

THE CHEMISTRY OF SOME FUSED
EIGHT-MEMBERED HETEROCYCLIC SYSTEMS

by

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Chapter 1

Introduction

It has been attempted in this thesis to compile information available in the literature on the synthesis of some eight-membered heterocyclic ring systems fused with one or two benzene rings (benzo- and dibenzo- respectively), having one nitrogen (azocines), two nitrogens (diazocines), and one nitrogen and one oxygen (oxazocines) in the ring system. Literature up to the end of 1978 has been covered.

While this work was in progress, a similar report appeared in *Rodd's Chemistry of Carbon Compounds*, Volume IV-K.¹ This review article covers the literature up to the end of 1972 only and does not include oxazocines.

With the growing interest in the pharmacological activity of medium rings, synthetic work in this area has seen a remarkable increase during the 1970's. Figures 1 and 2 show the distribution of publications during the period covered in this thesis, and it is evident that a large amount of work has been carried out after 1972. Synthetic work on dibenzodiazocines has been reported from the early 1880's, but only six publications appeared up to the end of 1920.

Relative positions of the hetero atoms and the ring fusion give rise to a number of structural isomers in each benzo- and dibenzo-system. The number of possible isomers and the number of isomers reported (to the end of 1978) in each case is given in Table 1. All the structural isomers of benz- and dibenzazocines are known, whereas those ring systems containing nitrogen and oxygen, oxazocines, are less well known and should provide a fertile area for future synthetic

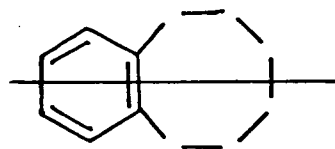
endeavours.

The calculation of the number of isomers possible for the benzo-fused eight-ring systems, was based on the following general equation:

$$\text{Total Number of Isomers} = \left(\frac{A-M}{2}\right) + M$$

where,

$$A = \frac{P!}{P_C! \cdot P_N! \cdot P_O!}$$



and M equals the number of arrangements in the ring in which 'mirror symmetry' is shown about the central horizontal line. Hence, for one nitrogen atom, $M = 0$, for two nitrogen atoms, $M = 3$ and for nitrogen and oxygen, $M = 0$. In the calculation of A , P is the number of possible replacement sites (6) in the eight-membered ring, while P_C , P_N and P_O are the numbers of carbon, nitrogen and oxygen atoms (if present) respectively.

The number of isomers for the dibenzo systems were worked out manually.

The nomenclature of all these ring systems is as given in *Chemical Abstracts*. The synthesis of each group is discussed separately in the following Chapters, and each Chapter is divided according to the methods employed to construct these ring systems. An attempt has been made to include not only the basic synthetic work, but also further functional group manipulations together with key pharmacological properties of the azocines, diazocines and oxazocines fused with one or two benzene rings.

Table 1

Type of compound		Number of possible isomers	Number of known isomers
Benz(o)	azocines	3	3
	diazocines	9	7
	oxazocines	15	7
Dibenz(o)	azocines	6	6
	diazocines	11	5
	oxazocines	16	8

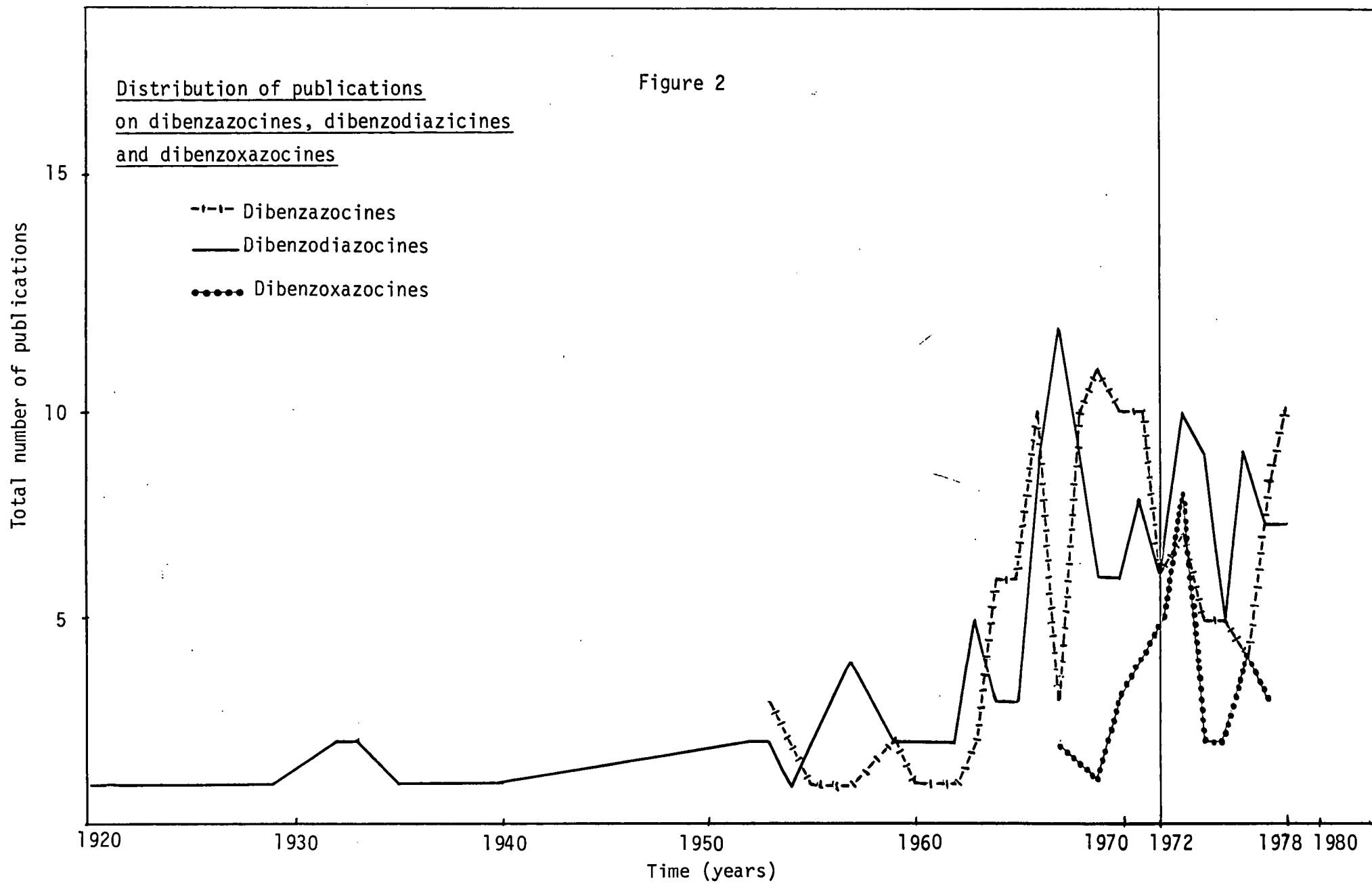
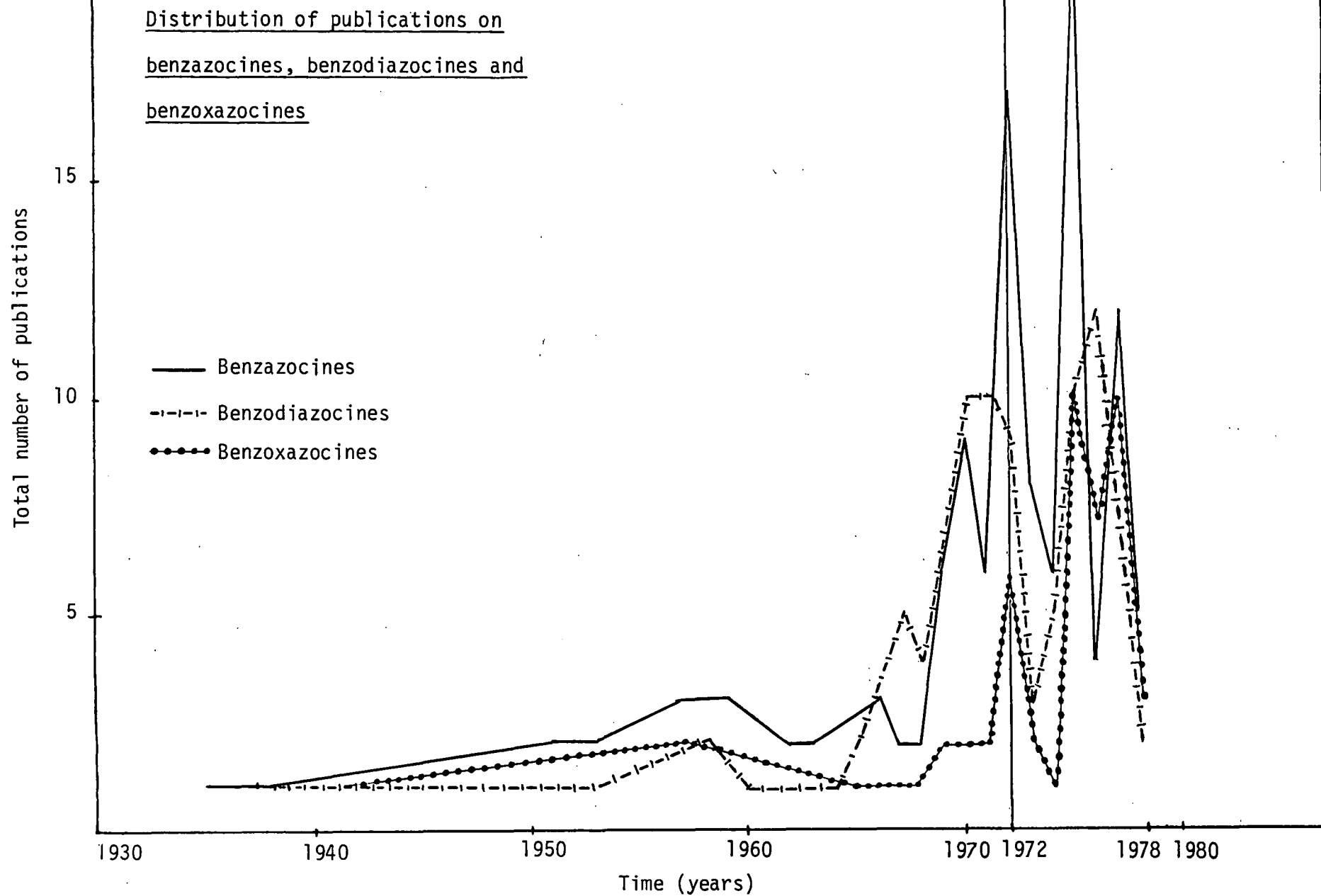


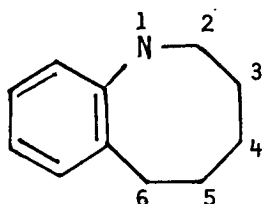
Figure 1



Chapter 2

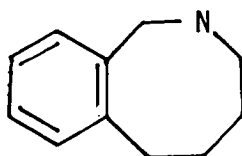
Benzazocines

All three structural isomers of benzazocines are known and the widely prepared isomer is the 1-benzazocine (Figure 3).



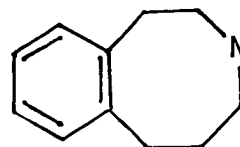
1-Benzazocine

(A)



2-benzazocine

(B)



3-benzazocine

(C)

Figure 3

Methods of Preparation

The construction of 1-, 2-, and 3-benzazocine derivatives can be divided into three major groups according to their methods of preparation. These are,

- (A) ring enlargements
- (B) ring closure, and
- (C) photocyclization.

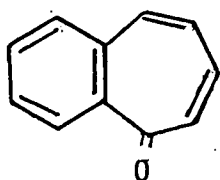
(A) Ring enlargements

The expansion of smaller rings to heterocyclic eight-membered rings has been achieved by,

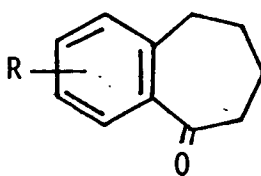
- (i) rearrangements
 - (ii) ring enlargement by cleavage of an internal C-C or C-N bond,
- and,
- (iii) addition followed by ring enlargement.

A(i) RearrangementsA(i) (a) Beckmann rearrangementA(i)a-(1) 1-Benzazocines

The Beckmann rearrangement is a widely used method for the synthesis of 1-benzazocines. In many cases the precursors are 7H-benzocycloheptene-5-one (1)^{2,3} or 5,6,7,8-tetrahydro-7H-benzocycloheptene-5-ones (2-9)⁴⁻¹⁵ (Table 2).



(1)

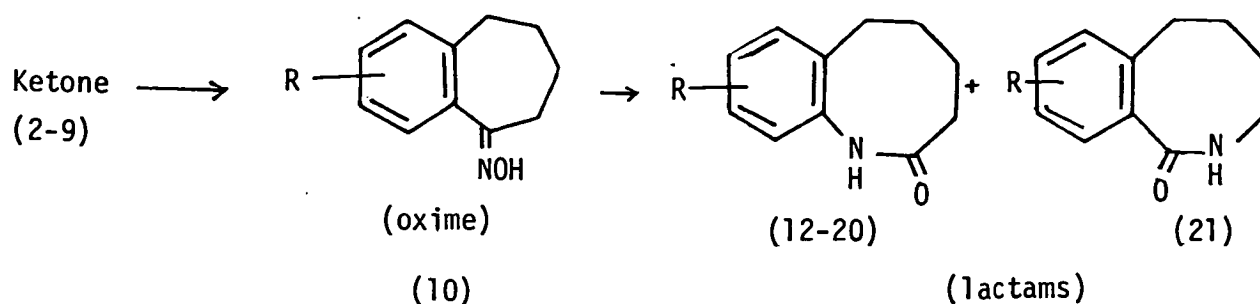


(2-9)

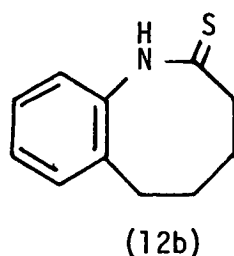
In theory, the Beckmann rearrangement of asymmetrical ketones can form a mixture of isomeric products, due to the concurrent alkyl and aryl migration. In addition, fragmentation of the oxime also may occur during the rearrangement. However, in the above cyclic ketones, formation of only one isomer was reported.

For example in the rearrangement of benzocycloheptanone oximes, only phenyl migration occurred rather than alkyl migration resulting in 1-benzazocine-2-ones.^{4,5} This was shown by hydrolysis of the lactams followed by diazotization and β -naphthol coupling.

The oximes (1) and (2-9) were rearranged in the presence of a suitable dehydrating agent such as polyphosphoric acid,⁴ phosphorus pentachloride or sulfuric acid^{6,7} to yield the corresponding 1-benzazocine-2-ones (12-20). The general reaction is illustrated in Scheme 1.



Scheme 1



Many substituted lactams were prepared in high yields by the Beckmann rearrangement. Then these lactams were converted into many other derivatives by reduction and alkylation.¹⁶ The 1-benzazocine-2-(1H)-thione (12b) was prepared by the reaction of (12a) and thioacetic acid.¹⁷ Attempts to prepare 10-substituted hexahydro-1-benzazocines were unsuccessful, however, but no explanation was given.⁶

The yields and conditions employed in the Beckmann rearrangement are given in Table 2.

A(i)a-(2) 2-Benzazocines

Unlike the 1-benzazocines, the application of the Beckmann rearrangement to the synthesis of 2-benzazocines is limited. The only case reported, by Huisgen and co-workers,¹¹ was the preparation of 2-(2,4,6-trinitro)-2-benzazocine-1(2H)one (25a) in 84% yield by the rearrangement of the *syn*-oxime (24) in dichloromethane. When the

Table 2

A(i)a-(1) 1-BenzazocinesBeckmann rearrangement

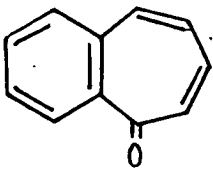
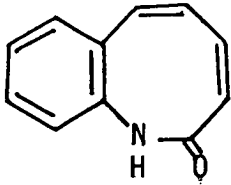
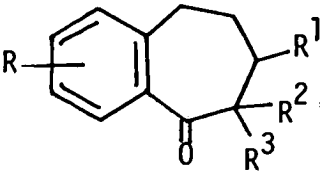
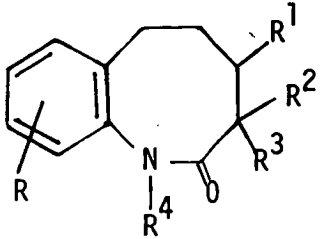
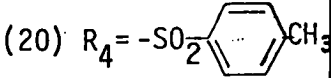
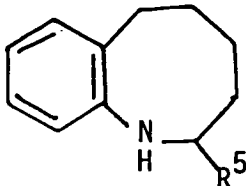
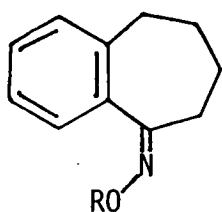
Starting material	Reaction conditions	Product(s)	Yield %	Ref.
 (1)	(i) NH_2OH /pyridine EtOH Δ , and (ii) $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$ 0° -room temperature	 (11)	68 59	2 3
 (2) $\text{R}=\text{R}^1=\text{R}^2=\text{R}^3=\text{H}$ (3) $\text{R}=6\text{-Cl}$ (4) $\text{R}=7\text{-Cl}$ (5) $\text{R}=8\text{-NO}_2$ (6) $\text{R}=8\text{-Cl}$	(i) $\left\{ \begin{array}{l} \text{NH}_2\text{OH}/\text{pyridine} \\ \text{EtOH and} \end{array} \right.$ (ii) $\left\{ \begin{array}{l} \text{H}_2\text{SO}_4/\text{glacial} \\ \text{acetic acid} \end{array} \right.$ (2:1) or $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$ ^{6,7}	 (12) $\text{R}=\text{R}^1=\text{R}^2=\text{R}^3=\text{R}^4=\text{H}$ (13) $\text{R}=7\text{-Cl}$ (14) $\text{R}=8\text{-Cl}$ (15) $\text{R}=9\text{-NO}_2$ (16) $\text{R}=9\text{-Cl}$	88 85 90 29 50	6,7 6
(7) $\text{R}^2=\text{R}^3=\text{CH}_3$ (8) $\text{R}^2+\text{R}^3=-(\text{CH}_2)_2-$ (9) $\text{R}^1=\text{C}_6\text{H}_5$	(i) $\left\{ \begin{array}{l} \text{NH}_2\text{OH}/\text{pyridine} \\ \text{EtOH, and} \end{array} \right.$ (ii) $\left\{ \begin{array}{l} \text{polyphosphoric} \\ \text{acid}^4 \text{ or } \text{PCl}_5^5 \end{array} \right.$ $\text{pyridine}/\text{HCl}$ and $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$	(17) $\text{R}^2=\text{R}^3=\text{CH}_3$ (18) $\text{R}^2+\text{R}^3=-(\text{CH}_2)_2-$ (19) $\text{R}^1=\text{C}_6\text{H}_5$	98 92	4
(10) (oxime)	(A) (1) acetone/pyridine picryl chloride (2) CH_2Cl_2 and	 (20) $\text{R}_4 = -\text{SO}_2-\text{C}_6\text{H}_4-\text{CH}_3$	80	9,10 11

Table 2 continued

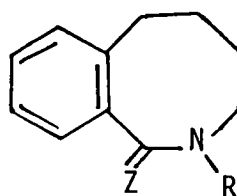
(10) (oxime)	(B) $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$ or $\text{CH}_3\text{SO}_2\text{Cl}$			
(10) (oxime)	$\text{LiAlH}_4/\text{AlCl}_3$ $\text{LiAlH}_4/\text{ether}$	(22) $\text{R}^5 = \text{SO}_2\text{-C}_6\text{H}_4\text{Cl-p}$ (23) $\text{R}^5 = \text{H}$	75 -	12 13-15

† when not specified, $\text{R}^n = \text{H}$ ($n=1,2,3,\dots$)

anti-oxime was used, the formation of a 1-benzazocine derivative was observed. Therefore the direction of the migration was determined by the configuration of the oxime as has been noted in other systems.²⁻⁶



(24)



- (25a) $\begin{cases} \text{Z}=\text{O} \\ \text{R}=2,4,6\text{-trinitro} \end{cases}$
 (25b) $\begin{cases} \text{Z}=\text{S} \\ \text{R}=\text{H} \end{cases}$

The reaction of (25a) with thioacetic acid, gave the 2-benzazocine-1-(2H)thione (25b).^{17,18}

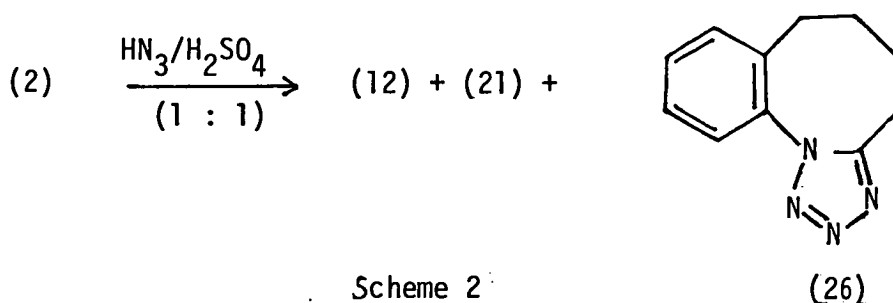
The preparation of 3-benzazocines by the Beckmann rearrangement has not been reported although this should provide a convenient route

to these systems.

A(i)b Schmidt reaction

A(i)b-(1) 1-Benzazocines

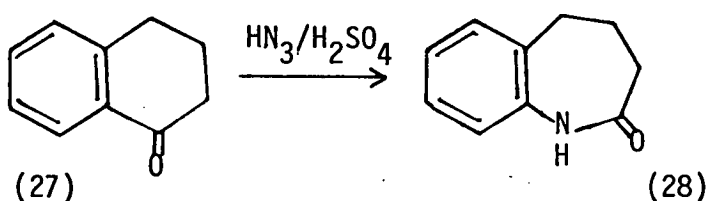
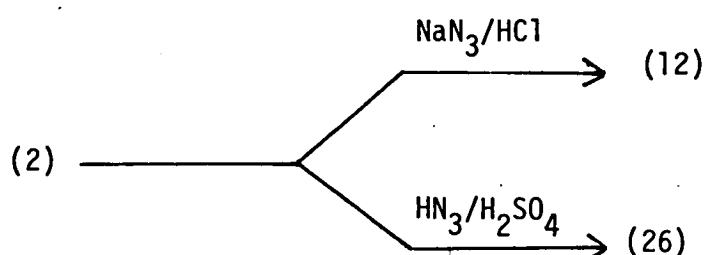
The Schmidt reaction has also been employed to synthesise various 1-benzazocine derivatives from benzocycloheptanones. When an appropriate cyclic ketone (2) was treated with a mixture of hydrazoic acid and sulfuric acid, it underwent both aryl and alkyl migration to produce a mixture of two isomeric products (12 and 21) respectively. Another side reaction, the formation of fused tetrazole, (26), may also occur (Scheme 2).



However, many workers^{19,20} have observed that the aryl migration in seven-membered bicyclic ketones is favoured over alkyl migration, resulting in a higher yield of 1-benzazocine derivatives. The reported alkyl migration of benzocycloheptanone was only 20%.¹⁹ It has been found when five- and six-membered benzo fused ketones having electron releasing substituents are subjected to the Schmidt reaction, the alkyl migration is greater than the aryl migration; conversely electron withdrawing substituents favour aryl migration. The use of trichloroacetic acid or polyphosphoric acid was also found to increase the aryl migration products. However these effects on the aryl migration was less with benzocycloheptanones, because of the flexibility

of the seven-membered ring.¹⁹

Huisgen²² has reported that under the more usual Schmidt reaction conditions, i.e. hydrazoic and sulfuric acid in benzene, 5,6,7,8-tetrahydro-7H-benzocycloheptene-5-one (2) gave the ring expanded tetrazole (26, R=H), whereas 1-tetralone (27) yielded the expected seven-membered lactam (28). Replacing the sulfuric acid with hydrochloric acid,²¹ the ketone (2) did yield the expected lactam (12).



Therefore it is evident from these contrasting results, that the Schmidt reaction is more sensitive than the Beckmann rearrangement to the conditions used, and that the former is less satisfactory as a preparative method.

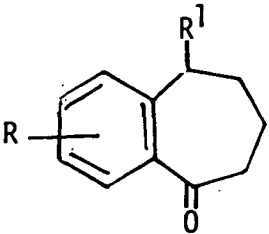
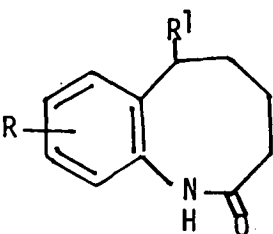
The synthesis of 1-benzazocines by the Schmidt reaction is shown in Table 3.

A(i)b-(2) 2-Benzazocines

A low yield (20%) of 2,4,5,6-tetrahydro-2-benzazocine-1-(2H)-one (21), (R=H) was obtained by the Schmidt reaction of the ketone (2).¹⁹ As described for 1-benzazocines, the major product was the lactam (12) which was formed by the aryl migration. Hence the Schmidt reaction is

Table 3

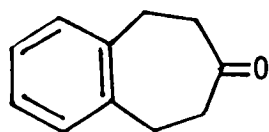
A(i)b-(1) 1-BenzazocinesSchmidt reaction

Starting material	Reaction conditions	Product(s)	Yield %	Ref.
 <p>(2) $R=R^1=H$</p> <p>(29) $R=7-OCH_3$</p>	<p>(A) H_2SO_4/NaN_3 60-64° or (B) molten CCl_3COOH NaN_3 or (C) $PPA/NaN_3$¹⁸ or (D) NaN_3/methanesulphonic acid¹⁹ or (E) HCl/NaN_3, below 8°C^{20,22} or (F) $CHCl_3/HN_3/H_2SO_4$²¹</p>	 <p>(12) $R=R^1=H$</p> <p>(31) $R=8-OCH_3$</p>	<p>80-82</p> <p>80</p>	<p>9,19-21 23</p> <p>19</p>
<p>(30) $R=7,8-(OCH_3)_2$ $R^1=pCl \cdot C_6H_4-$</p>	<p>NaN_3/H_2SO_4</p>	<p>(12) + (26)</p> <p>(32) $\begin{cases} R=8,9-(OCH_3)_2 \\ R^1=C_6H_4 \cdot Cl \cdot p \end{cases}$</p>	<p>-</p> <p>-</p>	<p>22,24</p> <p>25</p>

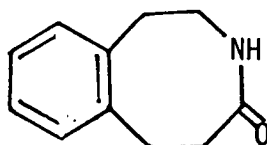
not suitable for the preparation of 2-benzazocine derivatives.

A(i)b-(3) 3-Benzazocines

The Schmidt reaction of 5,6,7,8-tetrahydro-7H-benzocycloheptene-7-one (33) gave the expected lactam (34) in 88% yield, on treatment with sodium azide and hydrochloric acid.^{6,21,26} The formation of isomeric products and tetrazoles or other side reactions were not reported.^{6,21}



(33)

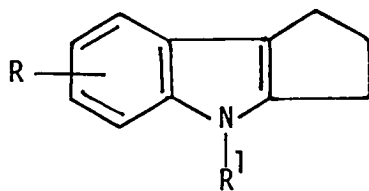


(34)

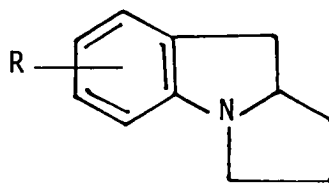
A(ii) Ring enlargement by cleavage of an internal C-C or C-N bond

A(ii)-(1) 1-Benzazocines

The ring enlargement of cyclopent[b]indoles (35-43) and pyrrolo-[1,2-a]-indoles (44-46) to 1-benzazocines is one of the most widely used methods.



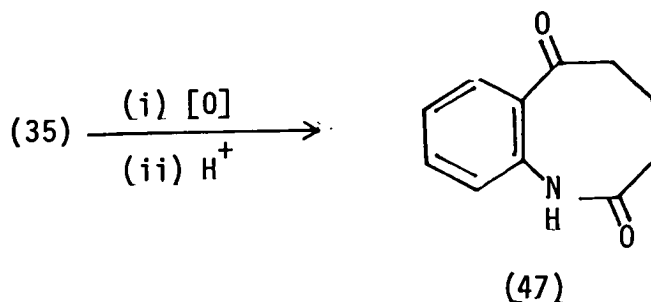
(35-43)



(44-46)

The oxidative cleavage of cyclopent[b]indoles by sodium periodate gave the 1-benzazocine-2,6-diones (47-55).²⁷⁻³⁴ (Table 4). This reaction proceeds through the formation of an intermediate hydroperoxide. The cyclopent[b]indoles are highly unstable in solution and undergo rapid auto-oxidation to give the final product (47), and the intermediate hydroperoxide was not isolable.²⁹ With higher analogues

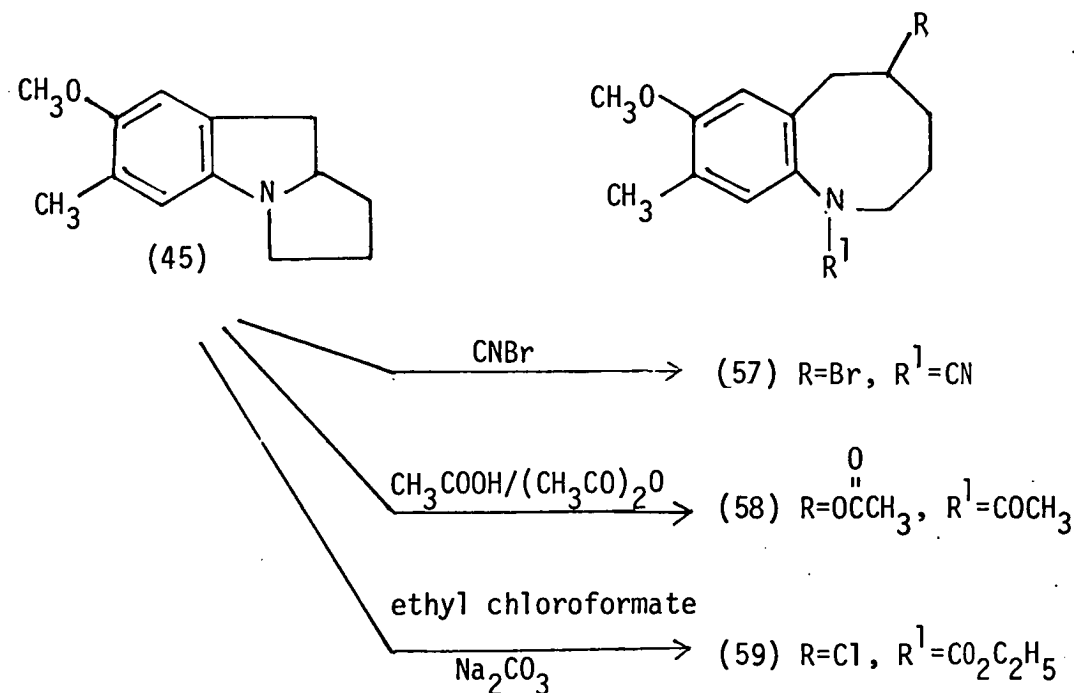
of cycloalkylindoles this intermediate can be isolated, and they form mixtures of ring expanded lactams together with highly oxygenated products which were not investigated further.



These 2,6-dione derivatives were converted into 6-hydroxy derivatives by the action of phenyl magnesium bromide followed by reduction with lithium aluminium hydride.³⁵⁻³⁷

The von Braun reaction of pyrrolo[1,2-a]indoles (44,46) gave the 1-benzazocine derivatives in moderate yields.³⁸⁻⁴² (Table 4).

Kametani and co-workers⁴¹ have reported an alternative transformation of the pyrrolo[1,2-a]indole (45) into 1-benzazocines (57-59) in good yields using ethyl chloroformate and sodium carbonate or acetic anhydride and acetic acid. (Scheme 3).



Scheme-3

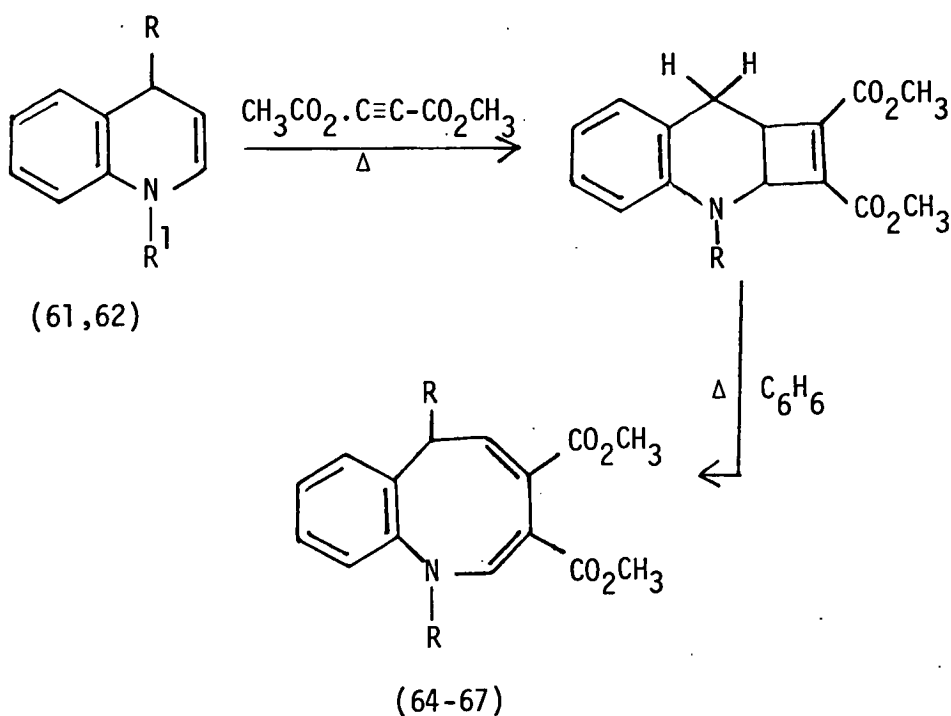
The ring enlargements of cyclopent[b]indoles and pyrrolo[1,2-a]indoles are summarized in Table 4.

A(iii) - Addition followed by ring enlargement

A(iii)-(1) 1-Benzazocines

In recent years dimethylacetylenedicarboxylate (DMAD) has been used in the synthesis of medium size ring carbocycles and heterocycles. The cycloaddition of DMAD to cyclic enamines forms a fused cyclobutene system, which may undergo step-wise thermal ring expansion to yield the corresponding ring diene.

To synthesise 1-benzazocines, quinoline derivatives (61-63) were used as the cyclic enamines.⁴³⁻⁴⁵ The construction of the 1-benzazocines involved formation of an intermediate which underwent thermal electrocyclic ring opening. The cyclo-addition and ring expansion⁴³ of cyclic enamines (61,62) (Table 4) is shown in Scheme 4.



Scheme 4

Table 4

A(ii)-(1) 1-BenzazocinesRing enlargement by cleavage of an internal bond

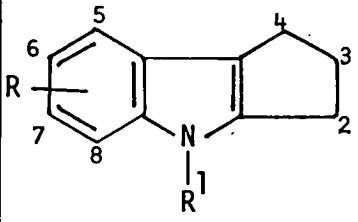
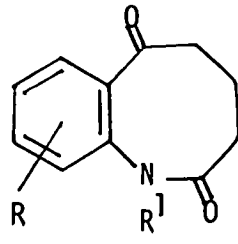
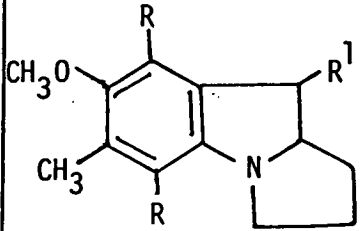
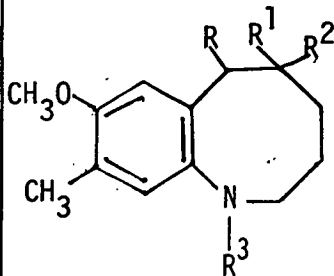
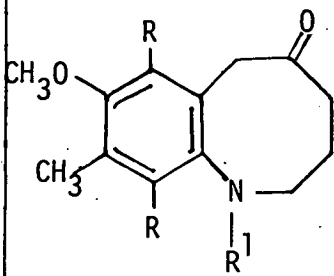
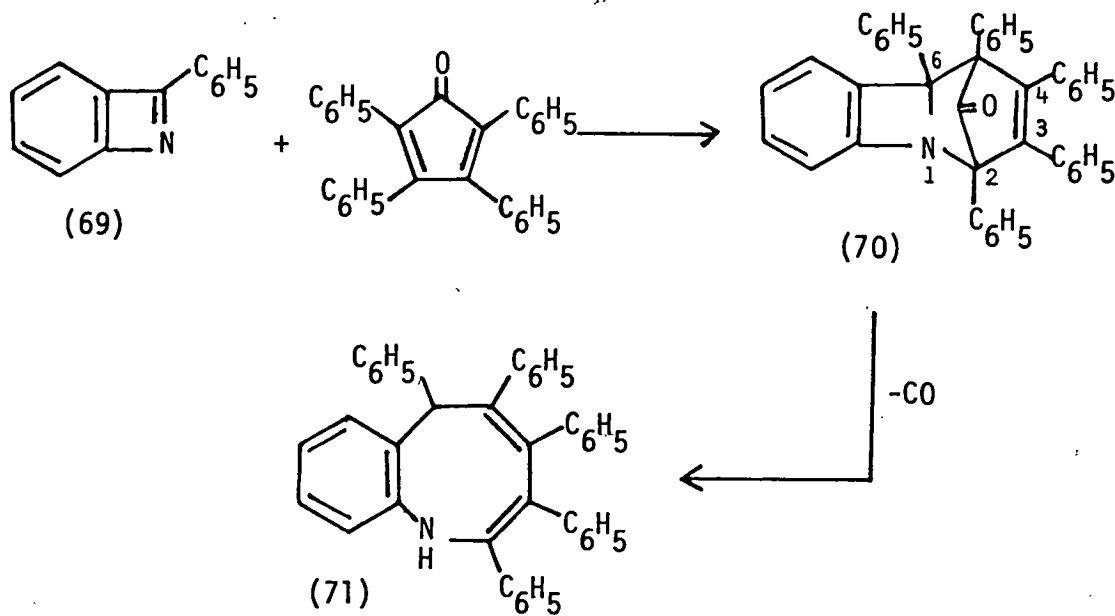
Starting materials	Reaction conditions	Product(s)	Yield %	Ref.
				
(35) $R=R^1=H$	$NaIO_4$ in CH_3OH/H_2O	(47) $R=R^1=H$	-	27-30
(35)	$PtO_2/CH_3CO_2C_2H_5/O_2$	(47)	-	29
(35)	(i) $CHCl_3-C_2H_5OH/H_2O$ (ii) $KOH \Delta$	(47) HCl salt	-	31
(36) $R=6-isopropyl$	$\left\{ \begin{array}{l} NaIO_4 \text{ in} \\ CH_3OH-H_2O \end{array} \right.$	(48) $R=8-isopropyl$	-	30
(37) $R=6-OCH_2C_6H_5$		(49) $R=8-OCH_2C_6H_5$	-	30
(38) $R=5-C_6H_5$		(50) $R=7-C_6H_5$	-	30
(39) $R=6-C_6H_5$		(51) $R=8-C_6H_5$	-	30
(40) $R=7-C_6H_5$		(52) $R=9-C_6H_5$	-	30
(41) $R=6-C_2H_5$		(53) $R=8-C_2H_5$	-	32
(42) $\left\{ \begin{array}{l} R=6-Cl \\ R^1=CH_2CONH_2 \end{array} \right.$	CH_3COOH/O_3	(54) $\left\{ \begin{array}{l} R=8-Cl, \\ R^1=CH_2CONH_2 \end{array} \right.$	-	33

Table 4 continued

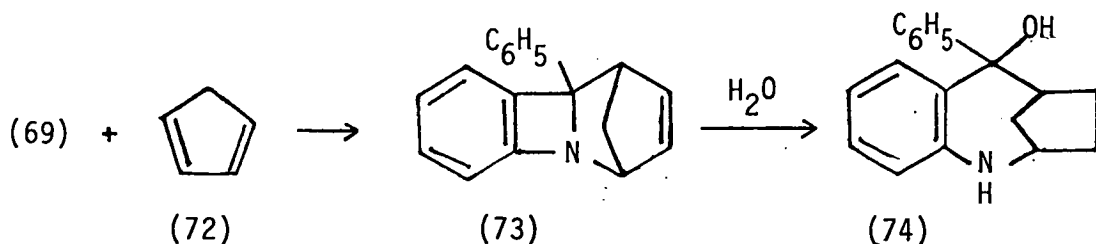
<p>(43) $\begin{cases} R=6,7,8-(OCH_3)_2 \\ R^1=CH_2C_6H_5 \end{cases}$</p>  <p>(44) $R^1=CH_3, R=H$ (45) $R^1=R=H$</p> <p>(45)</p> <p>(45)</p> <p>(46) $\begin{cases} R=OCOCH_3 \\ R^1=H \end{cases}$</p>	<p>$h\nu$-(200 w) halogen lamp, O_2, CH_3OH, CH_2Cl_2 25°</p> <p>$C_6H_6/BrCN/N_2$</p> <p>$CH_3COOH/(CH_3CO)_2O$</p> <p>ethyl chloroformate/ Na_2CO_3</p> <p>(i) trifluoro- acetic anhydride/ (ii) hydrolysis and (iii) oxidation</p>	<p>(55) $\begin{cases} R=8,9,10-(OCH_3)_3 \\ R^1=CH_2C_6H_5 \end{cases}$</p>  <p>$R \quad R^1 \quad R^2 \quad R^3$ (56) $CH_3 \quad H \quad Br \quad CN$ (57) $H \quad H \quad Br \quad CN$</p> <p>(58) $\begin{cases} R=R^1=H \\ R^2=O \parallel CCH_3 \\ R^3=COCH_3 \end{cases}$</p> <p>(59) $\begin{cases} R=R^1=H, R^2=Cl_2 \\ R^3=CO_2C_2H_5 \end{cases}$</p>  <p>(60) $\begin{cases} R=OCOCH_3 \\ R^1=COCF_3 \end{cases}$</p>	<p>82</p> <p>43</p> <p>40</p> <p>-</p> <p>-</p> <p>-</p>	<p>34</p> <p>38-40</p> <p>38</p> <p>41,42</p> <p>41</p> <p>42</p>
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Apart from this method, highly reactive and easily generated benzazetes were used to synthesise 1-benzazocines.^{46,47} The benzazete (69) also formed an initial adduct (70) with cyclopentadiene-ones, which underwent cleavage of the N-C₆ bond to form the corresponding 1-benzazocine derivative (71) (Scheme 5).



Scheme 5

The strain in the initial adduct (70) was relieved by the extrusion of carbon monoxide.⁴⁶ When cyclopentadiene (72) was reacted with 2-phenyl benzazete (69) it only gave an amino alcohol (74). In this case, the strain in the intermediate (73) was less than that in (68), and the amino alcohol (74) did not undergo further ring enlargement. (Scheme 6). Unlike cyclobutadiene, 2-phenylbenzazete does not react with DMAD, but does give conjugated addition products resulting from nucleophilic attack.⁴³



Scheme 6

The synthesis of 1-benzazocines by addition followed by ring enlargement is given in Table 5.

Table 5

A(iii)-(1) 1-Benzazocines

Addition followed by ring enlargement

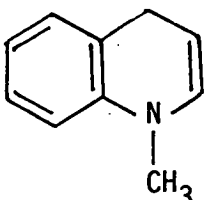
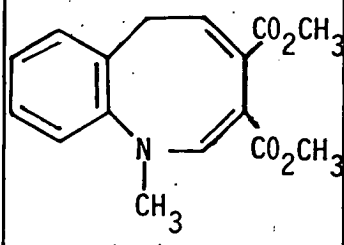
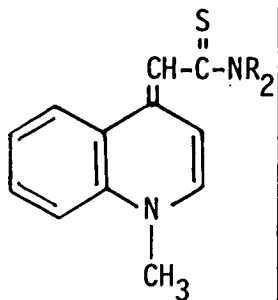
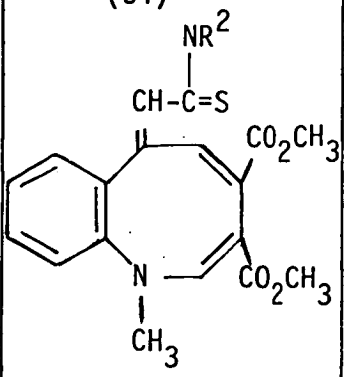
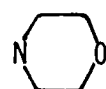
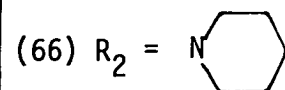
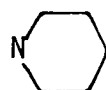
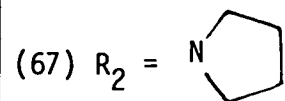
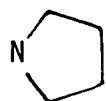
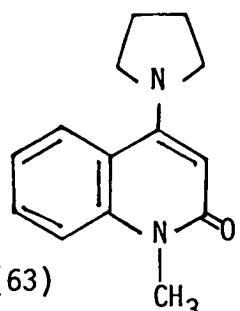
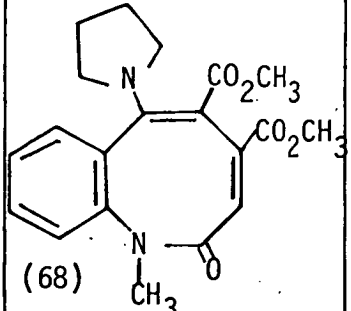
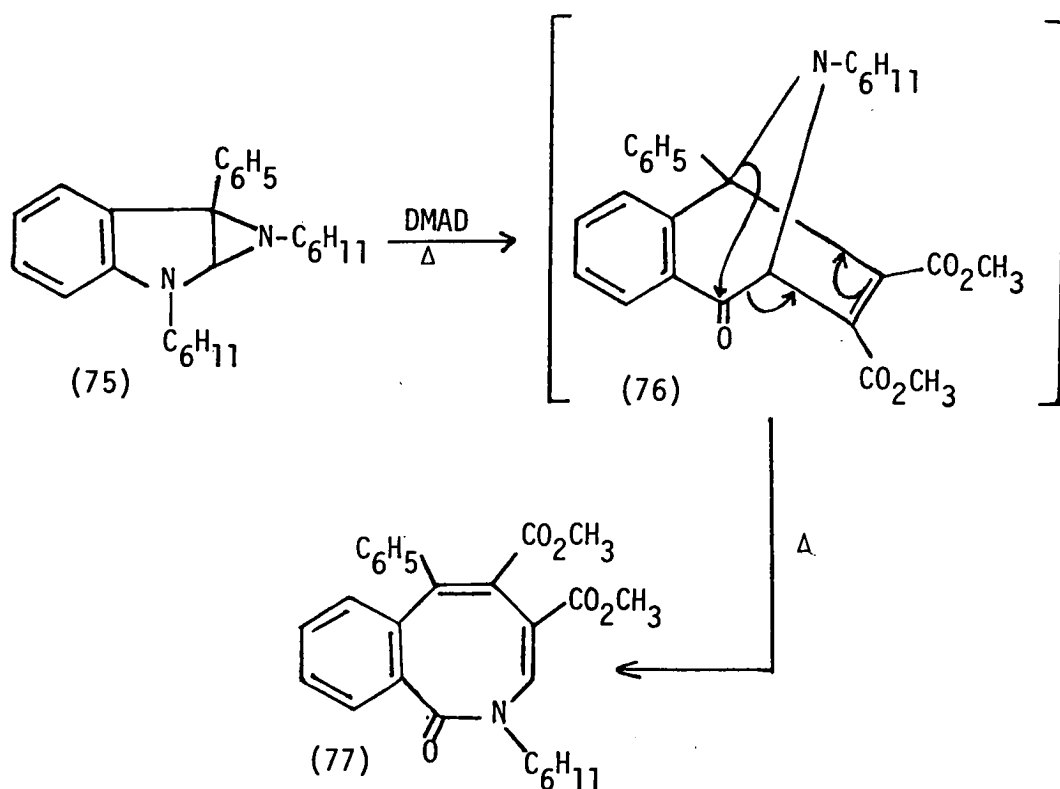
Starting material	Reaction conditions	Product(s)	Yield %	Ref.
 (61)	(i) DMAD $\text{CH}_2\text{CN}/\text{N}_2$ (ii) dry C_6H_6 reflux	 (64)	78	43
 (62)	DMAD in dioxane	 (65) $\text{R}_2 = $ 	55	44
		 (66) $\text{R}_2 = $ 	40	44
		 (67) $\text{R}_2 = $ 	45	44
 (63)	DMAD in dry C_6H_6 reflux	 (68)	58	45

Table 5 continued

<p>(69) + (71)</p>	CH_2Cl_2 -78°	<p>(71)</p>	<p>52 52</p>	<p>46 47</p>
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A(iii)-(2) 2-Benzazocines

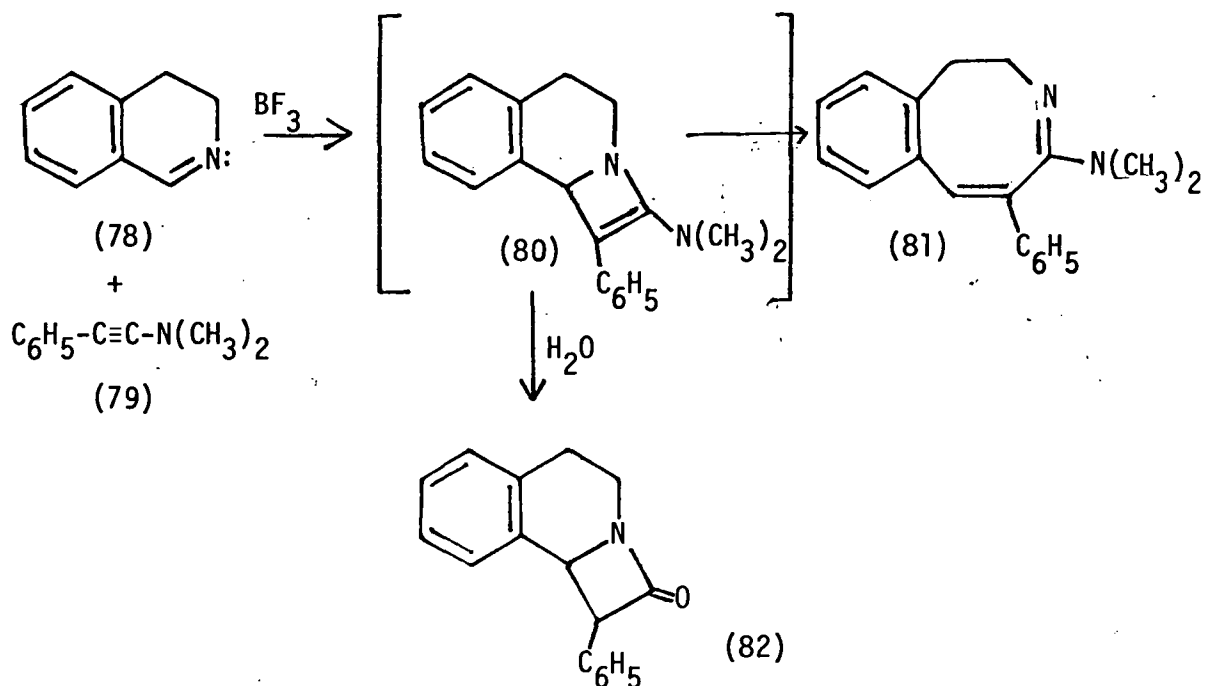
The cyclo-adduct (76), which was obtained by the reaction of (75) with dimethylacetylenedicarboxylate, underwent a novel rearrangement giving rise to 2-benzazocine (77).⁴⁸ The proposed electrocyclic reaction was given in Scheme 7.



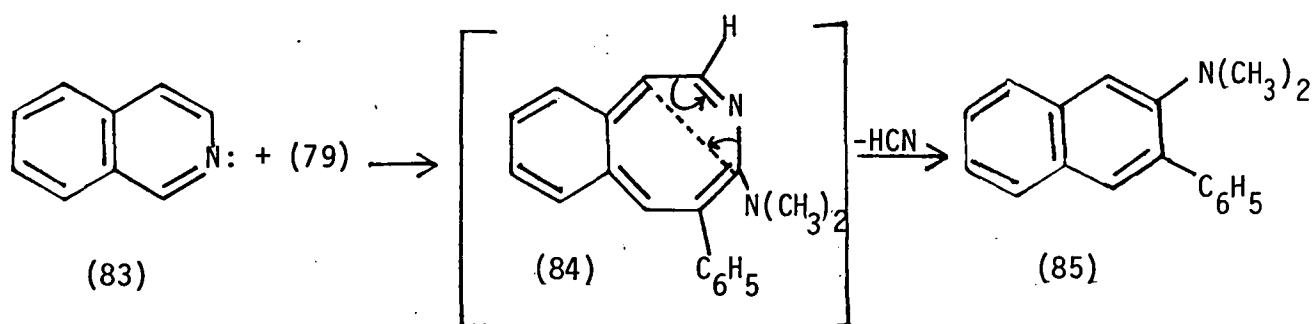
Scheme 7

A(iii)-(3) 3-Benzazocines

In the presence of boron trifluoride, the acetylene derivative (79) and 3,4-dihydroisoquinoline (78) gave the intermediate (80), which afforded the 3-benzazocine (81) in 75% yield. If water was added to the reaction mixture, the formation of lactam (82) was observed.⁴⁹

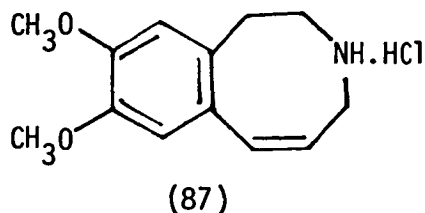
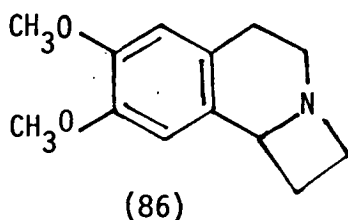


However the reaction of isoquinoline (83) and (79) gave 3-dimethylamino-2-phenylnaphthalene (85) as the only isolable product.⁴⁹ A possible pathway for this reaction is shown in Scheme 8.



Scheme 8

Treatment of 6,7-dimethoxy-1,4,5,9b-tetrahydro-2H-azeto[2-1a]-isoquinoline (86) with 15% hydrochloric acid afforded the tetrahydrobenzazocine derivative (87).⁵⁰

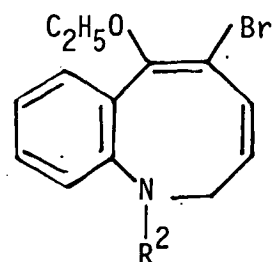
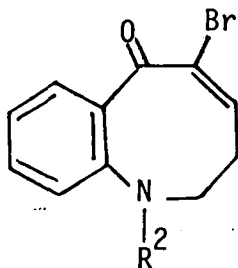
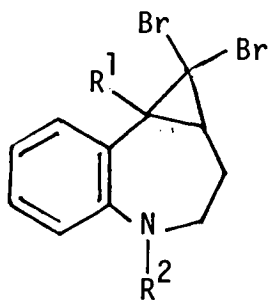


A(iv) Other ring enlargements

A(iv) 1-Benzazocines

A paper by Ross and Proctor⁵¹ described the synthesis of 1-benzazocines from the 1-benzazepine derivatives. This ring expansion was achieved in two ways. First the treatment of the dibromocyclopropane derivative (88) with ethanolic silver nitrate solution gave the benzazocine (89) in 50% yield. A higher yield (81%) of benzazocine (90) was obtained by the ring expansion of (88) in pyridine and water. With anhydrous pyridine, the yield of (90) was only 14%. This implies the assistance of water in the transfer of a proton from the intermediate alkyl cation to the base, pyridine.

Hydrolysis of (90) gave a 78% yield of 5-bromo-2,3-dihydro-1-p-tolylsulphonyl-1-benzazocine (89).

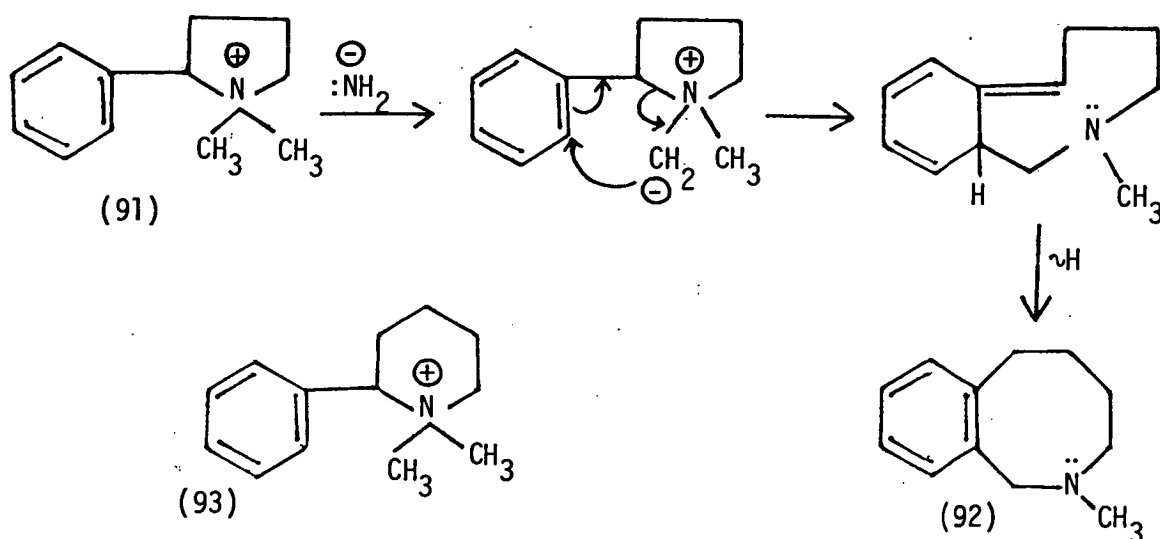


$R^2 = \text{tosyl group}$

A(iv)-(2) 2-Benzazocines

Ring expansion of the 1,1-dimethyl-2-phenylpyrrolidinium ion (91) in the presence of sodium amide in liquid ammonia afforded the tertiary amine (92) and a polymeric material in yields of 41 and 38% respectively.⁵²

The benzazocine (92) was a product of ortho substitution and rearrangement involving the expansion of a five-membered ring to an eight-membered ring. The polymeric material formed through the β -elimination reaction of the quaternary ammonium ion (91). It has been found that the rearrangement of six-membered quaternary ammonium



ion (93) occurred exclusively to form the corresponding nine-membered ring product. Hence the conformation of quaternary ammonium ion (91) appears to be less favourable for the rearrangement than that of (93).⁵² The structure of (92) was established by Hofmann degradation and spectral data.

(B) Ring closureB(i) C-C type

The synthesis of benzazocine derivatives has been achieved by ring closure with the formation of a C-C bond, of the types A to E, as

shown in the Figure 4.

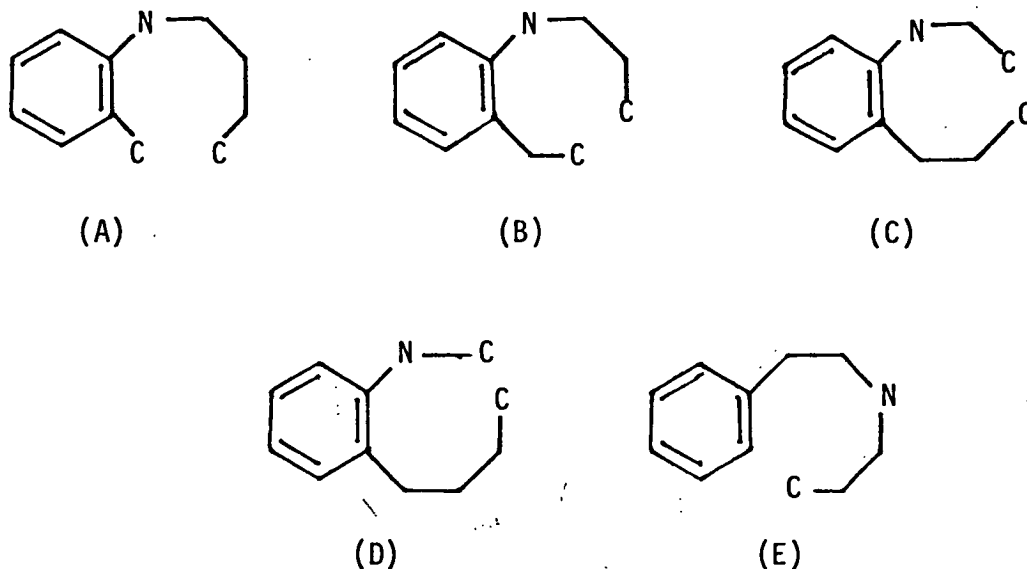


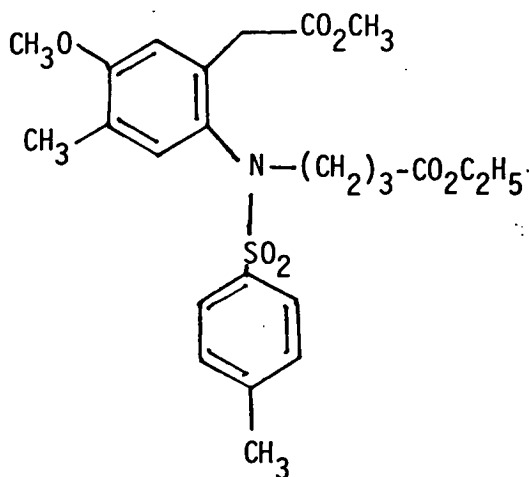
Figure 4

Ring closures of type A to D were employed to synthesise 1-benzazocines by Dieckmann cyclization of the appropriate esters. Ring closure of type E were used to synthesise 3-benzazocines by the Friedel-Crafts reaction and the intramolecular cyclizations with polyphosphoric acid. No synthesis of 2-benzazocines by C-C ring closure has been reported.

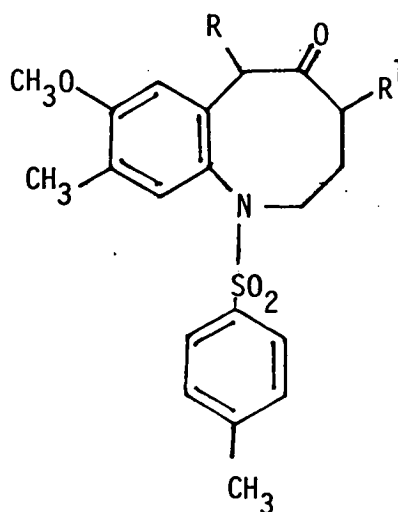
B(i)a Dieckmann cyclization

B(i)a-(1) 1-Benzazocines

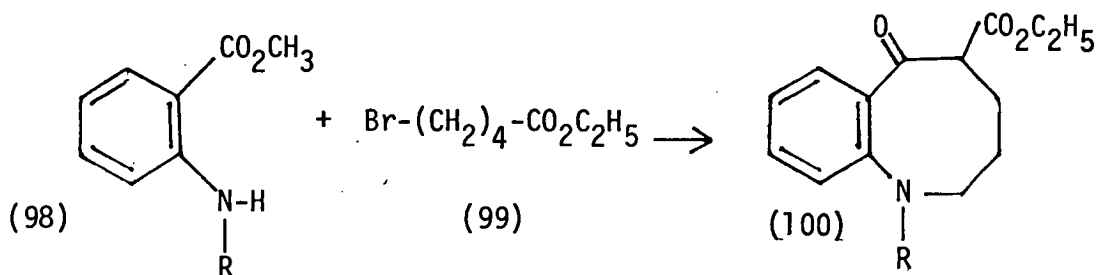
The direct cyclization of amino ester (94), in the presence of potassium *tert*-butoxide⁵³⁻⁵⁵ or sodium in liquid ammonia⁵⁶ gave 25% to 75% of (95) together with two other benzazocines (96,97), in trace amounts.



(94)

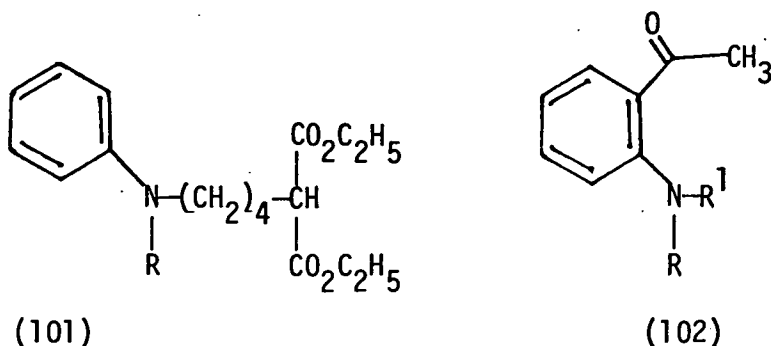
(95) $R=R^1=H$ (96) $R=CO_2CH_3$, $R^1=H$ (97) $R=H$, $R^1=CO_2C_2H_5$

The 1-benzazocine-6(5H)-one derivative (100) was obtained by the cyclization of (98) with (99) in anhydrous dimethylformamide containing sodium hydride.⁵⁷

 $R = \text{tosyl}$

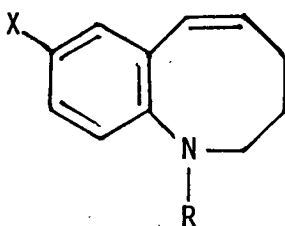
Attempts to prepare tetrahydro-1-benzazocine-5(6H)-ones (95), from diesters of type (94) with sodium hydride were unsuccessful because of the base catalysed elimination of the tosyl group.⁵⁷ This elimination was seen to operate only between carbon-nitrogen atoms already joined by a δ -bond. Suitable model compounds were prepared to explore this possibility. Thus the ester (101) and ketone (102) were treated with

various bases and in every case, the starting material was recovered.



R = tosyl

Several other derivatives were prepared from these benzazocines.⁵⁸⁻⁶⁵ In a series of patents, Okamoto and co-workers⁶⁶⁻⁷⁰ reported the conversion of 1,2,3,4-tetrahydro-1-benzazocine (103) into the N-substituted derivative (104), but the synthesis of (103) was not given.



(103) R=H, X=H or Cl

(104) R=COCH:CHC₆H₅, X=H or Cl

B(i)b Friedel-Crafts reaction

B(i)b-(1) 3-Benzazocines

The Friedel-Crafts reaction of various substituted glycol chlorides (105-107, 111) has been employed to prepare 3-benzazocine derivatives. The cyclization occurred smoothly and in fair yields in the presence of anhydrous aluminium chloride at room temperature.⁷¹⁻⁷⁵ At higher temperatures the recorded yields were poor and at -10° no reaction was observed.^{74,75} Comer and co-workers⁷³ found that the

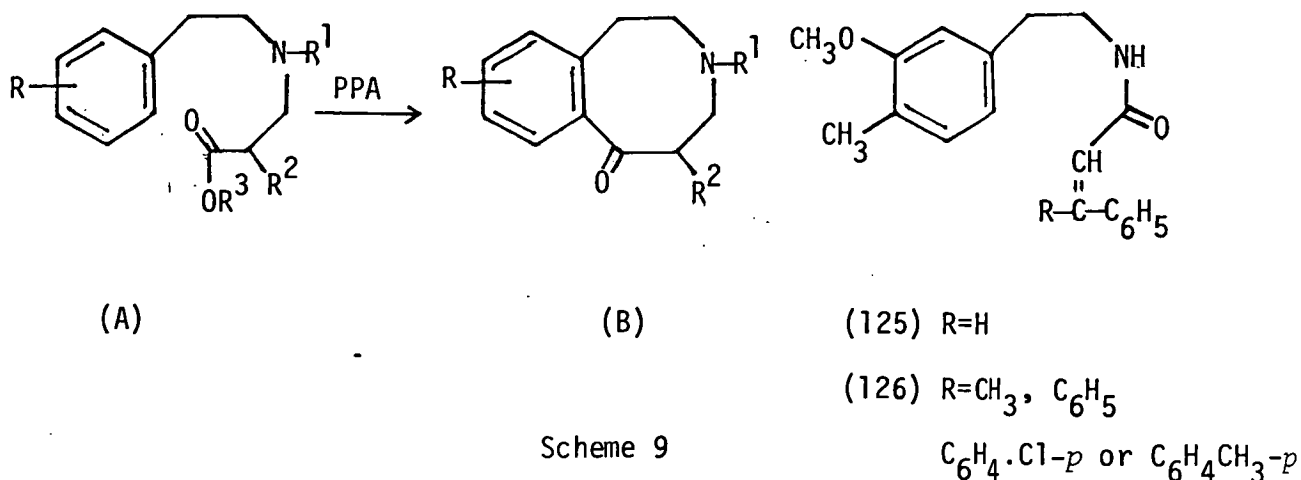
prolonged reaction of glycyll chlorides with excess aluminium chloride resulted in the selective cleavage of the 9-methoxy group. Therefore the formation of the final product mainly depends upon the temperature of the reaction.

The 3-benzazocines obtained by the intramolecular Friedel-Crafts reaction are summarized in Table 6.

B(i)c Other C-C type ring closures

B(i)c-(1) 3 Benzazocines

This method is closely related to the Friedel-Crafts cyclization of glycyll chlorides, but the cyclodehydration was carried out in the presence of polyphosphoric acid (PPA) instead of aluminium chloride. The general reaction is given in Scheme 9.



In the presence of phosphorus oxychloride, the amide (125) did not undergo the expected cyclodehydration giving rise to a heterocyclic ring system. However, the polyphosphoric acid, the compound (125) did yield the 3-benzazocine derivative (128) (Table 6) in 25% yield.⁹¹

In the case of amides of type (126), (R¹=H), the cyclodehydration with phosphorus oxychloride resulted in the formation of the corresponding 1-styryl-3,4-dihydroisoquinoline derivatives.⁹¹ Unlike aluminium

Table 6

B(i)b-(1) 3-Benzazocines

Friedel-Crafts reaction

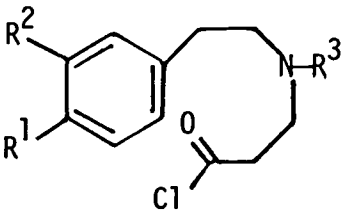
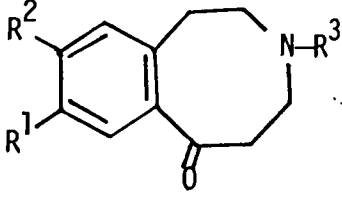
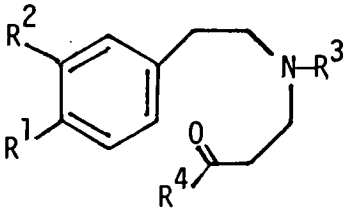
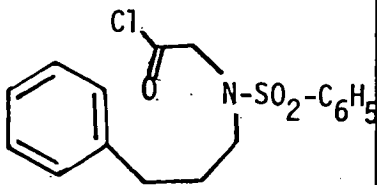
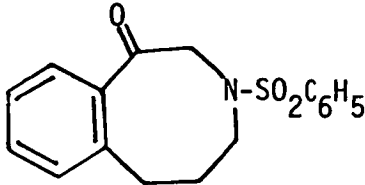
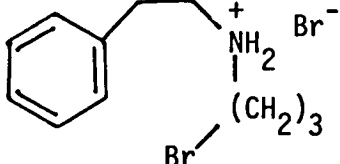
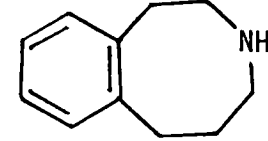
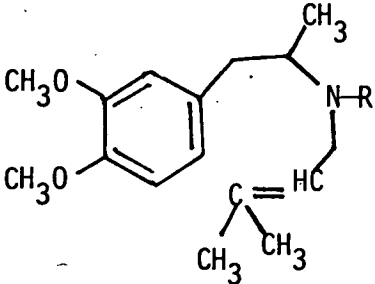
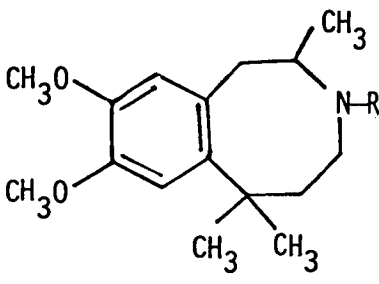
Starting materials	reaction conditions	Products	Yield %	Ref.
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 <p>(108) $\begin{cases} R^1=R^2=OCH_3, \\ R^4=H \\ R^3=COC_6H_5 \end{cases}$</p> <p>(109) $\begin{cases} R^1=R^2=OCH_3, \\ R^4=H \\ R^3=SO_2C_6H_5 \end{cases}$</p> <p>(110) $\begin{cases} R^1=R^2=OCH_3, \\ R^4=CH_3 \\ R^3=COC_6H_5 \end{cases}$</p>	<p>$AlCl_3$</p> <p>$AlCl_3$</p> <p>$AlCl_3$</p>	<p>(118) $\begin{cases} R^1=R^2=OCH_3, R^4=H \\ R^3=COC_6H_5 \end{cases}$</p> <p>(119) $\begin{cases} R^1=R^2=OCH_3, R^4=H \\ R^3=SO_2C_6H_5 \end{cases}$</p> <p>(120) $\begin{cases} R^1=R^2=OCH_3, R^4=CH_3 \\ R^3=COC_6H_5 \end{cases}$</p>	-	67
			-	73
			-	73

Table 6 continued

 <p>(111)</p>	$\text{AlCl}_3\text{-CH}_2\text{Cl}_2$ 15° to room temperature	 <p>(121)</p>	36	74
 <p>(112)</p>	AlCl_3 room temperature	 <p>*(122)</p>	50	75
 <p>(113) $\text{R}=\text{COC}_6\text{H}_5$</p>	$\text{BF}_3/\text{H}_2\text{SO}_4$	 <p>(123) $\text{R}=\text{COC}_6\text{H}_5$</p>	-	76
<p>(114) $\text{R}=\text{CH}_2\text{C}_6\text{H}_5$</p>	$\text{BF}_3/\text{H}_2\text{SO}_4$	<p>(124) $\text{R}=\text{CH}_2\text{C}_6\text{H}_5$</p>	-	76

The hexahydro-3-benzazocine (122) was converted into several N-substituted derivatives by alkylation.⁷⁷⁻⁸⁸

chloride, polyphosphoric acid does not cleave the aromatic methoxy group. Therefore the latter is a better dehydrating agent than the former and this ring closure reaction is more satisfactory as a preparative method.

Other C-C type ring closures employed to synthesise 3-benzazocines are given in Table 7.

Table 7

B(i)c-(1) 3-BenzazocinesOther C-C type ring closures

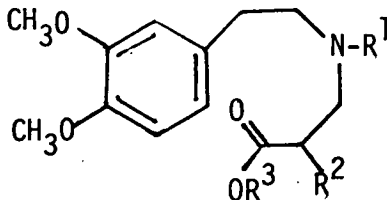
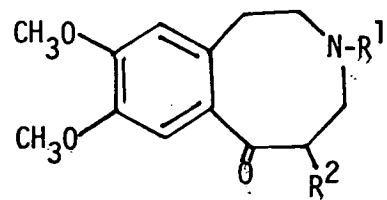
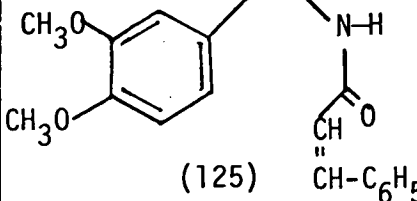
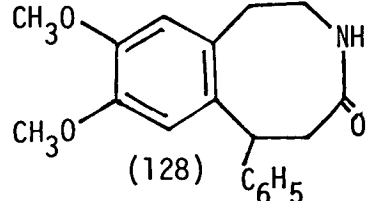
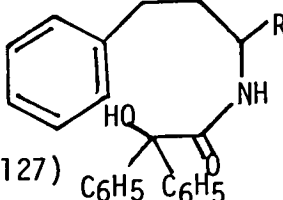
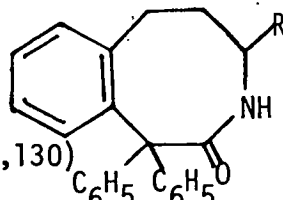
Starting materials	reaction conditions	Product	Yield %	Ref.
 <p>(108) $R^1 = \text{COC}_6\text{H}_5$, $R^2 = R^3 = \text{H}$</p> <p>(109) $R^1 = \text{SO}_2\text{C}_6\text{H}_5$, $R^2 = R^3 = \text{H}$</p> <p>(110) $R^1 = \text{COC}_6\text{H}_5$, $R^2 = \text{CH}_3$, $R^3 = \text{H}$</p>	<p>PPA/75°</p>	 <p>(118) $R^1 = \text{COC}_6\text{H}_5$, $R^2 = \text{H}$</p> <p>(119) $R^1 = \text{SO}_2\text{C}_6\text{H}_5$, $R^2 = \text{H}$</p> <p>(120) $R^1 = \text{COC}_6\text{H}_5$, $R^2 = \text{CH}_3$</p>	<p>79</p> <p>85</p> <p>76</p>	<p>73</p> <p>73</p> <p>73</p>
(114)	PPA	(124)	-	89
(114)	80% H_2SO_4	(124)	-	90
 <p>(125)</p>	<p>PPA/ 120°-130° 15 minutes</p>	 <p>(128)</p>	25	91
 <p>(126,127)</p>		 <p>(129,130)</p>		

Table 7 continued

(126) R=H	CH ₃ COOH and H ₂ SO ₄	(129) R=H	-	92
(127) R=CH ₃	SnCl ₄	(130) R=CH ₃	-	93,94

B(ii) C-N type

Ring closure with the formation of a C-N bond, of the types A to D, (Figure 5) has been employed to synthesise derivatives of all three benzazocines.

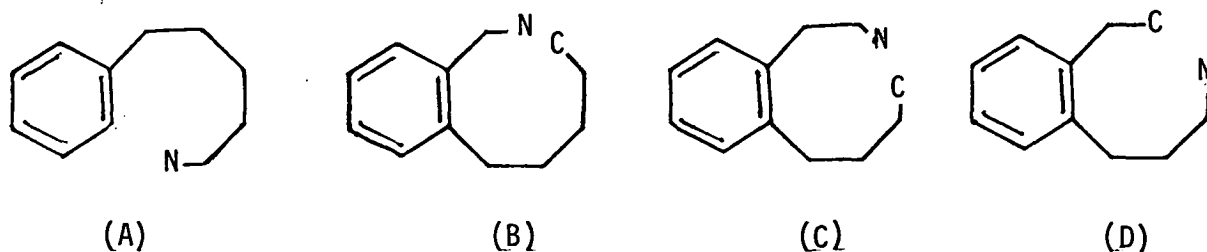
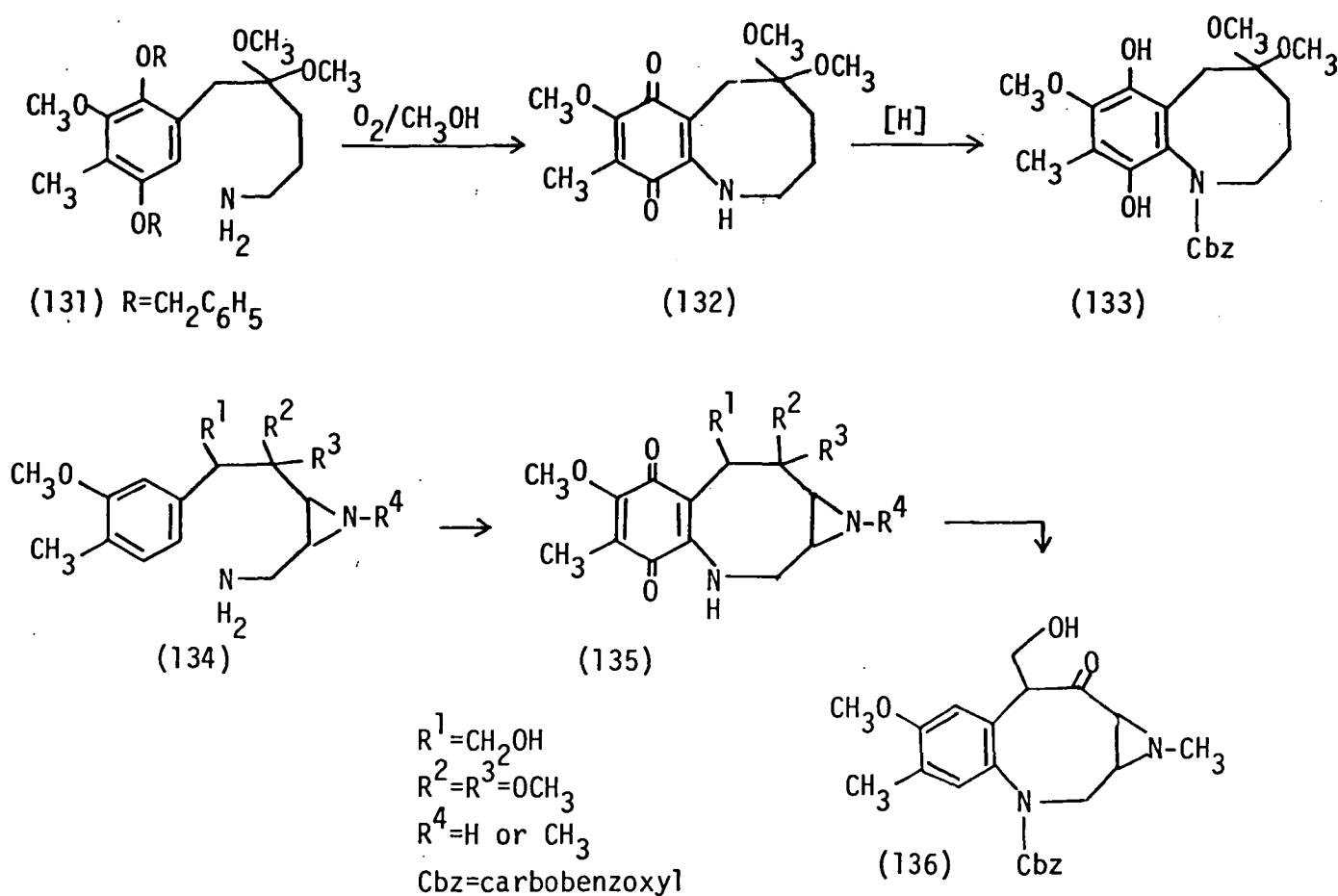


Figure 5

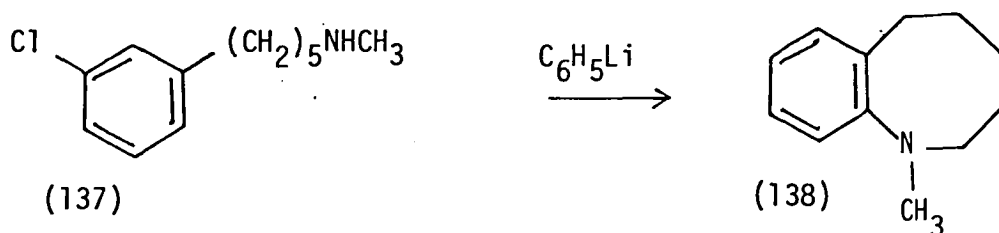
B(ii)-(1) 1-Benzazocines

The construction of eight-membered rings by the formation of a C-N bond has been mainly employed to synthesise the eight-membered quinones (132,135) rather than the 1-benzazocines. These compounds were prepared by the intramolecular Michael reaction of primary amines (131,134).⁹⁵⁻¹⁰¹ The Michael reaction on the aziridine (134) gave a small amount of the eight-membered quinone (135), together with another product.⁹⁸ This latter major product was likely to be formed by the interaction of the aziridine nitrogen atom with carbonyl group.

Recently, a paper by Yoshito¹⁰¹ described the conversion of the quinone moiety of (132) and of (135) into the corresponding hydroquinones (133,136). This was achieved by reduction, and N-carbobenzoylation followed by acid hydrolysis resulted in the formation of 1-carbobenzoxy-8-methoxy-9-methyl-1,2,3,4,5,6-hexahydro-1-benzazocine-5(6H)-one in high yield. These eight-membered quinones were prepared as precursors in the synthesis of mitomycins, which are a class of antibiotics with activity against Gram-positive and Gram-negative bacteria and also against several kinds of tumors.

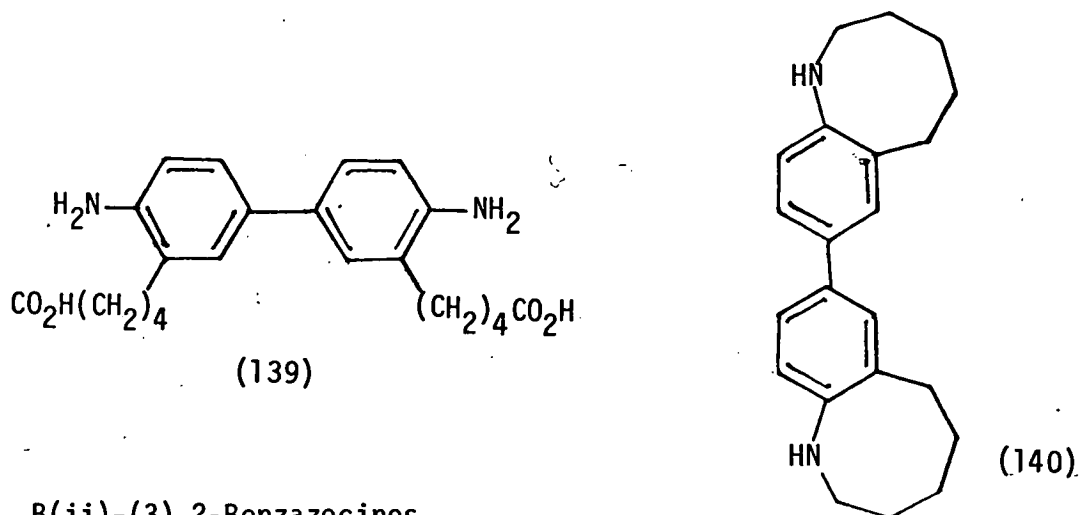


The hexahydro-1-benzazocine (138) was prepared by the cyclization of (137) in the presence of phenyl lithium in ether.¹⁵

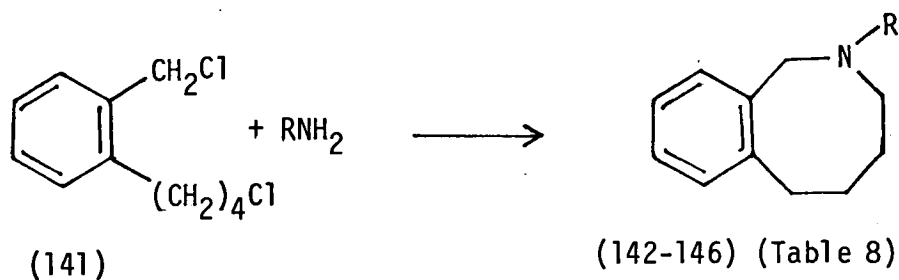


B(ii)-(2) Bis-1-Benzazocines

In a series of patents, Jonsson and co-workers¹⁰²⁻¹⁰⁴ reported the preparation of the bis-1-benzazocine (140) by the intramolecular cyclization of the amine (139). The experimental details and yields of the products were not reported.

B(ii)-(3) 2-Benzazocines

Several 2-benzazocines (142-146) were prepared by the condensation of 1-chloro-4-(2-chloromethylphenyl)butane (141) with an appropriate amine in the presence of sodium carbonate⁶ or lithium bromide.¹⁰⁵ (Table 8).



The compound (147) (Table 8) was prepared by the cyclization of (149) with phosphorus pentachloride or aluminium chloride.¹⁰³

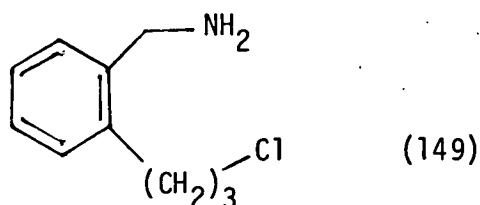


Table 8

B(ii)-(3) 2-Benzazocines

(C-N ring closure)

Product	R	Yield %	Reference
(142)	$-(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	24	105
(143)	$-\text{CH}_2\text{CHCH}_3\text{CH}_2\text{N}(\text{CH}_3)_2$	22	105
(144)	$-\text{CH}_2)_2-\text{N}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{CH}_2$	8	105
(145)	$-(\text{CH}_2)_2\text{OH}$	-	6
(146)	$-(\text{CH}_2)\text{Cl}$	80	6
(147)	H	-	106
(148)	COH or COCH_3	-	107

Hassner and Amit¹⁰⁷ reported on conformational studies of (148).

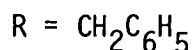
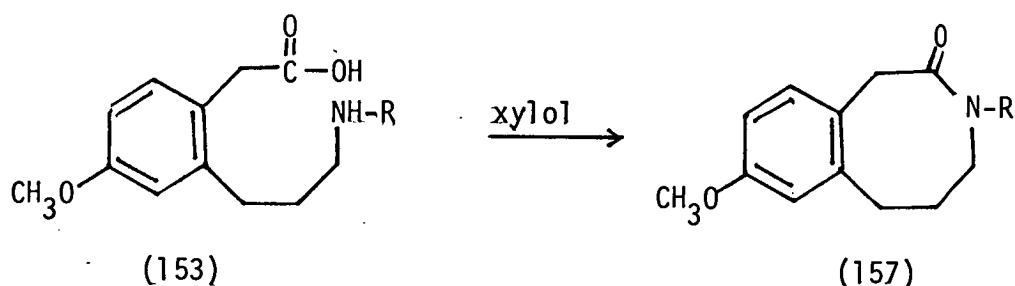
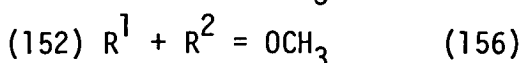
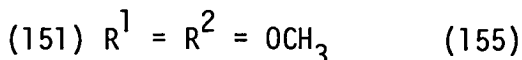
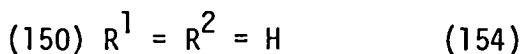
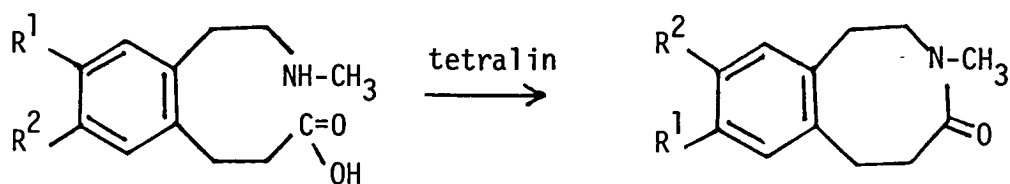
B(ii)-(4) 3-Benzazocines

The synthesis of 3-benzazocines by the ring closure of C-N type can be further divided into two groups. These are

- (a) ring closure by condensation, and
- (b) reductive ring closure.

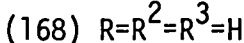
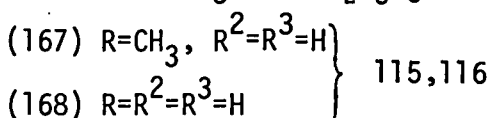
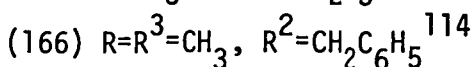
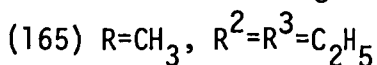
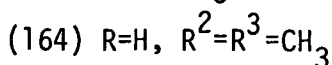
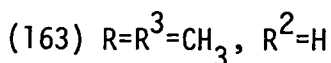
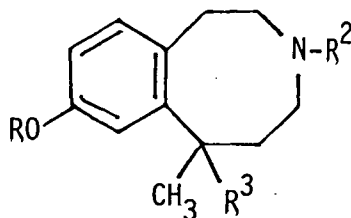
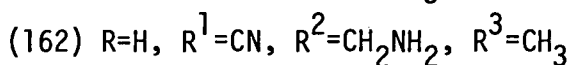
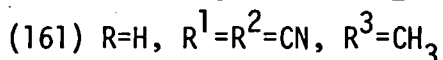
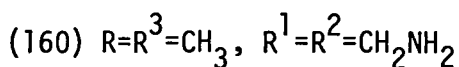
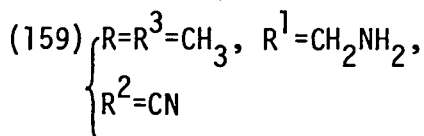
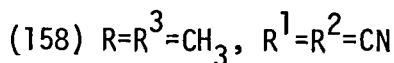
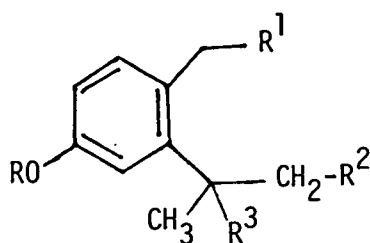
B(ii)-4a Ring closure by condensation

The condensation of o-substituted amines (150-153) in tetralin¹⁰⁸ or xylol¹⁰⁹ gave the corresponding 3-benzazocines (154-157) in 55% to 98% yields.



B(ii)-4b Reductive ring closure

The reductive ring closure of nitriles takes place in the presence of a suitable catalyst such as Raney nickel or Raney cobalt or palladium on charcoal in methanol.¹¹⁰⁻¹¹³ The reduction of the dinitrile (158) with Raney cobalt, which is considered to be a mild catalyst, gave the 3-benzazocine (163) together with amines (159) and (160). The yields of these by-products were increased by addition of small amounts of water to the reaction mixture. When Raney nickel was used, the addition of water greatly influenced the yield of (163).¹¹⁰ However addition of more water decreased the yield of (163). The best yield of (163) was obtained by the reaction carried out in methanol containing acetic acid. In this case acetic acid depressed the formation of by-products.



The conditions used in this reductive ring closure are summarized in Table 9.

(C) Photocyclization

C(i)-(1) 1-Benzazocines

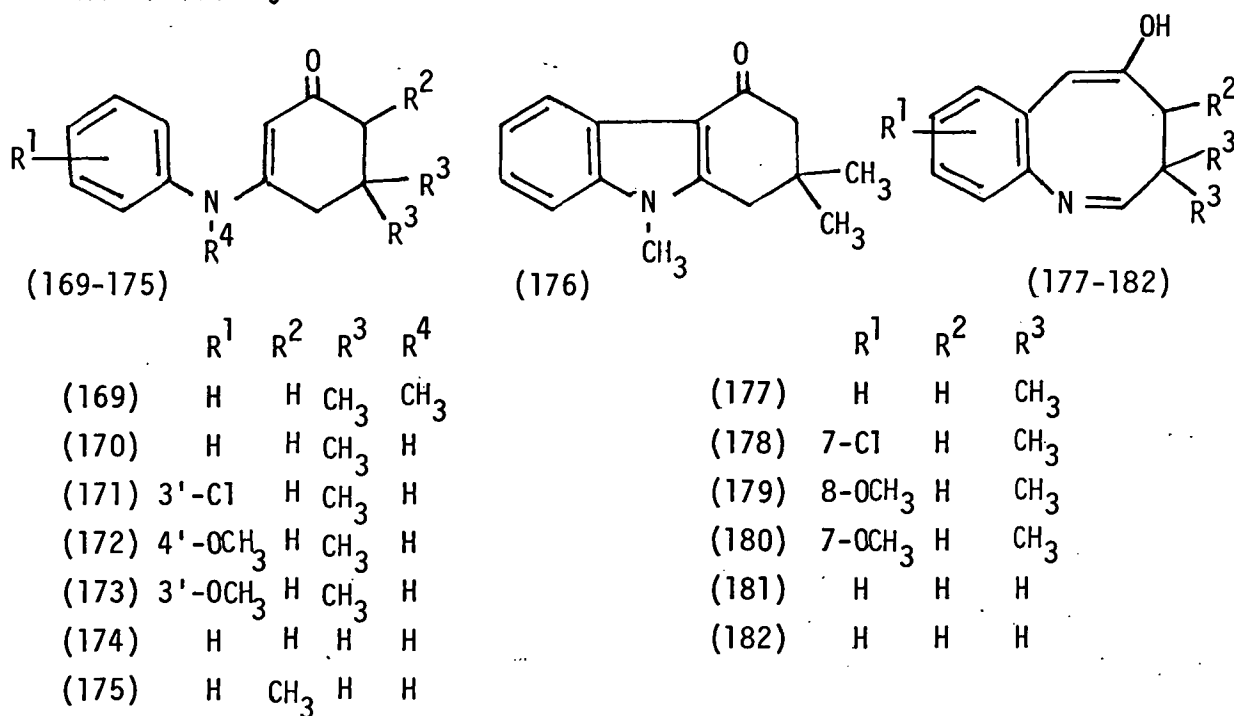
In recent years, photochemical reactions of *N*-aryl enamino ketones, examined by Yamada and co-workers,¹¹⁷⁻¹²⁰ have opened a new route for the synthesis of 1-benzazocines. These workers have studied both *N*-substituted and *N*-unsubstituted aryl enamines to investigate the possibilities in the preparation of benzazocines.

On irradiation with a pyrex-jacketed immersion lamp, the *N*-substituted enamino ketone (169) gave a carbazole (176) instead of the anticipated eight-membered ring product. Under the same conditions, the *N*-unsubstituted enamino ketones (170-175) gave the 1-benzazocine derivatives (177-182) together with a ketene adduct and a lactone.¹¹⁷ In this case no corresponding carbazole was detected.

Table 9

B(ii)-4b 3-BenzazocinesReductive ring closure

Starting material	Reaction conditions	Product	Yield %	Ref.
(158)	(a) $\text{R}\bar{\text{a}}^*\text{-Co/CH}_3\text{OH-H}_2$ 100° high pressure autoclave	(163)	small amount	110,111
	(b) W-2 $\text{R}\bar{\text{a}}\text{-Ni/CH}_3\text{OH-H}_2$ high pressure autoclave	(163)·HCl salt	21	110,111
	(c) W-2 $\text{R}\bar{\text{a}}\text{-Ni/CH}_3\text{OH-H}_2$ CH_3COOH -high pressure autoclave	(163)	65	110,111
	(d) W-2 $\text{R}\bar{\text{a}}\text{-Ni}$		42	110,111
(160)	Pd-C/H_2 or Pd/BaSO_4 in xylene	(163)	78	110
(161), (162)	$\text{R}\bar{\text{a}}\text{-Ni/H}_2$	(164)	92	112
(162)	$\text{R}\bar{\text{a}}\text{-Ni/H}_2\text{O}$	(164)	-	113

* $\text{R}\bar{\text{a}}\text{-Ni} \equiv \text{Raney Nickel}$ 

However the yields of 1-benzazocines obtained by photocyclization was poor (between 3%-20%) when compared with the other methods.

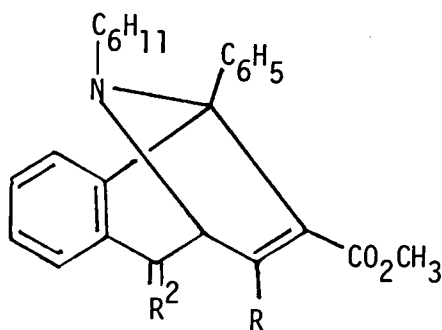
In order to investigate the mechanism of these photochemical reactions, the irradiation of enamino ketones was carried out with a low pressure mercury lamp, and no eight-membered ring product was isolated. When a high pressure mercury lamp was used, the formation of benzazocines were observed.¹¹⁷ These results indicate that the excited state in this photoreaction is the $n \rightarrow \pi^*$ triplet.

The benzazocine derivative (182) was synthesised from the corresponding ketone (175) using a high pressure mercury lamp.¹¹⁹⁻¹²⁰

Kinetic studies involving potentially aromatic dihydrobenzazocine anions have been reported by Johnson.¹²¹

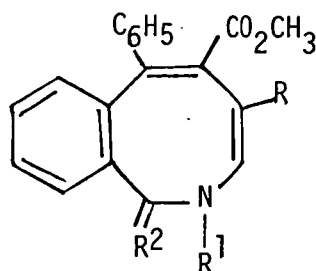
C(2) 2-Benzazocines

The ketone (183) underwent a novel rearrangement on irradiation giving rise to the 2-benzazocine (185) in 93% yield. Action of heat on (173) in toluene also resulted in the formation of (185).¹²² On further irradiation, the benzazocine (185) gave a mixture of ring contracted products.



(183) $R^2=O$, $R=CO_2CH_3$ or H

(184) $R^2=N-C_6H_{11}$, $R=CO_2CH_3$ or H



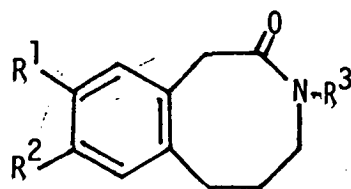
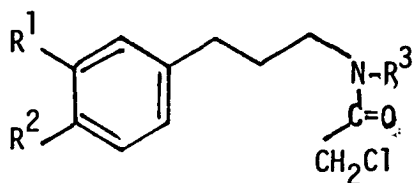
(185) $R^2=O$, $R=CO_2CH_3$ or H

(186) $R^2=N-C_6H_{11}$, $R=CO_2CH_3$ or H

C(3) 3-Benzazocines

Photochemical ring closure of *N*-(chloroacetyl)phenylpropylamine

derivatives (187-190) resulted in the formation of 3-benzazocines (191-194) in 25%-30% yield.¹²³⁻¹²⁶ Irradiation of (188) with a low pressure mercury lamp gave the benzazocine (192) along with a dimeric product having the molecular formula $C_{22}H_{26}N_2O_4$.¹²³ The related 3-benzazocine (192) was prepared in 30% yield using a high pressure mercury immersion lamp.¹²⁴ In this case no dimeric products were detected.



(187) $R^1=R^2=R^3=H$

(188) $R^1=H$, $R^2=OH$, $R^3=CH_3$

(189) $R^1=R^3=H$, $R^2=OCH_3$

(190) $R^1=R^2=OCH_3$, $R^3=H$

(191) $R^1=R^2=R^3=H$

(192) $R^1=H$, $R^2=OH$, $R^3=CH_3$

(193) $R^1=R^3=H$, $R^2=OCH_3$

(194) $R^1=R^2=OCH_3$, $R^3=H$

Chapter 3

Benzodiazocines

The number of possible isomers for the benzodiazocine system is nine, and seven of them are known (Figure 6).

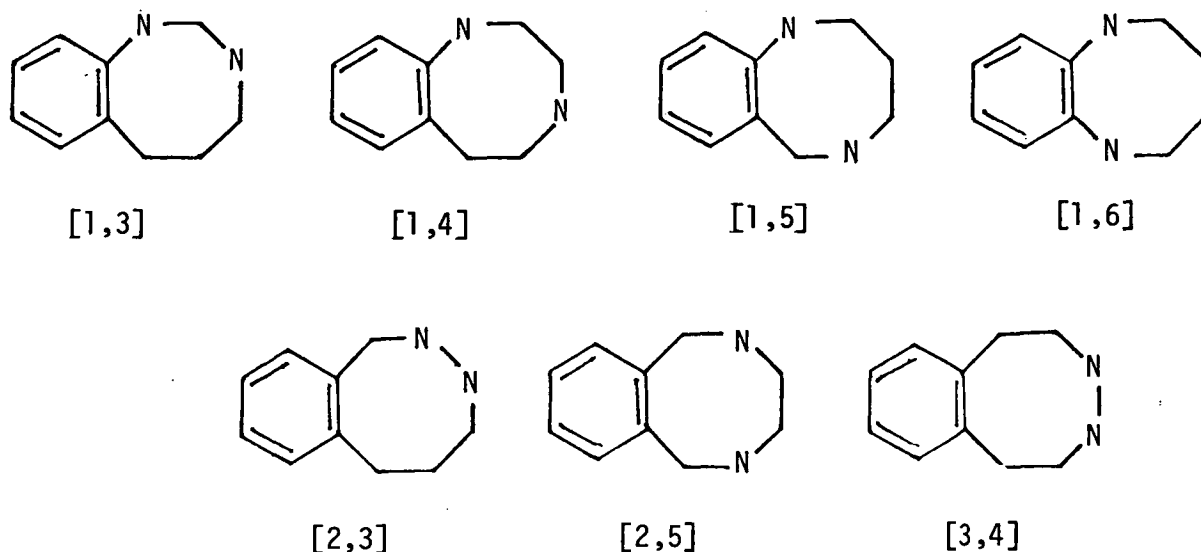


Figure 6

As with the benzazocines, the methods employed for the synthesis of benzodiazocines are (A) ring enlargements, (B) ring closures and (C) photochemical reactions. In addition to these methods, 1,5-benzodiazocines were prepared from bridge-head compounds by the cleavage of an endo-methano bridge.

Methods of Preparation

(A) Ring enlargements

The ring enlargement reactions can be further divided into four sub-divisions and these are,

- (i) rearrangements - Schmidt reaction,
- (ii) ring enlargement of benzodiazepines and indole derivatives,

(iii) addition followed by ring enlargement and,

(iv) ring enlargement by cleavage of an internal C-N bond.

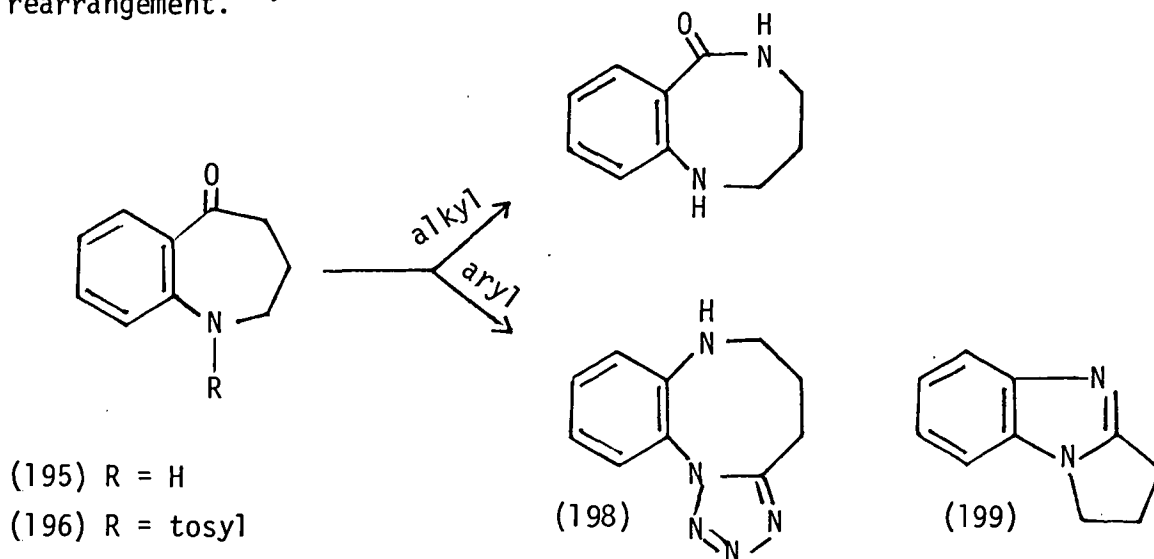
A(i) Rearrangements

The Beckmann rearrangement of benzo fused ketones has not been employed to synthesise benzodiazocine derivatives. The only rearrangement reaction used is the Schmidt reaction. The reported yields of the Schmidt reaction were very poor and the formation of by-products was observed. Hence this has not been used as a major preparative method.

A(i) a Schmidt reaction

A(i) a-(1) 1,5- and 1,6-benzodiazocines

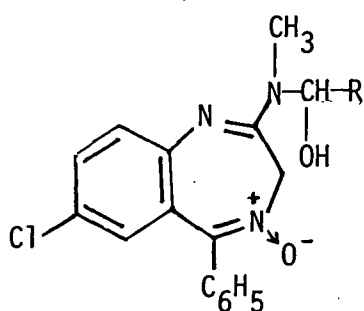
Misiti *et al*²⁴ reported that the Schmidt rearrangement of 1,2,3,4-tetrahydro-1-benzazepine-5-one (195) gave only 2% of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazocine-6-one (197) and 6% of 4,5,6,7-tetrahydrotetrazolo-[5,1-*e*]-1,6-benzodiazocine (198). The major product (83%) was a benzimidazole (199), which was formed by aryl migration (Scheme 11). The *N*-tosyl derivative (196) also gave a similar result showing that aryl migration is predominant in this rearrangement.^{24,127}



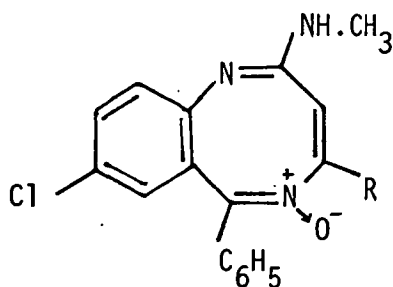
Scheme 11

A(ii) a Ring enlargement of benzodiazepinesA(ii) a-(1) 1,5-benzodiazocines

The ring expansion of the benzodiazepine (200) to the benzodiazocine (201) was achieved by treatment with 10% aqueous sodium hydroxide at room temperature.^{128,129}



(200)



(201)

R = 2-furyl

A(ii) b Ring enlargement of indoles

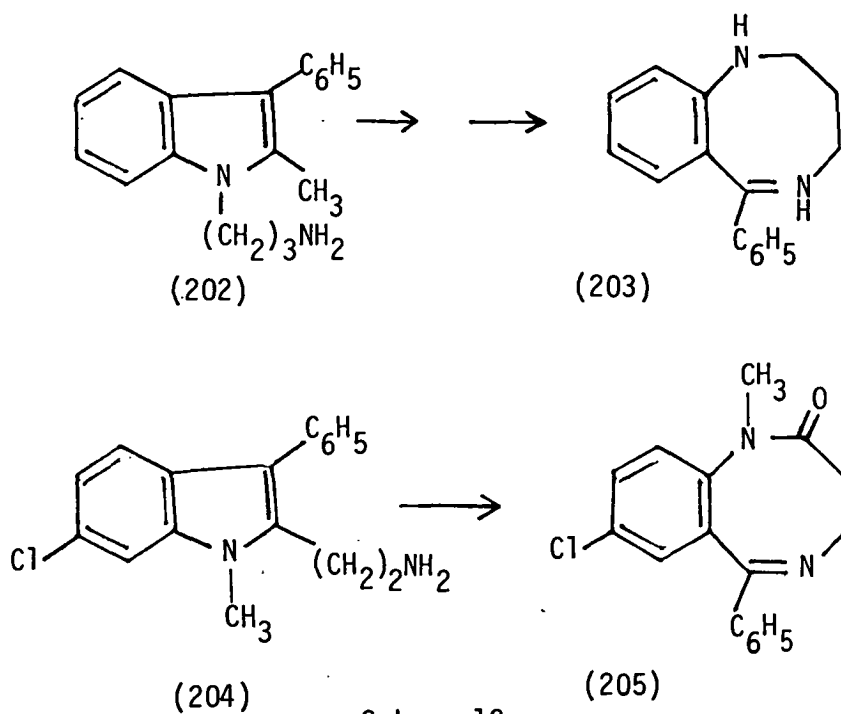
Both 1,5- and 1,4-benzodiazocines have been synthesised by the ring enlargement of indole derivatives.

A(ii) b (1) 1,5-Benzodiazocines

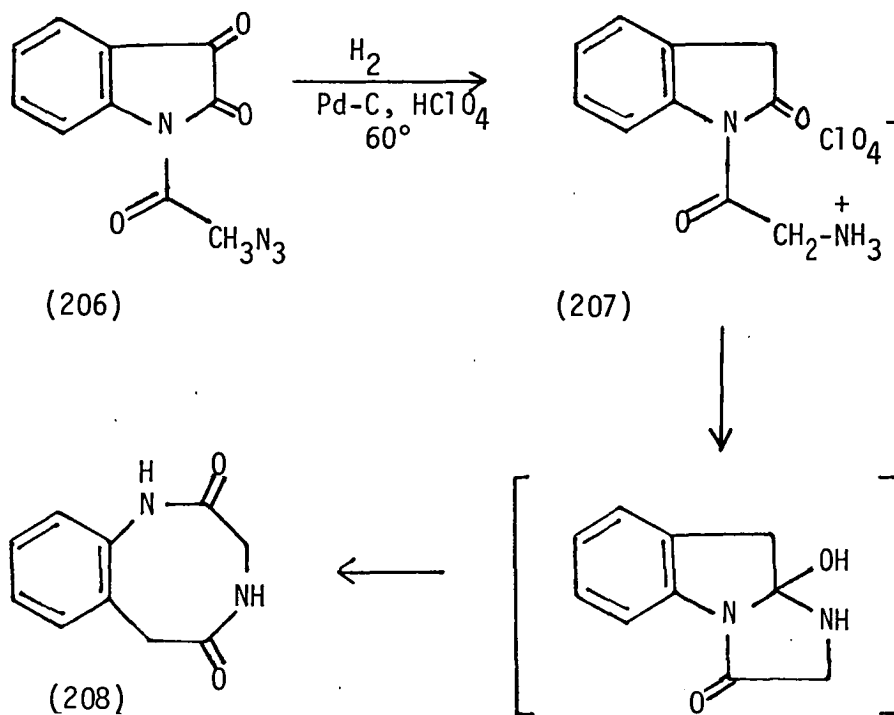
Sodium periodate oxidation of the indole derivative (202) followed by a series of reductions gave 6-phenyl-1,2,3,4,5,6-hexahydro-1,5-benzodiazocine (203).¹³⁰ (Scheme 12). The related indole (204) oxidised with chromic trioxide gave the 8-chloro-3,4-dihydro-1-methyl-6-phenyl-1,5-benzodiazocine-2-(1H)-one (205).^{131,132} Sharbatyan and co-workers¹³³ have reported on the mass spectral behaviour of (205).

A(ii) b-(2) 1,4-Benzodiazocines

Hydrogenolysis of the azido compound (206) gave the aminoacetyl-oxindole (207). Then continuous extraction of (207) with aqueous sodium bicarbonate solution resulted in the formation of the dione



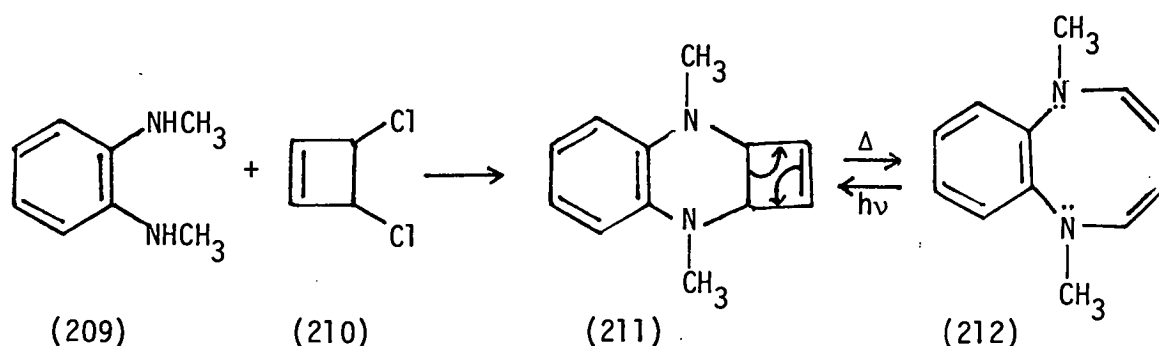
derivative (208).¹³⁴ (Scheme 13).



A(iii) Addition followed by ring enlargement

A(iii) (1) 1,6-Benzodiazocines

The cyclobutene adduct (211) was readily obtained by the reaction of *N,N*-dimethyl-*o*-phenylenediamine (209) and *cis*-3,4-dichlorocyclobutene (210) in the presence of *n*-butyl lithium. The gas phase thermolysis of (211) at 285° gave the 1,6-benzodiazocine (212) as the only detectable product; this ring expansion was reversed on irradiation.¹³⁵



A(iii)-(2) 2,3-Benzodiazocines

The cycloaddition of dimethylacetylenedicarboxylate (DMAD) to 1-oxido-3-phenylphthalazinium (213) in chloroform under reflux gave the 2,3-benzodiazocine derivative (214).^{136,137} Replacing chloroform with xylene afforded only the cycloadduct (215). However the reaction of (213) with phenylacetylene in xylene gave the ring expanded product (217). It has been suggested that both (214) and (217) are formed by the electrocyclic reaction of the normal cycloadducts (215 and 216) respectively. (Figure 7).

The catalytic hydrogenation of (217) with 10% palladium-charcoal gave the tetrahydro derivative (218) in 80% yield.¹³⁷ Harlow and Simonsen¹³⁸ have reported the X-ray crystal structure of (218).

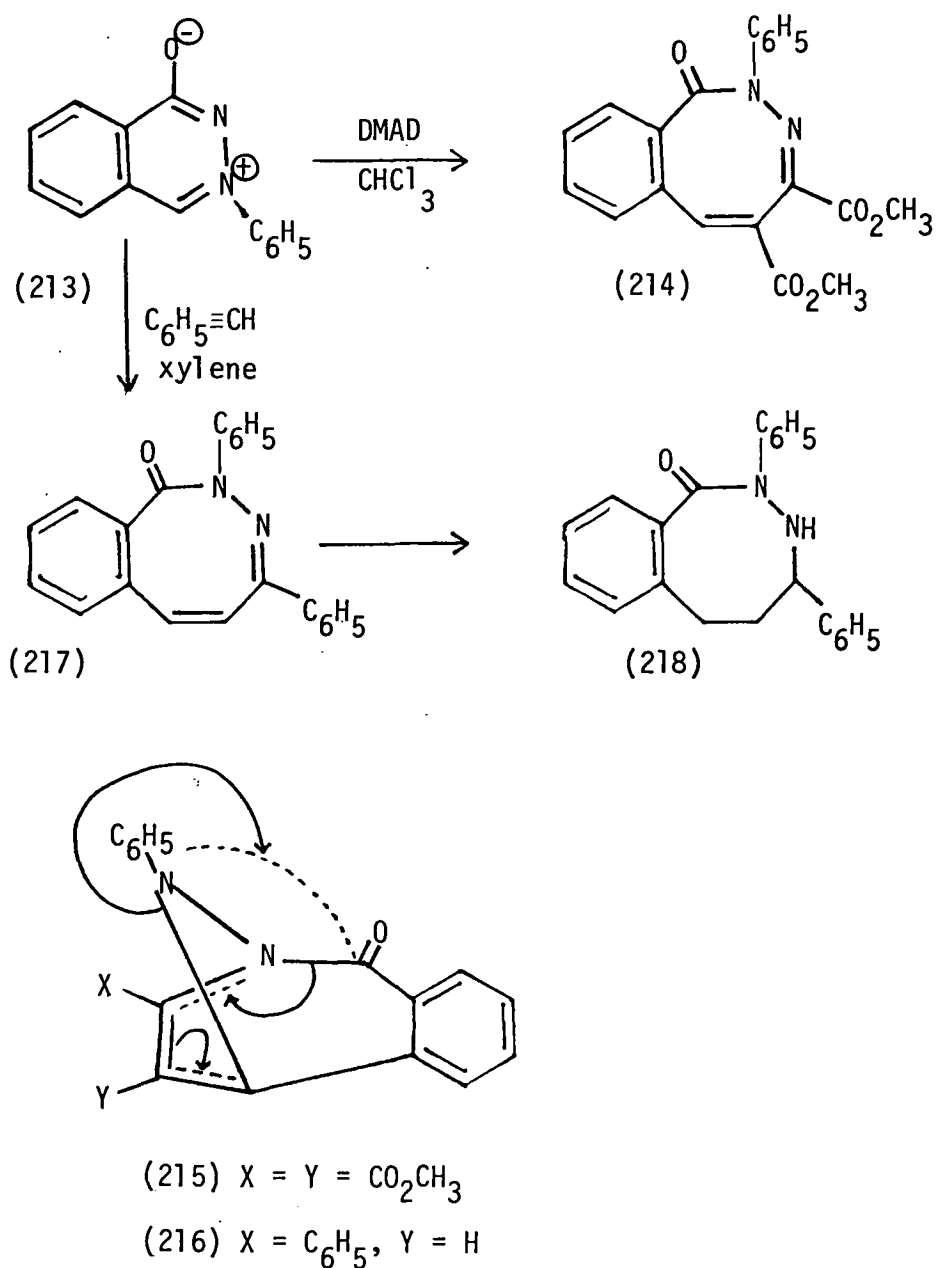
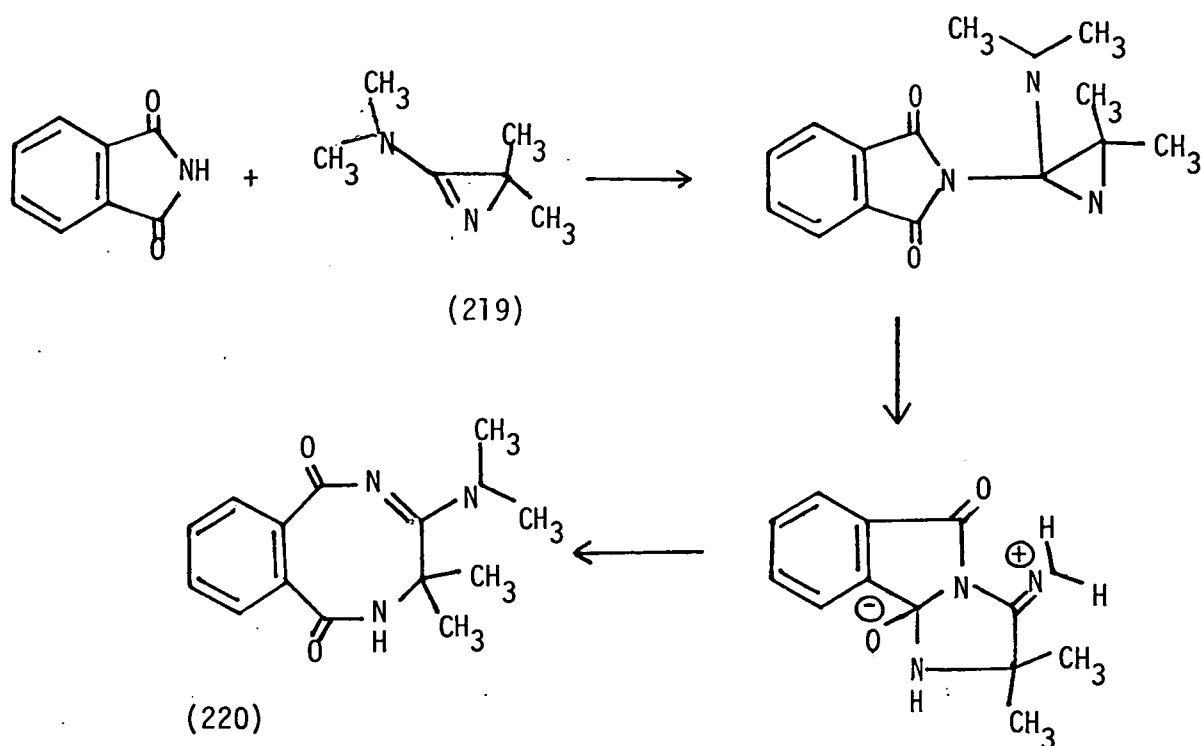


Figure 7

A(iii)-(3) 2,5-Benzodiazocines

The reaction of 3-dimethylamino-2,2-dimethyl-2H-azirine (219) and phthalimide in dimethylformamide gave the ring expanded product, 4-dimethylamino-3,3-dimethyl-1,2,3,6-tetrahydro-2,5-benzodiazocine-1,6-dione (220).¹³⁹ A suggested pathway for the formation of (220) is given in the Scheme 14.



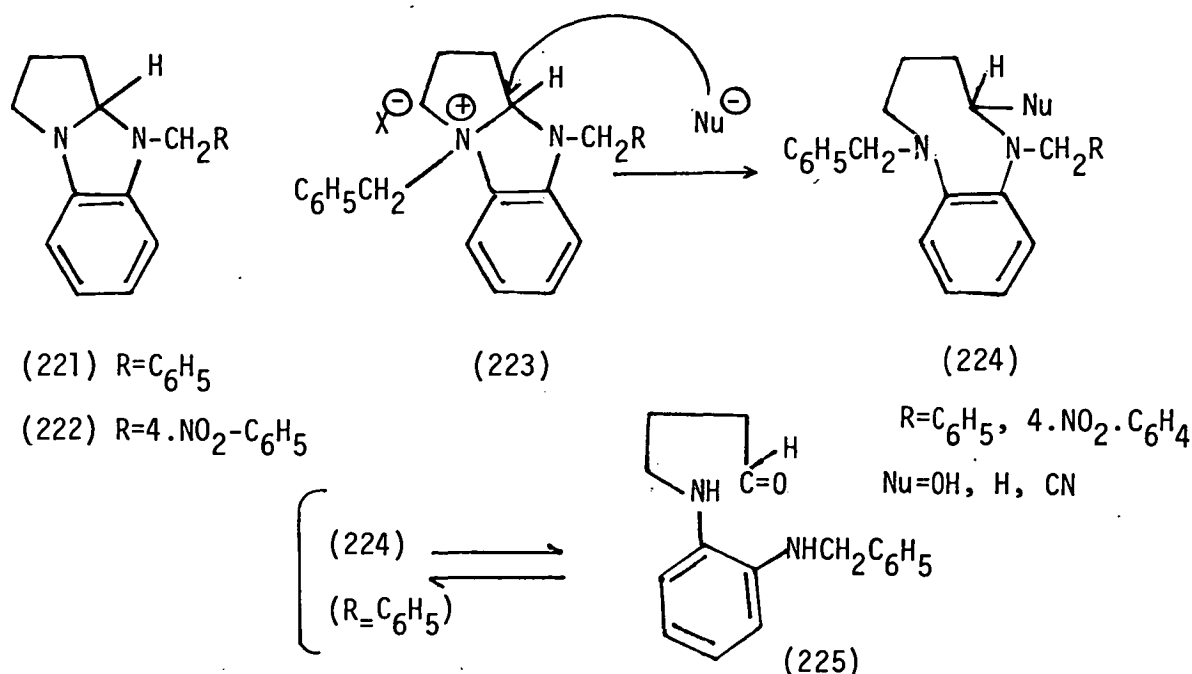
Scheme 14

A(iv) Ring enlargement by cleavage of an internal C-N bond

This method has been employed to synthesise 1,6- and 2,5-benzodiazocine derivatives.

A(iv)-(1) 1,6-Benzodiazocines

The tetrahydropyrrolo[1,2- α]benzimidazoles (221,222) underwent benzylation at the bridge-head nitrogen to give the quaternary ammonium ion (223). (Scheme 15). Treatment of (223) with aqueous solutions of sodium hydroxide, sodium tetrahydroborate or sodium cyanide in the cold, resulted in the cleavage of the C-N bond between the quaternized nitrogen atom and the adjacent carbon atom-C₅, giving rise to an eight-membered ring product (224).^{140,141} The reaction of sodium hydroxide with (221) gave a tautomeric mixture of ring expanded product (224) and a ring opened product (225) in equal yields.

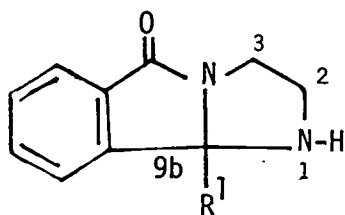


Scheme 15

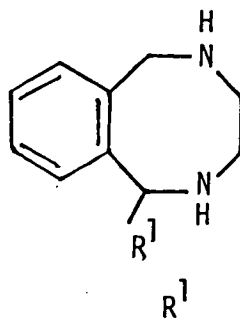
A(iv)-(2) 2,5-Benzodiazocines

In a series of patents, Sulkowski *et al*¹⁴²⁻¹⁴⁸ and Winn^{149,150} described the ring expansion of 9-(4-chlorophenyl)-1,2,3-9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]-isoindol-5-one (226) to the 2,5-benzodiazocine derivative (227), in moderate yield. Unlike 1-benzazocines, the cleavage of the internal C-N bond was achieved by reduction with lithium aluminium hydride in anhydrous ether. Similarly, benzodiazocines (228-232) were prepared from the corresponding imidazoisindolones.^{146,147,151}

This type of reduction can only be applied to the *N*-unsubstituted imidazoisindolones, with *N*-substituted derivatives, lithium aluminium hydride reduction caused the cleavage of the N-1/C-9*b* bond and no eight-membered ring products were obtained.¹⁴² Instead the unstable isoindoles were formed.¹⁵¹



(226) 4-ClC₆H₄



(227) 4-Cl-C₆H₄

(228) 2,4-(OCH₃)₂·C₆H₃

(229) 3,4-Cl·C₆H₃

(230) 4-OCH₃·C₆H₄

(231) C₆H₅

(232) CH₃

The 2,5-benzodiazocine (227) was converted into various *N*-substituted derivatives^{152,154} and oxidation of (227) resulted in the formation of tricyclic imidazoisindoles.¹⁵⁵⁻¹⁶⁰ The pharmacological studies of (227) also were carried out by several workers.^{161,164} The benzadiazocine (227) was found to be an effective anorexic agent and caused primary depression of cardiovascular function.^{162,163}

(B) Ring closure

B(i) C-C type

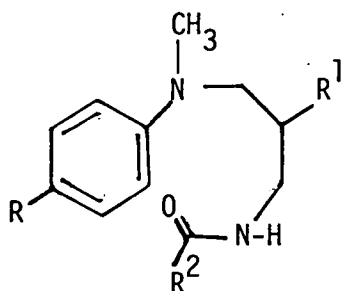
The Bischler-Napieralski reaction is the only method employed to synthesise 1,5- and 2,5-benzodiazocines by ring closure of the C-C type. This is a widely used method for the synthesis of 1,5-benzodiazocines.

B(i)a Bischler-Napieralski reaction

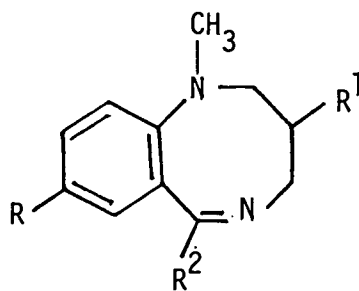
B(i) a-(1) 1,5-Benzodiazocines

The cyclodehydration of amide (233) was carried out in the presence

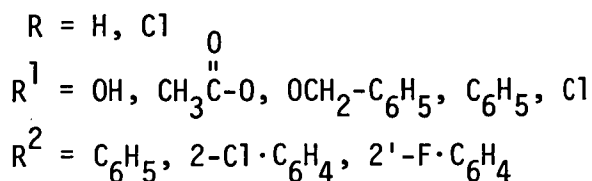
of phosphorus oxychloride under reflux to give the corresponding 1,5-benzodiazocines,¹⁶⁵⁻¹⁷⁰ but the yields were not reported.



(233)



(234)

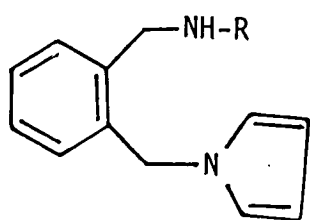


B(i)-(2) 2,5-Benzodiazocines

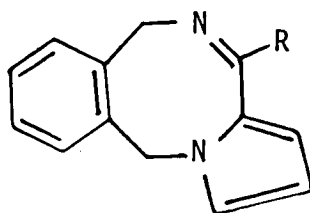
De Martino *et al*¹⁷¹ reported the synthesis of 6,11-dihydropyrrolo-[1,2-*b*][2,5]benzodiazocines (238-240), containing a new heterocyclic system, from 1-(2-acetylaminoethylbenzyl) pyrroles (235-237). The ring closure of (235) and (236) in phosphorus oxychloride proceeded smoothly and in high yields to give the corresponding benzodiazocines (238,239). The lactam (241) was prepared by the intramolecular cyclization of (237) with zinc chloride.¹⁷¹

B(ii) C-N type

The C-N type of ring closure is the most widely used preparative method in the construction of benzodiazocine derivatives. Out of the nine possible isomers for the benzodiazocines, six isomers (A-F)



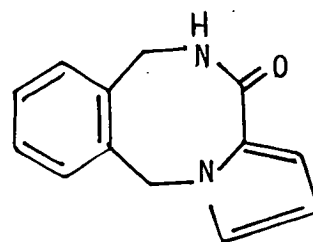
R

(235) COCH_3 (236) COC_6H_5 (237) $\text{CO}_2\text{C}_2\text{H}_5$ 

R

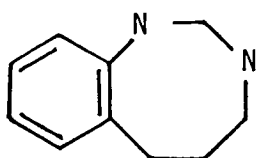
(238) CH_3 (239) C_6H_5

(240) H



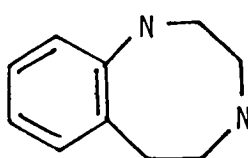
(241)

(Figure 8) have been prepared by this method. The formation of the carbon-nitrogen bond was achieved by intramolecular cyclizations and condensation reactions.



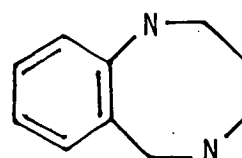
1,3

(A)



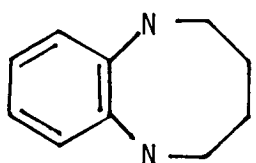
1,4

(B)



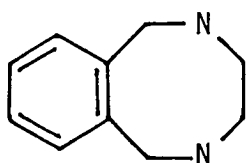
1,5

(C)



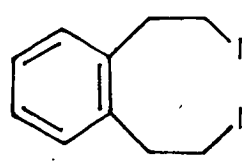
1,6

(D)



2,5

(E)



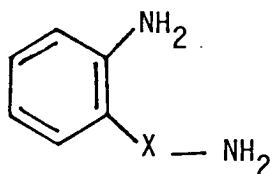
3,4

(F)

Figure 8

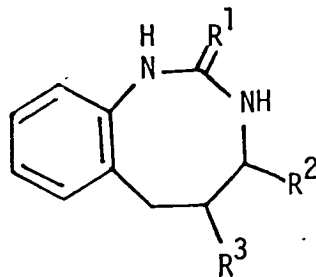
B(ii)-(1) 1,3-Benzodiazocines

The condensation of amines (242-245) with COCl_2 or CS_2 afforded the corresponding 1,3-benzodiazocine derivatives (246-250) in fair yields.^{172,173}



X

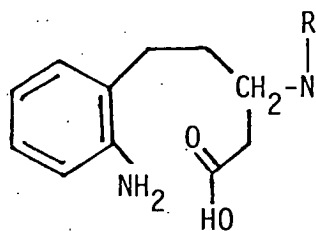
- (242) $(\text{CH}_2)_3$
 (243) $(\text{CH}_2)_2\text{CHCH}_3$
 (244) $\text{CH}_2\text{-CH}\cdot\text{CH}_3\text{-CHCH}_3$
 (245) $(\text{CH}_2)_2\text{CH}\cdot\text{C}_6\text{H}_5$

R¹ R² R³

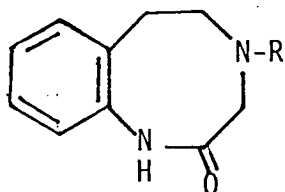
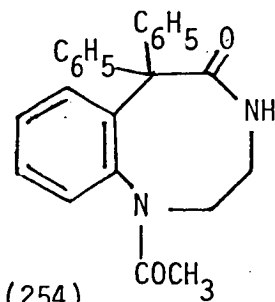
- (246) O H H
 (247) S H H
 (248) S CH₃ H
 (249) S CH₃ CH₃
 (250) S C₆H₅ H

B(ii)-(2) 1,4-Benzodiazocines

The 1,4-benzodiazocines (252,253) were prepared by the intramolecular cyclization of *N*-2-(2-aminophenyl)ethylglycine (251) in acetonitrile. The cyclization was induced by the use of dicyclohexylcarbodiimide (DCC); this reaction did not proceed in pyridine.¹⁷⁴ No explanation is available for the influence of the solvent in the above cyclization. However this ring closure method was reported by the same author to be more versatile than the previously described method¹³⁴ (p. 43) for the synthesis of 1,4-derivatives.



(251)

(252) R=CH₃(253) R=SO₂-C₆H₅

(254)

The lactam (252) was readily reduced to the corresponding diamine, but no basic product was obtained from (253), under the same conditions.

The 1,4-benzodiazocine-5-one (254) was synthesised in 94% yield by the condensation of β -(*N*-phenylacetamide)ethanamide, in a mixture of sulfuric and acetic acids.¹⁷⁵

B(ii)-(3) 1,5-Benzodiazocines

Synthesis of 1,5-benzodiazocines by the formation of a C-N bond has been used extensively¹⁷⁶⁻¹⁹² and they consist of ring closures of type A to E. (Figure 9).

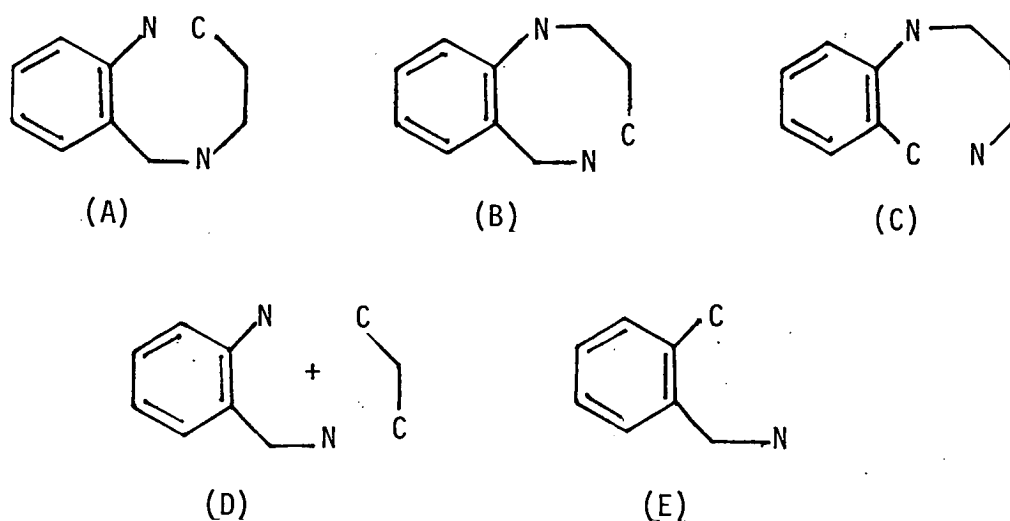


Figure 9

The starting materials and the reaction conditions employed for the synthesis of 1,5-benzodiazocines by the C-N ring closure reactions are summarized in Table 10.

Bagataskii and co-workers¹⁹⁸ have reported the synthesis of a triazolo derivative of 8-chloro-6-phenyl-3,4-dihydro-1,5-benzodiazocine by the ring closure of the corresponding benzophenone derivative. The corresponding tetrahydro-1,5-benzodiazocine-2-(1*H*)-one was obtained

Table 10

B(ii)-(3) 1,5-Benzodiazocines

(C-N type ring closure)

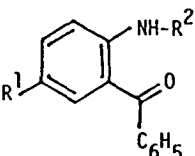
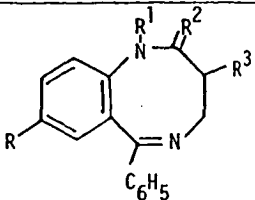
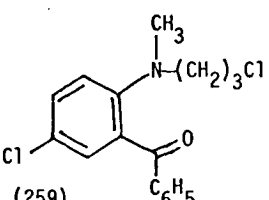
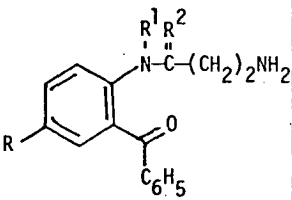
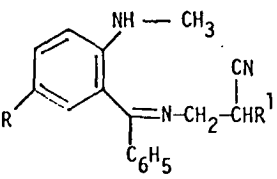
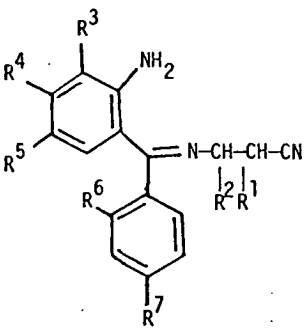
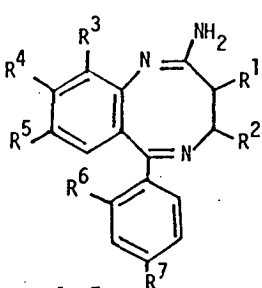
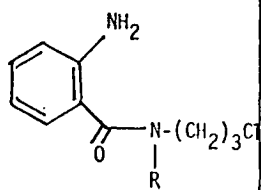
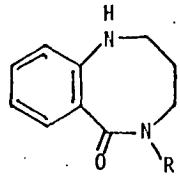
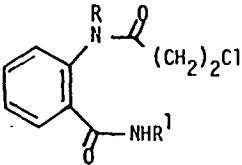
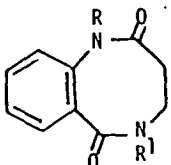
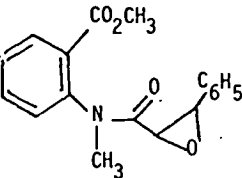
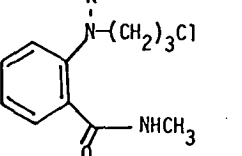
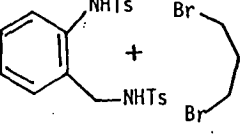
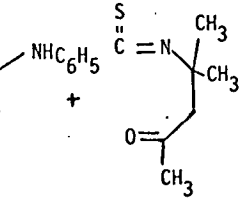
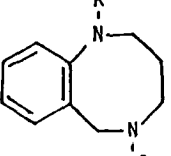
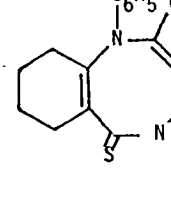
Starting materials	Reaction conditions	Products	Yield %	Reference
 <p>(255) $R^1 = \text{Cl}, R^2 = \text{H}$</p> <p>(255)</p> <p>(257) $R^1 = \text{Br}, R^2 = \text{H}$</p>	<p>(i) $\text{Cl}(\text{CH}_2)_2\text{COCl}/$ (ii) NH_3</p> <p>condensation with an amino acid</p> <p>$\text{Cl}(\text{CH}_2)_2\text{COCl}$ and NH_3</p>	 <p>(256) $\begin{cases} R = \text{Cl}, R^2 = \text{O}, \\ R^1 = R^3 = \text{H} \end{cases}$</p> <p>(256) and several other derivatives</p> <p>(258) $\begin{cases} R = \text{Br}, R^1 = R^3 = \text{H}, \\ R^2 = \text{O} \end{cases}$</p>	<p>51</p> <p>179</p> <p>45</p>	<p>176,177 178</p> <p>179</p> <p>176,177</p>
 <p>(259)</p>	<p>$\text{KI}/\text{C}_2\text{H}_5\text{OH}/\text{NH}_3$ under pressure</p>	<p>(260) $\begin{cases} R = \text{Cl}, R^1 = \text{CH}_3, \\ R^2 = 2\text{H}, R^3 = \text{H} \end{cases}$</p>	<p>74</p>	<p>180</p>
 <p>(261) $R = \text{Cl}, R^1 = R^2 = \text{H}$</p> <p>(261)</p> <p>(263) $\begin{cases} R = \text{Cl}, R^1 = \text{CH}_3, \\ R^2 = \text{H}_2 \end{cases}$</p> <p>(265) $\begin{cases} R = \text{Cl}, R^1 = \text{CH}_3, \\ R^2 = \text{O} \end{cases}$</p> <p>(265)</p>	<p>$\text{POCl}_3/\text{pyridine}$</p> <p>pyridine/$\Delta$</p> <p>"</p> <p>pyridine/HCl</p> <p>toluene/Δ</p>	<p>(262) $R = \text{Cl}, R^1 = R^2 = R^3 = \text{H}$</p> <p>(262)</p> <p>(264) $\begin{cases} R = \text{Cl}, R^1 = \text{CH}_3, \\ R^2 = R^3 = \text{H} \end{cases}$</p> <p>(205) $\begin{cases} R = \text{Cl}, R^1 = \text{CH}_3, \\ R^2 = \text{O}, R^3 = \text{H} \end{cases}$</p> <p>(205)</p>	<p>40</p> <p>-</p> <p>-</p> <p>23</p>	<p>180</p> <p>180,181</p> <p>180</p> <p>182</p> <p>180</p>
 <p>(266) $R = \text{NO}_2, R^1 = \text{H}$</p>	<p>dry $\text{HCl}/\text{C}_6\text{H}_6$</p>	<p>(267) $\begin{cases} R = \text{NO}_2, R^1 = \text{CH}_3, \\ R^2 = \text{NH}, R^3 = \text{H} \end{cases}$</p>	<p>-</p>	<p>183</p>

Table 10 continued

(268) $R=Cl, R^1=H$	dry HCl/C_6H_6	(269) $\begin{cases} R=Cl, R^1=CH_3, \\ R^2=NH, R^3=H \end{cases}$	-	183
(270) $R=CF_3, R^1=H$	"	(271) $\begin{cases} R=CF_3, R^1=CH_3, \\ R^2=NH, R^3=H \end{cases}$	-	183
(272) $R=Cl, R^1=CH_3$	"	(273) $\begin{cases} R=Cl, R^1=CH_3, \\ R^2=NH, R^3=CH_3 \end{cases}$	-	183
(274) $R=CF_3, R^1=CH_3$	"	(275) $\begin{cases} R=CF_3, R^1=CH_3, \\ R^2=NH, R^3=CH_3 \end{cases}$	-	183
				
(276) $R^1 \rightarrow R^7=H$	CH_3OH dry HCl room	(277)*	60	184
(278) $R^5=Cl$	temperature	(279)*	85	"
(280) $R^5=CH_3$	"	(281)	70	"
(282) $R^5=CF_3$	"	(283)	74	"
(284) $R^5=NO_2$	"	(285)	46	"
(286) $R^5=OCH_3$	"	(287)	47	"
(288) $R^5=R^7=Cl$	"	(239)	38	"
(290) $R^5=Cl, R^7=OCH_3$	"	(291)	60	"
(292) $R^4=R^5=OCH_3$	"	(293)	77	"
(294) $R^3=OCH_3, R^5=Cl$	"	(295)	74	"
(296) $R^1=CH_3, R^5=Cl$	"	(297)	86	"
(298) $R^2=CH_3, R^5=Cl$	"	(299)	66	"
(300) $R^2=CH_3, R^5=R^7=Cl$	"	(301)	25	"
(302) $R^1=CH_3, R^5=R^7=Cl$	"	(303)	82	"
(304) $R^2=CH_3, R^4=R^5=OCH_3$	"	(305)	32	"
(305) $R^1=CH_3, R^4=R^5=OCH_3$	"	(307)	53	"
(308) $R^5=R^2=CH_3$	"	(309)	40	"
(310) $R^1=R^5=CH_3$	"	(311)	69	"
(312) $R^1=CH_3, R^5=R^6=Cl$	"	(313)	29	"
				
(314,316,318)		(315,317,319)		

*These 2-amino-3,4-dihydro-1,5-benzodiazocines were converted into many other derivatives. 193-197

Table 10 (continued)

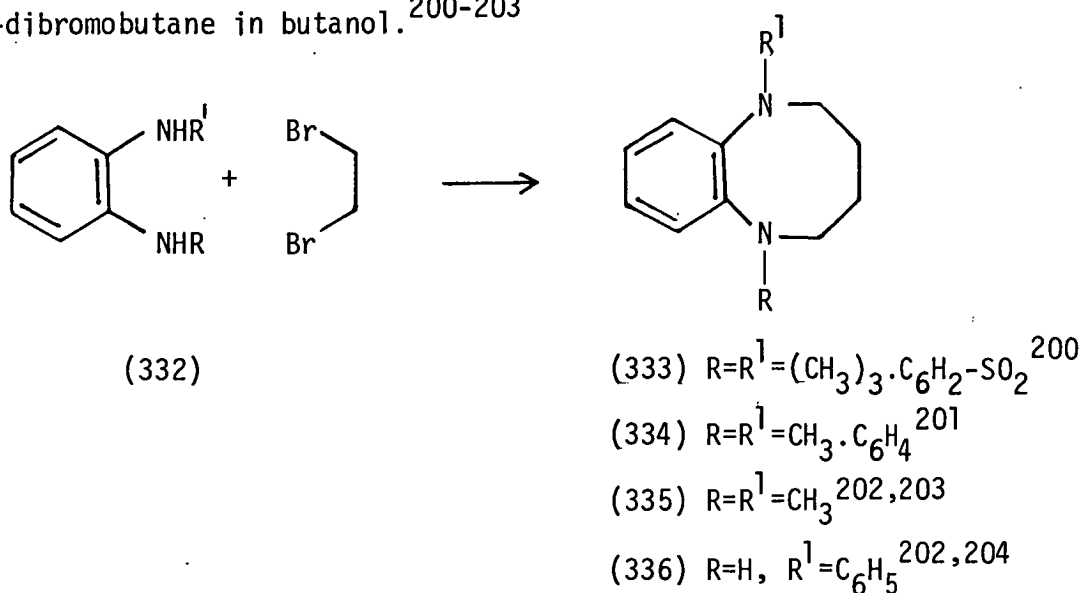
<p>(314) $R=CH_2C_6H_5$</p> <p>(316) $R=C_6H_5$</p> <p>(318) $R=4-CH_3 \cdot C_6H_4 \cdot SO_2$</p>  <p>(320) $R=H, R^1=C_6H_5$</p> <p>(322) $R=H, R^1=CH_2C_6H_5$</p>	<p>$K_2CO_3/DMF/\Delta$</p> <p>"</p> <p>"</p> <p>dioxane/$(C_2H_5)_3\Delta$</p> <p>"</p>	<p>(315) $R=CH_2-C_6H_5$</p> <p>(317) $R=C_6H_5$</p> <p>(319) $4-CH_3 \cdot C_6H_4 \cdot SO_2$</p>  <p>(321) $R^1=C_6H_5, R=H$</p> <p>(323) $R^1=CH_2C_6H_5, R=H$</p>	<p>64</p> <p>29</p> <p>185</p> <p>185</p> <p>186</p> <p>187</p>	<p>185</p> <p>185</p> <p>185</p>
<p>(324)</p>  <p>(326) $R=4-ClC_6H_5$</p>  <p>(328)</p> <p>Ts = tosyl</p>  <p>(330)</p> 	<p>$CH_3/NH_2/\Delta$</p> <p>THF/diborane</p> <p>BuOH/Na</p> <p>Δ</p> <p>condensation</p>	<p>(325) $R=R^1=CH_3$</p>  <p>(327) $\begin{cases} R=4-ClC_6H_5 \\ R^1=CH_3 \end{cases}$</p> <p>(329) $R=R^1=\text{tosyl}$</p>  <p>(331)</p>	<p>70</p> <p>189</p> <p>189</p> <p>190</p> <p>191</p> <p>192</p>	<p>188</p> <p>189</p> <p>190</p> <p>191</p> <p>192</p>

When not specified $R^n=H$. ($n=1,2,3,\dots$)

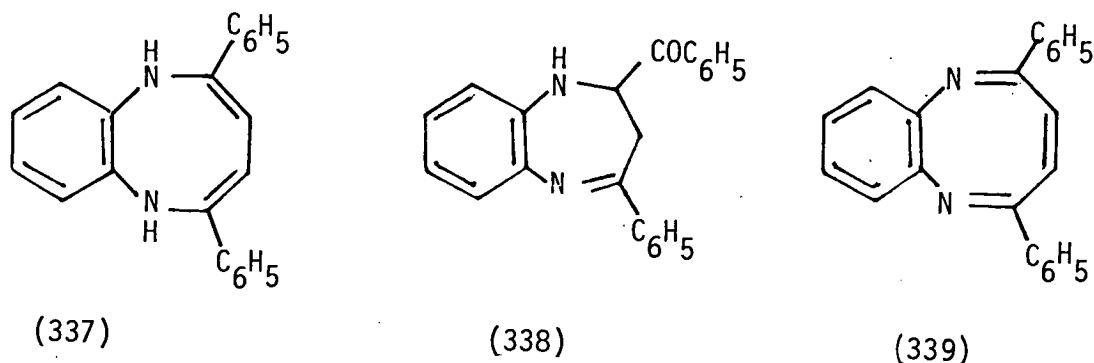
by the reduction of the dihydro derivative.¹⁹⁸ The hexahydro derivative of (306) was converted into the pyrido[3,2-*l*-*k*]-1,5-benzodiazocine derivative by cyclization with β -propiolactone.¹⁹⁹

B(ii)-(4) 1,6-Benzodiazocines

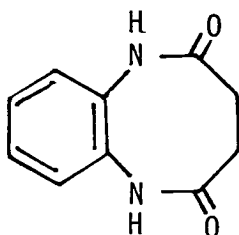
Several 1,6-benzodiazocines were prepared in moderate yields by the condensation of *o*-phenylenediamine derivatives (322) with 1,4-dibromobutane in butanol.²⁰⁰⁻²⁰³



The condensation of *o*-phenylenediamine (322, R=H) with 1,2-dibenzoylthane resulted in the formation of 2,5-diphenyl-1,6-dihydro-1,6-benzodiazocine (337) and a seven-membered ring product (338),²⁰⁵ but not the earlier reported²⁰⁶ 2,5-diphenyl-1,6-benzodiazocine (339). However the yield of (337) was only 7%, and (338) was the major product.



The reaction of (332, R=H) and diethyl succinate in a solution of dimethylformamide containing sodium hydride afforded the 3,4-dihydro-1,6-benzodiazocine-2,5-(1*H*,6*H*)-dione (340) in 8% yield.^{207,208}

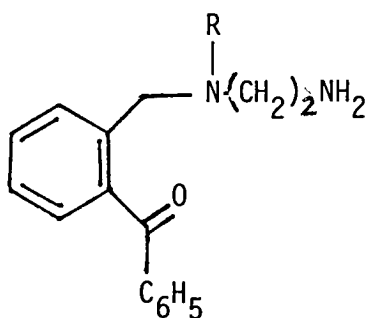


(340)

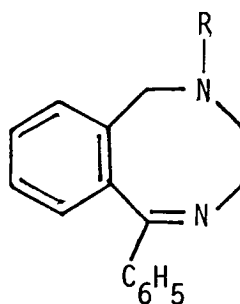
The parent ring system, 1,6-benzodiazocine, having molecular formula $C_{10}H_8N_2$, appears in the Ring Index,²⁰⁹ but further details could not be obtained.

B(ii)-(5) 2,5-Benzodiazocines

Sulkowski and co-workers^{148,210,211} described the synthesis of (343,344) by the cyclodehydration of (341,342) in the presence of pyridine. The early work carried out by the same authors¹⁴⁸ reported that the cyclodehydration was effected by refluxing (341) in pyridine containing a catalytic amount of pyridine hydrochloride. In the absence of the catalyst, only starting material was recovered.



(341)

R = $SO_2C_6H_5$ 

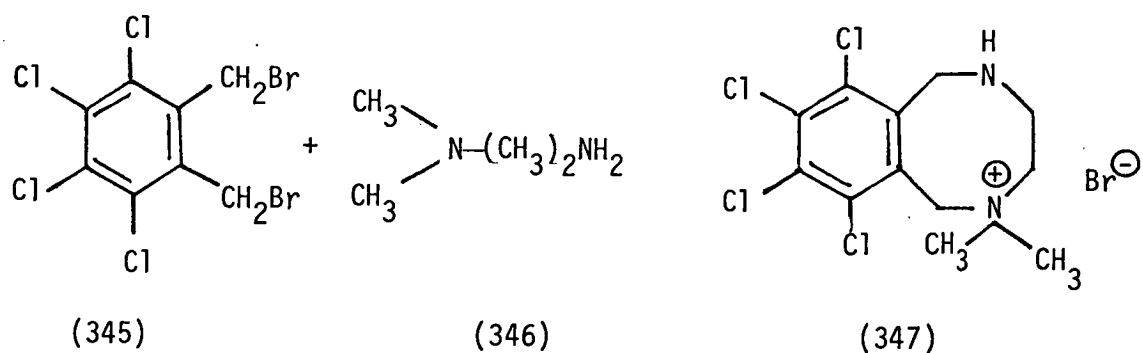
(343)

(342)

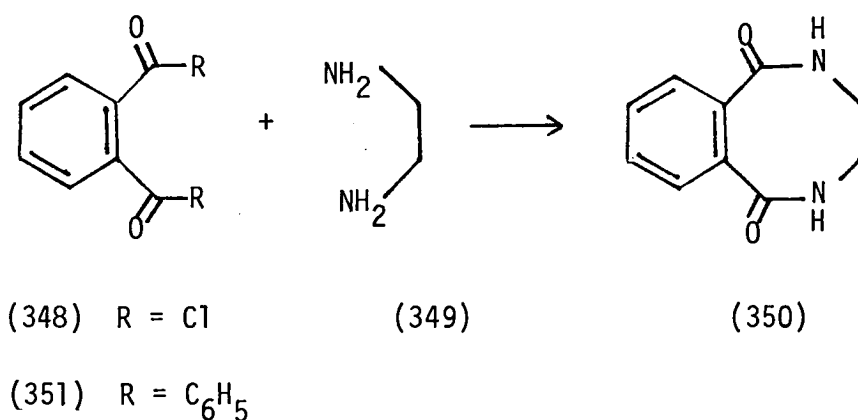
R = $SO_2 \cdot C_6H_4CH_3$

(344)

The 2,5-benzodiazocinium bromide (347) was prepared in high yield by the condensation of (345) and 2-dimethylaminoethylamine (346) in hydrobromic acid.^{212,213}



The dione derivative (350) was also prepared in 32% yield by the condensation of (348) and ethylenediamine (349).²¹⁴



Attempts to synthesise (350) from 2-aminoethylphthalimide were unsuccessful because of competing inter- and intramolecular reactions.^{215,216}

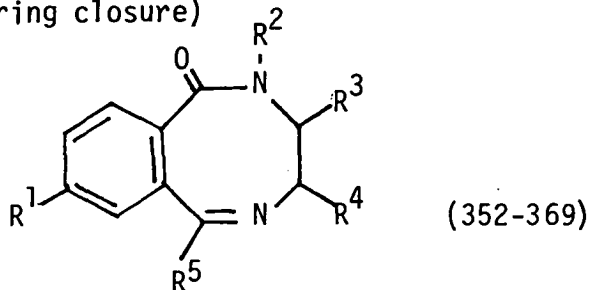
The condensation of (351) with (349) resulted in the formation of a lactam (352).²¹⁷ Several other 2,5-benzodiazocines (353-369) were reported similarly.²¹⁷ (Table 11).

The hexahydro derivatives (370,371) also appear to have been

Table 11

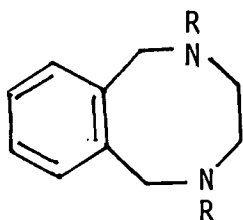
B(ii)-(5) 2,5-Benzodiazocines

(C-N type ring closure)



Compound number	R ¹	R ²	R ³	R ⁴	R ⁵
(352)	H	H	H	H	C ₆ H ₅
(353)	H	C ₂ H ₅	H	H	C ₆ H ₅
(354)	H	H	H	H	4-Cl C ₆ H ₄
(355)	H	C ₂ H ₅	H	H	4-Cl C ₆ H ₄
(356)	H	H	H	H	4-OCH ₃ C ₆ H ₄
(357)	H	H	CH ₃	CH ₃	C ₆ H ₅
(358)	H	H	CH ₃	H	C ₆ H ₅
(359)	H	H	H	H	CH ₂ -C ₆ H ₅
(360)	H	H	CH ₃	H	4-Cl C ₆ H ₄
(361)	NO ₂	H	H	H	C ₆ H ₅
(362)	H	H	H	H	2-thienyl
(363)	H	H	CH ₃	CH ₃	2-thienyl
(364)	H	H	H	H	4-F-C ₆ H ₄
(365)	H	H	OH	OH	4-OH C ₆ H ₄
(366)	H	H	H	H	4,3-Cl(NH ₂)C ₆ H ₃
(367)	H	H	H	CH ₃	4-Cl C ₆ H ₄
(368)	H	CH ₃	H	H	4,3-Cl(NH ₂)C ₆ H ₃
(369)	H	CH ₃	H	H	4-Cl C ₆ H ₄

prepared by the condensation of (349) with the corresponding ortho-substituted benzene derivative.²¹⁸



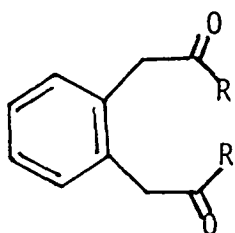
(370) R = H

(371) R = tosyl

B(ii)-(6) 3,4-Benzodiazocines

The reaction of the diketone (372) and hydrazine hydrobromide in dimethylformamide, under high dilution conditions, afforded a low yield of 2,5-diphenyl-1,6-dihydro-3,4-benzodiazocine (375).²¹⁹

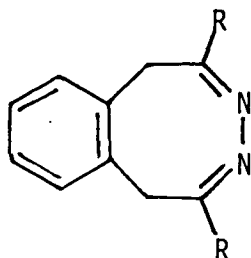
Similarly (376) and (377) were prepared from the corresponding diketone. Attempted isomerization of (375) into (378), using 5% palladium on charcoal was unsuccessful.²¹⁹



(372) R = C₆H₅

(373) R = 2,4-xylyl

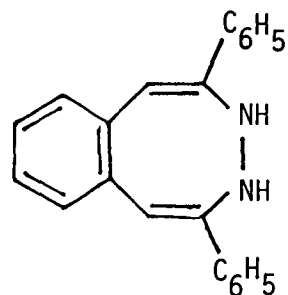
(374) R = H



(375)

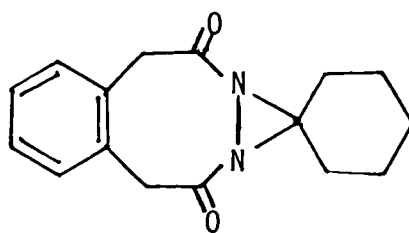
(376)

(377)



(378)

The novel spiro derivative (379) was synthesised by the reaction of *o*-benzenediacylchloride and 3,3-pentamethylenediaziridine in anhydrous ether.²²⁰



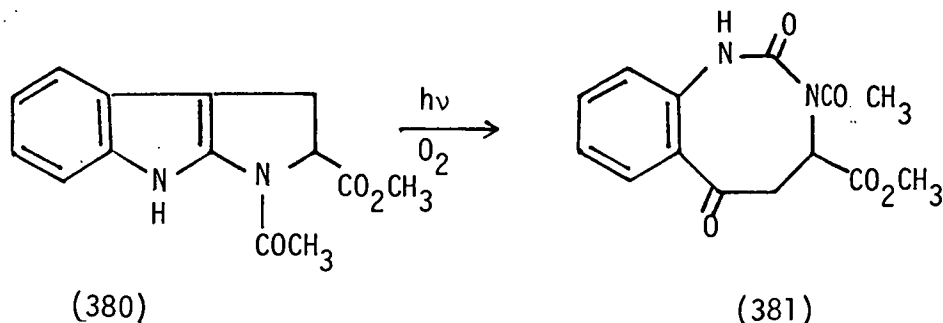
(379)

(C) Photochemical preparations

Photochemical reactions have not been widely used for the synthesis of benzodiazocine derivatives. One isomer of 1,3-benzodiazocine and two isomers of 1,5-benzodiazocine were prepared by photochemical methods.

C-(1) 1,3-Benzodiazocines

The photooxygenation of (380) in methanol gave the eight-membered ring dione (381).²²¹

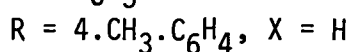
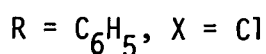
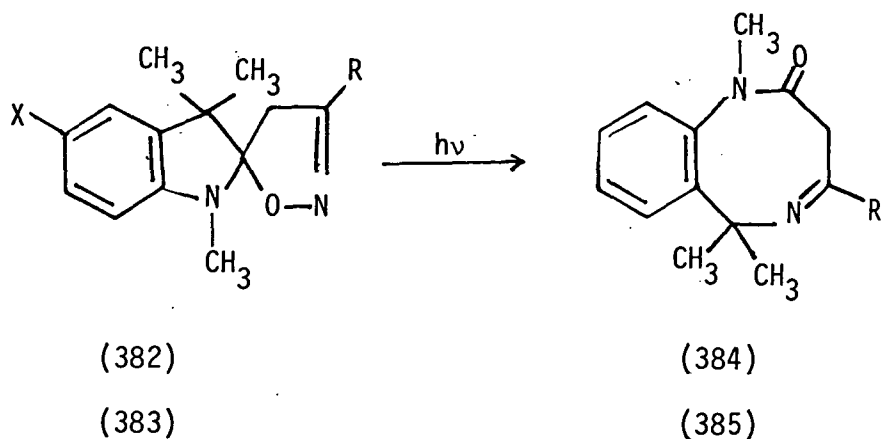


(380)

(381)

C-(2) 1,5-Benzodiazocines

Irradiation of (382,383) in tetrahydrofuran, for one hour, resulted^{222,223} in the formation of 1,5-benzodiazocines (384,385) in 70% yield in each case.

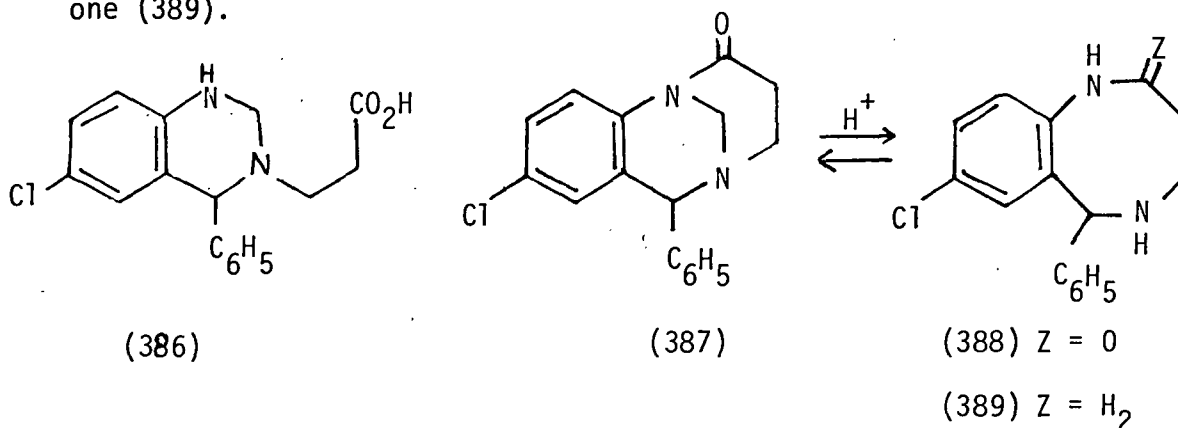


(D) Synthesis of benzodiazocines from bridge-head compounds

This method was used to synthesise derivatives of 1,5-benzodiazocines alone.

(D)-(1) 1,5-Benzodiazocines

Denzer and Ott²²⁴⁻²²⁶ reported a novel route for the preparation of 1,5-benzodiazocines, by bridging the two nitrogen atoms of tetrahydroquinazoline (386) to form the 1,5-methano derivative (387). Then (387) was reacted with hydrochloric acid in dioxan and water to yield (388) in 89% yield. On the other hand hydrogenolysis of the bridge-head lactam (387) with platinum in glacial acetic acid afforded 8-chloro-5-methyl-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocine-2(1H)-one (389).



Ferretti and co-workers²²⁷ have discussed the aromaticity of dihydro-1,6-, -2,5- and -3,4-benzodiazocines

Chapter 4

Benzoxazocines

Out of the fifteen possible isomers of benzoxazocine ring systems, only seven (A-G) have been synthesised so far. (Figure 10).

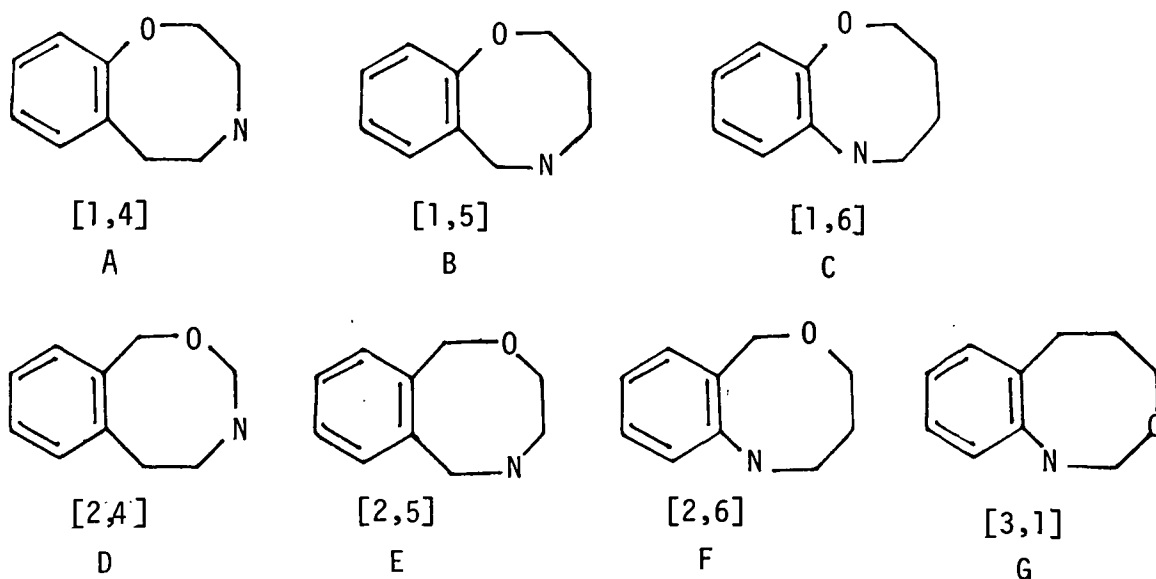


Figure 10

The preparative methods employed to construct these eight-membered rings are (A) ring enlargements and (B) ring closure reactions. Unlike the situation with benzazocines and benzodiazocines, photochemical reactions have not been employed to synthesise benzoxazocines.

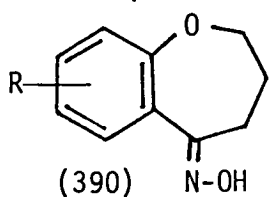
Methods of Preparation

(A) Ring enlargements

The Beckmann and the Schmidt rearrangements have been employed to synthesise 1,5- and 1,6-benzoxazocines, while a 2,4-benzoxazocine was synthesised by the ring expansion of an isoquinoline derivative. The applications of these rearrangements are few and the Beckmann and the Schmidt reaction always gave mixtures of 1,5- and 1,6-isomers.

A(i) RearrangementsA(i) (a) Beckmann rearrangementA(i)a-(1) 1,5-Benzoxazocines

Beckmann rearrangement of the benzoxepine oximes (390a-d) gave a mixture of 1,5- and 1,6-benzoxazocines (391,392) due to concurrent alkyl and aryl migrations respectively. Attempted rearrangement of (390f) was not successful, and it was found that both electronic and steric factors were operative in this rearrangement.²²⁸ The rearrangement of (390e) with phosphorus pentachloride in a mixture of benzene and ether yielded only a small amount of the lactam (391e).²²⁹ The yield of (391e) and the formation of isomers were not reported.

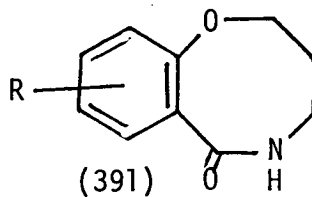


R

(a), H

(b), 8-CH₃(c), 6,8-(CH₃)₂(d), 7,8-(CH₃)₂

(e), 8-Cl

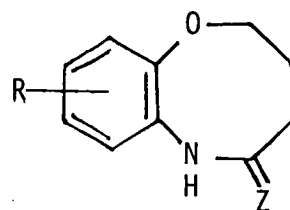
(f), 7-CH₃

R

(a), H

(b), 9-CH₃(c), 7,9-(CH₃)₂(d), 8,9-(CH₃)₂

(e), 9-Cl

(f), 8-CH₃

(392a) Z=O

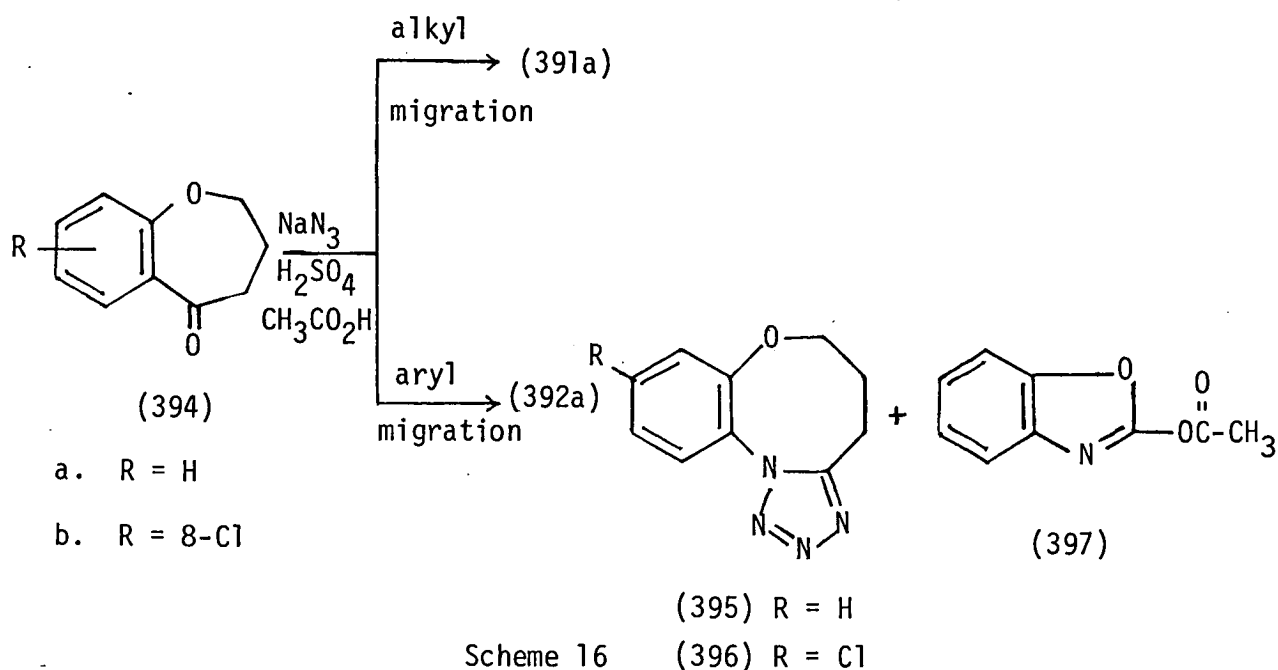
(393) Z=2H

A(i)a-(2) 1,6-Benzoxazocines

The 1,6-benzoxazocine (392c) was obtained in 66% yield by the Beckmann rearrangement of (390c).²³⁰ The formation of the 1,5-isomer was not reported.

A(b) Schmidt reactionA(b)-(i) 1,6- and 1,5-Benzoxazocines

When 2,4-dihydro-1-benzoxepin-5(2*H*)one (394a) was subjected to the Schmidt reaction in concentrated sulfuric acid and sodium azide in glacial acetic acid, a mixture of 3,4-dihydro-2*H*-1,6-benzoxazocine-5-(6*H*)one (392a, 54%), 4,5-dihydro-6*H*-tetrazolo[5,1-*e*]-1,6-benzoxazocine (395, 4%), 2-(3-acetoxy-propyl)benzoxazole (397, 13%) and 2,3,4,5-tetrahydro-1,5-benzoxazocine (391a, 5%) were obtained.^{24,231} The 1,6-benzoxazocine derivatives and compound (397) were formed by aryl migration, while the 1,5-benzoxazocine was formed by alkyl migration (Scheme 16); a subsequent ring contraction is also involved in the case of (397).

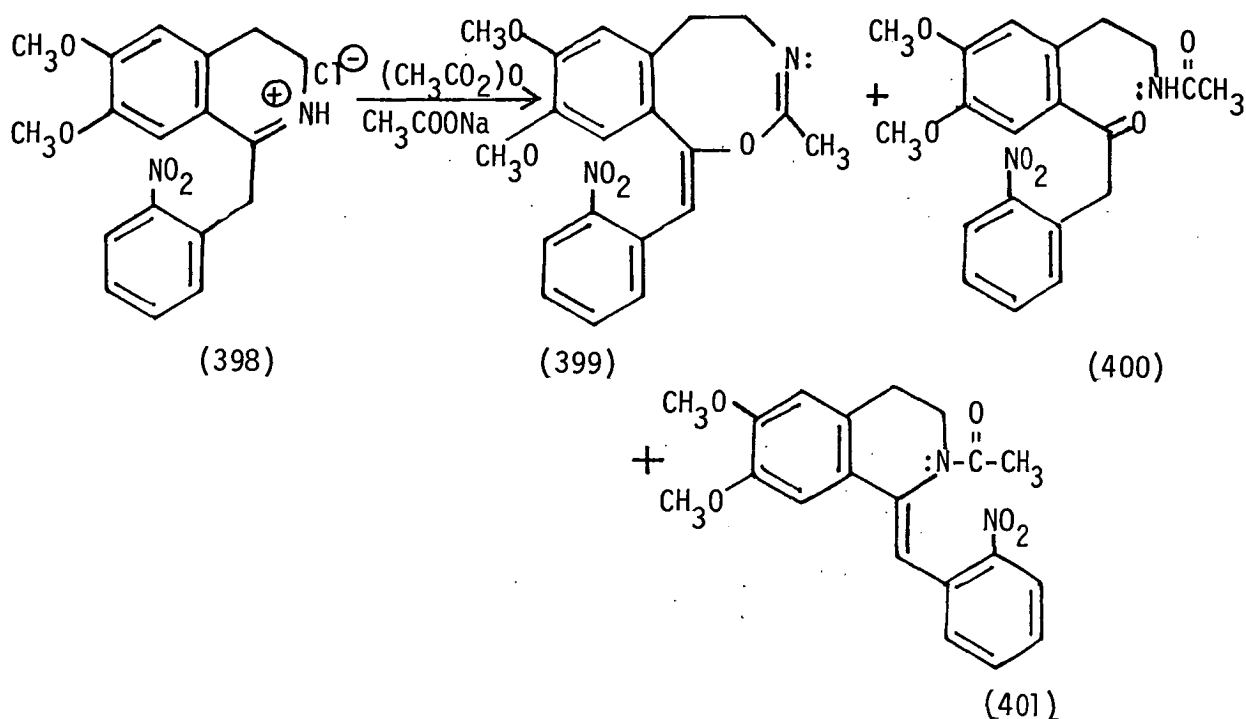


It has been reported that the Schmidt reaction on (394b) only gave the tetrazole derivative (396) in 23% yield.²²⁹

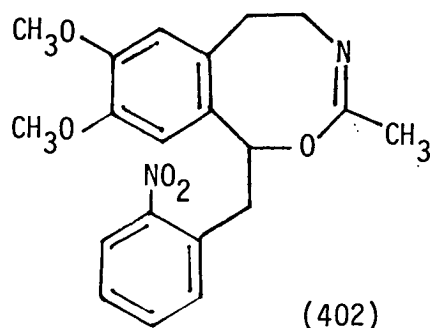
In five and six-membered fused ring ketones the alkyl migration is predominant and it is influenced by the electronic effects of the hetero atom ortho to the carbonyl group. These effects do not operate in the seven-membered cyclic ketones because of the

A(ii) Ring enlargement of six-membered ringsA(ii)-(1) 2,4-Benzoxazocines

The acetylation of 3,4-dihydro-6,7-dimethoxy-1-(2-nitrobenzyl)-isoquinoline hydrochloride (398) with acetic anhydride and sodium acetate afforded the 2,4-benzoxazocine (399) together with two other products (400 and 401).²³⁴ The reported yield of (399) was 60% and it was found to be the *cis*-isomer, on the basis of the spectroscopic data and the chemical analysis. A mechanism for this interesting ring expansion was not given.

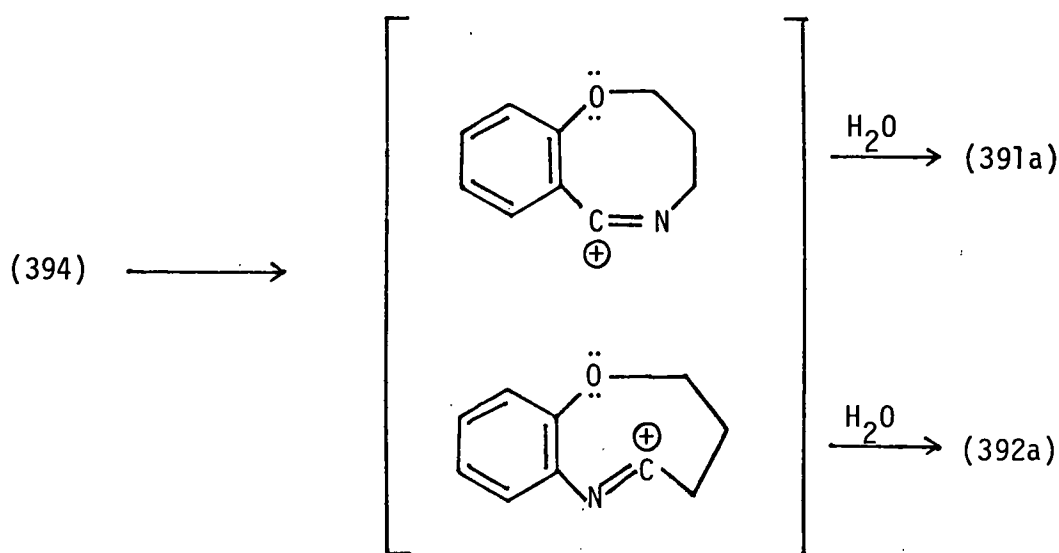


The action of 98-100% formic acid and formamide on (399) gave the compound (402).



flexibility of the ring. Therefore the aryl migration products are formed in an increased ratio.²⁴ It has been found by the same workers, that the eight-membered cyclic ketones undergo only aryl migration.

Kawamoto and co-workers²³¹ have reported the formation of 1,6- and 1,5-isomers in a ratio of 7:3 when the ketone (394a) was treated with trichloroacetic acid and sodium azide. The mechanism proposed is illustrated in Scheme 17.



Scheme 17

A paper by Tandon and co-workers²³² described the synthesis of (392f) and (392d) by the Beckmann rearrangement of the corresponding ketones. However in this case, the formation of the 1,5-isomer was not reported. The reduction of these lactams resulted in the formation of the amines (393d and 393f), while the oximes (390b) and (390c), afforded (393 and 393) respectively, along with the 5-amino-benzoxazepine derivative in equal yields.²³² The compound (393f) was converted into various *N*-substituted derivatives.²³³

(B) Ring closures

Derivatives of 1,5-, 2,5-, 2,6-, 3,1-, and 1,4-benzoxazocines have been synthesised by ring closure of the C-O and C-N type. The synthesis of benzoxazocines by ring closure of the C-C type has not been reported to date.

B-(i) Ring closure of C-O type

Ring closures of the types A to E shown in Figure 9 have been employed to construct the 1,5-, 2,5-, 2,6-, 3,1- and 1,4-benzoxazocines.

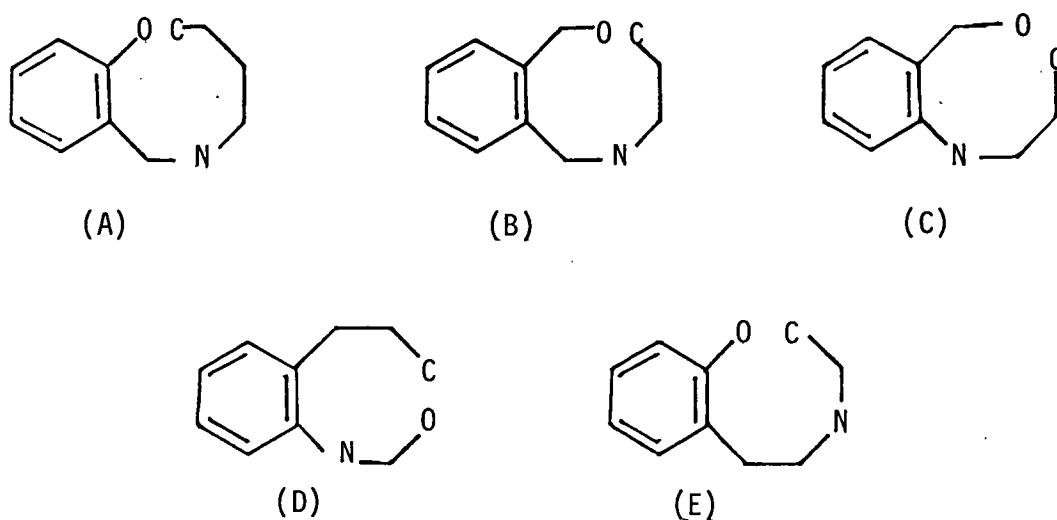
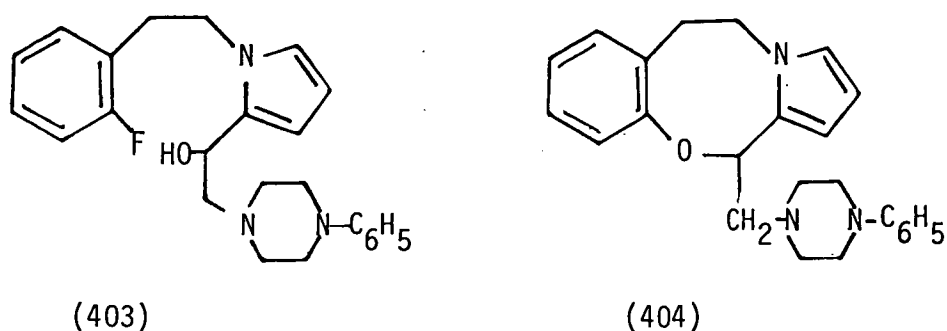


Figure 9

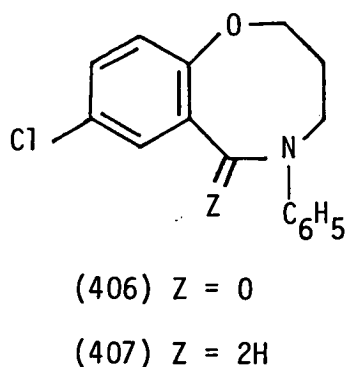
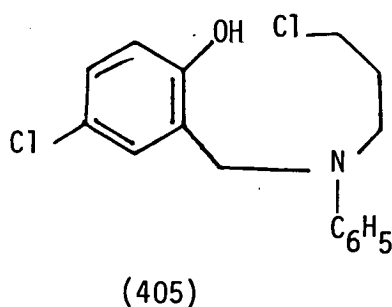
B(i)-(1) 1,4-Benzoxazocines

The treatment of (403) with sodium hydride afforded the 1,4-benzoxazocine (404). The yield of (404) was not reported.²³⁵

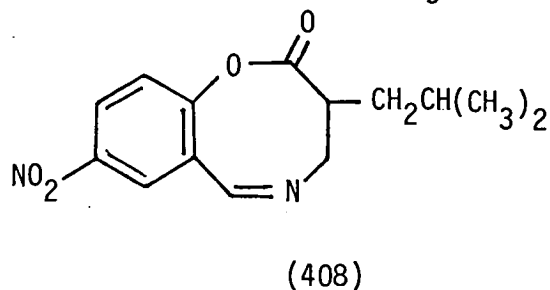


B(i)-(2) 1,5-Benzoxazocines

The cyclization of the compound (405) with sodium carbonate gave the lactam (406), which on reduction afforded the tertiary amine (407).²³⁶

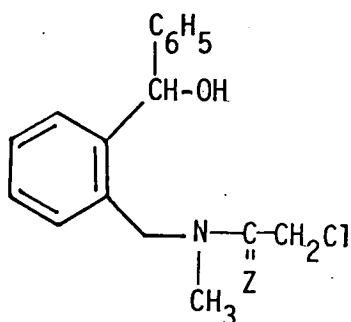


In a patent by Bodanszky,²³⁷ the synthesis of 8-nitro-3,4-dihydro-3-(2-methylpropyl)-2*H*-1,5-benzoxazocine-2-one (408) was reported, although no experimental details were given.

B(i)-(3) 2,5-Benzoxazocines

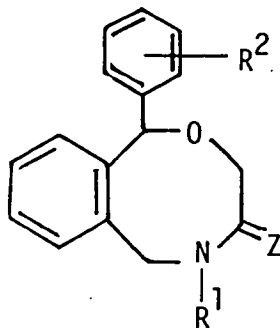
The ring closure of (409) with potassium-*t*-butoxide in dimethylsulfoxide gave the lactam (411), which afforded 5-methyl-1-phenyl-1,3,4,6-tetrahydro-2,5-benzoxazocine (412) on lithium aluminium hydride reduction.²³⁸ Apart from this method, the compound (412) could be prepared directly by the ring closure of (410) with *p*-toluenesulfonic acid in xylene,²³⁸ or in benzene²³⁹ or with aqueous hydrobromic acid in chloroform.^{240,241} The yield of (412)

was 81% and 95% respectively. The 2,5-benzoxazocines (413-417) were prepared similarly.²³⁸



(409) Z=O

(410) Z=2H



(411) Z=O, R¹=CH₃, R²=H

(412) Z=2H, R¹=CH₃, R²=H

(413) Z=2H, R¹=CH₃, R²=4-Cl

(414) Z=2H, R¹=CH₃·HCl, R²=5-Cl

(415) Z=2H, R¹=CH₃, R²=2-CH₃

(416) Z=2H, R¹=CH₃·HCl, R²=5-OCH₃

(417) Z=2H, R¹=C₂H₅·HCl, R²=H

(418) Z=2H, R¹=R²=H, R²=H

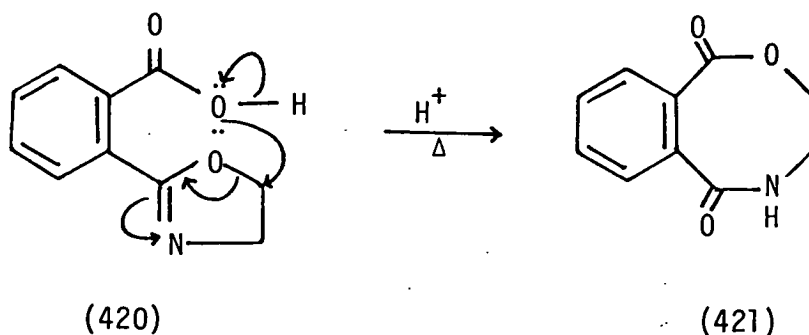
(419) Z=2H, R¹=(CH₂)₃NH₂, R²=H

The cyclization of *o*-benzylbenzoyl chloride with 2-(dimethylamino) ethanol followed by reduction also afforded the 2,5-benzoxazocine (412).²⁴² The hydrochloride salt of (412) is known as *Nefopam*, which is being used as a pain-relieving agent.²⁴⁶⁻²⁶⁶ A number of metabolic and analytical studies on *Nefopam* have been reported.²⁴³⁻²⁴⁵

The action of acrylonitrile on (418) followed by reduction with 5% palladium on carbon, afforded the 5-(3-aminopropyl)-derivative (419) which was a central nervous system depressant.²⁶⁷ The synthesis of (418) was not given in the patent.

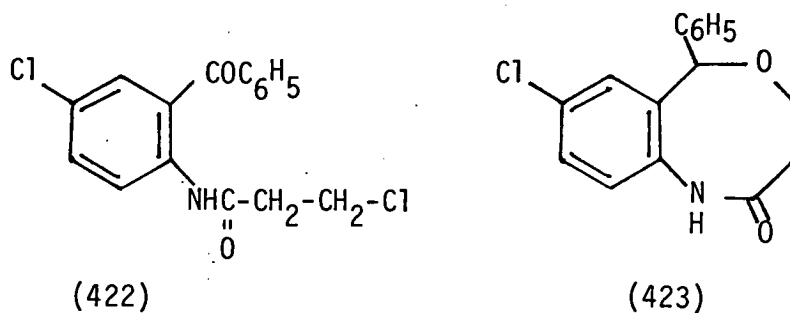
The 2,6-dione derivative (421) was prepared in 77% yield by the action of 15% potassium bromide and hydrochloric acid on 2-bromo-ethylphthalimide.^{268,269} It has been found that nucleophilic

displacement of the bromo group by the carboxyl oxygen could yield (421), while (420) could be obtained by a displacement involving the amide oxygen.²⁶⁸ The isomer (420) can be rearranged into (421).

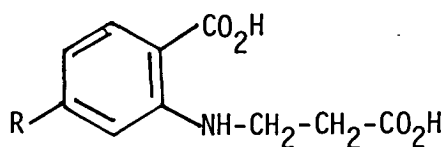


B(i)-(4) 2,6-Benzoxazocines

The sodium tetrahydroborate reduction of 2-(β -chloropropi-amido)5-chlorobenzophenone (422) in methanol gave an intermediate which afforded the lactam (423) on treatment with sodium in methanol.²⁷⁰ The yield of (423) and the structure of the intermediate were not given in the patent.



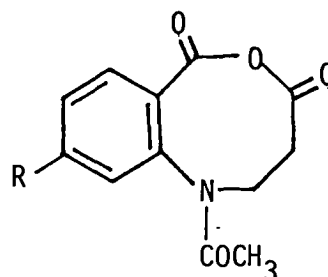
The cyclization of (420a,b) in the presence of potassium acetate in acetic anhydride gave the 2,6-benzoxazocine-1,3-dione derivatives (425a,b) as intermediates, which underwent ring contraction to form quinoline derivatives.²⁷¹



(424)

a, R = H

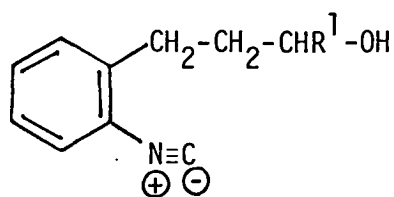
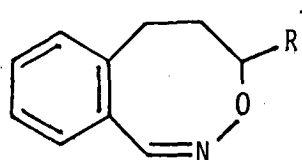
b, R = Cl



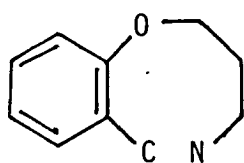
(425)

B(i)-(5) 3,1-Benzoxazocines

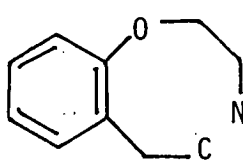
Ito *et al*²⁷² reported the formation of 4*H*-5,6-dihydro-4-methyl-3,1-benzoxazocine (427a) and 4-ethyl-3,1-benzoxazocine (427b) in low to moderate yields by the intramolecular cyclization of isonitriles (426a,b) respectively in the presence of copper oxide.

(426) a, R¹ = CH₃b, R¹ = C₂H₅(427) R¹ = CH₃(428) R¹ = CH₂CH₃B(ii) Ring closure C-N type

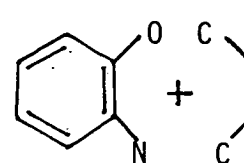
The 1,5- and 1,4-benzoxazocines have been synthesised by the formation of a C-N bond, and the types of C-N bond construction are given in Figure 11.



(A)



(B)

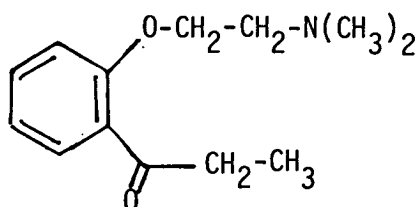


(C)

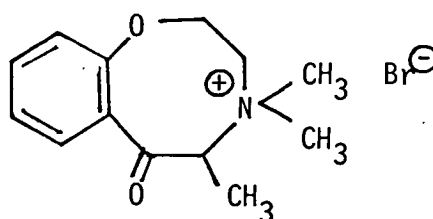
Figure 11

B(ii)-(1) 1,4-Benzoxazocines

The reaction of *o*-(2-dimethylaminoethoxy)propiophenone (429) with bromine followed by treatment with 20% sodium hydroxide in the cold resulted in the 1,4-benzoxazocine derivative (430).²⁷³



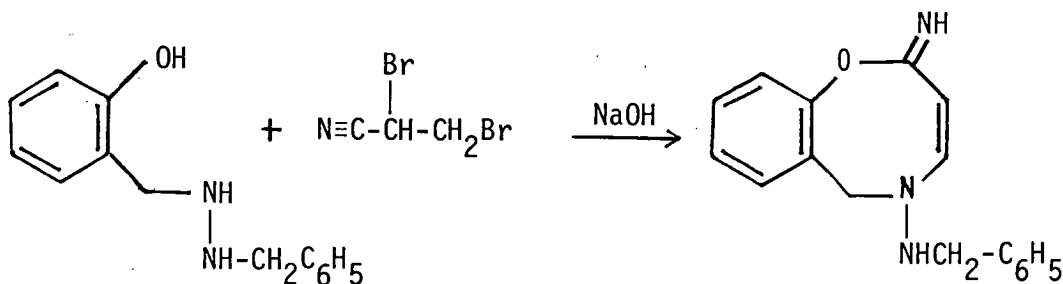
(429)



(430)

B(ii)-(2) 1,5-Benzoxazocines

The condensation of 2,3-dibromopropionitrile and (431) gave 2-imino-5-benzylamino-5,6-dihydro-1,5-benzoxazocine (432) in 32% yield.²⁷⁴



(431)

(432)

A series of 1,5-benzoxazocines were prepared by the treatment of an appropriate *o*-acetylphenoxy propane epoxide (433) with ammonia in anhydrous methanol at room temperature.²⁷⁵ The cyclization proceeded slowly through the formation of an intermediate amino alcohol (434). Attempts made to accelerate this process resulted in decreased yields. The 1,5-benzoxazocines obtained by this method are given in Table 13. Pharmacological studies of (435) have been reported by Caputi and

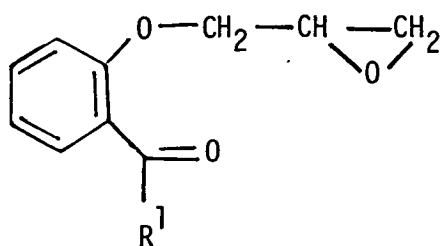
Table 13

B(ii)-(2) 1,5-Benzoxazocines

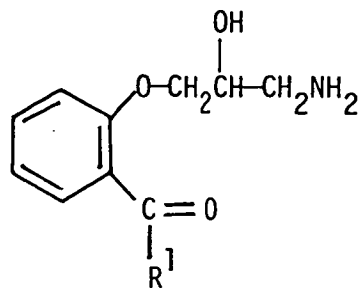
(C-N type ring closure)

Compound No.	R ¹	Other substituents	Yield %
(435)	CH ₃	-	38
(436)	C ₂ H ₅	-	23
(437)	<i>n</i> -C ₃ H ₇	-	8
(438)	<i>i</i> -C ₃ H ₇	-	5
(439)	<i>t</i> -C ₄ H ₉	-	2
(440)	C ₆ H ₅	-	12
(441)	4-CH ₃ C ₆ H ₄	-	5
(442)	CH ₂ -C ₆ H ₅	-	6
(443)	(CH ₂) ₂ -C ₆ H ₅	-	7
(444)	CH=CH-C ₆ H ₅	-	-
(445)	4-NO ₂ ·C ₆ H ₄ -CH=CH	-	-
(446)	2-C ₅ H ₄ O	-	5
(447)	CH ₃	3-CH ₃	19
(448)	CH ₃	8-Cl	6
(449)	CH ₃	8-C ₆ H ₅	4
(450)	CH ₃	8-NO ₂	-
(451)	CH ₃	9-C ₆ H ₅	15
(452)	CH ₃	8- <i>n</i> C ₃ H ₇ CONH	58
(453)	CH ₃	7,9-Cl ₂	8
(454)	CH ₃	8,10-Cl ₂	12
(455)	CH ₃	8,10-(CH ₃) ₂	4
(456)	CH ₃	9,10-C ₆ H ₂	34
(457)	CH ₃	5,6-H ₂	-

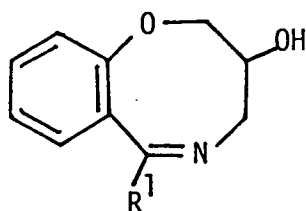
co-workers.²⁷⁶



(433)



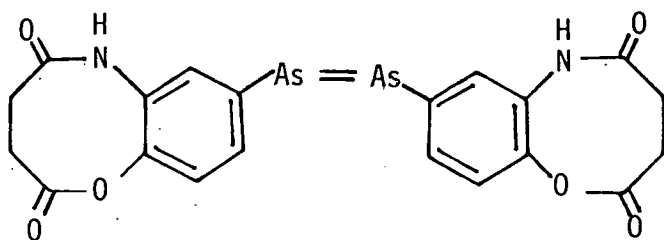
(434)



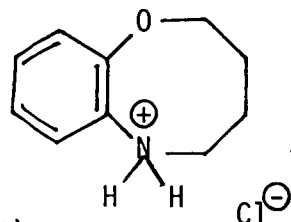
(435-457)

B(ii)-(3) 1,6-Benzoxazocines

A dimeric product (458) of 1,6-benzoxazocine was obtained by the reaction of 4-hydroxy-3-aminobenzenearsonic acid with an equal quantity of succinic anhydride.²⁷⁸



(458)



(459)

Orlova and co-workers²⁷⁸ reported the alkylation of the 1,6-benzoxazocine (459).

Chapter 5

Dibenzazocines

Examples of all six possible isomers of dibenzazocines have been synthesised and the skeleton of each isomer is illustrated in Figure 12.

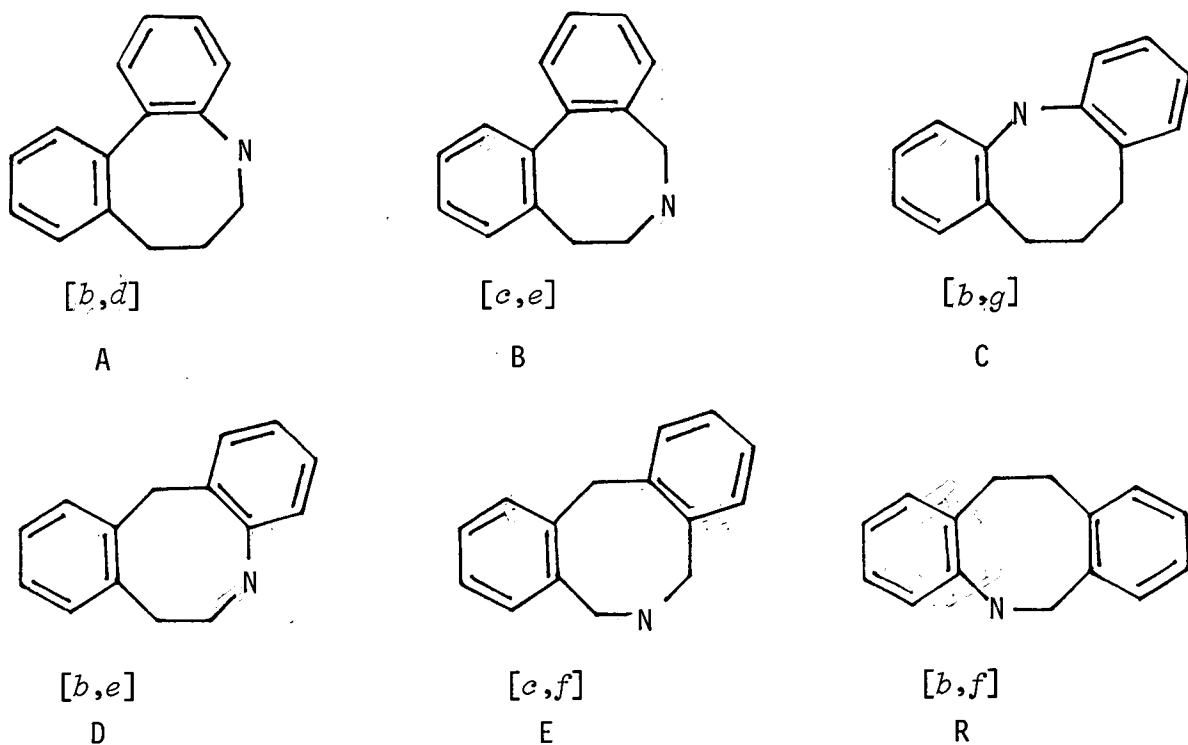


Figure 12

Derivatives of $[c,e]$ and $[b,f]$ dibenzazocines have been prepared in a larger number than the other isomers.

The synthetic methods employed to construct these tricyclic systems are similar to those for benzazocine derivatives, i.e.

- (A) ring enlargements
- (B) ring closures
- (C) photochemical preparations and
- (D) from bridge-head compounds.

The types of ring enlargements used are,

- (i) rearrangements
- (ii) ring enlargement followed by cleavage of an internal bond and,
- (iii) addition followed by ring enlargement.

As with the benzo analogues, the rearrangements employed are the Beckmann and the Schmidt reactions. The Beckmann rearrangement of tricyclic ketones is one of the most widely used methods while the application of the Schmidt reaction is limited to one case.

Methods of preparation

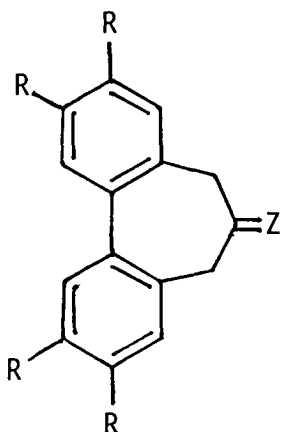
(A) Ring enlargements

(A)i Rearrangements

A(i)a Schmidt reaction

A(i)a-(1) Dibenz[*c,e*]azocines

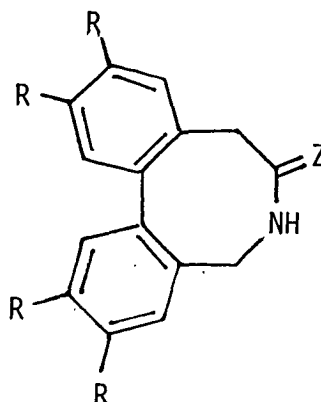
The reaction of tricyclic ketone (460) with sodium azide in trichloroacetic acid gave the ring expanded lactam, 5,6,7,8-tetrahydro-dibenz[*c,e*]azocine-6-one (463) in 60% yield.^{279,280} The formation of by-products were not reported. The reduction of (463) with lithium aluminium hydride afforded the tertiary amine (464).²⁸¹



(460) Z = O, R = H

(461) Z = NOH, R = H

(462) Z = NOH, R = OCH₃

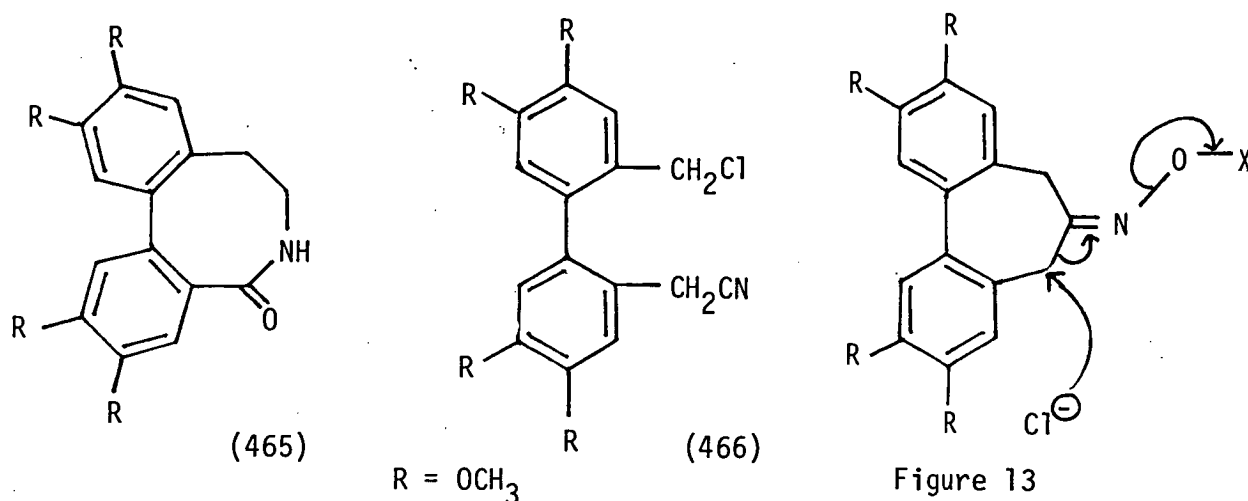


(463) Z = O, R = H

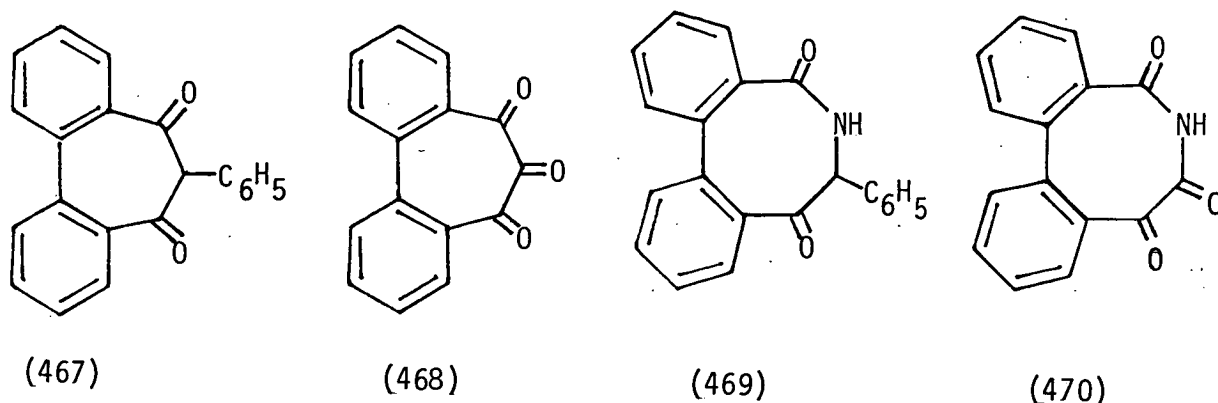
(464) Z = 2H, R = H

A(i)b Beckmann rearrangementA(i)b-(1) Dibenz[*c,e*]azocines

The Beckmann rearrangement of the oxime (461) in pyridine and benzenesulfonyl chloride yielded 67% of (463).²⁸² However the rearrangement of the substituted oxime (462) with phosphorus pentachloride in anhydrous benzene, proceeded with difficulty, giving rise to the lactam (465) in poor yield (10-40%).²⁸³ The major product was a nitrile (466) which was formed by the attack of chloride ion on the strained ring system. (Figure 13).



The treatment of polyphosphoric acid (PPA) at 100°, on the mono-oximes of (467) and (468) gave 7-phenyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine-5,8-dione (469) and 5,6,7,8-tetrahydrodibenz[*c,e*]azocine-5,7,8-trione (470) respectively.²⁸⁴

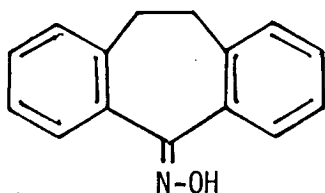


A(i)b-(2) Dibenz[*b,f*]azocines

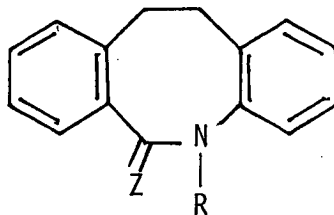
In the presence of phosphorus pentachloride at room temperature, the oxime (471), underwent the Beckmann rearrangement giving rise to a 65-90% yield of lactam (472).²⁸⁵⁻²⁸⁷ The reduction of (472) yielded the 5,6,11,12-tetrahydrodibenz[*b,f*]azocine (473) which was converted into various *N*-substituted derivatives.²⁸⁸⁻²⁹⁸

N-substituted derivatives of the lactam (472) have also been prepared.²⁹⁹⁻³⁰² Ollis and Stoddart³⁰³ have reported on conformational studies with the lactam (474). The lactam (476) was obtained in 90% yield by the Beckmann rearrangement of oxime (475) with polyphosphoric acid.^{286,304-308}

Replacing polyphosphoric acid with thionyl chloride in benzene, the oxime (475) afforded the 6-chlorodibenz[*b,f*]azocine (478) in 90% yield.^{309,310} The 6-methoxy derivative (479) was obtained by the reaction of (472) with trimethyloxonium fluoroborate followed by treatment with *N*-bromosuccinimide/benzoyl peroxide and then potassium-*tert*-butoxide.³ The *N*-methyl derivative of (477) was prepared³¹¹ by methylation of (476) followed by reduction.

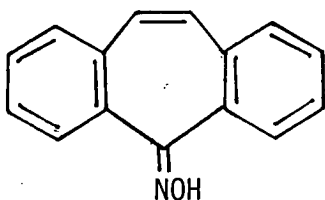


(471)

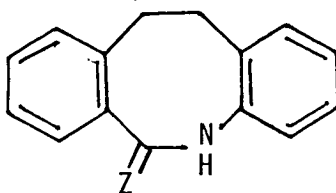


(472) Z = O, R = H

(473) Z = 2H, R = H

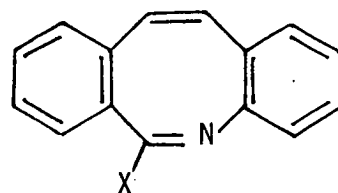
(474) Z = O, R = CH₂C₆H₅

(475)



(476) Z = O

(477) Z = 2H

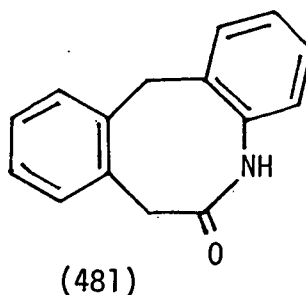
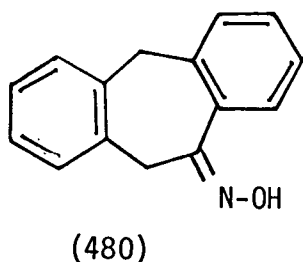


(478) X = Cl

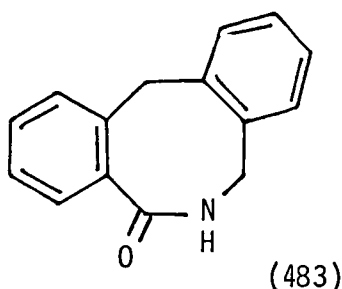
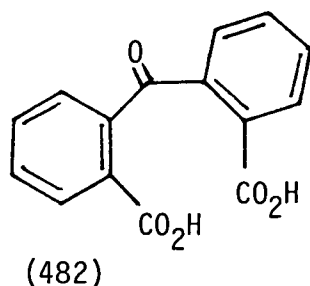
(479) X = OCH₃

A(i)b-(3) Dibenz[*b,e*]azocines

The treatment of (480) with phosphorus pentachloride in benzene gave the lactam (481), but the yield and any occurrence of side reactions were not reported.³¹² However, with phosphorus trichloride, the oxime (480) afforded (481) in 59% yield.³¹³

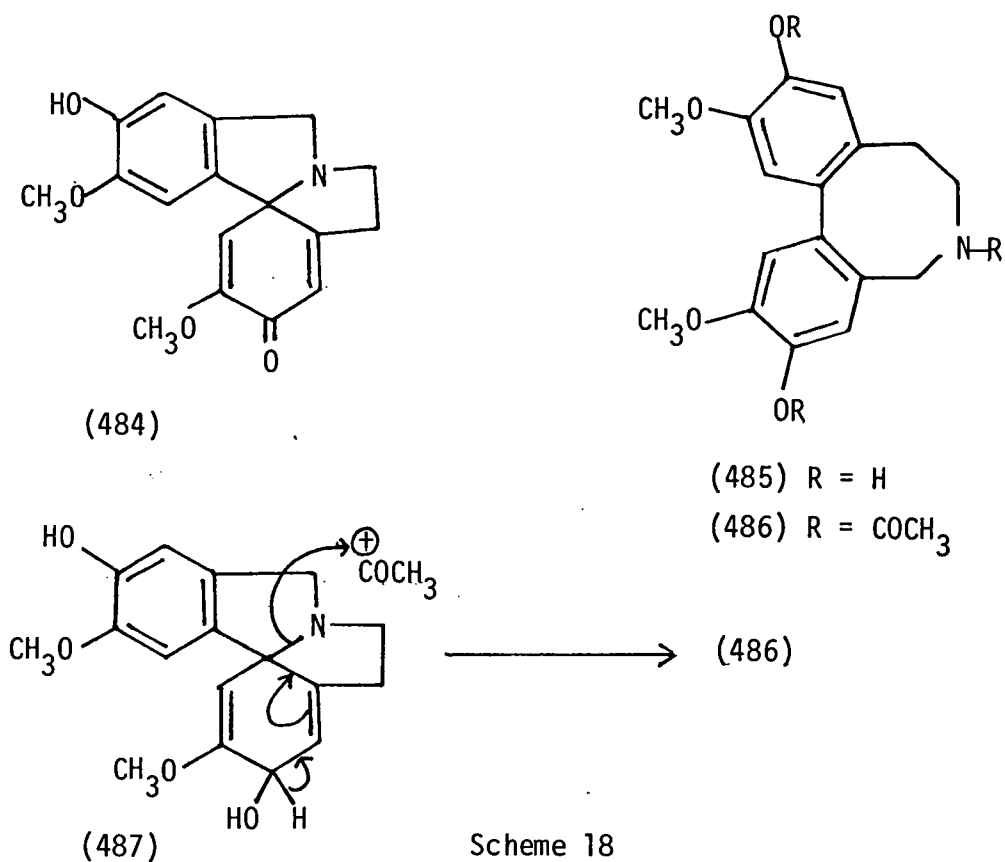
A(i)b-(4) Dibenz[*c,f*]azocines

The dibenz[*c,f*]azocine (483) was obtained from (482) via a lactone intermediate and subsequent reaction with ammonium hydroxide and ethanol.³¹⁴

A(i) Ring enlargement followed by cleavage of an internal bondA(ii)-(1) Dibenz[*c,e*]azocines

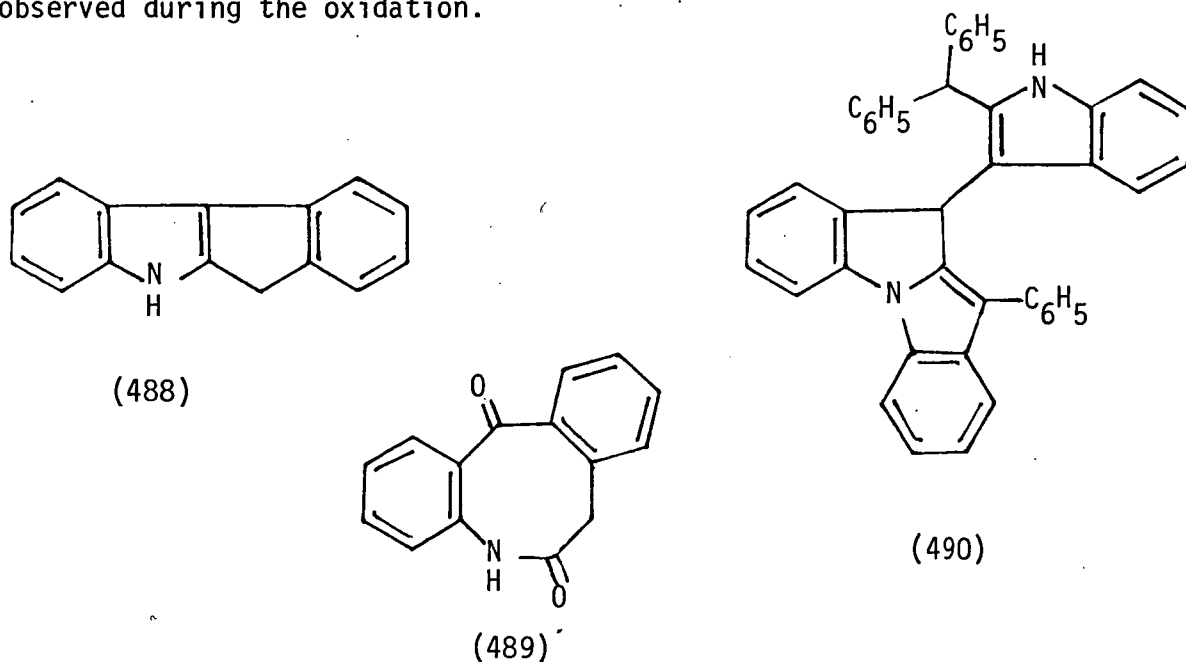
The dibenz[*c,e*]azocine (485) was obtained by the reductive cleavage of the dienone (484) on hydrogenation over 10% palladium-charcoal in ethanol.³¹⁵ The triacetate derivative (486) was obtained by a similar ring enlargement of (487) in the presence of 98% sulfuric

acid and acetic anhydride.³⁰⁹ (Scheme 18).



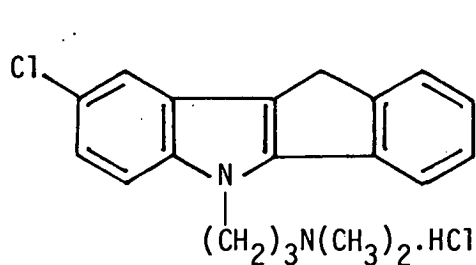
A(ii)-(2) Dibenz[b,e]azocines

Periodic acid or sodium metaperiodate oxidation of (488) gave 5,7-dihydrodibenz[b,e]azocine-6,12-(6*H*)-dione (489) in 71% and 49% yields respectively.³¹⁶ The formation of a dimer (490) was also observed during the oxidation.

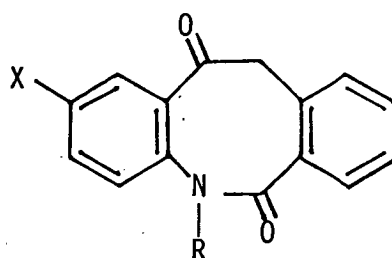


A(ii)-(3) Dibenz[*b,f*]azocines

The oxidative cleavage of 10-(2-dimethylaminoethyl)-7-chloro-5,10-dihydroindeno[1,2-*b*]indole hydrochloride (491) with ozone in acetic acid gave 2-chloro-5-(3-dimethylaminopropyl)-5,6,11,12-tetrahydrodibenz[*b,f*]-azocine-6,12-dione (492).³¹⁷ Similarly the diones (493-495) were prepared from the corresponding indeno[1,2-*b*]indole derivatives.^{317,318}



(491)

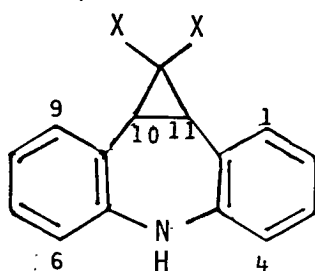
(492) R = (CH₂)₃N(CH₃)₂, X = Cl(493) R = (CH₂)₃N(CH₃)₂, X = Br(494) R = (CH₂)₃N(CH₃)₂, X = H(495) R = X = H.³¹⁸

Scheme 19

The reduction and dehydration of (492) resulted in the formation of the 2-chloro-5(3-dimethylaminopropyl)- derivative of (477).³¹⁹ Landquist and Sandstrom³²⁰ have investigated the barriers to ring inversion in the dibenzazocinone series.

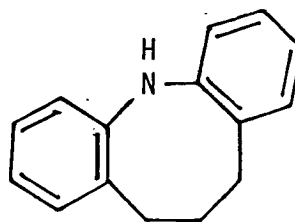
A(ii)-(4) Dibenz[*b,g*]azocines

A large excess of sodium in liquid ammonia, caused the cleavage of the C₁₀-C₁₁ bond of (496) and (497) giving rise to 5,6,7,12-tetrahydrodibenz[*b,g*]azocine (498) in 50% yield.³²¹



(496) X = Cl

(497) X = H



(498)

A(iii) Addition followed by ring enlargement

Only the dibenz[*c,e*]azocines have been prepared by this method, which has not been as widely used as the other preparative methods.

A(iii)-(1) Dibenz[*c,e*]azocines

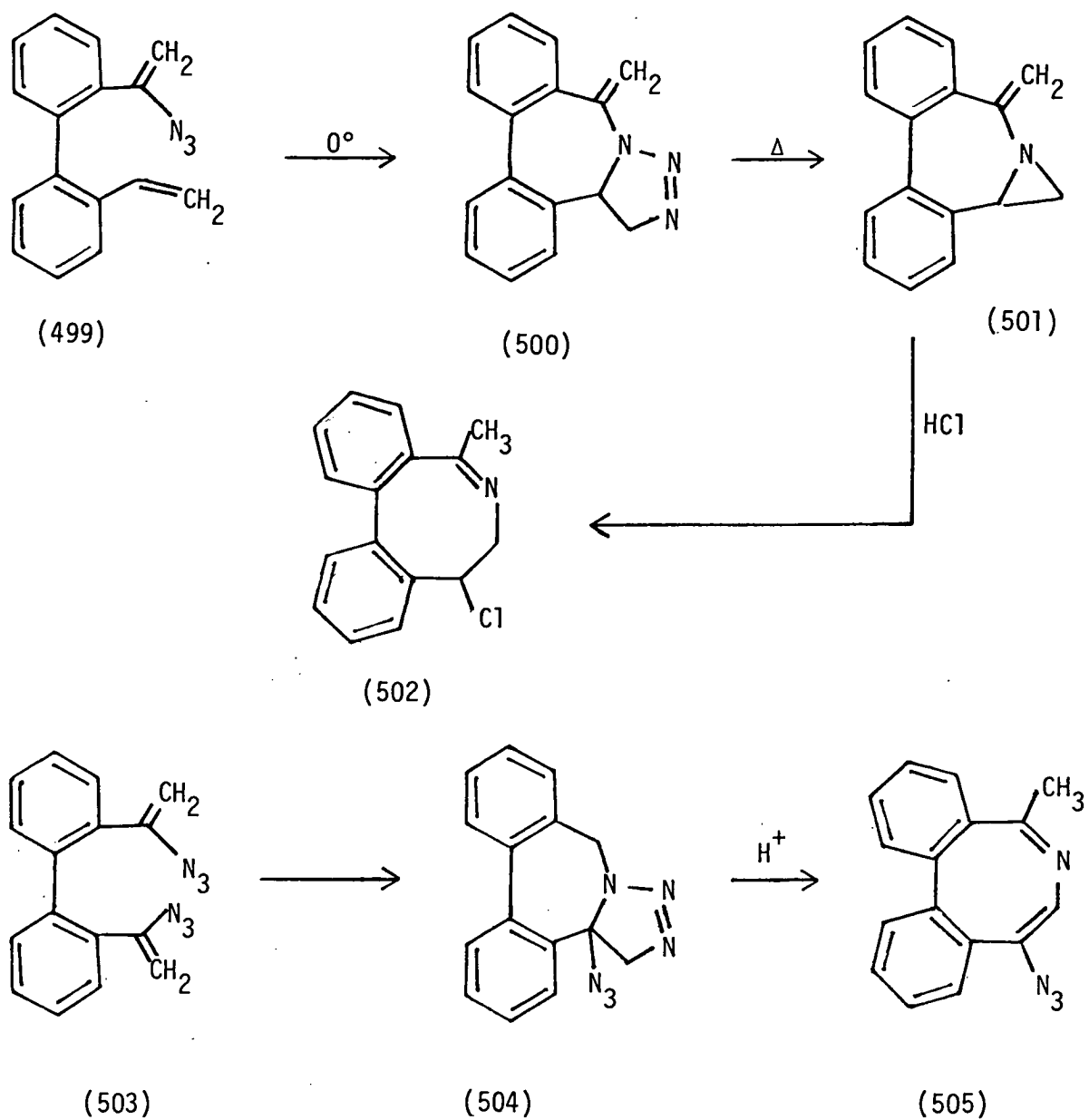
The mono-vinyl azide (499), which was obtained by the reaction of 2,2'-divinylbiphenyl and iodine azide, gave the cyclo-adduct (500), when allowed to stand at 0° for three days; thermal rearrangement of (500) then afforded (501). Addition of hydrochloric acid to (501) gave the ring expanded dibenzazocine derivative (502) in 68% yield.^{322,323} The cyclo-adduct (504) obtained by the thermolysis of divinyl azide (503) gave 8-azido-5-methyldibenz[*c,e*]azocine (505) when treated with acid.³²² (Scheme 19).

(B) Ring closure

B(i) C-C type

The methods employed for the synthesis of dibenzazocines by the formation of a C-C bond can be divided into three sub-divisions as,

- (a) Bischler-Napieralski type reactions,
- (b) Friedel-Crafts reaction and
- (c) Aryl-aryl coupling reactions.

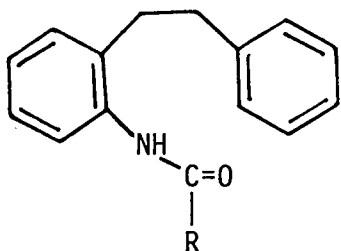
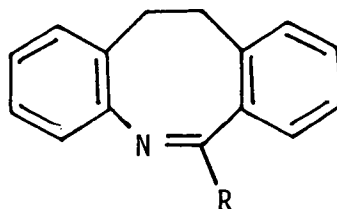


Scheme 19

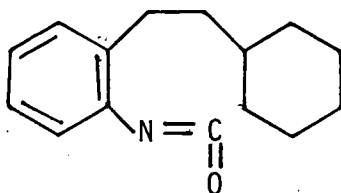
The applications of the Bischler-Napieralski and the Friedel-Crafts intramolecular cyclizations are limited to two cases of dibenz[*b,f*]azocines.

B(i)a Bischler-Napieralski reactionB(i)a-(1) Dibenz[*b,f*]azocines

In the presence of polyphosphoric acid and phosphorus pentachloride, the amides (506) and (507) gave 6-methyl and 6-phenyl-11,12-dihydrodibenz[*b,f*]azocine (508) and (509) respectively.³²⁴

(506) R = CH₃(507) R = C₆H₅(508) R = CH₃(509) R = C₆H₅B(i)b Friedel-Crafts cyclizationB(i)b-(1) Dibenz[*b,f*]azocines

The intramolecular cyclization of the isocyanate (510) in the presence of aluminium chloride in *o*-dichlorobenzene gave the dibenz[*b,f*]azocine-6-one (472) in high yield.^{325,326}



(510)

B(i)c Aryl-aryl coupling reactions

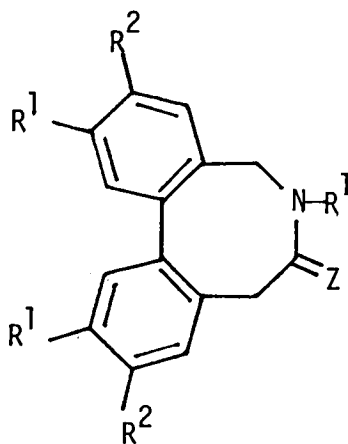
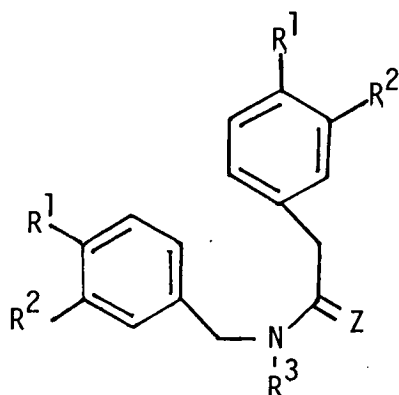
This method has been employed to synthesise derivatives of [*c,e*], [*b,g*] and [*b,d*] dibenzazocines.

B(i)c-(1) Dibenz[*c,e*]azocines

The electrolysis of compound (511) in a solution of 10% sodium perchlorate and acetonitrile containing anhydrous sodium carbonate gave the dibenz[*c,e*]azocine (514) in 60% yield, by aryl-aryl coupling.³²⁷ The electrolysis was conducted at a controlled anode potential of 1.15v. Similarly (515) was prepared from (512). The reported yield of (515) was 45%.³²⁷

The ring closure of (513) gave the dibenz[*c,e*]azocine (516).³²⁸

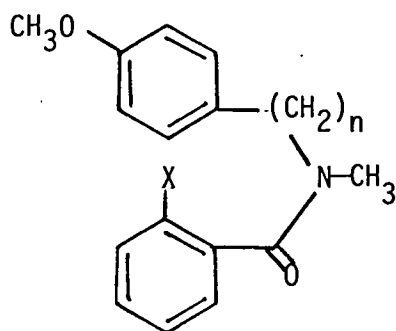
The Pschorr reaction of (517) afforded the lactam (519), whereas the analogue (518) afforded a triazinone;³²⁹ inaccuracies exist in the abstract, however, and these results need to be investigated further.



(511) $R^1=R^2=OCH_3$, $R^3=COCH_3$, $Z=2H$ (514)

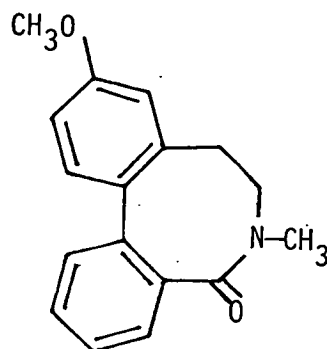
(512) $R^1=R^2=OCH_3$, $R^3=COCH_3$, $Z=O$ (515)

(513) $R^1=OCH_3$, $R^2=OH$, $R^3=SO_2CH_3$, $Z=2H$ (516)



(517) $X = NH_2$, $n = 2$

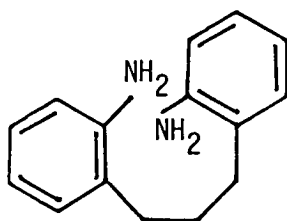
(518) $X = NH_2$, $n = 1$



(519)

B(i)c-(2) Dibenz[*b,g*]azocines

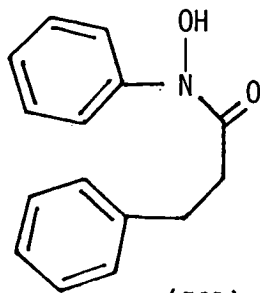
The phosphate of 1,3-bis(2-aminophenyl)propane (520) gave the dibenz[*b,g*]azocine (498) in 43% yield, when heated at 290-300° for 90 minutes.³³⁰⁻³³²



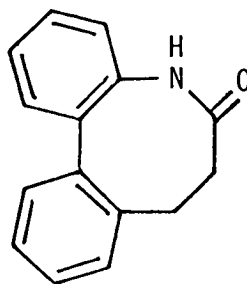
(520)

B(i)c-(3) Dibenz[*b,d*]azocines

The dibenz[*b,d*]azocine-6-one (522) was prepared in 41% yield by the aryl-aryl coupling of (521) in the presence of trifluoromethanesulfonic acid (TFSA).³³³ Under the same reaction conditions, the seven-membered analogue was prepared in 76% yield.



(521)



(522)

B(ii) C-N type ring closure

The C-N type of ring closure is a most widely used method for the synthesis of dibenz[*c,e*]and [c,*f*]azocines. The general types employed to construct a carbon-nitrogen bond are shown in Figure 14.

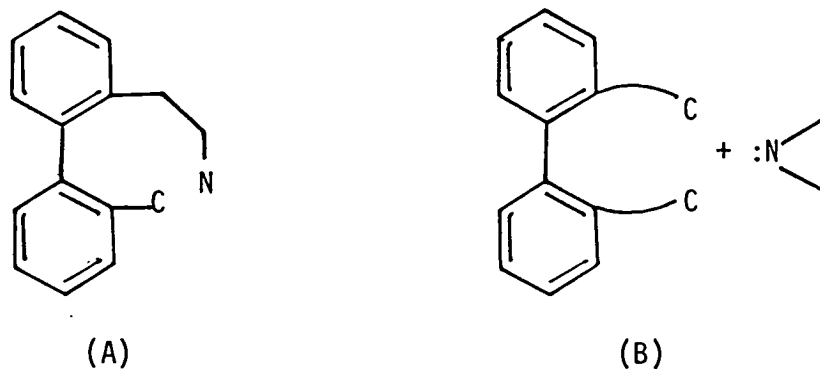
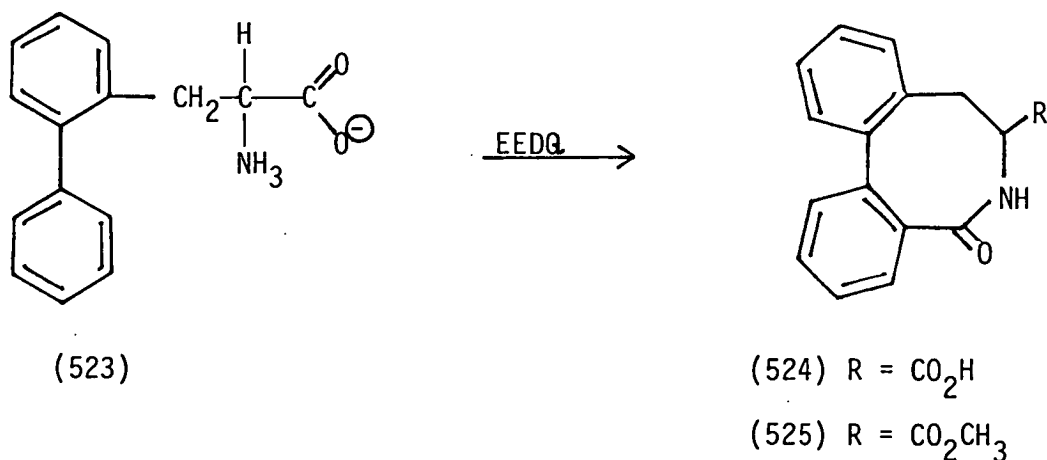


Figure 14

B(ii)-(1) Dibenz[*c,e*]azocines

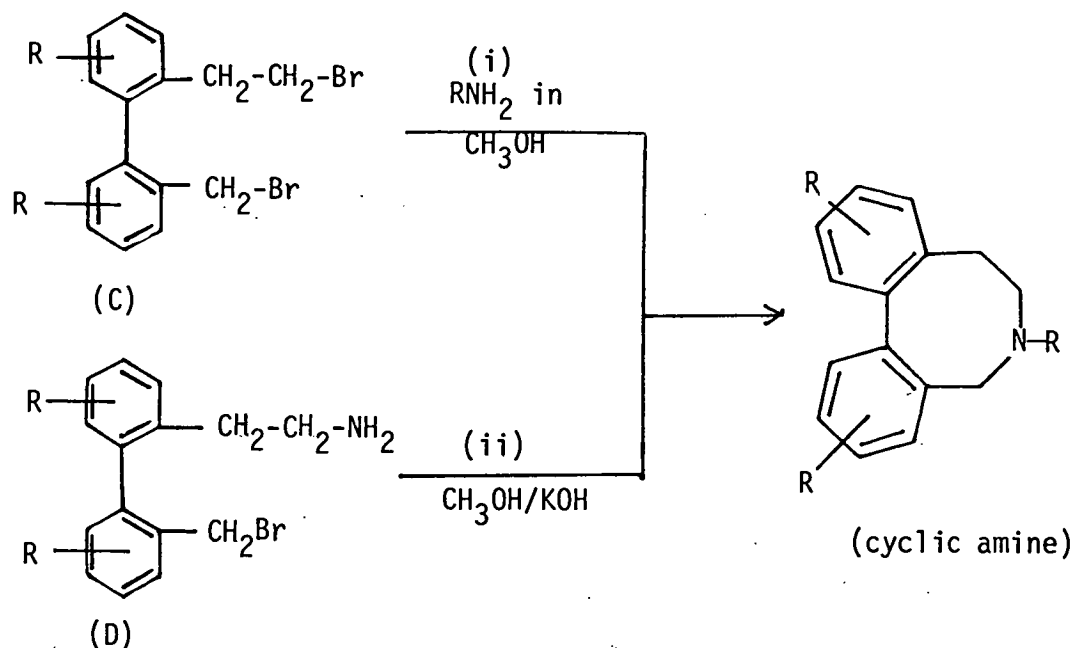
Reaction of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) with compound (523) directly afforded (524) which was isolated as the methyl ester (525) in 24% yield.³³⁴ It has been found that EEDQ can readily induce the formation of peptide linkages.³³⁵



Belleau and Schuber³³⁶ reported the molecular rotation and conformational studies of (525).

Several other dibenz[*c,e*]azocines were prepared by two different procedures: (i) intramolecular cyclization of the dibromide (C) with an amine,^{279,237-242} and (ii) intramolecular cyclization of the bromoamine (D) in the presence of a base.³⁴²⁻³⁴⁵ It has been reported that the yield of cyclic amines obtained by procedure (i) was better

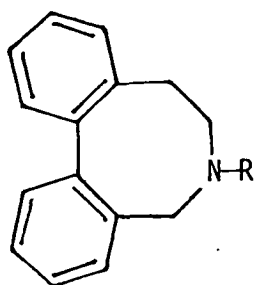
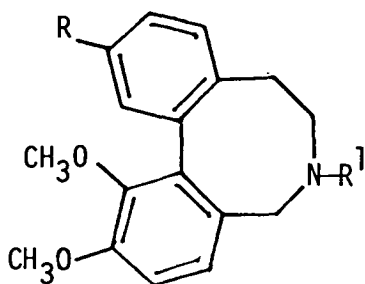
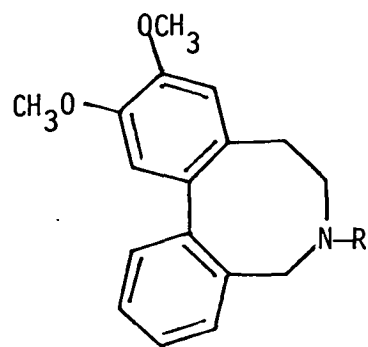
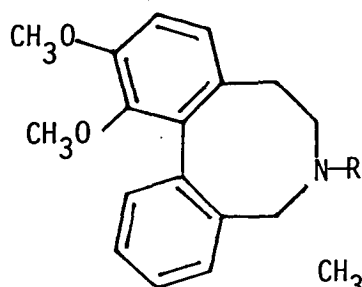
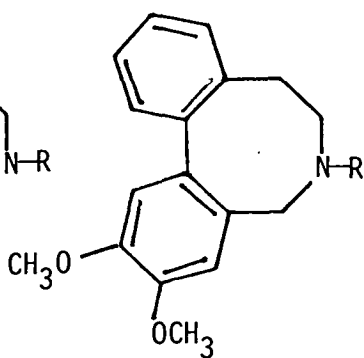
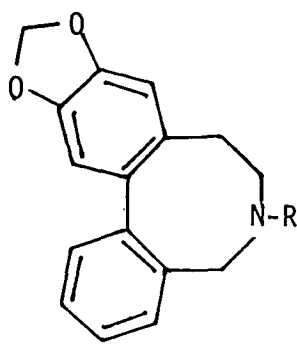
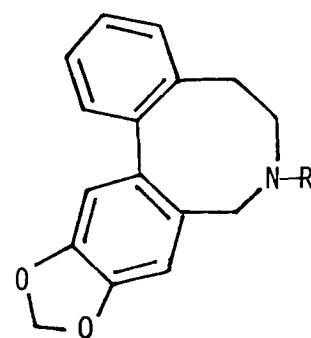
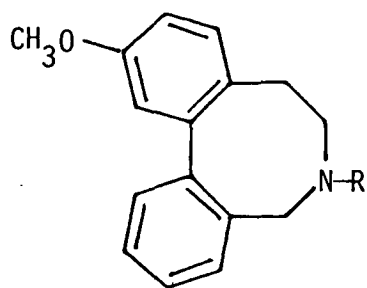
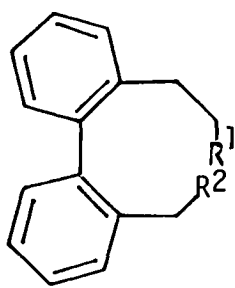
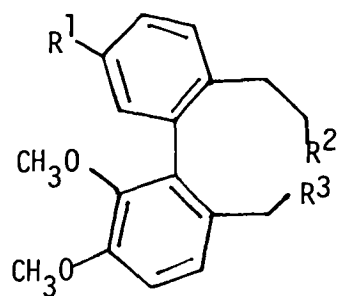
than that from procedure (ii)^{279,337,338} (Scheme 20).

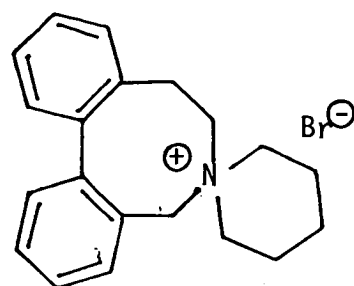
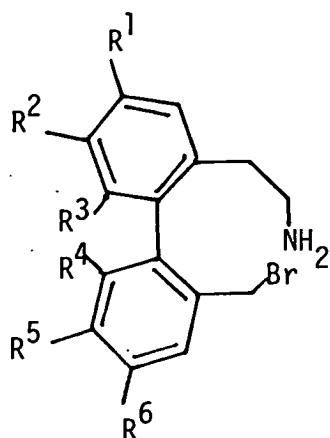


Scheme 20

The intramolecular cyclization of the dibromo compounds (543,545,547) with methylamine in methanol gave the cyclic amines (527,532,530, and 526) respectively.^{279,337-342} The *N*-ethylated derivative (528) was obtained directly by the reaction of (543) with ethylamine in benzene.³³⁹ The compounds (526,532,533,535,537,538,540 and 542) were prepared from the bromo-amines (544,546,548-550 and 552-554) respectively, in the presence of methanolic potassium hydroxide.^{343,346}

The reported yields of the cyclic amines were between 10-30%. In this case the *N*-ethylated derivatives (528,534,539 and 541) were formed as by-products of the cyclization of (544,548,553 and 554) respectively. Kotera and co-workers³⁴⁶ reported the conversion of (526) and (542) to their *N*-methylated derivatives.

(526) $R=H$ (527) $R=CH_3$ (528) $R=C_2H_5$ (529) $R=CH_2C_6H_5$ ³⁴²(530) $R=H, R^1=CH_3$ (531) $R=OCH_3, R^1=CH_3$ (532) $R=OCH_3, R^1=H$ (533) $R=H$ (534) $R=C_2H_5$ (535) $R=H$ (536) $R=C_2H_5$ (537) $R=H$ (538) $R=H$ (539) $R=C_2H_5$ (540) $R=H$ (541) $R=C_2H_5$ (542) $R=H$ (543) $R_1=R_2=Br$ (544) $R_1=NH_2, R_2=Br$ (545) $R_1=OCH_3, R_2=R_3=Br$ (546) $R_1=OCH_3, R_2=NH_2, R_3=Br$ (547) $R_1=H, R_2=R_3=Br$



(555)

(548) $R_1=R_2=OCH_3$, $R_3=R_4=R_5=R_6=H$

(549) $R_2=R_3=OCH_3$, $R_1=R_4=R_5=R_6=H$

(550) $R_1=R_2=R_3=R_4=H$, $R_5=R_6=OCH_3$

(551) $R_2=OCH_3$, $R_1=R_3=R_4=R_5=R_6=H$

(552) $R_1=R_2=R_3=R_4=H$, $R_5=R_6=OCH_3$

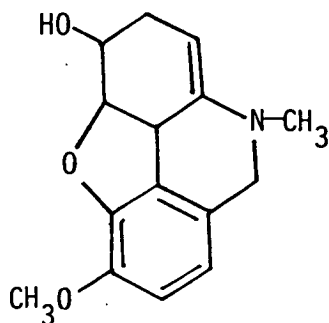
(553) $R_1,R_2=OCH_2O$, $R_3=R_4=R_5=R_6=H$

(554) $R_1=R_2=R_3=R_4=H$, $R_5=R_6=O-CH_2O$

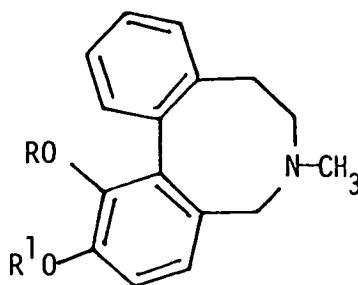
The condensation of (543) with piperidine gave the quaternary ammonium salt (555).³⁴⁷ The calculation of the enthalpy and entropy of activation and the Arrhenius parameters for this reaction were reported by Hall and Harris.³⁴⁸

Many workers^{337,338,349-356} have reported the transformation of galanthamine (556) into 1,2-dihydroxy-6-methyl-5,6,7,8-tetrahydro-dibenz[*c,e*]azocine (557), known as apogalanthamine. Galanthamine is an alkaloid, frequently encountered in the bulbs of plants of the Amaryllidaceae. The reaction of 48% hydrobromic acid and acetic acid^{337,338,349,350} or 20% hydrochloric acid³⁵¹⁻³⁵³ and galanthamine (556) yielded 90% and 78% of hydrobromide and hydrochloride salt of (557). In order to establish the structure, (557) was further converted into the 1-hydroxy-2-methoxy- (558) and 1,2-dimethoxy (530)

derivatives by methylation.



(556)



(557) $R=R^1=H$

(558) $R=H$, $R^1=CH_3$

(559) $R=C_6H_5$, $R^1=CH_3$

The reaction of (558) with bromobenzene in pyridine containing potassium carbonate and copper powder gave the 1-phenoxy-2-methoxy-6-methyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (559).³⁵⁷

The mass spectral fragmentation³⁵⁸ and spectrophotometric determinations³⁵⁹⁻³⁶¹ of (557), and (558), have also been reported.

The compound (558) has been tested for antiarrhythmic³⁶²⁻³⁶⁶ and hypotensive³⁶⁷⁻³⁷⁰ activities. The effects of (558) on regional blood circulation,³⁷¹ and other pharmacological activities of (558) have also been investigated.^{372,373}

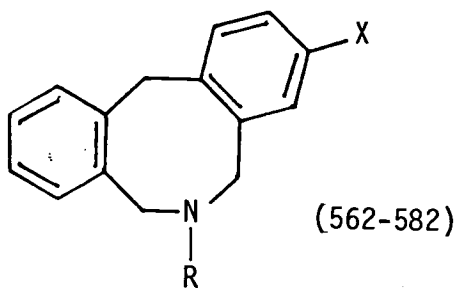
B(ii)-(2) Dibenz[*c,f*]azocines

Derivatives of dibenz[*c,f*]azocines have also been synthesised by the condensation of the dibromo compound (560) (page 96) with various amines. For example, the reaction of (560) with methylamine in anhydrous benzene under reflux gave 5,6-dihydro-6-methyl-7*H*,12*H*-dibenz[*c,f*]azocine (561) in 57-80% yield.³⁷⁴⁻³⁷⁶ The 5,5,7,7-tetradeutero compound of (561) also was prepared in 97% yield.^{374,375} Similarly several other dibenz[*c,f*]azocines (562-575) were prepared in high yields.³⁷⁵⁻³⁸⁰ (Table 14).

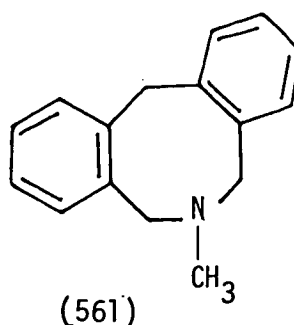
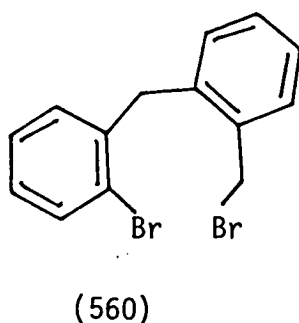
Table 14

B(ii)1-Dibenz[*c,f*]azocines

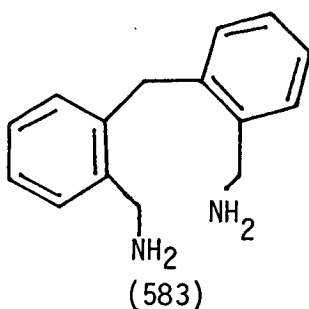
(2) C-N type ring closure



Compound number	X	R	Yield %	Reference
(562)	H	C ₂ H ₅	74	375
(563)	H	<i>n</i> -C ₃ H ₇	54	"
(564)	H	<i>i</i> -C ₃ H ₇	86	"
(565)	H	CH ₂ =CH-CH ₂	50	"
(566)	H	<i>n</i> -C ₄ H ₉	58	"
(567)	H	1-methyl-3-piperidylethyl	78	"
(568)	H	2-(1-methyl-1-piperidyl)ethyl	78	"
(569)	H	4-C(CH ₃) ₃ -C ₆ H ₄ -CH ₂	62	"
(570)	H	4-Cl-C ₆ H ₄ , CHC ₆ H ₅	52	"
(571)	H	CH ₃ CH(OH)CH ₂	74	"
(572)	H	HO-(CH ₂) ₂ -	67	"
(573)	H	HO-(CH ₂) ₃ -	78	"
(574)	H	CH ₂ -C ₆ H ₅	-	377,378
(575)	H	CD ₂ -C ₆ H ₅	-	376
(576)	H	CH-(CH ₃) ₂	-	374,376,377
(577)	H	C(CH ₃) ₃	-	376,377
(578)	H	H	35	374,376,377
(579)	H	CN	55	377,381
(580)	CH ₃	CH ₃	-	380
(581)	OCH ₃	CH ₃	-	380
(582)	Br	CH ₃	-	380



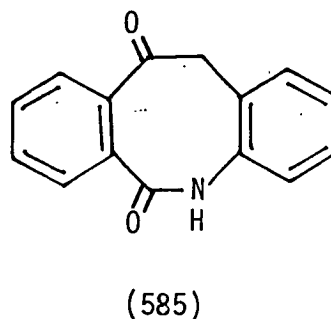
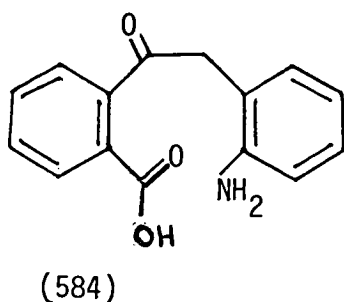
The cyano compound (579) was prepared^{377,381} by the reaction of (560) and cyanamide in dimethylsulfoxide containing sodium hydride. The 5,6-dihydro-7*H*,12*H*-dibenz[*c,f*]azocine (578) was obtained by heating the dihydrochloride of (583) at 300°, in a sealed tube containing water.³⁷⁷ Then this was converted into many other derivatives.³⁸²⁻³⁸⁶



The structural studies of (577),³⁸⁷ (580)³⁸⁸ and (582),³⁸⁹ and nmr studies of (562)³⁹⁰ also were reported.

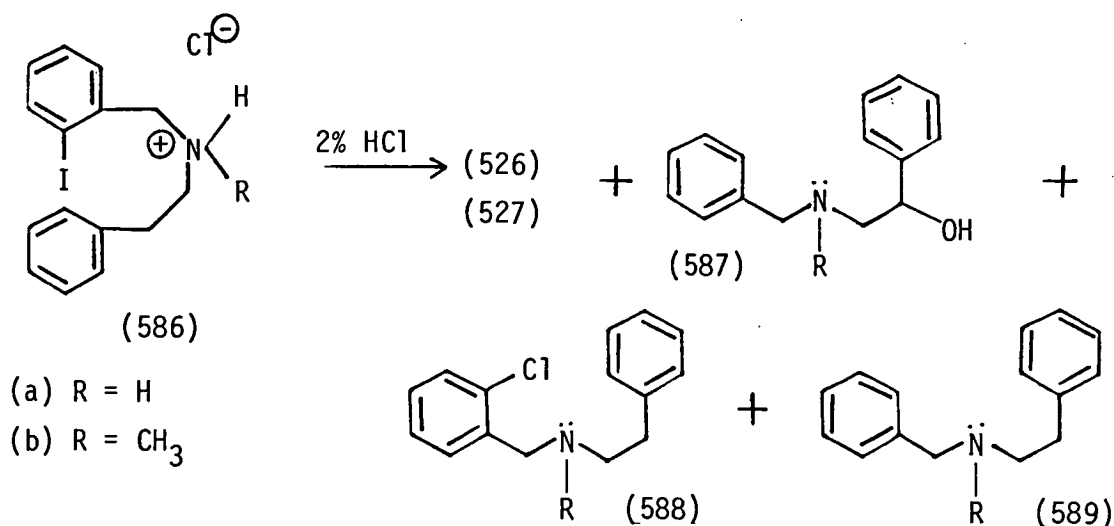
B(ii)-(3) Dibenz[*b,f*]azocines

The action of heat on compound (584) gave the dibenz[*b,f*]azocine-6,11-dione (585).³⁹¹



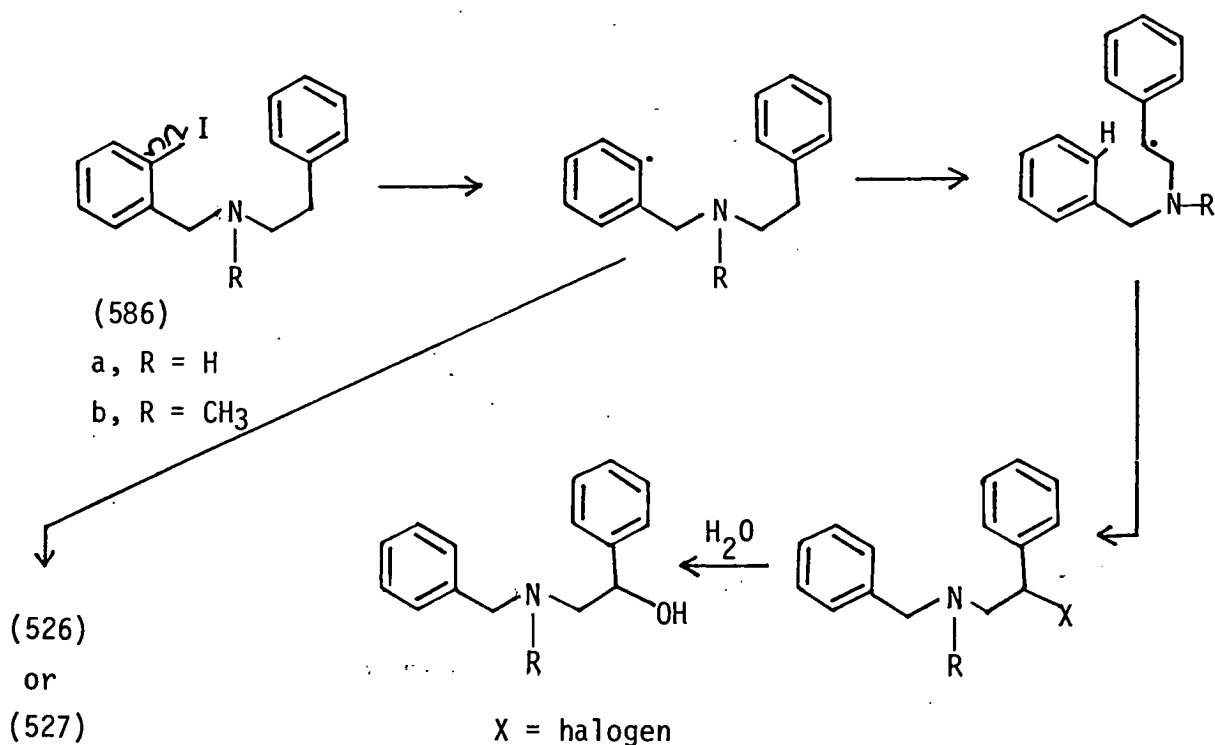
(C) PhotocyclizationC-(1) Dibenz[*c,e*]azocines

Photolysis of aryl iodides in benzene provided a new route for the synthesis of substituted biphenyls. Irradiation of the hydrochloride of *N*-(β -phenethyl)-2-iodobenzylamine (586a) in water for 113 hours gave the photocyclized product (526) in 25% yield, together with 10% of *N*-(β -phenethyl)benzylamine.^{341,392} The structure of (526) was established by the comparison with an authentic sample. The prolonged irradiation of (586a) gave a slightly improved yield (33%) of compound (526). The *N*-methyl derivative (586b) also gave the corresponding ring closed product (527) in 33% yield together with three other by-products (587-589).

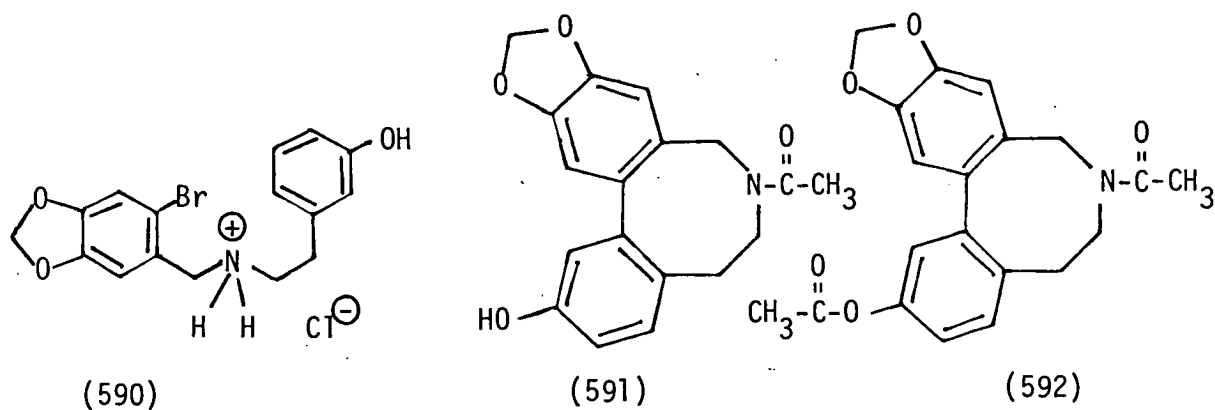


It has been suggested³⁴¹ that the photolysis of (586) proceeds through the formation of an aryl radical by the homolysis of the carbon-iodine bond. The proposed mechanism is given in Scheme 21.

The formation of (587) supports this mechanism. The drawback of this photocyclization reaction is the long reaction times. However, in contrast to the above results, irradiation of (590) for ten hours, followed by acetylation, gave 6,11-diacetoxy-2,3-methylene-

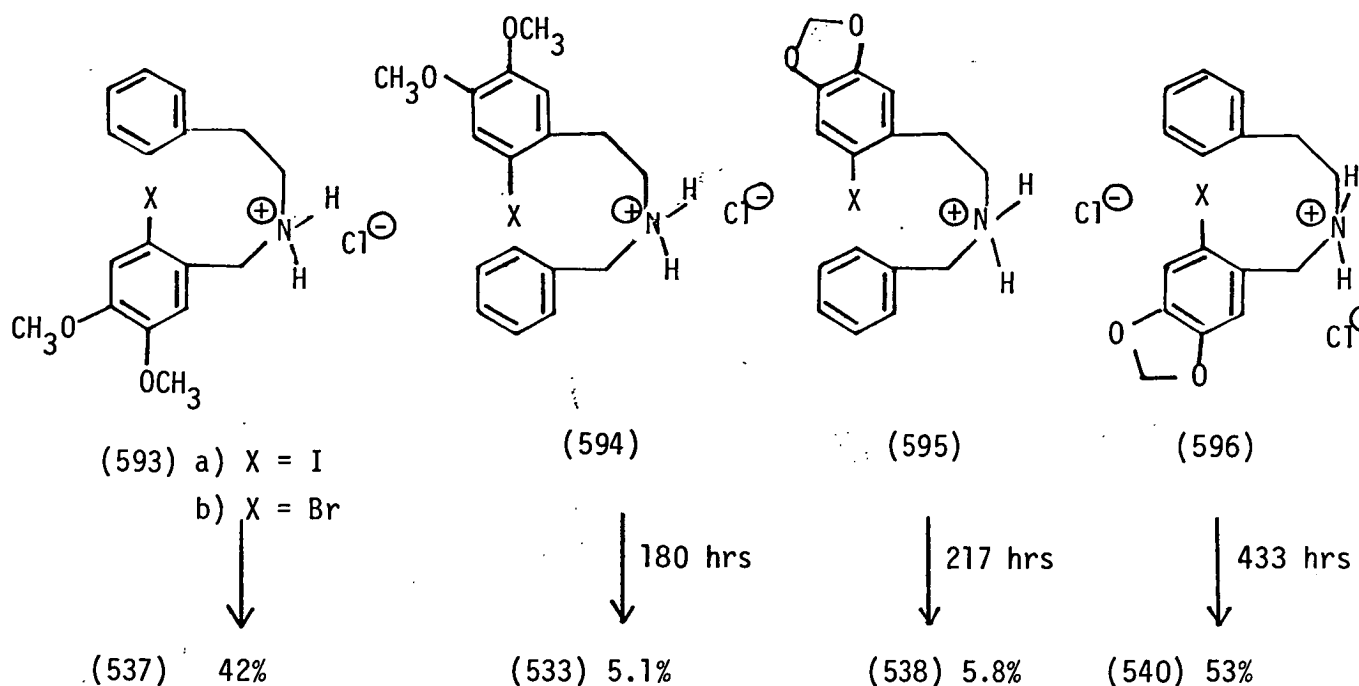


dioxy-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (592) in 22% yield, and 57% of the starting material was recovered. Furthermore, it was found that the length of the reaction could be shortened to two hours without decreasing the yield, by using a Corex filter.³⁴¹



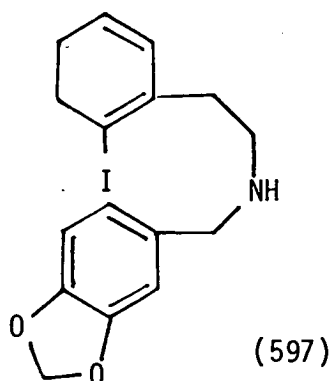
Recently Kobayashi and Kihara³⁹³⁻³⁹⁶ described the photolysis of similar iodo-amines. Irradiation of (593a) in aqueous solution gave 2,3-dimethoxy-5,6,7,8-tetrahydrodibenz[*c,e*]azocine (537) in 42% yield.

The dibenz[*c,e*]azocines (533, 538 and 540) also were prepared similarly from the iodo-amines (594a-596a) respectively.³⁹³

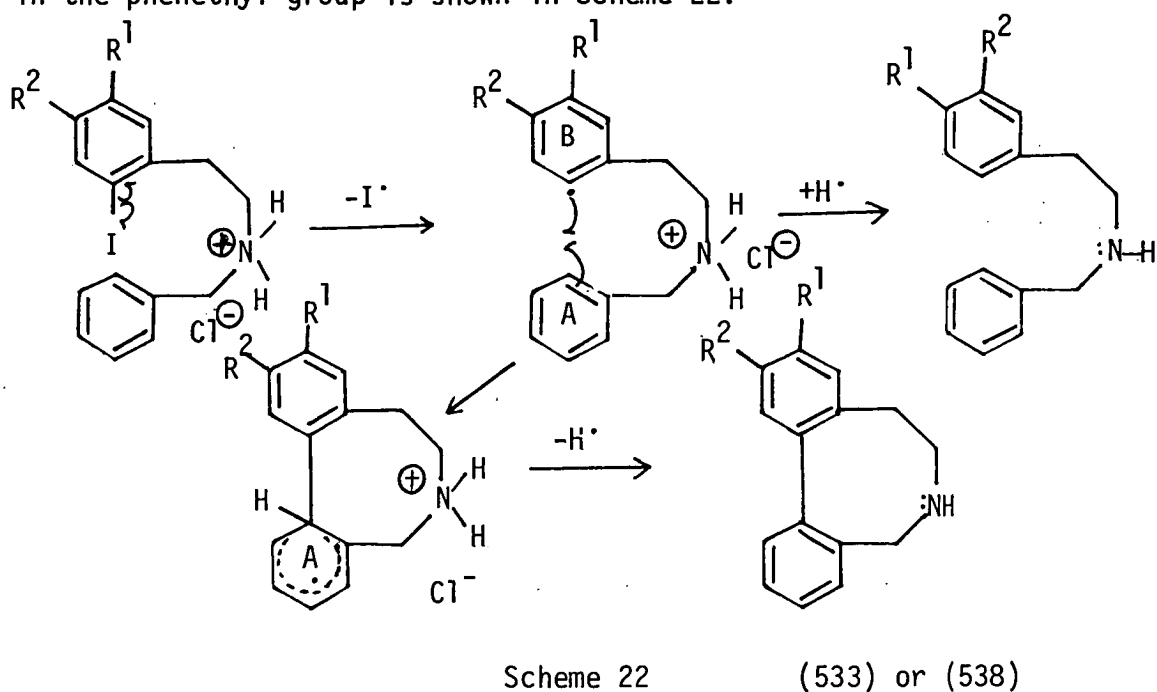


On irradiation, the bromo-amines (593b-596b) also gave 40% of (537), 7% of (533), 8% of (538) and 11% of (540).³⁹⁴ The irradiation periods of bromo-amines were between forty minutes and nine hours.

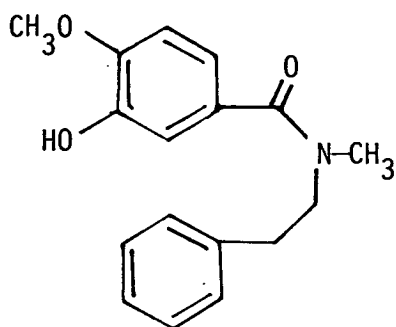
From these results, it is evident that the yields of the dibenzazocines (537,540) obtained from the halides having a halogen atom in the benzyl group (593,596) were better than those of the dibenzazocines (533,538) which were obtained from the halides (594,595) having a halogen atom in the phenethyl group. Attempted cyclization of *N*-(3,4-methylenedioxybenzyl)-2-iodo- β -phenethylamine (597) by irradiation was unsuccessful.³⁹³



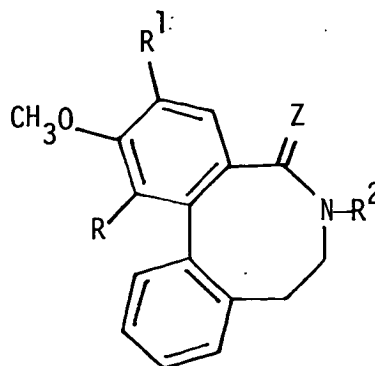
The suggested³⁹⁴ mechanism for the photocyclization with the halogen in the phenethyl group is shown in Scheme 22.



Yoneda *et al*³⁹⁷ reported that the irradiation of (598) in aqueous sodium hydroxide gave a mixture of (599) and (600) in 37% and 15% yield respectively. Compound (601) was prepared similarly.



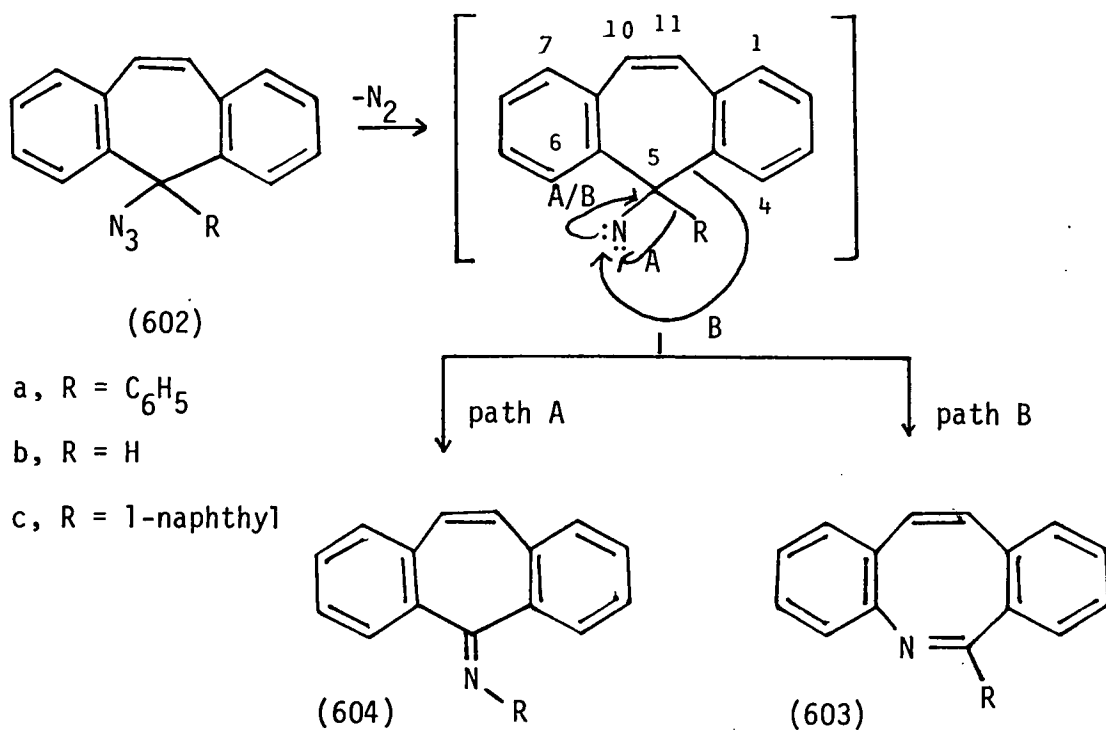
(598)

(599) $R=H$, $R^1=OH$, $R^2=CH_3$ (600) $R=OH$, $R^1=OH$, $R^2=CH_3$ (601) $R=OH$, $R^1=H$, $R^2=H$

Similar results were observed, when (598) was irradiated in a solution of sodium nitrite and 10% sulfuric acid.³⁹⁸

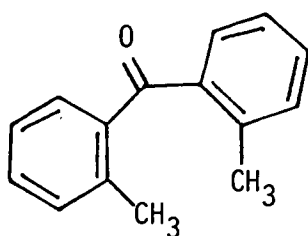
C-(3) Dibenz[*b,f*]azocines

The photolysis of cycloheptatriene (602a) gave 4% of the dibenz[*b,f*]azocine (603a) together with 58% of (604a).³⁹⁹ The major product (604a) was formed by nitrene insertion into the C_5 -R bond (path A), and the dibenzazocine (603a) was formed by insertion into the C-C bond of the seven-membered ring (path B). The photolysis of (602b) gave (604b) as the only identifiable product and (602c) gave 14% of dibenzazocine (603c) and 46% of (604c).

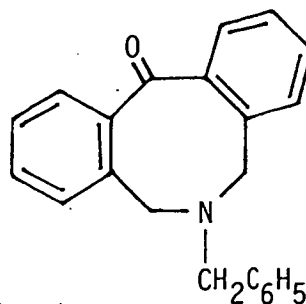


C-(4) Dibenz[*c,f*]azocines

Irradiation of (605) and *N*-bromosuccinimide in the presence of benzoyl peroxide gave a low yield (4%) of the lactam (606).³⁷⁸



(605)



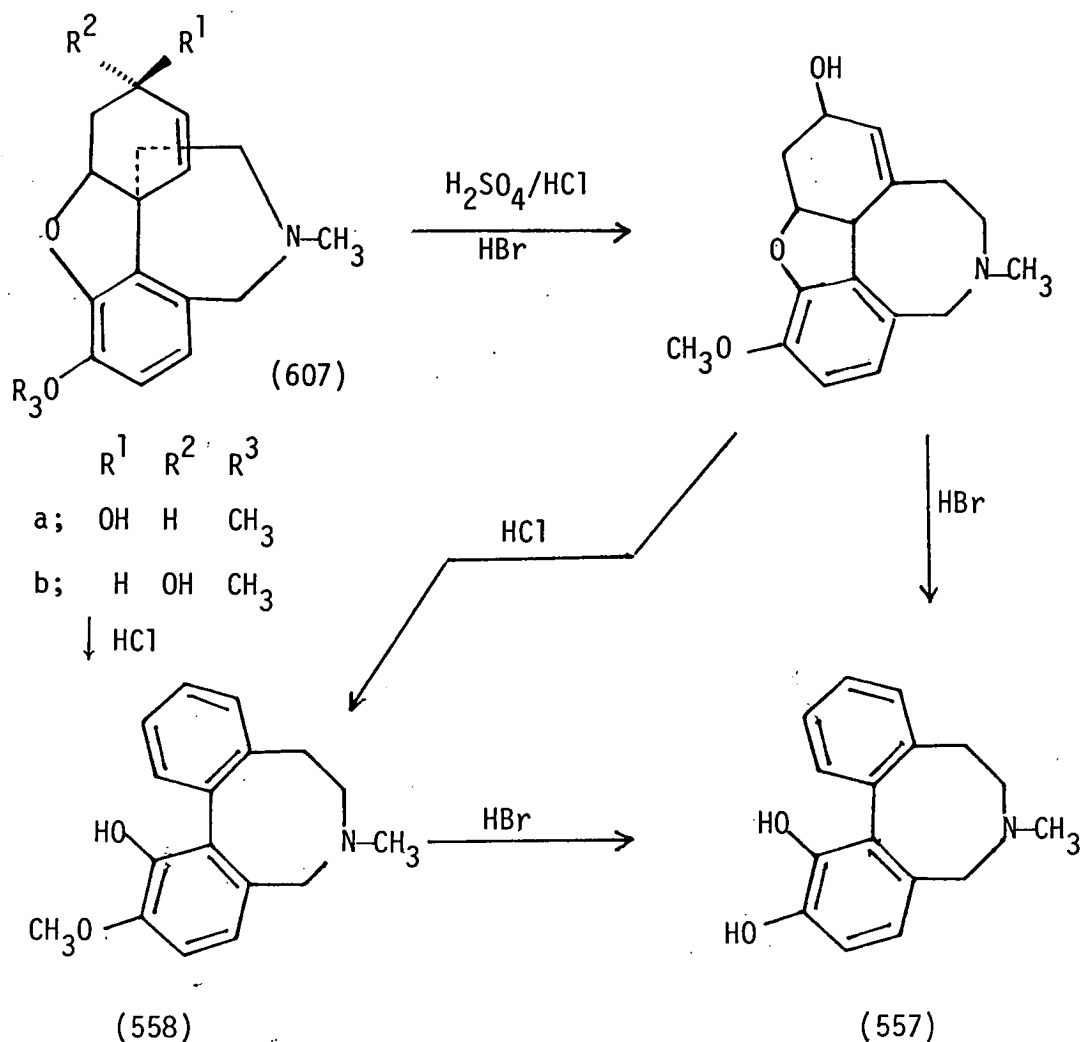
(606)

(D) From bridge-head compounds

(D)-(1) Dibenz[*c,e*]azocines

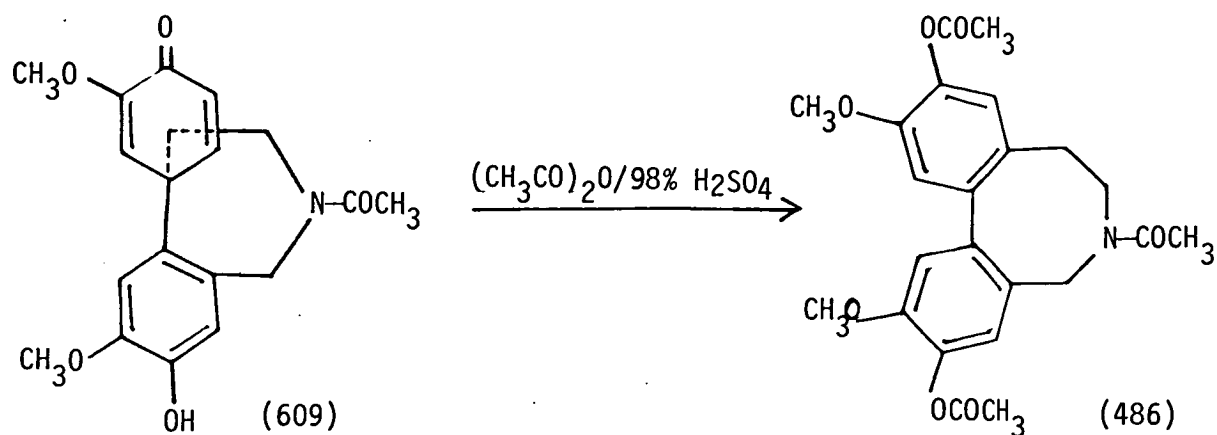
When galanthamine (607a) was treated with potassium hydroxide and hydrazine hydrate in diethylene glycol at 200° it afforded the

dibenzazocine (558), together with three other products.⁴⁰⁰ The compound (558) was obtained from (607a) by heating with hydrochloric acid⁴⁰⁰ and was synthesised in moderate yield from (607b) by heating with 12% hydrochloric acid.^{400,401} The reactions involved in the transformation⁴⁰² are illustrated in Scheme 23.



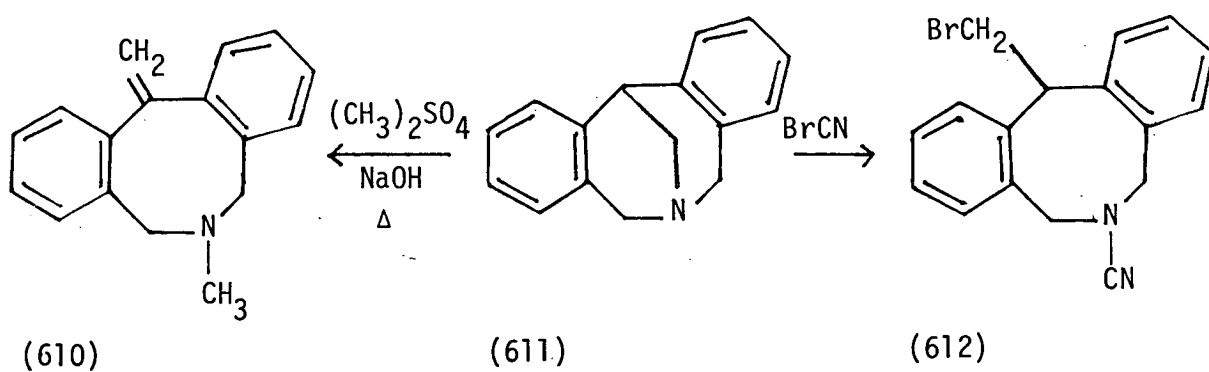
Scheme 23

The triacetate derivative (486) was prepared by rearrangement of (609) in the presence of acetic anhydride and 98% sulfuric acid.³¹⁵

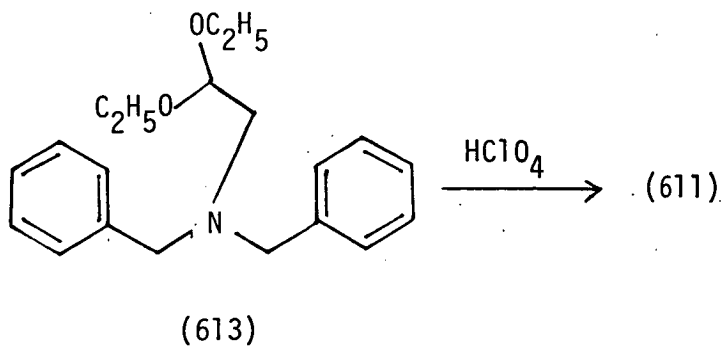


(D)-(2) Dibenz[*e,f*]azocines

The dibenz[*e,f*]azocines (610) and (612) were obtained from compound (611) by the Hofmann and the von Braun reactions respectively.⁴⁰²



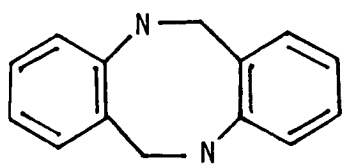
The bridge-head compound (611) was prepared by the intramolecular Friedel-Crafts reaction of (613).⁴⁰²



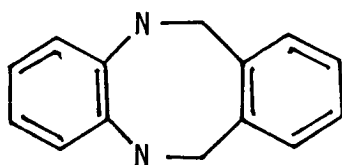
Chapter 6

Dibenzodiazocines

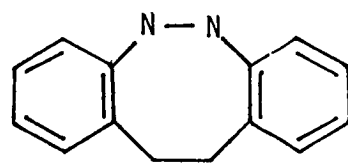
Only five out of the eleven possible isomers of dibenzadiazocines (A-E) have been synthesised so far and the commonest isomer is the dibenzo[*b,f*][1,5]diazocine [A] (Figure 15).

[*b,f*][1,5]

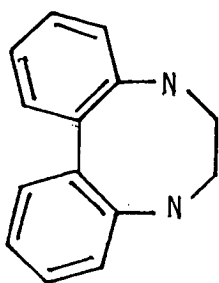
(A)

[*b,f*][1,4]

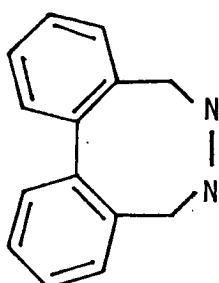
(B)

[*c,g*][1,2]

(C)

[*e,g*][1,4]

(D)

[*d,f*][2,3]

(E)

Figure 15

The most widely used preparative method in constructing this ring system was the dimerization (self-condensation) of 2-aminobenzophenone derivatives. Other synthetic methods employed were similar to those previously described for the benz- and dibenzazocine compounds.

Methods of preparation(A) Ring enlargements

Ring enlargement types used for the synthesis of dibenzazocines are the (a) Beckmann rearrangement

(b) rearrangement of quinazolines

(c) ring enlargement followed by cleavage of an internal bond,

and (d) other ring enlargements.

However the application of these methods are few, and limited to the construction of dibenz[*b,f*][1,5], [1,4] and [1,2]diazocines (isomers (A), (B) and (C) respectively).

A(a) Beckmann rearrangement

A(a)-(1) Dibenz[*b,f*][1,5] and [1,4]diazocines

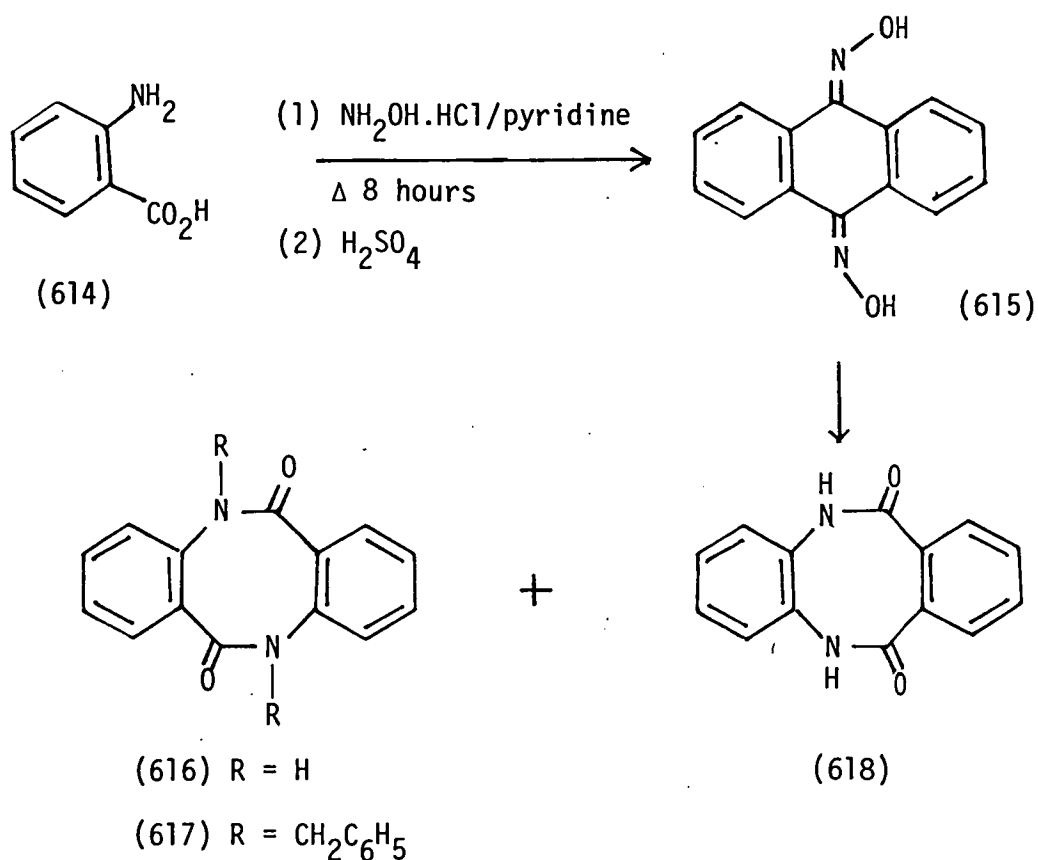
The Beckmann rearrangement of dianthraquinone dioxime (615) in the presence of polyphosphoric acid gave dibenzo[*b,f*][1,5]diazocine-6,12-(5*H*,11*H*)-dione (616) and dibenzo[*b,f*][1,4]diazocine 6,11-(5*H*, 12*H*)-dione (618).⁴⁰³⁻⁴⁰⁵ The dioxime (615) was prepared by the reaction of *o*-aminobenzoic acid (614) and hydroxylamine hydrochloride in refluxing pyridine.⁴⁰⁴ (Scheme 24). The dibenzo[*b,f*][1,5]azocine (616) was converted into several *N*-substituted derivatives.⁴⁰⁶ Ollis and co-workers^{303,407,408} reported on the conformational analysis of (617).

The reactions⁴⁰⁹ and the mass spectral fragmentation of diketone (616)⁴¹⁰ have also been reported.

A(b) Rearrangement of quinazolines

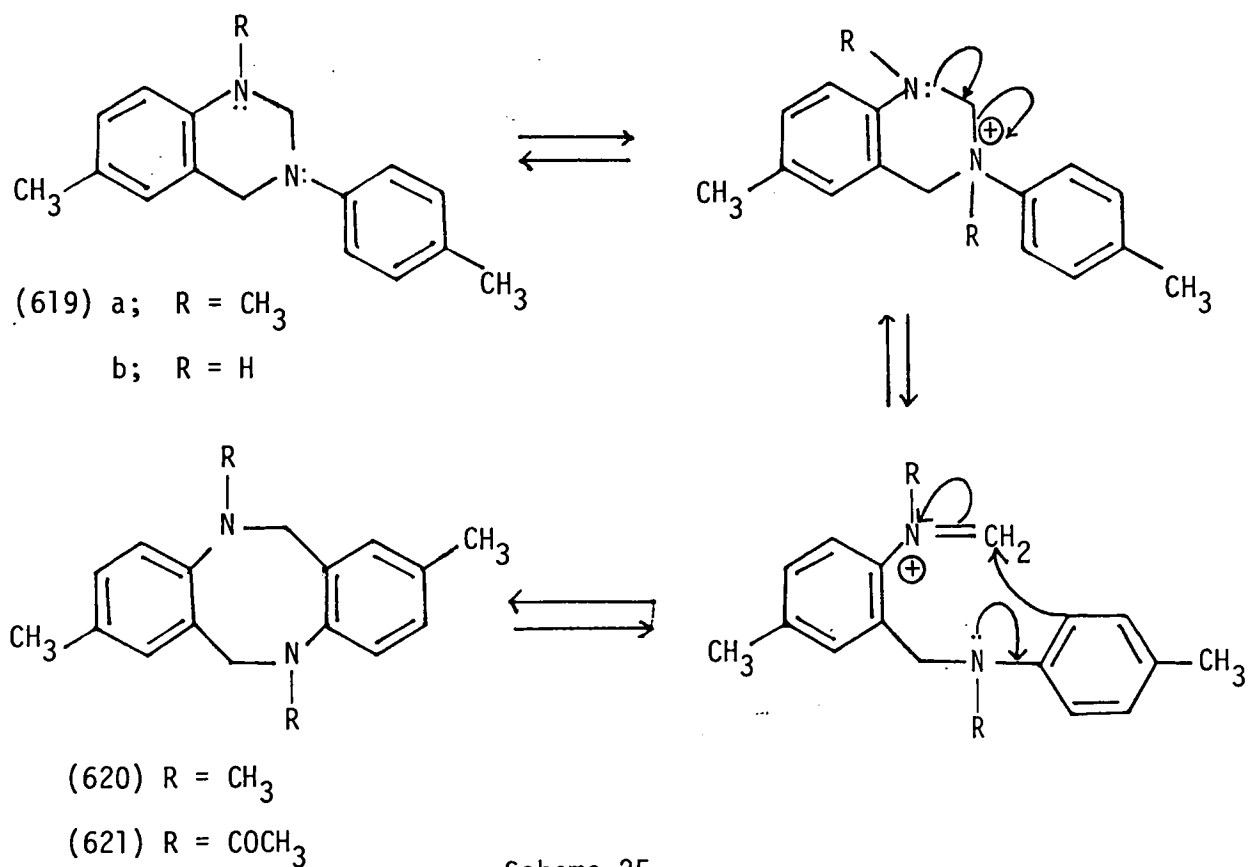
A(b)-(1) Dibenzo[*b,f*][1,5]diazocines

Treatment of the quinazoline (619a) with methyl iodide or methyl bromide in chloroform for two days at room temperature, followed by three hours refluxing, afforded the ring expanded product (620).^{411,412} When the reaction mixture was refluxed over six hours most of the



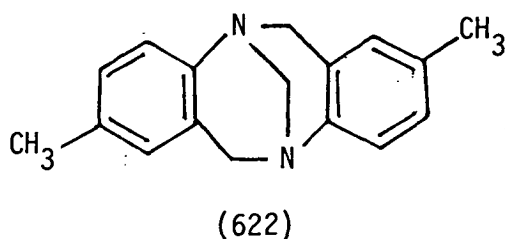
Scheme 24

starting material was recovered.⁴¹² The suggested mechanism for the rearrangement is shown in Scheme 25.



Scheme 25

In the presence of acetic anhydride, the quinazoline (619b) also underwent the same rearrangement giving rise to dibenzo[*b,f*][1,5]-diazocine (621) and the bridge-head compound (622) which is commonly known as Tröger's Base.⁴¹³

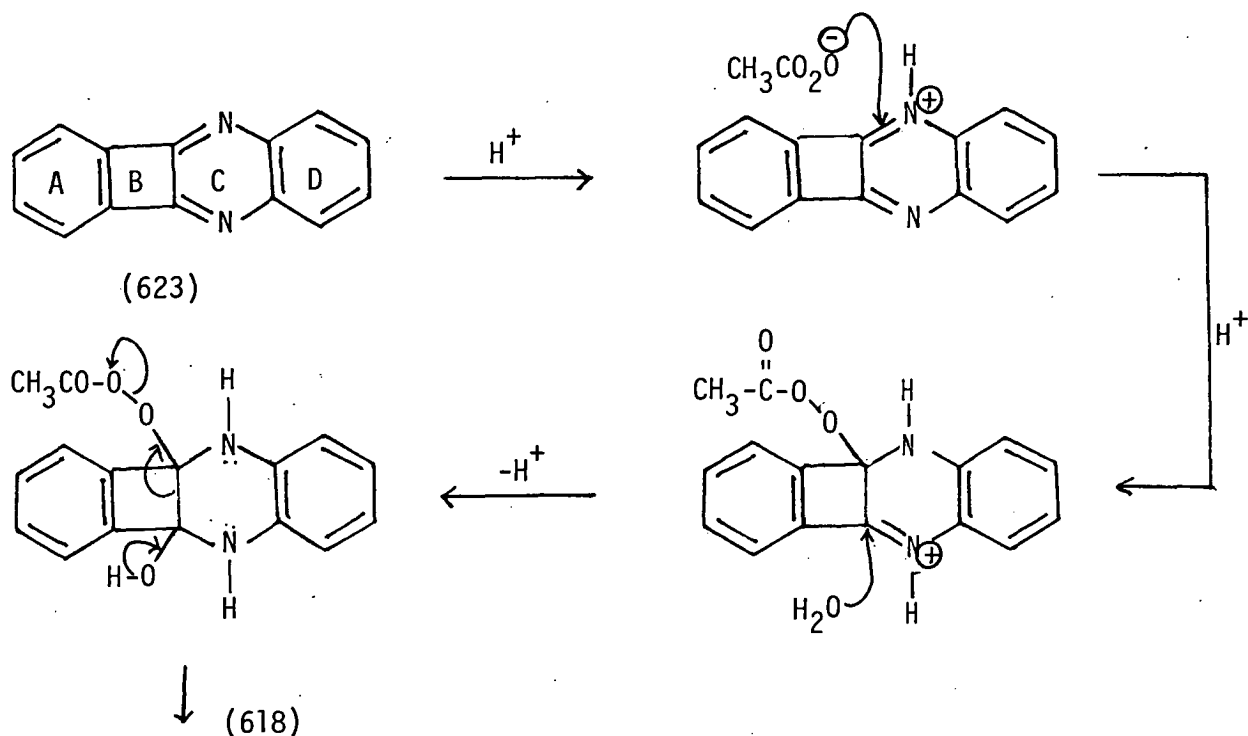


A(c) Ring enlargement followed by cleavage of an internal bond

A(c)-(1) Dibenzo[*b,f*][1,4]diazocines

In the presence of 30% hydrogen peroxide in acetic acid, the compound (623) underwent an oxidative cleavage of the C-C bond common to rings B and C, giving rise to 30% of dibenzo[*b,f*][1,4]diazocine-6,12-(5*H*, 11*H*)-dione (618), together with a small amount of *o*-nitro aniline.⁴¹⁴

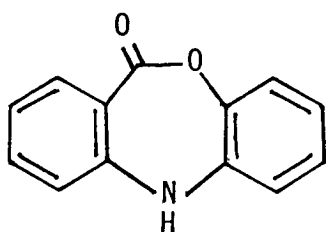
The proposed mechanism is given in Scheme 26.



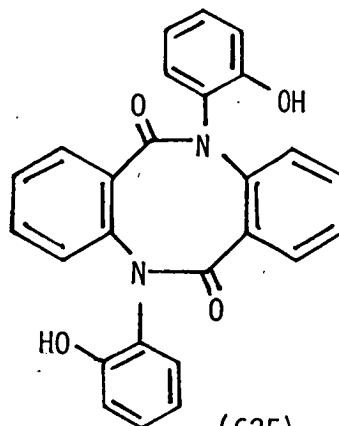
Scheme 26

A(d) - Other ring enlargementsA(d)-(1) Dibenzo[*b,f*][1,5]diazocines

The ring enlargement of the dibenzo[*b, e*][1,4]oxazepine (624), in the presence of sodium hydride in benzene and dimethylformamide gave 40% of the dibenzo[*b,f*][1,5]diazocine-6,12-dione (625).⁴¹⁵



(624)



(625)

The diazocine derivative (625) may have formed through nucleophilic attack by the nitrogen anion on the carbonyl group. (Figure 16).

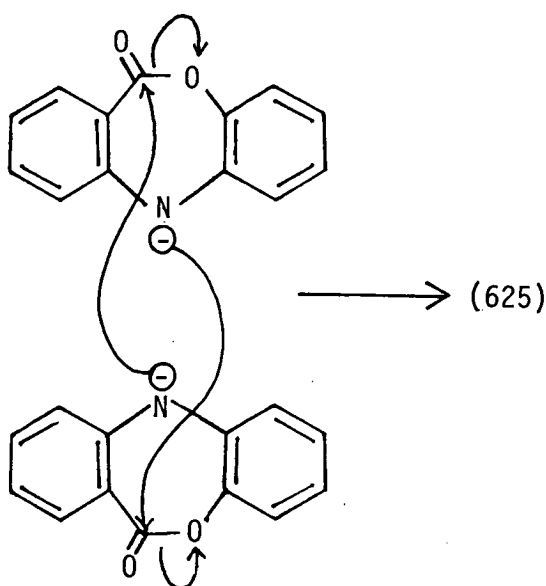
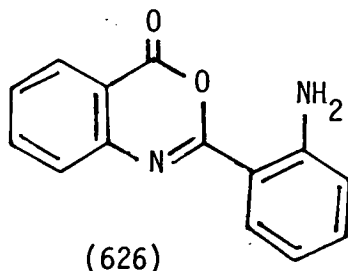


Figure 16

A(d)-(2) Dibenzo[*b,f*][1,4]diazocines

The reaction of (626) with dry ammonia afforded 51% of 5,12-dihydrobenzo[*b,f*][1,4]diazocine-6,12-dione (618).⁴¹⁶ Derivatives of the corresponding tetrahydrodibenzo[*b,f*][1,4]diazocine, were also prepared.³⁰¹

A(d)-(3) Dibenzo[*d,f*][1,2]diazocines

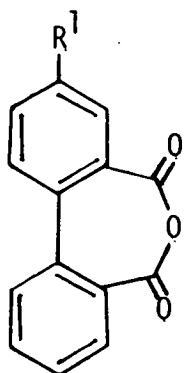
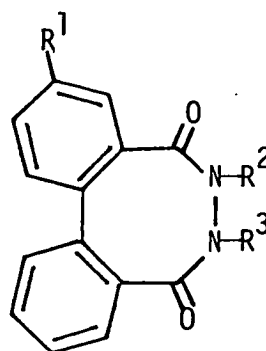
The reaction of hydrazine hydrate with diphenic anhydride (627) followed by subsequent ring closure at 200° under vacuum, afforded the dibenzo[*d,f*][1,2]diazocine-5,8-(6*H*,7*H*)-dione (630).⁴¹⁷⁻⁴²² Similarly, the 3-nitro derivative (631) also was prepared.⁴¹⁸ The 6-substituted dibenzo[*d,f*][2,3]diazocines (632-635) were synthesised by the reaction of (627) and *N*-substituted hydrazine hydrates of type (629).^{419,420}

(B) Ring closure

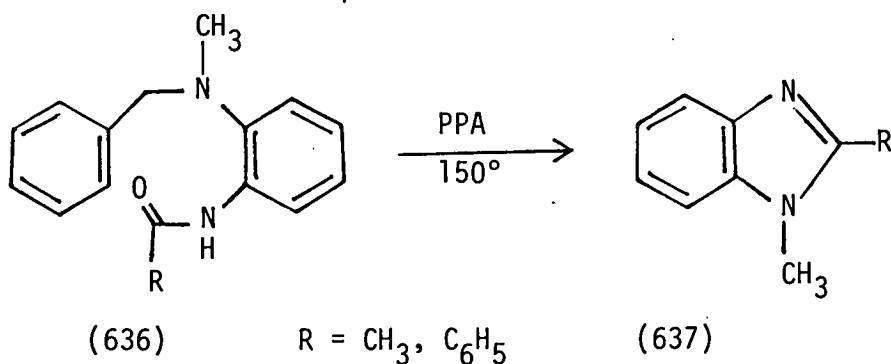
Ring closure of the types a) C-N and

b) N-N have been employed to

synthesise many dibenzodiazocine derivatives. The more widely used ring closure is the C-N type. The few preparative methods involved with the formation of a C-C bond will be discussed later in the self-condensation section. A few workers^{423,424} have reported that the attempted Bischler-Napieralski reaction of amide (636) with polyphosphoric acid was unsuccessful; the final product obtained by

(627) $R^1 = H$ (628) $R^1 = NO_2$ (629) $R-NH-NH_2 \cdot H_2O$ $(R = CH_3, C_2H_5, C_3H_7, C_4H_9)$ (630) $R^1 = R^2 = R^3 = H$ (631) $R^1 = NO_2, R^2 = R^3 = H$ (632) $R^1 = R^3 = H, R^2 = CH_3$ (633) $R^1 = R^3 = H, R^2 = C_2H_5$ (634) $R^1 = R^3 = H, R^2 = C_3H_7$ (635) $R^1 = R^3 = H, R^2 = C_4H_9$

this reaction was (637). No other work on ring closures of the C-C type seem to have been reported so far.



B(a) C-N type

The reaction types A and B, shown in the Figure 17 have been used for the formation of a C-N bond.

Ring closure of type (A) results in the formation of dibenzo[*b,f*]-[1,5]- and [1,4]-diazocines, while ring closure of type (B) results in the formation of dibenzo[*e,g*][1,4]diazocines.

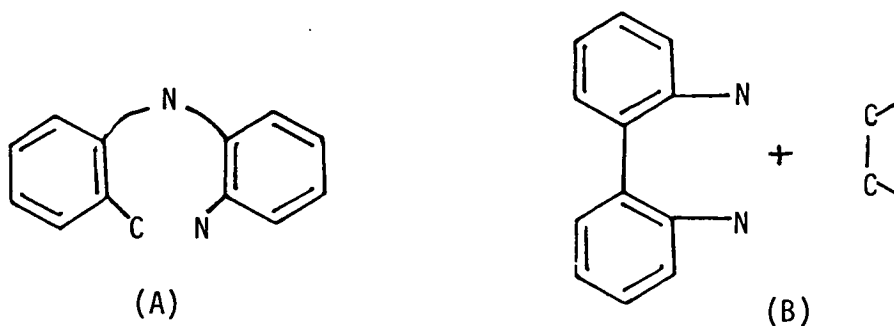
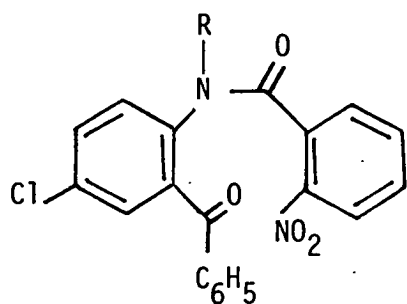


Figure 17

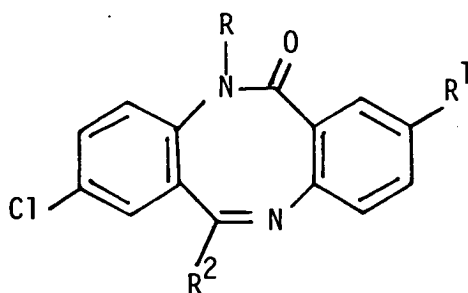
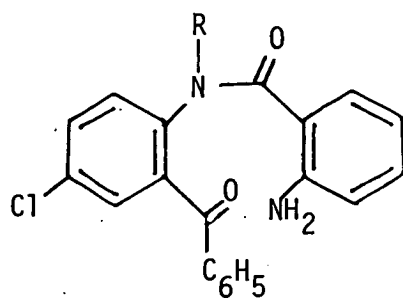
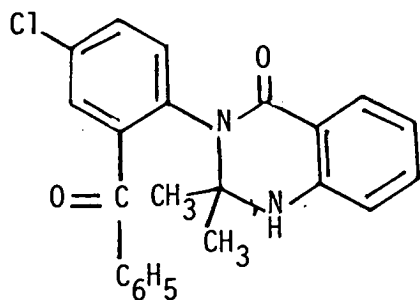
B(a)-(1) Dibenzo[*b,f*][1,5]diazocines

Topliss and co workers^{423,425} have reported the formation of 8-chloro-6-phenyl-11-methyl-dibenzo[*b,f*][1,5]diazocine-12-one (639) in 69% yield by the reductive cyclization (638a) in the presence of ammonium chloride in 2-methoxyethanol and water containing iron filings. Dibenzo[*b,f*][1,5]diazocines (640-642) were prepared similarly.⁴²⁵ Under the same reaction conditions the *N*-unsubstituted nitro compound (638b) did not undergo the cyclodehydration giving rise to the expected dibenzodiazocine (640). The final product obtained was (645). Attempted cyclization of the amine with acetone gave a quinazoline derivative (646). However the dibenzodiazocine (640) was obtained in 95% yield, by refluxing the amine (645) in xylene for 6 hours.⁴²³ Nakano and co-workers⁴²⁶ reported the synthesis of (643) by azeotropic dehydration of (638b) in pyridine.

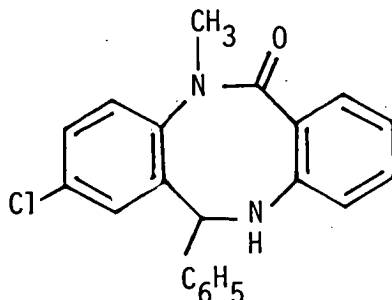
The 5,6-dihydro derivative (647) was obtained either by reduction of (638a) with 5% palladium charcoal in ethanol at room temperature for seven hours or with platinum oxide in glacial acetic acid at room temperature. The longer reaction periods resulted in the formation of (644) instead of the expected dibenzodiazocine (647).⁴²³



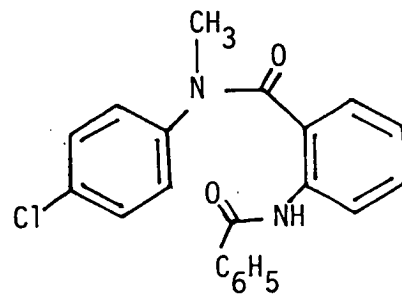
(638)

a: $R=CH_3$ b: $R=H$ (639) $R=CH_3$, $R^1=H$, $R^2=C_6H_5$ (640) $R=R^1=H$, $R^2=C_6H_5$ (641) $R=(CH_3)_2N(CH_3)_2$, $R^1=H$,
 $R^2=C_6H_5$ (642) $R=(CH_3)_2N(CH_3)_2$, $R^1=R^2=H$ (643) $R=H$, $R^1=Cl$, $R^2=C_6H_5$ (644) $R=CH_3$ (645) $R=H$ 

(646)

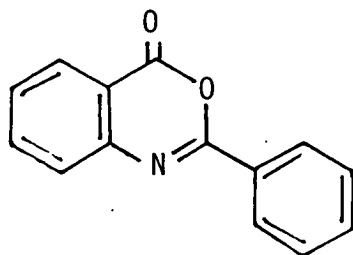


(647)



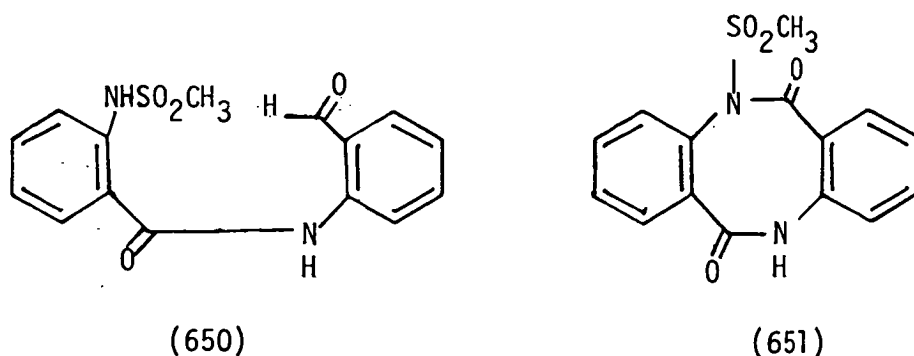
(648)

These workers⁴²⁴⁻⁴²⁵ also tried to obtain (639) from the amide (648) by the Bischler-Napieralski reaction. However the attempted cyclodehydration with polyphosphoric acid only gave the benzoxazone (649).



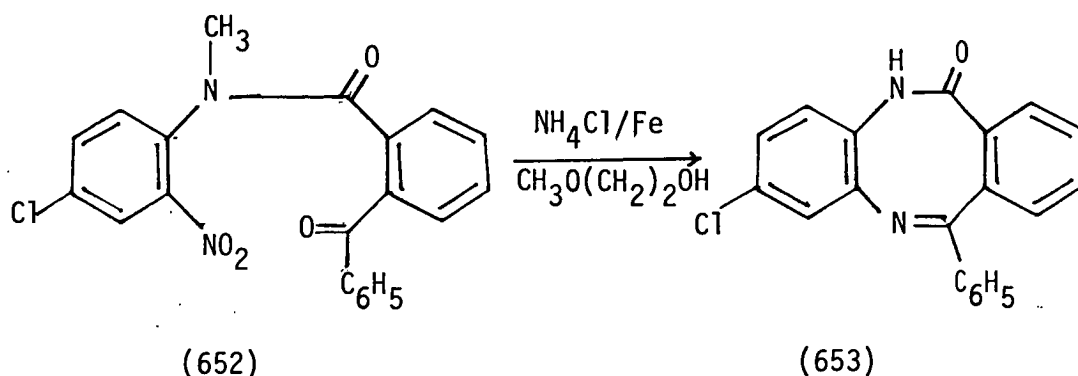
(649)

The dione derivative (651) was obtained by the intramolecular cyclization of compound (650).⁴²⁷

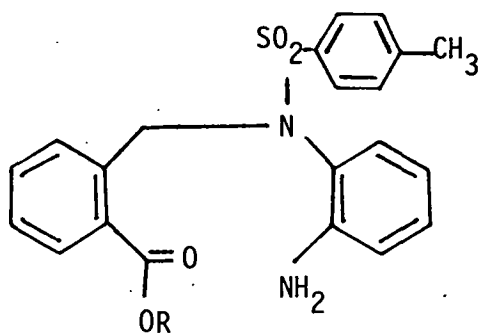
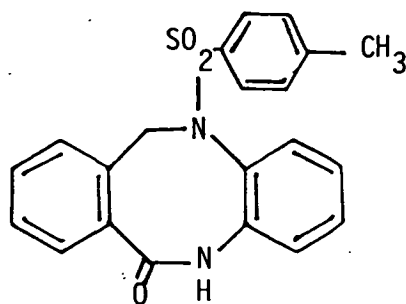


B(a)-(2) Dibenz[*b,f*][1,4]diazocines

The reductive cyclization of (652) in the presence of ammonium chloride and iron filings gave 29% yield of the dibenz[*b,f*][1,4]-diazocine derivative (653).^{423,425}

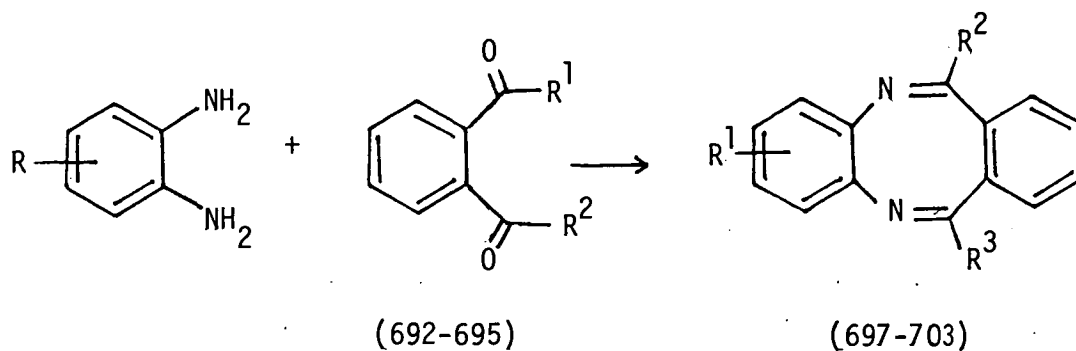
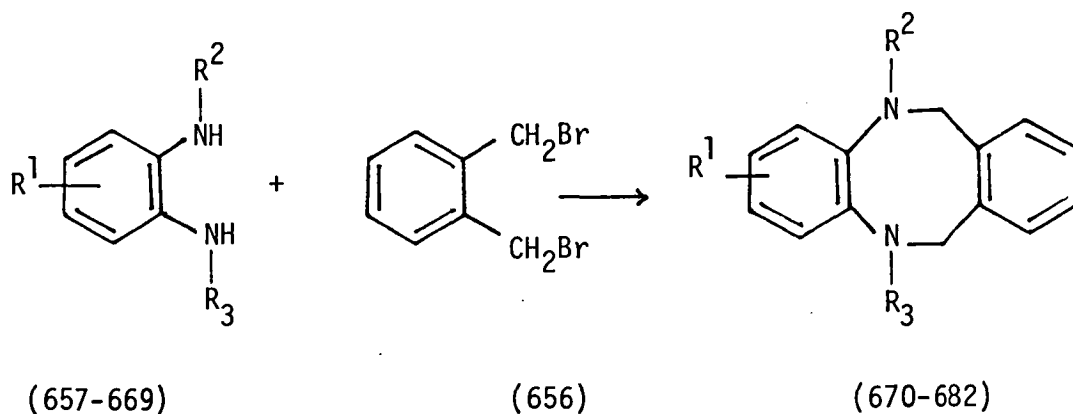


Saunders and Sprake⁴²⁴ synthesised 11,12-dihydro-12-*p*-tolyl-dibenzo[*b,f*][1,4]diazocine-6(5*H*)-one (655) in 73% yield by the reaction of (654a) and sodium hydride in dioxane. Treatment of the amino acid (654b) with dicyclohexylcarbodiimide in ethyl acetate or ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate in tetrahydrofuran, also gave (655) in 64% yield.⁴²⁴

(654) (a) $R=C_2H_5$ (b) $R=H$ 

(655)

A number of dibenzo[*b,f*][1,4]diazocines (670-682 and 697-703) (Tables 15 and 16) were synthesised by the reaction of *o*-phenylenediamine derivatives (657-669, 684-691) and α,α' -dibromo-*o*-xylene (656) (Table 15) or with *o*-diketobenzene compounds (692-695) (Table 16). The general reactions are given in the Scheme 27.

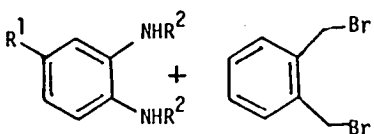
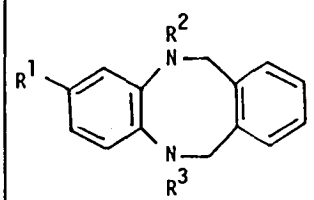


Scheme 27

Table 15

B(a)-(2) Dibenzo[b,f][1,4]diazocines

(C-N type ring closure)

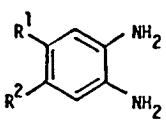
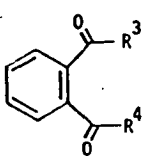
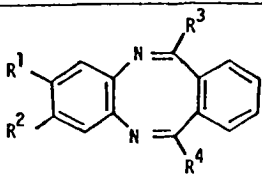
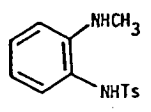
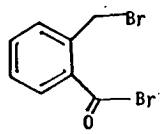
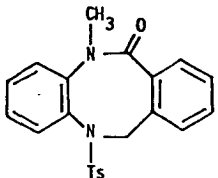
Starting materials	Reaction conditions	Products	Yield %	Reference
 (657-669)				
<div> <div>R¹</div> <div>R²</div> <div>R³</div> </div>		<div> <div>R¹</div> <div>R²</div> <div>R³</div> </div>		
(657) H CH ₃ CH ₃	{ anhydrous K ₂ CO ₃ /toluene reflux }	(670) H CH ₃ CH ₃	85	428-431
(658) H Ts Ts		(671) H Ts Ts	85	431
(659) H SO ₂ C ₆ H ₅ SO ₂ C ₆ H ₅	KOH/H ₂ O reflux 8 hours	(672) H SO ₂ C ₆ H ₅ SO ₂ C ₆ H ₅	90	432
(660) Cl Ts Ts	in boiling toluene	(673) Cl Ts Ts	-	430
(661) OCH ₃ Ts Ts		(674) OCH ₃ Ts Ts	-	"
(662) CF ₃ Ts Ts		(675) CF ₃ Ts Ts	-	"
(663) NO ₂ Ts Ts		(676) NO ₂ Ts Ts	-	"
(664) OCH ₃ SO ₂ C ₆ H ₅ Ts	"	(677) OCH ₃ SO ₂ C ₆ H ₅ Ts	-	"
(665) OCH ₃ Ts SO ₂ C ₆ H ₅	"	(678) OCH ₃ Ts SO ₂ C ₆ H ₅	-	"
(666) H CH ₃ CH ₃	K ₂ CO ₃ /toluene reflux	(679) H CH ₃ CH ₃	-	433
(667) H COCH ₃ COCH ₃	"	(680) H COCH ₃ COCH ₃	-	"
(668) H CHO CHO	DMF/K ₂ CO ₃ /N ₂ reflux	(681)* H CHO CHO	60	434
(669) Cl CHO CHO	"	(682) Cl CHO CHO	77	435
		(683) H H CHO	-	"

*The reaction of 85% potassium hydroxide with (681) (Table 13) yielded (683)⁴³⁴ and this was further converted into several 12-substituted dibenzo[b,f][1,4]diazocine derivatives.⁴⁴¹

Table 16

B(a)-(2) Dibenzo[*b,c*][1,4]diazocines

(C-N type ring closure)

Starting materials	Reaction conditions	Products	Yield %	Reference
  (684) $R^1=R^2=H$ + (692) $R^3=R^4=H$ (685) $R^1=R^2=H$ + (693) $R^3=R^4=C_6H_5$ (686) $R^1=CH_3$, $R^2=H$ + (693) (687) $R^1=C_2H_5$, $R^2=H$ + (693) (688) $R^1=iso-C_3H_7$, $R^2=H$ + (693) (689) $R^1=Cl$, $R^2=H$ + (693) (690) $R^1=R^2=Cl$ + (693) (684) + (694) $R^3=R^4=Cl$ (684) + (695) $R^3=R^4=OC_2H_5$	$AlCl_3/Cl \cdot C_6H_5$ $p-CH_3C_6H_4 \cdot SO_3H /$ $C_6H_6 / reflux$ Δ $NaH / dimethyl formamide$ $5\% NaH$ in anhydrous dioxane	 (697) $R^1=R^4=H$ (698) $R^1=R^2=H$, $R^3=R^4=C_6H_5$ (699) $R^1=CH_3$, $R^2=H$, $R^3=R^4=C_6H_5$ (700) $R^1=C_2H_5$, $R^2=H$, $R^3=R^4=C_6H_5$ (701) $R^1=iso-C_3H_7$, $R^2=H$, $R^3=R^4=C_6H_5$ (702) $R^1=Cl$, $R^2=H$, $R^3=R^4=C_6H_5$ (703) $R^1=R^2=Cl$, $R^3=R^4=C_6H_5$ (618) (618)	- 72 73 69 72 73 72	436 436-438 438 " " " "
 (691)	 (699)	 (704)	91	424

The starting materials, reaction conditions and yields of the dibenzo[*b,f*][1,4]diazocines obtained are recorded in Tables 15 and 16.

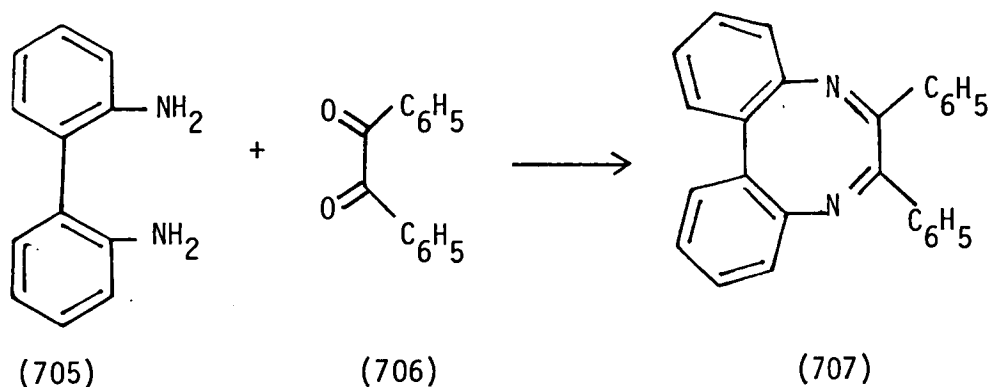
Ruxer and co-workers have reported the interconversions of (699),⁴⁴² while others have reported kinetic⁴⁴³ and structural^{444,227} studies on the dibenzo[*b,f*][1,4]diazocines (697 and 698).

The reduction of dione (618) with phosphorus pentachloride, hydrazine and copper acetate afforded (697),⁴⁴⁰ and the mass spectral behaviour of this compound has been reported.^{445,446}

The 6,6-dideutero derivative of (704) was prepared by the reduction of (704) with lithium tetradeutero aluminate.⁴⁴⁷

B(a)-(3) Dibenzo[*e,g*][1,4]diazocines

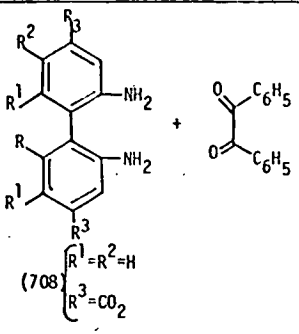
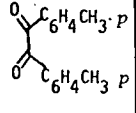
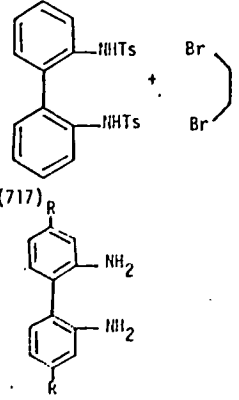
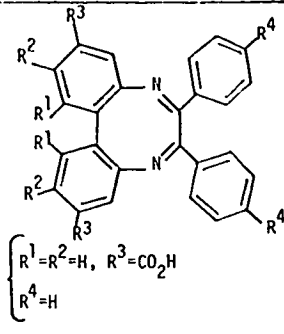
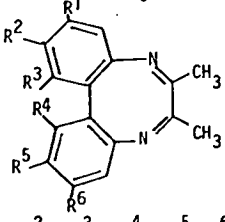
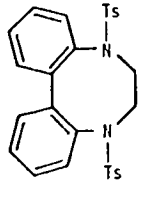
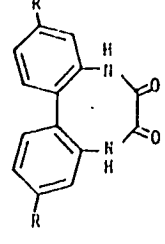
Many workers⁴⁴⁸⁻⁴⁵⁷ have reported the preparation of 6,7-diphenyl-dibenzo[*e,g*][1,4]diazocine (707) in 70-80% yields by the interaction of 2,2'-diaminodiphenyl (705) and phenanthraquinone (706) in the presence of glacial acetic acid under reflux, for one hour to twenty-four hours.



Similarly several other dibenzo[*e,g*][1,4]diazocine derivatives (720-731) (Table 15) were prepared.⁴⁵⁹⁻⁴⁶⁸ The reaction conditions and the products obtained are tabulated in Table 17.

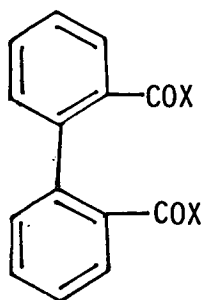
Table 17

B(a)-(3) Dibenzo[*c,g*][1,4]diazocines
(C-N type ring closure)

Starting materials	Reaction conditions	Products	Yield %	Reference
 <p>(708) $R^1=R^2=H$ $R^3=CO_2$</p> <p>(709) $R^1=CH_3$, $R^2=R^3=H$</p> <p>(710) $R^1=R^3=H$, $R^2=Br$</p> <p>(711) $R^1=R^2=H$, $R^3=CO_2CH_3$</p> <p>(712) $R^1=R^3=F$, $R^2=H$</p> <p>(713) +  $R^1=R^2=R^3=H$</p> <p>+ biacetyl</p> <p>(714) CH_3 CH_3 H H H H</p> <p>(715) H H CH_3 CH_3 H H</p> <p>(716) CO_2H H H H H CO_2H</p> <p>(717) </p> <p>(718) $R=C_6H_5$ + oxalyl chloride</p> <p>(719) $R=H$ + oxalic acid</p>	<p>glacial acetic acid Δ 24 hours</p> <p>in boiling propionic acid</p> <p>acetic acid Δ 8 hours</p> <p>30 minutes/Δ</p> <p>in ethylene glycol 1 hour, Δ</p> <p>Na in butanol</p> <p>dry toluene/reflux</p> <p>"</p>	 <p>(720) $R^1=R^2=H$, $R^3=CO_2H$ $R^4=H$</p> <p>(721) $R^1=CH_3$, $R^2=R^3=H^4=H$</p> <p>(722) $R^1=R^3=R^4=H$, $R^2=Br$</p> <p>(723) $R^1=R^2=R^4=H$, $R^3=CO_2CH_3$</p> <p>(724) $R^1=R^3=F$, $R^2=R^4=H$</p> <p>(725) $R^1=R^2=R^3=H$, $R^4=CH_3$</p>  <p>(726) CH_3 CH_3 H H H H</p> <p>(727) H H CH_3 CH_3 H H</p> <p>(728) CO_2H H H H H CO_2H</p> <p>(729) </p>  <p>(730) $R=C_6H_5$</p> <p>(731) $R=H$</p>	<p>73</p> <p>24</p> <p>—</p> <p>20</p> <p>—</p> <p>—</p> <p>—</p> <p>39</p> <p>9</p> <p>24</p> <p>43</p> <p>82</p> <p>77</p>	<p>451,453, 456,458, 459</p> <p>460</p> <p>451,456</p> <p>460</p> <p>455</p> <p>451,456</p> <p>461</p> <p>462</p> <p>460</p> <p>460</p> <p>463</p> <p>464, 465, 466</p> <p>467</p>

B(a)-(4) Dibenzo[*d,f*][1,2]diazocines

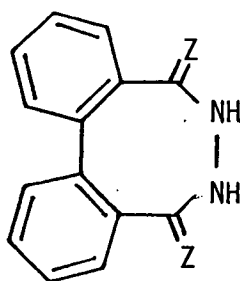
The dibenzo[*d,f*][1,2]diazocine (630), which was obtained by the ring enlargement of diphenic anhydride, was also synthesised by the reaction of the methyl ester (732) or dichloride (733) with hydrazine hydrate.^{417,468}

(732) X = OCH₃

(733) X = Cl

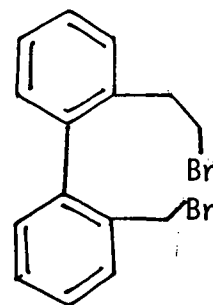
(734) X = CH₃

(735) X = H

(736) X = C₆H₅

(630) Z = O

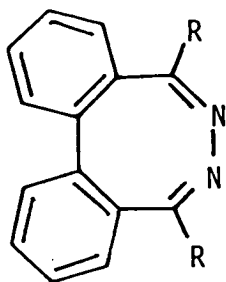
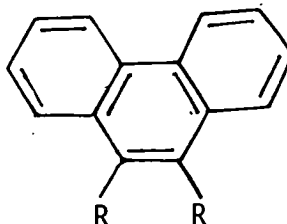
(737) Z = O



(738)

The tetrahydro derivative (737) was prepared in 38% yield by the reaction of (738) with *tert*-butyl hydrazodiformate and potassium in butanol and dimethylformamide.⁴⁶⁹ Compound (630) was further converted into *N*-substituted derivatives.⁴⁷⁰

The condensation of diketone (734) with aqueous hydrazine hydrate gave 53% of the dibenzodiazocine (739), along with 4% of the phenanthrene derivative (741a).^{471,472} Under the same reaction conditions, the dialdehyde (735), gave (741b) as the only product. The 5,8-diphenyl derivative (740) was synthesised in 60% yield, by the reaction of (736) with hydrazine in diethylene glycol, and the formation of by-products was not observed.^{473,474}

(739) $R = \text{CH}_3$ (740) $R = \text{C}_6\text{H}_5$ (741) a, $R = \text{CH}_3$ b, $R = \text{H}$

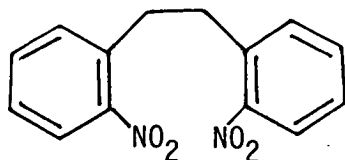
A paper by Beaven and Johnson⁴⁷⁵ described the uv spectrum of (739).

B(b) *N-N* type ring closure

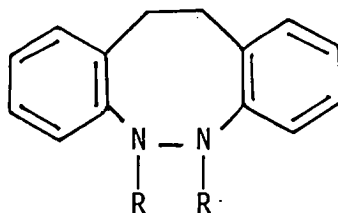
B(b)-(1) Dibenzo[*c,g*][1,2]diazocines

The reductive ring closure of *N,N'*-dinitrobibenzyl (742) with zinc dust in barium hydroxide and ethanol under reflux, gave 5,6,11,12-tetrahydrodibenzo[*c,g*][1,2]diazocine (743) in 60% yield.⁴⁷⁶⁻⁴⁸⁰

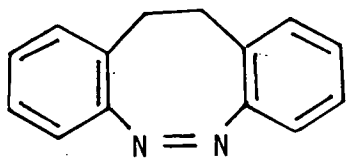
Treatment of (743) with dilute acids afforded a *spiro*-1,2,3,4-tetrahydroquinoline derivative,⁴⁸¹ and the reaction of (743) with methyl iodide gave (744).⁴⁸² Neugebauer and Wegar⁴⁸³ have reported the ESR spectrum of this methylated derivative.



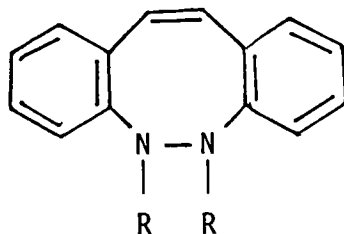
(742)

(743) $R = \text{H}$ (744) $R = \text{CH}_3$

In the presence of yellow mercuric oxide in ethanol, (743) gave 81% of 6,12-dihydrodibenz[*c,g*][1,2]diazocine (745), which was converted into (746),⁴⁷⁶ and (747),⁴⁸⁴ by a series of reactions.



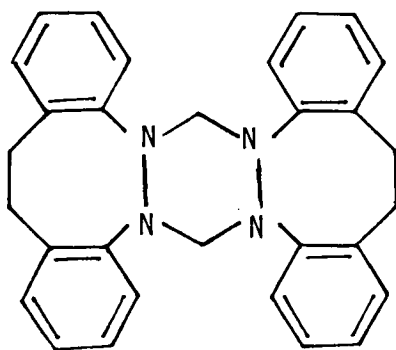
(745)



(746) R = H

(747) R = CH₃

With butyl lithium and methyl sulfate, (745) underwent a dimerization reaction giving rise to (748).⁴⁸² Gersson *et al*^{485,486} described the ultraviolet absorption spectrum of (745).



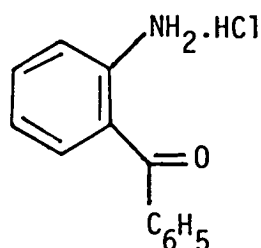
(748)

(C) Self-condensation (dimerization)

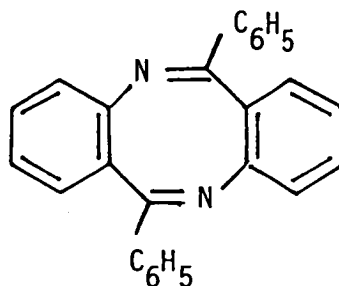
(C)-(1) Dibenzo[*b,f*][1,5]diazocines

Self-condensation of 2-aminobenzophenone derivatives is the most widely employed method for the synthesis of dibenzo[*b,f*][1,5]diazocines.

In 1896, Sandheimer⁴⁵⁰ obtained a dimeric product by heating 2-aminobenzophenone hydrochloride (749) alone. This compound was described as a "phenhomazine" derivative, now known as 6,12-diphenyl-dibenzo[*b,f*][1,5]diazocine (750).



(749)

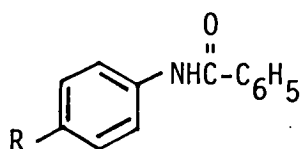


(750)

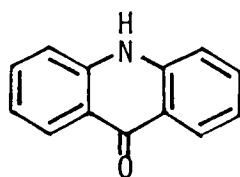
In 1966, Metlesics and co-workers⁴⁸⁷ reported the synthesis of the same dibenzodiazocine (750) in 71% yield by the self-condensation of (749) in the presence of a catalytic amount of aluminium chloride in refluxing chlorobenzene. Replacing aluminium chloride with zinc chloride, a poor yield (22%) of (750) together with two minor by-products (751,752) were obtained.^{488,489}

A 100% yield of (750) was isolated by heating 2-aminodiphenyl-methyleneimine (753) at 200° in a nitrogen stream.⁴⁹⁰ Phosphorus oxychloride also was used as a catalyst for this bimolecular condensation.⁴⁹¹

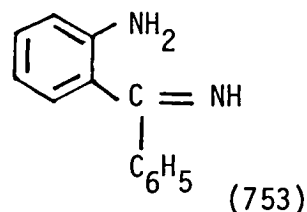
A patent by Yamamoto⁴⁹² *et al* reported the synthesis of (750) in yields of 41-85%, but the experimental details were not given.



(751)



(752)



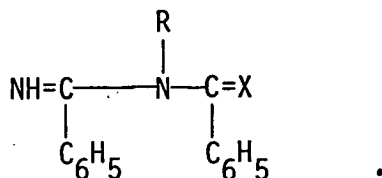
(753)

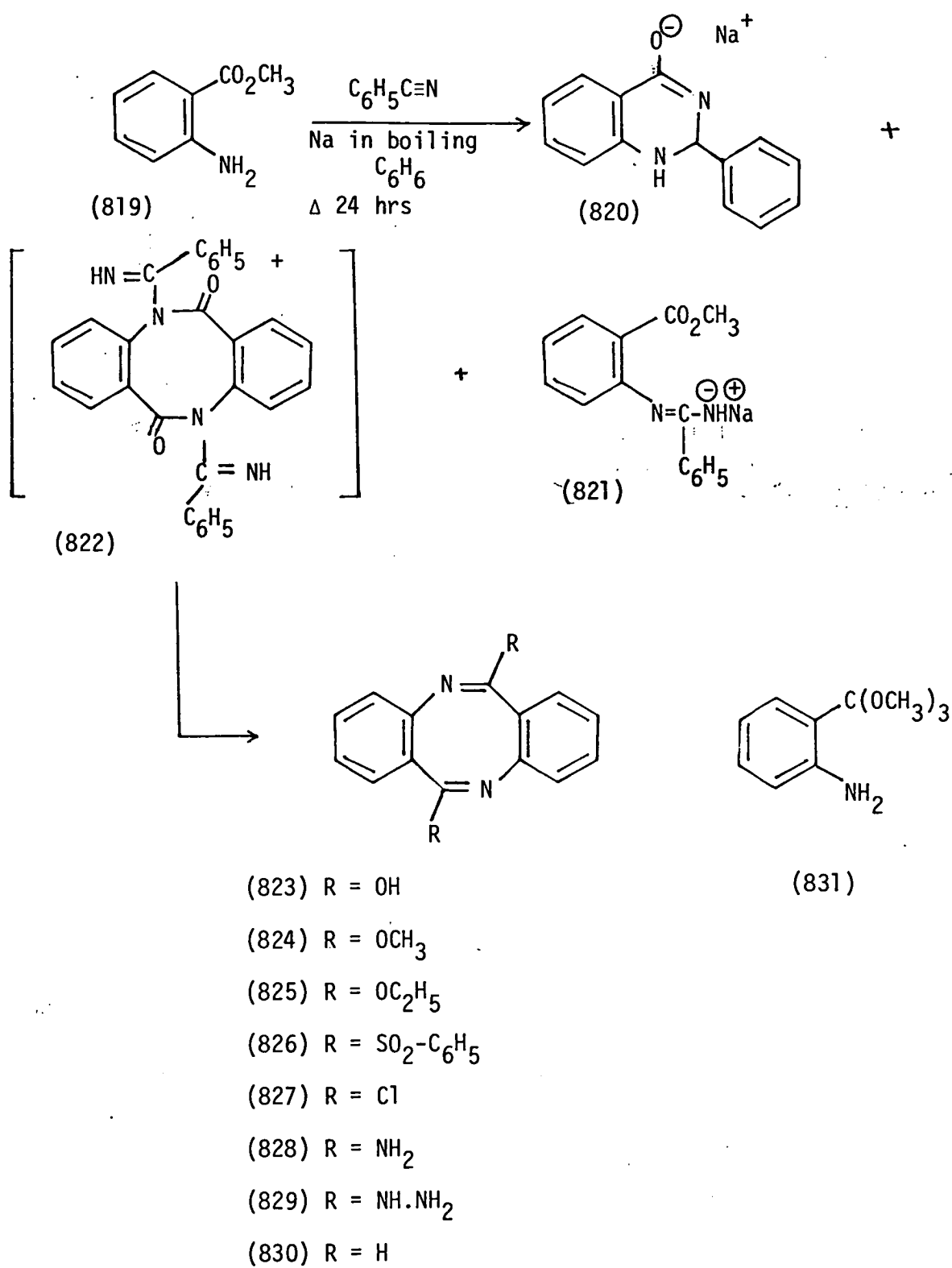
Other dibenzo[*b,f*][1,5]diazocines (787-818) prepared by the self-condensation reactions⁴⁸⁷⁻⁵⁰⁰ are given in Table 18.

Many other dibenzo [*b,f*][1,5]diazocines were prepared by the bimolecular condensation of 2-aminobenzoic acid derivatives. For

example, 5,11-dihydroxydibenzo[*b,f*]diazocine (823) was synthesised from 2-aminomethylbenzoate (819).^{508,509} (Table 18). The reaction was carried out in benzonitrile containing "powdered" sodium in benzene, to give 55-60% yield of (823) together with two other products (820,821).^{509,512} (Scheme 28). Replacing benzonitrile with acetonitrile, the yield of (823) decreased and the reaction with sodium in benzene or ethanol alone gave a poor yield (4%) of (823).^{508,509} Hence this reaction could not be a simple base-catalysed condensation as thought at first, and it is possible that benzonitrile may act as a catalyst. In contrast to these results, 6,12-demethoxydibenzo[*b,f*][1,5]diazocine (824) was obtained in 81% yield by the condensation of (831) in the presence of glacial acetic acid.⁵⁰⁸

The decomposition of (822) to (823) was similar to that observed in a number of open-chain analogues having the structure,



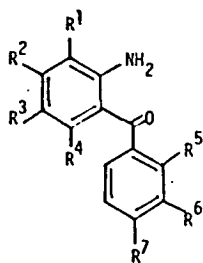


Scheme 28

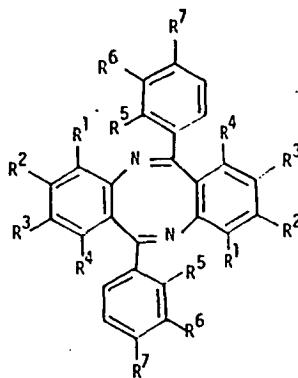
Table 18

(C)-(1) Dibenzo[*b,r*][1,5]diazocines

(Self-condensation)



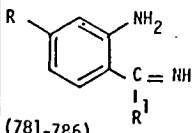
Starting material

Product (R_1 to R_7 as with the starting material)

Starting material	Solvent	Catalyst	Reaction (h) time or t°C	Product	Yield %	Reference
(754) $R^3=Cl$	xylene	$BF_3-(C_2H_5)_2O$	6/15 hr	(787)	88	487,492,493
	-	$ZnCl_2$	180°	"	68	
	-	$ZnCl_2$	200°	(787)*	43	
	-	$ZnCl_2$	200°	"	10	
	-	$ZnCl_2$	240°	"	8	
	-	-	200°	"	42	
	-	$AlCl_3$	200°	"	78	
	C_6H_5Cl	$AlCl_3$	3 hr	"	-	
	C_6H_5Cl	PPA	18 hr	"	-	
	xylene	$HSO_3 \cdot C_6H_5-p-Me$	16 hr	"	62	
(755) $R^3=F$	-	$POCl_3$	reflux	"	41-85	488,489
	heating in a N_2 stream					
	C_6H_5Cl	BF_3-Et_2O	17 hr	(788)	65	
	-	$POCl_3$	reflux		-	
	C_6H_5Cl	$AlCl_3$	-	(789)	-	
	-	BF_3-Et_2O	17 hr		23	
	C_6H_5Cl	$POCl_3$	reflux	(790a)	-	
	-	$AlCl_3$	"		-	
	benzene	$TiCl_4$	2 hr	(791)	23	
	heating in a nitrogen stream				-	
(756) $R^3=Br$	C_6H_5Cl	$BF_3-(C_2H_5)_2O$	6 hr	(790b)	65	487,492,493
	"	$AlCl_3$	-		-	
(757) $R^3=CF_3$	C_6H_5Cl	$BF_3-(C_2H_5)_2O$	16 hr	(791)	63	487,492,493
	"	"	-		-	
(758) $R^3=OCH_3$	C_6H_5Cl	$BF_3-(C_2H_5)_2O$	16 hr	(791)	63	487,492,493
	"	"	-		-	
(759) $R^3=Br, R^5=F$	C_6H_5Cl	$BF_3-(C_2H_5)_2O$	16 hr	(791)	63	487,492,493
	"	"	-		-	

*When not specified $R^n=H$. ($n=1,2,3,4,5$, or 6)

Table 18 continued

(760) $R^3=Cl, R^5=OCH_3$	$\left\{ \begin{array}{l} C_6H_5Cl \\ " \\ " \\ " \\ " \\ " \\ " \\ " \end{array} \right.$	$BF_3 \cdot (C_2H_5)_2O$	16 hr	(792)	43	487,492,493
(761) $R^3=R^6=Cl$	"	"	"	(793)	64	
(762) $R^3=Cl, R_7=F$	"	"	"	(794)	76	
(763) $R^2=Cl$	"	"	"	(795)	84	
(764) $R^4=Cl$	"	"	"	(796)	52	
(765) $R^2=R^3=Cl$	"	"	"	(797)	64	
(766) $R^3=R^5=Cl$	"	$TiCl_4$	"	(798)	60	487,493
(767) $R^3=Cl, R^5=CH_3$	"	"	"	(799)	60	"
(768) $R^3=NO_2$	"	"	"		87	498,499
	heating in a nitrogen stream				-	493
	"	$AlCl_3$	18 hr	(800)	87	491
	"	$POCl_3$	reflux		-	492
	xylene	$BF_3 \cdot (C_2H_5)_2O$	15 hr		-	493
(769) $R^3=C_2H_5S$	C_6H_5Cl	$TiCl_4$	reflux	(801)	-	487,493
(770) $R^1=Cl$	"	$BF_3 \cdot TiCl_4$	16 hr	(802)	52	"
(771) $R^1=R^3=Br$	"	$BF_3/TiCl_4$	"	(803)	63	493
(772) $R^1=R^2=R^3=R^4=Cl$	"	$BF_3/TiCl_4$	reflux	(804)	-	491
	-	$POCl_3$	"	(805)	-	488
(773) $R^3=CH_3$	-	$ZnCl_2$	200°		18	489
	-	$ZnCl_2$	220°		11.4	492
	xylene	$BF_3 \cdot Et_2O$	15 hr		-	500
	EtOH	HCl	Δ		50	498,499
(774) $R^3=Cl, R^7=CH_3$	heating in a nitrogen stream			(806)	-	497
(775) $R^3=Cl, R^7=OCH_3$	toluene and p-toluenesulfonic acid		16 hr	(807)	-	"
(776) $R^7=OCH_3$	$C_6H_5CH_3/HSO_3 \cdot C_6H_4-p-CH_3$	-	"	(809)	-	491
(777) $R^7=NO_2$	-	$POCl_3$		(810)	41%-85%	"
(778) $R^6=NO_2$	-	"	reflux	(811)	"	"
(779) $R^5=R^6=R^7=Br$	-	"	"	(812)	"	"
(780) $R^5=Cl$	-	"	"			
<div style="display: flex; align-items: center;"> <div style="margin-right: 20px;">  <p>(781-786)</p> </div> <div> <p>* structures of the products are given below</p> </div> </div>						

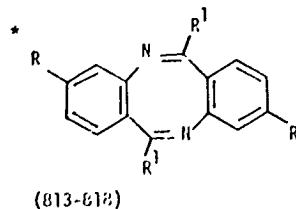


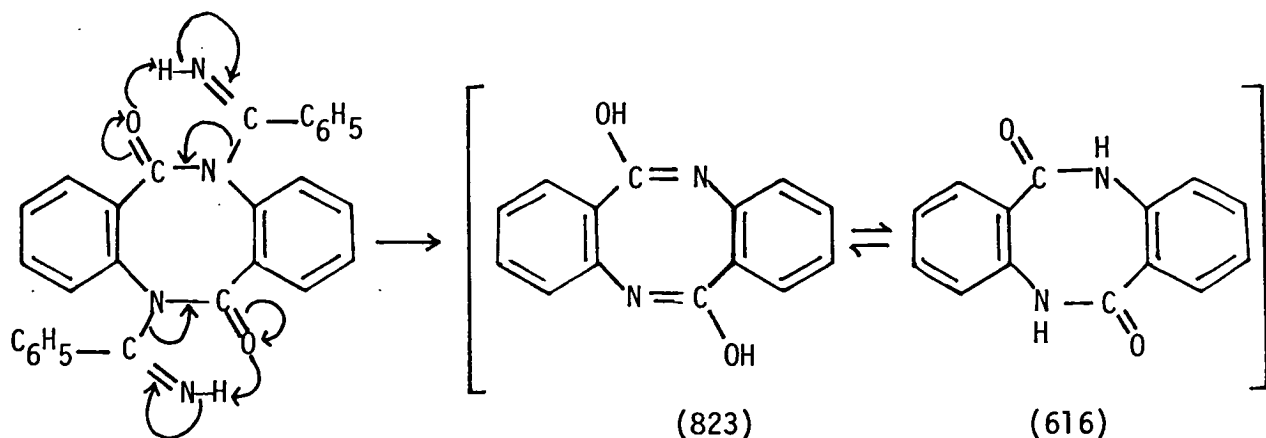
Table 18 continued

R	R ¹						
(781)	Cl C ₆ H ₅	heating in a N ₂ stream at 220°	—	4 hr	(813)	—	490,492
(782)	NO ₂ C ₆ H ₅	"	—	"	(814)	—	"
(783)	CF ₃ C ₆ H ₅	"	—	"	(815)	—	"
(784)	Cl o-tolyl	"	—	"	(816)	—	"
(785)	H 2-thienyl	xylene	BF ₃ ·(C ₂ H ₅) ₂ O	15 hr	(817)	—	492
(786)	H 2-pyridyl	"	"	"	(818)	—	499

*The reduction of (787) (page 126) afforded 2,8-dichloro-6,12-diphenyl-5,6-dihydro and 5,6,11,12-tetrahydrodibenzo-[b,f][1,5]diazocine.⁵⁰¹⁻⁵⁰⁴

Ruxer and co-workers⁵⁰⁵ reported on the NMR spectrum of (787), and the pharmacological studies showed that (787) possessed significant antigonadotropic activity in rats.^{506,507}

On the basis of this assumption, these workers have proposed the following mechanism for the decomposition of (822). (Scheme 29).



Scheme 29

A thermochromic rearrangement (Figure 18) has also been observed⁵¹³ for the dibenzodiazocine (823).

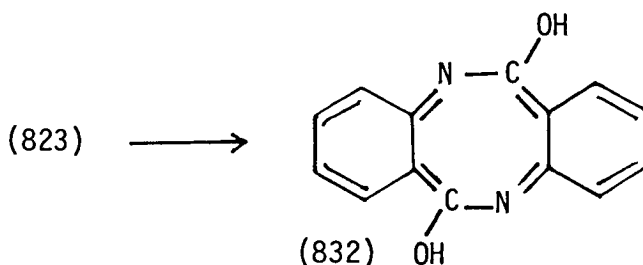
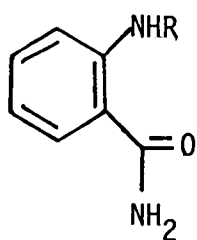


Figure 18

The compound (823) can be obtained from the hydrolysis of (826) which was prepared from the self-condensation of *o*-arylsulphonamido benzyl chloride.⁵⁰⁹ The reaction of (823) with phosphorus pentachloride resulted in the formation of 6,12-dichlorodibenzo[*b,f*]-[1,5]diazocine (827). This was further converted into diamino (828) and dialkoxy (824 and 825) derivatives by treatment with methanolic ammonia or by reaction with an appropriate alkoxide respectively.⁵⁰⁹ (Scheme 28).

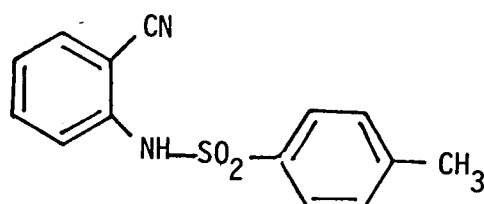
A paper by Pakrashi⁵¹⁴ described the synthesis of the diamino derivative (828) directly from the self-condensation of anthranilamide

(833) in anhydrous xylene and phenylacetic acid containing excess phosphorus pentoxide. Formation of several other by-products was a disadvantage of this method. Under the same reaction conditions, *N*-methylantranilamide (834) did not give an eight-membered ring product. In addition to these methods, 6,12-diaminobenzo[*b,f*][1,5]-diazocine (828) can be prepared from the self-condensation of *o*-cyanoanilinium toluene-*p*-sulphonate (835).⁵¹⁰



(833) R = H

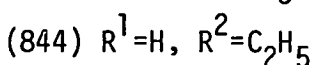
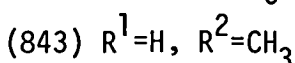
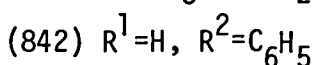
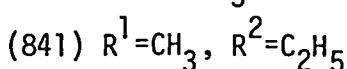
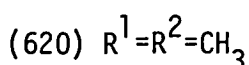
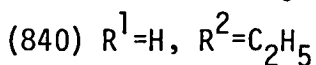
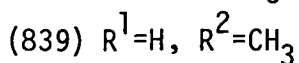
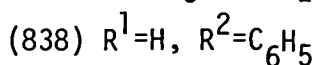
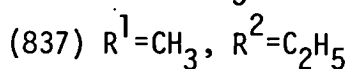
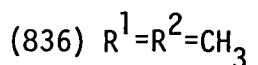
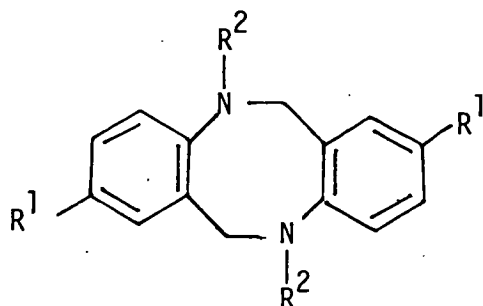
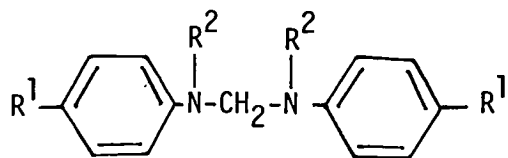
(834) R = CH₃



(835)

The reaction of 6,12-dichlorodibenzo[*b,f*][1,5]diazocine (827) with hydrazine gave (829) which afforded (830) on reduction with copper acetate.⁵¹⁵ Reduction of (830) followed by alkylation gave derivatives of 5,6,12-tetrahydrodibenz[*b,f*]diazocine.^{513,516} The formation of 5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocines have been achieved by the self-condensation of α -diamines of type (A). (836-840). The reaction of (836) either in benzoic acid in pure dry chloroform or benzoyl chloride in chloroform afforded 2,5,8,11-tetramethyldibenzo[*b,f*][1,5]diazocine (620). The former method gave a higher yield (70%) than the latter method.⁴¹¹

Similarly dibenzo[*b,f*][1,5]diazocines (841-844) were prepared from the corresponding diamine (837-840).⁴¹¹ When the benzene rings of the α -diamine were unsubstituted (838-840), the yield of dibenzodiazocines (842-844) were only 35-40%, whereas α -diamines

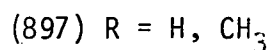
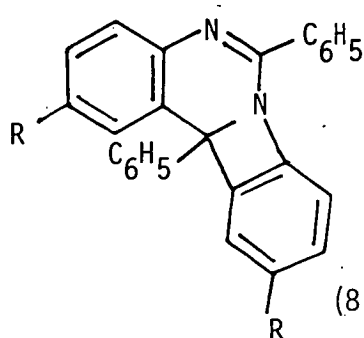
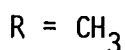
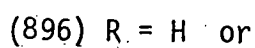
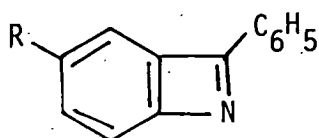


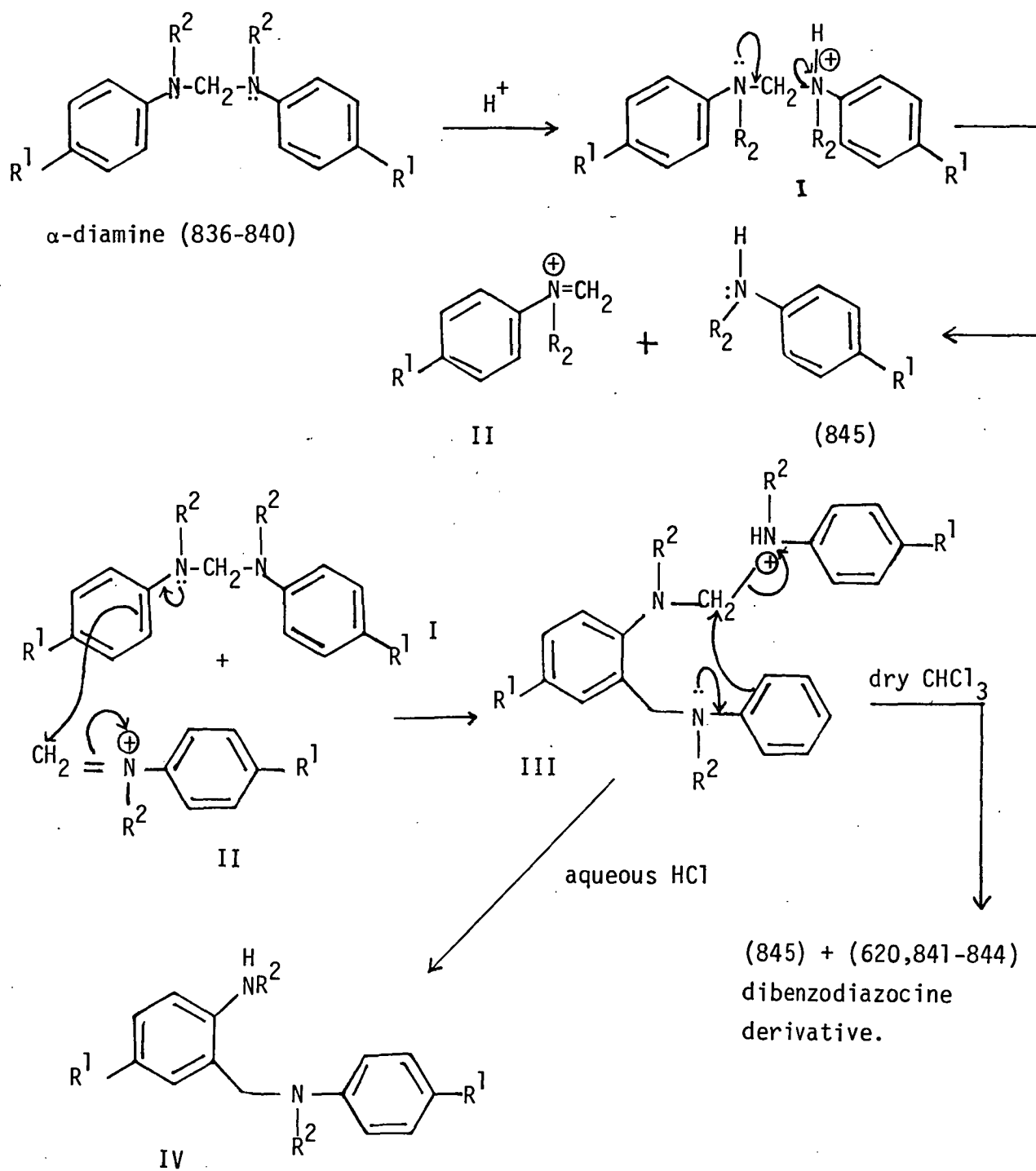
having substituents on the benzene rings (836,837) gave 70% yield of the corresponding diazocine (620,841).

The suggested mechanism for the condensation of α -diamines unsubstituted on the benzene ring is illustrated in Scheme 30.

Other dibenzo[*b,f*][1,5]diazocines (869-896) obtained by dimerization⁵¹⁷⁻⁵³² are summarized in Table 19.

The dibenzo[*b,f*][1,5]diazocines (893-895) were prepared by the reaction of paraformaldehyde and saccharine with *o*, *m*, and *p*-hydroxy aniline respectively.⁵³⁴ In the presence of aluminium chloride, silver tetrafluoroborate, or boron trifluoride-etherate, the 2-phenylbenzoazetes (896a,b) gave a mixture of dibenzo[*b,f*][1,5]-diazocine (750,807) and an angular dimer (897).⁵³⁵



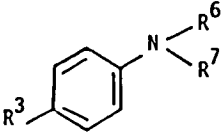
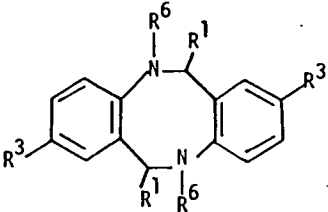
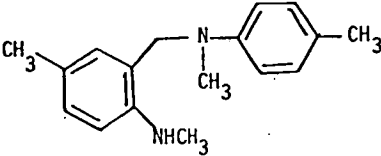
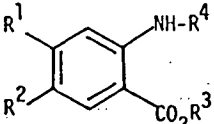
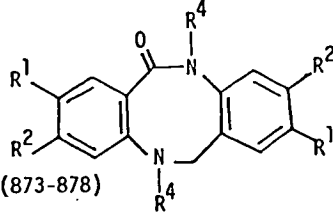


(Scheme 30)

Table 19

(C)-(1) Dibenzo[*b,c'*][1,5]diazocines

(Condensation)

Starting materials	Reaction conditions	Products	Yield %	Reference
				
(846) $R^3=CH_3$	40% formaldehyde conc. HCl and $NaNO_2/HCl$, and cuprous chloride	(869) $R^3=CH_3$	32	517
(847) $R^6=R^7=CH_3$	benzoyl peroxide	(843) $R^6=CH_3$ in cumene (0°) in tetralin (0°) in decane	70 low "	410 518
(848) $R^3=CH_3$, $R^6=H$, $R^7=NH_2$	$ZnCl_2$	(870) $R^3=CH_3$, $R^1=C_6H_5$, $R^6=N:CHC_6H_5$	-	519,520
(849) $R^3=R^6=R^7=CH_3$	<div> <div>benzoyl peroxide in ethyl acetate or $CHCl_3$, N_2</div> <div>or</div> <div>C_6H_6 or CH_3CN at 5-45°</div> </div>	(620) $R^3=R^6=C_6H_5$ (page 107)	79	518
		no 8-membered ring product was obtained	-	"
	<div> <div>oxidation $Hg(II)$acetate in acetic acid or copper(II) chloride in EtOH or MeCN</div> </div>	(620) $R^3=R^6=CH_3$	250	411
(850) $R^3=R^6=CH_3$	40% HCHO 2N HCl after 14 days at 20°C	(620)* $R^3=R^6=CH_3$ and 	equal yields	521, 522
(851) $R^6=C_6H_5$	HCHO	(872) $R^6=C_6H_5$	78	523
 (852-b57)		 (873-878)		
(852) $R^3=CH_3$, $R^4=C_6H_5$	aziridine/ $AlCl_3$	(873) $R^4=C_6H_5$	30	524

* On addition of excess formaldehyde to the reaction mixture, the compound (871) was rapidly converted into (620). The formation of (871) was observed at low acid concentration. At higher acid concentration (>2N) only (872) was obtained. 522

Table 19 continued

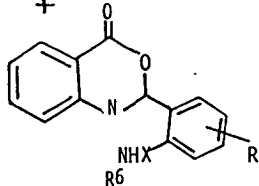
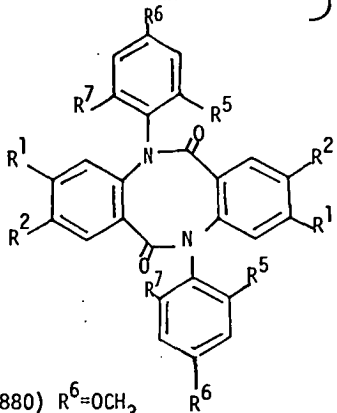
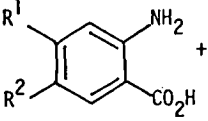
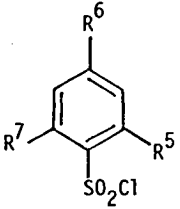
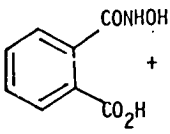
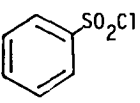
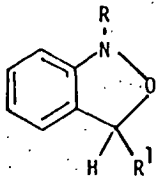
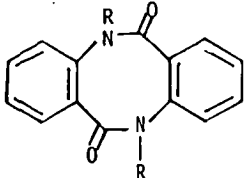
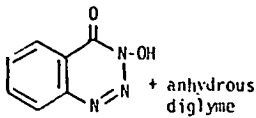
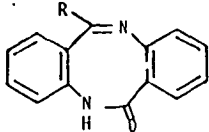
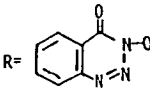
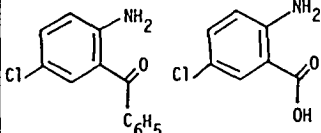
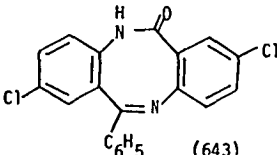
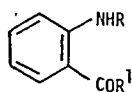
<p>(853) $\begin{cases} R^1 = Cl \\ R^3 = CH_3 \\ R^4 = C_6H_5 \end{cases}$</p> <p>(854) $\begin{cases} R^3 = H \\ R^4 = CH_3 \end{cases}$</p> <p>(855) $\begin{cases} R^2 = Cl \\ R^3 = H \\ R^4 = C_6H_5 \end{cases}$</p> <p>(856) $R^1 = OCH_3$</p> <p>(857) $R^2 = OCH_3$</p>	<p>$AlCl_3$/aziridine</p> <p>$SOCl_2/C_6H_6 \Delta/2 \text{ hours}$</p> <p>condensation</p> <p>$p\text{-CH}_3C_6H_4SO_2Cl$ in pyridine 30° to 114°</p>	<p>(874) $R^1 = Cl, R^6 = C_6H_5$</p> <p>(875) $R^4 = CH_3$</p> <p>(876) $R^2 = Cl, R^4 = C_6H_5$</p> <p>(877) $\begin{cases} R^1 = OCH_3 \\ R^4 = SO_2-C_6H_4-p-CH_3 \end{cases}$</p> <p>(878) $\begin{cases} R^2 = OCH_3 \\ R^4 = SO_2-C_6H_4-p-CH_3 \end{cases}$ + </p> <p></p>	<p>28</p> <p>50</p> <p>-</p> <p>-</p> <p>-</p> <p>-</p>	<p>524</p> <p>525</p> <p>527</p> <p>527</p> <p>528</p> <p>529</p> <p>"</p> <p>"</p> <p>"</p> <p>"</p> <p>"</p> <p>530</p> <p>531</p> <p>"</p> <p>"</p> <p>"</p>
<p> + </p> <p>(858) $R^1 = R^2 = H$ + (859) $R^6 = OCH_3$</p> <p>(858) + (860) $R^6 = NO_2$</p> <p>(858) + (861) $R^5 = R^6 = R^7 = CH_3$</p> <p>(857) + (862) $\left. \begin{matrix} \\ \end{matrix} \right\} R^6 = CH_3$</p> <p>(856) + (862)</p> <p> + </p> <p>(863)</p> <p></p> <p>(864) $R = CH_3, R^1 = OCH_3$</p> <p>(865) $R = CH_2CH_3, R^1 = CN$</p> <p>(866) $R = CH(CH_3)_2$</p> <p>(867) $R = C(CH_3)_3$</p>	<p>pyridine</p> <p>"</p> <p>"</p> <p>"</p> <p>"</p> <p>in alkali</p> <p>xylene</p> <p>reflux</p>	<p>(880) $R^6 = OCH_3$</p> <p>(881) $R^6 = NO_2$</p> <p>(882) $R^5 = R^6 = R^7 = CH_3$</p> <p>(883) $R^2 = OCH_3, R^5 = CH_3$</p> <p>(884) $R^1 = OCH_3, R^6 = CH_3$</p> <p></p> <p>$R = SO_2-C_6H_5$</p> <p>(866) $R = CH_3$</p> <p>(887) $R = CH_2CH_3$</p> <p>(888) $R = CH(CH_3)_2$</p> <p>(889) $R = C(CH_3)_2$</p>	<p>45</p> <p>15</p> <p>3</p> <p>67</p> <p>31</p> <p>-</p> <p>-</p> <p>-</p> <p>-</p>	<p>529</p> <p>"</p> <p>"</p> <p>"</p> <p>"</p> <p>530</p> <p>531</p> <p>"</p> <p>"</p> <p>"</p>

Table 19 continued

 <p>(868) + anhydrous diglyme</p>	reflux	 <p>(890)</p> <p>R = </p>	-	532
	p-toluenesulfonic acid/ C ₂ H ₅ OH and pyridine	 <p>(643)</p>	70	533

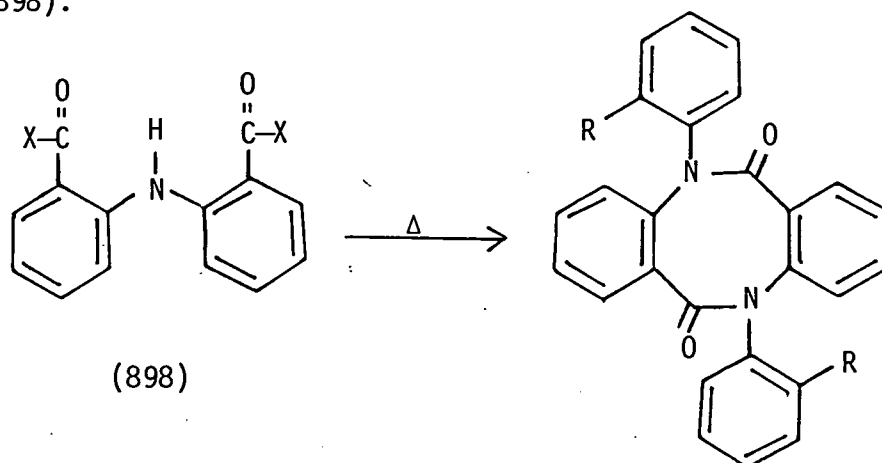
The reaction of (864) in refluxing xylene gave a mixture of dibenzodiazocine (886) and (891), and thermolysis of (865) gave (892) as the only isolable product.⁵³¹



(891) R=CH₃, R¹=OCH₃

(892) R=CH₂CH₃, R¹=CN

The dibenzodiazocine (899) was obtained by the pyrolysis of (898).^{536,537}



X = imidazol-1-yl

(899) 1-imidazolyl

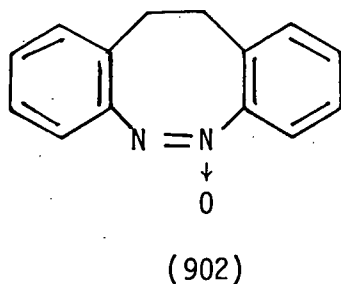
(900) $\text{R}=\text{CO}_2\text{H}$

(901) $\text{R}=\text{CO}_2\text{CH}_3$

Hydrolysis of (899) gave (900) which was converted into the diester (901).⁵³⁷

C-(2) Dibenzo[*c,g*][1,2]diazocines

Unlike the situation with the dibenzo[*b,f*][1,5]diazocines, dimerization reactions have not been widely used in constructing the dibenzo[*c,g*][1,2]diazocines. The only case reported was the dimerization of 2-nitrotoluene in alkali-*tert*-butoxide under a nitrogen atmosphere.⁵³⁸ However, this reaction also resulted in the formation of a small amount of dibenzo[*c,g*][1,2]diazocine (902).

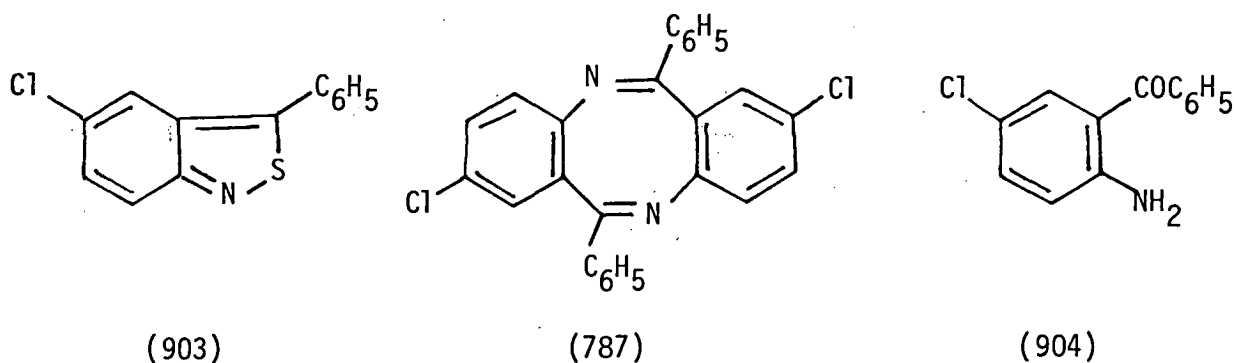


(D) Photochemical preparations

Photochemical reactions have been employed only to synthesise a few derivatives of dibenzo[*b,f*]diazocine and dibenzo[*b,g*][1,5]-diazocines so far. These reactions always resulted in the formation of mixtures. Therefore as a preparative method, photolysis is not so widely used as the condensation reactions.

D-(1) Dibenzo[*b,f*][1,5]diazocines

Irradiation of the benzo[*c*]isothiazole derivative (903) in methyl cyanide, with a pyrex-filtered medium pressure mercury arc lamp gave 39% of (787) along with 8% of 2-amino-5-chlorobenzophenone (904).⁵³⁹ When the reaction was carried out in methanol, the only product isolated was (904). Hence the solvent appears to influence the course of the reaction.

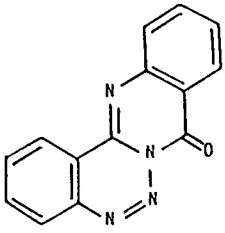
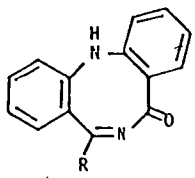
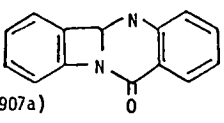
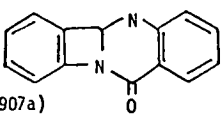
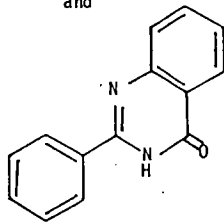
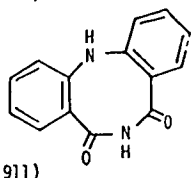


D-(2) Dibenzo[*b,g*][1,5]diazocines

Photolysis of 8-oxo-8*H*-quinazolino[3,2-*c*]1,2,3-benzotriazine (905) in methanol gave 82% yield of dibenzo[*b,g*][1,5]diazocine (906) along with 9% of (907). Irradiation of (905) in different solvents gave derivatives of dibenzo[*b,g*][1,5]diazocines.⁵⁴⁰ These are given in Table 20.

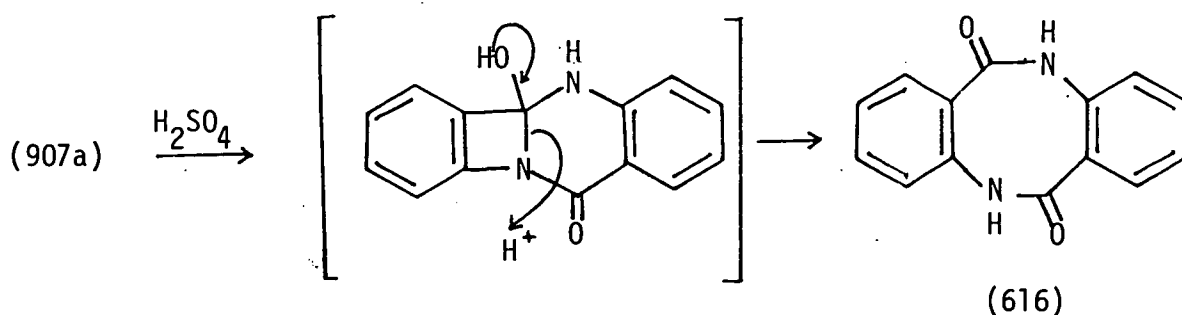
Table 20

O-(2) Dibenzo[*b*,*d*][1,5]diazocines

Starting material	Solvent	Products	Yield %
 (905)	CH ₃ OH	 (906) R=OCH ₃ and	82
	iso-propyl alcohol	 (907a)	9
	Tetrahydrofuran + morpholine	 (908) R=OCH(CH ₃) ₂ and (907a)	52 16
		(909) R = N-morpholino and	47
	Tetrahydrofuran methylene chloride	 (910)	46
(905)		 (911) + (907a)	47 38

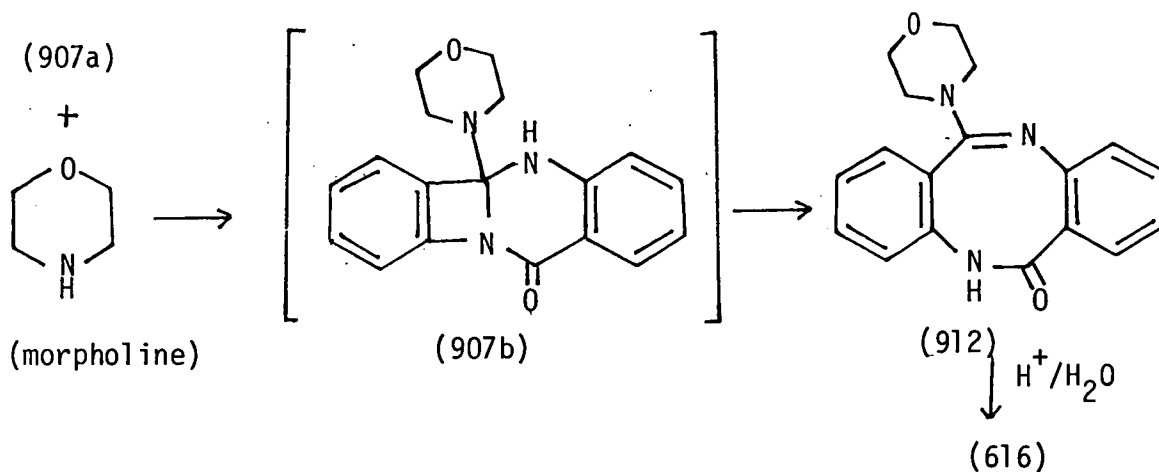
Hydrolysis of the photo-product (907a) gave 95% of dibenzo [*b,f*][1,5]diazocine-6,12(5*H*,11*H*)dione (616).

A suggested pathway for this ring enlargement, somewhat different from that proposed by Ege and co-workers⁵⁴⁰ is given in Scheme 31.



Scheme 31

The morpholino derivative (912), was obtained in 99% yield from (907a), and acid hydrolysis of (912) gave the dione (616).⁵⁴⁰

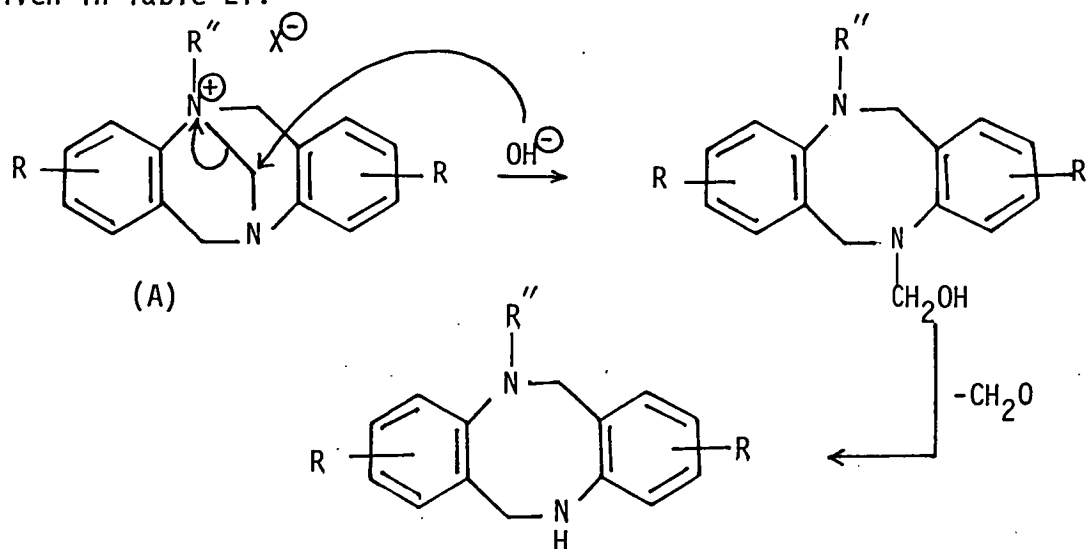


(E) From bridge-head compounds

(E)-(1) Dibenzo[*b,f*][1,5]diazocines

Methylation of compounds of type (A), derivatives of Tröger's base, with dimethylsulfate in alkali resulted in the fission of the endomethylene bridge giving rise to the corresponding dibenzodiazocine derivatives (Scheme 32).

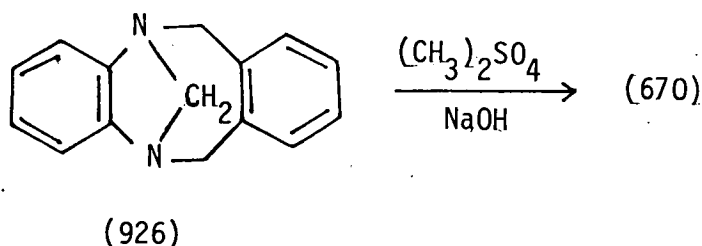
The dibenzodiazocine derivatives obtained by this method are given in Table 21.



Scheme 32

(E)-(2) Dibenzo[*b,f*][1,4]diazocines

Treatment of dimethylsulfate and sodium hydroxide with the bridge-head compound (926) afforded the dibenzo[*b,f*][1,4]diazocine (670).⁴²¹



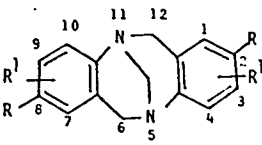
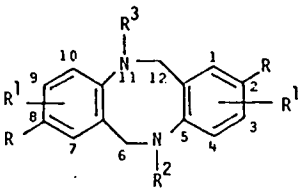
Polymers of dibenzodiazocines

In the presence of polyphosphoric acid, 3,3'-benzidine-dicarboxylic acid (927) gave a yellowish-brown, heat-resistant polymer in 64% yield.^{459,546} The formation of eight-membered rings

Table 21

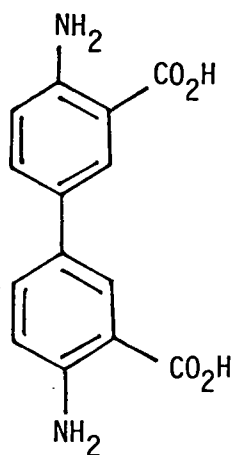
(E)-(1) Dibenzo[*b,f'*][1,5]diazocines

(from bridge-head compounds)

Starting material	Reaction conditions	Product	Yield %	Reference
				
(622) [†] R=CH ₃ , R ¹ =H	(CH ₃) ₂ SO ₄	(620)* R=R ² =CH ₃ , R ¹ =R ³ =H	96	541
(913) R=SCH ₃ , R ¹ =H	CHCl ₃ /(CH ₃) ₂ SO ₄	(919) R=SCH ₃ , R ¹ =R ³ =H, R ² =CH ₃	-	"
(914) R=CH ₃ , R ¹ =Cl	(CH ₃) ₂ SO ₄	(920) R=R ² =CH ₃ , R ¹ =Cl, R ³ =H	-	"
(915) R=R ¹ =CH ₃	(CH ₃) ₂ SO ₄ /NaOH	(921) R=R ¹ =R ² =CH ₃ , R ³ =H	32	"
(916a) R=OCH ₃ , R ¹ =H	dioxane/H ₂ O	(922) { R=OCH ₃ , R ¹ =H, R ² =CH ₃ R ³ =H	75	"
(916b) R=OC ₂ H ₅ , R ¹ =H	HCHO/HCl	(923) R=OC ₂ H ₅ , R ¹ =H, R ² =R ³ =CH ₃	-	542
(917) R=CH ₃ , R ¹ =H	allylbromide	(924) { R=CH ₃ , R ¹ =R ³ =H R ² =CH ₂ -CH=CH ₂	-	541
(917)	p-toluenesulfonyl chloride	(925) { R=CH ₃ , R ¹ =H R ² =Ts	-	524
(918) R=OCH ₂ C ₆ H ₅	CH ₃ COOH/formalin	(926) { R=OCH ₂ C ₆ H ₅ R ¹ =3,9(OCH ₂ C ₆ H ₅) ₂	-	543

[†](Position of R¹ is not given).⁵⁴¹*The crystal structure of (620)⁵⁴⁴ and complex formation with Cu(II), Zn(II) and Ni(II) have also been reported.⁵⁴⁵

containing two lactam links was suggested from infrared spectroscopy.



(927)

Chapter 7

Dibenzoxazocines

Out of the sixteen possible dibenzoxazocines, only eight (A-H) have been synthesised, and these are given in Figure 19.

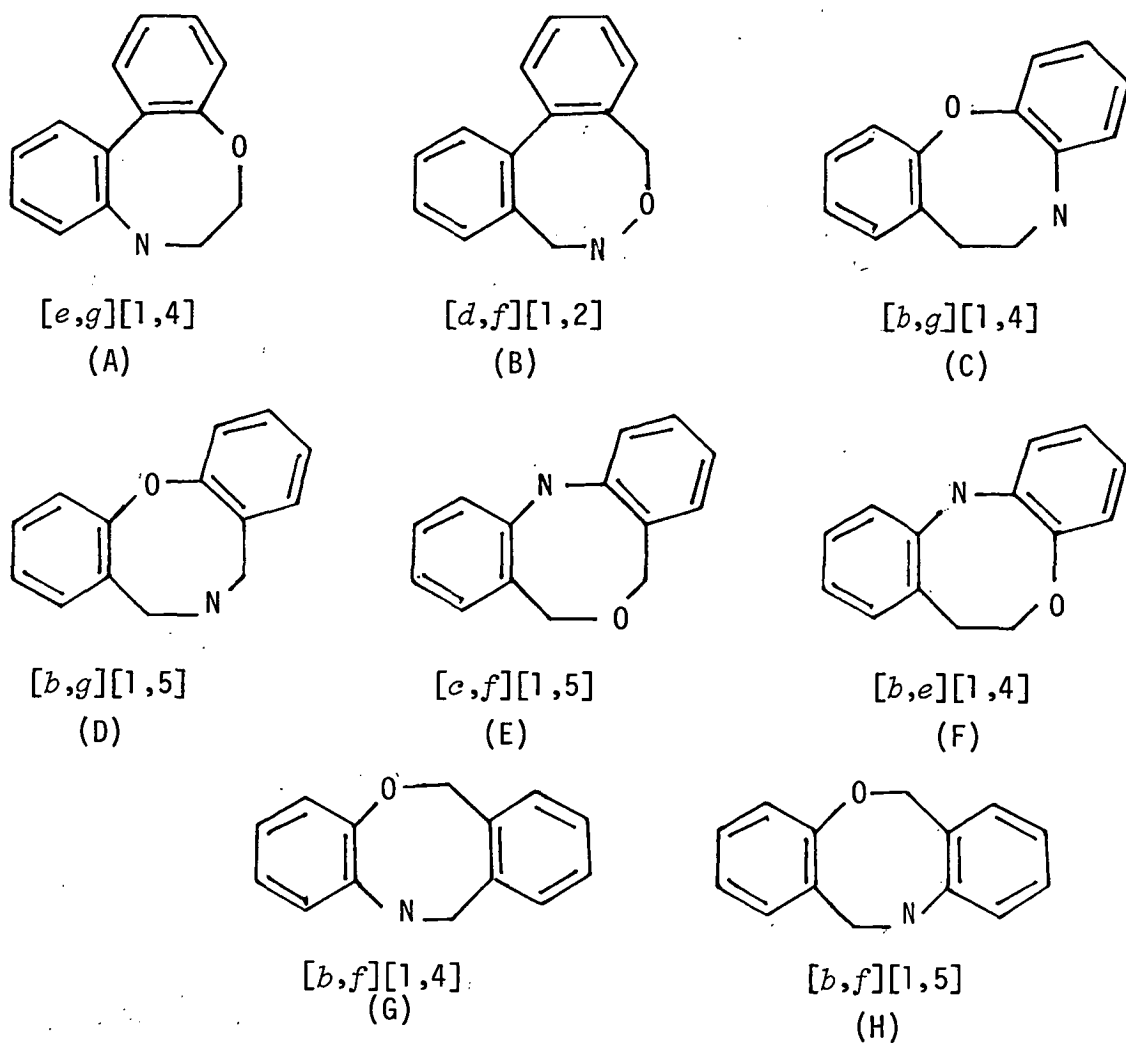


Figure 19

Unlike other benzo and dibenzo derivatives, dibenzoxazocines have not been widely prepared. The preparative methods employed to synthesise these isomers are similar to those for benzoxazocines, i.e. ring enlargements and ring closure reactions.

Ring enlargement reactions used are the Beckmann and the Schmidt reactions. Application of these were few and limited to the construction of dibenz- $[e,g][1,4]$ - and $[b,g][1,4]$ oxazocines. The other five isomers have been synthesised by ring closure reactions.

The formation of a carbon-nitrogen bond is the most commonly used ring closure type, while the C-O type ring closure was employed to synthesise a dibenz $[b,f][1,5]$ oxazocine. The C-C type of ring closure has not been used for the synthesis of these ring systems.

(A) Ring enlargements

(A)a Rearrangements

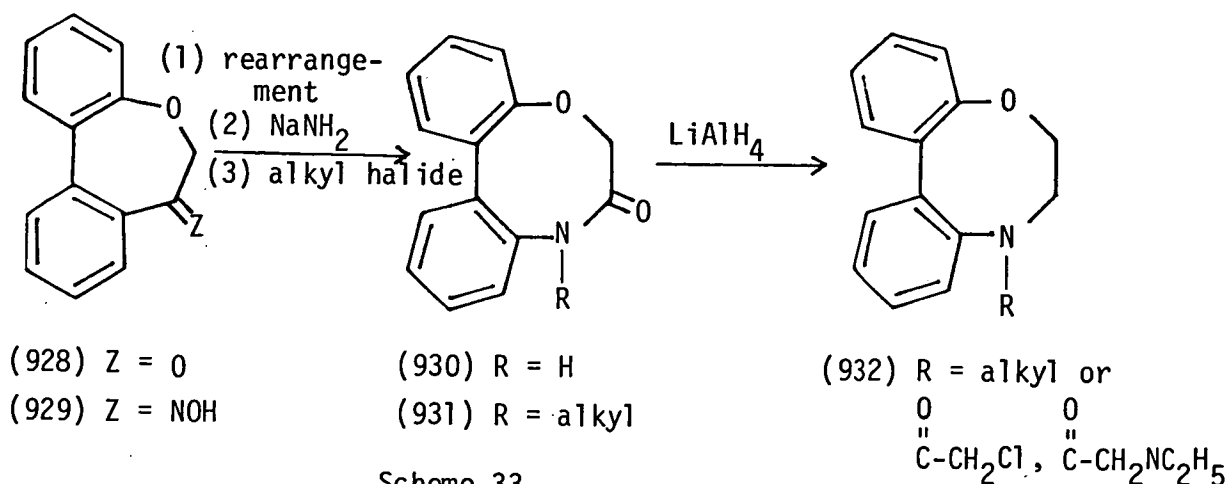
A(a) i Beckmann and the Schmidt rearrangements

A(a) i - Dibenz $[e,g][1,4]$ oxazocines

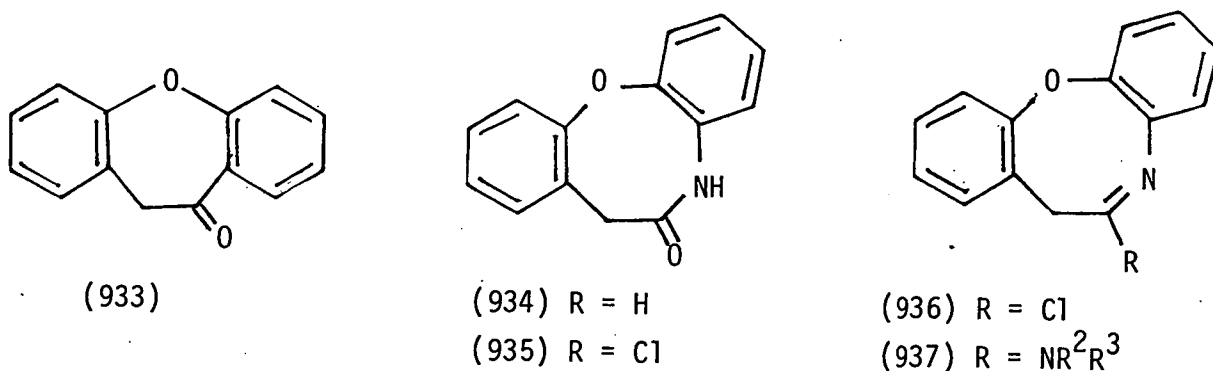
Harrow and co-workers⁵⁴⁷ described the synthesis of dibenz $[e,g][1,4]$ -oxazocine-7(8H)-one (930) from the oxepine (928), either by the Beckmann or by the Schmidt reaction. The Beckmann rearrangement of the oxime (929) with polyphosphoric acid afforded 71% yield of (930), whereas the Schmidt reaction with sodium azide in polyphosphoric acid or in concentrated sulfuric acid gave 38% and 58% of yields respectively. In both reactions the formation of isomeric products or fragmentation products were not reported although expected theoretically. A number of *N*-substituted dihydrobenzoxazocines (932) were prepared by the action of alkyl halides on *N*-sodio derivatives followed by reduction with lithium aluminium hydride. The reaction sequence is given in Scheme 33.

A(a) i-(2) Dibenz $[b,g][1,4]$ oxazocines

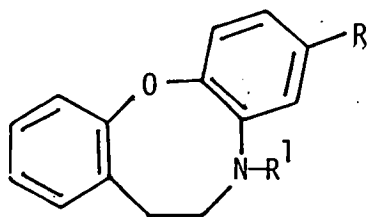
In a patent by Mashimo *et al*,⁵⁴⁸ it was reported that under the usual Schmidt reaction conditions, (i.e. using sodium azide and



concentrated sulfuric acid in benzene), the dibenz[*b,f*]oxepine-5-one (933) gave the dibenz[*b,g*][1,4]oxazocine-6-(5*H*)-one (934) in 67% yield. The 3-chloro derivative (935) was also prepared similarly. Unlike the benzoxazocines, the formation of tetrazole derivatives and the isomeric products were not recorded.



The action of phosphorus pentachloride on lactams (934,935) afforded the 6-chloro derivative (936) which was further converted into the 6-amino derivatives (937).⁵⁴⁹ The *N*-substituted tetrahydro derivatives (938) were obtained by the reaction of lactams (934,935) with an alkyl halide followed by reduction.^{550,551}



(938)

$R = H \text{ or } Cl$

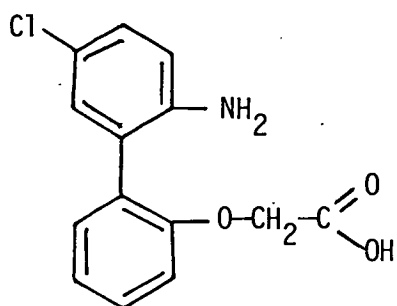
$R^1 = \text{alkylene, lower alkyl, morpholine, pyrrolidino group etc.}$

(B) Ring closure

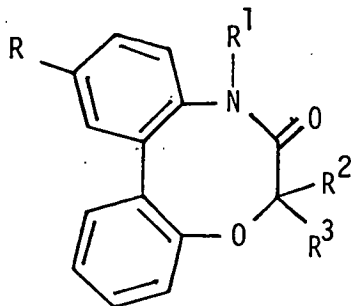
(B) i C-N type

B(i)-(1) Dibenz[*e,g*][1,4]oxazocines

The action of heat on the amino acid (939) gave the dibenzoxazocine (940) by cyclodehydration.⁵⁵² Similarly five other benzoxazocines (941-945) were prepared from the corresponding amino acids.



(939)



(940) $R=Cl, R^1=R^2=R^3=H$

(941) $R=R^1=R^2=R^3=H$

(942) $R^2=CH_3, R=R^1=R^3=H$

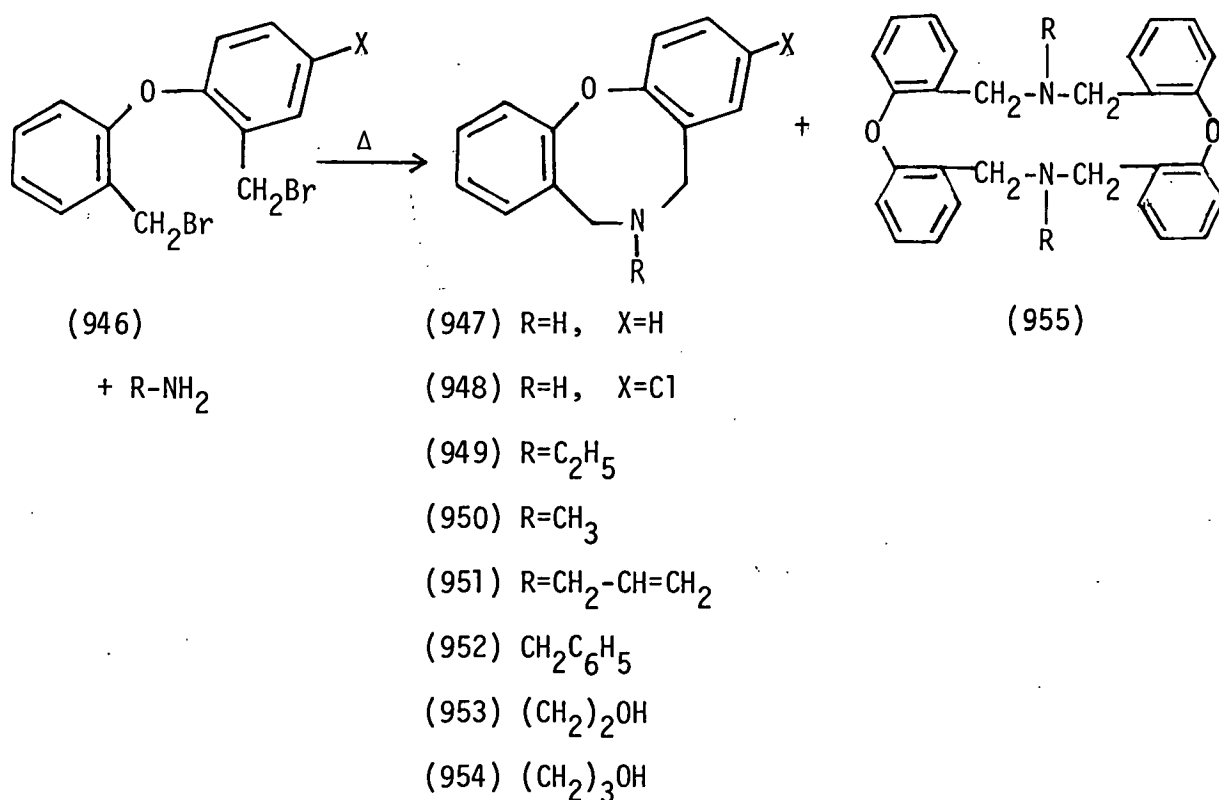
(943) $R^2=R^3=CH_3, R=R^1=H$

(944) $R^2=C_2H_5, R=R^1=R^3=H$

(945) $R^2=C_6H_5, R=R^1=R^3=H$

B(i)-(2) Dibenz[*b,g*][1,5]oxazocines

As described for the dibenz[*c,f*]azocines, several dibenz[*b,g*][1,5]-oxazocines were prepared by the reaction of dibromo compound (946) with various primary amines.⁵⁵³⁻⁵⁶¹ An interesting feature of this reaction was the formation of a sixteen-membered ring product (955). The yields of the dibenzoxazocines obtained by this method were generally satisfactory, but the yield of (952) was only 10%.⁵⁵³

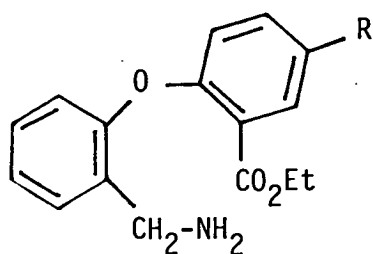


X = Cl or H

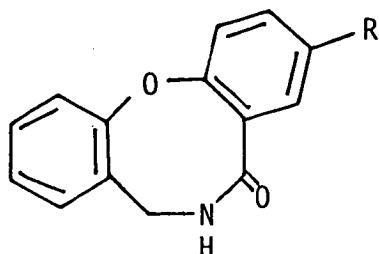
The lactams (957 and 958) were prepared by the base catalysed cyclization of (956).⁵⁶²

B(i)-(3) Dibenz[*b,f*][1,4]oxazocines

In the presence of dicyclohexylcarbodiimide (DCC) and ethyl aceto acetate, the amino acid (959) afforded dibenz[*b,f*][1,5]oxazocine-



(956)

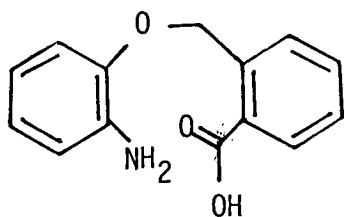


(957) R = H

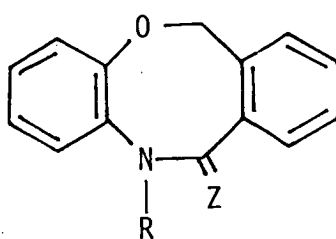
(958) R = Cl

12(11*H*)-one (960) in 39% yield.⁵⁶⁵⁻⁵⁶⁹ A similar preparative method was described previously for the synthesis of benzo[1,4]diazocines. (page 52).

The lactam (960) was reduced to the secondary amine (961) and converted to the *N*-substituted derivatives in fair yields.^{563,565-568} A dimeric product (962) was obtained by the reaction of (960) and carbonyl chloride in a solution of toluene containing sodium hydride.^{556,567}

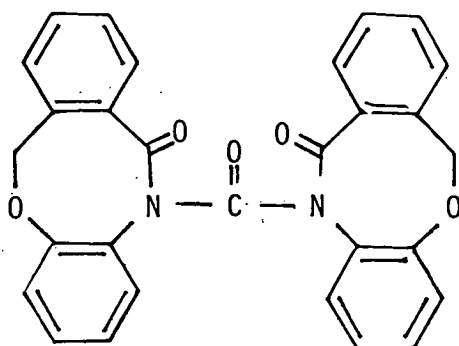


(959)



(960) R = H, Z = O

(961) R = H, Z = 2H

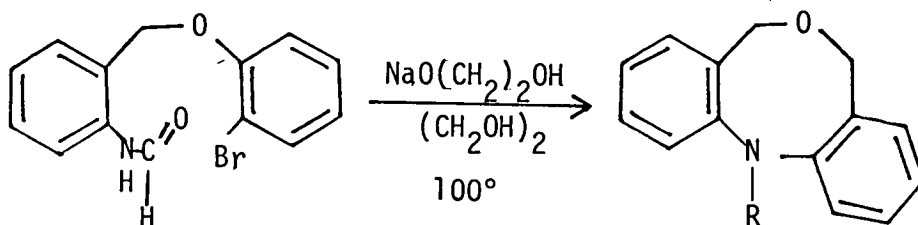


(962)

Puar and co-workers⁵⁷⁰ have reported the conformational and spectral behaviour of 6,11-dihydro-12*H*-dibenz[*b,f*][1,4]oxazocines (961). The mass spectral fragmentation of (961) also was reported.⁵⁷¹

B(i)-(4) Dibenz[*c,f*][1,5]oxazocines

In two patents, Yale and co-workers^{572,573} reported that the intramolecular cyclization of (963) in ethylene glycol gave an 85% yield of the dibenz[*c,f*][1,5]oxazocine (964). This was converted into various *N*-substituted derivatives (965-967) by reaction with the appropriate alkyl halide.⁵⁷²⁻⁵⁷⁸



(963)

(964) R=H

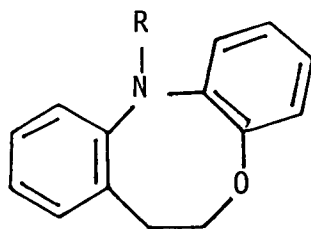
(965) R=(CH₃)₂NCH₃C(=O)NH₂

(966) R=(CH₃)₂N(CH₃)₂

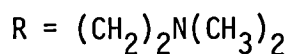
(967) R=(CH₂)₂N(CH₃)₂

(968) R=piperidinocarbonyl

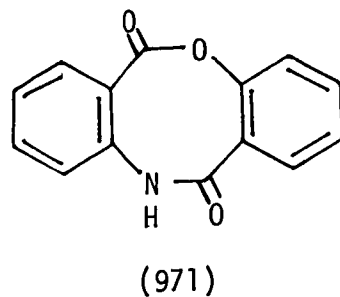
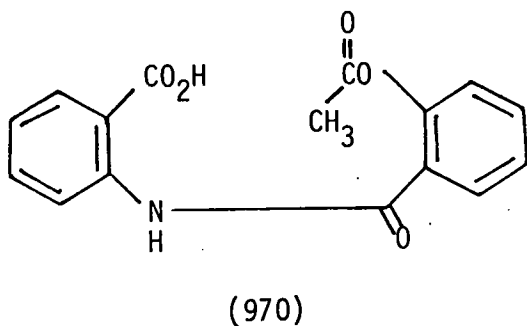
The dibenz[*c,f*][1,4]oxazocines (964,966,967), and dibenz[*b,e*][1,4]oxazocine (969) were mentioned in one patent by Yale and co-workers,⁵⁷³ although there seems to be an error in the starting material given in the abstract.



(969).

B(ii) C-O type of ring closureB(ii)-(1) Dibenz[*b,f*][1,5]oxazocines

In the presence of *N,N'*-carbonyldimidazole or dicyclohexylcarbodiimide, the cyclization of (970) in dimethylformamide at 100° gave 73% yield of dibenzo[*b,f*][1,5]oxazocine dione (971).⁵⁷⁹

B(ii)-(2) Dibenz[*b,f*][1,2]oxazocines

Johnstone and co-workers⁵⁸⁰ have reported the mass spectral fragmentation of a dibenz[*d,f*][1,2]oxazocine, but no preparative details were given.

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