STUDIES ON

THE CHEMISTRY OF TRIAZOLES.

by

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being a Thesis submitted for the degree
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in the Faculty of Science
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I wish to record my thanks to Professor E. E. Kurth, Head of the Chemistry Department, for the active interest he has taken in my studies and for his valuable advice on many occasions.

Dr. J. B. Polya, Senior Lecturer in Organic Chemistry, has been my supervisor during this course, and I am particularly indebted to him for his generous assistance in both theoretical and experimental aspects of the investigation.

Dr. E. A. Parkes has kindly permitted the inclusion of some of his spectroscopic measurements on 1:2:4-triazoles.

The frequent assistance and advice of Drs. J. A. Allen, I. R. C. Bick, A. A. Komzak and L. E. Smythe, staff members of the Chemistry Department, is gratefully acknowledged, as is the microanalytical service provided by C.S.I.R.O. Melbourne, under the direction of Dr. K. W. Zimmermann.

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calculations (made with Mr. I. M. Bassett) on electron distributions.

My wife has kindly checked portions of the manuscript and a number of the calculations.

An I.C.I.A.N.Z. Research Fellowship is acknowledged with thanks.

MEMORANDUM.

The rules of the degree of Doctor of Philosophy in the University of Tasmania require that where results already submitted for another degree are incorporated in the Doctorate thesis their extent should be clearly specified.

In order to present a unified treatment of the problems discussed in this thesis, it has seemed most desirable to include some preliminary experiments which were among those submitted in a thesis for the degree of Bachelor of Science with Honours in the University of Tasmania. All such experiments have been indicated by inclusion of the letter (H) with the experiment number in the body of the thesis.

A number of the preparations of compounds required for spectroscopic investigation were conducted largely or partly by my supervisor, Dr. J. B. Polya. In all these cases the author assisted at least in the final purification of the compounds. Such experiments are indicated in the experimental part by the letters (JP).

This thesis contains a section on the spectroscopy of triazoles. A number of the results included in the composite table of spectroscopic features, and several of the curves used for comparison purposes., were

obtained by the author in the earlier investigation mentioned above, or by Dr. E. A. Parkes (Ph. D. Thesis, Tasmania, 1953). These compounds have been indicated in the composite table by the letters (H) or (AP).

It has been necessary to repeat a considerable number of reactions which have been described in the literature, and in general details of such preparations have only been given when repetition has presented novel features. In such cases reference has been made to the original authors.

The preparation of new compounds has been indicated by underlining the name of the compounds in the body of the experimental part. Where the same new compound was prepared by a number of methods the name is underlined in the experiment which also presents the relevant analytical data.

TABLE OF CONTENTS.

INTRODUCTION.

During the last eight years a number of aspects of amide chemistry have been studied in the Chemistry Department, University of Tasmania, under the direction of Dr. J. B. Polya. Acylation of amides to diacylamines was investigated, and satisfactory syntheses were developed for unsymmetrical diacylamines ($R^1.CO.NH.CO.R^2$; $R^1 \neq R^2$). In some cases such diacylamines, through reacylation, may form mixtures of the two corresponding symmetrical diacylamines. Diacylamines react with hydrazines to form 1:2:4-triazoles, which are convenient derivatives indicating the structure of the diacylamine. With a hydrazine $R.NH.NH_2$ an unsymmetrical diacylamine of the type indicated could form $1R\text{-}3R^1\text{-}5R^2$- and $1R\text{-}3R^2\text{-}5R^1$-1:2:4-triazole. Proving the orientations of the products from a number of diacylamines seemed a promising way to investigate the mechanism of this triazole synthesis. Mr. P. L. Tardrew, Demonstrator in the Chemistry Department, reported the reaction of N-acetylpropionamide with phenylhydrazine in a thesis dealing with diacylamines. A crude picrate and mercuric chloride adduct were isolated, indicating the structure of the ethylmethylphenyltriazole formed. The results presented here follow from this work.

As part requirement for the degree of Bachelor of Science with Honours in the University of Tasmania the author isolated the triazoles formed in the reaction of N-acetylpropionamide, N-acetylbenzamide and N-formylbenzamide with phenylhydrazine. Structural proofs were attempted from the reaction of amides and 1-acyl-2-phenylhydrazines, but considerable doubt was thrown on the validity of these proofs by the frequency with which mixtures of triazoles were obtained in this reaction. Meanwhile biological investigation of a number of the triazoles prepared showed a marked C-mitotic effect on dividing cells. It seemed very desirable to develop unambiguous syntheses of 1:2:4-triazoles.

Since work for submission in this thesis was started one reaction has been found suitable for unambiguous synthesis of 1:2:4-triazoles. This is the reaction of amidrazones, $R.NH.N:C(NH_2).R^2$ with acylating agents, $R^1.CO.X$, to give 1-R-3-R^2-5-R^1-1:2:4-triazole. Using this reaction the work mentioned in the previous paragraph was finalized, and was published in the Journal of the Chemical Society (c.f. Triazoles I). 1:3-Diphenyl-1:2:4-triazole has been the suoject of some confusion. Following a note by Thompson in the Journal of the American Chemical Society pointing out that the

1:5-diphenyl- isomer had been incorrectly identified in the earlier literature, we have been able to prepare the 1:3-isomer in modified amidrazone reaction using formic acid as the acylating agent. This result is reported as a note in the American Journal.

1:2:4-Triazoles are among the simplest compounds in which N-substitution may be studied and correlated with the results of π-electron density calculations. When the substituents on the two carbon atoms are identical, the adjacent "hydrazinic" nitrogen $N_{1(2)}$ atoms are indistinguishable, but chemically distinct from the isolated nitrogen, N_4. Methylation and acetylation of this simple system with various substituents on $C_{3(5)}$ is reported, with structural proofs of the products, in the Journal of the Chemical Society (Triazoles 11). When the substituents on C_3 and C_5 are different the three nitrogen atoms of the triazole are chemically distinguishable. No unambiguous synthesis of 1-methyl-3-R^1-5-R^2-1:2:4-triazole was available, since the structure of the required N-methylamidrazone was not known. After this structure had been proved by cyclization with ethyl chloroformate to a hydroxytriazole of known structure, such unambiguous syntheses were possible. Methylations of unsymmetrically substituted triazoles were then

conducted. The same reference substances served to prove the structures of the triazoles obtained from methylhydrazine and unsymmetrical diacylamines. These results were reported in a paper recently submitted for publication in the Journal of the Chemical Society.

A note on the opening of triazole rings, and on a correction to the literature of this subject has been accepted for publication in "Chemistry and Industry".

Aminotriazole formation from aminoguanidine and its derivatives was investigated, with particular reference to aminotriazoles derived from aromatic and heterocyclic acids. Some of these compounds will be tested for tuberculostatic activity.

Amidrazone syntheses from iminoethers and hydrazines were studied, and with the improvements found, these intermediates may be conveniently prepared.

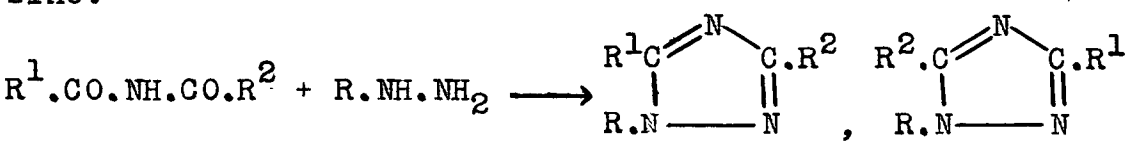
A study of the ultraviolet absorption spectra of 1:2:4-triazoles was partly reported in the author's B.Sc. (Hons.) thesis, was continued by Dr. E. A. Parkes, and is further extended in this thesis. As indicated in the introductory memorandum, work presented for the previous degree has been clearly marked, as have the contributions of other workers in this Department.

SECTION 1.

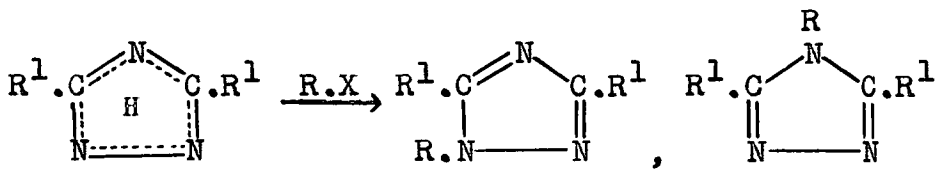
UNAMBIGUOUS SYNTHESES OF TRIAZOLES.

Discussion.

The investigations reported in Section 2 deal principally with reactions of diacylamines and hydrazines. In the case of unsymmetrical diacylamines, two triazoles may be formed in the reaction with a substituted hydrazine.



In Section 3, investigations on N-substitution of triazoles are reported. These are of the types:



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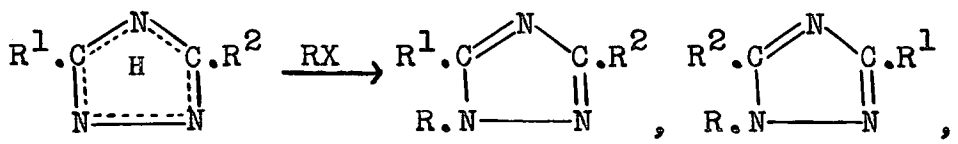
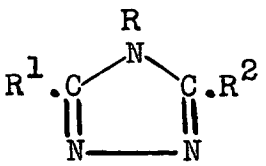


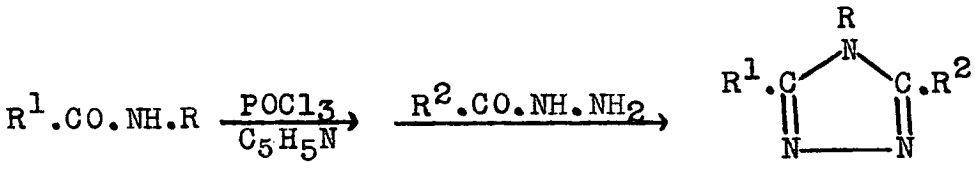


where RX represents an acylating or alkylating agent.

Both these classes of reactions lead to products of unknown orientation, and to obtain information about

them it has been essential to find independent syntheses of triazole isomers which would indicate the structures of products obtained. Some general observations on methods which are available or have been developed here precede the experimental part of Section 1, where specific examples are given.

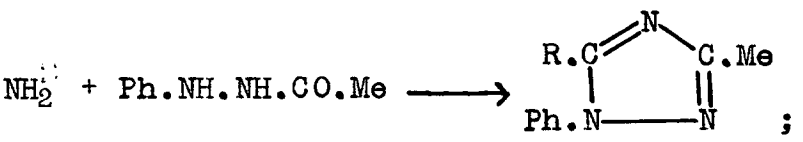
Satisfactory unambiguous syntheses of 4-substituted triazoles are available. The condensation of N-substituted amides and hydrazides in inert solvents (e.g. chloroform, carbon tetrachloride) under the influence of phosphorus oxychloride and pyridine:

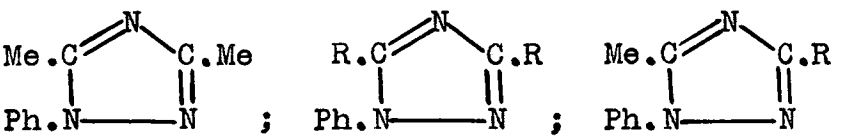


takes place without rearrangement. Reports of extensive use of this reaction are found in the patent literature (1,2,3.) 4-Ethyl-3:5-dimethyl- and 4-methyl-3:5-diphenyl-1:2:4-triazole were thus prepared during this investigation. An attempt to use this synthesis in the case of reactants of the type $R^1.CO.NH_2$ + $R.NH.NH.CO.R^1$ failed although phosphorus oxychloride addition was conducted below 0^o. With benzamide much benzonitrile was formed. On the other hand both the above types of amide-hydrazide pairs will react to give triazoles under the near-

pyrolytic conditions of Pellizzari's reaction [4,5]. Reaction temperatures of 200-260° are generally used.

Pellizzari's reaction is almost valueless for unambiguous syntheses when R^1, R^2 are different. Thus reactions of the type:



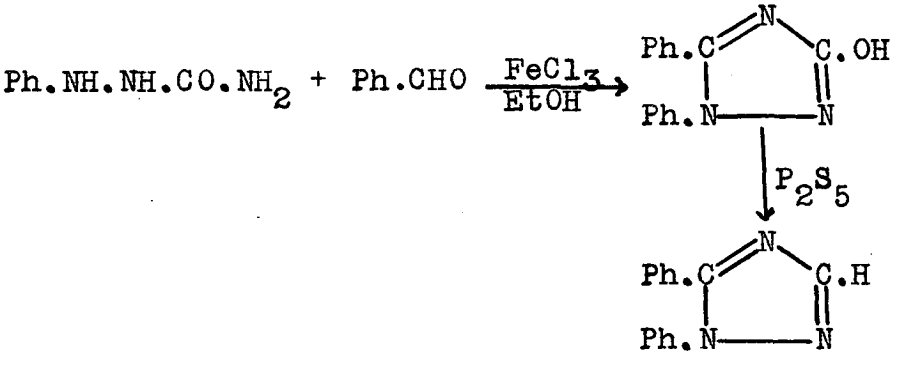


are possible, presumably through exchange of acyl groups. In this work 3-ethyl-5-methyl-1-phenyl-1:2:4-triazole was the only new triazole prepared solely by a Pellizzari reaction (from acetamide and 1-phenyl-2-propionylhydrazine). In other reactions reported here the products obtained from various combinations of formamide, acetamide and benzamide with 1-formyl, 1-acetyl and 1-benzoyl-2-phenylhydrazine were also prepared by independent methods.

When benzamide and 1-acetyl-2-phenylhydrazine were heated together below 200° cyclization to a triazole did not take place. Instead a compound was obtained which analyzed as an equimolar adduct of the reactants. The

same compound was obtained when a chloroform solution of these reactants was concentrated. Under these mild conditions it is not likely that the components' structures are much modified. Hydroxylic solvents decompose the adduct to its components.

Structures of unsymmetrically substituted triazoles have previously been proved by reduction of hydroxytriazoles, many of which may be obtained in a known orientation. Thus Young was able to prepare 1:5-diphenyl-1:2:4-triazole. (22)



This reaction was repeated to check the structure of a diphenyltriazole described in Section 2. Young and Oates (38) wished to compare 1-methyl-3-phenyl- and 1-methyl-5-phenyl-1:2:4-triazole, in an investigation of triazole tautomerism, but they were unable to prepare these compounds. When they heated 5-hydroxy-1-methyl-3-phenyl-1:2:4-triazole with phosphorus pentasulphide they

obtained 3-phenyl-1:2:4-triazole. This lack of an unambiguous synthesis for 1-methyl-3-R^1-5-R^2-1:2:4-triazole was a serious handicap in the present investigation, since work reported in Sections 2 and 3 involved a number of such compounds. The problem has finally been solved through the use of amidrazones as intermediates.

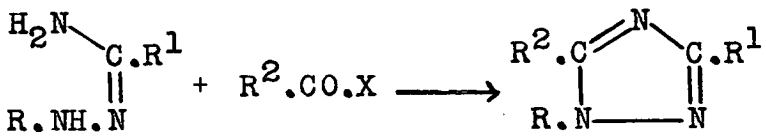
When iminoethers and hydrazines are reacted in water, ethanol or ether, amidrazones are formed:

$$R.NH.NH_2 + R^1.C(=NH)(OEt) \longrightarrow R.NH.N=C(NH_2).R^1 \text{ or } R.C(=NH).NH.NH_2$$

1. 11.

The formulation 1 has always been assumed (c.f. Voswinkel[6] Jerchel and Fischer [7]) and in the cases where R = Ph this formulation is justified by independent syntheses from, for instance, benzylidene-phenylhydrazone. In the case of methylhydrazine, however, structure 11 is quite likely, since the nucleophilic centre of the hydrazine is $N_{(1)}$, a result which is discussed more fully in Section 2. Further, unambiguous syntheses of 1 or 11 for R = Me are not available.

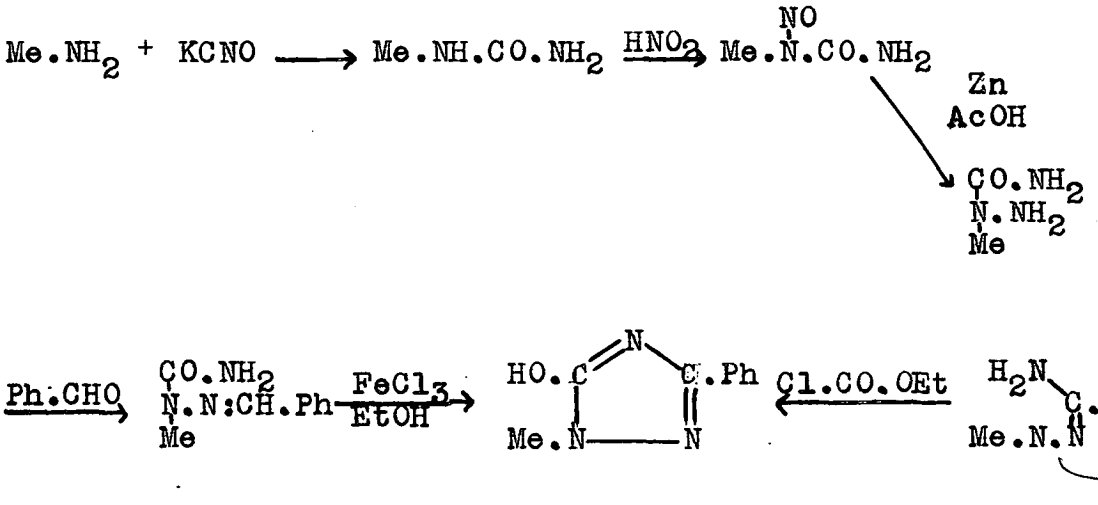
The interest in amidrazones arises from the fact that with acylating agents they are cyclized to triazoles, a result observed by Pinner [8] and investigated further by Ponzio. [9]



(X = Cl; .O.CO.R^2)

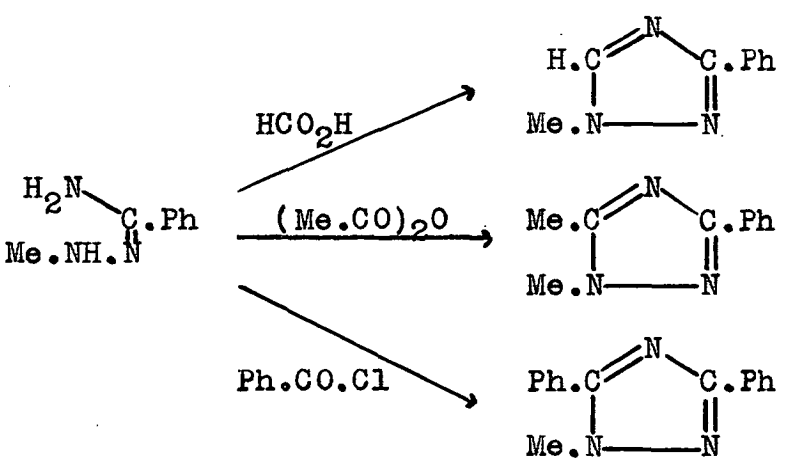
This reaction takes place at room temperature or on a steam bath, and does not afford mixtures of triazole isomers. In this investigation triazole synthesis from amidrazones was extended to the case R^2 = H by acylating with formic acid. Also it was found in the later stages of the work that amidrazone hydrochlorides could be cyclized directly without preliminary liberation of the base. Thus the new compounds 1:3-diphenyl- and 1:3-diphenyl-5-styryl-1:2:4-triazole were obtained from benzamide phenylhydrazone by the action of formic acid and of cinnamoyl chloride.

The structure of the amidrazone obtained from methylhydrazine and ethyl benziminether has now been proved by cyclization to 5-hydroxy-3-phenyl-1-methyl-1:2:4-triazole with ethyl chloroformate. The same compound was obtained by Young in a sequence of reactions which is not likely to involve a changed orientation in the product.



The amidrazone therefore has the structure indicated.

With formic acid and with acetic anhydride it was cyclized to 1-methyl-3-phenyl- and 1:5-dimethyl-3-phenyl-1:2:4-triazole. With benzoyl chloride 1-methyl-3:5-diphenyl-1:2:4-triazole was obtained.

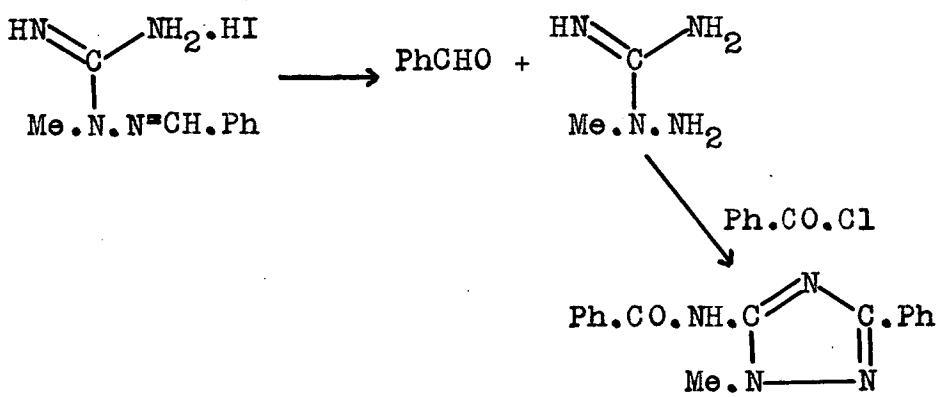


The compounds obtained in the reaction of N-formyl-benzamide and of N-acetylbenzamide with methylhydrazine were isomeric with the methylphenyl- and

dimethylphenyltriazole obtained from the amidrazone.

Before the ethyl chloroformate reaction was found to prove the structure of benzamide methylhydrazone, an independent method of obtaining 1-methyl-3-phenyl-1:2:4-triazole was investigated. Having an authentic sample of this compound, it would have been possible to deduce the amidrazone's structure from a cyclization with formic acid.

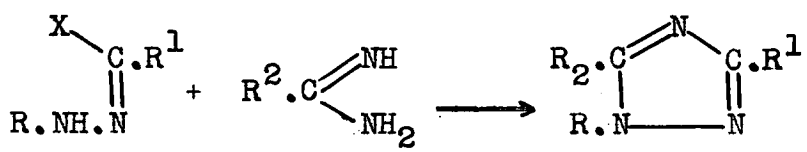
1-Benzylidenamino-1-methylguanidine hydriodide, prepared by the method of Finnegan, Henry and Smith (10) was hydrolyzed and treated with benzoyl chloride and sodium hydroxide. 5-Benzoylamino-1-methyl-3-phenyl-1:2:4-triazole was obtained:



Hydrolysis and removal of the amino group by treatment of the corresponding diazo-compound with hypophosphorous acid would probably have afforded the required methyl-phenyltriazole, but these steps were not carried out,

since the problem was meanwhile solved by the methods indicated earlier.

As reported in Section 3 of this thesis, methylation of triazole sodium salts with methyl iodide has been investigated as a means of locating the more nucleophilic nitrogen atoms of the anion. Clearly, the various syntheses above permit comparisons to be made for any of the N-methyl derivatives of 3-phenyl- and 3-methyl-5-phenyl-1:2:4-triazole. At an earlier stage, when it seemed that reference materials would not be available for methylation experiments, 1-chloro-2:4-dinitrobenzene was considered as a substituting agent. Amidines will react with α-halo-hydrazones to form triazoles (c.f. Fusco and Musante [11].



(X = halogen)

The relevant compounds in this case would have R = 2:4-dinitrophenyl, R^1 = Ph, R^2 = H, Me. Benzylidene-2:4-dinitrophenylhydrazone, treated with bromine in acetic acid and in carbon tetrachloride, did not react, but after several months in carbon disulphide a monobromo derivative was formed.

EXPERIMENTAL PART.

N-alkyl amides required for triazole syntheses.

A convenient preparation of N-methylacetamide from acetamide and methylamine hydrochloride has been described by Galat and Elion [12]. This method was found satisfactory for the preparation of N-methylacetamide and was extended to the case of N-ethylacetamide.

Experiment No. 1.1. Preparation of N-ethylacetamide.

Ethylamine hydrochloride (36 g.) and acetamide (30 g.) were mixed and heated at 200° until no more ammonium chloride separated from the melt. The product was extracted with chloroform (100 cc.) and the extract distilled. N-ethylacetamide, b.p. 205-206°/760 mm. (29.6 g., 78%) was collected; (lit., b.p. 205°) [13]

N-methylbenzamide.

This material was prepared by the standard method of benzoylating a solution of methylamine in benzene with benzoyl chloride in the presence of pyridine. [14] Recrystallized from benzene-light petroleum (b.p. 60-80°) the product was obtained as colourless plates, m.p. 75-77° (lit., m.p. 78°).

Ethyl benzimino-ether hydrochloride.

Benzonitrile was reacted with ethanol and hydrogen chloride, and ethyl benzimino-ether hydrochloride m.p. 116°(d), was obtained.[15]

Ethyl acetimino-ether hydrochloride was prepared similarly (Dox, loc. cit.) from dry acetonitrile, ethanol and hydrogen chloride.

Anhydrous methylhydrazine.

Methylhydrazine sulphate was prepared from benzylidene-azine by the action of dimethylsulphate, following the procedure outlined in Organic Syntheses [16]. The anhydrous hydrazine has generally been obtained from its salts by heating in a sealed tube with barium oxide [17]. The following procedure was found to be more convenient. Methylhydrazine sulphate (57.6 g.) and powdered potassium hydroxide (100 g.) were mixed. Water was added (50 cc.) and the solution distilled from an oil-bath until the distillate, which had b.p. 105-110°/760 mm., no longer reduced Fehling's solution. The distillate was saturated with potassium hydroxide (70 g.), and the upper layer separated and distilled, again until no more reducing material passed over. The distillate was boiled under reflux with barium oxide (10 g.) in an atmosphere of dry nitrogen for 12 hours. On distillation in an atmosphere

of nitrogen, anhydrous methylhydrazine (9.2 g., 50%) was obtained as a colourless liquid, b.p. 87°/760 mm. From the combined aqueous alkaline residues and solids a further 4.4 g. (24%) of methylhydrazine in 8 cc. of aqueous solution was obtained by distillation. The hydrazine content was determined by iodate titration. All glass joints used in this work were lubricated with Dow-Corning silicone grease, and it may be mentioned that a pink colour developed where air had access to the lubricant and hydrazine.

Experiment No. 1.2. Preparation of benzamide methylhydrazone hydrochloride.

Methylhydrazine (4.6 g.) was added to a mixture of ethyl benzimino-ether hydrochloride (18.5 g.) and dry pyridine (40 cc.). The initial vigorous reaction was moderated by cooling to 30-35° in a water-bath. After 0.5 hour the crystalline mass was filtered, and the residue washed with dry ether (3 x 20 cc.). Dried at 105°, these colourless prisms (12.6 g., 68%) had m.p. 185°, unchanged on crystallization from a mixture of ethanol and ether. Jerchel and Fischer [7] report m.p. 185° for their preparation of benzamide methylhydrazone hydrochloride. Dilution of the mother liquors of the crystals with ether (60 cc.) precipitated more of the same material (3.3 g.)

(18%), m.p. 185°.

The advantages of using pyridine in promoting the condensation of hydrazines and iminoether salts to form amidrazones is well illustrated in this case. The conventional procedure, which has been outlined by Jerchel and Fischer (loc.cit.) involves reaction in ethanol for 8 days. A troublesome purification is usually involved.

In the earlier experiments on triazole syntheses involving cyclization of this amidrazone with acylating agents, the free base was used. It was subsequently found desirable to acylate the amidrazone hydrochloride. The base was not obtained in an analytically-pure condition, due to its instability, but was used directly for triazole syntheses.

Experiment No. 1.3. Preparation of benzamide methylhydrazone.

Benzamide methylhydrazone hydrochloride (11.1 g.) was dissolved in aqueous sodium carbonate (10%, 50 cc.) and the solution extracted with chloroform (4 x 50 cc.). The extract was dried (Na_2SO_4) and the solvent removed under reduced pressure (below 30°) leaving benzamide methylhydrazone (7.0 g., 78%) as a colourless oil which decomposed when set aside for several hours, and more rapidly on heating.

When a chloroform solution of the base was shaken with a neutral aqueous solution containing cobaltous or nickelous ion, deep purple or green colours respectively developed in the organic phase. In the former case the reaction was positive with solutions containing 5 p.p.m. cobalt.

Experiment No. 1.4. Conversion of benzamide methylhydrazone to 5-hydroxy-1-methyl-3-phenyl-1:2:4-triazole.

Benzamide methylhydrazone hydrochloride (3.71 g.) was converted to the free base (Experiment No. 1.3). The liberated base was treated without delay with ethyl chloroformate (3 cc.). Water-cooling was used to moderate the initial vigorous reaction, and cyclization was completed by heating the reactants for ten minutes on a steam-bath. Removal of excess solvent at 20 mm. pressure left a colourless fibrous solid, which was mixed with 2N aqueous sodium carbonate (to pH 8) and extracted with ether (4 x 30 cc.). Evaporation of the dried solution (Na_2SO_4) left crude 5-hydroxy-1-methyl-3-phenyl-1:2:4-triazole. Crystallization from benzene-light petroleum (b.p. 60-80°, 1:1) and sublimation at 150°/2 mm. gave the pure triazole (1.9 g., 54%), as colourless prisms, m.p. 219° alone or admixed with 5-hydroxy-1-methyl-3-phenyl-1:2:4-triazole prepared from 2-methyl semicarbazide

and benzaldehyde by the method of Young and Oates [38].

Analysis:	C	H	N
Found:	61.8	5.1	24.2%.
Calculated for $C_9H_9ON_3$:	61.7	5.2	24.0%.

The triazole did not give a picrate with an ethanolic solution of picric acid.

For comparison purposes this triazole was prepared by Young and Oates' method.

Unambiguous preparation of 5-hydroxy-1-methyl-3-phenyl-1:2:4-triazole.

Nitrosomethylurea (20.6 g.) was suspended in glacial acetic acid (55 cc.) and added gradually to a stirred suspension of zinc dust (55 g.) in ethanol (50 cc.). The temperature was maintained at -10 to 0° by cooling the flask in an ice-salt bath. At one stage of the reaction (after 0.75 hour) the temperature rose rapidly to 40°, with gas evolution and decomposition of much of the reactants. Addition was complete in 1.5 hour, and stirring was continued for a further hour. After filtration, benzaldehyde was added to the filtrate and the solution was set aside overnight. Water (50 cc.) was added, and solvents removed on the steam-bath until a crystalline mass was obtained. Recrystallization from 10% aqueous

ethanol gave benzylidene-2-methylsemicarbazide (6.9 g., 20%) as colourless needles, m.p. 161° (lit., m.p. 159-160°). Benzylidene-2-methylsemicarbazide (4.4 g.) and ferric chloride trihydrate (6.75 g.) in ethanol (30 cc.) were heated in a stoppered bottle at 105° for 6 hours. Ethanol was removed by steam-distillation, and after concentration of the involatile portion to 20 cc. and cooling, colourless needles of 5-hydroxy-1-methyl-3-phenyl-1:2:4-triazole, m.p. 215-218° separated (2.6 g., 59%). Recrystallization from a mixture of benzene and light petroleum (b.p. 60-80°) gave colourless prismatic needles, m.p. 218° alone or admixed with the triazole derived from the amidrazone. Young and Oates found m.p. 218-219°.

Experiment No. 1.5. Preparation of 1-methyl-3-phenyl-1:2:4-triazole.

Benzamide methylhydrazone hydrochloride (3.7 g.) and formic acid (99-100%; 4.6 g.) were mixed at room temperature. After 0.5 hour the reactants were boiled under reflux for 1 hour. No unreacted benzamide methylhydrazone remained at this stage of the reaction, cobalt chloride causing no purple colour when mixed with a small portion of the neutralized reactants. The whole product was poured into aqueous sodium carbonate (10%, 50 cc.) and extracted with chloroform (3 x 50 cc.). The dried

chloroform extract was evaporated and the residue distilled at reduced pressure, affording 1-methyl-3-phenyl-1:2:4-triazole (2.2 g., 69%) as a colourless oil, b.p. 110°/1 mm., which set to colourless prisms, m.p. 23°.

Analysis:	C	H	N
Found:	68.3	6.15	26.2%.
$C_9H_9N_3$ requires:	67.6	6.1	26.3%.

The triazole was evaporated with a chloroform solution of picric acid, and the residue recrystallized from ethanol, giving 1-methyl-3-phenyl-1:2:4-triazole picrate, yellow needles, m.p. 183°.

Analysis:	C	H	O
Found:	46.4	3.1	28.8%.
$C_{15}H_{12}O_7N_6$ requires:	46.6	3.0	28.4%.

The triazole and its picrate differ from the isomeric compounds derived from N-formylbenzamide and methylhydrazine sulphate, as indicated by the non-identity of their melting points and the depression of the melting points of the picrates in admixture (c.f. Figure 2).

An inferior preparation which used the free amidrazone instead of its hydrochloride gave a lower yield of 1-methyl-3-phenyl-1:2:4-triazole and purification was more difficult.

Experiment No. 1.6. Reaction of benzamide methylhydrazone with formic acid.

Benzamide methylhydrazone was obtained from the hydrochloride (3.71 g.) as in Experiment No. 1.3, and dissolved in formic acid (99%, 5 cc.). The initial vigorous reaction was moderated by cooling in a water-bath. The reactants were heated on a steam-bath for 0.5 hour, and then gave no amidrazone reaction (with cobaltous chloride, c.f. Experiment No. 1.3). The product was neutralized with 2N aqueous sodium carbonate. Extraction with chloroform (3 x 30 cc.) and evaporation of the dried (Na_2SO_4) extract left a pale brown oil (1.63 g.). Filtration of a benzene solution of this oil through a column of alumina (15 x 1 cm.) gave 1-methyl-3-phenyl-1:2:4-triazole (0.87 g., 27%), colourless prisms, m.p. 23° after sublimation at 80°/1 mm. The triazole gave a picrate, m.p. 184°. The triazole and its picrate did not depress the melting points of the materials prepared in Experiment No. 1.5.

Experiment No. 1.7. Preparation of 1:5-dimethyl-3-phenyl-1:2:4-triazole.

Benzamide methylhydrazone was obtained from the hydrochloride (3.71 g.) as in Experiment No. 1.3. The base was treated with acetic anhydride (3 cc.), the

initial reaction being moderated by cooling. After heating the solution on the steam-bath for 0.5 hour an aliquot tested with cobaltous chloride indicated the absence of unchanged benzamide methylhydrazone. The solution was neutralized with 2N aqueous sodium carbonate and extracted with chloroform (3 x 30 cc.). The extract was dried (Na_2SO_4), and the solvent removed, leaving 1:5-dimethyl-3-phenyl-1:2:4-triazole, colourless rosettes m.p. 113° (2.0 g., 58%). Crystallization from benzene and sublimation at 120°/2 mm. gave colourless prisms, m.p. 117°.

Analysis:	C	H	N
Found:	69.6	6.2	24.6%.
$C_{10}H_{11}N_3$ requires:	69.4	6.4	24.3%.

On evaporation with a chloroform solution of picric acid the triazole gave 1:5-dimethyl-3-phenyl-1:2:4-triazole picrate, m.p. 164°, which crystallized from ethanol as yellow silky needles, m.p. 166°.

Analysis:	C	H
Found:	48.1	3.7%.
$C_{16}H_{14}O_7N_6$ requires:	47.8	3.6%.

The triazole and its picrate differ from the isomeric compounds derived from N-acetylbenzamide and methylhydrazine sulphate (m.p. and mixed m.p.).

Experiment No. 1.8. Preparation of 1-methyl-3:5-diphenyl-1:2:4-triazole.

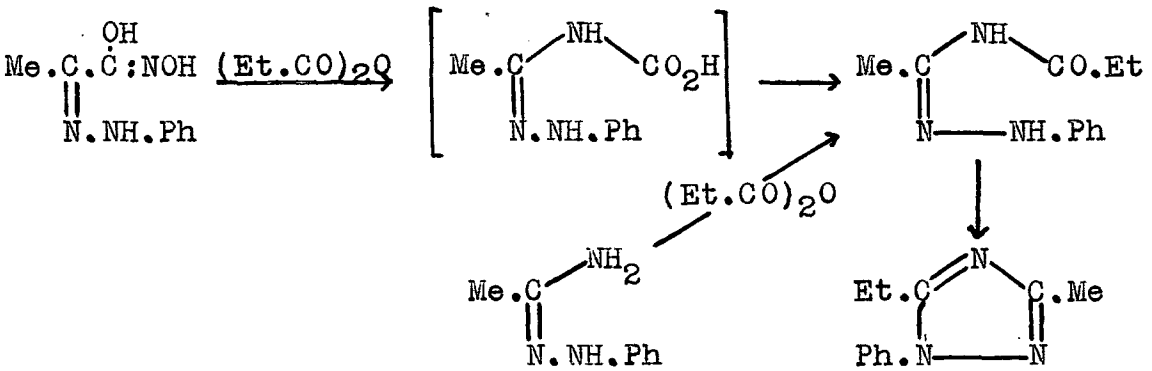
Benzamide methylhydrazone hydrochloride (0.5 g.) and benzoyl chloride (3 cc.) were heated together at 120° for 12 hours, and the resultant clear solution was poured into 2N aqueous sodium carbonate (25 cc.). After boiling for 4 hours the mixture was cooled and extracted with chloroform (3 x 50 cc.). The extract was dried (Na_2CO_3), and the solvent removed, leaving 1-methyl-3:5-diphenyl-1:2:4-triazole (0.59 g., 94%), colourless rosettes, m.p. 80°. Crystallization from benzene-light petroleum (b.p. 60-80°) gave colourless prisms (0.51 g.) m.p. 84°. When warmed with an ethanolic solution of picric acid the triazole precipitated 1-methyl-3:5-diphenyl-1:2:4-triazole picrate, which crystallized from ethanol as yellow needles, m.p. 135°.

The triazole and its picrate did not depress the melting points of the triazole and picrate derived from dibenzamide and methylhydrazine sulphate, or obtained by the methylation of 3:5-diphenyl-1:2:4-triazole (Sections 2 and 3).

5-Ethyl-3-methyl-1-phenyl-1:2:4-triazole.

This material was needed for reference purpose, since it appeared that the product obtained in the reaction of N-acetylpropionamide and phenylhydrazine (Section 2) was identical with this triazole, already prepared by Gastaldi [18]. Pyruvylhydroxamic acid phenylhydrazone was treated with propionic anhydride, as outlined by Gastaldi, and the resultant base separated from hydroxytriazoles and other products by extraction of their solution in aqueous sodium carbonate with ether. As only 0.3 cc. of the required triazole was obtained, and this oily product was not easy to purify, it was treated with picric acid, and the resultant 5-ethyl-3-methyl-1-phenyl-1:2:4-triazole picrate obtained as yellow rhombs (m.p. 139-139.5°). With the triazole obtained in the above-mentioned reaction of N-acetylpropionamide, the mixed m.p. was 139-140°, while with 3-ethyl-5-methyl-1-phenyl-1:2:4-triazole picrate, derived from the product of the reaction of acetamide and 1-phenyl-2-propionylhydrazine the mixed m.p. was 128-132°.

This triazole synthesis from pyruvylhydroxamic acid phenylhydrazone probably involves cyclization of an amidrazone obtained by rearrangement.



The same triazole was obtained when acetamide phenylhydrazone was treated with propionic anhydride.

Acetamide phenylhydrazone.

Ethyl acetimino-ether and phenylhydrazine were reacted in ether for 1 day, as outlined by Voswinkel[c] (19), and acetamide phenylhydrazone isolated from the product as its hydrochloride, which crystallized from ethanol on addition of light petroleum (b.p. 100-120°). The hydrate had m.p. ca. 140°, and the anhydrous hydrochloride m.p. 200-205° (lit., m.p. 140° and 205° respectively).

Experiment No. 1.9. Reaction of acetamide phenylhydrazone with propionic anhydride.

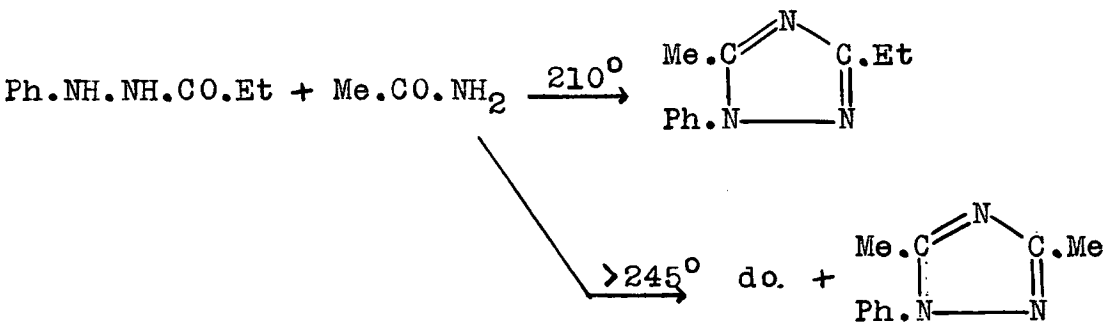
Acetamide phenylhydrazone (1.2 g.) was obtained from the hydrochloride by ether extraction of its solution in 2N aqueous sodium carbonate. Propionic anhydride (6 cc.) was added, and the mixture was boiled under

reflux for 10 minutes. The product was poured into aqueous sodium carbonate (2N, 50 cc.), and after excess propionic anhydride had reacted with the alkali, basic material was extracted with ether (4 x 40 cc.). The ether extract was dried (Na_2SO_4) and evaporated, leaving an oil, which was treated with ethanolic picric acid. 5-Ethyl-3-methyl-1-phenyl-1:2:4-triazole picrate was obtained as yellow rhombs, m.p. 139°(1.05 g.). Recrystallized from a mixture of ethanol and ether the product had m.p. 139°, and caused a small depression in the m.p. of 5-ethyl-3-methyl-1-phenyl-1:2:4-triazole picrate derived from triazole obtained in the Einhorn-Brunner reaction of N-acetylpropionamide and phenylhydrazine. When the two picrates were crystallized in similar conditions from ethanol they had m.p. 139-140°, and the melting point was not depressed on admixture. With the isomeric 3-ethyl-5-methyl-1-phenyl-1:2:4-triazole a 6° depression in the mixed melting point was observed.

3-Ethyl-5-methyl-1-phenyl-1:2:4-triazole.

To prepare this compound, isomeric with the ethylmethylphenyltriazole obtained by reacting N-acetylpropionamide and phenylhydrazine, 1-phenyl-2-propionylhydrazine and acetamide were heated together to 210°. When another batch of the reactants was heated above

254°, and then distilled to 240°/25 mm., considerable contamination of the product with dimethylphenyltriazole took place.



After heating the reactants for 9 hours at 175°, unchanged hydrazide was recovered in 96% yield.

Experiment No. 1.10(H). Reaction of 1-phenyl-2-propionylhydrazine and acetamide.

2-Phenyl-1-propionylhydrazine (180 g.) and dry, freshly distilled acetamide (60 g.) were heated at 60° for 14 hours. The temperature was then raised to 210°, and maintained thereat for 6 hours, while volatile products distilled off. The residual viscous oil was fractionated, giving acetamide, b.p. 108-109°/15 mm. (33 g.), the triazole, b.p. 152-162°/12 mm. (20 g.), and 1-phenyl-2-propionylhydrazine, b.p. 164°/12 mm., m.p. 158-159° (85 g.). On refractionation a mixture of the triazole and acetamide, b.p. 92-110°/2 mm. (1.5 g.) was first

obtained, then 3-ethyl-5-methyl-1-phenyl-1:2:4-triazole (16 g., 17% on unrecovered 1-phenyl-2-propionylhydrazine or 21% on unrecovered acetamide) distilled at 116-118°/2 mm. The pure triazole had b.p. 278°/755 mm., d_{20}^{20}: 1.058, n_D^{20}: 1.5505.

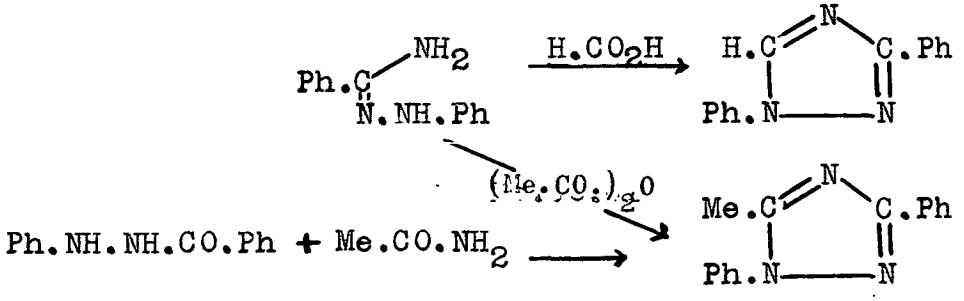
Analysis:	C	H	N
Found:	70.7	6.9	21.9%.
$C_{11}H_{13}N_3$ requires:	70.6	6.9	22.5%.

With an ethanolic solution of picric acid, 3-ethyl-5-methyl-1-phenyl-1:2:4-triazole picrate was obtained as yellow monoclinic prisms, m.p. 138-140°. Recrystallization from chloroform-ethanol (1:2) and then from 90% ethanol gave a product with m.p. 141-142°. The mercuric chloride adduct crystallized from 50% ethanol as colourless needles, m.p. 138-140°, and the hydrochloride, obtained by evaporating the base with hydrochloric acid, had m.p. 208-210°.

These compounds differed from 5-ethyl-3-methyl-1-phenyl-1:2:4-triazole and its derivatives obtained from N-acetylpropionamide and phenylhydrazine. The melting points were depressed in admixture.

1:3-Diphenyl- and 5-methyl-1:3-diphenyl-1:2:4-triazole.

Isomers of these triazoles were obtained (Section 2) when N-formylbenzamide and N-acetylbenzamide respectively were reacted with phenylhydrazine. Both structures were supported by syntheses from amides and hydrazides, and the former had been prepared from phenylsemicarbazide by Young (22), but as rearrangements in this high-temperature reaction (Pellizzari reaction) are the rule rather than the exception, a more rigorous proof of their structure was needed. Einhorn and Szelinski (21) considered that the product they obtained in the reaction of N-formylbenzamide and phenylhydrazine to be 1:3-diphenyl-1:2:4-triazole. From the present investigation, and from the work of Thompson (54) it was clear that the product was really 1:5-diphenyl-1:2:4-triazole, and it seemed desirable to prepare the unknown 1:3-diphenyl-isomer. This was achieved by cyclizing benzamide phenylhydrazone with formic acid. Jerchel and Kuhn's preparation of 5-methyl-1:3-diphenyl-1:2:4-triazole from benzamide phenylhydrazone and acetic anhydride was also repeated.



Benzamide phenylhydrazone.

This was prepared from ethyl benzimino-ether hydrochloride and phenylhydrazine in ethanol in a reaction taking 8 days for completion. Again the method is essentially that of Voswinkel[6]. The amidrazone was separated from phenylhydrazine hydrochloride by crystallization from ethanol, in which the former is more soluble. Benzamide phenylhydrazone hydrochloride hemihydrate crystallized from ethanol or hydrochloric acid as colourless prisms, m.p. 122-125° (Jerchel and Kuhn[20] report m.p. 122-124°). The picrate had m.p. 196-198° (Jerchel and Kuhn report m.p. 197-198°).

Experiment No. 1.11.

Benzamide phenylhydrazone hydrochloride was also obtained when equimolar amounts of ethyl benziminoether hydrochloride and phenylhydrazine were reacted in pyridine. The product from a 0.1 molar scale experiment was crystallized from dilute ethanol as the hemihydrate, m.p. 125° (19.5 g.). The water was removed on storing for 1 month over strong sulphuric acid at 0.1 mm.

Experiment No. 1.12. Reaction of benzamide phenylhydrazone with formic acid.

Benzamide phenylhydrazone was purified through its picrate as outlined above, and the base was liberated with cold saturated aqueous lithium hydroxide (13%). Lithium picrate is very soluble in water. The basic portion was dried, but did not crystallize. The amidrazone (7.2 g.) and formic acid (99%, 8.0 cc.) were heated under reflux at 100° for 1.5 hour. The product was adjusted to pH 8 with aqueous sodium carbonate (10%) and extracted with ether (3 x 50 cc.). The ether extract was dried and evaporated. Distillation of the residue gave a fraction with b.p. 160-220°/2 mm. which set to oily crystals (4.5 g.). These were dissolved in dry ether (150 cc.) and treated with dry hydrogen chloride to precipitate 1:3-diphenyl-1:2:4-triazole hydrochloride (5.7 g.) as a colourless powder, m.p. 192-194°.

Analysis:	Cl
Found:	13.7%.
$C_{14}H_{12}N_3Cl$ requires:	13.8%.

The hydrochloride was decomposed with aqueous sodium carbonate (10%, 100 cc.) and extracted with ether (3 x 50 cc.). Evaporation of the dried extract left 1:3-diphenyl-1:2:4-triazole (2.7 g., 36%) as colourless

prismatic crystals, m.p. 79-81°. This material was further purified through the picrate, which crystallized from ethanol as yellow needles, m.p. 161-161.5°.

Analysis:	C	H	N
Found:	53.4	3.2	17.7%.
$C_{20}H_{14}O_7N_6$ requires:	53.3	3.1	18.7%.

The liberated base after two recrystallizations from light petroleum (b.p. 60-80°) had m.p. 82.5-83°.

Analysis:	C	H	N
Found:	76.3	5.3	19.2%.
$C_{14}H_{11}N_3$ requires:	76.0	5.0	19.0%.

The base and picrate depressed the melting points of the corresponding products from the N-formylbenzamide reaction.

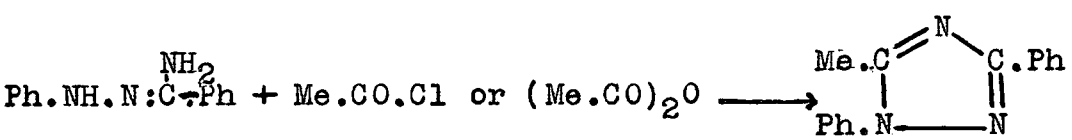
Experiment No. 1.13(H) Reaction of 1-formyl-2-phenylhydrazine and benzamide.

1-Formyl-2-phenylhydrazine (27.2 g.) and benzamide (25 g.) were heated to 220° during 4 hours, volatile products being allowed to distill off during the reaction (4 g.). The mixture was then poured into 10% potassium hydroxide solution (200 cc.) and extracted with ether (3 x 50 cc.), the extract evaporated and the residue fractionated, giving 1-phenyl-1:2:4-triazole (2.0 g., 7%) b.p. 144-148°/10 mm.; the picrate had m.p. 156-158° alone

or mixed with that of the triazole prepared by Pellizzari and Ferro's method [71]. A second fraction (1.7 g., 4%) b.p. 158-160°/4 mm., m.p. 60-70° (after sublimation, m.p. 85-90°), was 1:5-diphenyl-1:2:4-triazole; neither this nor its picrate (m.p. 136-138°) depressed the m.p. of authentic material prepared from benzylidene phenylsemicarbazide.

When 1-formyl-2-phenylhydrazine and benzonitrile were boiled under reflux for several hours all the nitrile could be recovered from the mixture, and no triazole formation took place.

When N-acetylbenzamide and phenylhydrazine were reacted with one another in the presence of various buffer systems (Section 2) a diphenylmethyltriazole was obtained which had m.p. 81°, forming a picrate which had m.p. 154°. Meanwhile Jerchel and Kuhn [20] had obtained 5-methyl-1:3-diphenyl-1:2:4-triazole by reacting acetic anhydride or acetyl chloride with benzamide phenylhydrazone:



This product was reported to have m.p. 92°. Their preparation was repeated using acetic anhydride, and

5-methyl-1:3-diphenyl-1:2:4-triazole was obtained, m.p. 91°. This product gave a melting point depression of ca. 30° with the isomeric triazole obtained from N-acetylbenzamide, but did not depress the melting point of the methyldiphenyltriazole obtained (Experiment No. 1.16b.) from 1-benzoyl-2-phenylhydrazine and acetamide. The triazole gave a picrate, m.p. 184-186°, which did not depress the melting point of the triazole picrate from 2-benzoyl-1-phenylhydrazine, but which was clearly different from the isomeric picrate (m.p. 154°) obtained in the N-acetylbenzamide reaction. From this it follows that the product in the reaction of N-acetylbenzamide with phenylhydrazine is 3-methyl-1:5-diphenyl-1:2:4-triazole.

Experiment No. 1.14.(H). Reaction of 1-acetyl-2-phenylhydrazine and benzamide.

1-Acetyl-2-phenylhydrazine (10 g.) and benzamide (10 g.) were heated on an oil bath to 185° during 1 hour then kept at 175-185° for 4 hours and finally at 200° for 1 hour. The residual pale brown oil solidified on cooling. It was dissolved in water (300 cc.), boiled with Norite, filtered, brought to pH 8 with ammonia, and cooled, giving a mixture of rhombic prisms and needles, m.p. 96-120° (10.6 g.). When dissolved in warm 0.1N hydrochloric acid and cooled this afforded benzamide,

m.p. 128-129° (4.6 g.). The acid solution was extracted with ether (2 x 50 cc.) affording 1-acetyl-2-phenylhydrazine, m.p. 128-130° (2.8 g.). The aqueous solution was brought to pH 10 with ammonia and extracted with ether (3 x 100 cc.) from which colourless prisms, m.p. 105-107° were obtained. (2.3 g., 18% on unrecovered 1-acetyl-2-phenylhydrazine, 19% on unrecovered benzamide).

Analysis:	C	H	N
Found:	66.2	6.3	15.5%.
Ph.NH.NH.Ac + Ph.CO.NH_2 i.e. $C_{15}H_{15}O_7N_2$ requires:	66.4	6.3	15.5%.

The substance gave neither picrate nor mercuric chloride adduct, it deteriorated on sublimation or recrystallization from aqueous ethanol.

More recently further evidence regarding the structure of this compound has been obtained. When equimolar proportions of benzamide and 1-acetyl-2-phenylhydrazine were dissolved in chloroform, and the solution evaporated below 40°, the colourless prismatic material which separated had m.p. 106° alone or admixed with the product obtained in the high temperature reaction mentioned above. The adduct is probably a result of simple association of the two components.

Experiment No. 1.15(H). 1-Acetyl-2-phenylhydrazine (11.5 g.) and benzamide (9.1 g.) were heated together in an oil-bath at 180° for 4 hours and at 245° for 4 hours, with evolution of water and ammonia. The oily product was poured into aqueous potassium hydroxide (40%, 100 cc.) and extracted with ether (3 x 100 cc.). The extract was freed from phenylhydrazine and 1-acetyl-2-phenylhydrazine as far as possible by Brunner's method (26). Fractionation gave a partially crystallizing forerun (0.8 g.) then 1-acetyl-2-phenylhydrazine, b.p. 158-165°/2-4 mm., m.p. 129-130° (2.9 g.) and 3-methyl-1:5-diphenyl-1:2:4-triazole, b.p. 170-195°/2-4 mm., m.p. 79-80° (0.75 g., 6% on unrecovered 1-acetyl-2-phenyl-hydrazine).

Analysis:	C	H	N
Found:	76.6	5.5	17.5%.
$C_{15}H_{13}N_3$ requires:	76.6	5.5	17.9%.

The forerun was separated by filtration into crystalline 1-acetyl-2-phenylhydrazine (0.1 g.) m.p. 129°, and an oil identified as 3:5-dimethyl-1-phenyl-1:2:4-triazole (0.6 g.) through the picrate, m.p. and mixed m.p. 155-157°.

When 1-acetyl-2-phenylhydrazine and benzamide were reacted in chloroform solution in the presence of

phosphorus oxychloride-pyridine most of the amide was converted to benzonitrile, but a small amount of the hydrazide-amide complex (m.p. and mixed m.p. 106°) was isolated. No methyldiphenyltriazole could be detected among the products of the reaction.

Experiment No. 1.16(H). 1-Benzoyl-2-phenylhydrazine and acetamide.

a.(H). The reaction between 1-benzoyl-2-phenylhydrazine and acetamide at 140° during 1 hour and then at 175° during 4 hours did not afford triazoles, but 90% of the reactants were recovered.

b.(H). 1-Benzoyl-2-phenylhydrazine (6.0 g.) and dry, freshly distilled acetamide (15 g.) were boiled under reflux in an oil bath at 250° for 4 hours. The unreacted acetamide was distilled off at atmospheric pressure, and the residue extracted with ether (2 x 50 cc.) leaving undissolved 1-benzoyl-2-phenylhydrazine, m.p. 166°,(2.1 g.). The crude triazole extract (3.8 g.) was fractionated to give as main fraction a pale yellow oil b.p. 210-215°/25 mm., which solidified after several months (2.1 g.). Recrystallization from light petroleum (b.p. 40-60°) removed insoluble 1-acetyl-2-phenylhydrazine, m.p. 129° (0.08 g.). The petroleum extract was sublimed at 40°/2 mm. to afford crude 5-methyl-1:3-

diphenyl-1:2:4-triazole, m.p. 80-85°. The picrate was obtained as flat prisms, m.p. 180-182°, which, recrystallized from ethanol, had m.p. 184-186°.

Analysis:	C	H	N
Found:	54.6	3.6	17.0%.
$C_{21}H_{16}O_7N_6$ requires:	54.3	3.45	18.1%.

The substance and its derivative were not identical with the various samples of 3-methyl-1:5-diphenyl-1:2:4-triazole and its picrate, but were identical with 5-methyl-1:3-diphenyl-1:2:4-triazole picrate prepared according to Jerchel and Kuhn. (loc. cit.)

c.(H). 1-Benzoyl-2-phenylhydrazine (95 g.) and acetamide (50 g.) were heated at 260-280° for 3 hours, water and other volatile materials being allowed to distil off (40 g.). The residue was poured into 10% aqueous sodium hydroxide (250 cc.) and the resulting mixture was extracted with ether (3 x 50 cc.). The oil (85 g.) from the extract was fractionated, giving a forerun 110-120°/14 mm. (6.1 g.), 3:5-dimethyl-1-phenyl-1:2:4-triazole, b.p. 134-138°/3 mm., and 118-124°/2 mm. (27.6 g., 70% on unrecovered 1-benzoyl-2-phenylhydrazine) (picrate m.p. 154-156°; mercuric chloride adduct, m.p. 186-189°) and 1-benzoyl-2-phenylhydrazine, b.p. 172-180°/2 mm., m.p. 167-168° (47 g.).

Experiment No. 1.17. Reaction of cinnamoyl chloride with benzamide phenylhydrazone.

Benzamide phenylhydrazone (16.8 g.) and cinnamoyl chloride (14.2 g.) were heated together at 100° for 12 hours. The product was poured into aqueous sodium carbonate (10%, 100 cc.) and extracted with benzene (200 cc.). The extract was dried (Na_2SO_4) and evaporated, leaving crude 1:3-diphenyl-5-styryl-1:2:4-triazole (11.0 g., 40%) m.p. 128-132°. Recrystallized from ethanol or purified by sublimation at 120°/0.1 mm. this material had m.p. 134°.

Analysis:	C	H	N
Found:	81.6	5.2	13.7%.
$C_{22}H_{17}N_3$ requires:	81.7	5.3	13.0%.

Bromination of benzylidine-2:4-dinitrophenylhydrazone.

Benzylidine-2:4-dinitrophenylhydrazone, prepared from the hydrazine and benzaldehyde, was recrystallized from acetic acid, and had m.p. 237° (lit., m.p. 237°). When the hydrazone was stirred overnight with an acetic acid solution of an equimolar amount of bromine, no reaction took place; the starting materials were recovered in nearly quantitative yield. Similarly no reaction took place after several days with a bromine solution in boiling carbon tetrachloride.

Experiment No. 1.18.

Benzylidine-2:4-dinitrophenylhydrazone (20 g.) and bromine (11.2 g.) in dry carbon disulphide (100 cc.) were set aside at room temperature for 6 months. The bright orange product was recrystallized from glacial acetic acid as orange prisms, m.p. 198-200° (16.6 g., 65%). Further recrystallization gave a product with m.p. 199-200°, which analyzed as a bromobenzylidene-2:4-dinitrophenylhydrazone.

Analysis:	C	H
Found:	41.9	2.7%.
$C_{13}H_9O_4N_4Br$ requires:	42.7	2.5%.

Acetylhydrazine.

Considerable difficulty has been experienced on a number of occasions in isolating this material in good yield from the reaction products of ethyl acetate and hydrazine hydrate. Curtius and Hofmann (72) recommend extraction of the product with ether, and crystallization of the residue, but in several experiments it has only been possible to crystallize out small yields (ca. 30%) of the hydrazide in this way. By fractionation of the residue a good yield of acetylhydrazine has been obtained.

Preparation of acetylhydrazine.

Hydrazine hydrate (150 g.) was heated on a steam bath, and ethyl acetate (220 g.) was run in at such a rate that only a small upper layer of liquid was present in the reaction flask. Addition was complete in 5 hours. The products were then boiled under reflux for 36 hours and distilled. Acetylhydrazine, b.p. 97-101°/2 mm. (134 g., 73%) was obtained as colourless crystals, m.p. 67° (lit., m.p. 67°).

Formylhydrazine was prepared from hydrazine hydrate and ethyl formate [73].

Benzoyl hydrazine was prepared from ethyl benzoate [74] or better, methyl benzoate, and hydrazine hydrate.

The following 1-acyl-2-phenylhydrazines prepared by recorded methods were: formyl (H)[75]: propionyl (H) [76] and benzoyl (H) [77].

1:2-Diformylhydrazine was obtained as a byproduct in the preparation of formylhydrazine reported above.

1:2-Diacetyl- [78] and 1:2-dibenzoylhydrazine [79] were also prepared by standard methods.

Experiment No. 1.19. Preparation of 4-ethyl-3:5-dimethyl-1:2:4-triazole from N-ethylacetamide and acetylhydrazine.

Phosphorus oxychloride (15.3 g.) in dry, ethanol-free chloroform (100 cc.) was added with stirring during 0.5 hour to N-ethylacetamide (8.7 g.) in dry pyridine (16.0 g.), the temperature being kept below 20°. After 12 hours at 20°, acetylhydrazine (7.4 g.) in boiling chloroform (200 cc.) was added, and stirring and boiling continued for 1 hour. The cooled product was extracted with water (2 x 100 cc.) and 10% aqueous sodium hydrogen carbonate (2 x 50 cc.). The combined aqueous extract was made strongly alkaline with sodium hydroxide, and extracted with chloroform (4 x 100 cc.). This extract was combined with the original chloroform layer, dried (Na_2SO_4), and the solvent removed. 4-Ethyl-3:5-dimethyl-1:2:4-triazole, (2.84 g., 23%) b.p. 170-175°/12 mm., m.p. 113-114° was obtained on distillation of the residue. This product was chromatographed in benzene solution on alumina (60 g.), and eluted with benzene-chloroform (20:1), yielding colourless hygroscopic prisms, m.p. 115-116°.

Analysis:	C	H	N
Found:	56.7	9.6	33.8%.
$C_6H_{11}N_3$ requires:	57.6	8.9	33.6%.

The base with picric acid in ethanol precipitated 4-ethyl-3:5-dimethyl-1:2:4-triazole picrate, which crystallized from ethanol as yellow leaflets, m.p. 146-147°.

Analysis:	C	H
Found:	41.1	4.4%.
$C_{12}H_{14}O_7N_6$ requires:	40.7	4.0%.

The extremely hygroscopic nature of the base probably accounts for discrepancies in its analysis.

4-Methyl-3:5-diphenyl-1:2:4-triazole.

This triazole was obtained from N-methylbenzamide and benzoylhydrazine when they were reacted in carbon tetrachloride, using phosphorus oxychloride-pyridine as a condensing agent. The preparation only differs from that of Scheuing and Walach [2] in that these authors used phosphorus trichloride as a condensing agent. Recrystallized from ethanol the compound had m.p. 242° (lit., m.p. 243°).

4-Methyl-3:5-diphenyl-1:2:4-triazole picrate was obtained on mixing an ethanolic solution of the base and picric acid. It crystallized from ethanol as yellow rhombs, m.p. 155°.

Analysis:	C	H
Found:	54.5	4.0%.
$C_{21}H_{16}O_7N_6$ requires:	54.3	3.5%.

Benzylideneamino-guanidine and its 1-methyl derivative.

This compound was prepared from benzaldehyde and aminoguanidine sulphate in the presence of sodium hydroxide (80). The product had m.p. 178-179° (lit., m.p. 179°). With methyl iodide in methanol 1-benzylidene-amino-1-methylguanidine hydriodide was obtained, as described by Finnegan, Henry and Smith (10). The hydriodide (30.4 g.) was steam distilled in the presence of concentrated sulphuric acid (50 cc.). Iodine and benzaldehyde and small amounts of benzoic acid distilled off with about 1500 cc. of water. The residue was boiled under reflux over-night and steam distilled again. After the collection of 7000 cc. of distillate benzaldehyde could no longer be detected in the distillate. Half of the residue in the distilling flask was treated with 10% sodium hydroxide until strongly alkaline, the temperature being maintained below 30° with external cooling. Benzoyl chloride (14 g.) was added and the mixture shaken for 1 hour. The product was extracted with chloroform (3 x 75 cc.) and the solvent removed, leaving colourless prisms (4.6 g.) m.p. 125-128°, mixed m.p. with benzamide

below 116°. Recrystallization from benzene gave 5-benzoylamino-1-methyl-3-phenyl-1:2:4-triazole (4 g., 17%), m.p. 134°.

Analysis:	C	H
Found:	69.5	5.3%.
$C_{16}H_{14}ON_4$ requires:	69.1	5.1%.

1-Benzylideneamino-1-methylguanidine hydriodide (0.35 g.) was shaken with aqueous sodium hydroxide (20%, 5 cc.) and benzoyl chloride (1.5 cc.) in acetone (5 cc.) for 10 minutes. The product crystallized throughout to colourless needles which had m.p. 187° after washing with a little water. Recrystallization from benzene with the addition of light petroleum (b.p. 40-60°) gave 1-benzylideneamino-3-benzoyl-1-methyl-guanidine (0.23 g., 80%), m.p. 187°.

Analysis:	C	H	N
Found:	68.9	5.7	20.4%.
$C_{16}H_{16}ON_4$ requires:	68.6	5.7	20.0%.

SECTION 2.

TRIAZOLE SYNTHESIS FROM IMIDES AND HYDRAZINES.

Discussion.

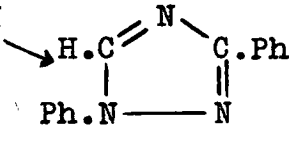
Einhorn and Szelinski [21] prepared the methylol derivatives of a large number of amides, and in several cases obtained N-formyl amides from these by oxidation. Thus N-formylbenzamide was obtained from benzamide.

$$Ph.CO.NH_2 + CH_2O \longrightarrow Ph.CO.NH.CH_2.OH \longrightarrow Ph.CO.NH.CHO$$

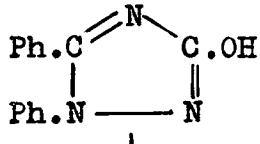
These workers investigated the reaction of N-formylbenzamide with phenylhydrazine. In ethanol the hydrazine was formylated to 1-formyl-2-phenylhydrazine, but in acetic acid a diphenyl triazole was obtained. On the basis of the melting-points of this compound and its derivatives, which differed from those of 1:5-diphenyl-1:2:4-triazole and its derivatives prepared by Young [22] from 1-phenyl-semicarbazide, the triazole was assigned the structure 1:3-diphenyl-1:2:4-triazole.

$$Ph.CO.NH.CHO + Ph.NH.NH_2 \xrightarrow{Et.OH} Ph.NH.NH.CHO$$

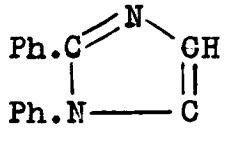
$$\xrightarrow{Ac.OH}$$



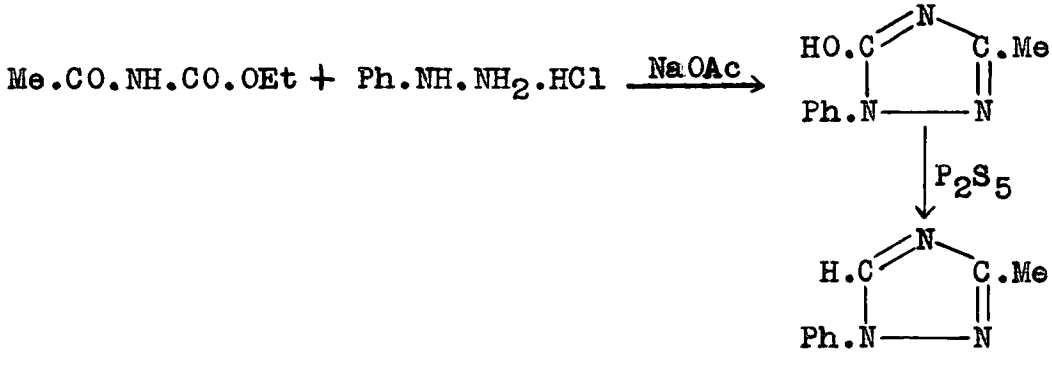
$$Ph.NH.NH.CO.NH_2 + Ph.CHO \xrightarrow[Et.OH]{FeCl_3}$$



$$\xrightarrow{P_2S_5}$$

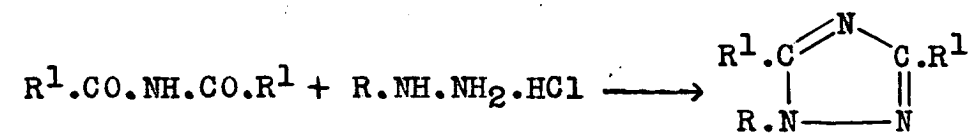


Andreocci [23] had obtained a hydroxytriazole in a related reaction. When acetylurethane, which contains the .CO.NH.CO. structure present in diacylamines of the type $R^1.CO.NH.CO.R^2$, was condensed with phenylhydrazine hydrochloride, 5-hydroxy-3-methyl-1-phenyl-1:2:4-triazole was obtained. The comparable hydroxypyrazole synthesis from phenylhydrazine and ethyl-acetoacetate was already well known. The structure was proved by reducing the hydroxytriazole to 3-methyl-1-phenyl-1:2:4-triazole.[24]



Nine years after the triazole synthesis of Einhorn and Szelinski, Brunner [25,26] reported his synthesis of triazoles from diacetamide and salts of hydrazine, semicarbazide and phenylhydrazine ("Eine neue Darstellungsweise von Triazolen"). Following this work other investigators in Brunner's school condensed symmetrical aromatic and higher aliphatic diacylamines with semicarbazide and phenylhydrazine salts.[27,28] Finally diacetamide was condensed with aromatic hydrazines to give a

considerable number of 1-aryl-3:5-dimethyl-1:2:4-triazoles.



(R^1 = alkyl, aryl; R = aryl)

When semicarbazide salts were used (R = $.CO.NH_2$) the $.CO.NH_2$ did not appear in the triazole, which, in these cases, was of the imino or acidic type.

Polya and a series of co-workers at the University of Tasmania have investigated the synthesis and chemistry of diacylamines, and have, in particular, developed syntheses for unsymmetrical diacylamines $R^1.CO.NH.CO.R^2$.[29] Reacylation may lead to mixtures of the type ($R^1.CO.NH.CO.R^1$ + $R^2.CO.NH.CO.R^2$) which have the same empirical composition as the unsymmetrical diacylamine indicated above. Triazole formation from diacylamines, a reaction which would reveal the presence of such isomeric mixtures, has now been investigated from this point of view. Optimum conditions for the preparation of 3:5-dimethyl-1-phenyl-1:2:4-triazole from phenylhydrazine and diacetamide have been investigated by Komzak and Polya [30] after preliminary work by Mr. P. L. Tardrew, and with the assistance of the author. It was found satisfactory to heat the reactants under reflux in

pyridine or in acetic acid - sodium acetate buffers. More recently most of these reactions have been carried out at about 150° in the absence of solvent.

At this stage, considering also the results of Brunner and co-workers, the following points were apparent:

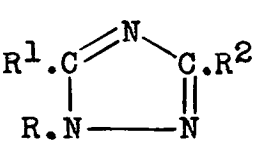
1. Triazole formation did not take place in basic media.
2. Acylhydrazines were substantial by-products, the diacylamine acting as an acylating agent.
3. Reactivity of the hydrazine $R.\overset{1}{N}H.\overset{2}{N}H_2$ was increased by electron withdrawal from $N_{(1)}$ (as judged from yields in comparable experiments). Thus, yields from semicarbazide and phenylhydrazine were higher than those from hydrazine. Yields from m-tolylhydrazine were higher than those from p-tolylhydrazine while with nitrophenylhydrazines the reverse was the case. Ortho substituents in both cases led to low yields, probably through steric effects.
4. Aliphatic diacylamines were more reactive

than aromatic diacylamines.

It was found in this work that several of the triazoles tested had colchicine-like effects on dividing cells, and this, with other results mentioned in the introduction, indicated the desirability of preparing more triazoles of known structure. Further, the possibility of identifying the triazole isomers obtained from a number of unsymmetrical diacylamines seemed a promising method of investigating this triazole synthesis.

Phenylhydrazine has been reacted with N-acetylpropionamide, N-formylbenzamide, N-acetylbenzamide, N-acetylcinnamamide and N-acetylurethane. Methylhydrazine has been reacted with N-formylbenzamide and N-acetylbenzamide. The results of these reactions are tabulated below; details of the procedures are given in the experimental part. In each case only one triazole isomer was obtained. The product was that in which the 3-substituent of the triazole was derived from the "more acidic" portion of the diacylamine,

$$R^1.CO.NH.CO.R^2 + R.NH.NH_2 \longrightarrow$$



where $Ka_{R^2.CO_2H} > Ka_{R^1.CO_2H}$

			TRIAZOLE SUBSTITUENTS.			
R	R^1	R^2	1	3	5	EXPT.NO.
Ph	Et	Me	Ph	Me	Et	2.9
Ph	Ph	H	Ph	H	Ph	2.10
Ph	Ph	Me	Ph	Me	Ph	2.11
Ph	Ph.CH=CH.	Me	Ph	Me	Ph.CH=CH.	2.12
Ph	CO_2Et	Me	Ph	Me	OH	2.14
Me	Ph	H	Me	H	Ph	2.6
Me	Ph	Me	Me	Me	Ph	2.7

Most of these reactions were carried out under various conditions, as outlined in the experimental part, but in no case was a second isomer isolated. From tests on artificial mixtures it is thought that 5% of a second isomer could have been detected.

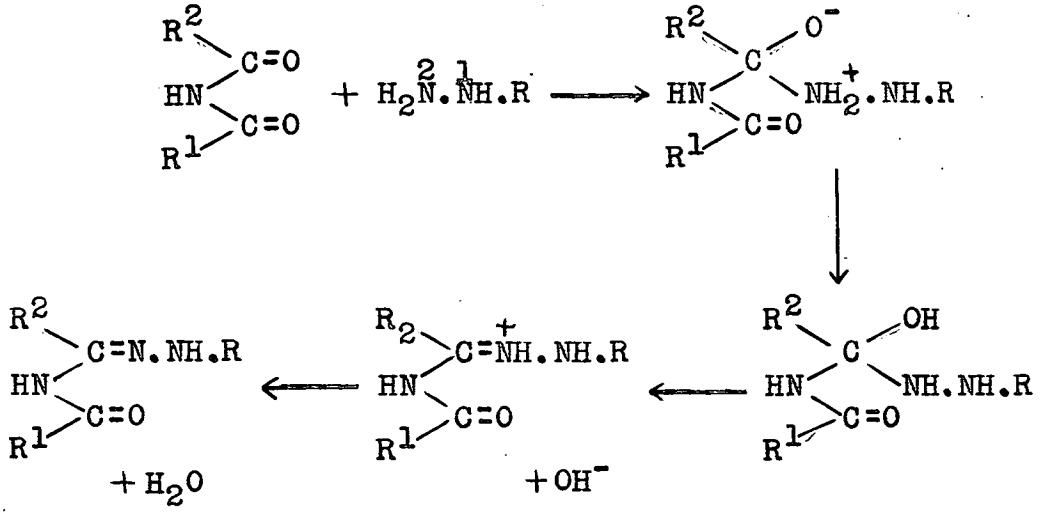
It will be noticed that Andreocci's reaction of acetylurethane and phenylhydrazine hydrochloride was repeated; in the absence of solvent much more vigorous conditions were investigated, but with the same result. Of particular interest is the observation that N-formylbenzamide and phenylhydrazine give 1:5-diphenyl-1:2:4-triazole, not the 1:3-isomer which had been reported by Einhorn and Szelinski (loc. cit.). Thompson, working independently at the University of Wisconsin [54], had cause to check some discrepancies in the characterization

of N-formylbenzamide reported by Einhorn and Szelinski and he too observed that with phenylhydrazine it gave the 1:5-isomer. Melting points reported in the older communication showed a constant error which had apparently been neglected. Synthetic proofs of structures of the triazole isomers reported in this and the next section have been collected in Section 1, where the synthesis of 1:3-diphenyl-1:2:4-triazole is reported.

N-formylbenzamide and N-acetylbenzamide were reacted with semicarbazide hydrochloride, but the resultant 3-phenyl and 3-methyl-5-phenyl-1:2:4-triazoles, formed by loss of $-CONH_2$, were valueless in indicating orientation of attack by the reagent. Diacetamide was also reacted with methylhydrazine sulphate to give 1:3:5-trimethyl-1:2:4-triazole ($R = R^1 = R^2 = Me$, above). The reaction took place less readily than that of diacetamide and phenylhydrazine salts, which is consistent with the third generalization above, dealing with the effect of the hydrazine substituent on cyclization.

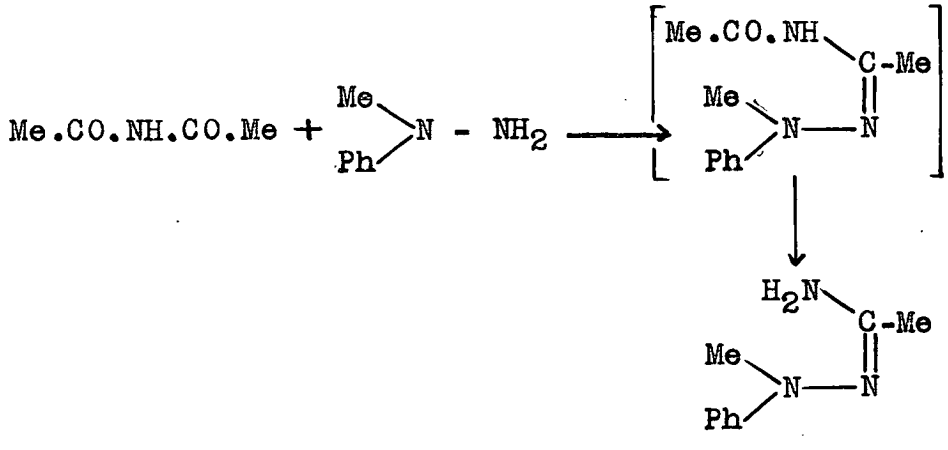
Some attempt may now be made to unify these observations. Optimum conditions of somewhat acidic buffering indicate the similarity between hydrazine-diacylamine reactions and hydrazone formation. On this assumption the first intermediates would appear to be

acylamidrazones or their tautomers.



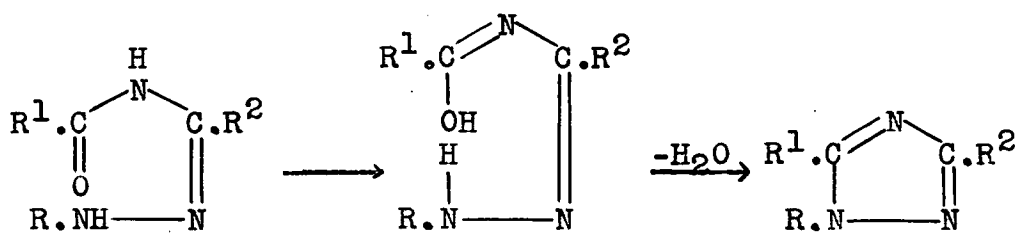
The hydrazine has been formulated as making the initial attack from its nucleophilic $N_{(2)}$ at the .CO. group adjacent to R^2, supposing that $Ka_{R^2CO_2H} > Ka_{R^1CO_2H}$ It may be noted that if this relationship exists, R^2.CHO also forms hydrazones more rapidly than R^1.CHO (where steric factors are not involved). One finds the sequence of reaction rates H.CHO > Me.CHO > Ph.CHO (55) with carbonyl reagents. A similar relationship exists in the synthesis of pyrazoles from unsymmetrical diketones. (56) The transition state for the attack indicated in the first step resembles that for a $-S_2$ replacement, and is stabilized by methyl R^2 to a greater extent than by the more -I ethyl R^1 for instance. All the aliphatic substituents and hydrogen would be more

favourable than phenyl, since if attack was initiated at the .CO. group adjacent to phenyl the mesomerism of the Ph.CO.NH. (or Ph.C(OH)=N-) group would be destroyed in the transition state, and the activation energy consequently increased. On this basis the products obtained are consistent with the view that a nucleophilic hydrazine $N_{(2)}$ attacks the more electrophilic .CO. of the diacylamine. As further evidence for this type of intermediate it may be mentioned that when diacetamide reacts with 1-methyl-1-phenylhydrazine the corresponding hydrazone of acetamide is isolated. (57) The conditions of isolation were such that an acylamidrazone would be readily hydrolyzed.



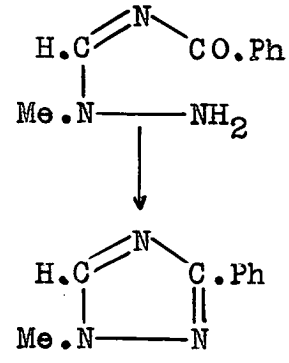
When the hydrazine has hydrogen on $N_{(1)}$, elimination of a second molecule of water would lead to triazole formation. A tautomeric shift is almost certain to take

place first, (though Polya and Spotswood [58] have advanced spectrographic evidence that some diacylamines exist to a significant extent as the N-acylimidic acid $R^1.\overset{OH}{C}=N.CO.R^2$).



The effect of the substituent R on the nucleophilic character of $N_{(2)}$ is probably minimized by the intervening $N_{(1)}$ atom of the hydrazine. Consequently the effect of R on progress of the reaction is almost certainly related to its influence on $N_{(1)}$. As mentioned above, electron withdrawal by R favours cyclization; this is probably because increased acidity of the hydrogen on $N_{(1)}$ would favour elimination of the second molecule of water.

While $N_{(2)}$ is quite clearly the nucleophilic centre of an arylhydrazine [8b], methylhydrazine is attacked by electrophilic reagents primarily at $N_{(1)}$. [59] It was anticipated that with unsymmetrical diacylamines methylhydrazine might lead to triazoles having the opposite orientations to those specified above.

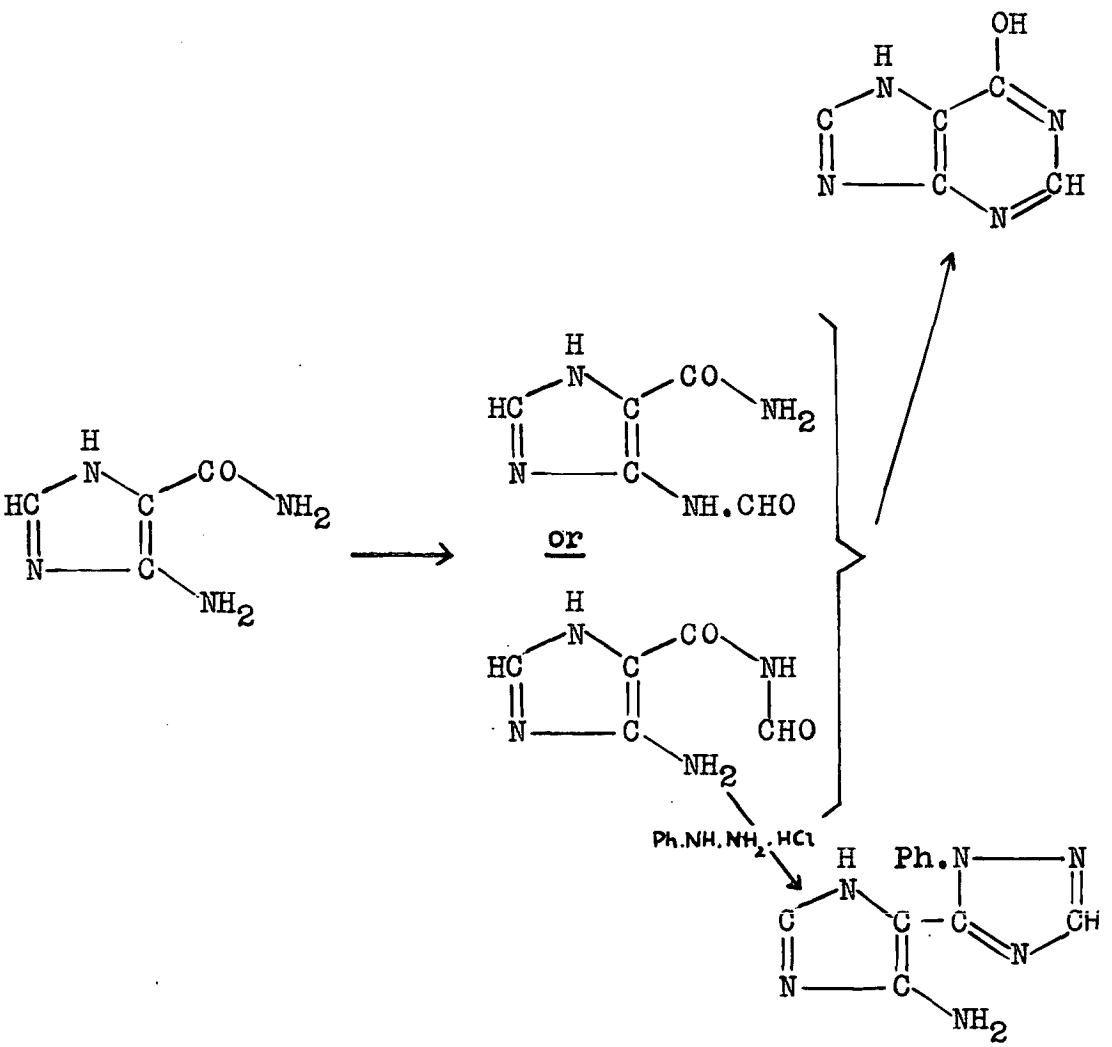
eg: $Me.NH.NH_2 + Ph.CO.NH.CHO \longrightarrow$ 

That this was not the case may give some significance to the fact that this intermediate can not take the structure $-\overset{|}{N} - N = \overset{|}{C} - N = \overset{|}{C} - OH$, which is evidently favourable for cyclization.

The possibility of investigating this reaction kinetically has been considered. Decrease of hydrazine or diacylamine concentration could be determined, but since they are also involved in side-reactions such as acylhydrazine formation they are not suitable. Triazoles were found to resist polarographic reduction (Section 4), and in the absence of other methods for their determination ultraviolet absorption measurements were considered. As mentioned in Section 5 interfering absorption by the diacylamine has prevented this approach. Since more recent work has brought out the uniformities mentioned above, permitting the prediction of the course and approximately of the facility of triazole formation in any

case, these mechanistic studies have not been elaborated further in this investigation.

It is hoped that this reaction may be of value in proving the structure of an intermediate in purine biosynthesis. Triazole formation with a hydrazine is one of the few reactions which would demonstrate the presence of an N-formylamide in, for instance, the following possible precursor of hypoxanthine.



The easy formation of triazoles from N-formylamides would probably permit cyclization before hydrolysis of the labile formyl group took place.

EXPERIMENTAL.

Preparation of Starting Materials.

N-acetylurethane.

Urethane (66 g.), acetic anhydride (204 g.) and acetyl chloride (1 cc.) were gently boiled under reflux for 1 hour, and the product was distilled. After removal of volatile material, N-acetylurethane, b.p. 105-106°/18 mm., was collected (80.5 g., 83%). This material solidified to colourless prisms, m.p. 78° (M'Creath [60] reports m.p. 77-78°).

It was found that M'Creath's preparation was best modified as above. An attempted repetition of the original preparation is given below.

Urethane (89 g.) and acetic anhydride (112 g.) were heated for 3 hours on a steam-bath. The product set to a mass of prisms and needles on cooling. Recovery of this material by filtration gave unchanged urethane, m.p. and mixed m.p. 51° (70 g., 78%).

Diacetamide.

Material prepared by the action of acetic anhydride on acetamide as described by Polya and Tardrew [61] was best purified by continuous extraction from concentrated aqueous solution with light petroleum (b.p. 60-80°).

N-acetylpropionamide and N-acetylbenzamide were prepared as described by Polya and Spotswood. (29)

N-formylbenzamide.

Considerable difficulty was experienced in this preparation, and it has been reported in some detail (c.f. Thompson, loc.cit.).

Reaction of benzamide with formaldehyde.

Benzamide (140 g.) and potassium carbonate (4 g.) were stirred with water (140 cc.). Formalin (38%; 100 cc.) was added, and the reactants were heated at 80° until a clear solution was obtained. The mass of crystals obtained on setting the product aside overnight was drained on a Buchner funnel, washed with water (150 cc.) and again drained. The material was dried for 2 hours at 40°/1 mm., leaving N-methylolbenzamide (170 g., 95%), m.p. 104°. The preparation is essentially that of Einhorn, Bishkopff and Szelinsky (62) who report m.p. 104-106°.

In other experiments the formalin was replaced by an equivalent amount of paraformaldehyde, but in all cases yields were approximately the same.

A number of attempts to prepare N-formylbenzamide from N-methylolbenzamide by oxidation with acidic dichromate by the method of Einhorn and Szelinski (21) have

led to extremely variable, and often quite small yields of the required material. Too low a temperature results in little oxidation, while high temperatures were found to result in almost quantitative formation of methylene-bis-benzamide. Some benzamide is always formed by hydrolysis of the methylol compound in the presence of acid. Because of these difficulties a number of different methods of obtaining this compound were investigated, such as oxidation with pyridine-copper sulphate or potassium ferricyanide. Only a modification of Einhorn and Szelinski's method gave a small yield of N-formylbenzamide.

Oxidation of N-methylolbenzamide to N-formylbenzamide.

N-methylolbenzamide (60 g.) was made to a slurry with water (50 cc.) and a solution of sodium dichromate (92 g.) in concentrated sulphuric acid (36N, 50 g.) and water (270 g.) was gradually added. The reactants were stirred at 25-30° for 0.25 hour, during which time the original solid dissolved, and crystallization started. The mixture was then extracted with portions of ether at 5 minute intervals (4 x 150 cc.). The combined ether extract was washed with 10% aqueous sodium hydrogen carbonate (100 cc.), dried (Na_2SO_4) and evaporated, leaving colourless prisms, m.p. 90-100° (21.5 g.) This

material was recrystallized from water (400 cc.) giving N-formylbenzamide (7.7 g., 13%) colourless prismatic needles, m.p. 112°. The mother liquors were set aside for 2 days, and a further 5.0 g. (8%) of the same material, m.p. 110-112°, crystallized out. Einhorn and Szelinski (loc.cit.) give m.p. 120° for their material, but this investigation confirms the findings of Thompson (loc. cit), who describes N-formylbenzamide as colourless needles m.p. 113°. Thompson obtained N-formylbenzamide by the decomposition of N-formyldibenzamide hydrate obtained in low temperature dibenzoylation of formamide with benzoyl chloride-pyridine.

Experiment No. 2.1 (H). Acetylcinnamamide.

Cinnamamide was prepared from cinnamic acid through the acid chloride. Cinnamamide (2.6 g.) and acetic anhydride (2.0 g.) with acetyl chloride (0.1 cc.) were boiled under reflux for 0.5 hour. Volatile material was removed by distillation to 60°/25 mm. and crystallization of the residue from chloroform gave N-acetylcinnamamide (1.4 g., 44%) as colourless rhombic plates, m.p. 125°. Recrystallized from chloroform the substance had m.p. 127°. (Lit., m.p. 122-124°; Rodionov and Kiseleva[63] c.f. also Thompson[64] who reports m.p. 131-132°.

Analysis:	C	H	N
Found:	69.9	5.8	7.6%.
Calculated for $C_{11}H_{11}O_2N$:	69.8	5.8	7.4%.

Rodienov and Kiseleva and Thompson used less convenient procedures.

Dibenzamide.

Barth and Senhofer's reaction of benzonitrile with phosphoric oxide and strong sulphuric acid[65] gave dibenzamide, provided a temperature of 25-40° was maintained by cooling during addition of benzonitrile. When the temperature was maintained at 5-10° in an ice-bath most of the benzonitrile was recovered unreacted; on the other hand when no cooling was employed the temperature of the reactants rose to ca.100°, and almost complete hydrolysis of benzonitrile to benzamide took place. Recrystallized from 10% ethanol the dibenzamide had m.p. 147° (lit., m.p. 147°)

3-Hydrazino-1:2:4-triazole hydrochloride.

This compound was prepared by the method of Manchot and Noll[66]. 3-Diazo-1:2:4-triazole-5-carboxylate was reduced in hydrochloric acid with stannous chloride, tin was precipitated as the sulphide, and the resultant hydrazine was isolated as the hydrochloride, m.p. 221°(d) Manchot and Noll report m.p. 224°(d).

Experiment No. 2.2. Reaction of N-formylbenzamide and semicarbazide hydrochloride.

N-formylbenzamide (0.55 g.) and semicarbazide hydrochloride (0.42 g.) were mixed and melted at 160° for 1 hour. After water (5 cc.) had been added the product was neutralized with sodium carbonate, and insoluble material recovered by filtration. This was hydrazodicarboxyamide (125 mg., 29%), m.p. 257°(d). The melting point was not changed by recrystallization from water. Auwers and Keil report the m.p. of this compound as 257°(67) The filtrate was extracted with ether (2 x 50 cc.), dried with sodium sulphate and evaporated, leaving colourless needles, m.p. 114-115°. These were purified by sublimation at 140°/1 mm., affording 3-phenyl-1:2:4-triazole (160 mg., 30%), m.p. 118°; mixed m.p. with authentic material, 119°. Hoggarth (68) reports m.p. 121° in a preparation from benzoyl semicarbazide, but in repeating this work we have only been able to obtain material with m.p. 119°.

Experiment No. 2.3. Reaction of N-acetylbenzamide and semicarbazide hydrochloride.

N-acetylbenzamide (8.2 g.) and semicarbazide hydrochloride (5.6 g.) were mixed and heated in an oil-bath at 160° for 1 hour. Hydrazodicarboxyamide (1.22g., 21%)

m.p. 257°(decomp.), was isolated as in the reaction of semicarbazide hydrochloride and N-formylbenzamide. Extraction of the residue and filtrate with ether (3 x 150 cc.) and evaporation of the dried (Na_2SO_4) extract gave 7.3 g. of colourless crystals with an indefinite melting point between 105 and 135°. When this material was crystallized from toluene-petroleum (b.p. 100-120°) the least soluble portion was 3-methyl-5-phenyl-1:2:4-triazole (1.4 g., 18%) m.p. 164.5°, which was sublimed at 140°/1 mm. with a rise of melting point to 166°.

Analysis:	C	H
Found:	68.4	5.8%.
Calculated for $C_9H_9N_3$:	67.6	6.1%.

Heller [69] reports that this triazole has m.p. 164.5°.

Reaction of dibenzamide with semicarbazide hydrochloride.

Dibenzamide (2.2 g.) and semicarbazide hydrochloride (2.2 g.) were heated together at 160° for 4 hours (c.f. Wolchowe [27]). The product was poured into aqueous sodium hydrogen carbonate (10%, 20 cc.) and extracted with ether, (3 x 30 cc.). The extract was dried (Na_2SO_4) and evaporated, leaving a mixture of benzamide and 1:2-dibenzoylhydrazine, which was separated by sublimation and crystallization from water, giving benzamide

(0.5 g., 41%) m.p. and mixed m.p. 128°, and 1:2-dibenzoylhydrazine (0.77 g., 32%) m.p. 238° and mixed m.p. 238-239°.

Wolchowe isolated some 3:5-diphenyl-1:2:4-triazole in this experiment.

Experiment No. 2.4. Reaction of acetylhydrazine and diacetamide.

Acetylhydrazine (7.4 g.) and diacetamide (10.1 g.) were dissolved in chloroform (100 cc.) containing pyridine (10 cc.). After 1 month at room temperature the solvent was removed by distillation and the residue evaporated down with several portions of carbon tetrachloride. Sublimation at reduced pressure afforded acetamide (4.2 g., 71%), m.p. and mixed m.p. 78°. The sublimate gives a negative test for diacylamines (Polya and Tardrew,[70]). The residue was recrystallized from 2-propanol-ether affording 1:2-diacetylhydrazine (9.1 g., 78%), m.p. and mixed m.p. 135-136°. No triazoles could be detected among the products of the reaction.

Experiment No. 2.5. Reaction of diacetamide with methylhydrazine sulphate.

Diacetamide (15.0 g.) and methylhydrazine sulphate (14.4 g.) were heated for 5 hours at 145°. Water (5 cc.) was added, and after boiling under reflux for 1 hour the product was brought to pH 5 with cold 2N sodium carbonate then to pH 8 with cold concentrated ammonia. The alkaline solution was extracted with chloroform (3 x 80 cc.), the extract dried (Na_2SO_4), and the solvent removed, leaving a pale brown oil (6.3 g., 57%), b.p. 194-197°/760 mm. This crude 1:3:5-trimethyl-1:2:4-triazole was fractionated, giving a colourless oil, b.p. 72-74°/11 mm. b.p. 193-195°/760 mm.; after redistillation, b.p. 193°/755 mm.

d_{20}^{20} 1.037, n_D^{20} 1.4652

Analysis:	C	H	N
Found:	54.5	8.3	37.3%.
$C_5H_9N_3$ requires:	54.0	8.2	37.8%.

This base gave a precipitate with ethanolic picric acid. The 1:3:5-trimethyl-1:2:4-triazole picrate crystallized from ethanol as yellow prismatic needles, m.p. 134-135.5°.

Analysis:	C	H	N
Found:	39.2	3.6	24.2%.
$C_{11}H_{12}O_7N_6$ requires:	38.8	3.6	24.7%.

In duplicate experiments the yield and quality of product did not differ significantly from those reported in this experiment. When the reactants were heated together in acetic acid/sodium acetate buffers the yield was very low (ca.20%).

Experiment No.2.6. Reaction of N-formylbenzamide with methylhydrazine sulphate.

N-formylbenzamide (7.45 g.) and methylhydrazine sulphate (7.2 g.) were melted together and the temperature of the mixture was maintained at 120° for 4 hours. The clear liquid was neutralized with aqueous sodium carbonate (10%), and the mixture was extracted with chloroform (3 x 50 cc.). Evaporation of the dried (Na_2SO_4) solution left 1-methyl-5-phenyl-1:2:4-triazole 5.0 g., 63%), tan prisms, m.p. 57-58°. Crystallization from benzene-light petroleum ether (b.p. 60-80°) and sublimation at 60°/2 mm. gave colourless prisms, m.p. 59°.

Analysis:	C	H	N
Found:	67.8	5.6	26.5%.
$C_9H_9N_3$ requires:	67.6	6.1	26.3%.

With an ethanolic solution of picric acid the triazole gave a precipitate of 1-methyl-5-phenyl-1:2:4-triazole picrate, flat yellow needles, m.p. 178°.

Analysis:	C	H
Found:	47.0	3.3%.
$C_{15}H_{12}O_7N_6$ requires:	46.6	3.0%.

This triazole and its picrate differ from the isomeric 1-methyl-3-phenyl-1:2:4-triazole and its picrate (obtained from the reaction of benzamide methylhydrazone with formic acid), since the melting points are non-identical, and the melting points of the picrates are depressed on admixture.

A melting point diagram for the system: 1-methyl-3-phenyl-1:2:4-triazole picrate -- 1-methyl-5-phenyl-1:2:4-triazole picrate has been constructed (Section 3).

Experiment No. 2.7. Reaction of N-acetylbenzamide with methylhydrazine sulphate.

a. N-acetylbenzamide (6.1 g.) and methylhydrazine sulphate (3.60 g.) were melted together at 160° for 6 hours. The product was neutralized with 2N aqueous sodium carbonate, extracted with chloroform (4 x 50 cc.), and the extract dried (Na_2SO_4). Removal of the solvent left a mixture of oil and crystals (4.4 g.), from which a small amount of benzamide (m.p. and mixed m.p. 127°) was obtained by crystallization from methanol. The impure material was chromatographed in benzene on alumina (1.5 x 40 cm.) affording crude 1:3-dimethyl-5-phenyl-1:2:4-triazole (2.6 g., 65%) colourless prisms, m.p. 66-68°. Crystallization from benzene-light petroleum (b.p. 60-80°) and sublimation at 60°/2 mm. gave colourless prisms, m.p. 72°.

Analysis:	C	H	N
Found:	70.0	6.4	24.1%.
$C_{10}H_{11}N_3$ requires:	69.4	6.4	24.3%.

With an ethanolic solution of picric acid the triazole gave a precipitate of 1:3-dimethyl-5-phenyl-1:2:4-triazole picrate which was recrystallized from methanol as yellow prismatic needles, m.p. 172°.

Analysis:	C	H	O
Found:	48.3	3.5	27.3%.
$C_{16}H_{14}O_7N_6$ requires:	47.8	3.5	27.9%.

The triazole and picrate depress the melting points (in admixture) of 1:5-dimethyl-3-phenyl-1:2:4-triazole and its picrate. (c.f. Section 1)

b. N-acetylbenzamide (8.15 g.) and methylhydrazine sulphate (7.20 g.) were dissolved in a mixture of glacial acetic acid (15 cc.), anhydrous sodium acetate (4.0 g.) and water(10 cc.). After boiling the reactants under reflux for 10 hours the products were isolated in essentially the manner outlined in Experiment 2.7a. The reaction afforded benzamide (3.0 g., 50%) and 1:3-dimethyl-5-phenyl-1:2:4-triazole (0.46 g., 5%).

Experiment No. 2.8. Reaction of dibenzamide with methylhydrazine sulphate.

Dibenzamide (2.25 g.) and methylhydrazine sulphate (1.44 g.) were heated together for 4 hours at 160°. The product was poured into water (100 cc.), brought to pH 6 with sodium carbonate and the slurry extracted with benzene-ether (2:1) (4 x 25 cc.). The dried extract (Na_2SO_4) was evaporated, and the non-crystalline residue was crystallized from light petroleum (b.p. 60-80°),

affording 1-methyl-3:5-diphenyl-1:2:4-triazole (0.95 g., 40%), colourless crystals, m.p. 84-85° alone or admixed with the 1-methyl-3:5-diphenyl-1:2:4-triazole obtained by the methylation of 3:5-diphenyl-1:2:4-triazole, or by benzoylation of benzamide methylhydrazone (Sections 3, 1). This triazole gave a picrate, yellow needles from 20% ethanol, m.p. and mixed m.p. 135°.

Experiment No.2.9(H). Reaction of phenylhydrazine and N-acetylpropionamide.

a. Phenylhydrazine hydrochloride (31.5 g.) N-acetylpropionamide (25.0 g.) and dry pyridine (100 cc.) were refluxed for 4 hours. The product was poured into 5% aqueous sodium hydroxide (250 cc.) and extracted 3 times with ether, the ethereal extracts being combined with the pyridine layer. Removal of ether and pyridine left an oil (39.1 g.) which was extracted with ether. Fractionation of the extract gave an oil, b.p. 147-155°/12 mm. (21.5 g.), and 1-acetyl-2-phenylhydrazine, m.p. 128-130° (4 g.), as residue. The oil was redistilled to afford 5-ethyl-3-methyl-1-phenyl-1:2:4-triazole, b.p. 122-122.5°/2 mm. (18 g., 65%).

Analysis:	C	H	N
Found:	70.8	6.9	21.8%.
Calc. for $C_{11}H_{11}N_3$:	70.6	6.9	22.5%.

b. Freshly crystallized phenylhydrazine hydrochloride (7.3 g.), N-acetylpropionamide (7.3 g.), glacial acetic acid (1.5 g.), and hydrated sodium acetate (3.5 g.) were refluxed in water (80 cc.) for 16 hours at initial and final pH 5. The resulting mixture of aqueous phase and oil was treated with 5% mercuric chloride solution, with stirring at 60°, until no further precipitation occurred. Recrystallization from water afforded the mercuric chloride adduct of 5-ethyl-3-methyl-1-phenyl-1:2:4-triazole, m.p. 148-152° (14.3 g., 62%); it had m.p. 156° on further recrystallization from 1:1 ethanol - ether.

Analysis:	C	H	N
Found:	29.2	2.9	8.6%.
Calc. for $C_{11}H_{11}N_3.HgCl_2$:	28.8	2.8	9.2%.

The adduct was dissolved in cold 4N-hydrochloric acid (100 cc.) and extracted with ether. The extract was discarded and the acid solution treated with hydrogen sulphide, neutralized to pH 5 with ammonia, and precipitated with sodium carbonate. Ether-extraction of the precipitate and filtrate afforded

5-ethyl-3-methyl-1-phenyl-1:2:4-triazole, b.p. 281-282°/760 mm., d_{20}^{20} 1.075, n_D^{20} 1.5450 (4.5 g., 77% recovery from the adduct, 48% overall); this gave a picrate, yellow rhombs, m.p. 139-140.5°, and a hydrochloride, m.p. 205-206°, which did not depress the m,p.s of those prepared from 5-ethyl-3-methyl-1-phenyl-1:2:4-triazole obtained by Gastaldi's method (c.f. Section 1).

c. Phenylhydrazine (base), N-acetylpropionamide, glacial acetic acid, and anhydrous sodium acetate (each 0.1 mole) were heated on the water-bath for 16 hours and worked up as in (b), to afford the same triazole, b.p. 151-155°/9-12 mm. (8.3-8.5 g., 45-48%), as shown by the identity of picrates, hydrochlorides, and mercuric chloride adducts.

Experiment No. 2.10(H). Reaction of phenylhydrazine and N-formylbenzamide.

Phenylhydrazine hydrochloride (14.5 g.) and N-formylbenzamide (14.7 g.) in pyridine (50 cc.) were refluxed for 4 hours although most of the reaction is completed in about 15 minutes, as judged by the volume of oil separating in the reaction. On cooling, prismatic needles of 1:5-diphenyl-1:2:4-triazole, m.p. 89-90°, were obtained (11.5 g.) (52%), raised to 90-90.5° after

recrystallization from light petroleum (b.p. 60-80°)

Analysis:	C	H	N
Found:	76.1	5.1	18.5%.
Calc. for $C_{14}H_{11}N_3$:	76.0	5.0	19.0%.

The triazole, its picrate, m.p. 142-143°, and mercuric chloride adduct, m.p. 126-128° (from 80% ethanol), were identical with 1:5-diphenyl-1:2:4-triazole (Young, loc. cit.) and its derivatives.

Experiment No. 2.11(H). Reaction of phenylhydrazine and N-acetylbenzamide.

Phenylhydrazine hydrochloride (14.5 g.), N-acetylbenzamide (16.5 g.), glacial acetic acid (30 cc.) and anhydrous sodium acetate (10 g.) were refluxed for 10 hours. The product was made alkaline with 40% sodium hydroxide solution and extracted with ether. The pale oil obtained from the extract solidified slowly and consisted of 3-methyl-1:5-diphenyl-1:2:4-triazole, which formed prisms, m.p. 80-81° on recrystallization from 90% ethanol and then light petroleum (b.p. 60-80°) (18.4 g., 78%).

Analysis:	C	H	N
Found:	76.6	5.5	17.6%.
$C_{15}H_{13}N_3$ requires:	76.6	5.5	17.9%.

The hydrochloride is precipitated when an ethereal solution of the triazole is treated with dry hydrogen chloride; it has m.p. 221-223°; the picrate forms yellow prisms (from ethanol), m.p. 152-154°, and the mercuric chloride adduct needles (from 50% ethanol), m.p. 121-124°. The triazole and its derivatives depress the m.p.s of 5-methyl-1:3-diphenyl-1:2:4-triazole (prepared according to Jerchel and Kuhn, loc.cit.) and its derivatives. (c.f. Section 1).

Experiment No. 2.12. Reaction of N-acetylcinnamamide with phenylhydrazine hydrochloride.

N-acetylcinnamamide (13.9 g.) and phenylhydrazine hydrochloride (10.6 g.) were heated at 140-150° for 4 hours. The product was neutralized with aqueous sodium carbonate (10%) and extracted with chloroform (3 x 150 cc.). The extract was dried (Na_2SO_4) and evaporated. The residue was dissolved in 90% ethanol (100 cc.) and boiled for 10 hours after the addition of potassium hydroxide (15 g.). Most of the ethanol was removed by evaporating with water (150 cc.), and the residual solution (150 cc.) was extracted with ether. The ether extract was washed with sodium carbonate solution (100 cc.) (10%), dried and evaporated. The residue thus obtained was treated with Fehling's solution (100 cc.) at 100°

and the triazole was extracted with ether. Removal of the solvent after drying left crystalline material (9.8 g.), m.p. 68-72°. Distillation at 2 mm. (material boiling above 190°) led to considerable resinification. Triazole was recovered from this material as the picrate which was recrystallized from 80% ethanol as monoclinic crystals, m.p. 172°. An unstable modification was obtained, with m.p. 154°, but this resolidified, and melted at 172°. This was apparently pure 3-methyl-1-phenyl-5-styryl-1:2:4-triazole picrate.

Analysis:	C	H
Found:	56.9	3.8%.
$C_{23}H_{18}O_7N_6$ requires:	56.3	3.7%.

The picrate was decomposed by filtration through a column of chromatographic alumina in chloroform solution, the base passing through with the eluate. The apparatus illustrated in Figure 4 was used in this experiment. Evaporation of the eluate left 3-methyl-1-phenyl-5-styryl-1:2:4-triazole, m.p. 72-74°, which sublimed at 145°/0.1 mm. as colourless prisms, m.p. 74°.

Analysis:	C	H	N
Found:	78.5	5.7	16.4%.
$C_{17}H_{15}N_3$ requires:	78.1	5.8	16.1%.

In a duplicate experiment essentially the same yield and quality of product were obtained.

The above orientation is assigned on the basis of oxidative degradation reported below.

Experiment No. 2.13. Oxidation of 3-methyl-1-phenyl-5-styryl-1:2:4-triazole.

Methylphenylstyryltriazole picrate (1.0 g.) was crushed with 4N sulphuric acid (10 cc.), filtered and extracted with ether (50 cc.). The acid solution was treated with water (50 cc.) and potassium permanganate (5 g.). After stirring for 10 minutes at room temperature, the mixture was treated with ethanol (50 cc.), and the residue removed by filtration and washed with ethanol (10 cc.). The combined washings and filtrate were concentrated to 30 cc. and again filtered from solid. The acid solution was neutralized with sodium hydroxide and evaporated to dryness. The residue was heated at 200° for 0.5 hours, cooled and extracted with ether (50 cc.). Evaporation of the ether left a colourless oil (20 mg.) which partially crystallized. With methanolic picric acid a precipitate of fine needles was obtained. Recrystallized from methanol these had m.p. 169-170° and mixed m.p. with the picrate of 3-methyl-1-phenyl-1:2:4-triazole 169.5° (lit., m.p. 171°).

Andreocci [23] found that when acetylurethane and phenylhydrazine were reacted together in buffered aqueous solution the only triazole produced was 5-hydroxy-3-methyl-1-phenyl-1:2:4-triazole. In an investigation of the possibility that a second isomer might be formed under more vigorous conditions acetylurethane and phenylhydrazine hydrochloride were heated together at 150-160°, but again only one isomer was formed.

Experiment No. 2.14. Reaction of acetylurethane and phenylhydrazine hydrochloride.

Acetylurethane (11.8 g.) and phenylhydrazine hydrochloride (11.8 g.) were melted together and heated at 150-160° for 12 hours. The product was neutralized with aqueous sodium carbonate (10%) and extracted with ether (3 x 50 cc.). The ether extract was dried (Na_2SO_4) and evaporated, leaving 5-hydroxy-3-methyl-1-phenyl-1:2:4-triazole (4.3 g., 30%) as colourless prisms, m.p. 167°. The melting point was not raised by recrystallizing from ethyl acetate or by sublimation. Andreocci found m.p. 167° for this material.

Experiment No. 2.15. Reaction of diacetamide with 3-hydrazino-1:2:4-triazole hydrochloride.

Diacetamide (6.1 g.) and 3-hydrazino-1:2:4-triazole hydrochloride (2.70 g.) were heated in glacial acetic acid (1.0 g.) with anhydrous sodium acetate (1.4 g.) for 14 hours at 110-120°. The product was diluted with water (70 cc.) and extracted continuously for 4 hours with ether. The ether extract was dried (Na_2SO_4) and the solvent removed, leaving a residue which was purified by sublimation at 160°/1 mm. 3:5-Dimethyl-1-(1:2:4-triazol-3-yl)-1:2:4-triazole was obtained as colourless prisms, m.p. 191° (0.30 g., 9%).

Analysis:	C	H	N
Found:	44.2	5.0	51.3%.
$C_6H_8N_6$ requires:	43.9	4.9	51.2%.

With ethanolic picric acid the triazole gave a precipitate of yellow prismatic needles, which were crystallized from ethanol to give 3:5-dimethyl-1-(1:2:4-triazol-3-yl)-1:2:4-triazole picrate as long, flat yellow prisms, m.p. 219°.

In a similar experiment these proportions of the reactants were heated in aqueous solution, but the yield was even lower (4%).

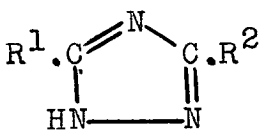
The low yields obtained in these reactions are not readily explained from the properties of the reactants, but it seems probable from later work that the imino group of the triazole ring may be acylated in these conditions.

SECTION 3.

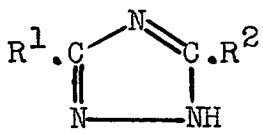
SUBSTITUTION REACTIONS OF 1:2:4-TRIAZOLES.

Discussion.

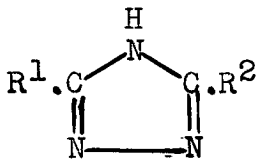
As in the case of pyrazoles and glyoxalines, 1:2:4-triazoles which bear no substituent other than hydrogen on a ring nitrogen atom have been isolated only in one form. In the absence of evidence for the existence of a particular isomer (1, 11 or 111) it has seemed desirable to use the more general formulation 1V.



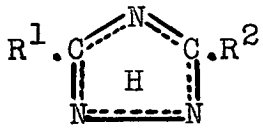
1.



11.

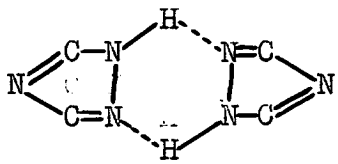


111.



1V.

Hückel has advanced evidence (96) that 1:2:4-triazole has a tendency to associate as a hydrogen-bonded dimer.



It is obvious that substitution reactions will not give unambiguous evidence on the location of hydrogen in an "acidic" triazole. (The term "acidic" conveniently describes the triazoles without N-substituents, which form metal salts). At the same time, it seemed

desirable to study alkylation and acylation of acidic triazoles in order to determine the reactive centre of the molecule. Thus while methylation of a triazole with diazomethane would not indicate the location of hydrogen in the unmethylated compound, it would indicate the least nucleophilic ring nitrogen in the neutral molecule. Similarly methylation of a sodium triazolate with methyl-iodide would indicate the most nucleophilic nitrogen in the anion. As the relative reactivities of nitrogen atoms in a triazole molecule or in triazolate anion could be calculated, the possibility of obtaining a correlation between predicted and observed orientations of substitution seemed to justify such an investigation.

Pellizzari and Soldi [97] isolated only 1-methyl-1:2:4-triazole when they treated 1:2:4-triazole and sodium methoxide with methyl iodide (R^1 = H)

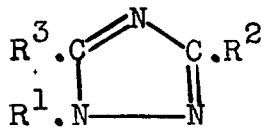
The same orientation has now been shown in the methylation of 3:5-dimethyl- (R^1 = Me) and 3:5-diphenyl-1:2:4-triazole (R^1 = Ph) using the same reagent. Ethylation of 3:5-dimethyl-1:2:4-triazole with ethyliodide and sodium ethoxide, gave, in addition to the 1-ethyl

derivative a small amount of 4-ethyl-3:5-dimethyl-1:2:4-triazole in the ratio 60:1. Pellizzari and Soldi's experiment was repeated, but their observation that methylation of the anion took place exclusively at $N_{(1)}$ was confirmed. It was then found that diazomethane and diazoethane also led to substitution at $N_{(1)}$. In the case of the three acidic triazoles considered above, there are only two chemically distinguishable nitrogen atoms, the isolated N_4 and the "hydrazinic" $N_{1(2)}$, since C_3 and C_5 are symmetrically substituted.

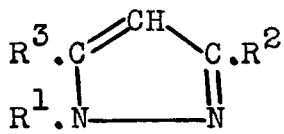
Treatment of the neutral triazole with acetic anhydride or of the alkali metal salt with acetyl chloride gave the same acetyl-, acetyldimethyl- or acetyldiphenyl-1:2:4-triazole with each of the three corresponding acidic triazoles. Acetyltriazoles were found to be active acetylating agents, hygroscopic and decomposed by water. An attempted synthesis of 1-acetyl-3:5-dimethyl-1:2:4-triazole from acetylhydrazine and diacetamide failed, the products being 1:2-diacetylhydrazine and acetamide. Reduction of this triazole to an ethyldimethyltriazole with lithium aluminium hydride resulted in cleavage to acetaldehyde and 3:5-dimethyl-1:2:4-triazole. Although chemical evidence on the location of the acetyl group has not been obtained, it has been tentatively called a

1-acetyl group on the basis of the good fit in a boiling point relationship with the pyrazoles.

Although the available information is limited to a small number of cases, it appears that a monotonic relationship exists between the boiling points of 1-substituted 1:2:4-triazoles



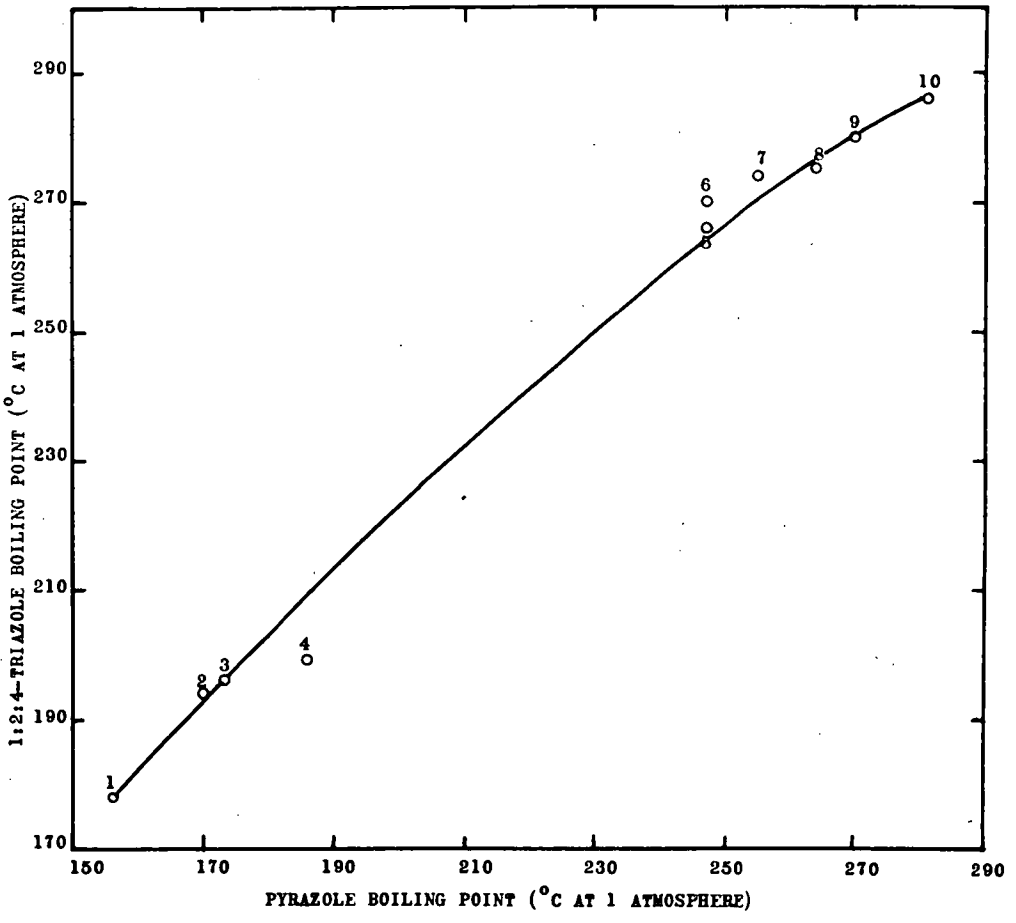
and the boiling points of corresponding pyrazoles



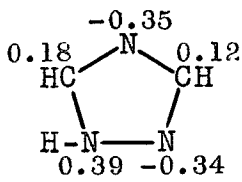
The relationship is shown graphically in Figure 1.

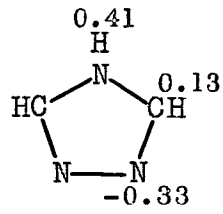
	R^1	R^2	R^3	Boiling points at atmospheric pressure. Pyrazole	1:2:4-triazole
1.	Ac(?4Ac)	H	H	156°	178°
2.	Me	Me	Me	170	194
3.	Et	Me	Me	173	196
4.	Ac(?4Ac)	Me	Me	186	199
5.	Ph	H	H	247	266
6.	o-tolyl	H	H	247	270
7.	Ph	Me	H	255	274
8.	Ph	H	Me	264	275
9.	Ph	Me	Me	270	280
10.	Ph	H	n-C_3H_7	281	286

FIGURE 1.


290
270
250
230
210
190
170
1:2:4-TRIAZOLE BOILING POINT (°C AT 1 ATMOSPHERE)
150
170
190
210
230
250
270
290
PYRAZOLE BOILING POINT (°C AT 1 ATMOSPHERE)
1
2
3
4
6
7
8
9
10

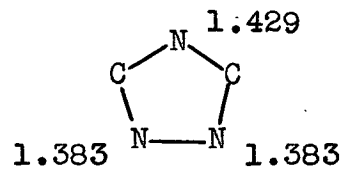
Before considering the substitution of triazoles which have different groups on C_3 and C_5, the results for symmetrically substituted triazoles may be compared with those predictable from calculations of π-electron density in triazoles and their anions. Orgel, Cottrell, Dick and Sutton [98] have calculated the π-electron densities in 1H- and 4H-1:2:4-triazole.





(relative charges on ring atoms)

In this form the data is not useful for predicting the reactive centre of the neutral molecule. Using the value h = 1 of the electronegativity parameter, the density distribution, including overlap integrals, for neutral 1:2:4-triazole is indicated:

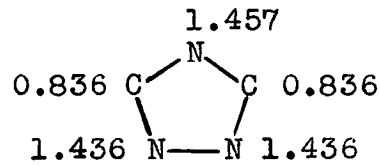


triazole, h = + 1
(including overlap integrals)

This result has been obtained for me by Dr. R. D. Brown, and is presented with his permission. The exact calculation for triazolate ion (h = -1/3) and the approximate

calculation (neglecting overlap integrals) for triazolate (h =-1) and for triazole (h = +1), are also from Dr. Brown. The last of these was obtained independently (Appendix A) by the author.

A calculation, neglecting overlap integrals, for the triazole molecule, has been made. Nitrogen has been assigned an electronegativity parameter of +1, but the ring-carbon atoms have been treated as though they were carbon atoms of a benzene ring. Since they more closely resemble the α-carbon atoms of pyridine a small correction, with the same sign as that for nitrogen, would have been a closer approximation. When ring-carbons carry a methyl group it is desirable to apply a correction for the resultant change in electronegativity [117] which is of the opposite sign and comparable magnitude. Thus the values obtained in the approximate calculation:



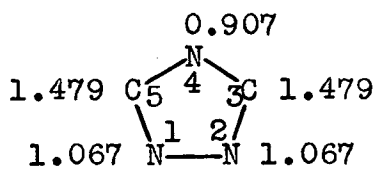
triazole h = +1
(neglecting overlap integrals)

are probably a better representation of the π-electron densities in 3:5-dimethyl-1:2:4-triazole than in 1:2:4-triazole.

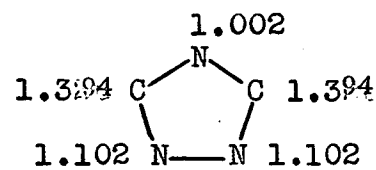
The "hydrazinic" nitrogen atoms, N_1 and N_2 are less nucleophilic than N_4, and it is here that attack by diazoalkanes takes place.

In calculating electron densities for triazolate ions, selection of a value for the electronegativity parameter of nitrogen presents some difficulties. Using the value h = -1 for glyoxaline anion, Dr. Brown has calculated electron densities which correctly predict the relative reactivities of ring carbon atoms. He has communicated an approximate triazolate π-electron density calculation (neglecting overlap integrals) for h = -1, and also a more refined calculation including overlap integrals for h = -1/3.

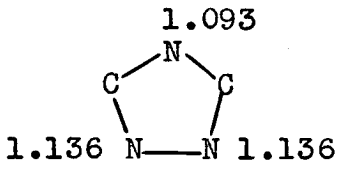
It seems reasonable to select the value h = -2/3 for triazole anion if h = -1 is a satisfactory value for glyoxaline anion, on the basis of the relative numbers of ring nitrogen atoms. Calculations for this case, neglecting overlap integrals are presented here (c.f. Appendix A for the calculations with h = -2/3)



h = -1 (approx)



h = -2/3 (approx)



h = -1/3
(overlap integrals included)

For all these values of h, N_1 and N_2 are more nucleophilic than N_4, as might be expected from the formation of 1-alkyl derivatives when sodium triazolate reacts with alkyliodides.

Acetyl derivatives, of unproved structure, deserve less attention, but these calculations are consistent with the supposition that both modes of acetylation led to 1-acetyl compounds.

It has been suggested that in the acylation of amides by anhydrides in the absence of strongly acidic catalysts protonation of the anhydride by the amide may precede attack by the resultant cation on the anion derived from the amide. (83) This argument may be extended to the case of the triazole, and as in the acylation of the sodium salt by acetyl chloride, the reagent would be attacking the triazolate anion.

$$(CH_3.CO)_2O + H.Tr \longrightarrow (H.(CH_3.CO)_2O)^+ + Tr^-$$

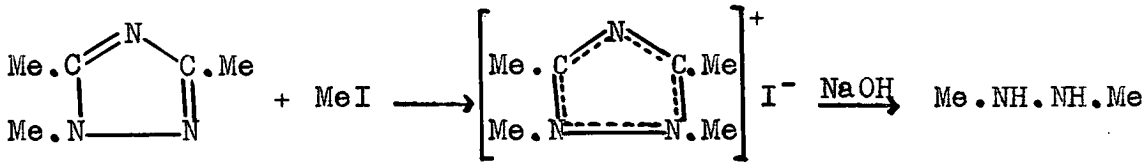
where Tr^- represents the triazolate anion.

It is therefore not surprising that reaction of

sodium triazolate with acetyl chloride and acetylation of the free triazole with acetic anhydride lead to the same isomer.

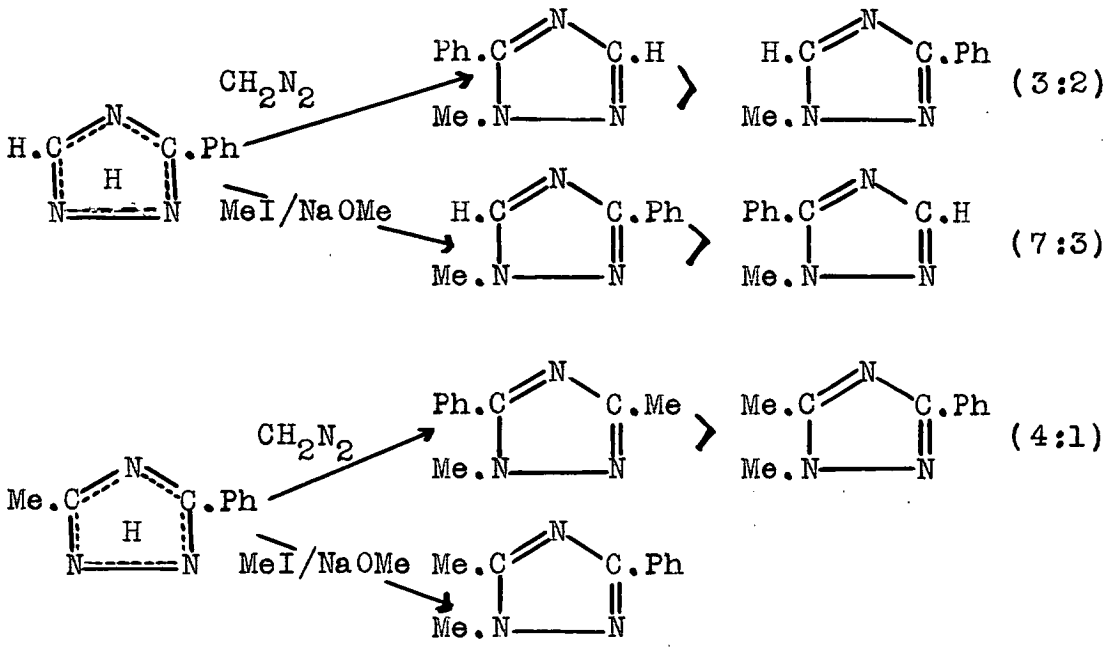
The great increase in π-electron density at $C_{3(5)}$ (from 0.84 to 1.48) when neutral triazole is converted to the anion is of interest. The anion should show a reactivity at these positions comparable to that in the α-position of pyridine. Thus coupling of triazolate with diazonium salts should be possible.

It has now been shown that the methiodide of 1:3:5-trimethyl-1:2:4-triazole carries methyl groups on both N_1 and N_2 unless a migration occurs during opening of the triazole ring.



The triazoles of known structure derived from amidrazones (Section 1) and from diacylamines (Section 2) provided the reference materials needed for an investigation of the relative reactivities of N_1 and N_2 when an element of asymmetry was introduced by the presence of different groups on C_3 and C_5. 3-Phenyl- and 3-methyl-5-phenyl-1:2:4-triazole were methylated with diazomethane, and with methyliodide in the presence of

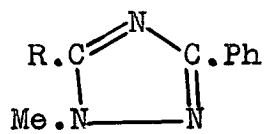
sodium methoxide, and the products are indicated below.



Limits of detection of absent isomers are estimated from tests on artificial mixtures to be about 5%. Proportions of the mixtures above are thought to be accurate to 10%. Without calculations on π-electron densities of these two acidic triazoles methylation results can only be discussed in a qualitative way. As with the three symmetrically substituted triazoles considered earlier, substitution at N_4 was not observed. The calculations of Orgel et al. indicated little double bond character for the N_1-N_2 link of triazole, and this is possibly true for its C-methyl and C-phenyl derivatives. If these C-substituents influence principally the

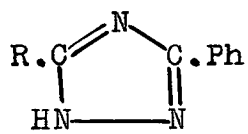
adjacent "hydrazinic" nitrogen in either the neutral molecule or the anion these results can be expected. Thus the $N_{1(2)}$ atom nearer to C-phenyl is the site of attack by diazomethane, while methyl iodide attacks the anion at $N_{1(2)}$ nearer to hydrogen or methyl respectively, and this is presumably the most nucleophilic nitrogen in the anion. The tendency towards formation of one isomer in the case of 3-methyl-5-phenyl-1:2:4-triazole (compared to 3-phenyl-1:2:4-triazole) is probably due to the reinforced effects of phenyl and -I methyl.

The ultraviolet absorption spectra of these two acidic triazoles each resembled the spectrum of one of their N-methyl derivatives. In both cases this was the isomer with the 1-methyl-3-phenyl orientation:



(R = H or Me)

but this is not sufficient evidence to propose the formulations



(R = H or Me)

as most closely resembling the actual structures of the corresponding acidic triazoles.

This investigation has further demonstrated the labile nature of N-acylazoles, and the presence of "active" acyl groups in such compounds will probably prove significant in metabolic studies. Acetyltriazoles were found to give hydroxamic acids with buffered hydroxylamine, and they were readily cleaved by hydroxylic solvents and even by picric acid in benzene.

In the experimental part of this section details of purification and characterization of individual acidic triazoles precede accounts of their alkylation and acylation.

1:2:4-Triazole.

This material may be prepared from formylhydrazine and formamide or from hydrazine hydrochloride and two moles of formamide as pointed out by Pellizzari [4]. In each case the product is obtained by distillation at ca. 260°/760 mm. In this investigation both preparations have been repeated several times. The former gives yields of the order of 30%, while with the latter the highest yield obtained was about 20%. The lower yield is offset by the convenience of starting materials which are readily available. An interesting point observed in the reaction using two moles of formamide is the vigorous spontaneous heating on mixing. This is probably sufficient to lead to cyclization.

Reaction of hydrazine dihydrochloride and formamide.

Formamide (184 g.) and hydrazine dihydrochloride (215 g.) were mixed. The temperature rose spontaneously to 160°, and after 0.5 hour decreased to 120°. The material was distilled, and the fraction with b.p. 260-265°/760 mm. was collected (30.0 g., 21%), m.p. 115-120°. Extraction with benzene (Soxhlet) gave colourless prisms, which were dried at 75°/1 mm., and had m.p. 120-121°. By sublimation at atmospheric pressure it was possible to obtain pure 1:2:4-triazole as colourless needles,

m.p. 122°. The benzene extraction left a small residue, which contained 1:2-diformylhydrazine.

When the material boiling above 265°/760 mm. was extracted with boiling water (800 cc.) gelatinous material was recovered, which was dried (1.1 g.) and had m.p. above 320°. The brown, water-insoluble residue (15 g.) also had m.p. above 320°. These residues were not investigated further.

In another experiment formylhydrazine (60 g.) and formamide (45 g.) were heated at 100° for 0.5 hour and then distilled at atmospheric pressure. Material with b.p. 160-162° (21.5 g.) was collected and purified by Soxhlet extraction with benzene, giving 1:2:4-triazole as colourless needles, m.p. 121° (19.3 g., 28%). As in the former experiment 1:2-diformylhydrazine and high boiling unidentified residues were obtained.

1:2:4-Triazole in chloroform with an equimolar amount of picric acid precipitated 1:2:4-triazole picrate, m.p. 167-168°. This crystallized from a mixture of benzene and methanol (9:1) as yellow triclinic crystals, and had m.p. 168°.

Analysis:	C	H
Found:	32.8	2.2%.
$C_8H_6O_7N_6$ requires:	32.2	2.0%.

Experiment No. 3.1. Methylation of the sodium salt of 1:2:4-triazole.

1:2:4-Triazole (10.0 g.) was dissolved in a solution of sodium (3.33 g.) in dry methanol (60 cc.). Methyl iodide (20.6 g.) was added to the solution, and the reactants were placed in a glass vessel contained in an autoclave. After 1 hour at 20°, the autoclave was heated to 120°, and maintained at this temperature for 1 hour. This departure from the methylation procedure of Pellizzari and Soldi (loc. cit.) was made in order to test the possibility that 4-methylation might take place at higher temperatures than those (i.e. on a steam bath) which were used by the earlier investigators. Methanol was removed from the oily paste by distillation at atmospheric pressure, and the residue was extracted with hot benzene (50 cc.) and hot chloroform (3 x 50 cc.). Preliminary extraction with benzene removes most of the triazole free from sodium iodide. Sodium iodide is appreciably soluble in concentrated chloroform solutions of triazoles. The combined extract precipitated 1:2:4-triazole (1.86 g., 19%) on cooling. This had m.p. and mixed m.p. 120-121°, and crystallized as colourless needles. Solvent was removed from the mother liquor of these needles, and the residual oil was distilled.

1-Methyl-1:2:4-triazole was obtained as a colourless oil (9.44 g., 78%) and had b.p. 177°/755 mm. d_{20}^{20} 1.105, n_D^{20} 1.4650; Pellizzari and Soldi give b.p. 178° and d_4^{24} 1.097. The residue after fractionation consisted principally of sodium iodide. Chloroform extraction of its solution in water removed 1-methyl-1:2:4-triazole (50 mg.), b.p. 178-180°/760 mm. No 4-methyl-1:2:4-triazole could be isolated at any stage of the purification.

1-Methyl-1:2:4-triazole picrate separated when warm ethanolic solutions of the base and picric acid were mixed. The picrate crystallized from ethanol or benzene as yellow monoclinic crystals, m.p. 137°.

Analysis:	C	H
Found:	35.4	2.6%.
$C_9H_8O_7N_6$ requires:	34.6	2.6%.

To investigate the possibility that N-alkyl groups of triazoles migrated on heating, the N-methyl and N-ethyl-1:2:4-triazoles prepared in this investigation were heated in sealed tubes at 140-160° for 4-6 hours, but in no case was there a change in physical properties (m.p. of solids; b.p., density and refractive index of liquids).

Experiment No. 3.1. Acetylation of 1:2:4-triazole with acetic anhydride.

1:2:4-Triazole (3.45 g.) was boiled under reflux for 1 hour with acetic anhydride (6 cc.). Distillation to 150°/760 mm. through a vacuum-jacketed Vigreux column removed acetic acid and acetic anhydride. The fraction boiling at 178-180°/760 mm. was almost pure acetyl-1:2:4-triazole (4.41 g., 80%), and set to colourless triclinic crystals, m.p. 38-39°. After sublimation at 40°/2 mm. or crystallization from a mixture of benzene and light petroleum (b.p. 40-60°) the product was obtained as triclinic crystals, m.p. 39°, and had b.p. 178°/755 mm.

Analysis:	C	H	N
Found:	44.5	4.7	37.5%.
$C_4H_5ON_3$ requires:	43.2	4.5	37.8%.

Acetyl-1:2:4-triazole is a hygroscopic substance which is hydrolyzed almost immediately by water. Samples exposed to the atmosphere for several minutes were found to be partially decomposed. The analytical sample was sublimed and stored under dry nitrogen. Methanol and ethanol were rapidly esterified by this compound, with the liberation of 1:2:4-triazole. The presence of the active acetyl group is indicated by a positive reaction with hydroxylamine under the modified conditions of

Polya and Tardrew [70]. This test gives positive results with diacylamines.

A solution of acetyl-1:2:4-triazole and picric acid in chloroform or benzene-carbon tetrachloride (1:1) on warming and concentration precipitated picric acid. When set aside 1 week in anhydrous conditions a precipitate of 1:2:4-triazole picrate, m.p. and mixed m.p. 167° was obtained.

Experiment No. 3.2. Reaction of the sodium salt of 1:2:4-triazole with acetyl chloride.

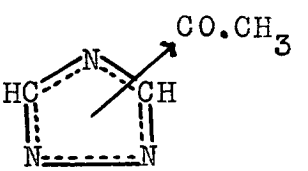
1:2:4-Triazole (0.69 g.) was added to a solution of sodium (0.23 g.) in ethanol (50 cc.) and evaporated to dryness. The residue was then covered with benzene (20 cc.) and acetyl chloride (1 cc.) in benzene (20 cc.) was added with stirring. The reactants were boiled under reflux and stirred for 0.5 hour. The liquid phase was removed by filtration, the residue washed with benzene (30 cc.) and the combined benzene solution evaporated. The pale brown oil obtained (0.21 g., 19%) was crystallized from a benzene solution on addition of light petroleum (b.p. 40-60°) giving acetyl-1:2:4-triazole, colourless triclinic crystals, b.p. 179°/760 mm., m.p. 38-39° alone or admixed with the acetyl-1:2:4-triazole prepared from 1:2:4-triazole and acetic anhydride.

Position of the acetyl group in the acetylation product of 1:2:4-triazole.

In both these cases only one of the two possible isomeric acetyl triazoles was isolated. In the reaction with acetyl chloride the low yield was due to incomplete reaction, since much of the unused triazole was recoverable from the benzene-insoluble residue. Because of the remarkable instability of acetyltriazole, efforts to determine the location of the acetyl group by chemical means were not concentrated on this compound, but rather on the more stable acetyl-3:5-dimethyl-1:2:4-triazole. The results of these investigations are discussed below. Reduction to 1-ethyl or 4-ethyl-1:2:4-triazole with lithium aluminium hydride was not attempted, since it was found in the case of the 3:5-dimethyl compound that this reagent removed the acyl group as the corresponding aldehyde, with simultaneous formation of the original triazole. This behaviour resembles that recently reported for acyl carbazoles, (82) and is probably general among those heterocyclic compounds with acidic imino groups. As mentioned above a monotonic relationship has been shown to exist between the boiling points of a number of 1-substituted pyrazoles. Acetyl-1:2:4-triazole fits closely to this relationship, and in view of the almost

exclusive 1-substitution which is now evident in this series it might be considered reasonable to assign to this compound the structure 1-acetyl-1:2:4-triazole.

On these considerations it is quite likely that we have a 1-acetyl compound with the N-Ac link approximately in the plane of the triazole ring. While there is no evidence to justify questioning the conventional formulation in this case, it might be suggested that these unstable acetyl-triazoles can only exist in one form, a positively charged acetyl group being associated



with the π-electron system of the triazole ring. It has been suggested that a similar association of a proton with the heterocyclic ring may account for phenomena of pyrazole tautomerism. (84)

Benzoyl-1:2:4-triazole.

One of the better known reactions quoted in the literature of 1:2:4-triazoles is the reported formation of 1:2-dibenzoylhydrazine from 1:2:4-triazole by the action of benzoyl chloride (85, c.f. 86). Heller obtained the hydrazine in high yield using a sample of 1:2:4-

triazole prepared from formylhydrazine and formamide by the method of Pellizzari [4]. Since the triazole ring has been found extremely stable towards a number of reagents, and in this investigation has only been opened by a sequence of reactions involving the quaternary methiodide it was thought desirable to repeat Heller's work using a purified sample of 1:2:4-triazole.

Experiment No. 3.3. Reaction of 1:2:4-triazole with benzoyl chloride.

Benzoyl chloride (10.9 g.) was added to 1:2:4-triazole (1.07 g.) at 20°. The temperature of the reactants rose to 35°, and after the initial exothermic reaction was complete the mixture was heated to 100° for 3 hours. At the end of the reaction 1:2:4-triazole hydrochloride (0.61 g., 38% of total triazole) was recovered by filtration. It had m.p. 168-170° (lit., m.p. 168-169° [87]), and after crystallization twice from a mixture of ethanol and ether was obtained as colourless plates, m.p. 170°.

Analysis:	C	H	N
Found:	22.9	3.9	39.4%.
Calculated for $C_2H_4N_3Cl$:	22.7	3.8	39.9%.

The filtrate from the first precipitate of triazole

hydrochloride was warmed with methanol (20 cc.) for 0.5 hour. A further 0.90 g. (56%) of the hydrochloride was precipitated, and had the same melting point as the first batch.

The filtrate after removal of the second batch of triazole hydrochloride was steam distilled, and the aqueous residue was boiled with an equal volume (30 cc.) of concentrated hydrochloric acid for 4 hours. The absence of hydrazine at the end of this treatment was indicated by the fact that the solution did not liberate iodine from potassium iodate or reduce Fehling's solution.

To test the possibility that dibenzoylhydrazine formation resulted from attack of the intermediate by aqueous alkali in Heller's work, the excess benzoyl chloride was decomposed with aqueous sodium carbonate or sodium hydroxide, but in neither case could any acylhydrazine formation be demonstrated by the presence of hydrazine after hydrolysis.

The near-quantitative (96%) recovery of triazole as hydrochloride and the absence of any hydrazine on hydrolysis of the remaining material throws some doubt on Heller's observations, and a possible explanation is given below. The formation of 1:2:4-triazole hydrochloride during the benzoylation indicates the simultaneous

formation of an equimolar amount of benzoyl-1:2:4-triazole, which would remain in solution in the excess benzoyl chloride. Even neglecting the solubility of 1:2:4-triazole hydrochloride in this solvent the yield of benzoyl compound must have been at least 75% from the amount of hydrochloride isolated. On decomposition of excess benzoyl chloride with dry methanol this compound must have been decomposed either by methanol or hydrogen chloride to 1:2:4-triazole, which precipitated as the second batch of hydrochloride.

This apparent discrepancy is almost certainly caused by the contamination of Heller's triazole sample with considerable amounts of 1:2-diformylhydrazine. On checking the Pellizzari synthesis of 1:2:4-triazole it has been observed several times that substantial proportions of the hydrazine remain at the end of the reaction as the diformyl compound. The depression of the melting point of the triazole is not always very great, and one must usually recrystallize the triazole from a suitable solvent (e.g. benzene with the use of a Soxhlet apparatus) to obtain a pure product. Assuming that all the dibenzoylhydrazine obtained in Heller's reaction was derived from diformylhydrazine, it follows that the apparent yield of 60% based on "triazole" corresponds to 77%

contamination of the starting materials, even if a quantitative conversion is assumed.

Experiment No. 3.4. Reaction of benzoyl chloride with 1:2-diformylhydrazine.

1:2-Diformylhydrazine (0.40 g.) was mixed with benzoyl chloride (3.5 g.) and heated at 100° for 3 hours. At the end of the reaction the product was poured into aqueous sodium carbonate (2N, 50 cc.), and when the benzoyl chloride was completely decomposed, insoluble 1:2-dibenzoylhydrazine was recovered by filtration (0.78 g 72%), m.p. 135-137°. Recrystallization from ethanol gave pure 1:2-dibenzoylhydrazine (0.67 g., 69%) m.p. and mixed m.p. 137°.

3:5-Dimethyl-1:2:4-triazole.

The samples of this triazole used in alkylation and acylation experiments were prepared from acetylhydrazine and acetamide by Silberrad's method. (88) In a typical case, acetamide (23.6 g.) and acetylhydrazine (29.6 g.) were heated together under reflux for 4 hours in a bath at 230°. Water was allowed to escape at the head of an 80 cm. column. After this time the product was distilled. The fraction boiling at 255-260°/760 mm. was collected and recrystallized from benzene. After drying at

75°/0.1 mm. the weight of the pure triazole was 29.4 g. (76%), and the colourless prisms had m.p. 143° alone or in admixture with 3:5-dimethyl-1:2:4-triazole prepared from diacetamide and semicarbazide hydrochloride.

It has been reported [26] that 3:5-dimethyl-1:2:4-triazole does not form a precipitate with picric acid. This has been confirmed for the system with water, methanol or ethanol as solvent, but with some of the higher alcohols or with non-hydroxylic solvents it is not the case.

3:5-Dimethyl-1:2:4-triazole picrate separated from a warm solution of the triazole and picric acid in chloroform. It crystallized from benzene-methanol (12:1) as orange needles with m.p. 170°, which could be dried at 75°/1 mm.

Analysis:	C	H
Found:	37.2	3.1%.
$C_{10}H_{10}O_7N_6$ requires:	36.8	3.1%.

Quantitative isolation of amphoteric triazoles such as 3:5-dimethyl-1:2:4-triazole presents considerable difficulties, since they are frequently obtained in the presence of amides and hydrazides of similar physical properties, and since they form few characteristic insoluble derivatives. Of the metal salts the most useful

was found to be the silver salt, from which the triazole could be isolated in high yield by solution in hydrochloric acid, neutralization and extraction of the dried residue with benzene.

3:5-Dimethyl-1:2:4-triazole does not give a precipitate with a solution of nickel chloride in carbon bisulphide.

Experiment No. 3.5. Methylation of the sodium salt of 3:5-dimethyl-1:2:4-triazole with methyl iodide.

3:5-Dimethyl-1:2:4-triazole (7.50 g.) was dissolved in a solution of sodium (1.78 g.) in methanol (40 cc.) and methyl iodide (11.0 g.) was added. After 1 hour at room temperature and 1 hour at 120° in a sealed vessel the product was worked up as in the case of 1-methyl-1:2:4-triazole. The basic portion of the product on distillation at 194-195°/760 mm. was found to consist entirely of 1:3:5-trimethyl-1:2:4-triazole (6.95 g., 81%). Redistilled at 193°/755 mm. the triazole had d_{20}^{20}: 1.037; n_D^{20}: 1.4653. The base gave a picrate which had m.p. 134-135.5° alone or admixed with 1:3:5-trimethyl-1:2:4-triazole picrate from the base obtained in the reaction of diacetamide with methylhydrazine sulphate (Section 2).

The residue remaining after distillation of 1:3:5-trimethyl-1:2:4-triazole was unchanged 3:5-dimethyl-1:2:4-

triazole, (0.15 g., 2%), which was identified by its m.p. and mixed m.p.

None of the previously described [89] 3:4:5-trimethyl-1:2:4-triazole could be detected at the end of the reaction.

This methylation was conducted at 120°, since a corresponding ethylation (Experiment No. 3.7) led to the formation of a small amount of the 4-ethyl isomer in addition to a high yield of 1-ethyl-3:5-dimethyl-1:2:4-triazole. In an earlier experiment with the same reactants, but involving reaction at room temperature for 1 hour and at 100° for 1.5 hours a yield of 8.7 g. (76%) 1:3:5-trimethyl-1:2:4-triazole was obtained from 10.0 g. of 3:5-dimethyl-1:2:4-triazole. Formation of the 4-methyl isomer was not observed.

Experiment No. 3.6. Methylation of 3:5-dimethyl-1:2:4-triazole with diazomethane.

3:5-Diemthyl-1:2:4-triazole (1.00 g.) was dissolved in methanol (20 cc.), and ethereal diazomethane generated from nitrosomethylurea (total 13 g.) was added in 3 portions during 3 days. Solvent was removed, and the residual oil distilled at 1.5 mm. The distillate, 1:3:5-trimethyl-1:2:4-triazole (0.93 g., 81%), was a colourless oil with b.p. 195-196°/755 mm., and gave a picrate,

m.p. 134°, which did not depress the m.p. of 1:3:5-trimethyl-1:2:4-triazole picrate.

The residue remaining after distillation of the lower-boiling fraction set to colourless prisms, m.p. 138-142°, which were washed with a few drops of benzene, and then had m.p. 143° alone or admixed with 3:5-dimethyl-1:2:4-triazole (0.14 g., 14% recovery).

Experiment No. 3.7. Ethylation of the sodium salt of 3:5-dimethyl-1:2:4-triazole with ethyl iodide.

3:5-Dimethyl-1:2:4-triazole (10.0 g.) was dissolved in a solution of sodium (2.37 g.) in ethanol (60 cc.). Ethyl iodide (16.1 g.) was added, and after reaction for 1 hour at room temperature and 1.5 hours at 120° the products were worked up as in the methylation experiments. Distillation afforded 1-ethyl-3:5-dimethyl-1:2:4-triazole (7.50 g., 58%) as a colourless oil, b.p. 80.5-81.5°/12 mm. b.p. 196°/755 mm. This material when redistilled at 196°/755 mm. had d_{20}^{20}: 0.990, n_D^{20}: 1.4690.

Analysis:	C	H	N
Found:	57.2	8.9	33.7%.
$C_6H_{11}N_3$ requires:	57.6	8.9	33.6%.

1-ethyl-3:5-dimethyl-1:2:4-triazole picrate crystallized from a solution of the base and picric acid in warm

ethanol, and was recrystallized from ethanol as flat yellow prisms, m.p. 125-126°. The picrate was dried at 75°/1 mm.

Analysis:	C	H
Found:	40.9	3.9%.
$C_{12}H_{14}O_7N_6$ requires:	40.7	4.0%.

The residue remaining after distillation of 1-ethyl-3:5-dimethyl-1:2:4-triazole was hygroscopic, and with ethanolic picric acid gave 4-ethyl-3:5-dimethyl-1:2:4-triazole picrate (0.4 g., 1%). This had m.p. 145-147° alone or admixed with an authentic sample of 4-ethyl-3:5-dimethyl-1:2:4-triazole picrate obtained from N-ethylacetamide and acetylhydrazine (Section 1). The picrate was decomposed with 4N hydrochloric acid, and after extraction of the picric acid with ether the triazole hydrochloride was treated with dilute sodium hydroxide, and the triazole extracted with chloroform. After drying (Na_2SO_4) the solvent was removed, leaving tan prisms (0.13 g.), m.p. 111-114°. This product was chromatographed on alumina (6 g.) in benzene, and eluted with benzene-chloroform (10:1), giving colourless hygroscopic prisms, m.p. 115°. The melting point of 4-ethyl-3:5-dimethyl-1:2:4-triazole was not depressed on admixture with this material.

Experiment No. 3.8. The reaction of 3:5-dimethyl-1:2:4-triazole with diazoethane.

3:5-dimethyl-1:2:4-triazole (1.00 g.) in ethanolic solution was treated with an ethereal solution of diazoethane generated from nitrosoethylurea (total 21 g.) in 3 portions during 3 days. The product was worked up as in the corresponding methylation experiment, and afforded 1-ethyl-3:5-dimethyl-1:2;4-triazole (1.20 g., 93%), b.p. 194.5°/745 mm. The picrate had m.p. 125-126° alone and in admixture with the 1-ethyl-3:5-dimethyl-1:2:4-triazole picrate obtained in the ethyl iodide ethylation. In addition unchanged 3:5-dimethyl-1:2:4-triazole (0.03 g., 3%) was recovered and identified as in the former case.

Quaternary salt formation from 1:2:4-triazoles.

When the sodium salt of a triazole which has an acidic hydrogen is treated with an equimolar amount of an alkyl halide the corresponding N-alkyl triazole is formed, often in high yield. Under these conditions the quaternary alkyl ammonium compound does not appear to be formed to a significant extent. When, however, a basic triazole (i.e. one without an imino group) is treated with an excess of an alkyl halide it is possible to obtain the quaternary monohalide. Introduction of a

second quaternary centre in the molecule by using a large excess of the halide has not been successful.

Experiment No. 3.9. Reaction of 1:3:5-trimethyl-1:2:4-triazole with methyl iodide.

1:3:5-trimethyl-1:2:4-triazole (2.0 g.) was heated with methyl iodide (10.2 g.) and benzene (15 cc.) under reflux for 4 hours. The solvent and excess methyl iodide were partially removed by evaporation, and the colourless crystalline product recovered by filtration. This was 1:3:5-trimethyl-1:2:4-triazole methiodide (2.9 g., 64%) m.p. 133-136° after drying at 75°/2 mm. Two recrystallizations from methanol-ether gave colourless hygroscopic prisms, m.p. 138°.

Analysis:	C	H	I
Found:	27.5	5.5	50.2%.
$C_6H_{12}N_3I$ requires:	28.5	4.8	50.1%.

The hygroscopic nature of this compound possibly accounts for discrepancies in the analysis.

The methyl groups of many heterocyclic methohalides may be condensed with Folin's amino acid reagent (the sodium salt of 1:2-naphthoquinone-4-sulphonic acid) to give coloured condensation products [90]; the reaction failed in this case. In order to locate the newly

introduced methyl group, the methiodide was decomposed with strong alkali.

Experiment No. 3.10. Decomposition of 1:3:5-trimethyl-1:2:4-triazole methiodide with sodium hydroxide.

1:3:5-Trimethyl-1:2:4-triazole methiodide (2.15 g.) was dissolved in water (50 cc.) and potassium hydroxide (30 g.) was added. The solution was steam-distilled, and after condensation of 1 litre of distillate the material passing over no longer reduced Fehling's solution. The distillate was evaporated on a water bath with concentrated hydrochloric acid (5 cc.) and finally evaporated under reduced pressure with ethanol (2 x 10 cc.). The residue set to colourless needles of indefinite melting point, but crystallization from a mixture of ethanol and ether containing a few drops of hydrochloric acid gave 1:2-dimethylhydrazine dihydrochloride (0.51 g., 45%), colourless prismatic powder, m.p. 167° (lit., m.p. 168° (91)). With picric acid in 20% ethanol 1:2-dimethylhydrazine picrate was precipitated as yellow plates, m.p. 145-147°. Recrystallized from water as yellow needles it had m.p. 148-150° (lit., m.p. 147-150° (92)).

The yield was reduced by the loss of dimethylhydrazine in the vigorous reaction which followed the addition of solid potassium hydroxide. Loss of hydrogen

chloride during the final stages of evaporation probably accounts for the unsharp melting point of the first crystals obtained. Hatt [93] has commented on this behaviour of the dihydrochloride, which decomposes to the monohydrochloride, but may be readily crystallized if a little hydrochloric acid is added to the solvent.

Discounting the possibility of migration of a methyl group this reaction may be considered to prove the structure of 1:3:5-trimethyl-1:2:4-triazole methiodide as 1:2:3:5-tetramethyl-1:2:4-triazolium iodide.

Experiment No. 3.11. Acetylation of 3:5-dimethyl-1:2:4-triazole with acetic anhydride.

3:5-Dimethyl-1:2:4-triazole (2.0 g.) and acetic anhydride (4 cc.) were boiled under reflux for 1 hour, and the solid remaining after distillation of acetic acid and excess acetic anhydride was sublimed at 70°/2 mm. This gave acetyl-3:5-dimethyl-1:2:4-triazole (2.4 g., 84%) as colourless prisms, m.p. 90-91°, b.p. 199°/760 mm.

Analysis:	C	H	N
Found:	51.9	6.4	30.9%.
$C_6H_9ON_3$ requires:	51.8	6.5	30.2%.

Acetyl-3:5-dimethyl-1:2:4-triazole in chloroform was warmed with a 5% excess of picric acid. On partial

removal of the solvent acetyl 3:5-dimethyl-1:2:4-triazole picrate crystallized as yellow prisms, m.p. 119-120°. This product was recrystallized from carbon tetrachloride-benzene (10:1) as yellow monoclinic needles, m.p. 120°.

Analysis:	C	H
Found:	39.2	3.2%.
$C_{12}H_{12}O_8N_4$ requires:	39.1	3.2%.

Evaporation of the chloroform mother liquors gave a residue which was washed with benzene, leaving clusters of orange needles, m.p. 167-169°. These were recrystallized from ethanol and had m.p. 170° alone or admixed with 3:5-dimethyl-1:2:4-triazole picrate.

As in the case of acetyl-1:2:4-triazole, picric acid in non-hydroxylic solvents is capable of cleaving acetyl-3:5-dimethyl-1:2:4-triazole to the acetyl-free triazole, but in this case the acetyl compound is sufficiently stable to be partially precipitated as the picrate. Here also the active acetyl group may be demonstrated by a hydroxamic acid reaction, but the reaction is more vigorous than in the case of acetyl-1:2:4-triazole. A similar positive test was also given by the acetyl derivative of 3-hydroxy-5-phenyl-1:2:4-triazole (kindly provided by Dr. E. A. Parkes). The test was negative with acetyl-3:5-diphenyl-1:2:4-triazole.

When 3:5-dimethyl-1:2:4-triazole was treated with acetic acid-acetic anhydride (1:1) and sodium acetate at 100° for 0.5 hour, and the product was poured into ice-water a few crystals, m.p. 91°, of acetyl-3:5-dimethyl-1:2:4-triazole were obtained by filtration, but practically all the unsubstituted triazole used in the reaction was recovered from the aqueous solution.

Experiment No. 3.12. Reaction of the potassium salt of 3:5-dimethyl-1:2:4-triazole with acetyl chloride.

3:5-Dimethyl-1:2:4-triazole (1.0 g.) was dissolved in a solution of potassium (0.39 g.) in methanol (10 cc.). Ether (200 cc.) precipitated colourless needles which were suspended in benzene (50 cc.). Acetyl chloride (0.80 g., 0.01 mole) in benzene (25 cc.) was added, and the suspension was boiled under reflux for 0.5 hours with stirring. The residue was removed by filtration, washed with benzene (20 cc.), and the combined benzene solution evaporated, leaving acetyl-3:5-dimethyl-1:2:4-triazole (0.86 g., 60%) as colourless prisms, m.p. 89-91° after sublimation. This material did not depress the melting point of the acetyldimethyltriazole obtained by the action of acetic anhydride on dimethyltriazole.

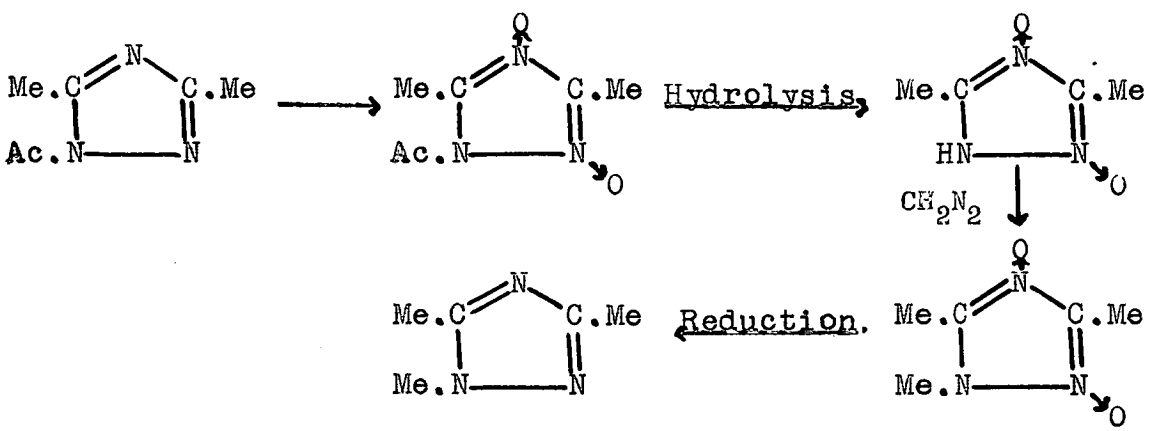
Some reasons for supposing that the acetyl group, in this case, is located at N_1 have been given in

connection with the structure of acetyl-1:2:4-triazole. Several attempts to prove the location of this acetyl group by chemical means are reported below.

Acetyl-3:5-dimethyl-1:2:4-triazole was recovered unchanged in almost quantitative yield after being heated with an equimolar amount of methyl iodide in benzene at 100° for 6 hours. The material obtained at the end of the reaction, and its picrate, did not depress the melting points of the starting material or its picrate.

This failure to obtain a quaternary salt from an acetyl triazole prevented several approaches to a proof of location of the acetyl group.

Reaction of the triazole with hydrogen peroxide solutions led to rapid hydrolysis of the acetyl group. If it had been possible to form the dioxide of the acetyldimethyltriazole it is possible that the location of the acetyl group could have been demonstrated. Thus, supposing the compound to be acylated on N_1:



the indirect replacement of an acetyl group by a methyl group to give one of the known isomeric trimethyltriazoles would have been a fairly conclusive proof of the location of the acetyl group. The possibility of preparing a dioxide of an azole has not been established yet, and the system might not be sufficiently stable to permit isolation. There would also be a small chance of oxide formation on the amide nitrogen.

A direct synthesis of 1-acetyl-3:5-dimethyl-1:2:4-triazole using diacetamide and acetylhydrazine was attempted, but instead of a cyclized product, the only compounds isolated were acetamide and 1:2-diacetylhydrazine, resulting from acetylation of acetylhydrazine.

Experiment No. 3.13. Reduction of acetyl-3:5-dimethyl-1:2:4-triazole with lithium aluminium hydride.

Acetyl-3:5-dimethyl-1:2:4-triazole (1.75 g.) in ether (100 cc.) was added to a slurry of lithium aluminium hydride (1.5 g.) in ether (50 cc.), and the mixture was boiled under reflux with an atmosphere of nitrogen for 20 hours. Excess lithium aluminium hydride was decomposed with water, and sufficient 4N sulphuric acid was added to give a clear solution. The ether layer was separated, and the aqueous layer extracted with chloroform (3 x 50 cc.), the combined extracts dried (Na_2SO_4)

and the solvent removed, affording traces of non-crystalline material which did not give a picrate with ethanolic picric acid. This extract had a strong odour of acetaldehyde, and gave a positive reaction with Schiff's reagent. The aqueous layer was made strongly alkaline with 10% sodium hydroxide containing sodium tartrate and extracted continuously with ether without the removal of any organic material. The alkaline solution was neutralized, evaporated to dryness at 12 mm. over sulphuric acid and the residue extracted with chloroform (100 cc.). Removal of the solvent left 3:5-dimethyl-1:2:4-triazole (0.84 g., 69%) m.p. 141-142°, which crystallized from benzene as colourless prisms, m.p. and mixed m.p. 142-143°.

The reduction of an acetyl triazole to acetaldehyde and de-acetylated triazole may be compared to the corresponding aldehyde formation when acyl carbazoles are reduced with lithium aluminium hydride. (94) The failure to obtain one of the two possible N-ethyl-3:5-dimethyl-1:2:4-triazoles, which had already been unambiguously prepared in this investigation, prevented a structural proof on the starting material.

Experiment No. 3.14. Reaction of 3:5-dimethyl-1:2:4-triazole with 2:4-dinitrochlorobenzene.

3:5-Dimethyl-1:2:4-triazole (1.7 g.) and 2:4-dinitrochlorobenzene (3.4 g.) were fused with anhydrous sodium acetate (2.6 g.). After heating the reactants for 0.25 hour at 100°, water (5 cc.) was added and heating was continued for a further 0.5 hour. The product was poured into aqueous sodium hydrogen carbonate (10%, 50 cc.) and extracted with ether (3 x 50 cc.). The extract was dried (Na_2SO_4) and evaporated, leaving pale yellow crystals (3.3 g.), m.p. 48-52°. Recrystallization from dilute ethanol gave pale yellow crystals (2.6 g.), m.p. 51-53° alone or mixed with 2:4-dinitrochlorobenzene. The mother liquors of these did not give a picrate with aqueous picric acid. By evaporation of the sodium hydrogen carbonate solution and extraction of the residue with chloroform 3:5-dimethyl-1:2:4-triazole (1.5 g., 89%) m.p. and mixed m.p. 240-242° was recovered.

From the recovery of the starting materials and the failure to demonstrate the formation of 3:5-dimethyl-1-(2:4-dinitrophenyl)-1:2:4-triazole it is concluded that no reaction occurred. The triazole would be ether soluble, and would form an insoluble picrate.

3-Phenyl-1:2:4-triazole.

3-Phenyl-1:2:4-triazole was required for the investigation of orientation effects in the formation of its N-methyl derivatives. Considerable difficulty was experienced in obtaining sufficient material for this purpose. As mentioned in Section 2, 3-phenyl-1:2:4-triazole was obtained from N-formylbenzamide by an Einhorn-Brunner reaction, but at that time it was only possible to obtain the diacylamine in very low yields, so other methods were investigated. A Pellizzari type reaction of formylhydrazine and benzamide was attempted, but the yield of the required material was extremely small.

Experiment No. 3.15. Reaction of benzamide and formylhydrazine.

Benzamide (60.5 g.) and formyl hydrazine (30 g.) were mixed and heated for 16 hours (internal temperature 220-240°). Water and ammonia distilled off during the reaction. The residual oil was distilled, and after collection of benzonitrile a fraction with b.p. 195-200°/12 mm. was obtained. This material (1.5 g.) had m.p. 110-125°, and could not be purified by recrystallization. The whole fraction was treated with ethanolic silver nitrate. The precipitate was filtered and washed with ether, then rubbed with hydrochloric acid (5N). The

solution was decanted from silver chloride, neutralized with aqueous sodium carbonate (2N), and extracted with chloroform (30 cc.) which extracted ca. 50 mg. of oily material. The aqueous solution was evaporated to dryness and extracted with hot benzene (10 cc.). On concentration and dilution with light petroleum (b.p. 40-60°) 3-phenyl-1:2:4-triazole (0.42 g., below 1%) crystallized as colourless needles, m.p. 118°. This was later found to give no depression of melting point with 3-phenyl-1:2:4-triazole prepared by Hoggarth's method [68] from benzoylthiosemicarbazide. A fraction of material with b.p. 210-215°/12 mm. (12.5 g.) contained 1:2-diformylhydrazine, which had m.p. 157° after crystallization from 50% aqueous ethanol. (Lit., m.p. 158°; Curtius, Schofer and Schwan [73]). Higher boiling material remained in the distillation flask as a glassy residue, insoluble in water, ethanol or acetone.

Recourse was finally made to the sequence of reactions described by Hoggarth (loc. cit.).

Semicarbazide was benzoylated in dry pyridine, and the benzoylsemicarbazide was cyclized with sodium ethoxide to 3-phenyl-1:2:4-triazole-5-thiol. Removal of the -SH group in boiling acetic acid with perhydrol gave 3-phenyl-1:2:4-triazole. This crystallized from light

petroleum (b.p. 100-120°) with m.p. 116-118°, and after sublimation at 120°/0.1 mm. had m.p. 119°. Hoggarth gives m.p. 121° for the final product, but apart from this small discrepancy the set of reactions was found to be reliably described, both as to yields and quality of products.

Experiment No. 3.16. Methylation of the sodium salt of 3-phenyl-1:2:4-triazole.

3-Phenyl-1:2:4-triazole (2.9 g.) was added to a solution of sodium (0.46 g.) in methanol (10 cc.). Methyl iodide (2.8 g.) was added and the tube containing the reactants was sealed. After 1 hour at 20° the tube was heated to 100° for 12 hours. After removing methanol by distillation the residual oil was treated with 20% aqueous sodium hydroxide (50 cc.) and extracted with ether. The ether extract was dried with sodium sulphate and solvent was removed, leaving a pale oil (2.9 g.). Assuming that this material consists entirely of N-methyl-3-phenyl-1:2:4-triazoles the total yield is 91%. An aliquot of this material was evaporated in chloroform solution with an equimolar amount of picric acid, and the resultant mixed picrate recrystallized from the minimum amount of ethanol. The product was a mixture of stout prismatic rods, identical in appearance with

1-methyl-3-phenyl-1:2:4-triazole picrate, and a smaller proportion of flat needles or laminae characteristic of 1-methyl-5-phenyl-1:2:4-triazole picrate. Assuming that these were the only products present (an assumption which seems to be supported by the distillation studies reported below) a melting point diagram was constructed for the system of these two picrates. Consistent results were obtained using well-ground samples and observing the "all-clear" point. (Figure 2). The composition of the mixed picrate was determined on this basis to include 63% 1-methyl-3-phenyl-1:2:4-triazole picrate. The position on the eutectic curve at m.p. 73.5° was determined with close agreement by altering the composition of the unknown with pure samples of the two components, and interpolating to the original composition.

Chromatography of the mixed triazoles in benzene on alumina did not effect a separation. A partial separation of the components of the mixture was achieved by decomposition of the mixed picrate on a column of alumina in dry ether solution. Samples of the two pure isomeric triazoles (1-methyl-3-phenyl- and 1-methyl-5-phenyl-) were obtained, but the separation was not complete. This method is discussed in Section 5 as an illustration of the use of this technique for recovering triazoles

from their picrates. From the picrates used in this investigation the original mixture of bases was quantitatively regenerated on the alumina column by elution with chloroform-ether. Distillation was attempted as a means of separation, and the fraction with b.p. 114-116°/2-3 mm. had m.p. 55-57° (0.89 g, 28% on starting material). After sublimation at 60°/2 mm. it had m.p. 58° and mixed m.p. 59° with 1-methyl-5-phenyl-1:2:4-triazole. The picrate prepared from this triazole had m.p. 176-178°, and after recrystallization from ethanol it had m.p. and mixed m.p. 178°.

Discarding an intermediate fraction of less than 100 mg., the fraction with b.p. 120-122°/2-3 mm. (1.79 g. 56%) was collected and sublimed onto a condenser cooled with liquid air. 1-Methyl-3-phenyl-1:2:4-triazole was obtained as colourless prisms, m.p. and mixed m.p. 23°. The picrate was obtained as a precipitate with ethanolic picric acid, m.p. 179-182°. Recrystallized from ethanol it had m.p. 181°, and mixed m.p. 181-182°.

4-Methyl-3-phenyl-1:2:4-triazole was not detected among the products of the reaction. The ratios of isomers demonstrated by the two methods are shown.

	1-Methyl-3-phenyl-	1-Methyl-5-phenyl-
Picrate eutectic:	73%	27%
Fractionation:	67%	33%

Even this small discrepancy may be partly explained by the fact that the solubilities of the picrates in ethanol are not identical.

System 1-methyl-3-phenyl-1:2:4-triazole picrate --- 1-methyl-5-phenyl-1:2:4-triazole picrate.

In order to determine the composition of mixtures of the above picrates obtained in methylation experiments the composition-melting point diagram of the system was constructed. Melting points were determined as the all-clear point, using a metal-block apparatus calibrated against pure compounds in the same manner. Mixtures were weighed on an analytical balance, finely ground and mixed. Melting points were the average of four determinations, and were found to be closely reproducable. An equimolar eutectic, m.p. 159.8^{o} was observed.

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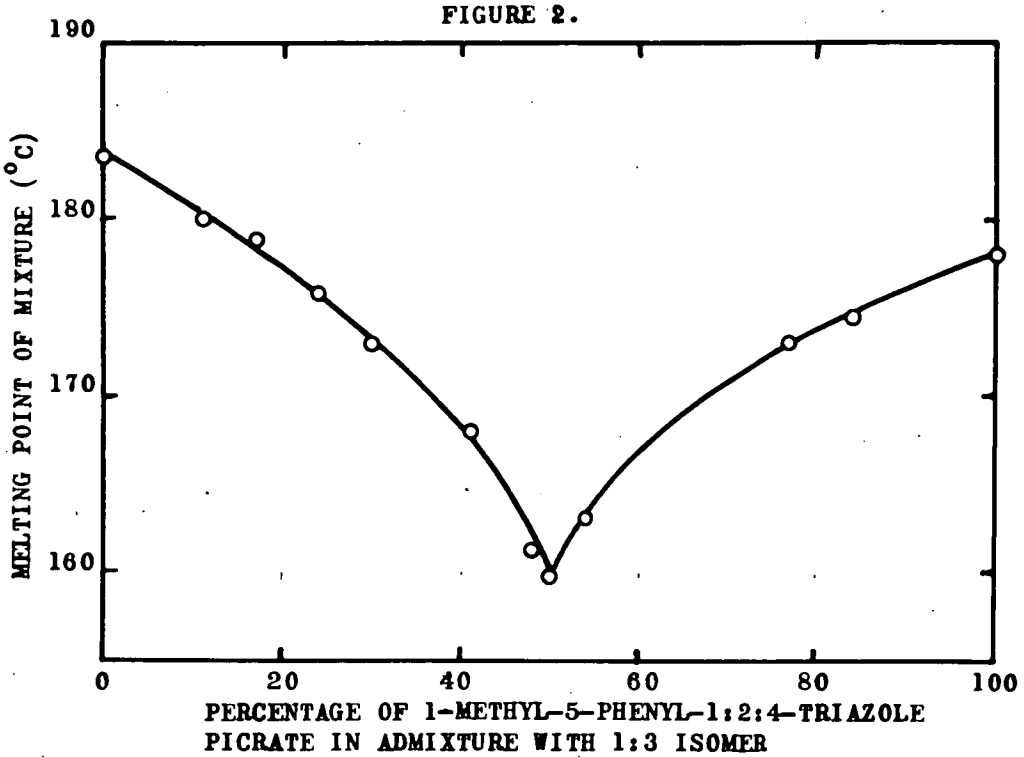
Percentage of 1-methyl-5-phenyl-1:2:4-triazole picrate in mixture with 3-phenyl isomer.	Melting point of mixture.
0	183.5°
11	180.0
17	178.8
24	175.8
30	173.0
41	167.0
48	161.1
50	159.8
54	163.0
77	173.0
84	174.5
100	178.0

The curve is shown in Figure 2.

While artificial mixtures were found to give consistent results, it was found that starting from a mixture of the two pure triazoles, estimation of composition by determining the melting point of the resultant mixed picrate could lead to errors of up to 10%, since the solubilities of the picrates were not identical. The best method of preparing the mixed picrate was found to be evaporation of a chloroform solution of the triazoles and an equimolar amount of picric acid. The composition was determined from the melting point of an unknown mixture by also altering the composition of the mixture in each direction with known amounts of the pure components

FIGURE 2.


190
180
170
160
MELTING POINT OF MIXTURE (°C)
0
20
40
60
80
100
PERCENTAGE OF 1-METHYL-5-PHENYL-1:2:4-TRIAZOLE
PICRATE IN ADMIXTURE WITH 1:3 ISOMER

and interpolating. Such interpolations usually agreed within 3% of the original value.

Experiment No. 3.17. Methylation of 3-phenyl-1:2:4-triazole with diazomethane.

3-Phenyl-1:2:4-triazole (1.45 g.) was dissolved in dry methanol (10 cc.) and ethereal diazomethane from nitrosomethylurea (10 g.) was added in three lots during six days. After removal of the solvent the residue was poured into aqueous sodium hydroxide (10%) and extracted with chloroform (2 x 50 cc.). Evaporation of the dried extract left a colourless oil (1.51 g.) which was fractionally distilled.

The fraction boiling at 112-116°/2-3 mm. solidified on cooling, giving colourless crystals, m.p. 52-55° (0.89 g., 56%) of 1-methyl-5-phenyl-1:2:4-triazole. The picrate had m.p. 177°, and crystallized from ethanol as flat needles, m.p. and mixed m.p. 178°.

After discarding a small intermediate fraction material with b.p. 119-122°/2-3 mm. (0.54 g., 34%) was collected, and on cooling with liquid air set to a glass which crystallized, and gave material with m.p. 18-20°. This was converted to the picrate, which had m.p. 180-181°, and after crystallization from ethanol had m.p. 181-182°. The mixed m.p. with 1-methyl-3-phenyl-1:2:4-triazole picrate was 182°.

3-Methyl-5-phenyl-1:2:4-triazole.

Heller [69] has reported the preparation of this material from benzoylhydrazine and acetamide. In this investigation the compound was required for methylation studies, and had been prepared in small quantities from N-acetylbenzamide and semicarbazide hydrochloride (Section 2). For the larger quantities required it was decided to attempt a preparation by Heller's method.

Experiment No. 3.18. Preparation of 3-methyl-5-phenyl-1:2:4-triazole.

Benzoylhydrazine (41.5 g.) and acetamide (18 g.) were mixed and heated by means of a Wood's metal bath under a short column. The internal temperature was gradually increased from 230° to 260° during 6 hours, and maintained at 260° for 6 hours. The product was poured into hydrochloric acid (5N, 100 cc.), boiled for a few minutes and cooled. The crystalline product was filtered and dried at 100°/0.1 mm. It had m.p. 185-190°, and was crude 3:5-diphenyl-1:2:4-triazole (15.5 g., 23%). A portion recrystallized from benzene had m.p. and mixed m.p. 191°.

The acidic filtrate was neutralized with ammonia and with sodium carbonate, and extracted with benzene (4 x 50 cc.). After evaporation of the dried (Na_2SO_4)

extract the residue was pressed on a porous tile, leaving 3-methyl-5-phenyl-1:2:4-triazole (14.4 g., 30%) as colourless prisms, m.p. 160-164°. Recrystallized from benzene-light petroleum (b.p. 100-120°) this material had m.p. 165°, and did not depress the melting point of material obtained in the Einhorn-Brunner reaction (lit., m.p. 164.5°; Heller, loc. cit.).

In two other experiments with the same reactants, but at lower temperatures (200-220°) no triazoles were isolated, but substantial yields of 1:2-diacetylhydrazine, 1:2-dibenzoylhydrazine and mixed hydrazides, which could be hydrolysed to hydrazine, were obtained. In one case a compound with m.p. 164° was obtained, but this was recovered unchanged after heating for 12 hours with methyl iodide and sodium methoxide. The m.p. of the compound was not changed by recrystallization from benzene, but the analytical figures have not been interpreted.

Analysis:	C	H	N
Found:	79.58.	5.35	7.83%.

The compound in ethanolic solution had a light absorption maximum at 264 millimicrons while a sample of 3-methyl-5-phenyl-1:2:4-triazole had maximum absorption at 244 millimicrons. The compound was not investigated further.

Instead of reacting benzoylhydrazine and acetamide, acetylhydrazine and benzamide were reacted in molar quantities, all details of the procedure being as in the preceding experiment (No. 3.18). The products of the reaction were 3:5-diphenyl-1:2:4-triazole (62 g., 56%), and 3-methyl-5-phenyl-1:2:4-triazole (21.3 g., 13%). In this case the yield of re-acylated product is much higher than in the former case, but the 3-methyl-5-phenyl-1:2:4-triazole was somewhat easier to purify.

An attempt was made to react benzamide and acetylhydrazine in chloroform, using phosphorus oxychloride-pyridine as a condensing agent, but almost all the benzamide was converted to benzonitrile, and no 3-methyl-5-phenyl-1:2:4-triazole was obtained.

3-Methyl-5-phenyl-1:2:4-triazole picrate was prepared from the triazole and picric acid in 2-propanol. It crystallized as yellow prisms, m.p. 156°, and then from methanol as yellow needles, m.p. 158°. Heller reports m.p. 158°.

Experiment No. 3.19. Methylation of the sodium salt of 3-methyl-5-phenyl-1:2:4-triazole with methyl iodide.

3-Methyl-5-phenyl-1:2:4-triazole (7.9 g.) was suspended in a solution of sodium (1.15 g.) in dry methanol (30 cc.). Methyl iodide (7.1 g.) was added, and the reaction vessel was sealed. After 1 hour at 20° the vessel was heated to 100° for 12 hours. Methanol was removed by distillation from the products, and the residue added to 100 cc. of 20% aqueous sodium hydroxide. Methylated material was extracted with ether (3 x 150 cc.) and the residue from the dried extract was distilled. The entire residue distilled at 116-118°/2-3 mm., and solidified to a crystalline mass (8.1 g., 93% crude) with m.p. 111-114°. Recrystallization from benzene-light petroleum (b.p. 60-80°) gave 1:5-dimethyl-3-phenyl-1:2:4-triazole as colourless prisms (7.8 g., 90%), m.p. and mixed m.p. 117°. No indications of the formation of the other two possible N-methyl derivatives were obtained. The crude product before distillation gave a picrate which had m.p. 164°, and which crystallized from ethanol as yellow needles with m.p. 166° alone or admixed with 1:5-dimethyl-3-phenyl-1:2:4-triazole picrate.

Experiment No. 3.20. Methylation of 3-methyl-5-phenyl-1:2:4-triazole with diazomethane

3-Methyl-5-phenyl-1:2:4-triazole (7.9 g.) was suspended in dry methanol (50 cc.) and was treated with diazomethane from 15 g. of nitrosomethylurea, in three lots, each in 100 cc. of ether, during one week. After all the diazomethane had decomposed the solvents were removed by distillation and the residue was distilled at reduced pressure through a vacuum-jacketed Vigreux column. The fraction with b.p. 93-96°/1 mm. crystallized, and was rubbed with 1 cc. of benzene-petroleum ether (b.p. 60-80°). This material (3.2 g., 37%) was almost pure 1:3-dimethyl-5-phenyl-1:2:4-triazole, and had m.p. and mixed m.p. 70-72°. With ethanolic picric acid 1:3-dimethyl-5-phenyl-1:2:4-triazole picrate was precipitated as yellow needles, m.p. 170-171° and mixed m.p. 171°.

A fraction with b.p. 96-105°/1 mm. (ca. 150 mg.) was discarded.

Material with b.p. 105-110°/1 mm. (0.9 g., 10%) solidified immediately on cooling, and had m.p. 113-115°. after washing with 1 cc. of benzene--light petroleum. The mixed m.p. with 1:5-dimethyl-3-phenyl-1:2:4-triazole prepared from benzamide methylhydrazone was 114-115°. This triazole gave a picrate from ethanol with m.p. 166°,

silky yellow needles, which did not depress the m.p. of the authentic picrate.

The residue from the distillation had m.p. 158-160° and was principally pure 3-methyl-5-phenyl-1:2:4-triazole, since rubbing on a sintered glass plate with benzene-light petroleum left 3.3 g. (42%) of material with m.p. 163° and mixed m.p. 164° with the starting material. A portion sublimed at 140°/1 mm. had m.p. and mixed m.p. 166°. The washings from the residue were collected and treated with picric acid, but afforded only a few mg. of 1:5-dimethyl-3-phenyl-1:2:4-triazole picrate, m.p. 165° and mixed m.p. 166°.

The ratio of the products of methylation N_1/N_2 = ca. 1.4:1. If formation of the N_4-methyl product occurred it was below the limit of detection by these methods (estimated at 2-5%).

3:5-Diphenyl-1:2:4-triazole.

This material was obtained from benzamide and benzoylhydrazine by Pellizzari's reaction. (5)

Experiment No. 3.21. Preparation of 3:5-diphenyl-1:2:4-triazole.

Benzamide (18.2 g.) and benzoylhydrazine (20.4 g.) were heated at 240° for 8 hours. The product was dissolved in warm aqueous sodium hydroxide (10%), a residue being separated by filtration. The alkaline solution was made slightly acidic with hydrochloric acid, and cooled overnight. The precipitated material was recrystallized from 30% ethanol, giving colourless prisms, m.p. 187-188° after drying at 20°/1 mm. Dried at 100°/1 mm. this product had m.p. 190-192° (lit., m.p. 192°). The yield of 3:5-diphenyl-1:2:4-triazole was 7.4 g. (22%).

3:5-Diphenyl-1:2:4-triazole crystallizes from water with one molecule of solvent associated with each molecule of the triazole. This water is not readily removed, and this phenomenon has possibly led to a mistake in the literature, as is discussed in Section 4.

3:5-Diphenyl-1:2:4-triazole and picric acid when mixed in chloroform precipitate yellow plates, m.p. 150°(d). This appears to be an unstable chloroform adduct, which is always formed when the material is recrystallized from mixtures of benzene and chloroform. On recrystallizing from dilute ethanol and then from

benzene, 3:5-diphenyl-1:2:4-triazole picrate was obtained, m.p. 172°. Recrystallization from 2-propanol gave yellow monoclinic crystals, m.p. 171°.

Analysis:	C	H	O
Found:	54.4	3.6	24.6%.
$C_{20}H_{14}O_7N_6$ requires:	53.3	3.1	24.9%.

Experiment No. 3.22. Methylation of the sodium salt of 3:5-diphenyl-1:2:4-triazole with methyl iodide.

3:5-Diphenyl-1:2:4-triazole (2.21 g.) was dissolved in a solution of sodium (0.23 g.) in methanol (5 cc.). Methyl iodide (1.42 g.) was added, and the solution was heated for 15 hours at 120°. The product was made to a slurry with 5% aqueous sodium carbonate and extracted with benzene-ether (1:1) (3 x 30 cc.). Evaporation of the dried extract gave a residue of tan crystals (1.55 g.) m.p. 78-81°. These were dissolved in benzene and filtered through a column of alumina (30 g.). Crystallization of the filtered material from benzene-light petroleum ether (b.p. 40-60°) gave 1-methyl-3:5-diphenyl-1:2:4-triazole (1.47 g., 62%), colourless prismatic needles, m.p. 84-85° alone or admixed with the product of the reaction of dibenzamide and methylhydrazine sulphate.

Analysis:	C	H	N
Found:	76.8	5.6	18.0%.
$C_{15}H_{15}N_3$ requires:	76.6	5.5	18.9%.

The triazole in 20% ethanol with picric acid deposits 1-methyl-3:5-diphenyl-1:2:4-triazole picrate, which was recrystallized from 20% ethanol as fine needles, m.p. 135°.

Analysis:	C	H
Found:	54.8	3.5%.
$C_{21}H_{16}O_7N_6$ requires:	54.3	3.5%.

Experiment No. 3.23. Reaction of 3:5-diphenyl-1:2:4-triazole with acetylating agents.

3:5-Diphenyl-1:2:4-triazole, sodium acetate and acetic anhydride were reacted on the water bath as described by Wolchowe.(95)

The acetyl-3:5-diphenyl-1:2:4-triazole which crystallized on addition of ice-water had m.p. 106-108° (lit., m.p. 107-108°) and was partially hydrolyzed to 3:5-diphenyl-1:2:4-triazole when recrystallization was attempted from dilute ethanol (Wolchowe, loc. cit.). Crystallization from ether-light petroleum afforded colourless prisms, m.p. 108°. Acetyl-3:5-diphenyl-1:2:4-triazole identical with that described by Wolchowe

(m.p. and mixed m.p.) was obtained by the action of acetyl chloride in benzene on the sodium salt of 3:5-diphenyl-1:2:4-triazole (45% yield on 3:5-diphenyl-1:2:4-triazole) or be refluxing the triazole with acetic anhydride (92%).

SECTION 4.

MISCELLANEOUS REACTIONS OF 1:2:4-TRIAZOLES AND HYDRAZINE DERIVATIVES.

In this section a number of somewhat unrelated investigations are reported, discussion of each being included with the corresponding experimental part.

Reduction of triazoles was considered with a view to comparing the stability of triazoles with other heterocyclic compounds. A satisfactory polarographic reduction would also have been valuable in kinetic studies on triazole formation.

Dr. E. A. Parkes was interested in 1:2:4-triazole aldehydes, none of which had been described, in connection with a study of other heterocyclic and aromatic aldehydes. Oxidation of a triazole C-methyl side chain to C-CHO by Etard's method was attempted.

Some aminotriazoles were prepared from aminoguanidine and carboxylic acids. A new intermediate was isolated.

Some replacement reactions of C-substituents of triazoles were investigated, with particular reference to the preparation of aziridino-1:2:4-triazoles of possible cytological interest.

The possibility of preparing bicyclic systems with a triazole ring fused to a six-membered ring was investigated.

Some details of paper chromatography of triazoles

and also of a chromatographic recovery of triazoles from their picrates are presented. An apparatus has been constructed for continuous elution and also one for continuous co-distillation of bases from mixtures.

Reported reactions of benzamidrazone have been investigated.

A synthesis of amidrazones from nitrile and hydrazinium sulphonate has been achieved.

Reduction of 1:2:4-triazoles.

Andreocci (99) reported in a preliminary note that he had reduced 1-phenyl-1:2:4-triazole with sodium and ethanol, obtaining a small amount of 1-phenyl-1:2:4-triazoline among the non-cyclic products resulting from opening of the triazole ring. The note was not amplified later, and it seems that the triazoline could not be characterized. Apart from this observation there do not appear to be any cases known in which a triazoline was prepared from a triazole by reduction.

Attempted polarographic reductions.

To get some idea of the stability of the triazole ring, 1:3:5-trimethyl- and 3:5-dimethyl-1:2:4-triazole (typical basic and amphoteric triazoles respectively) were examined as 0.01 molar solutions in 0.1 molar aqueous potassium chloride. In neither case was any diffusion current observed below the decomposition potential of the potassium chloride.

Hydrogenation with a platinum catalyst. Experiment No. 4.1

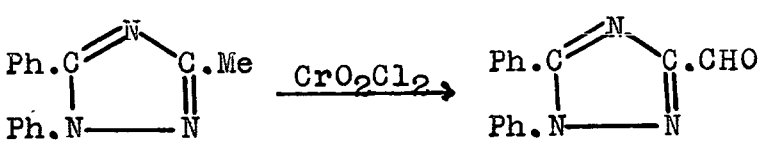
3:5-dimethyl-1:2:4-triazole (1 g.) in glacial acetic acid (200 cc.) was shaken with hydrogen at atmospheric pressure in the presence of a platinum catalyst. After one molar proportion of hydrogen had been absorbed

uptake ceased. After filtration the solution was diluted with water (400 cc.), made alkaline with potassium hydroxide and extracted with chloroform (3 x 75 cc.). The extract was dried (Na_2SO_4) and concentrated, leaving 1.02 g. of an oil, which was sublimed at 40°/1 mm. giving 0.95 g. of colourless prisms, m.p. 40-42°, mixed m.p. with the starting material, 41-42°. The product gave a picrate, m.p. and mixed m.p. with 3:5-dimethyl-1-phenyl-1:2:4-triazole, 155-156°.

This recovery of the starting material in essentially quantitative yield is hard to reconcile with the initial uptake of a molar equivalent of hydrogen. It is suggested that the triazole was reduced to unstable triazoline, which then reacted slowly with the solvent, being itself re-oxidized to a triazole. The hydrogenation itself was conducted as a laboratory exercise by students at this University.

Reaction of chromyl chloride with 3-methyl-1:5-diphenyl-1:2:4-triazole.

An attempt to prepare a triazole aldehyde by oxidation of a methyl substituent:

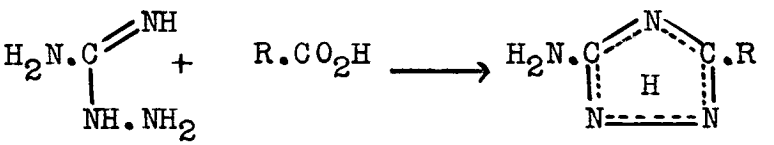


failed. The reason for this is not apparent.

3-Methyl-1:5-diphenyl-1:2:4-triazole was recovered unchanged in an essentially quantitative yield after treatment with chromyl chloride in boiling carbon tetrachloride for 0.5 hour.

Aminotriazoles.

Manchot and Noll[100] and Reilly and Madden [101] have prepared a number of aminotriazoles from aminoguanidine salts and aliphatic acids.



By conducting the reaction in concentrated acid solution aromatic and heterocyclic acids have now also been converted to aminotriazoles. The new 2- and 3-pyridyl-aminotriazoles were prepared in this way, and in the latter case an intermediate was isolated when the reactants were heated in water.

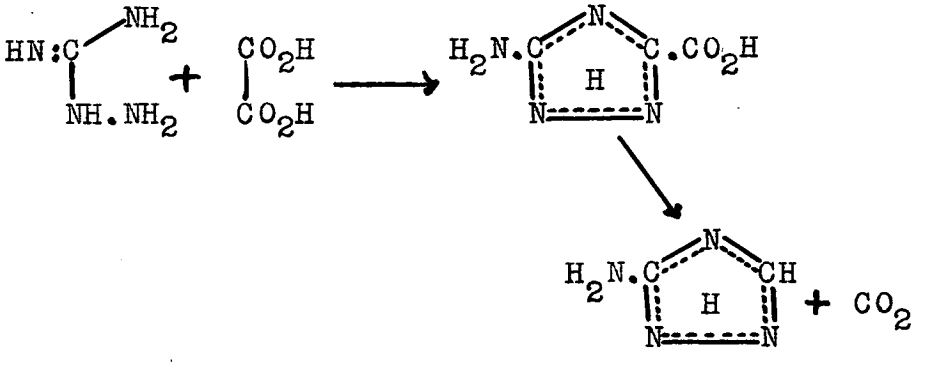
These compounds have similarities to a number of tuberculostatic hydrazides, and arrangements are being made at present for biological testing.

The preparation of the sodium salt of 3-amino-1:2:4-triazole -5-carboxylate (Manchot and Noll, loc. cit.) from oxalic acid and aminoguanidine bicarbonate was repeated to provide material for further synthetic work.

Experiment No. 4.2.

When oxalic acid and aminoguanidine sulphate were reacted in 40% hydrobromic acid for 1 day at 140° the only aminotriazole obtained on neutralizing with sodium carbonate and evaporating the product was 3-amino-1:2:4-triazole. Recrystallized from 2-propanol it had m.p. 159°. The mixed m.p. with 3-amino-1:2:4-triazole (102) was also 159°. The picrate had m.p. and mixed m.p. 230°.

Presumably the intermediate 3-amino-1:2:4-triazole-5-carboxylic acid was decarboxylated.



Experiment No. 4.3. Reaction of α-picolinic acid with aminoguanidine.

α-Picolinic acid hydrochloride (15.8 g.) and aminoguanidine sulphate (17.2 g.) were dissolved in hydrobromic acid (25 g., 40%) and boiled under reflux for 16 hours. The clear solution was neutralized with sodium carbonate and evaporated to dryness. Extraction of the

residue with ethyl acetate (Soxhlet) recovered the basic material present. Removal of the solvent left a residue, which was recrystallized from methanol giving colourless needles (6.8 g., 42%), m.p. 212-215°. Two recrystallizations from ethanol gave pure 3-amino-5-(2-pyridyl)-1:2:4-triazole as colourless prismatic needles, m.p. 217°.

Analysis:	C	H	N
Found:	52.4	4.4	42.2%.
$C_7H_7N_5$ requires:	52.2	4.4	43.3%.

With aqueous picric acid the base gave insoluble needles. The 3-amino-5-(2-pyridyl)-1:2:4-triazole picrate was recrystallized from ethanol as yellow needles, m.p. 229°.

Analysis:	C	H
Found:	39.4	2.9%.
$C_{13}H_{10}O_7N_8$ requires:	40.0	2.6%.

Experiment No. 4.4a. Reaction of nicotinic acid with aminoguanidine.

Nicotinic acid (24.6 g.) and aminoguanidine sulphate (34.4 g.) in hydrobromic acid (50 g., 40%) were boiled for 40 hours, and further treatment as in the preceding experiment gave 3-amino-5-(3-pyridyl)-1:2:4-triazole, (14.3 g., 44%) colourless needles from methanol, m.p. 233°.

Analysis:	C	H	N
Found:	52.3	4.3	43.5%.
$C_7H_7N_5$ requires:	52.2	4.4	43.3%.

3-Amino-5-(3-pyridyl)-1:2:4-triazole picrate was precipitated when aqueous solutions of the base and picric acid were mixed. It crystallized from water as yellow monoclinic needles, m.p. 269°.

Analysis:	C	H
	40.7	2.9%.
$C_{13}H_{10}O_7N_8$ requires:	40.0	2.6%.

This triazole gives a violet colour with an alkaline solution of 1:2-naphthoquinone-4-sulphonic acid (Folin's amino acid reagent). A similar colour is shown by 3-amino-5-phenyl-1:2:4-triazole, in distinction to the 2-isomer, which gives a green colour.

b. Nicotinic acid (12.3 g.) and aminoguanidine sulphate (17.2 g.) were dissolved in water (100 cc.)and the solution was boiled under reflux for 1 day. Neutralization with sodium carbonate and extraction of the dried residue with chloroform gave colourless material (9.0 g.) m.p. 155-158°, which was recrystallized from 2-propanol as colourless prisms, m.p. 165°. The substance appears to be an equimolar adduct of the starting

materials.

Analysis:	C	H	N
Found:	43.0	6.0	35.1%.
$C_7H_{11}O_2N_5$ requires:	42.6	5.6	35.5%.

1 g. of this substance was boiled with hydrobromic acid (5 g., 40%) for 1 day. After neutralization with sodium carbonate, aqueous picric acid was added to the solution and the precipitated picrate recovered by filtration and recrystallized from water. The yellow monoclinic needles (1.05 g.) obtained thus had m.p. 268° alone or admixed with 3-amino-5-(3-pyridyl)-1:2:4-triazole picrate.

Experiment No. 4.5a. 3-Amino-5-phenyl-1:2:4-triazole.

Benzoic acid (24.6 g.) and aminoguanidine sulphate (32.4 g.) with 40% hydrobromic acid (40.5 g.) were boiled under reflux for 24 hours. The product was brought to pH 8 with 2N aqueous sodium carbonate and evaporated to dryness. The residue was extracted with boiling absolute ethanol. The extract was evaporated and the residue re-extracted with dry ethanol-ether (1:1) (2 x 100 cc.). After evaporation of the solvent, material containing some inorganic matter was obtained (16.2 g.). 5% of this material was converted to the picrate which was re-crystallized from 80% ethanol and gave pure

3-amino-5-phenyl-1:2:4-triazole picrate (1.16 g., 30%) m.p. and mixed m.p. 219°. The residue of the material was treated with nitric acid. The nitrate, which was washed with benzene and recrystallized from water (9.35 g., 21%) had m.p. 207°(d).

b. The same experiment was repeated using the same quantities of reactants except for the replacement of hydrobromic acid by constant boiling hydrochloric acid (0.2 mole). A 5% aliquot of the crude product was converted to the picrate (1.24 g., 32%). The bulk was converted to the nitrate (7.97 g., 18%), m.p. 207°(d).

No aminotriazole was obtained when salicylic acid and aminoguanidine sulphate were heated in 40% hydrobromic acid for 1 day at 140°. Aminoguanidine was the only basic material present when the reactants were finally neutralized.

3-Diazo-1:2:4-triazole-5-carboxylate.

This compound was obtained in nearly quantitative yield as a white insoluble powder when 3-amino-1:2:4-triazole-5-carboxylic acid was diazotized at -5° in hydrochloric acid. The preparation has been described by Manchot and Noll (loc. cit.).

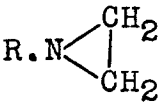
The explosive properties of this compound were not

unexpected, and it was, in fact, found to detonate violently when struck sharply though being quite stable at room temperature. This material was reduced to 3-hydrazino-1:2:4-triazole (Section 2) and also converted to 3-bromo-1:2:4-triazole. When a little of the dry product was treated with anhydrous ethylenimine the reaction was explosive.

3-Bromo-1:2:4-triazole.

This compound was obtained by the action of hydrobromic acid (40%) on 3-diazo-1:2:4-triazole-5-carboylate, as described by Manchot and Noll. The product had m.p. 185-186° (lit., m.p. 188-189°), but on heating above 100° for some hours it was found that hydrobromic acid was liberated, and the melting point of the resultant material became much less sharp. 2-Propanol was found to be a suitable solvent for recrystallization of the triazole.

Aziridinotriazoles.

A number of heterocyclic derivatives of ethylenimine  (R = pyrimidine, triazine) have been prepared, and many have been found to inhibit the growth of tumours (104). With this possibility in mind attempts have been made to prepare aziridinotriazoles, but the desired compounds have not been obtained. In the case of 3-bromo-

triazole the amphoteric nature of the compound probably resulted in opening of the ethylenimine ring and polymerization.

Experiment No. 4.6. Reaction of ethylenimine and 3-bromo-1:2:4-triazole.

Ethylenimine was prepared from ethanolamine by treatment with sulphuric acid and then with sodium hydroxide, as described by Leighton, Perkins and Renquist.(103) When equimolar amounts of ethylenimine and 3-bromo-1:2:4-triazole were warmed in aqueous solution at 30-35° for 1.5 hour, almost all the bromotriazole was recoverable at the end of this period.

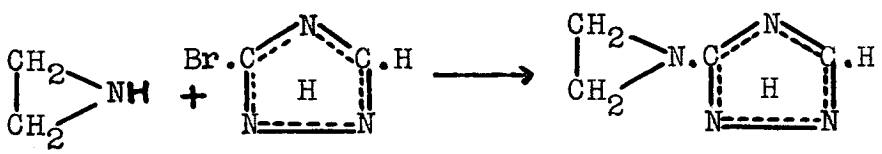
3-Bromo-1:2:4-triazole (10 g.) was added slowly to a solution of ethylenimine (3.2 g.) and pyridine (5.9 g.) in dry benzene (40 cc.). After stirring the product at 35-40° for 1 hour a semicrystalline syrup was obtained, and after cooling the product, the supernatant benzene layer was decanted and evaporated at 40°/25 mm. The residual resinous material could not be crystallized. When the semicrystalline material insoluble in benzene was neutralized with sodium carbonate and extracted with ether (50 cc.), a white powder was obtained which had m.p. 185-187°; the melting point was not raised by sublimation at 80°/0.1 mm. The mixed m.p. with bromotriazole

(which has m.p. 187°) was ca. 130°, and at 120° the mixed product turned a bright red colour. No structure has been assigned to this product.

Analysis:	C	H	N
Found:	18·48, 18·51	1·66, 1·70	27·87%

3:5-Dihydroxy-1:2:4-triazole.

After attempts to prepare aziridino triazoles from acidic halotriazoles, e.g.

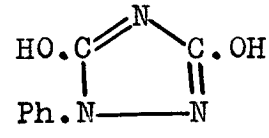


had proved abortive, (c.f. Experiment No. 4.6) it appeared that the principal cause of this difficulty was attack on the labile ethylenimine ring by the acidic triazole. To avoid this problem, and also to obtain a disubstituted compound somewhat analogous to disubstituted radiomimetic pyrimidines [104] it was decided to prepare 3:5-dichloro-1-phenyl-1:2:4-triazole and react it with ethylenimine. The preparation of the dichloro-compound has been described by Andreocci [105], who treated 3:5-dihydroxy-1-phenyl-1:2:4-triazole (1-phenyl-urazole) with phosphorus halides. The preparation of

this compound had been described by Pinner (106), who gave details for its preparation from phenylhydrazine hydrochloride and urea. When Pinner's directions were followed the product obtained was 1-phenylsemicarbazide. A greater excess of urea and twice the reaction time was needed to obtain 1-phenylurazole, a higher temperature being used in the second stage.

$$Ph.NH.NH_2.HCl + H_2N.CO.NH_2 \xrightarrow[5\ hrs.]{160^\circ} Ph.NH.NH.CO.NH_2$$

$$\downarrow CO(NH_2)_2,\ 200^\circ/5\ hrs.$$



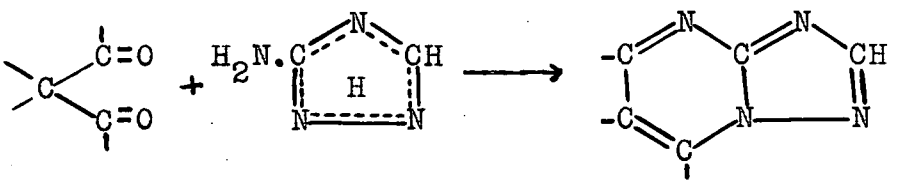
Andreocci's preparation of 3:5-dichloro-1-phenyl-1:2:4-triazole from phenylurazole requires a pressure vessel which may be heated to 180°, and which is not attacked by phosphorus pentachloride, phosphorus oxychloride or hydrogen chloride. It was hoped to use somewhat larger quantities than could be handled in a sealed tube. The reaction of phosphorus pentachloride and oxychloride with phenylurazole was therefore carried out at atmospheric pressure under a long air-condenser. It was found possible to attain a temperature of 175° in the reaction flask, but when the product was worked up as outlined in the literature, none of the expected steam-volatile

phenyl-dichlorotriazole was obtained.

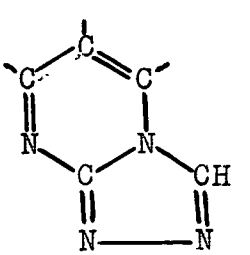
As the whole project was not closely linked to the main lines of investigation dealt with in this thesis it was deferred at this stage.

Bicyclic systems containing fused 1:2:4-triazole rings.

It has been observed (107) that 3-amino-1:2:4-triazole condenses with β-keto esters or β-diketones to give bicyclic compounds with a triazole ring fused to a 6-membered ring.

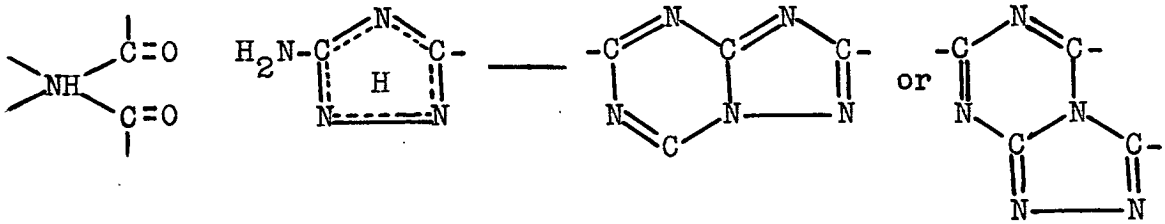


The alternative formulation,



if considered, was evidently dismissed as less likely.

Since diacylamines and β-diketo compounds show similar activity in cyclizing with hydrazines to 1:2:4-triazoles and pyrazoles, it was thought that diacylamines might condense with aminotriazoles.

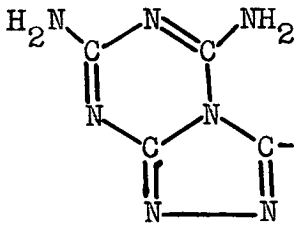


Compounds of this type may be formally related to purines. A reaction of 3-amino-5-methyl-1:2:4-triazole and diacetamide resulted in acetylation, and not cyclization, but it is hoped that by using more reactive diacylamines (e.g. acylurethanes) and modifying the reaction conditions cyclization may be achieved.

Experiment No. 4.7.

3-Amino-5-methyl-1:2:4-triazole (0.2 g.) and diacetamide (0.2 g.) were heated at 150° for 5 minutes. The mixture solidified throughout and was rubbed on a porous tile with benzene and light petroleum (b.p. 60-80°) leaving the monoacetyl derivative of the aminotriazole, m.p. 282° (lit., m.p. 284°) [108].

During 1953, Kaiser [109] has advanced evidence that the product obtained from hydrazine salts with two molecular proportions of dicyandiamide contains the last of the ring systems indicated above.



This is stated on the basis of an experiment involving oxidation cleavage in which molecular nitrogen is liberated. Such evidence does not seem sufficient to preclude the possibility that one of the "hydrazinic" nitrogen atoms occupies a bridgehead position.

Paper chromatography of 1:2:4-triazoles.

A number of the problems encountered in this investigation have involved the separation of isomeric triazoles, or the proof of purity of single isomers obtained in reactions. This is obviously an excellent field for application of the methods of paper chromatography. Failure to take advantage of this technique has principally been due to a lack of suitable methods for locating triazoles on paper in 20-50 microgram quantities. A satisfactory method has only been developed in the last months of the investigation. When triazole chromatograms were placed in an oven at 40° with iodine vapour, a satisfactory technique with many nitrogenous compounds, they failed to develop the brown spots of iodine adduct.(110)

Even at room temperature the triazole-iodine adducts were not stable enough to allow detection of triazoles at the required concentration. Eventually it was found that if the dried chromatogram was cooled to 0-5° and placed in a tall vessel, at the bottom of which iodine crystals were vaporized by the local application of external heat, spots were developed to maximum intensity in about five minutes. Faint spots were found to be much more prominent when exposed to ultraviolet light, but in all cases the adduct lost iodine very rapidly in the atmosphere. Attempts were made to render triazole spots on chromatograms permanently visible in a manner suitable for quantitative estimation. Application of 0.1% palladous chloride in neutral solution to the immediate vicinity of the brown spots gave permanent black stains in some cases, but the results were not uniformly applicable.

In order to separate isomeric triazoles by an ionophoretic method on paper it was necessary to have a method of detection applicable in the presence of large concentrations of ionic solids remaining when the buffer-saturated paper is dried. This problem has not yet been overcome in the case of 1:2:4-triazoles under investigation.

Some heterocyclic bases have been located by converting to the quaternary ammonium halide, and then condensing the N-methyl group with the sodium salt of 1:2-naphthoquinone-4-sulphonic acid to give coloured products.[90] With the triazoles tested this reaction was negative.

The possibility of detecting triazole spots on paper by their buffering effect was also investigated. Dried chromatograms were sprayed with oxalic acid solutions and then with the potassium salt of tetrabromophenolphthalein ethyl ester (c.f. Feigl's technique [111]). The ester was prepared by standard methods from phenolphthalein by reduction to phenolphthalin, esterification, bromination and finally oxidation with potassium ferricyanide. The method failed to show the position of triazoles on chromatograms when they were present in quantities suitable for chromatographic separation.

As little opportunity has remained for a study of the chromatography of triazoles on paper, good separation of isomers has not yet been obtained, but the following R_f values were observed, using Whatman No. 1 paper and descending elution. Observations were made at $20^{\circ} \pm 2^{\circ}$.

	butanol: water.
1-methyl-3-phenyl-1:2:4-triazole	0.85
1-methyl-5-phenyl-1:2:4-triazole	0.84
1:5-dimethyl-3-phenyl-1:2:4-triazole	0.88
1:3-dimethyl-5-phenyl-1:2:4-triazole	0.91

Recovery of triazoles from their picrates.

The picrates of hydrocarbons have been separated into their components on columns of alumina (113) and alkaloid picrates have likewise been dissociated on alumina which has previously been treated with acid.(114) Triazole picrates are less stable than those of many bases, and their solutions in benzene, ether or chloroform are decomposed on neutral alumina columns, picric acid being strongly adsorbed while the triazole component passes through in the eluate. Columns may be loaded much more heavily than is the case with normal chromatographic procedures. Thus it was convenient to use 8-10 parts by weight of alumina to 1 part of picrate. In the case of mixtures of picrates partial separations were obtained, depending on the stabilities of the components. The rate of movement of the coloured band on the column, in standard conditions, gave some idea of stability of the picrate, but the matter has not been investigated quantitatively.

When recovering triazoles from picrates which are very insoluble in solvents of low dielectric constant, use was made of the apparatus shown in Figure 3. The picrate was packed in the column above the alumina, and continuously eluted by condensate from the still head. By this re-cycling of eluent it was possible to use small volumes of solvents. The rate of flow could be measured by counting drops at the head of the column, and it could be adjusted by means of the taps.

This apparatus was also found to be very convenient for purification of a compound from strongly adsorbed impurities. Though such a simple arrangement could hardly be novel it has been reported, since a search of the literature available did not reveal any such description.

Continuous azeotropic distillation of bases.

A number of reactions in this investigation were carried out in pyridine buffers, and it was found difficult to remove pyridine from heat-sensitive bases by evacuation over drying agents. A method which has frequently been used to drive off pyridine from a residue is repeated evaporation with carbon tetrachloride. To avoid the inconvenience of this procedure an apparatus was built in which pyridine could be continuously

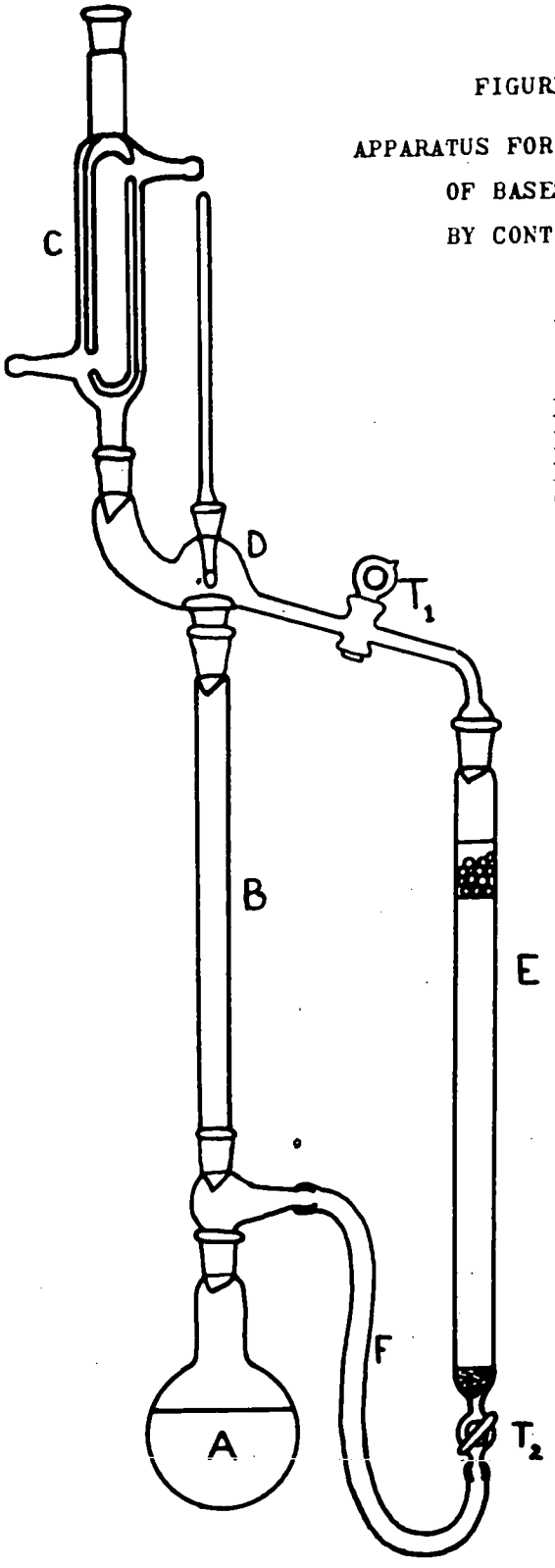


FIGURE 3.

APPARATUS FOR CHROMATOGRAPHIC ISOLATION OF BASES FROM THEIR PICRATES BY CONTINUOUS ELUTION.

A = Eluate.
B = Unpacked column.
C = Condenser.
D = Still-head with weir.
E = Alumina column.
F = Polythene tubing.
T_1, T_2 = Taps.

distilled off with liquids lighter than water (e.g. ligroin, benzene). Condensate from the condenser passed through a layer of hydrochloric acid, which removed pyridine, and then through a column of solid sodium hydroxide which removed any hydrochloric acid (Figure 4). Modification as shown by broken lines, and replacement of the central distributing tube with a set of baffles in the acid would permit the use of liquids heavier than water for co-distillation. Triazoles with low boiling points such as 1:3:5-trimethyl-1:2:4-triazole may be co-distilled with benzene and crystallize out from the aqueous phase as the hydrochloride.

Benzamidrazone. Experiment No. 4.8.

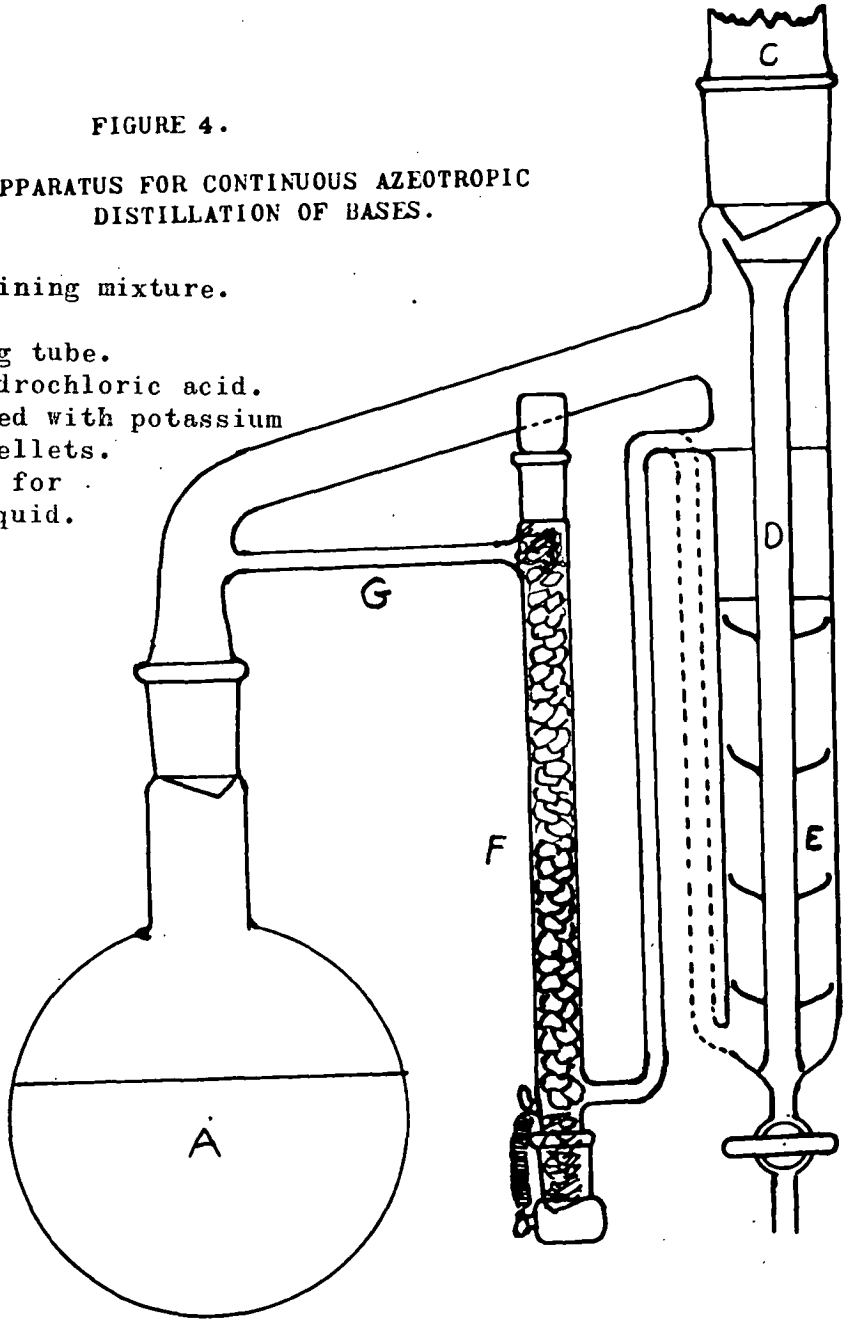
Hydrazine hydrate (2.8 g., 90%) and ethyl benzimino-ether hydrochloride (9.2 g.) were mixed in pyridine (15 cc.). The spontaneous reaction was moderated by cooling the reactants to 30°. After 12 hours insoluble material (6.5 g.) was filtered and washed with ether (2 x 15 cc.). It had a very indefinite melting point (125-190°), as observed by Pinner [8], and again it was not possible to obtain pure material, but with picric acid benzamidrazone picrate was obtained, m.p. 160-161° (lit., m.p. 163°)

100 mg. of crude benzamidrazone hydrochloride was

FIGURE 4.

APPARATUS FOR CONTINUOUS AZEOTROPIC DISTILLATION OF BASES.

A = Flask containing mixture.
C = Condenser.
D = Distributing tube.
E = Layer of hydrochloric acid.
F = Column packed with potassium hydroxide pellets.
G = Return tube for purified liquid.



heated with formic acid (1 cc.) for 1 hour at 100°, and the product was poured into water (5 cc.). 3:5-Diphenyl-1:2:4-triazole was obtained as a flocculent precipitate. The hydrate had m.p. ca. 120°, but when dried for 1 hour at 75°/0.1 mm. the material had m.p. 185-187°. Recrystallization from 2-propanol gave pure 3:5-diphenyl-1:2:4-triazole, m.p. and mixed m.p. with authentic material 191°. Similarly, with cold acetic anhydride or benzoyl chloride, benzamidrazone gave 3:5-diphenyl-1:2:4-triazole. Pinner reports the isolation of an intermediate benzoyl benzamidrazone in the last case. This was said to lose water at temperatures above 120°, and to give 3:5-diphenyl-1:2:4-triazole.

A synthesis of amidrazones involving addition to a nitrile.

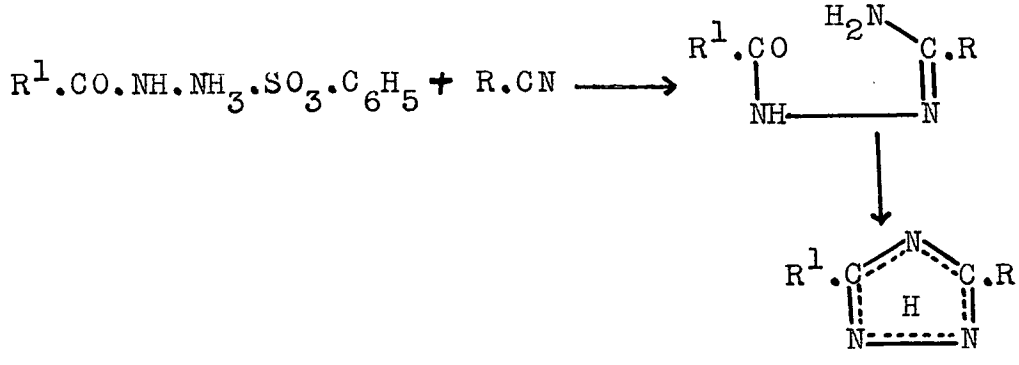
Phenylhydrazine is sufficiently activated, by conversion to the p-tolylsulphonate, to add to benzonitrile, forming benzamide phenylhydrazone.

$$Ph.CN + Ph.NH.NH_3.SO_3.C_6H_4.Me \longrightarrow Ph.C(NH.NH.Ph)=NH$$

This reaction has only been found at the conclusion of the present programme, but promises to be significant if its general nature can be established. Amidrazones

have recently shown promise as tuberculostatic agents [7] and for large scale production, a reaction involving nitriles without intermediate iminoether formation would be very desirable, since it would eliminate the use of anhydrous reagents.

A general triazole synthesis from acylhydrazinium sulphonates and nitriles should also be possible.



Phenylhydrazinium sulphonates.

These may be obtained from phenylhydrazine and sulphonic acids in boiling benzene. Thus p-toluene-sulphonic acid and phenylhydrazine gave phenylhydrazinium p-tolylsulphonate, m.p. 187° (lit., m.p. 188° (115)).

A more convenient preparation of phenylhydrazinium salts of sulphonic acids is precipitation from an aqueous solution of the sodium sulphonate and phenylhydrazine hydrochloride. In this way phenylhydrazinium benzenesulphonate was obtained in 74% yield from sodium benzene

sulphonate and phenylhydrazine hydrochloride. Recrystallized from ethanol it had m.p. 176-178°. A preparation from benzenesulphonic acid and phenylhydrazine was reported to have m.p. 179°. (116)

Experiment No. 4.9. Reaction of phenylhydrazinium p-tolylsulphonate and benzonitrile.

Phenylhydrazinium p-tolylsulphonate (2.9 g.) and benzonitrile (1.1 g.) were heated in a sealed tube at 200-220° for 1 hour. The product was added to cold aqueous sodium hydroxide (5N, 30 cc.) and extracted with chloroform (3 x 30 cc.). The chloroform extract was extracted with aqueous sodium hydrogen carbonate (10%, 20 cc.) and with hydrochloric acid (4N, 3 x 50 cc.). The acid extract was extracted with ether (50 cc.), neutralized with sodium hydroxide and extracted with chloroform (3 x 50 cc.). The chloroform extract was dried (Na_2SO_4) and evaporated, leaving crude benzamide phenylhydrazone as a red oil (0.72 g.). This was converted to the picrate, which had m.p. 186-189°, and after recrystallization from ethanol, m.p. 193°. The mixed m.p. with benzamide phenylhydrazone picrate obtained from benziminoether and phenylhydrazine (lit., m.p. 196° (20), found m.p. 194°) was 193-194°.

SECTION 5.

ULTRAVIOLET ABSORPTION SPECTRA OF 1:2:4-TRIAZOLES.

Experimental.

Light absorption measurements were made with a Unicam S.P.500 spectrophotometer. Matched 1 cm. cells were used. The solvent was ethanol, purified by the method of Clow and Reasbeck [31], unless some other solvent has been specified in the tables. n-Hexane was purified by Polya's modification of the method of Henri and Castille [32] and conductivity water was used for measurements in aqueous solution.

In the column marked "Measurement" the following initials have been used to specify the investigation: A = author during term of Ph.D. studies: A(H) = reported in author's B.Sc.(Hons.) thesis: AP = measurement reported in Ph.D. thesis of Dr. E. A. Parkes. (Hobart, 1953) c.f. introductory memorandum.

Credits for preparations are given in the footnotes of this table.

The position of mobile imino hydrogen has not been indicated.

Triazole Substituent.

No.	1	2	3	4	5	Measurement	λmax (mμ.)	εmax	Table No.
1	-	-	H	-	H	AP,A(H)	-	-	-
			do.	+HCl		AP	-	-	-
			do.	+KOH		AP	-	-	-
11	-	-	Me	-	Me	AP,A(H)	-	-	-
111	Me	-	Me	-	Me	AP	-	-	-
1V	Et	-	Me	-	Me	AP	-	-	-
V	-	-	Me	Et	Me	AP	-	-	-
V1	Ac(?4)	-	Me	-	Me	AP	220	5,100	-
			do.	(hexane)		AP	223	6,900	-
V11	3-triazolyl	-	Me	-	Me	AP	218	6,100	-
V111	Ph	-	H	-	H	A(H)	239	10,900	-
1X	-	-	H	Ph	H	A	224.5	10,900	1
X	Ph	-	Me	-	H	A	244	15,400	11
X1	Ph	-	Me	-	Me	A(H)	230	9,000	-
X11	-	-	Me	Ph	Me	A	259	300	111
X111	Ph	-	Me	-	Et	A(H)	230	10,600	-
X1V	Ph	-	Et	-	Me	A(H)	230	9,400	-
XV	-	-	Ph	-	H	A	241.5	14,100	V
			do.	(water)		A	239.5	14,100	V1
			do.	+HCl		A	241.5	14,400	V11
			do.	+KOH		A	237	13,500	V111
XV1	Me	-	Ph	-	H	A	243	15,100	1X
XV11	Me	-	H	-	Ph	A	235	11,900	X
XV111	-	-	Ph	Me	H	A	270	500	X1
X1X	Ph	-	Ph	-	H	AP	265	23,400	-
XX	Ph	-	H	-	Ph	AP	248	13,600	-
XX1	-	-	Ph	Ph	H	A	235.5	14,700	X11
XX11	-	-	Ph	-	Me	A	244	15,600	X111
			do.	KOH		A	261	15,100	X1V
XX111	Me	-	Ph	-	Me	A	245	15,300	XV1

Triazole substituents.

No.	1	2	3	4	5	Measurement	λ max	ε max	Table No.
XXIV	Me	-	Me	-	Ph	A	239	12,700	XV
XXV	Ph	-	Ph	-	Me	AP	253	22,100	-
XXVI	Ph	-	Me	-	Ph	AP	252	10,500	-
XXVII	-	-	Ph	-	Ph	AP	255	22,700	-
							234	21,800	
			do.	+KOH		AP	276	21,900	-
XXVIII	Me	-	Ph	-	Ph	A	247	21,300	XVII
XXIX	-	-	Ph	Me	Ph	A	251	24,400	-
XXX	Ph	-	Ph	-	Ph	A	244	29,200	XVIII
XXXI	-	-	Ph	Ph	Ph	A	256.5	8,000	XIX
XXXII	Ph	-	Me	-	Styryl	A	300	52,300	XX
XXXIII	Ph	-	OH	-	H	AP	282	9,100	-
			do.	+KOH		AP	284	11,500	-
XXXIV	Ph	-	Me	-	OH	A	249	16,800	XXI
			do.	+KOH		A	261	14,600	XXII
XXXV	-	-	OH	-	Ph	AP	264	10,900	-
			do.	+KOH		AP	273	6,650	-
							223.5	13,800	-
XXXVI	Me	-	Ph	-	OH	A	269.5	12,800	XXIII
			do.	+KOH		A	277	8,700	XXIV
							224	16,000	-
XXXVII	-	-	OH	-	Styryl	AP	297	22,600	-
							223	10,100	-
			do.	+KOH		AP	306	15,500	-
							272	13,300	-

Triazole substituent.

No.	1	2	3	4	5	Measurement.	λ max	ε max	Table No.
XXXVIII	-	-	OH	-	p-methoxy-styryl	AP	316	24,800	-
							223	9,600	-
			do.	+KOH		AP	304	19,200	-
XXXIX	Ph	-	OH	-	Ph	AP	294	5,700	-
							226	15,600	-
			do.	+KOH		AP	302	6,700	-
							230	15,500	-
XL	Ph	-	OH	-	p-hydroxy-phenyl	AP	289	7,700	-
							242	11,600	-
			do.	+KOH		AP	309	11,700	-
							265	12,700	-
XLI	Ph	Me	:O	-	H	AP	280	7,400	-
							216	14,500	-
XLII	-	-	NH_2	-	H	AP	-	-	-
XLIII	-	-	NH_2	-	Me	AP	-	-	-
XLIV	-	-	NH_2	-	n-C_3H_7	AP	-	-	-
XLV	-	-	NH_2	-	iso-C_3H_7	AP	-	-	-
XLVI	-	-	NH_2	-	n-C_6H_{13}	AP	-	-	-
XLVII	-	-	NH_2	-	Ph	AP	258	8,100	-
			do.	+HCl		AP	257	15,700	-
XLVIII	-	-	NH_2	-	2-pyridyl	A	283	8,100	XXV
			do.	+4,000 M. excess HCl		A	278	12,300	XXVI
							254.5	9,900	-
XLIX	-	-	NH_2	-	3-pyridyl	AP	273	6,300	-
							218	11,300	-
			do.	+ HCl 1:420		AP	256	8,400	-
			do.	+ HCl 1:900		AP	258	8,000	-
			do.	+ HCl 1:12,000		AP	276	7,500	-
							239	8,400	-

	Triazole substituent.							
No.	1	2	3	4	5	Measurement	λmax	εmax
L	-	-	OH	-	CHO	AP	374	25,800
	2:4-dinitrophenylhydrazone of acetyl derivative.						288	8,200

	Compound.	Spectrum determin.			Table No.
Ll	N-formylbenzamide (in water)	A	240	7,200	XXVll
Lll	benzamide-2-acetyl-phenylhydrazine adduct	AP	279	2,100	
			229	18,100	
Llll	nicotinic acid-aminoguanidine adduct	AP	258	8,100	

Notes on compounds tabulated above.

JP = Work of Dr. J. B. Polya; AK = Work of Dr. A. A. Komzak.

l. a. Preparation: Section 3. (A).
b. Purification: Recrystallization twice from benzene and sublimation. (AP).
c. Properties: m.p. 121-122.5° (lit., m.p. 121°)

ll. a. Section 3. (A).
b. Recryatallization from benzene and sublimation. (AP).
c. m.p. 141-142.5° (lit., m.p. 143-143.5°)

lll. a. Section 2. (A).
b. Fractional distillation. (A).
c. b.p. 193-195°/760 mm.

lV. a. Section 3. (A).
b. Fractional distillation. (A).
c. b.p. 196°/740 mm.

V. a. Section 3. (A).
b. Chromatographic purification. (A).
c. m.p. 115-116°

Vl. a. Section 3. (A).
b. Sublimation. (A).
c. m.p. 89.5-90.5°

Vll. a. Section 2. (A).
b. Sublimation. (A).
c. m.p. 193°

Vlll. a. Reaction of phenylhydrazine hydrochloride and formamide.[33] (AH).
b. Sublimation. (AH).
c. m.p. 46° (lit., m.p. 46-47°).

lX. a. Reaction of formanilide and 1:2-diformylhydrazine.[34] (JP).
b. Sublimed twice at 120°/0.1 mm. (A).
c. m.p. 120° (lit., m.p. 121°).

X. a. Reaction of acethydroxylamine phenylhydrazone with methyl iodide - sodium methoxide. (35) (JP).
b. Recrystallized from light petroleum (b.p. 60-80°) and sublimation at 60°/0.1 mm. (A).
c. m.p. 89.5° (lit., m.p. 87°).

Xl. a. Reaction of diacetamide with phenylhydrazine hydrochloride. (36) (AK).
b. Sublimation at 40°/0.1 mm. (AH).
c. m.p. 47-48°

Xll. a. Reaction of acetanilide and 1:2-diacetylhydrazine. (37) (JP).
b. Sublimation at 140°/0.1 mm. (A).
c. m.p. 236° (lit., m.p. 236°).

Xlll. a. Section 2. (AH).
b. Fractional distillation. (AH).
c. b.p. 281-282°/760 mm.

XlV. a. Section 1. (AH).
b. Fractional distillation. (AH).
c. b.p. 278°/755 mm.

XV. a. Section 3. (A).
b. Crystallization from ligroin and sublimation. (A).
c. m.p. 119° (lit., m.p. 121°).

XVl. a. Section 1. (A).
b. Sublimation at 40°/0.1 mm. (A).
c. m.p. 23°.

XVll. a. Section 2. (A).
b. Crystallization from benzene and sublimation at 40°/0.1 mm. (A).
c. m.p. 59°.

XVlll. a. Reaction of N-methylbenzamide and formylhydrazine. (38) (JP).
b. Sublimation at 80°/0.1 mm. (A).
c. m.p. 117° (lit., m.p. 116°).

XlX. a. Section 1. (A).
b. Sublimation. (A).
c. m.p. 83°.

XX. a. Section 2. (AH)
b. Sublimation. (AH)
c. m.p. 90.5° (lit., m.p. 91°).

XX1. a. Reaction of formamide and benzoylhydrazine (JP).
b. Sublimation at 150°/0.1 mm. (A).
c. m.p. 142.5° (lit., m.p. 142°).

XX11. a. Section 3. (A).
b. Sublimation at 140°/0.1 mm. (A).
c. m.p. 166° (lit., m.p. 164.5°).

XX111. a. Section 1. (A).
b. Sublimation at 0.1 mm. (A).
c. m.p. 117°.

XX1V. a. Section 2. (A).
b. Sublimation at 0.1 mm. (A).
c. m.p. 72°.

XXV. a. Section 1. (A).
b. Crystallization from light petroleum (b.p. 60-80°). (AP).
c. m.p. 92.5-93.5° (lit., m.p. 91°).

XXV1. a. Section 2. (AH).
b. Sublimation at 80°/0.1 mm. (AH).
c. m.p. 80-81°.

XXV11. a. Section 3. (A).
b. Crystallization from water. (A).
c. m.p. 190-192° (lit., m.p. 191°).

XXV111. a. Section 3. (A).
b. Sublimation at 0.1 mm. (A).
c. m.p. 84-85°.

XX1X. a. Section 1. (A).
b. Crystallization from ethanol.
c. m.p. 242° (lit., m.p. 243°).

XXX. a. Reaction of phenylhydrazine and benzonitrile with sodium. (JP). (39)
b. Sublimates at 0.1 mm. (A).
c. m.p. 120° (lit., m.p. 120°).

XXX1. a. Reaction of benzanilide and benzoylhydrazine (JP). (37)
b. Sublimation at 250°/760 mm.
c. m.p. 298-300° (lit., m.p. 304-5°).

XXXll. a. Section 2. (A).
b. Crystallization from ethanol. (A).
c. m.p. 74°.

XXXlll. a. Parkes, Ph.D. thesis.
b. " " "

XXXlV. a. Section 2. (A).
b. Sublimation at 80°/0.1 mm.
c. m.p. 167° (lit., m.p. 167°).

XXXV. a. Parkes, Ph.D. thesis.
b. " " "

XXXVl. a. Section 1. (A).
b. Sublimation at 0.1 mm.
c. m.p. 219° (lit., m.p. 218°).

XXXVll. a. Parkes, Ph.D. thesis.
b. " " "

XXXVlll. a. Parkes, Ph.D. thesis.
b. " " "

XXXlX. a. Parkes, Ph. D. thesis.
b. " " "

Xl. a. Parkes, Ph.D. thesis.
b. " " "

XLl. a. Parkes, Ph.D. thesis.
b. " " "

XLll. a. Reaction of formic acid and aminoguanidine sulphate. [40] (AK).
b. Crystallization from ethanol and sublimation (AP).
c. m.p. 158-159° (lit., m.p. 159°).

XLlll. a. Reaction of acetic acid and aminoguanidine sulphate. [112] (AK).
b. Crystallization from ethanol - ethyl acetate and sublimation. (AP).
c. m.p. 148-150° (lit., m.p. 150°).

XLIV. a. Reaction of n-butyric acid and aminoguanidine sulphate. (AK).
b. Crystallization from ethyl acetate. (AP).
c. m.p. 142-143° (lit., m.p. 143°).

XLV. a. Reaction of iso-butyric acid and aminoguanidine sulphate. (AK).
b. Crystallization from ethyl acetate. (AP).
c. m.p. 112° (lit., m.p. 112°).

XLVI. a. Reaction of hexanoic acid with aminoguanidine sulphate. (AK).
b. Crystallized from water. (AK).
c. m.p. 131-132°.

XLVII. a. Section 4. (AK).
b. Crystallization from butanol - ethylacetate. (AP).
c. m.p. 187-188° (lit., m.p. 186°)

XLVIII. a. Section 4. (A).
b. Crystallization from ethanol. (A).
c. m.p. 217°.

XLIX. a. Section 4. (A).
b. Crystallization from ethanol.
c. m.p. 233°.

L. a. Parkes, Ph.D. thesis.
b. " " "
c. m.p. 323-324°.

LI. a. Section 2. (A).
b. Crystallization from water. (A).
c. m.p. 112° (lit., m.p. 113°).

LII. a. Section 1. (AH).
b. Crystallization from carbon tetrachloride. (A).
c. m.p. 106-107°.

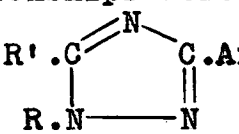
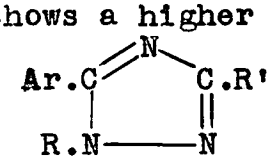
LIII. a. Section 4. (A).
b. Crystallized from 2-propanol. (A).
c. m.p. 165°.

Discussion.

Recent observations on the absorption spectra of series of heterocyclic compounds have revealed uniformities which have proved valuable in structural investigations and which have been correlated with other physical properties of the compounds concerned. Special reference may be made to work on pyrimidines (41) and pteridines (42). The investigation of absorption spectra of 1:2:4-triazoles reported here was undertaken principally for two reasons. It was hoped that a satisfactory method would be developed for estimation of triazoles, with a view to investigating the kinetics of their formation from diacylamines. Further, since this investigation has dealt largely with positional isomerism in triazoles, it seemed desirable to investigate the absorption spectra of a number of sets of isomeric triazoles available from the chemical investigation outlined in previous section of this thesis.

The first aim has not been realized. Triazoles without aromatic substituents do not have ultraviolet absorption maxima above 210 millimicrons. 3-Phenyl-1:2:4-triazole, however, has a well defined maximum at 239 millimicrons in water (ε = 14,100), and its formation from semicarbazide salts and N-formylbenzamide seemed a suitable reaction to investigate kinetically. It was found,

however, that in aqueous solution N-formylbenzamide also exhibited a maximum absorption (240 millimicrons, ε = 7,200) which prevented such an approach to the problem. Similar difficulties were experienced with other diacylamines, and this aspect of the work has not been pursued further.

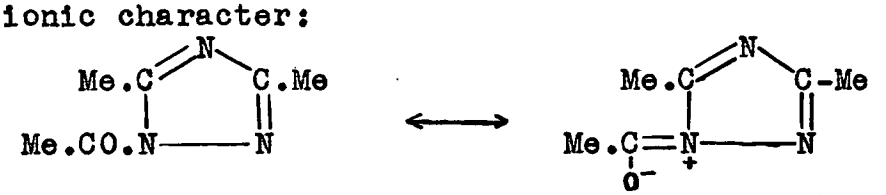
On investigating a series of isomeric triazoles with phenyl and methyl substituents and combinations of these, consistent relationships were observed between the isomers. Thus the isomer  has maximum absorption at longer wavelength, and shows a higher extinction coefficient than the triazole  where R = Ph-, Me-; R' = H-, Me-. This and other generalizations have been discussed below, and some explanations of these results have been possible.

Beer's law is obeyed quite closely by all the compounds investigated. The results for 3-phenyl-1:2:4-triazole, which was investigated with a view to its quantitative determination, are shown at the foot of Table VI.

1:2:4-Triazole and its alkyl derivatives like 3:5-dimethyl-, 1-ethyl-3:5-dimethyl-, 4-ethyl-3:5-dimethyl- and 1:3:5-trimethyl-1:2:4-triazoles display no band above

210 millimicrons. Attempts to shift possible maxima just below 210 millimicrons into the range of the instrument by adding excess potassium hydroxide or hydrochloric acid (anion or cation formation) failed.

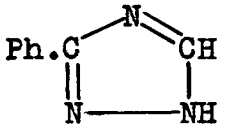
Acetyl-3:5-dimethyl-1:2:4-triazole (V1) which is probably the 1-acetyl compound (Section 3.) shows a band (λ_{max} 222 mμ, ε = 6,900). Its extinction is higher than that of other simple heterocyclic compounds. (43) The band may be regarded as a K-band, possibly due to extended conjugation in the ionic state of the acetyl compound. Thus assuming the 1-acetyl structure, the following partial ionic character:



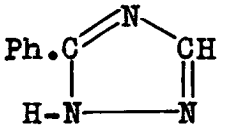
may be related to the excited state. This spectrum was determined in hexane to avoid rapid alcoholysis, which took place in ethanol. The ε value given for ethanol was obtained by extrapolation.

The three isomeric phenyl-1:2:4-triazoles display single bands of high intensity. These bands are obviously not B-bands and are not due to a summation of benzene and triazole spectra; they are best regarded as K-bands due to the conjugation of benzene and triazole chromophores. The three phenyltriazole chromophores are somewhat

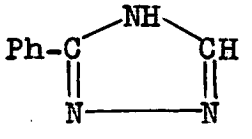
different. Their λ_{max} and ε decrease in the following order; 3-phenyl-1:2:4-triazole (XV) (241.5, 14,100): 1-phenyl-1:2:4-triazole (239, 10,900) (V111): 4-phenyl-1:2:4-triazole (224.5, 10,900) (1X). The difference between the spectra of V111 and 1X could be explained by the concepts of linear and cross conjugation which have been used in discussing the related problem of the spectrum of 5-phenyltetrazole by Elpern and Nachod. (44)



cross

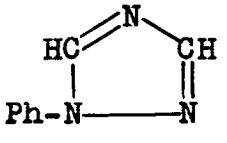


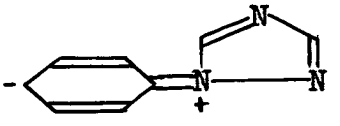
linear



linear

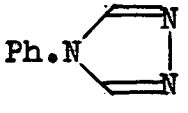
XV

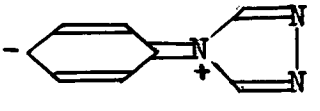




linear

V111





linear

1X

More appropriate might be the empirical comparison of (V111) and (1X) with phenylhydrazine and aniline respectively, (45) the K-bands of which are in the same relation.

Substitution of 1-phenyl-1:2:4-triazole by alkyl

groups results in small bathochromic or hypsochromic shifts. A bathochromic shift accompanied by a hyperchromic shift is illustrated by 3-methyl-1-phenyl-1:2:4-triazole (XVl) (λ_{max} 244 mμ, ε = 15,400). The practically identical spectra of 3:5-dimethyl-1-phenyl- (Xl), 3-ethyl-5-methyl-1-phenyl (XlV) and 5-ethyl-3-methyl-1-phenyl-1:2:4-triazoles (Xlll) show firstly that the effects of methyl and ethyl groups are practically the same and that the hypsochromic and hypochromic effects of 5-substitution outweigh the bathochromic effect of 3-substitution. Similar uncoupling effects by C-substituents vicinal to N-phenyl have been noted for 1:2:3-triazoles. (46, 47) The absorption maxima of 5-methyl-1:3-diphenyl- (XXV) and 3-methyl-1:5-diphenyl-1:2:4-triazoles (XXVl) are at almost the same wavelength (253 and 252 mμ), but in the former case the extinction is much higher (22,100 compared to 10,500). Braude, Sandheimer and Forbes (48) have recently analyzed a number of similar cases where steric interference has led to a reduction of absorption intensity without a shift to shorter wavelength, and have concluded that this results from "restriction of the transition to vibrational states allowing of a high degree of uniplanarity in the excited state." This appears to be the case with

N-phenyltriazoles with vicinal groups. 1:3-Diphenyl- (XIX, λ_{max}: 265, ε = 23,400) and 1:5-diphenyl-1:2:4-triazole (XX, λ_{max}: 248, ε = 13,600) show a similar effect on the extinction coefficient, but the 1:5-isomer, which would be expected to show the results of steric interference, absorbs at a shorter wavelength. The N-methyl isomer pairs 1:3-dimethyl-5-phenyl- (XXIV), 1:5-dimethyl-3-phenyl (XXIII), 1-methyl-5-phenyl- (XVII) and 1-methyl-3-phenyl-1:2:4-triazole (XVI) show the same relationship. Thus in each case the isomer with the aromatic component in position 5- has the absorption maximum at shorter wavelength and has the lower extinction coefficient.

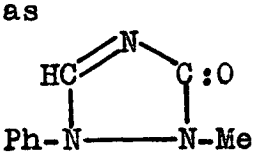
The spectra of 3-phenyl- and 3-methyl-5-phenyl-1:2:4-triazole closely resemble those of only one of their N-methyl derivatives respectively, namely 1-methyl- and 1:5-dimethyl-3-phenyl-1:2:4-triazole, (Figures 6,7). Present ignorance of the effect of an N-methyl group restricts the value of this observation, but there is a possibility that this implies that in the "acidic" triazole the mobile hydrogen is located principally in the corresponding position, namely on the hydrazinic nitrogen adjacent to the phenyl group.

Even taken as an empirical generalization this

observation might justify the investigation of the absorption spectra of these isomers, since chemical proofs have been quite laborious. Possibly the absorption band of the N-phenyl triazoles corresponds to an ionic excited state in which the phenyl and triazole rings are coplanar, the situation being similar to that of diphenyl and its derivatives. The absorption bands of XX and XXVl are much flatter (Figure lla) than those of the isomeric compounds XlX and XXV. The broader bands may be due to the effects of relatively uncoupled chromophores.

The introduction of a 5-phenyl group into 3-hydroxy-l-phenyl-l:2:4-triazole (XXXlll) produces a bathochromic effect combined with a hypochromic one (XXXlX). The higher band maximum of XXXlX is comparable with that of XXXVll although the extinction coefficient of the latter has the well-known exceptional high value characteristic of styryl derivatives. Comparison of the bands of XX and XXlX shows the importance of auxochromes like the hydroxy-group, which also appears to cause deconjugating effects, greater than expected from the size alone: compare the hypsochromic shift from XXXlll to 5-hydroxy-3-methyl-l-phenyl-triazole (XXXlV). (the hyperchromic shift may be due to the 5-methyl group XXXlV). This hypsochromic effect is much greater than that

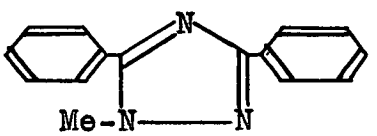
observed when passing from 3-hydroxy-5-methyl-1-phenyl-pyrazole to 5-hydroxy-3-methyl-1-phenylpyrazole. (49) It may be premature to compare the spectrographic behavious of hydroxytriazoles with that of triazoles substituted by alkyl and phenyl groups. In particular, XXXlll is methylated by dimethylsulphate to a methyl derivative which, on analysis, has no methoxyl group and must be formulated therefore as



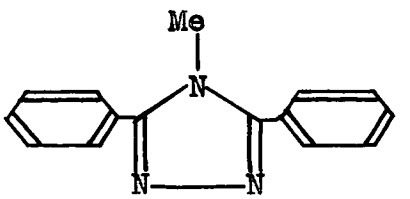
2-methyl-1-phenyl-1:2:4-triazol-3-one (XL1). The spectra of XL1, XXXlll and the anion of XXXlll are practically identical, which indicates a triazolone structure for (XXXlll).

A small bathochromic effect is found when passing from the spectrum of XV to 3-methyl-5-phenyl-1:2:4-triazole (XXll). The spectrum of 3:5-diphenyl-1:2:4-triazole (XXVll) presents two maxima of approximately equal intensities which suggests the presence of the tautomeric 1H-1:2:4- and 4H-1:2:4-triazole structures in equilibrium. The N-methyl derivative corresponding to the former, 1-methyl-3:5-diphenyl-1:2:4-triazole (XXVlll) has a spectrum with a single maximum. A hypsochromic effect would be expected on considering that in this

form the two phenyl rings cannot conjugate linearly through the triazole ring (XXVlla). The single band of 4-methyl-3:5-diphenyl-1:2:4-triazole (XXlX) on the other hand, might be thought to have undergone a bathochromic shift owing to the possibility of linear conjugation of two phenyls through the triazole ring (XXVlla)



XXVlla

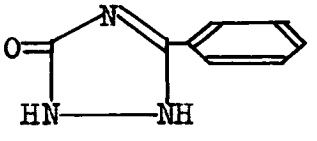


XXlXa

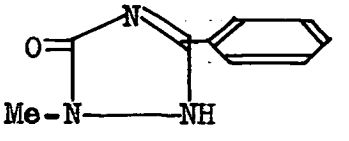
On these arguments one cannot identify the 234 mu band of XXVll as that of the 4H- and the 255 mu band as that of the 1H- form because the contribution of deconjugation by N-methyl groups cannot be assessed.

The actual location of the band of 1:3:5-triphenyl-1:2:4-triazole (XXX) is due to a number of effects: deconjugation through the interaction of $N_{(1)}$- and $C_{(5)}$-phenyl groups, which may magnify the effect of lack of linear conjugation between $C_{(3)}$ and $C_{(5)}$-phenyl. At the same time the presence of three "isolated" phenyl groups results in a hyperchromic effect. A similar phenomenon is observed on comparing p- and m- terphenyl (Braude, loc. cit.)

On comparison of the spectra of 3-hydroxy-5-phenyl- (XXXV) and 5-hydroxy-1-methyl-3-phenyl (XXXVl) 1:2:4-triazoles, one would expect the former to have a maximum at a higher wave-length owing to the steric deconjugating effect between the 1- and 5- substituents in the latter. The opposite is the case. It is readily seen that the optimum conjugated system is afforded by the forms XXXVa and XXXVla; methylation permits stabilization of the structure XXXVla.



XXXVa



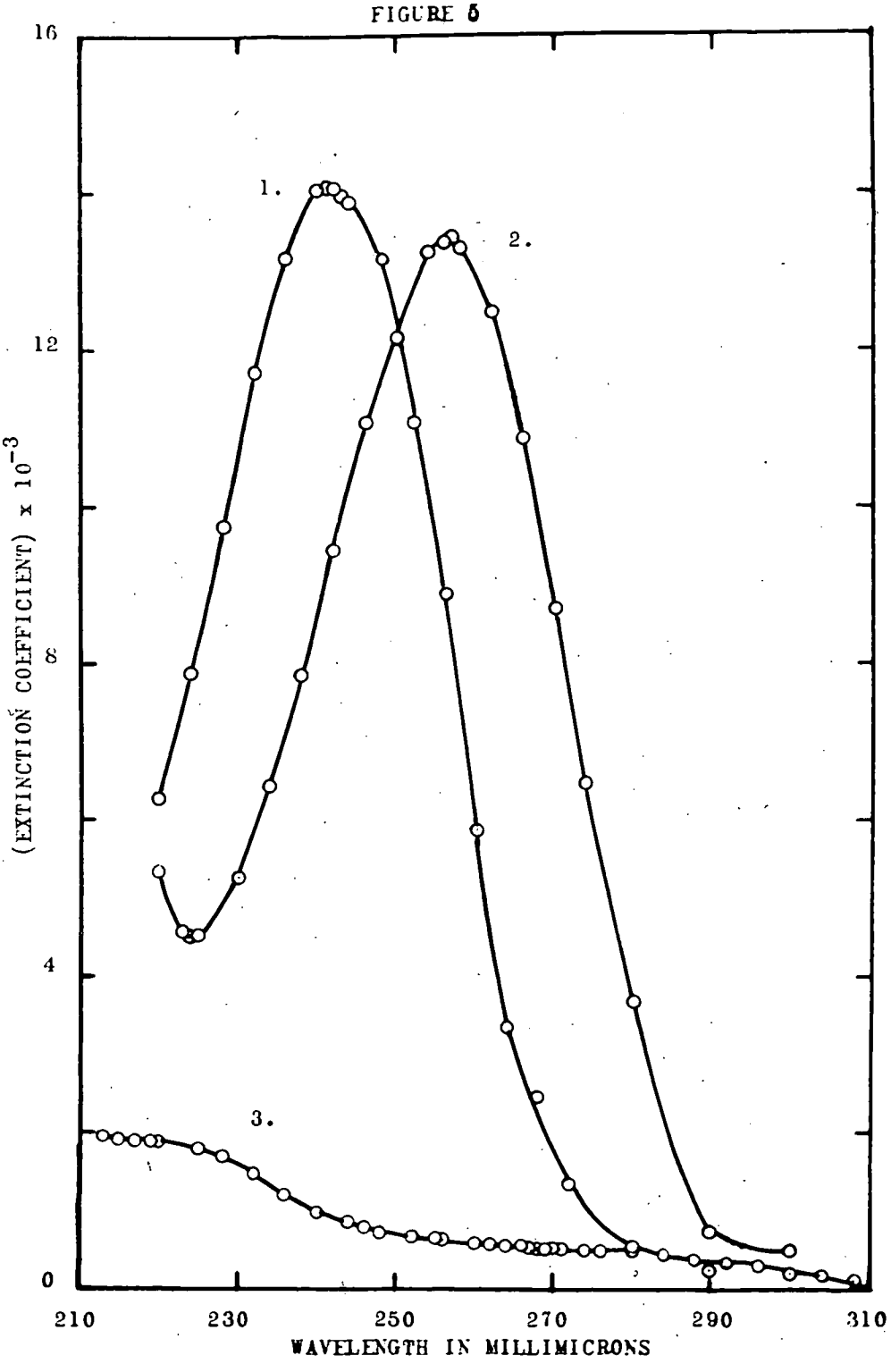
XXXVla

The anions of the investigated hydroxytriazoles and those of the acidic triazoles XV, XXll and XXVll absorb at longer wavelengths than the neutral substances, the bathochromic shifts being of the order of 8-17 mμ; the extinctions are lower except in the case of the anion of XXXlll and XXXlX, both of them derivatives of 1-phenyl-1:2:4-triazole. The spectrum of XV in ethanol with excess hydrochloric acid does not differ significantly from that of the neutral molecule, supporting the view that protonation would not affect the absorbing system. Similarly the spectra of XV in ethanol and water are

practically identical.

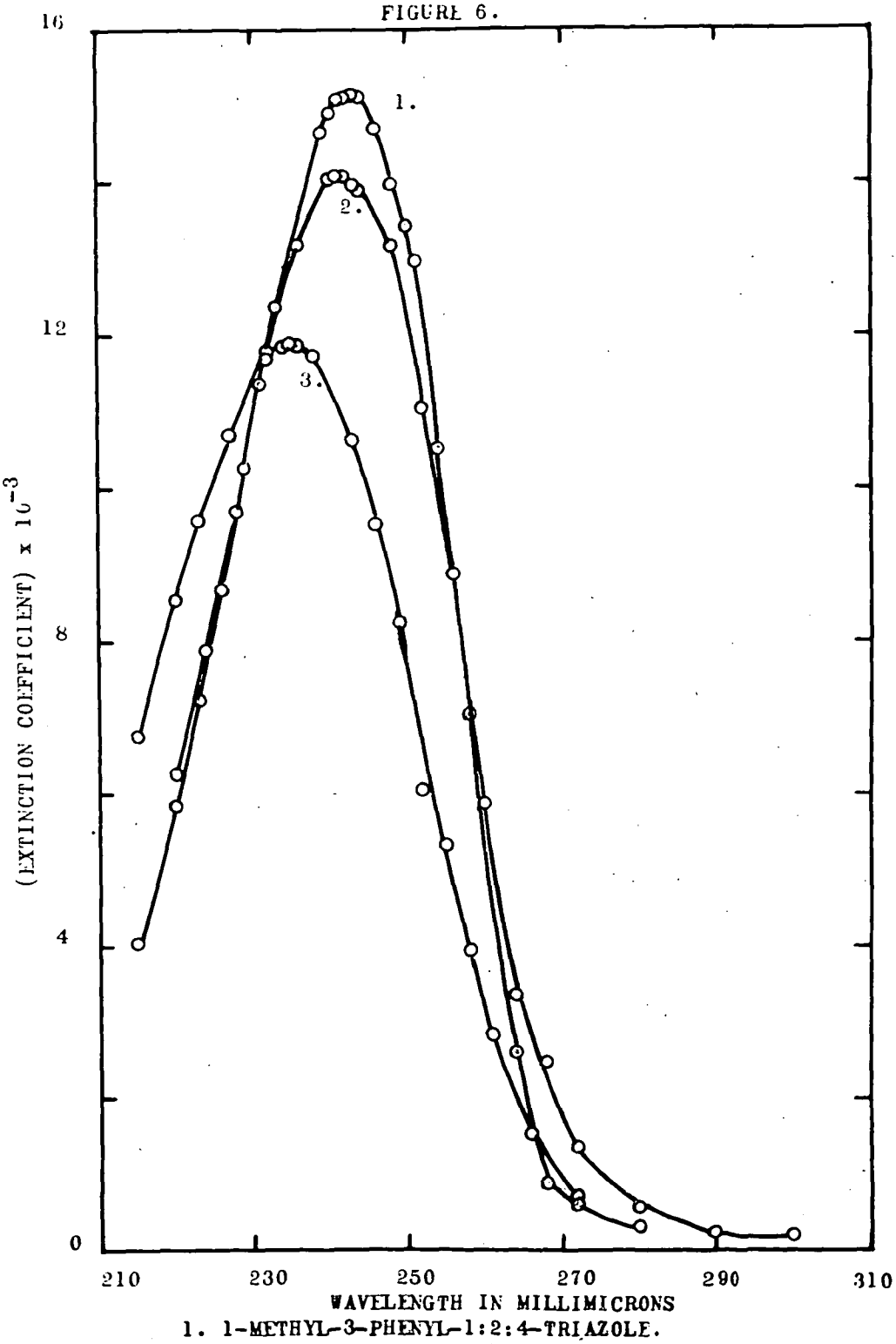
The aliphatic aminotriazoles in ethanolic solution exhibit no bands above 215 millimicrons. Dimethyltriazolyltriazole (Vll) has a band similar to that of acetyldimethyltriazole. If the spectroscopic similarity of the weak chromophores 3-triazolyl and acetyl may be assumed, this would strengthen previous arguments in favour of the 1-acetyl structure of the latter. The absorption spectrum of 3-amino-5-phenyltriazole (XLVll) is closely similar to that of 3-phenyl-5-hydroxy$_A$. The spectrum of the cation has practically the same λ_{max} although the extinction is increased.

FIGURE 5



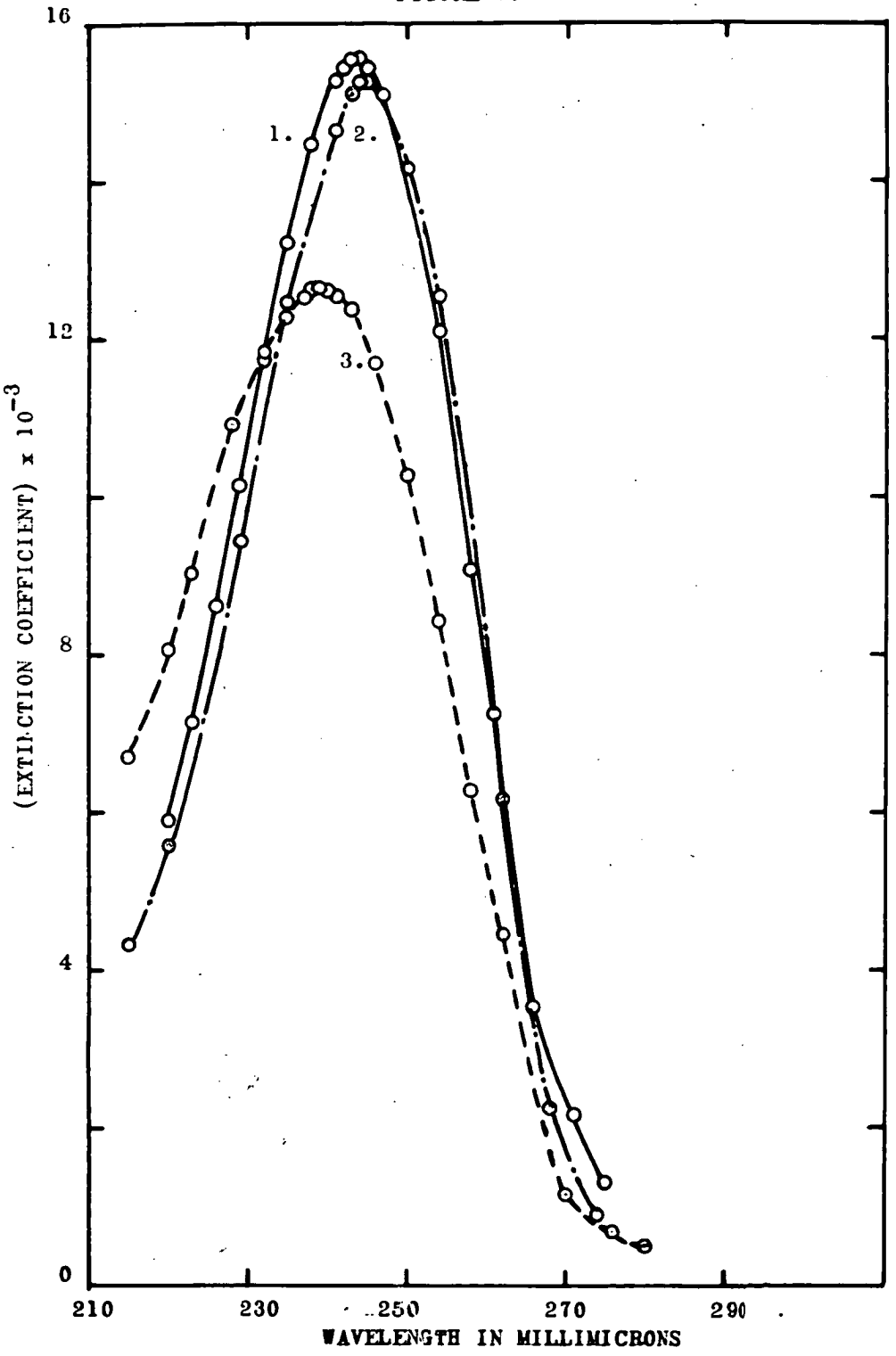
1. 3-PHENYL-1:2:4-TRIAZOLE.
2. ANION OF 3-PHENYL-1:2:4-TRIAZOLE.
3. 4-METHYL-3-PHENYL-1:2:4-TRIAZOLE.

FIGURE 6.



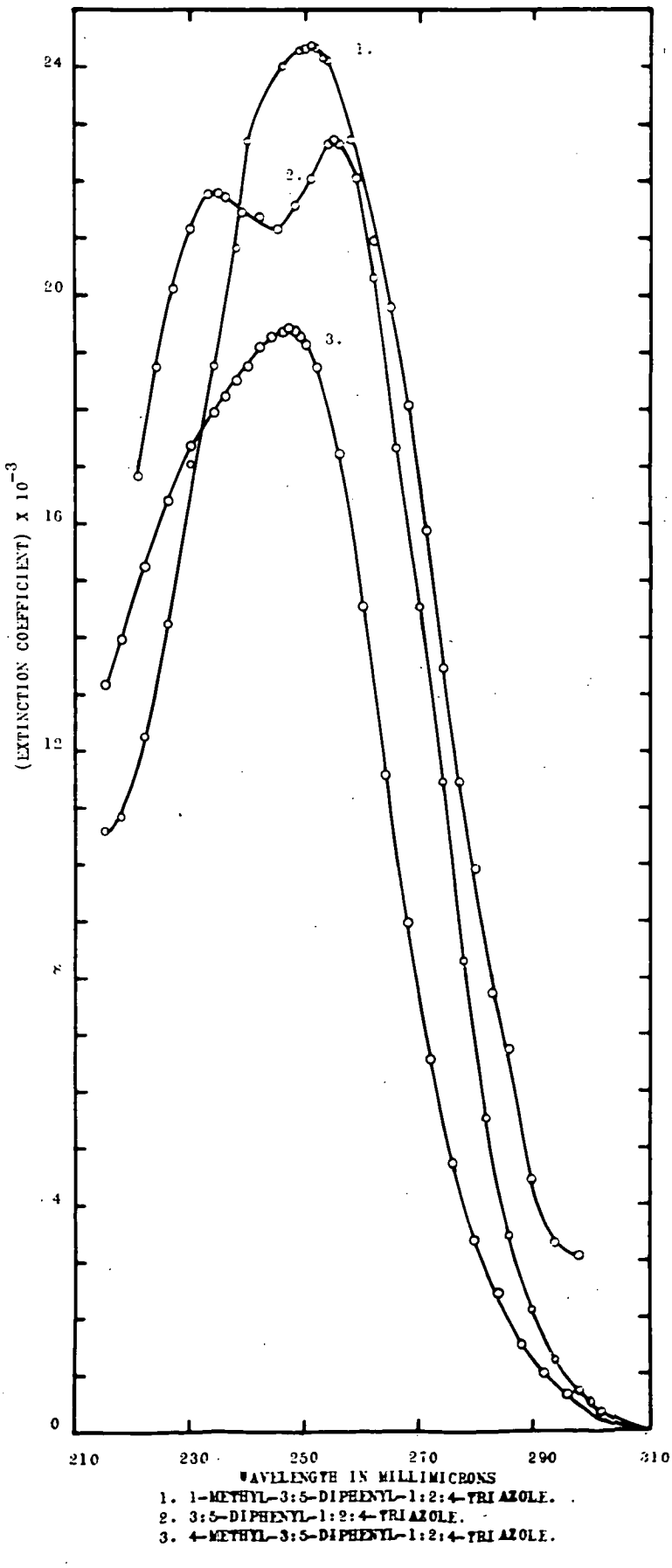
1. 1-METHYL-3-PHENYL-1:2:4-TRIAZOLE.
2. 3-PHENYL-1:2:4-TRIAZOLE.
3. 1-METHYL-5-PHENYL-1:2:4-TRIAZOLE.

FIGURE 7.



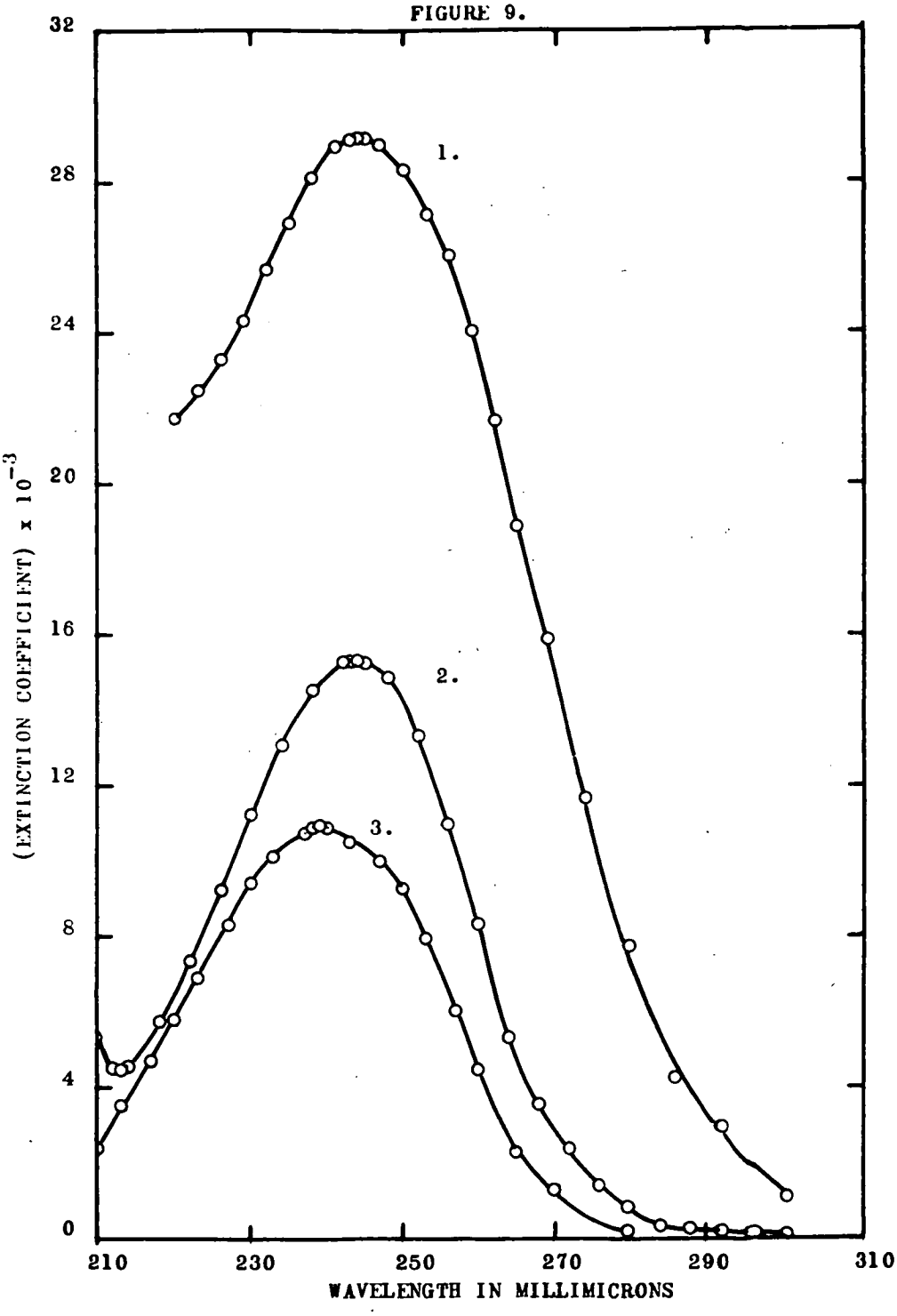
1. 3-METHYL-5-PHENYL-1:2:4-TRIAZOLE
2. 1:5-DIMETHYL-3-PHENYL-1:2:4-TRIAZOLE.
3. 1:3-DIMETHYL-5-PHENYL-1:2:4-TRIAZOLE.

FIGURE 1.



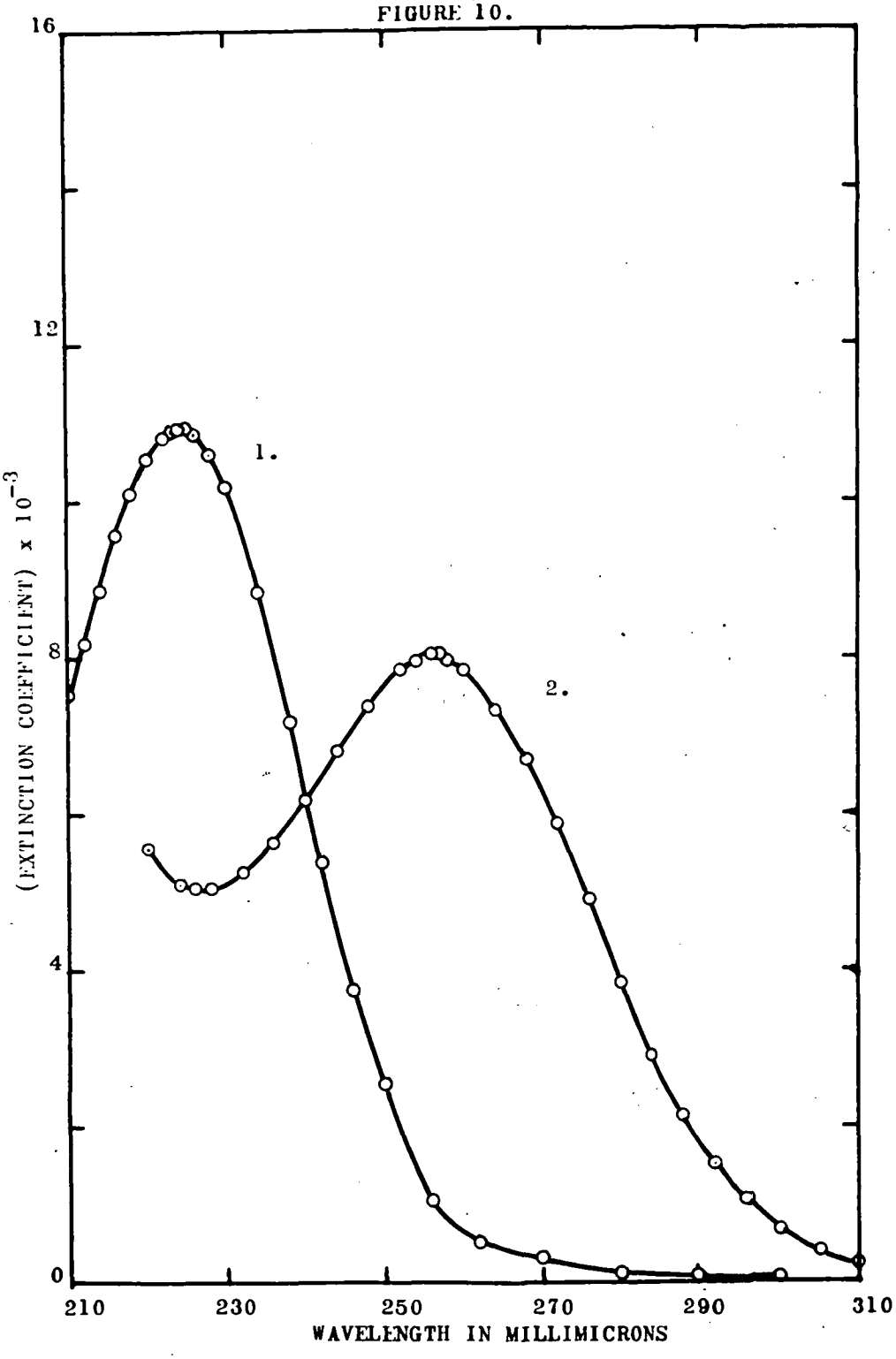
1. 1-METHYL-3:5-DIPHENYL-1:2:4-TRIAZOLE.
2. 3:5-DIPHENYL-1:2:4-TRIAZOLE.
3. 4-METHYL-3:5-DIPHENYL-1:2:4-TRIAZOLE.

FIGURE 9.



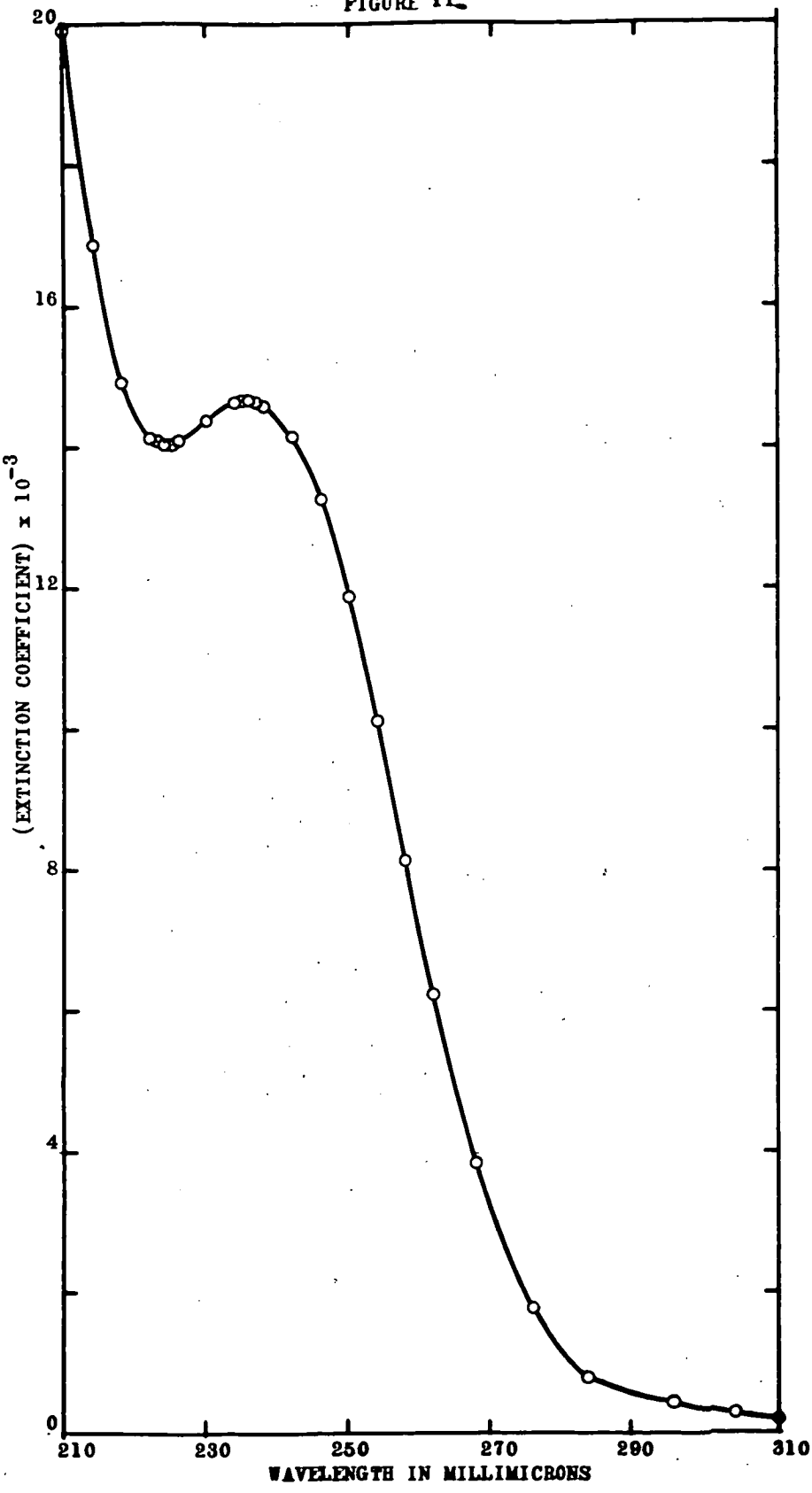
1. 1:3:5-TRIPHENYL-1:2:4-TRIAZOLE.
2. 3-METHYL-1-PHENYL-1:2:4-TRIAZOLE.
3. 1-PHENYL-1:2:4-TRIAZOLE.

FIGURE 10.



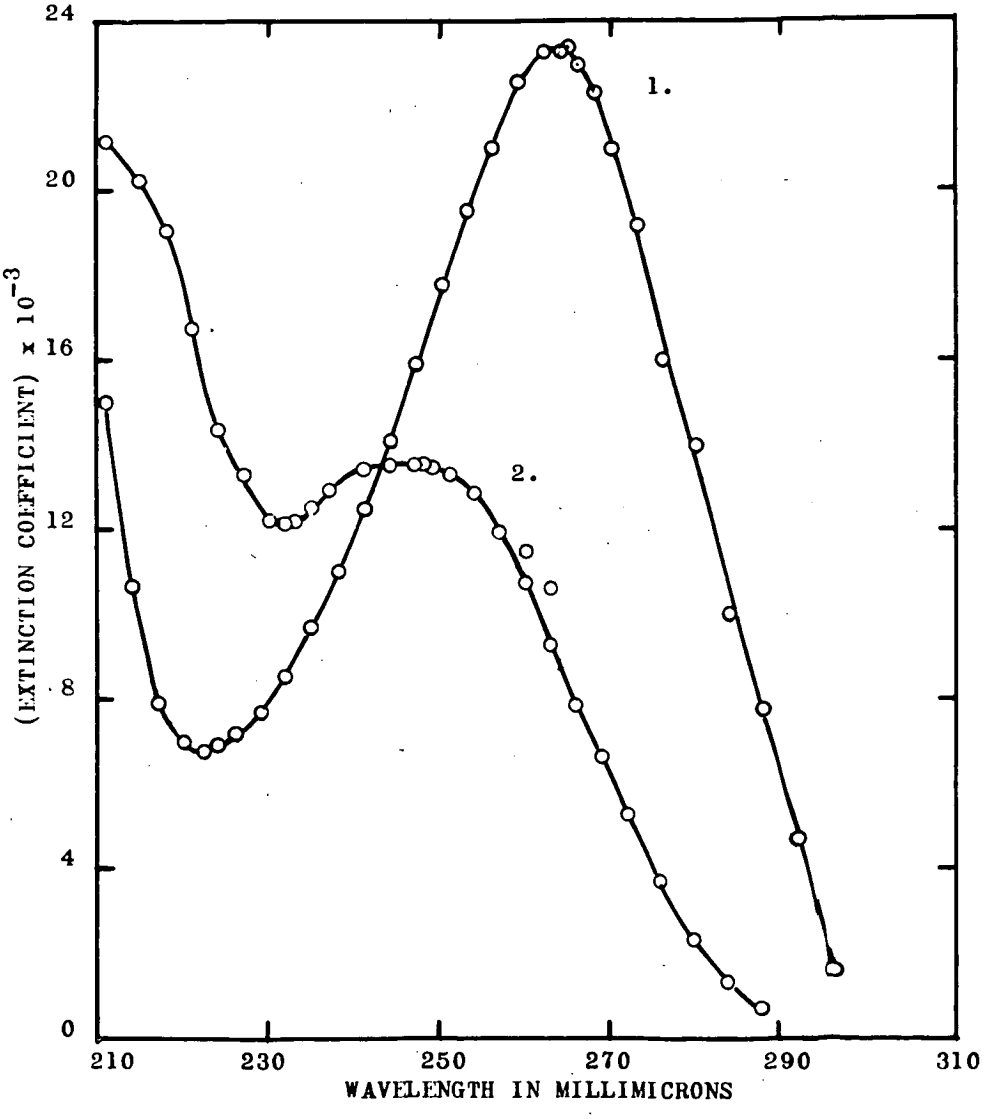
1. 4–PHENYL–1:2:4–TRIAZOLE.
2. 3:4:5–TRIPHENYL–1:2:4–TRIAZOLE.

FIGURE 11.



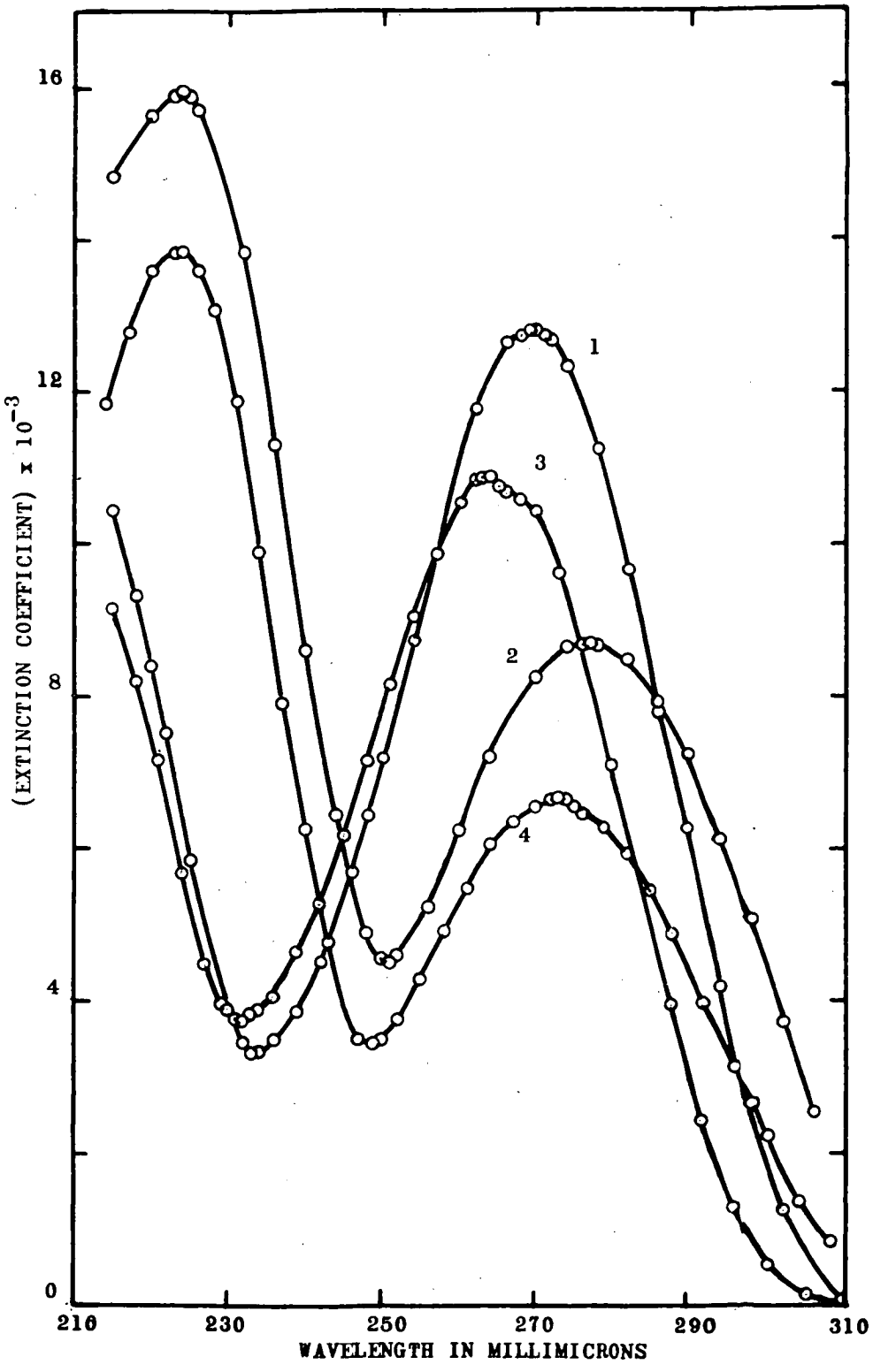
3:4-DIPHENYL-1:2:4-TRIAZOLE.

FIGURE 11 A.



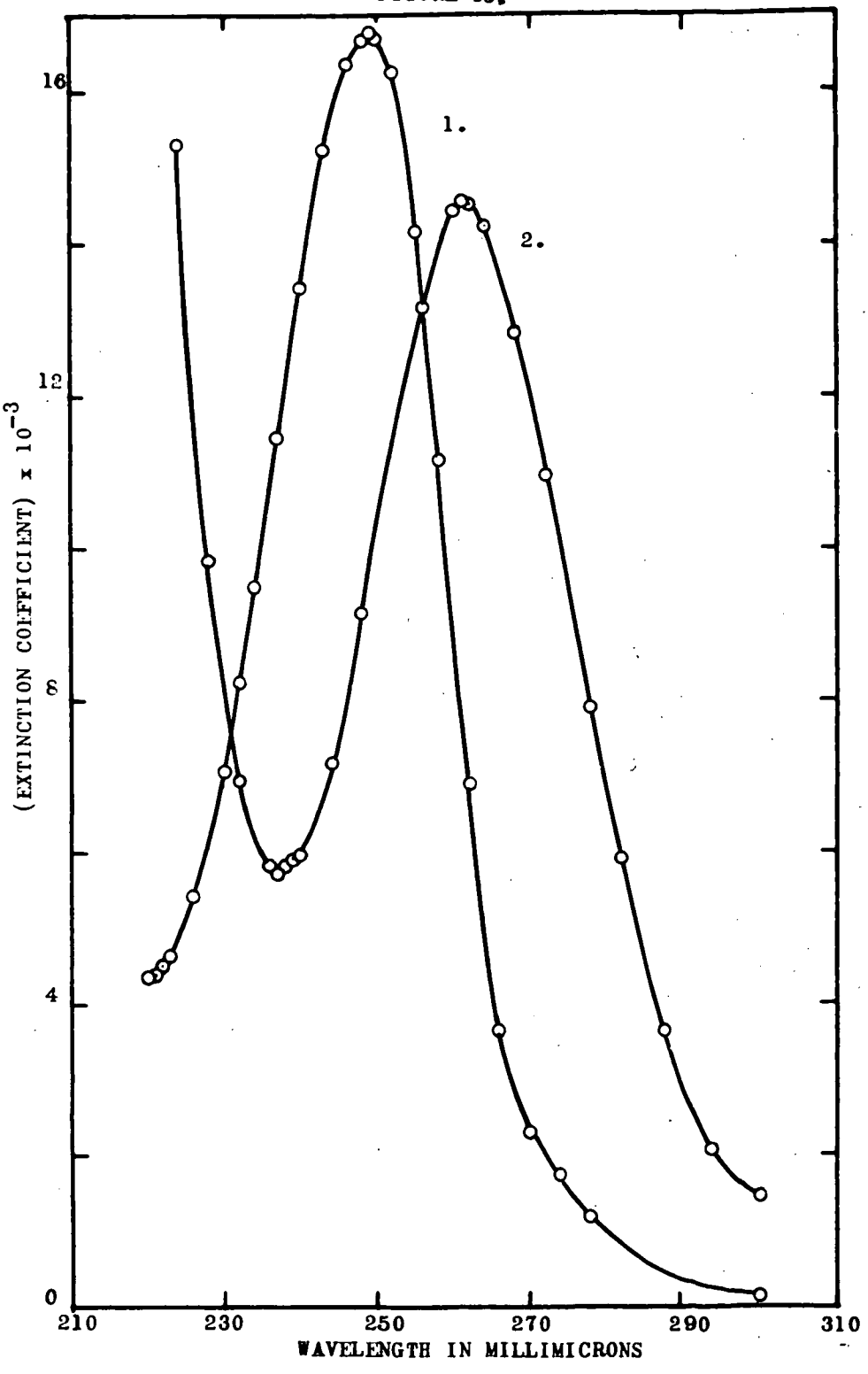
1. 1:3-DIPHENYL-1:2:4-TRIAZOLE.
2. 1:5-DIPHENYL-1:2:4-TRIAZOLE.

FIGURE 12.



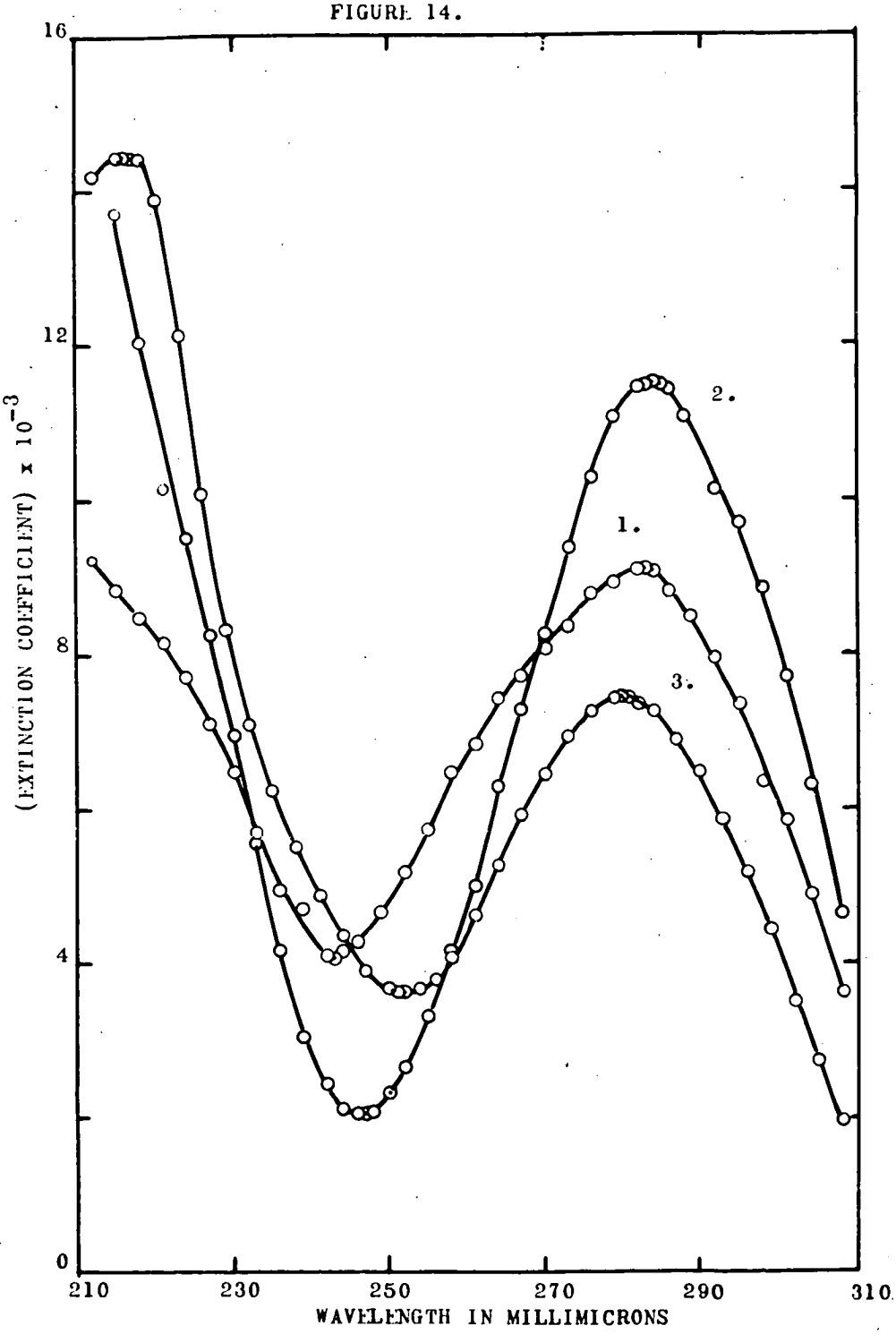
1. 5-HYDROXY-1-METHYL-3-PHENYL-1:2:4-TRIAZOLE.
2. DO. - ANION.
3. 3-PHENYL-5-HYDROXY-1:2:4-TRIAZOLE.
4. DO. - ANION.

FIGURE 13.



1. 5-HYDROXY-3-METHYL-1-PHENYL-1:2:4-TRIAZOLE.
2. DO. -ANION.

FIGURE 14.



1. 3-HYDROXY-1-PHENYL-1:2:4-TRIAZOLE.
2. DO. - ANION.
3. 2-METHYL-1-PHENYL-1:2:4-TRIAZOL-3-ONE.

TABLE 1.

4-Phenyl-1:2:4-triazole.

Concentration: 5.30×10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
210	0.400	7.55
212	0.434	8.19
214	0.470	8.86
216	0.508	9.58
218	0.563	10.11
220	0.560	10.57
222	0.574	10.83
223	0.578	10.91
224	0.580	10.94
225	0.580	10.94
226	0.575	10.85
228	0.562	10.60
230	0.540	10.19
234	0.468	8.83
238	0.381	7.19
242	0.285	5.38
246	0.198	3.74
250	0.134	2.53
256	0.055	1.04
262	0.028	0.53
270	0.017	0.32
280	0.006	0.11
290	0.004	0.08
300	0.002	0.04

Maximum: 224.5 mμ $\quad\quad$ ε_{max}: 10,900.

TABLE 11.

3-Methyl-1-phenyl-1:2:4-triazole.

Concentration: 8.10 x 10^{-5} molar.

λ(mu)	D	ε x 10^{-3}
210	0.436	5.38
212	0.368	4.54
213	0.366	4.51
214	0.373	4.60
218	0.465	5.74
222	0.597	7.37
226	0.748	9.23
230	0.910	11.23
234	1.062	13.11
238	1.176	14.52
242	1.237	15.27
243	1.244	15.35
244	1.245	15.37
245	1.238	15.28
246	1.232	15.20
248	1.204	14.86
252	1.081	13.35
256	0.890	10.99
260	0.674	8.32
264	0.436	5.38
268	0.291	3.59
272	0.194	2.40
276	0.115	1.42
280	0.068	0.84
284	0.031	0.38
288	0.023	0.28
292	0.018	0.22
296	0.015	0.19
300	0.013	0.16

Maximum: 244 mμ ε_{max}: 15,400.

Minimum: 213 mμ ε_{min}: 4,500.

TABLE 111.

3:5-Dimethyl-4-phenyl-1:2:4-triazole.

Concentration: 7.26×10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
210	0.514	7.08
213	0.467	6.43
216	0.390	5.37
219	0.304	4.19
222	0.239	3.29
226	0.125	1.72
230	0.056	0.77
234	0.018	0.25
238	0.007	0.09
240	0.006	0.08
241	0.005	0.07
242	0.006	0.08
246	0.009	0.12
250	0.014	0.19
252	0.016	0.22
255	0.018	0.25
258	0.019	0.26
259	0.020	0.28
260	0.019	0.27
263	0.018	0.25
265	0.016	0.22
270	0.009	0.12
275	0.008	0.11
280	0.007	0.09
285	0.005	0.07
290	0.004	0.06
300	0.002	0.03

Maximum: 259 mμ. ε_{max}: 280.

Minimum: 241 mμ. ε_{min}: 70.

TABLE IV.

3:5-Dimethyl-4-phenyl-1:2:4-triazole (cation).

Concentration: 7.03×10^{-5} molar in ethanol containing hydrochloric acid (4.22×10^{-3} molar)

λ (mμ)	D	$\varepsilon \times 10^{-3}$
210	0.458	6.52
214	0.372	5.29
218	0.282	4.01
222	0.200	2.84
226	0.133	1.89
230	0.087	1.24
234	0.066	0.94
238	0.053	0.75
239	0.052	0.74
240	0.051	0.73
241	0.050	0.72
242	0.052	0.74
246	0.056	0.80
250	0.062	0.88
254	0.068	0.97
257	0.068	0.97
258	0.070	1.00
259	0.069	0.98
260	0.068	0.97
262	0.062	0.88
266	0.056	0.80
270	0.045	0.64
275	0.041	0.58
280	0.037	0.53
282	0.035	0.50
285	0.033	0.47
290	0.028	0.40
295	0.025	0.36
300	0.021	0.30
310	0.017	0.24
320	0.014	0.20

Maximum: 258 mμ. ε_{max}: 1,000.

Minimum: 241 mμ. ε_{min}: 730.

TABLE V.

3-Phenyl-1:2:4-triazole.

Concentration: 7.40×10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
220	0.464	6.27
224	0.583	7.88
228	0.722	9.76
232	0.865	11.69
236	0.976	13.19
240	1.038	14.02
241	1.042	14.08
242	1.042	14.08
243	1.035	13.99
244	1.028	13.89
248	0.976	13.19
252	0.818	11.05
256	0.657	8.88
260	0.434	5.86
264	0.249	3.36
268	0.180	2.43
272	0.101	1.36
280	0.043	0.58
290	0.017	0.23
300	0.015	0.20

Maximum: 241.5 mμ ε_{max}: 14,100.

TABLE VI.

3-Phenyl-1:2:4-triazole.

Concentration: 1.66×10^{-4} molar in water.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
220	1.117	6.73
222	1.257	7.57
226	1.547	9.32
228	1.689	10.17
230	1.825	10.99
234	2.028	12.22
238	2.119	12.76
239	2.305	13.89
240	2.250	13.55
242	2.095	12.62
246	1.978	11.92
250	1.706	10.28
254	1.329	8.01
258	0.938	5.65
262	0.509	3.06
266	0.328	1.97
270	0.195	1.17
274	0.120	0.72
278	0.083	0.50
282	0.057	0.34

Concentration in water:	$D_{239\ m\mu}$	$\varepsilon \times 10^{-3}$
1.58×10^{-5} molar	0.224	14.2
3.95 " "	0.553	14.0
7.90 " "	1.104	14.1
16.6 " "	2.305	13.9
19.8 " "	2.47	12.5

TABLE V11.

3-Phenyl-1:2:4-triazole (cation).

Concentration: 7.22×10^{-5} molar in ethanol containing hydrochloric acid (5.67×10^{-3} molar).

λ(mμ)	D	$\varepsilon \times 10^{-3}$
220	0.438	6.06
224	0.568	7.87
228	0.710	9.83
232	0.858	11.88
236	0.975	13.50
240	1.039	14.39
241	1.042	14.43
242	1.042	14.43
243	1.037	14.36
244	1.032	14.29
248	0.980	13.57
252	0.840	11.63
256	0.655	9.07
260	0.430	5.96
264	0.244	3.38
270	0.172	2.38
280	0.037	0.48
290	0.011	0.15
300	0.007	0.10

Maximum: 241.5 mμ ε_{max}: 14,400.

TABLE V111.

3-Phenyl-1:2:4-triazole (anion).

Concentration: 7.40×10^{-5} molar in ethanol containing potassium hydroxide (2.2×10^{-3} molar).

λ (mμ)	D	$\varepsilon \times 10^{-3}$
220	0.397	5.36
223	0.339	4.58
224	0.334	4.51
225	0.335	4.53
230	0.389	5.26
234	0.475	6.42
238	0.580	7.84
242	0.698	9.43
246	0.820	11.08
250	0.922	12.18
254	0.981	13.26
256	0.990	13.38
257	0.995	13.45
258	0.985	13.31
262	0.925	12.50
266	0.805	10.88
270	0.645	8.72
274	0.479	6.47
280	0.272	3.68
290	0.056	0.76
300	0.038	0.51

Maximum: 257 mμ. ε_{max}: 13,500.

Minimum: 224 mμ. ε_{min}: 4,500.

TABLE IX.

1-methyl-3-phenyl-1:2:4-triazole.

Concentration: 4.49×10^{-5} molar in ethanol.

λ (mμ)	D	$\varepsilon \times 10^{-3}$
215	0.181	4.03
220	0.262	5.84
223	0.324	7.22
226	0.389	8.66
229	0.461	10.27
231	0.510	11.36
233	0.556	12.38
234	0.580	12.92
236	0.615	13.70
239	0.658	14.65
240	0.670	14.92
241	0.678	15.10
242	0.679	15.12
243	0.680	15.14
244	0.679	15.12
246	0.660	14.70
248	0.628	13.99
250	0.602	13.41
251	0.582	12.97
254	0.473	10.53
258	0.315	7.02
260	0.262	5.83
264	0.117	2.60
268	0.039	0.87
272	0.027	0.60
280	0.014	0.32

Maximum: 243 mμ ε_{max}: 15,100.

TABLE X.

1-methyl-5-phenyl-1:2:4-triazole.

Concentration: 4.29 x 10^{-5} molar in ethanol.

λ (mμ)	D	$\varepsilon \times 10^{-3}$
215	0.290	6.76
220	0.367	8.55
221	0.396	9.23
222	0.406	9.46
223	0.411	9.58
227	0.460	10.72
230	0.489	11.40
232	0.506	11.79
234	0.508	11.84
235	0.510	11.89
236	0.509	11.86
238	0.504	11.75
240	0.485	11.30
243	0.456	10.63
246	0.410	9.55
249	0.353	8.23
252	0.259	6.04
255	0.229	5.34
258	0.169	3.94
261	0.121	2.82
266	0.066	1.54
272	0.032	0.75
280	0.010	0.23

Maximum: 235 mμ ε_{max}: 11,900.

TABLE XI.

1-methyl-3-phenyl-1:2:4-triazole.

Concentration: 8.64×10^{-5} molar in ethanol.

λ (mμ)	D	$\varepsilon \times 10^{-3}$
213	0.170	1.97
215	0.166	1.92
216	0.165	1.91
217	0.164	1.90
219	0.162	1.88
220	0.162	1.88
225	0.155	1.79
228	0.146	1.69
232	0.127	1.47
236	0.104	1.20
240	0.085	0.98
244	0.074	0.86
246	0.068	0.79
248	0.062	0.72
252	0.058	0.67
255	0.055	0.64
256	0.054	0.62
260	0.051	0.59
262	0.050	0.58
264	0.048	0.56
266	0.048	0.56
267	0.047	0.54
268	0.046	0.54
269	0.047	0.54
270	0.0475	0.55
271	0.047	0.54
272	0.046	0.53
274	0.045	0.53
276	0.044	0.51
280	0.041	0.47
284	0.037	0.43
288	0.034	0.39
292	0.030	0.35
296	0.026	0.30
300	0.022	0.25
304	0.017	0.20
308	0.012	0.14

Maximum: 270 mμ ε_{max}: 500.

TABLE XII.

3:4-Diphenyl-1:2:4-triazole.

Concentration: 3.01×10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
210	0.598	19.88
214	0.508	16.88
218	0.450	14.94
222	0.425	14.12
223	0.424	14.09
224	0.422	14.02
225	0.422	14.02
226	0.424	14.09
230	0.433	14.39
234	0.440	14.62
235	0.441	14.65
236	0.441	14.65
237	0.440	14.62
238	0.439	14.58
242	0.426	14.15
246	0.399	13.26
250	0.358	11.89
254	0.305	10.13
258	0.245	8.14
262	0.187	6.21
268	0.115	3.82
276	0.054	1.79
284	0.024	0.80
290	0.016	0.53
296	0.013	0.43
304	0.009	0.30
310	0.006	0.20

Maximum: 235.5 mμ. ε_{max}: 14,700.

Minimum: 224.5 mμ. ε_{min}: 14,000.

TABLE XIII.

3-methyl-5-phenyl-1:2:4-triazole.

Concentration: 5.46×10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
220	0.323	5.92
223	0.391	7.16
226	0.470	8.61
229	0.555	10.16
232	0.648	11.87
235	0.723	13.24
238	0.790	14.47
241	0.835	15.29
242	0.842	15.42
243	0.849	15.55
244	0.850	15.57
245	0.842	15.42
247	0.825	15.11
250	0.791	14.49
254	0.660	12.09
258	0.495	9.07
261	0.396	7.25
266	0.189	3.46
271	0.118	2.16
275	0.072	1.32
280	0.028	0.51

Maximum: 244 mμ ε_{max}: 15,600.

TABLE XIV.

3-methyl-5-phenyl-1:2:4-triazole (anion).

Concentration: 5.46×10^{-5} molar in ethanol containing potassium hydroxide (1.6×10^{-3} molar).

λ(mμ)	D	$\varepsilon \times 10^{-3}$
220	0.510	9.34
224	0.335	6.14
228	0.260	4.76
229	0.256	4.69
230	0.255	4.67
231	0.260	4.76
232	0.266	4.87
236	0.316	5.79
240	0.393	7.20
244	0.489	8.96
248	0.593	10.86
252	0.694	12.71
256	0.779	14.27
260	0.824	15.09
261	0.826	15.13
262	0.825	15.11
263	0.824	15.09
264	0.818	14.98
267	0.768	15.11
271	0.694	12.71
275	0.570	10.44
280	0.413	7.56
285	0.264	4.84
290	0.128	2.34
300	0.020	0.37

Maximum: 261 mμ. ε_{max}: 15,100.

Minimum: 230 mμ. ε_{min}: 4,700.

TABLE XV.

1:3-dimethyl-5-phenyl-1:2:4-triazole.

Concentration: 5.00 x 10^{-5} molar in ethanol.

λ (mμ)	D	$\varepsilon \times 10^{-3}$
215	0.336	6.72
220	0.403	8.06
223	0.452	9.04
226	0.500	10.00
229	0.547	10.94
232	0.588	11.76
235	0.615	12.30
237	0.628	12.56
238	0.631	12.62
239	0.633	12.66
240	0.630	12.60
241	0.628	12.56
243	0.620	12.40
246	0.588	11.76
250	0.515	10.30
254	0.421	8.42
258	0.313	6.26
262	0.173	3.46
270	0.057	1.14
276	0.034	0.68
280	0.013	0.26

Maximum: 239 mμ. ε_{max}: 12,700.

TABLE XVl.

1:5-dimethyl-3-phenyl-1:2:4-triazole.

Concentration: 4.30 x 10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
215	0.186	4.33
220	0.240	5.58
223	0.235	5.49
226	0.344	8.00
229	0.406	9.44
232	0.473	11.00
235	0.536	12.47
238	0.590	13.72
241	0.630	14.65
243	0.650	15.12
244	0.656	15.26
245	0.656	15.26
246	0.654	15.21
247	0.650	15.12
250	0.610	14.19
254	0.540	12.56
258	0.491	11.42
262	0.265	6.16
268	0.096	2.23
274	0.039	0.91
280	0.024	0.56

Maximum: 245 mμ ε_{max}: 15,000.

TABLE XVll.

1-Methyl-3:5-diphenyl-1:2:4-triazole.

Concentration: 3.61 x 10^{-5} molar in ethanol.

λ(mμ)	D	ε x 10^{-3}
215	0.475	13.16
218	0.504	13.96
222	0.550	15.23
226	0.592	16.40
230	0.627	17.37
234	0.648	17.95
236	0.658	18.23
238	0.669	18.53
240	0.678	18.78
242	0.690	19.11
244	0.697	19.30
246	0.700	19.39
247	0.701	19.42
248	0.700	19.39
249	0.696	19.28
250	0.692	19.17
252	0.678	18.78
256	0.622	17.22
260	0.526	14.57
264	0.418	11.58
268	0.324	8.98
272	0.237	6.56
276	0.171	4.74
280	0.122	3.38
284	0.088	2.44
288	0.056	1.55
292	0.037	1.02
296	0.024	0.66
300	0.019	0.53

Maximum: 247 mμ. ε_{max}: 19,400.

TABLE XVIIa.

4-Methyl-3:5-diphenyl-1:2:4-triazole.

Concentration: 4.04 x 10^{-5} molar in ethanol.

λ(mμ)	D	ε x 10^{-3}
215	0.428	10.59
218	0.437	10.82
222	0.495	12.25
226	0.574	14.21
230	0.688	17.03
234	0.759	18.78
238	0.841	20.81
240	0.918	22.72
246	0.970	24.00
249	0.981	24.28
250	0.982	24.31
251	0.985	24.38
252	0.982	24.31
253	0.976	24.16
254	0.974	24.11
258	0.918	22.72
262	0.821	20.32
266	0.701	17.35
270	0.588	14.55
274	0.462	11.44
278	0.335	8.29
282	0.224	5.54
286	0.139	3.44
290	0.087	2.15
294	0.050	1.24
298	0.029	0.72
302	0.014	0.35

Maximum: 251 mμ ε_{max}: 24,000.

TABLE XVIII.

1:3:5-triphenyl-1:2:4-triazole.

Concentration: 5.28×10^{-5} molar in ethanol.

λ (mμ)	D	$\varepsilon \times 10^{-3}$
220	1.150	21.78
223	1.187	22.48
226	1.232	23.33
229	1.285	24.32
232	1.356	25.68
235	1.420	26.89
238	1.438	28.09
241	1.527	28.92
243	1.538	29.13
244	1.540	29.17
245	1.539	29.15
247	1.530	28.98
250	1.498	28.37
253	1.435	27.18
256	1.377	26.08
259	1.269	24.03
262	1.145	21.69
265	1.000	18.94
269	0.840	15.91
274	0.615	11.65
280	0.411	7.78
286	0.276	5.23
292	0.157	2.97
300	0.060	1.14

Maximum: 244 mμ. ε_{max}: 29,200.

TABLE XIX.

3:4:5-Triphenyl-1:2:4-triazole.

Concentration: 4.04 x 10^{-5} molar in ethanol.

λ (mμ)	D	$\varepsilon \times 10^{-3}$
220	0.225	5.57
224	0.206	5.10
226	0.204	5.05
228	0.204	5.05
232	0.212	5.25
236	0.227	5.61
240	0.250	6.18
244	0.275	6.80
248	0.298	7.38
252	0.316	7.82
254	0.321	7.95
256	0.324	8.02
257	0.324	8.02
258	0.322	7.97
260	0.316	7.82
264	0.296	7.33
268	0.270	6.68
272	0.238	5.86
276	0.198	4.90
280	0.154	3.81
284	0.117	2.90
288	0.086	2.13
292	0.061	1.51
296	0.042	1.04
300	0.028	0.69
305	0.016	0.40
310	0.010	0.25

Maximum: 256.5 mμ. ε_{max}: 8,000.

Minimum: 227 mμ. ε_{min}: 5,000.

TABLE XX.

3-Methyl-1-phenyl-5-styryl-1:2:4-triazole.

Concentration: 2.42×10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
210	0.669	27.64
214	0.662	27.36
218	0.670	27.69
221	0.706	29.17
222	0.709	29.30
223	0.700	28.93
226	0.654	27.02
230	0.627	25.90
234	0.510	21.07
238	0.445	18.39
242	0.417	17.23
246	0.395	16.32
250	0.372	15.37
254	0.359	14.83
258	0.374	15.45
262	0.420	17.36
266	0.486	20.08
270	0.560	23.14
274	0.651	26.90
278	0.764	31.57
282	0.890	36.78
286	1.012	41.82
290	1.103	45.58
294	1.204	49.75
298	1.262	52.12
299	1.266	52.31
300	1.267	52.35
301	1.265	52.27
302	1.262	52.15
306	1.244	51.40
312	1.155	47.73
318	0.880	36.36
324	0.660	27.27
330	0.405	16.73
336	0.157	6.49
342	0.041	1.69
348	0.010	0.41
352	0.004	0.17

Maxima: 222 mμ. ε_{max}: 29,300.
300 mμ. ε_{max}: 52,400.
Minimum: 254 mμ. ε_{min}: 14,800.

TABLE XXl.

5-hydroxy-3-methyl-1-phenyl-1:2:4-triazole.

Concentration: 2.46 x 10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
215	0.116	4.72
220	0.107	4.35
221	0.108	4.39
222	0.112	4.52
223	0.114	4.63
226	0.133	5.41
230	0.174	7.07
232	0.203	8.25
234	0.234	9.51
237	0.282	11.46
240	0.330	13.41
243	0.375	15.24
246	0.403	16.38
248	0.410	16.67
249	0.413	16.79
250	0.411	16.71
252	0.400	16.26
255	0.349	14.19
258	0.275	11.18
262	0.170	6.91
266	0.090	3.65
270	0.057	2.32
274	0.043	1.75
278	0.027	1.10
300	0.004	0.16

Maximum: 249 mμ. ε_{max}: 16,800.

TABLE XXll.

5-hydroxy-3-methyl-1-phenyl-1:2:4-triazole (anion).

Concentration: 2.46 x 10^{-5} molar in ethanol containing potassium hydroxide (7.5 x 10^{-4} molar).

λ(mμ)	D	ε x 10^{-3}
220	0.629	25.57
224	0.377	15.33
228	0.242	9.84
232	0.171	6.95
236	0.143	5.81
237	0.141	5.73
238	0.143	5.81
239	0.146	5.93
240	0.147	5.98
244	0.177	7.19
248	0.225	9.15
252	0.276	11.22
256	0.324	13.17
260	0.355	14.43
261	0.359	14.59
262	0.358	14.55
264	0.350	14.23
268	0.316	12.85
272	0.270	10.98
278	0.195	7.93
282	0.146	5.93
288	0.089	3.62
294	0.051	2.07
300	0.036	1.46

Maximum: 261 mμ. ε_{max}: 14,600.

Minimum: 237 mμ. ε_{min}: 5,700.

TABLE XXIII.

5-hydroxy-1-methyl-3-phenyl-1:2:4-triazole.

Concentration: 2.72×10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
215	0.283	10.40
218	0.253	9.30
220	0.228	8.38
222	0.204	7.50
223	0.190	6.98
224	0.174	6.40
225	0.158	5.81
226	0.144	5.29
229	0.108	3.97
232	0.093	3.42
233	0.089	3.27
234	0.090	3.31
236	0.094	3.46
239	0.104	3.82
242	0.122	4.49
246	0.154	5.66
248	0.174	6.40
250	0.195	7.17
254	0.237	8.71
256	0.282	10.37
262	0.320	11.76
266	0.343	12.61
268	0.346	12.72
269	0.348	12.79
270	0.348	12.79
271	0.346	12.72
272	0.344	12.65
274	0.335	12.32
278	0.305	11.21
282	0.262	9.63
286	0.212	7.79
290	0.170	6.25
294	0.113	4.15
298	0.072	2.65
302	0.033	1.21

Minimum: 233 mμ. ε_{min}: 3,300.

Maximum: 269.5 mμ. ε_{max}: 12,800.

TABLE XXIV.

5-hydroxy-1-methyl-3-phenyl-1:2:4-triazole (anion).

Concentration: 2.72×10^{-5} molar in ethanol containing potassium hydroxide (8.1×10^{-4} molar).

λ (mu)	D	$\varepsilon \times 10^{-3}$
215	0.403	14.82
220	0.426	15.66
223	0.433	15.92
224	0.434	15.96
225	0.432	15.88
226	0.427	15.70
232	0.376	13.82
236	0.308	11.32
240	0.234	8.60
244	0.175	6.43
248	0.133	4.89
250	0.124	4.56
251	0.123	4.52
252	0.125	4.60
256	0.142	5.22
260	0.169	6.21
264	0.196	7.20
270	0.224	8.24
274	0.235	8.64
276	0.236	8.68
277	0.237	8.71
278	0.236	8.68
282	0.231	8.49
286	0.216	7.94
290	0.197	7.24
294	0.167	6.14
298	0.138	5.07
302	0.103	3.79
306	0.070	2.57

Maxima: 224 mμ. ε_{max}: 16,000.
277 mμ. ε_{max}: 8,700.
Minimum: 251 mμ. ε_{min}: 4,500.

TABLE XXV.

3-Amino-5-(2-pyridyl)-1:2:4-triazole.

Concentration: 4.78×10^{-5} molar in ethanol.

λ(mμ)	D	$\varepsilon \times 10^{-3}$
215	0.512	10.71
218	0.500	10.46
222	0.491	10.27
226	0.484	10.13
230	0.460	9.62
234	0.411	8.60
238	0.339	7.09
242	0.267	5.59
246	0.224	4.69
248	0.215	4.50
250	0.214	4.48
252	0.216	4.52
254	0.224	4.69
258	0.243	5.08
262	0.265	5.54
266	0.290	6.07
270	0.316	6.61
274	0.345	7.22
278	0.372	7.78
282	0.386	8.08
283	0.387	8.10
284	0.385	8.05
286	0.380	7.95
290	0.356	7.45
294	0.309	6.46
298	0.256	5.36
302	0.190	3.97
306	0.138	2.89
310	0.099	2.07

Maximum: 283 mμ. ε_{max}: 8,100.

Minimum: 250 mμ. ε_{min}: 4,500.

TABLE XXVI.

3-Amino-5-(2-pyridyl)-1:2:4-triazole (cation).

Concentration: 4.78×10^{-5} molar in ethanol containing HCl (4×10^{-3} molar).

λ (mμ)	D	$\varepsilon \times 10^{-3}$
215	0.358	7.49
218	0.324	6.78
222	0.300	6.28
224	0.297	6.21
225	0.296	6.19
226	0.294	6.15
227	0.295	6.17
230	0.300	6.28
234	0.321	6.72
238	0.355	7.43
242	0.398	8.32
246	0.435	9.10
250	0.460	9.62
254	0.472	9.87
255	0.472	9.87
258	0.467	9.77
260	0.465	9.73
262	0.466	9.75
266	0.487	10.19
270	0.526	11.00
274	0.560	11.72
276	0.582	12.18
277	0.589	12.32
278	0.590	12.34
279	0.588	12.30
282	0.534	11.17
288	0.438	9.16
294	0.190	3.97
300	0.075	1.57

Maxima:	278 mμ.	ε_{max}: 12,300.
	254.5 mμ.	ε_{max}: 9,900.
Minima:	260 mμ.	ε_{min}: 9,700.
	226 mμ.	ε_{min}: 6,200.

TABLE XXVll.

N-formylbenzamide.

Concentration: 1.74 x 10^{-5} molar in water.

λ(mμ)	D	ε x 10^{-3}
200	1.379	7.93
204	1.225	7.04
208	0.830	4.77
212	0.825	4.74
216	0.900	5.17
220	0.978	5.62
224	1.045	6.00
228	1.126	6.47
232	1.186	6.82
236	1.235	7.10
239	1.243	7.14
240	1.250	7.18
241	1.235	7.10
244	1.224	7.03
248	1.127	6.48
252	0.955	5.49
258	0.535	3.07
262	0.288	1.65
268	0.167	0.96
274	0.143	0.82
280	0.123	0.71
290	0.071	0.41
300	0.029	0.17

Maximum: 240 mμ. ε_{max}: 7,200.

Appendix A.

Calculation of the distribution of electrons in 1:2:4-triazole molecules.

The method of calculation is that of Longuet-Higgins and Coulson [118]. The six π-electrons are assumed to exist in molecular orbitals ϕ, which may each be approximately represented as a linear combination of five atomic orbitals. Thus:

$$\phi = c_1\psi_1 + c_2\psi_2 + \ldots c_5\psi_5$$

where ψ_s has the usual significance as a wave function antisymmetric with respect to the plane of the triazole molecule (assuming a planar aromatic system), and having its greatest amplitude in the neighbourhood of atom s. For the best solution of the wave equation,

$$c_r(\alpha_r - E) + \sum_{s=1}^{5} \beta_{rs} c_s = 0; \quad r = 1, 2, \ldots 5$$

where the sum does not include the term with s = r.

E = energy of molecular orbital,

α_r = coulomb integral for the atomic orbital ψ_r,

β_{rs} = resonance integral between the atomic orbitals ψ_r and ψ_s.

In this calculation overlap between atomic orbitals is neglected, i.e. $\int \psi_r \psi_s dv = 0$, $r \neq s$.

The wave functions ψ_r and ϕ are in real form, and are normalised;

$$\int \psi_r^2 \, dv = 1 = c_1^2 + c_2^2 + \ldots\ldots c_5^2.$$

β_{rs} = β (resonance integral for a C-C bond in benzene) where atoms r, s are joined by a bond, otherwise,

$\beta_{rs} = 0$.

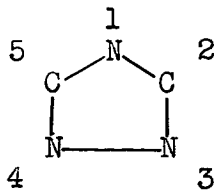
α_r = α (coulomb integral for a carbon atom in benzene) where r is a carbon atom;

$\alpha_r = \alpha + h\beta$ (h is the electronegativity parameter) where r is a nitrogen atom.

Following the advice of Dr. R. D. Brown, for neutral 1:2:4-triazole h has been assigned the value +1. To calculate the electron distribution in the anion α_C has again been assigned the value α, but for nitrogen the value $h = -2/3$ has been used. The value of α_C for C-methyl triazoles is considered in Section 3.

For 1:2:4-triazole or its anion the secular equations are:

$$c_1(\alpha + h\beta - E) + \beta(c_2 + c_5) = 0,$$
$$c_2(\alpha - E) + \beta(c_1 + c_3) = 0,$$
$$c_3(\alpha + h\beta - E) + \beta(c_2 + c_4) = 0,$$
$$c_4(\alpha + h\beta - E) + \beta(c_3 + c_5) = 0,$$
$$c_5(\alpha - E) + \beta(c_4 + c_1) = 0.$$



Putting $(\alpha - E)/\beta = y$, there are five values of y, and five sets of c_r which satisfy the secular equations. The six aromatic π-electrons will occupy in pairs the three molecular orbitals of lowest energy, i.e. these corresponding to the three lowest algebraic values of y.

1:2:4-TRIAZOLE (OR 3:5-DIMETHYL-1:2:4-TRIAZOLE-approx)

$h = +1.$

Solving for y in the secular equations,

$$(y^3 + 3y^2 - y - 5)(y^2 - 1) = 0.$$

The three lowest roots of these two equations are:

$$y = -2.675, -1.539, -1.000.$$

From each value of y, when substituted back into the secular equations, ratios of $c_1, \ldots c_5$ may be obtained; normalisation gives absolute values of c_r^2, and the total density of π-electrons at r is $2\Sigma c_r^2$.

	Values of c_r^2 —— Atom numbers:-				
y.	1.	2.	3.	4.	5.
-2.675	0.182	0.128	0.218	0.218	0.128
-1.539	0.5465	0.040	0.187	0.187	0.040
-1.000	0.000	0.250	0.250	0.250	0.250
Electron density:	1.457	0.836	1.436	1.436	0.836

1:2:4-TRIAZOLE ANION $h = -2/3$.

From the secular equations:

$$(9y^3 - 3y^2 - 29y)(3y^2 - 5y - 3) = 0.$$

The three lowest roots are:

$$y = -1.636, -0.468, 0.000.$$

	Values of c_r^2 — Atom numbers:-				
y.	1.	2.	3.	4.	5.
-1.636	0.191	0.253	0.151	0.151	0.253
-0.468	0.000	0.410	0.090	0.090	0.410
0.000	0.310	0.034	0.310	0.310	0.034
Electron density:	1.002	1.394	1.102	1.102	1.394

Appendix B.

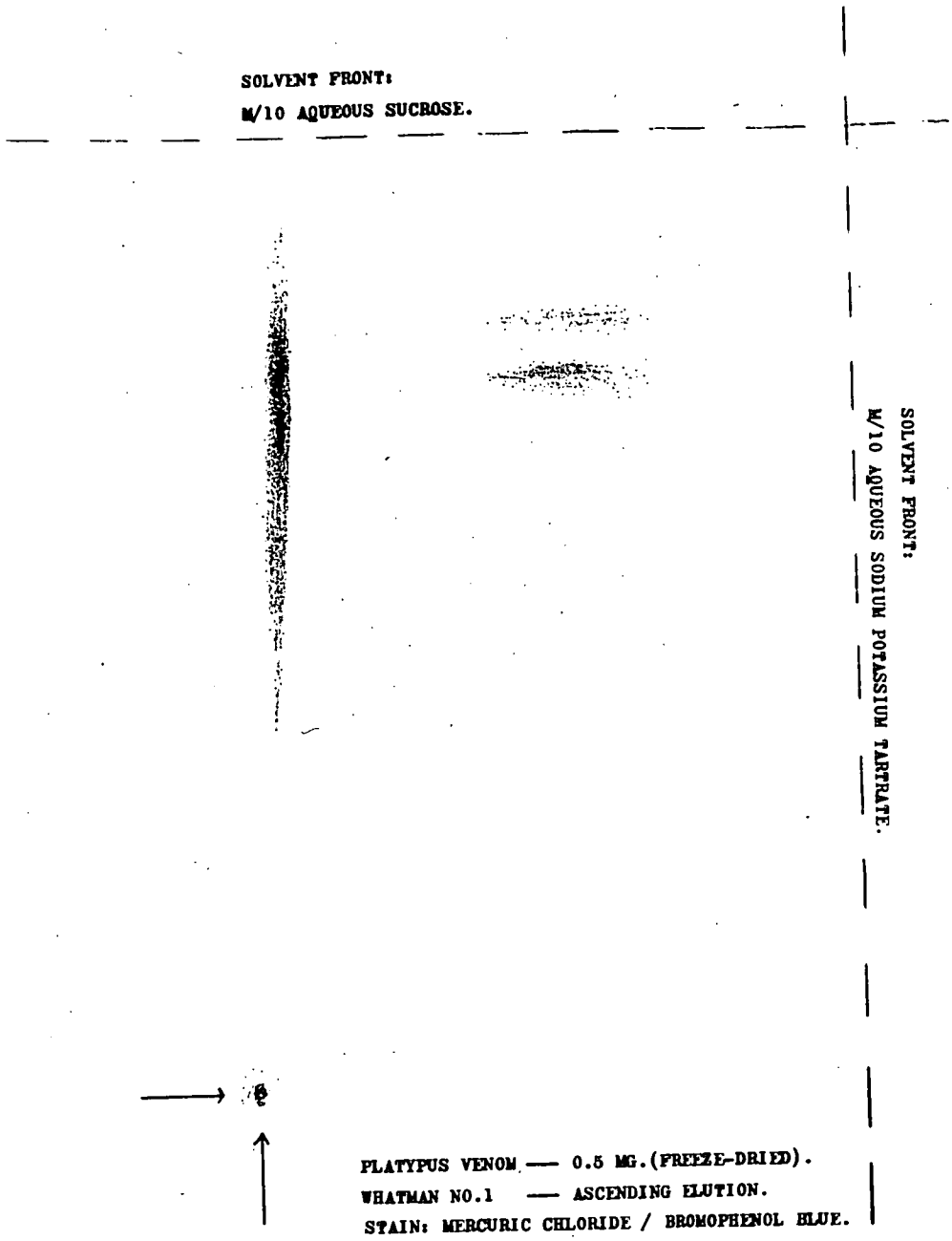
The Venom of the Platypus.

Historical: It was known for well over a century that the hind legs of the platypus bore canalised spurs through which venom, generated in the crural glands, could be ejected. Martin and Tidswell (50) in 1894 obtained some of the material which was precipitated on adding ethanol to expressed venom. The action of protein precipitants and colour reagents suggested to these authors that platypus venom contained proteins. From physiological examinations it seemed that similarities to viperine venoms existed. Kellaway (51) in 1935 examined whole venom aspirated from the ducts of a freshly killed adult Platypus. He also examined some of Martin and Tidswell's forty-year-old material. From a number of physiological experiments he concluded that the venom had haemolytic and cytolitic activity and caused a marked fall of blood pressure through peripheral vasodilation. The weakly viperine characteristics were again emphasized.

It seemed desirable to investigate the nature of platypus venom further, and in particular to attempt fractionation by electrophoresis or paper chromatography. Earlier reports that the proportion of males to females

was very low were confirmed, and we have not, in fact, been able to secure a sexually mature male Platypus in the period since this investigation was started. Two freshly killed young Platypus were kindly made available by the Salmon and Fresh Waters Fisheries Commission of Tasmania. The combined weight of the crural glands of the smaller specimen was 105 mg., the gland being composed of very firm tissue from which no liquid could be expressed. The larger specimen (combined weight of glands: 350 mg.) provided some water soluble material. The glands were frozen, crushed and extracted with water (5 cc.). The residue was centrifuged and extracted with aqueous sodium chloride (10%, 5 cc.). The first extract was freeze-dried, leaving amorphous tan material (13 mg.) which gave standard protein colour reactions. 0.5 mg. of this material was eluted on Whatman No. 1 paper with M/10 aqueous sucrose in the first dimension and with M/10 aqueous potassium sodium tartrate, in the second dimension. This empirical protein fractionation of Franklin, Quastel and Van Straten [52] was used since these authors had fractionated a number of snake venoms, providing comparison material for this examination. The pattern obtained (Figure 15) from platypus venom closely resembles those obtained from cobra and Russel

COPY OF PATTERN OBTAINED ON FRACTIONATION OF VENOM. Figure 15.



viper venom. The two components mobile in both dimensions might have similarities to the corresponding mobile components of the snake venoms. Staining was with mercuric chloride-bromophenol blue.

In the absence of facilities for physiological investigation of the venom fractions, small amounts (0.5 mg. in 50 mg. water of the aqueous extract) were injected into the leg muscles of frogs. Even at this low dose a significant increase in the rate of buccal inhalation took place. Control frogs which were injected with an equal volume of water did not show this effect, which is considered to be a consequence of the fall of blood pressure due to peripheral vasodilation which has been reported by Kellaway.

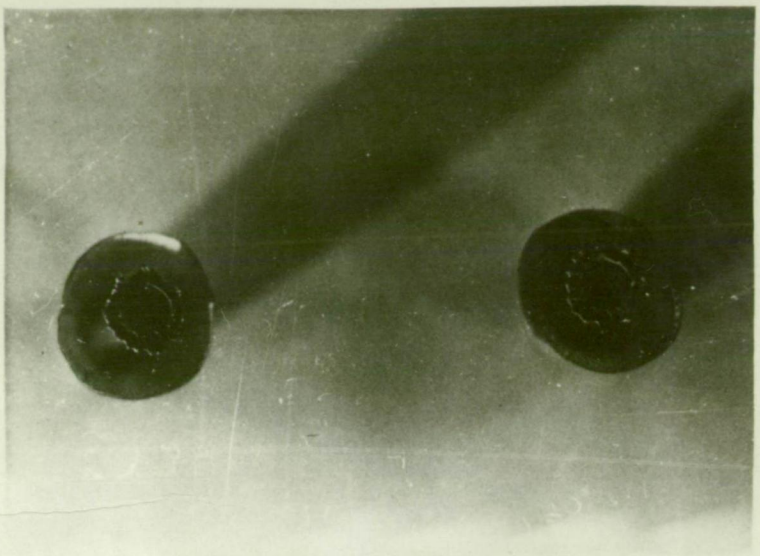
On dialysis of a portion of the water extract or saline extract in a collodion bag against distilled water, a dialysate was obtained which contained material giving a blue colour with mercuric chloride-bromophenol blue. It is thought that the dialysable components might correspond to the mobile components on the chromatogram. Dialysable components of bee and viper venoms have been demonstrated (53) and are considered to be low molecular weight protein. In view of the very small amounts of material available the investigation has been deferred

until larger supplies can be obtained from a mature animal, when it is hoped that electrophoretic separation of the venom components will be possible. The distinct toxic effects of the venom might be shown to be associated with individual components or combinations of these components.

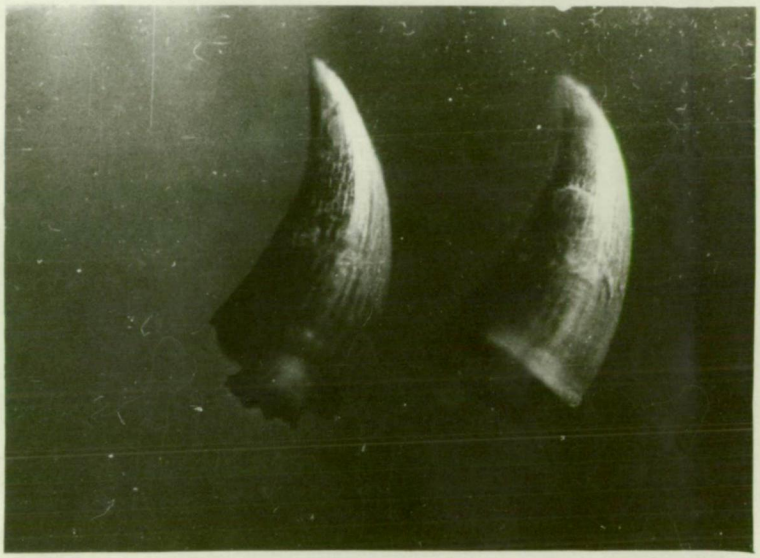
A problem of morphology has been encountered in this investigation which may have some phylogenetic significance. On examination of platypus spurs it was found that a central, canalized spur was covered by a horny conical process. In the smaller specimen obtained this cover was firmly attached at its apex to the spur which it surrounded (Figure *16*), while in the fully grown but sexually immature specimen the cover was not attached to the inner spur at the apex, and was only lightly held by a fold of tissue at the base. In the smaller animal the cover was imperforate and in the larger specimen it was perforated by an irregular opening which had apparently been formed by wear, and which had no direct contact with the venom canal. It is suggested that this cover is shed at maturity, and that possible regrowth and periodic "moulting" of the cover might explain the reported seasonal variation in the toxicity of the venom. Unless the cover was absent it seems unlikely that a wound

Figure 16.

A.



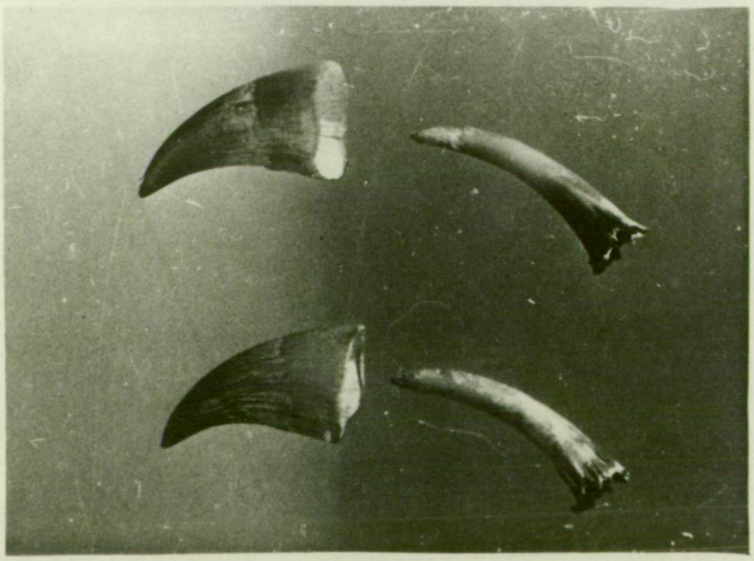
B.



A, B:
JUVENILE SPURS.

C: SPURS OF OLDER PLATYPUS.

C.



inflicted by the spur would be envenomed.

If a seasonal moulting of this spur cover was established it would provide an analogy with the moulting of the spur cover in many birds. This analogy would compare in significance with the better known similarity of Monotremes and birds in laying eggs.

Valued discussion with Professor V. V. Hickman, Head of the Zoology department at the University of Tasmania is gratefully acknowledged in connection with this section of the work.

SUMMARY.

Amidrazones may be conveniently prepared from imino-ethers and hydrazines. Cyclization to a hydroxy-triazole with ethyl chloroformate serves to prove the structure of an amidrazone. 1:2:4-Triazoles of known structure are available from amidrazones by the action of acylating agents. Formation of mixtures of triazoles in the reaction of amides and hydrazides reduces the value of this reaction in structural proofs.

Diacylamines react with hydrazines to form 1:2:4-triazoles. The unsymmetrical diacylamines investigated gave only one of the two possible triazoles when they reacted with substituted hydrazines. The orientation of the product may be predicted from the relative inductive and electromeric effects of the portions of the diacyl-amine, the portion related to the stronger acid providing the group which appears in position 3- of the triazole. Cyclization is thought to take place through an acyl-amidrazone structure.

Substitution of triazoles by diazoalkanes and of triazolates by alkyl iodides takes place predominantly at $N_{1(2)}$. A number of modes of acetylation lead to only one acetyl derivative. The orientation of substitution is consistent with that predictable from calculated

electron distributions.

Aromatic and heterocyclic acids react with aminoguanidine in strongly acid media to give the corresponding aminotriazoles. A sulphonic acid promotes the formation of benzamide phenylhydrazone from phenylhydrazine and benzonitrile.

The ultraviolet absorption spectra of a number of substituted triazoles have been studied, and an attempt has been made to explain some uniformities observed.

Platypus venom was found to contain dialyzable peptides.

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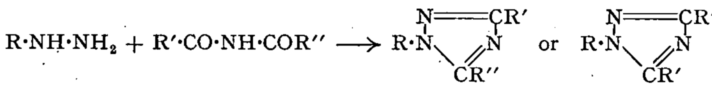
657. *Triazoles. Part I. Unsymmetrical Einhorn–Brunner and Related Pellizzari Reactions.*

By M. R. ATKINSON and J. B. POLYA.

Reactions of phenylhydrazine with *N*-formylbenzamide, *N*-acetylbenzamide, and *N*-acetylpropionamide in the presence of acid catalysts result in the formation of single triazoles, the substituent derived from the stronger acid related to the diacylamine appearing in the 3-position. The new compounds 3-ethyl-5-methyl-1-phenyl- and 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole were obtained, the former through the Pellizzari reaction and the latter through both the Pellizzari and the Einhorn–Brunner reaction, in addition to new compounds (not triazoles) of unknown structure.

CONDENSATION of a hydrazine with a diacylamine as in (1) (R, R′, and R″ = H, alkyl, aryl, etc.), to afford substituted 1 : 2 : 4-triazoles, may be termed the Einhorn–Brunner



(1)

reaction (Einhorn and Szelinsky, *Annalen*, 1905, **343**, 229; Brunner, *Ber.*, 1914, **47**, 2671; *Monatsh.*, 1915, **36**, 509). If R′ and R″ are different, the reaction is said to be unsymmetrical and could lead to two isomeric triazoles. The only recorded synthesis of this kind is that of 1 : 5-diphenyl-1 : 2 : 4-triazole from phenylhydrazine and *N*-formylbenzamide in aqueous acetic acid (Einhorn and Szelinsky, *loc. cit.*; Thompson, *J. Amer. Chem. Soc.*, 1951, **73**, 5914). A variation of this synthesis, and reactions of *N*-acetylpropionamide and *N*-acetylbenzamide with phenylhydrazine, are summarized in the Table.

Reaction of unsymmetrical diacylamines with equimolar amounts of phenylhydrazine in the presence of acid.

R′·CO·NH·COR″					Substituents in 1 : 2 : 4-triazoles					
R′	R″	Ph·NH·NH$_2$	Solvent	Time (hours)	1	3	5	Yield (%)	By-products and yields (%)	
Me	Et	Base	AcOH–NaOAc	16	Ph	Me	Et	45—48		
Me	Et	Hydro-chloride	do. +H$_2$O	16	Ph	Me	Et	48		
Me	Et	,,	Pyridine	4	Ph	Me	Et	65	Ph·NH·NHAc	18
Me	Ph	,,	AcOH–NaOAc	10	Ph	Me	Ph	78		
Me	Ph	,,	Pyridine	4	Ph	Me	Ph	35	$C_{28}H_{31}O_4N_5$	?
Me	Ph	,,	Pyridine–H$_2$O	5	—	—	—	0	NH_4Cl	36
									Ph·NH·NH·COPh	19
H	Ph	,,	Pyridine	4 [a]	Ph	H	Ph	52		
H	Ph	Base	30% AcOH	1	Ph	H	Ph	84 [b]		

[a] Main yield in few minutes. [b] Thompson, *loc. cit.*

Careful investigation failed to reveal the presence of more than one triazole in any reaction mixture and the same reactants afforded the same triazole irrespective of the composition of the solvent–catalyst system. The reactions investigated up to the present are not ambiguous and the substituent derived from the stronger acid related to the diacylamine appears in the 3-position of the resulting triazole. Further work is in progress to check the validity of these findings in general. A detailed discussion of the mechanism of the Einhorn–Brunner reaction will be presented in another communication but the following principles may be stated at present.

The participation of diacylamines in the reaction as *N*-acylimidic acid, R′·CO·N:C(OH)·R″, or a related structural form, was postulated by Brunner (*loc. cit.*) and made probable by other evidence (Titherley and Stubbs, *J.*, 1914, **105**, 299; Polya and Spotswood, *Rec. Trav. chim.*, 1949, **68**, 573; 1951, **70**, 146). The reaction takes place in

(*b*) Freshly crystallized phenylhydrazine hydrochloride (7·3 g.), *N*-acetylpropionamide (7·3 g.), glacial acetic acid (1·5 g.), and hydrated sodium acetate (3·5 g.) were refluxed in water (80 c.c.) for 16 hours at initial and final pH 5. The resulting mixture of aqueous phase and oil was treated with 5% mercuric chloride solution, with stirring at 60°, until no further precipitation occurred. Recrystallization from water afforded the mercuric chloride adduct of 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole, m. p. 148—152° (14·3 g., 62%); it had m. p. 156° on further recrystallization from 1 : 1 ethanol–ether (Found : C, 29·2; H, 2·9; N, 8·6. Calc. for $C_{11}H_{11}N_3,HgCl_2$: C, 28·8; H, 2·8; N, 9·2%). The adduct was dissolved in cold 4N-hydrochloric acid (100 c.c.) and extracted with ether. The extract was discarded and the acid solution treated with hydrogen sulphide, neutralized to pH 5 with ammonia, and precipitated with sodium carbonate. Ether-extraction of the precipitate and filtrate afforded 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole, b. p. 281—282/760 mm., d_{20}^{20} 1·075, n_D^{20} 1·5450 (4·5 g., 77% recovery from the adduct, 48% overall); this gave a picrate, yellow rhombs, m. p. 139—140·5°, and a hydrochloride, m. p. 205—206°, which did not depress the m. p.s of those prepared from 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole obtained by Gastaldi's method (*loc. cit.*).

(*c*) Phenylhydrazine (base), *N*-acetylpropionamide, glacial acetic acid, and anhydrous sodium acetate (each 0·1 mole) were heated on the water-bath for 16 hours and worked up as in (*b*), to afford the same triazole, b. p. 151—155°/9—12 mm. (8·3—8·5 g., 45—48%), as shown by the identity of picrates, hydrochlorides, and mercuric chloride adducts.

2-Phenyl-1-propionylhydrazine and Acetamide.—2-Phenyl-1-propionylhydrazine (3·7 g.) and acetamide (10 g.) were heated at 175° for 9 hours. Much acetonitrile was formed, no triazole could be isolated, and the hydrazine was recovered in a yield of 96%. 2-Phenyl-1-propionylhydrazine (180 g.) and dry, freshly distilled acetamide (60 g.) were heated at 60° for 14 hours; the temperature was raised slowly to 210° and kept thereat for 6 hours while volatile products distilled off. The residual viscous oil was fractionated, giving acetamide, b. p. 108—109°/15 mm. (33 g.), the triazole, b. p. 152—162°/12 mm. (20 g.), and 2-phenyl-1-propionylhydrazine, b. p. 164°/12 mm., m. p. 158—159° (85 g.). The triazole, refractionated, gave a mixture, b. p. 92—110°/2 mm., of acetamide and triazole (1·5 g.), *3-ethyl-5-methyl-1-phenyl-1 : 2 : 4-triazole* (16 g., 17% on unrecovered 1-propionyl-2-phenylhydrazine or 21% on unrecovered acetamide), b. p. 116—118°/2 mm., and a fraction, b. p. 120—134°/2 mm., contaminated with 2-phenyl-1-propionylhydrazine. The pure triazole (Found : C, 70·7; H, 6·9; N, 21·9. $C_{11}H_{13}N_3$ requires C, 70·6; H, 6·9; N, 22·5%) had b. p. 278°/755 mm., d_{20}^{20} 1·058, n_D^{20} 1·5505. When evaporated with excess of hydrochloric acid and dried *in vacuo* on porous plate over solid potassium hydroxide the triazole affords the hydrochloride, m. p. 208—210°, decomp. 220°. The mercuric chloride adduct crystallizes from 50% ethanol in colourless needles, m. p. 138—140°. The picrate, formed in ethanol solution without warming, consists of yellow, monoclinic prisms, m. p. 138—140°; on further recrystallizations from 1 : 2 chloroform–ethanol and then from 90% ethanol, it had m. p. 141—142°; it depressed the m. p. of picrates of 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole prepared by the Gastaldi or the Einhorn–Brunner method (7—8° for approximately 1 : 1 mixtures). The different crystal forms of the picrates of the closely similar isomeric triazoles in this case may be used for their rapid identification.

Phenylhydrazine and N-*Formylbenzamide.*—Phenylhydrazine hydrochloride (14·5 g.) and *N*-formylbenzamide (14·7 g.) in pyridine (50 c.c.) were refluxed for 4 hours although most of the reaction is completed in about 15 minutes, as judged by the volume of oil separating in the reaction. On cooling, prismatic needles of 1 : 5-diphenyl-1 : 2 : 4-triazole, m. p. 89—90°, were obtained (11·5 g., 52%), raised to 90—90·5° after recrystallization from light petroleum (b. p. 60—80°) (Found : C, 76·1; H, 5·1; N, 18·5. Calc. for $C_{14}H_{11}N_3$: C, 76·0; H, 5·0; N, 19·0%). The triazole, its picrate, m. p. 142—143°, and mercuric chloride adduct, m. p. 126—128° (from 80% ethanol), were identical with 1 : 5-diphenyl-1 : 2 : 4-triazole (Young, *J.*, 1895, **67**, 1063) and its derivatives.

1-Formyl-2-phenylhydrazine and Benzamide.—1-Formyl-2-phenylhydrazine (27·2 g.) and benzamide (25 g.) were heated to 220° for 4 hours, volatile products being allowed to distil off during the reaction (4 g.). The mixture was then poured into 10% potassium hydroxide solution (200 c.c.) and extracted with ether (3 × 50 c.c.), the extract evaporated, and the residue fractionated, giving 1-phenyl-1 : 2 : 4-triazole (2·0 g., 7%), b. p. 144—148°/10 mm.; the picrate had m. p. 156—158° alone or mixed with that of the triazole prepared by Pellizzari and Ferro's method (*Gazzetta*, 1898, **28**, II, 541). A second fraction (1·7 g., 4%), b. p. 158—160°/4 mm., m. p. 60—70° (after sublimation, m. p. 85—90°), was 1 : 5-diphenyl-1 : 2 : 4-triazole; neither this nor its picrate (m. p. 136—138°) depressed the m. p. of authentic material (Young, *loc. cit.*).

Phenylhydrazine and N-*Acetylbenzamide.*—(*a*) Phenylhydrazine hydrochloride (14·5 g.),

to afford oily crystals, m. p. 80—85°; it gave a *picrate*, flat prisms, m. p. 180—182°, which, recrystallized from ethanol, had m. p. 184—186° (Found: C, 54·6; H, 3·6; N, 17·0. $C_{21}H_{16}O_7N_6$ requires C, 54·3; H, 3·45; N, 18·1%). The substance and its derivative were not identical with the various samples of 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole and its picrate but identical with the 5-methyl-1 : 3-diphenyl-1 : 2 : 4-triazole (Jerchel and Kuhn, *loc. cit.*) and its picrate respectively. The triazole from the Pellizzari reaction is somewhat impure since its m. p. is lower than that of the triazole prepared according to Jerchel and Kuhn.

(*c*) 1-Benzoyl-2-phenylhydrazine (95 g.) and acetamide (50 g.) were heated at 260—280° for 3 hours, water and other volatile substances being allowed to distil off (40 g.). The residue was poured into 10% aqueous sodium hydroxide (250 c.c.), and the resulting mixture was extracted with ether (3 × 50 c.c.). The oil (85 g.) from the extract was fractionated, giving a forerun 110—120°/14 mm. (6·1 g.), 3 : 5-dimethyl-1-phenyl-1 : 2 : 4-triazole, b. p. 134—138°/3 mm., 118—124/2 mm. (27·6 g., 70% on unrecovered 1-benzoyl-2-phenylhydrazine) (picrate, m. p. 154—156°; mercuric chloride adduct, m. p. 186—189°), and 1-benzoyl-2-phenylhydrazine, b. p. 172—180°/2 mm., m. p. 167—168° (47 g.).

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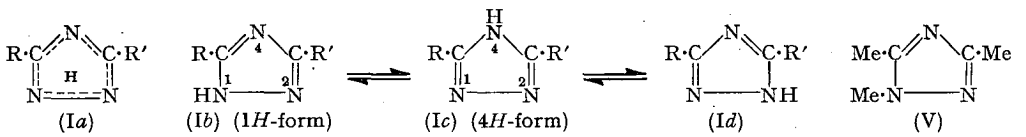
*Triazoles. Part II.** N-*Substitution of Some* 1 : 2 : 4-*Triazoles.*

By M. R. Atkinson and J. B. Polya.

[Reprint Order No. 4489.]

1 : 2 : 4-Triazole and its 3 : 5-dimethyl and 3 : 5-diphenyl derivatives have been methylated, ethylated, and acetylated by various methods. The orientation of the unstable acetyltriazoles could not be determined with certainty. Alkylation afforded mainly 1-alkyl-1 : 2 : 4-triazoles, the structures of which were established by alternative syntheses and comparison with known isomers. Some new triazole picrates have been prepared.

Like the analogous glyoxalines and pyrazoles, "acidic" triazoles (I; R = R′ = H, Alkyl, Aryl, etc.) which contain no *N*-substituent are obtained only in one form. This may be due to mesomerism (I*a*) or tautomerism (I*b*, *c*, *d*). Whichever representation is adopted, it appears probable that the acidic hydrogen will not be shared equally between the three nitrogen atoms. Alkylation of 1 : 2 : 4-triazole (II) (Pellizzari and Soldi, *Gazzetta*, 1905, **35**, I, 373) or 3 : 5-dimethyl- (III) or 3 : 5-diphenyl-1 : 2 : 4-triazole (IV) affords exclusively or mainly 1-alkyl-1 : 2 : 4-triazoles, that is, derivatives of (I*b* = I*d*). This suggests the uneven distribution of the acidic hydrogen between $N_{(1)}$ and $N_{(4)}$, without necessarily proving that the acidic hydrogen is more closely linked with either. More light may be thrown on this by a study of *N*-substitution of triazoles in which R and R′ are different which will be reported later.



(I*a*) (I*b*) (1*H*-form) (I*c*) (4*H*-form) (I*d*) (V)

R = R′ = H (II), Me (III), Ph (IV).

Methylhydrazine sulphate and diacetimide afford 1 : 3 : 5-trimethyl-1 : 2 : 4-triazole (V); under the mild conditions of the Einhorn–Brunner reaction (Part I *) rearrangement of methyl from $N_{(1)}$ to $N_{(4)}$ is unlikely. It was shown for (V) and all other 1 : 2 : 4-triazoles studied in this work that such rearrangements do not occur at higher temperatures and with longer reaction times than those applying in Einhorn–Brunner syntheses. Also the rearrangement of $N_{(4)}$-substituted 1 : 2 : 4-triazoles [*i.e.*, derivatives of (I*c*)] to $N_{(1)}$-substituted triazoles [*i.e.*, derivatives of (I*b*, *d*)] does not occur under such conditions. Methylation of 3 : 5-dimethyltriazole by diazomethane or by treatment of its sodium salt with methyl iodide affords (V) in good yield and free from the 3 : 4 : 5-trimethyl isomer (Meyer, G.P. 574,944; *Chem. Abs.*, 1933, **27**, 4541). Pure (V) with methyl iodide gives a very hygroscopic methiodide which is not obtained by reaction of equimolar amounts of methyl iodide and the sodium salt of the dimethyltriazole.

Ethylation of 3 : 5-dimethyl-1 : 2 : 4-triazole by diazoethane affords an ethyldimethyltriazole in almost quantitative yield. Treatment of the sodium salt with ethyl iodide affords the same main product with, in addition, a small quantity of an isomeric triazole. The latter is identified as 4-ethyl-3 : 5-dimethyl-1 : 2 : 4-triazole by its Pellizzari synthesis from acetylhydrazine and *N*-ethylacetamide. As the two compounds are not interconvertible by heating, the other must be the 1-ethyl isomer.

Methyl iodide and the sodium salt of 3 : 5-diphenyl-1 : 2 : 4-triazole afford 1-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole, the structure of which is established by an alternative synthesis from methylhydrazine sulphate and dibenzimide and by its difference from the

* Part I, *J.*, 1952, 3418.

1 : 2 : 4-Triazole (3·45 g.) was heated under reflux with acetic anhydride (6 c.c.) for 1 hr. The solvents were removed by distillation under atmospheric pressure; the fraction distilling at 178—180°/760 mm. set to colourless, triclinic crystals of *acetyl*-1 : 2 : 4-*triazole* (4·41 g., 79%), m. p. 38—39°, b. p. 178°/755 mm., which sublimes at 40°/2 mm. (Found: C, 44·5; H, 4·7; N, 37·5. $C_4H_5ON_3$ requires C, 43·2; H, 4·5; N, 37·8%). Only picric acid was precipitated when warm chloroform or benzene–carbon tetrachloride solutions of acetyltriazole and picric acid were mixed; the mother-liquor deposited 1 : 2 : 4-triazole picrate after a week.

Sodium (0·23 g.) was dissolved in ethanol (50 c.c.) and after addition of 1 : 2 : 4-triazole (0·69 g.) the solution was evaporated to dryness. The residue was covered with benzene (20 c.c.) and mixed with acetyl chloride (1 c.c.) in benzene (20 c.c.), and the suspension boiled under reflux with stirring for 30 min., then filtered. The residue was washed with benzene (30 c.c.), and the combined filtrate and washings were freed from solvent. The product was purified by distillation at 179—180°/760 mm. and crystallized from benzene–light petroleum (b. p. 40—60°) in triclinic crystals (0·21 g., 19%), m. p. 38—39° alone or on admixture with the former acetyltriazole.

Substitution of 3 : 5-*Dimethyl*-1 : 2 : 4-*triazole*.—(a) *Acetyl derivative*. 3 : 5-Dimethyl-1 : 2 : 4-triazole (2·0 g.) (Silberrad, *J.*, 1900, **77**, 1185) and acetic anhydride (4·0 c.c.) were boiled for 1 hr. under reflux, then the solvents were distilled off. The residue, sublimed at 70°/2 mm., gave colourless prisms of *acetyl*-3 : 5-*dimethyl*-1 : 2 : 4-*triazole* (2·41 g., 84%), m. p. 90—91°, b. p. 199°/760 mm. (Found: C, 51·9; H, 6·4; N, 30·9. $C_6H_9ON_3$ requires C, 51·8; H, 6·5; N, 30·2%).

3 : 5-Dimethyl-1 : 2 : 4-triazole (1·00 g.) was dissolved in a solution of potassium (0·39 g.) in methanol (10 c.c.). The potassium salt was precipitated with ether (200 c.c.), suspended in benzene (50 c.c.), and treated with acetyl chloride (0·80 g.) in benzene (25 c.c.) as in the preparation of acetyl-1 : 2 : 4-triazole. The product (0·86 g., 60%), purified by sublimation, had m. p. 89—91° alone and on admixture with the preceding sample. The picrates of the two materials were similarly proved to be identical.

Acetyldimethyltriazole (0·76 g.) and ethyl iodide (0·89 g.) were heated in a sealed tube with benzene (2 c.c.) at 100° for 6 hr. Removal of the solvent and sublimation of the residue gave unchanged acetyldimethyltriazole, m. p. 90° (0·71 g., 93%), identified as the picrate, m. p. 120°.

Diacetimide (10·1 g.) and acetylhydrazine (7·4 g.) were dissolved in a mixture of ethanol-free chloroform (100 c.c.) and dry pyridine (10 c.c.), and the solution was set aside at room temperature for a month. The solvent was removed by distillation and repeated evaporation with carbon tetrachloride. Sublimation of the residue at reduced pressure afforded acetamide (4·2 g., 78%), m. p. 78°. The less volatile portion, recrystallized from ether–*iso*propyl alcohol, gave *NN'*-diacetylhydrazine (9·1 g., 78%), m. p. 136° alone and on admixture with material prepared by Stollé's method (*Ber.*, 1899, **32**, 796). No dimethyltriazole or acetyldimethyltriazole could be detected.

Acetyldimethyltriazole (1·75 g.) was added to a slurry of lithium aluminium hydride (1·5 g.) in ether (50 c.c.), and the mixture was refluxed under nitrogen for 20 hr. After decomposition of the mixture with water, followed by 4N-sulphuric acid, the aqueous layer was extracted with chloroform (3 × 50 c.c.). Evaporation of the combined extracts left traces of an oil which gave no picrate. Extraction of the aqueous layer made alkaline with 10% sodium hydroxide gave similar results. Extraction of the residue, obtained on neutralization and concentration of the aqueous layer, with chloroform gave dimethyltriazole (0·84 g., 69%), m. p. and mixed m. p. 141—142°.

(b) *Methyl derivative*. Diacetimide (15·0 g.) and methylhydrazine sulphate (14·4 g.) were heated at 145° for 5 hr. Water (5 c.c.) was added, the solution boiled under reflux for another hour, and its pH adjusted to 5 with cold 2N-sodium carbonate and then to pH 8 with cold concentrated aqueous ammonia. Extraction with chloroform (3 × 80 c.c.) followed by the removal of the solvent and distillation of the residue at 193—195°/760 mm. left crude 1 : 3 : 5-*trimethyl*-1 : 2 : 4-*triazole* which was redistilled at 193°/755 mm. and 72—74°/11 mm. (6·3 g., 57%) and then had d_{20}^{20} 1·037, n_D^{20} 1·4652 (Found: C, 54·5; H, 8·3; N, 37·3. $C_5H_9N_3$ requires C, 54·0; H, 8·2; N, 37·8%).

A solution of trimethyltriazole (0·76 g.) and methyl iodide (3·4 g.) in benzene (20 c.c.) was boiled under reflux for 4 hr. and on cooling afforded very hygroscopic prisms of 1 : 3 : 5-*trimethyl*-1 : 2 : 4-*triazole methiodide*; dried at 75°/2 mm. and recrystallized twice from methanol–ether (1 : 2) they had m. p. 138° (Found: C, 27·5; H, 5·5; I, 50·2. $C_6H_{12}N_3I$ requires C, 28·5; H, 4·8; I, 50·1%). The hygroscopic nature of the substance no doubt accounts for

carbonate and extracted with benzene–ether (2 : 1; 4 × 25 c.c.). The extract was dried and evaporated. The residue, recrystallized from light petroleum (b. p. 60—80°), gave 1-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole (0·95 g., 40%), m. p. 85°, identical with the preceding preparation. Both preparations are clearly different from 4-methyl-3 : 5-diphenyl-1 : 2 : 4-triazole which has m. p. 242° (243° according to Scheuing and Walach).

All the triazole preparations were heated at 140—165° for 4—6 hr. without change of physical constants.

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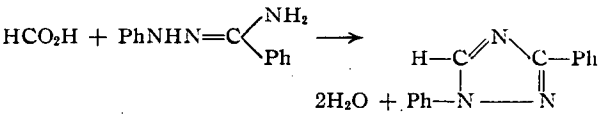
Synthesis of 1,3-Diphenyl-1,2,4-triazole

By M. R. Atkinson[1] and J. B. Polya

Received August 12, 1952

Einhorn, Bischkopff and Szelinski[2] reported the preparation of 1,3-diphenyl-1,2,4-triazole (I) from phenylhydrazine and N-formylbenzamide in 30% aqueous acetic acid. Thompson[3] showed that this reaction affords 1,5-diphenyl-1,2,4-triazole (II) identical with the preparations of Young[4] and Cleve.[5] We were able to confirm the work of Thompson and showed that II is obtained, although in inferior yield, when pyridine containing pyridinium hydrochloride is used instead of dilute acetic acid.[6]

It was necessary to synthesize I in order to assess the work of Einhorn and his collaborators as the physical data characterizing their triazole differ from those which apply to II by the agreement of other authors. The synthesis of I was accomplished by the method of Ponzio[7] which has been found useful in other triazole syntheses.[6,8] Benzamide phenylhydrazone heated with formic acid affords I in a yield of 36%. I, its hydrochloride and picrate differ from the corresponding products described by Einhorn and collaborators.



Experimental

Benzamide phenylhydrazone was prepared by the method of Voswinkel[9] and purified through its picrate, m.p. 196–198°. Benzamide phenylhydrazone (7.20 g.) was refluxed with 99% formic acid (8.0 ml.) on the water-bath for 90 minutes. The product was adjusted to *p*H 8 with aqueous 10% sodium carbonate and extracted with ether (3 × 50 ml.). Distillation of the dried ether extract between 160–220° (2 mm.) afforded oily crystals (4.5 g.) which were dissolved in dry ether (150 ml.) and treated with dry hydrogen chloride to precipitate the hydrochloride of I as a white, microcrystalline powder, m.p. 192–194° (Einhorn, *et al.*, 176°) in a yield of 5.73 g. *Anal.* Calcd. for $C_{14}H_{11}N_3 \cdot HCl$: Cl, 13.76. Found: Cl, 13.70.

The hydrochloride was decomposed with aqueous 10% sodium carbonate (100 ml.) and extracted with ether (3 × 50 ml.) to afford on removing the solvent colorless prismatic crystals of I, m.p. 79–81° (2.71 g., 36%). Purification through the picrate, yellow needles from ethanol, m.p. 161–161.5° (*Anal.* Calcd. for $C_{14}H_{11}N_3.C_6H_3O_7N_3$: C, 53.33; H, 3.11; N, 18.67. Found: C, 53.35; H, 3.24; N, 17.67) (Einhorn, *et al.*, 148°) and two recrystallizations from petroleum ether (60–80°) raised the m.p. to 82.5–83° (Einhorn, *et al.*, 96–97°).

Anal.[10] Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 76.34; H, 5.33; N, 19.18.

The triazole and its picrate depress the m.p.'s of authentic II and its picrate,[3] respectively.

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(10) Microanalyses by Dr. W. Zimmermann, Commonwealth Scientific and Industrial Research Organization, Melbourne.

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