

PHENETHYLISOQUINOLINE-DERIVED ALKALOIDS
AND RELATED SYSTEMS

by

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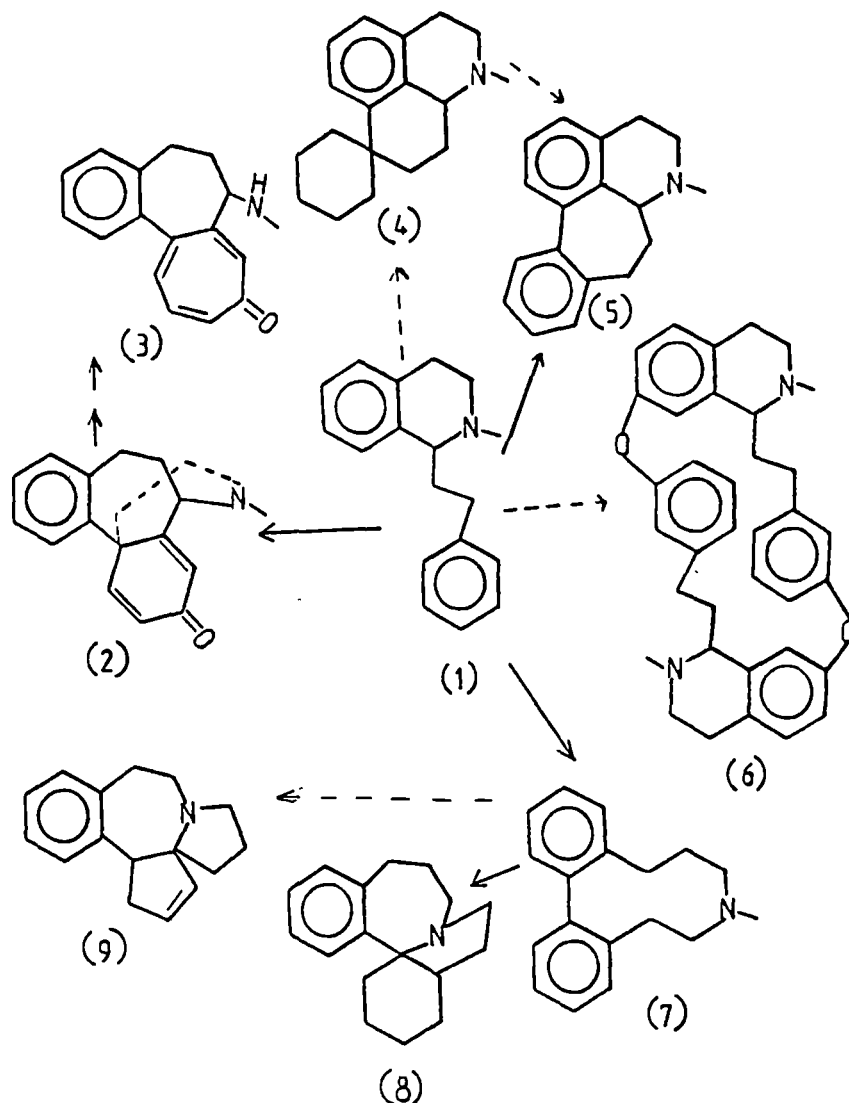
I also thank IDP for their support of my work.

1. GENERAL INTRODUCTION

1.1 Structures and Biosynthetic Relationships

The phenethylisoquinoline alkaloids comprise a relatively new class of alkaloids. They are structurally related to the very vast group of alkaloids based on the 1-benzylisoquinoline skeleton. Most of these alkaloids follow a biosynthetic pathway analogous to the benzylisoquinoline series. That is, they are biosynthesized from the 1-phenethylisoquinoline autumnaline (Table 1, A-1) and its relatives by phenolic oxidative coupling and subsequent reactions. At present, nine groups of alkaloids are identified as of the phenethylisoquinoline type (Scheme 1). This includes the simple 1-phenethylisoquinoline (1), homomorphinan (2), colchicine (3), homoproaporphine (4), homoaporphine (5), bisphenethylisoquinoline (6), dibenz[d,f]azecine (7), homoerythrina (8), and cephalotaxine (9) groups. The bold lines in Scheme 1 represent biosynthetic pathways indicated by tracer studies. No tracer studies have been done on those shown with dotted lines. One can see in the Scheme that, biosynthetically, homoerythrina and cephalotaxine may be related by a common precursor, the dibenz[d,f]azecine-type alkaloid (7).¹⁷⁷ Colchicine on the other hand is derived biosynthetically from a homomorphinan (2), specifically *O*-methylandrocymbine⁹² (Table 1, C-2).

The homoprotoberberine-type alkaloid skeleton (10), which may also be biosynthetically derived from a 1-phenethylisoquinoline precursor by a Mannich-type reaction, and which was anticipated by Battersby³ to occur in plants, has not yet been isolated. However, a homoprotoberberine (11) was isolated from Berberis acticantha⁴ but differs from (10) in the ring C structure. That is, nitrogen

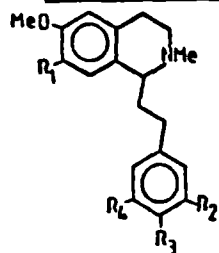


Scheme 1

and ring D are joined together by an ethylene group in (11) instead of a methylene group as in (10), the latter being characteristic of a Mannich-type ring closure. A complete list of the phenethylisoquinoline-derived alkaloids from plants, their sources, and their physical properties is given in Table 1 and summarised in Table 2. All the isolated alkaloids presented in Kamentani's review⁵ are included in Table 1 to provide a better view of the alkaloid profile.

TABLE I
Plant Sources and Physical Properties

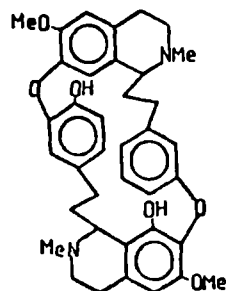
A. SIMPLE 1-PHENETHYLTETRAHYDROISOQUINOLINE



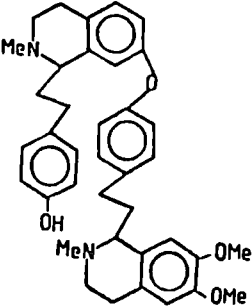
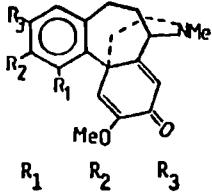
	R ₁	R ₂	R ₃	R ₄	PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION (°)	REFERENCES
1. Autumnaline	OH	OH	OMe	OMe	a) <u>Colchicum cornigerum</u> Schwein. Tackh. et Drar.	Liliaceae	166-168	$[\alpha]_D^{22} -5 \pm 3$ (CHCl ₃)	5,15,16,17,18
					b) <u>Colchicum latifolium</u> S.S.	Liliaceae			
					c) <u>Colchicum visiani</u>	Liliaceae			
					d) <u>Colchicum autumnale</u> L.	Liliaceae			
					e) <u>Colchicum doerfleri</u>	Liliaceae			
2. Dysoxylone	OMe	H	—OCH ₂ O—		a) <u>Dysoxylum lenticellari</u>	Meliaceae	154-156	$[\alpha]_D^{25} +22$ (C ₂ H ₅ OH)	19
3. S-(+)-homolaudanosine	OMe	H	OMe	OMe	a) <u>Dysoxylum lenticellari</u>	Meliaceae	78-79 ^a	$[\alpha]_D^{25} +11$ (C ₂ H ₅ OH)	19

B. BISPHENETHYLTETRAHYDROISOQUINOLINE

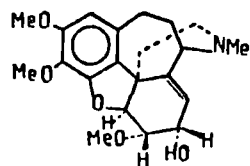
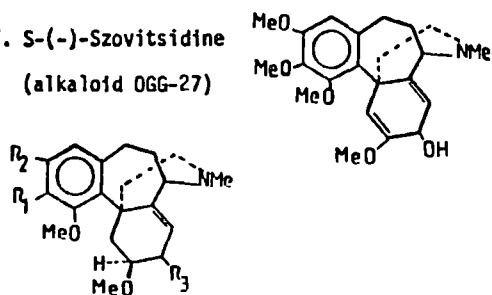
1. Melanthioidine

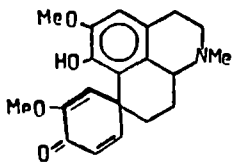


a) <u>Androcymbium melanthioides</u> Wild.	Liliaceae	142-144	$[\alpha]_D -63$ (CHCl ₃)	5,20,86, 181
b) <u>Androcymbium eucomides</u> (Jacq.) Wild.	Lilaceae			

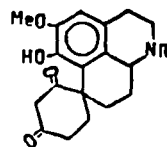
		PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION(°)	REFERENCES
2. jolantinine		a) <u>Merendera jolantae</u> E. Czerniak	Liliaceae	-	-	21
<u>C. HOMOPROMORPHINANE</u>						
						
1. androcymbine	R ₁ OMe R ₂ OH R ₃ OMe	a) <u>Androcymbium melanthioides</u> Wild. b) <u>Androcymbium eucomides</u> (Jacq.) Wild. c) <u>Androcymbium capense</u> (L.) Krause	Liliaceae Liliaceae Liliaceae	199-201	$[\alpha]_D^{22}$ -260 (CHCl ₃)	86,22,23
2. S-(-)-O-methyl-androcymbine	OMe OMe OMe	a) <u>Colchicum autumnale</u> b) <u>Colchicum cornigerum</u> Schwein. Tackh. et Drar. c) <u>Merendera trigyna</u> Stapf. d) <u>Androcymbium melanthioides</u> var. stricta	Liliaceae Liliaceae Liliaceae Liliaceae	154-155.5	$[\alpha]_D$ -295 (CHCl ₃)	15,23,24,25

	R ₁	R ₂	R ₃	PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION (°)	REFERENCES
3. S-(-)-collutine (alkaloid L-7)	OH	OMe	OMe	a) <u>Colchicum luteum</u> Baker	Liliaceae	192-194	$[\alpha]_D^{22} -182$ (CHCl ₃)	26
4. R-(+)-crociflorine (alkaloid K-2)	OMe	OMe	OMe	a) <u>Colchicum kesselringii</u>	Lilaceae			27
5. Alkaloid CC-10	OMe	OMe	OH	a) <u>Colchicum cornigerum</u> Schwein. Tackh. et Drar.	Liliaceae	209-212	$[\alpha]_D^{22} +308$ (CHCl ₃)	15,28
6. Alkaloid CC-20	OMe	—OCH ₂ O—		a) <u>Colchicum cornigerum</u> Schwein. Tackh. et Drar.	Liliaceae	210-212	$[\alpha]_D^{22} -324$ (CHCl ₃)	15,28
7. S-(-)-Szovitsidine (alkaloid OGG-27)				a) <u>Colchicum szovitsii</u> b) <u>Ornithoglossum glaucum</u> var. <i>grandiflora</i>	Liliaceae Liliaceae	-	-	29
8. R-(+)-alkaloid CC-36	OMe	OH	--OH	a) <u>Colchicum cornigerum</u> Schwein. Tackh. et Drar.	Liliaceae	210-212	$[\alpha]_D^{22} +25$ (CHCl ₃)	15,28
9. R-(+)-alkaloid CC-2	—OCH ₂ O—	OH		a) <u>Colchicum cornigerum</u> Schwein. Tackh. et Drar.	Liliaceae	172-174	$[\alpha]_D^{22} +40$ (CHCl ₃)	15,28



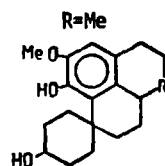
	R ₁	R ₂	R ₃	PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION (°)	REFERENCES
10. S-(-)-kreysiginine (alkaloid CC-21)				a) <u>Colchicum cornigerum</u> Schwein Tackh. et Drar.	Liliaceae	151-154	$[\alpha]_D^{22} -100$ (C ₃ H ₅ OH)	15
11. (+)-kreysiginine				a) <u>Kreysigia multiflora</u> Reichb.	Liliaceae	149	$[\alpha]_D^{24} +89$ (C ₂ H ₅ OH)	32,33, 30, 182
12. (+)-Floramultinine				b) <u>Iphigenia stellata</u> a) <u>Kreysigia multiflora</u> Reichb.	Liliaceae Liliaceae	165	$[\alpha]_D^{20} +118$	32
D. HOMOPROAPORPHINE								
1. Kreysiginone				a) <u>Kreysigia multiflora</u> Reichb.	Liliaceae	155-194(d)	-	34
								
2. 6 _a R-8 _a S-(+)- Bulbocodine (yolantamine =alk. k-8)				a) <u>Bulbocodium verum</u> b) <u>Merendera jolantae</u> E. Czerniak	Liliaceae Liliaceae	220-222	$[\alpha]_D +111$ (CHCl ₃)	35,36,37
3. (+)-yolantine				a) <u>Merendera jolantae</u> E. Czerniak	Liliaceae	269-270	-	38
4. R-(+)-crociflorinone (alkaloid k-16= umtaline=strumazine)				a) <u>Colchicum kesselringii</u> Rgl. b) <u>Wurmbea</u>	Liliaceae	246-248	-	39,91

	R ₁	R ₂	R ₃	PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION (°)	REFERENCES.
5. dihydrokreysiginone (luteidine)	OH	Me	OMe	a) <u>Kreysigia multiflora</u> Reichb. b) <u>Wurmbea</u>	Liliaceae Liliaceae	217-222	$[\alpha]_D^{25} -96$ (CH ₃ CH)	89,36,40,90 91
6. Alkaloid OGG-3	?			a) <u>Ornithoglossum glaucum</u> var. <u>grandiflora</u>	Liliaceae	228-230	$[\alpha]_D^{25} +11$ (CH ₃ OH-CHCl ₃)	27,35



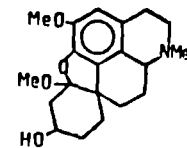
7. yollantimine	R=H			a) <u>Colchicum kesselringii</u> Rgl b) <u>Merendera jolantae</u> E. Czerniak	Liliaceae Liliaceae	272-273	$[\alpha]_D^{25} +98$ (C ₂ H ₅ OH)	41,42
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8. luteinone	R=Me			a) <u>Colchicum luteum</u> Baker	Liliaceae	234-235	$[\alpha]_D^{25} +325$ (CHCl ₃)	37,40
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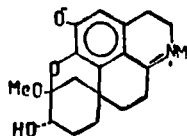


9. (-)-trigamine	R=N-Me			a) <u>Merendera trigina</u>	Liliaceae	169-170	$[\alpha]_D^{25} -7$ (CHCl ₃)	43
10. trigamine N-oxide	R=NO-Me			a) <u>Merendera jolantae</u> E. Czerniak	Liliaceae	201-202	$[\alpha]_D^{25} -10$ (CHCl ₃)	44

11. luteicine				a) <u>Colchicum luteum</u> Baker	Liliaceae	210-211 ⁶	$[\alpha]_D^{25} +112$ (CHCl ₃) ⁶	45
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12. regecoline				a) <u>Colchicum kesselringii</u> Rgl.	Liliaceae			
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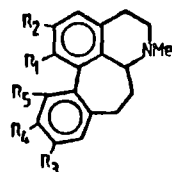


				PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION (°)	REFERENCES
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13. regelinone	R= --OH	a) <u>Colchicum kesselringii</u> Rgl.	Liliaceae	316-317	-	46
14. isoregelinone	R= — OH	a) <u>Colchicum kesselringii</u> Rgl.	Liliaceae	321-323	-	47

	R ₁	R ₂	R ₃	R ₄					
15. R-(+)-Regeline (alkaloid k-15)	OMe	Me	--OH	OMe	a) <u>Colchicum kesselringii</u> Rgl.	Liliaceae	198-200	[α] _D +93	48
16. R-(+)-kessel- ringine	OH	Me	--OH	OMe	a) <u>Colchicum kesselringii</u> Rgl.	Liliaceae	194-196	[α] _D ²² +53 (CH ₃ OH)	49,50
17. R-(+)-Luteine (alkaloid L-1)	OH	H	--OH	OMe	a) <u>Colchicum luteum</u> Baker	Liliaceae	228-230	[α] _D +93 (CH ₃ OH)	8
18. regelinine	OMe	Me	OH	OMe	a) <u>Colchicum kesselringii</u> Rgl.	Liliaceae	253-254	-	51
19. S-(-)-kessel- ridine	OH	Me	--OH	OH	a) <u>Colchicum kesselringii</u> Rgl.	Liliaceae	232-234	[α] _D -50	52
20. R-(-)-regelamine (alkaloid G-2)	OMe	Me	--OH	OH	a) <u>Colchicum kesselringii</u> Rgl.	Liliaceae	225-226	[α] _D +33 (CH ₃ OH)	53, 183
21. yolantidine	OMe	H	OH	--OH	a) <u>Merendera jolantae</u> E. Czerniak	Liliaceae	275-277	[α] _D +102 (CH ₃ OH)	54

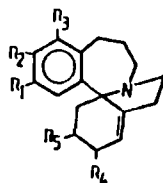
E. HOMOAPORPHINE



						PLANT SOURCE	FAMILY	MELTING POINT(°C)	OPTICAL ROTATION(°)	REFERENCES
	R ₁	R ₂	R ₃	R ₄	R ₅					
1. (+)-kreysigine	OH	OMe	OMe	OMe	OMe	a) <u>Kreysigia multiflora</u> Reichb.	Liliaceae	187-188	inactive	32,55,56
2. (-)-kreysigine (alkaloid CC-1)	OH	OMe	OMe	OMe	OMe	a) <u>Colchicum cornigerum</u> Schwein. Tackh. et Drar.	Liliaceae	123-125	$[\alpha]_D^{22} -70$ (CHCl ₃)	57
3. R-(-)-multifloramine	OH	OMe	OMe	OH	OMe	a) <u>Kreysigia multiflora</u> Reichb.	Liliaceae	190	$[\alpha]_D^{22} -112$ (CHCl ₃)	33,58,59
						b) <u>Iphigenia stellata</u>	Liliaceae			
						c) <u>Colchicum szovitsii</u>				
4. R-(-)-floramultine	OH	OMe	OH	OMe	OMe	a) <u>Kreysigia multiflora</u> Reichb.	Liliaceae	230(d)	$[\alpha]_D^{18} -97$ (C ₂ H ₅ OH)	16,32,55,60
						b) <u>Colchicum macedonium</u>	Liliaceae			
5. S-(+)-floramultine (Merenderine=bechuanine)	OH	OMe	OH	OMe	OMe	a) <u>Iphigenia stellata</u>	Liliaceae	232-235(d)	$[\alpha]_D^{22} +76$ (CHCl ₃)	43,52,61,62,63
						b) <u>Iphigenia bechuanica</u>	Liliaceae			
						c) <u>Iphigenia pallida</u> Baker	Liliaceae			
						d) <u>Iphigenia indica</u> Gray	Liliaceae			
						e) <u>Colchicum szovitsii</u> Fisch.	Liliaceae			
						f) <u>Colchicum latifolium</u>	Liliaceae			
						g) <u>Gloriosa superba</u>	Liliaceae			
						h) <u>Merendera raddeana</u> Regel.	Liliaceae			
						i) <u>Merendera trigina</u>	Liliaceae			
6. R-(-)-alkaloid CC-24	OH	OMe	OMe	OMe	OH	a) <u>Colchicum cornigerum</u> Schwein. Tackh. et Drar.	Liliaceae	245-249	-	15,28,62
						b) <u>Gloriosa superba</u>	Liliaceae			
7. szovitsinine	OMe	OH	OMe	OMe	OH	a) <u>Colchicum szovitsii</u> Fisch.	Liliaceae	-	-	64
8. R-(-)-szovitsamine	OMe	OMe	OMe	OMe	OH	a) <u>Colchicum szovitsii</u> Fisch.	Liliaceae	188-190	$[\alpha]_D^{20} +86$	65,66

	R ₁	R ₂	R ₃	R ₄	R ₅	PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION (°)	REFERENCES
9. 0-methylkresigine	OMe	OMe	OMe	OMe	OMe	a) <u>Colchicum szovitsii</u> Fisch.	Liliaceae	150-153	$[\alpha]_D^{21} +81$ (CHCl ₃)	66,67

F. HOMOERYTHRINA

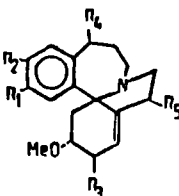
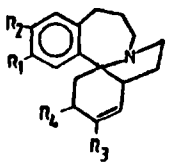


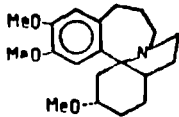
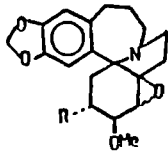
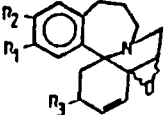
1(6) alkene series

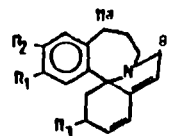
	R ₁	R ₂	R ₃	R ₄	R ₅					
1. schelhammerine (alkaloid D)	-OCH ₂ O-	H	--OH	OMe		a) <u>Schelhammera pedunculata</u> F. Muell.	Liliaceae	173-174	$[\alpha]_D +186$ (CHCl ₃)	68,69
2. 3-epischelhammerine (2-epihomoerythraline = alkaloid H)	-OCH ₂ O-	H	--OH	--OMe		a) <u>Schelhammera pedunculata</u> F. Muell. b) <u>Phelline comosa</u> Labill. c) <u>Phelline brachyphylla</u> d) <u>Athrotaxis cupressoides</u>	Liliaceae Aquifoliaceae Aquifoliaceae Taxodiaceae	182-185	$[\alpha]_D^{19} +170$	70,71,72
3. schelhammericine (alkaloid F)	-OCH ₂ O-	H		H	OMe	a) <u>Schelhammera pedunculata</u> F. Muell. b) <u>Cephalotaxus harringtonia</u> K. Koch var. harringtonia	Liliaceae Cephalotaxaceae	76-77	$[\alpha]_D +122$ (CHCl ₃)	69,73,74
4. 3-epischelhammericine (alkaloid E=alkaloid IV)	-OCH ₂ O-	H		H	--OMe	a) <u>Schelhammera pedunculata</u> F. Muell. b) <u>Schelhammera multiflora</u> R. Br. c) <u>Schelhammera undulata</u>	Liliaceae Liliaceae Liliaceae	169-172	$[\alpha]_D +123$	19,71,72,73, 74,75,76

	R ₁	R ₂	R ₃	R ₄	R ₅	PLANT SOURCE	FAMILY	MELTING POINT(°C)	OPTICAL ROTATION(°)	REFERENCES
						d) <u>Cephalotaxus harringtonia</u> K. Koch var. harringtonia	Cephalotaxaceae			
						e) <u>Cephalotaxus hainensis</u> Li	Cephalotaxaceae			
						f) <u>Cephalotaxus harringtonia</u> var. drupaceae	Cephalotaxaceae			
						g) <u>Cephalotaxus wilsoniana</u> Hayata	Cephalotaxaceae			
						h) <u>Dysoxylum lenticellari</u>	Meliaceae			
						i) <u>Phelline sp. aff. P. lucida</u>	Aquifoliaceae			
						j) <u>Phelline comosa</u> Labill.	Aquifoliaceae			
						k) <u>Athrotaxis selaginoides</u>	Taxodiaceae			
						l) <u>Athrotaxis laxifolia</u> Hook.	Taxodiaceae			
5. taxodine (2,7-dihydrohomo- erysovine =alkaloid V = alkaloid B)	OH	OMe	H	H	--OMe	a) <u>Schelhammera pedunculata</u> F. Muell.	Liliaceae	150-152	$[\alpha]_D^{19} +111$	1,71,74,75, 77,78,79
						b) <u>Schelhammera undulata</u>	Liliaceae			
						c) <u>Cephalotaxus harringtonia</u> K. Koch var. harringtonia	Cephalotaxaceae			
						d) <u>Cephalotaxus harringtonia</u> var. drupaceae	Cephalotaxaceae			
						e) <u>Phelline sp. aff. P. lucida</u>	Aquifoliaceae			
						f) <u>Athrotaxis selaginoides</u>	Taxodiaceae			
						g) <u>Athrotaxis laxifolia</u> Hook.	Taxodiaceae			
						h) <u>Athrotaxis cupressoides</u>	Taxodiaceae			

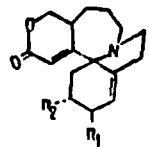
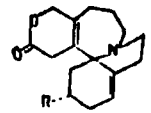
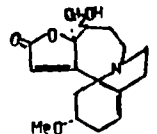
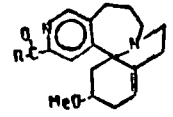
	R ₁	R ₂	R ₃	R ₄	R ₅	PLANT SOURCE	FAMILY	MELTING POINT(°C)	OPTICAL ROTATION(°)	REFERENCES
6. Alkaloid II	OH	OMe	H	H	OMe	a) <u>Cephalotaxus harringtonia</u> K. Koch. var. harringtonia	Cephalotaxaceae	-	[α] _D +76 (CHCl ₃)	74,93
7. Alkaloid III (3-epihomo-2,7- dihydro-erysotrine)	OMe	OMe	H	H	OMe	a) <u>Cephalotaxus harringtonia</u> K. Koch. var. harringtonia	Cephalotaxoaceae	-	[α] _D +118	74,93
8. 2,7-dihydrohomo- erysotrine	OMe	OMe	H	H	--OMe	a) <u>Cephalotaxus harringtonia</u> K. Koch. var. harringtonia b) <u>Cephalotaxus harringtonia</u> var. drupaceae c) <u>Dysoxylum lenticellari</u> d) <u>Phelline sp. aff.P.lucida</u>	Cephalotaxaceae Cephalotaxaceae Meliaceae Aquifoliaceae	-	[α] _D +122	1,19,74,76
9. homoerythratine	-OCH ₂ O-		H	H	--OMe	a) <u>Phelline brachyphylla</u> b) <u>Athrotaxis selaginoides</u> c) <u>Athrotaxis laxifolia</u> Hook. d) <u>Athrotaxis cupressoides</u>	Aquifoliaceae Texodiaceae Taxodiaceae Taxodiaceae	176	[α] _D +75 (CHCl ₃)	70,71,78
10. O-methylathro- cupressine (alkaloid 5)	OMe	OMe	OMe	H	OMe	a) <u>Athrotaxis cupressoides</u> b) <u>Phelline comosa</u> Labill.	Taxodiaceae Aquifoliaceae	100-110	[α] _D ¹⁹ +91	71
11. 2-hydroxytaxodine	OMe	OH	H	OH	--OMe	a) <u>Athrotaxis cupressoides</u> b) <u>Athrotaxis selaginoides</u> c) <u>Athrotaxis laxifolia</u> Hook.	Taxodiaceae Taxodiaceae Taxodiaceae	192-193	[α] _D ¹⁹ +51.47	71,78
12. 2-hydroxyisotaxodine	OH	OMe	H	OH	--OMe	a) <u>Athrotaxis cupressoides</u> b) <u>Athrotaxis selaginoides</u> c) <u>Athrotaxis laxifolia</u> Hook. d) <u>Phelline sp. aff.P.lucida</u>	Taxodiaceae Taxodiaceae Taxodiaceae Aquifoliaceae	-		71,78,80

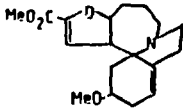
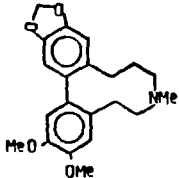
	R ₁	R ₂	R ₃	R ₄	R ₅	PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION (°)	REFERENCES
13. 2-epihydroxyiso-taxodine	OH	OMe	H	--OH	--OMe	a) <u>Athrotaxis cupressoides</u> b) <u>Athrotaxis selaginoides</u> c) <u>Athrotaxis laxifolia</u> Hook.	Taxodiaceae Taxodiaceae Taxodiaceae	-	-	71,78
14. athrocupressine	OMe	OMe	OH	H	--OMe	a) <u>Athrotaxis cupressoides</u> b) <u>Athrotaxis selaginoides</u>	Taxodiaceae Taxodiaceae	152-153	$[\alpha]_D^{19} +102.3$	71,78
15. 2-acetoxytaxodine	OMe	OH	H	OAc	--OMe	a) <u>Athrotaxis cupressoides</u>	Taxodiaceae	-	-	71
16. 2-acetoxyisotaxodine	OH	OMe	H	OAc	--OMe	a) <u>Athrotaxis cupressoides</u>	Taxodiaceae	-	-	71
17. dyshomerythrine (3-epi-18-methoxyschelhammericine)	--OCH ₂ O--	OMe	H	--OMe		a) <u>Dysoxylum lenticellari</u>	Meliaceae	-	-	81
18. holidinine	OH	OMe	OMe	H	--OMe	a) <u>Phelline sp. aff. P. lucida</u>	Aquifoliaceae	164-165	$[\alpha]_D^{19} +91$ (CHCl ₃)	76,79
										
19. 3-epi-12-hydroxy-schelhammericine	--OCH ₂ O--	H	OH	H		a) <u>Dysoxylum lenticellari</u>	Meliaceae	-	-	81
20. Cephalofortuneine	OMe	OMe	--OH	H	OH	a) <u>Cephalotaxus fortunei</u>	Cephalotaxaceae	-	-	82
										

	R ₁	R ₂	R ₃	R ₄	PLANT SOURCE	FAMILY	MELTING POINT(°C)	OPTICAL ROTATION(°)	REFERENCES
21. 3-epi-6α,7-dihydrohomoerythraline (alkaloid A)	-OCH ₂ O-		H	OMe	a) <u>Schelhammera pedunculata</u>	Liliaceae	188-189 ^a	[α] _D -100 (CHCl ₃)	73,93
22. comosidine	OMe	OMe	H	--OMe	a) <u>Phelline comosa</u> Labill. b) <u>Phelline Sp. aff. Lucida</u>	Aquifoliaceae Aquifoliaceae	-	-	76
23. 6α,7-dihydrohomoerythraline	-OCH ₂ O		H	--OMe	a) <u>Phelline comosa</u> Labill.	Aquifoliaceae	260(d)	[α] _D +75	93
24. 6α,7-dihydrohomoerysotrine (alkaloid 2)	OMe	OMe	H	H	a) <u>Phelline comosa</u> Labill.	Aquifoliaceae	143-145	[α] _D +72	93
25. lucidinine	OH	OMe	H	--OMe	a) <u>Phelline sp. aff. Lucida</u>	Aquifoliaceae	-	[α] _D +73	76
26. 1,2-dihydrocomosidine					a) <u>Phelline sp. aff. Lucida</u>	Aquifoliaceae	-	-	79
									
									
27. Phellinine	R = ---OH				a) <u>Phelline brachyphylla</u>	Aquifoliaceae	230	[α] _D +45 (CHCl ₃)	70
28. O-methylphellinine	R = ---OMe				a) <u>Phelline brachyphylla</u>	Aquifoliaceae	202	[α] _D +45 (CHCl ₃)	70
									

	R ₁	R ₂	R ₃	PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION (°)	REFERENCES
29. wilsonine	OMe	OMe	OMe	a) <u>Cephalotaxus wilsoniana</u> Hay. b) <u>Cephalotaxus fortunei</u> c) <u>Cephalotaxus harringtonia</u> k. koch. var. harringtonia	Cephalotaxaceae Cephalotaxaceae Cephalotaxaceae	150-151	[α] _D -51 (CHCl ₃)	83,84,85
30. 3-epi wilsonine	OMe	OMe	--OMe	a) <u>Cephalotaxus wilsoniana</u> Hay. b) <u>Cephalotaxus fortunei</u> c) <u>Cephalotaxus sinensis</u>	Cephalotaxaceae Cephalotaxaceae Cephalotaxaceae	103-104 215-216	[α] _D +76 (C ₂ H ₅ OH) [α] _D -74 (CH ₃ OH)	83,85
31. 6,7-epoxy-3α-methoxy- 15,16-methylenedioxy-C- homoerythrinan-2(1)-ene (alkaloid 6)	-OCH ₂ O-		--OMe	a) <u>Phelline comosa</u> Labill.	Aquifoliaceae	126	[α] _D +63	93
32. cycloxschelhammericine	-OCH ₂ O-		OMe	a) <u>Cephalotaxus hainensis</u> b) <u>Cephalotaxus sinensis</u>	Cephalotaxaceae Cephalotaxaceae	-	-	1
 <p>1,6 diene series</p>								
33. schelhammeridine (alkaloid C)	-OCH ₂ O-		OMe	a) <u>Schelhammera pedunculata</u>	Liliaceae	118	[α] _D -108 (CHCl ₃)	68,69
34. 3-epischelhammeridine (alkaloid G)	-OCH ₂ O-		--OMe	a) <u>Schelhammera pedunculata</u>	Liliaceae	131-133	[α] _D +24 (CHCl ₃)	73
35. Fortuneine	OMe	OMe	OMe	a) <u>Cephalotaxus fortunei</u>	Cephalotaxaceae	110	[α] _D ²⁴ -121 (MeOH)	85
36. 8-oxoschelhammeridine	-OCH ₂ O-		OMe	a) <u>Schelhammera pedunculata</u>	Liliaceae	-	[α] _D +35 (CHCl ₃)	73

C=O at 8

	R ₁	R ₂	R ₃	PLANT SOURCE	FAMILY	MELTING POINT(°C)	OPTICAL ROTATION(°)	REFERENCES
37. 11a-oxoschelhammeridine	-OCH ₂ O-		OMe	a) <u>Schelhammera pedunculata</u>	Liliaceae	151-153	[α] _D -47 (CHCl ₃)	73
				C=O at 11a				
38. Phellibiline	R ₁ = H	R ₂ = OH		a) <u>Phelline billiardieri</u>	Aquifoliaceae	-	-	86,87
39. Phellibilidene	R ₁ = OH	R ₂ = OMe		a) <u>Phelline billiardieri</u> b) <u>Phelline sp.aff.P.Lucida</u>	Aquifoliaceae Aquifoliaceae	114	[α] _D -11 (CHCl ₃)	80,87
								
40. isophellibiline		R = OH		a) <u>Phelline billiardieri</u>	Aquifoliaceae	186-188	[α] _D +143	88
41. O-methylisophellibiline (2,7-dihydrohomo-β-erythroidine)		R = OMe		a) <u>Phelline billiardieri</u> b) <u>Phelline sp.aff.P.Lucida</u>	Aquifoliaceae Aquifoliaceae	133	[α] _D +140	76,88
42. isophellibilidene				a) <u>Phelline billiardieri</u>	Aquifoliaceae	132	[α] _D +204	89
								
								
43. Phellinamide		R = NH ₂		a) <u>Phelline sp.aff.P.Lucida</u> b) <u>Phelline billiardieri</u>	Aquifoliaceae Aquifoliaceae	206	[α] _D +186 (CHCl ₃)	76
44. holidine		R = OMe		a) <u>Phelline sp.aff.P.Lucida</u>	Aquifoliaceae	-	[α] _D +175 (CHCl ₃)	76

		PLANT SOURCE	FAMILY	MELTING POINT (°C)	OPTICAL ROTATION (°)	REFERENCES
45. selaginoidine		a) <u>Athrotaxis selaginoides</u>	Taxodiaceae	62-63	$[\alpha]_D +167$	78
G. <u>DIBENZ(d,f)AZECINE</u>						
1. dysazecine		a) <u>Dysoxylum lenticellari</u>	Meliaceae	217-219 ^a	$[\alpha]_{25} +83$	19

a picrate

b acetate

TABLE 2
A SUMMARY OF THE TYPE OF ALKALOIDS ISOLATED
FROM PLANTS ARRANGED ACCORDING TO FAMILIES

	A	B	C	D	E	F
A. Class Liliatae						
(Monocotyledons)						
I. Family Liliaceae						
1. Subfamily <u>Wurmbaeoideae</u>						
a. tribe Gloriosae						
genus <u>Gloriosa</u> (3) ^a			+ ^b	+	+	
<u>Littonia</u> (?)				+		
<u>Sandersonia</u> (?)				+		
b. tribe Iphigenieae						
genus <u>Iphigenia</u> (4)			+		+	
<u>Ornithoglossum</u> (1)			+	+		
c. tribe Baeometrae						
genus <u>Baeometra</u> (?)			+			
d. tribe Colchiceae						
genus <u>Colchicum</u> (11)	+		+	+	+	
<u>Merendera</u> (5)		+	+	+	+	
<u>Bulbocodium</u> (1)				+	+	
<u>Androcymbium</u> (3)		+	+	+		
e. tribe Kreysigieae						
genus <u>Kreysigia</u> (1)			+	+	+	
f. tribe Wurmbaeae						
genus <u>Wurmbea</u> (3)					+	
<u>Anguillaria</u> (1)						

	A	B	C	D	E	F
2. genus <u>Schelhammera</u> (3)						+
B. Class Magnoliatae (Dicotyledons)						
I. Family Aquifoliaceae						
genus <u>Phelline</u> (3)						+
II. Family Meliaceae ^c						
genus <u>Dysoxylum</u> (1)	+					+
C. Gymnosperms						
I. Family Cephalotaxaceae						
genus <u>Cephalotaxus</u> (6)						+
II. Family Taxodiaceae						
genus <u>Athrotaxis</u> (3)						+

A 1-phenethylisoquinoline-type

B bisphenethylisoquinoline-type

C homomorphinan-type

D homoproaporphine-type

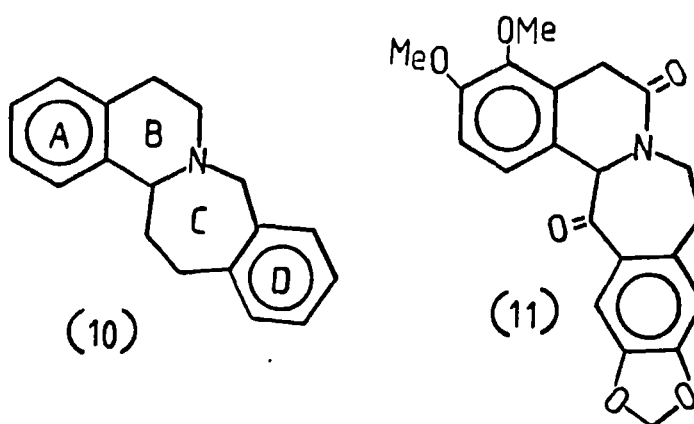
E homoaporphine-type

F homoerythrina-type

^a Number of plant species analyzed

^b Indicates occurrence of the alkaloid type including those whose actual structure have not yet been determined

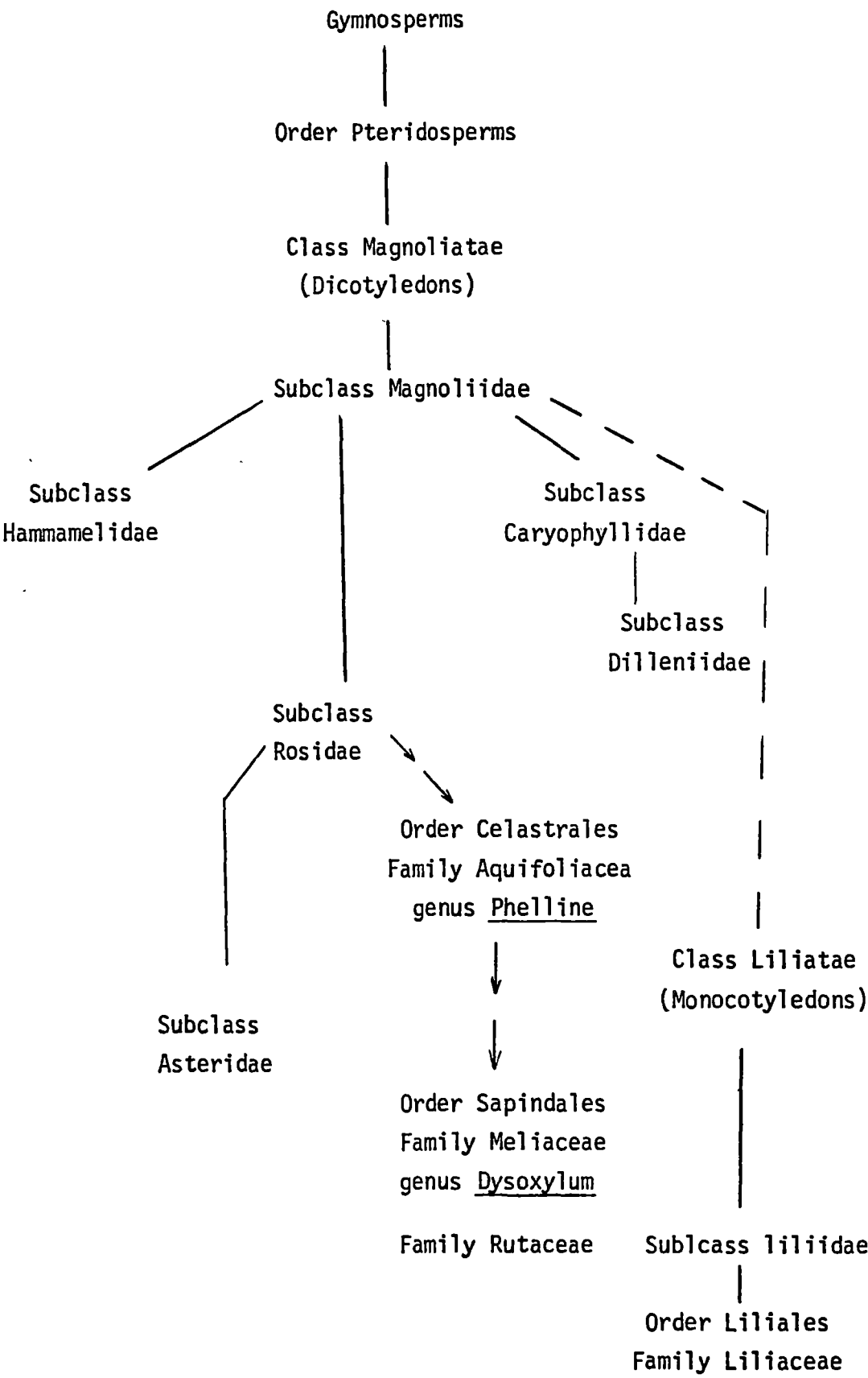
^c Also contains G (dibenz(d,f)azecine-type) alkaloid



1.2 Chemotaxonomic Aspects

Since the isolation of the first homoerythrina alkaloids schelhammerine and schelhammeridine, from Schelhammera pedunculata F. Muell. (Liliaceae), many other alkaloids of this type have been isolated from other species of Schelhammera (Liliaceae), from Phelline (Aquifoliaceae)^d, from Cephalotaxus (Cephalotaxaceae), and recently from Dysoxylum (Meliaceae) and Athrotaxis (Taxodiaceae). The relationship of these plant genera is illustrated in Scheme 2. From the recent review on homoerythrina alkaloids,⁹³ it appeared that each plant genus had a distinct alkaloid profile. However the isolation of more homoerythrina alkaloids are rather ubiquitous. Some of these are common to gymnosperms, monocotyledons and dicotyledons; to monocotyledons and dicotyledons; to gymnosperms and monocotyledons (Table 1). The seemingly distinct alkaloid profile of the genera Phelline, Athrotaxis, and Dysoxylum may just be due to the limited number of plant species studied rather than to being a characteristic of these particular plant groups. Homoazaerythrina and homoerythroidine-type homoerythrina alkaloids (Table 1, F 34-38) for instance are restricted to the Phelline species. The homoazaerythrina compounds are however suspected to be artefacts. No further studies have so far been reported to

^d Also classified in the Phellinaceae¹⁸⁴



Scheme 2

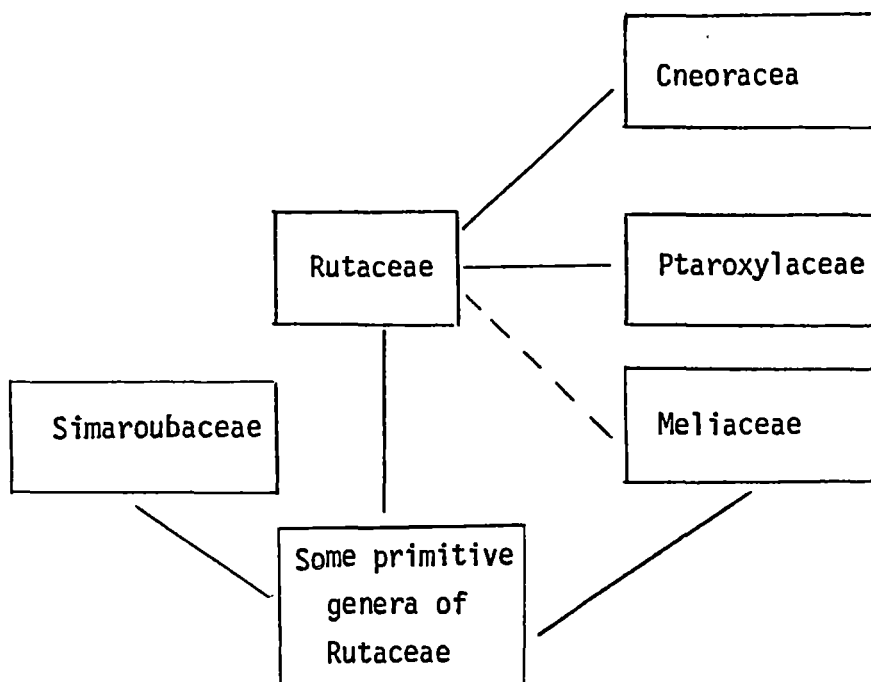
verify this. In the genus Cephalotaxus, the homoerythrina alkaloids were found to co-occur with the cephalotaxine-type alkaloids whose esters¹⁸⁵ are biologically active.

While the homoerythrina alkaloids were isolated from all the five phenethylisoquinoline-containing plant families, no alkaloids of this type were isolated from the plant species of the subfamily Wurmbaeoideae (Liliaceae). The subfamily Wurmbaeoideae was set apart from the rest of the Liliaceae species by Buxbaum.⁶ This subfamily formed more diverse phenethylisoquinoline types which are divided into two main groups namely, the tropolonic and the non-tropolonic alkaloids. The tropolonic group is composed of colchicine and its relatives. The simple phenethylisoquinoline alkaloids, which was also isolated from Dysoxylum (Meliaceae), the bisphenethylisoquinolines, homomorphinanes, homoproaporphines and homoaporphines, compose the non-tropolonic group. The types and the quantities of the non-tropolonic alkaloids formed in a given plant species are presumed to be dependent upon the stage of botanical development of the plant i.e. primitive or advanced. The more primitive ones like those in the tribe Colchiceae favour the formation of the colchicine-type intermediates: the 1-phenethylisoquinoline and the homomorphinane alkaloids. The more advanced tribes like Gloriosae, Iphigenieae, Baeometrae, and Neodregeae, form the companion alkaloids homoaporphine and homoproaporphine in greater quantities. A detailed chemotaxonomic study of the subfamily Wurmbaeoideae was reported by Santavy⁶. The alkaloid data led to the inclusion of the genus Kreysigia in this subfamily. Although in Hutchinson's classification the genus Kreysigia and Schelhammera belong to the same tribe Uvularieae⁷, the latter does not form the characteristic Wurmbaeoideae alkaloids

and is therefore excluded from this subfamily. Many other plants of the subfamily Wurmbaeoideae have been studied and many of them were found to contain non-tropolonic alkaloids but their actual structures have not yet been elucidated.^{8,17,27,40,62,94,95,96,97,98}

The presence of the homoerythrina-type alkaloids in Schelhammera presents an interesting possibility. Boulter⁹ suggested the possibility of a monophyletic origin for both monocotyledons and dicotyledons based on amino acid sequence studies on cytochrome C. Earlier, Cronquist, Bessey, and Stebbins, independently proposed different possible lines of origin for monocotyledons⁹. This remains unresolved up to the present due to very limited information being available, including chemical data. To date, there are only a very few cases of the same alkaloid type being found in both the monocotyledons and the dicotyledons. The homoerythrina alkaloids are therefore a new addition to this chemical data pool.

The genus Phelline have been classified in the family Rutaceae by Bentham and Hooker¹⁰, Illicaceae (Aquifoliaceae) by Guillamen¹⁰, and Araliaceae by Airy-Shaw¹⁰. Since the isolation of the homoerythrina alkaloids from this genus, it has been relegated to the family Aquifoliaceae¹¹. On the other hand, the family Meliaceae has been placed by many authors, together with the family Rutaceae, under order Rurales¹². Although Cronquist⁹⁹ classified it under order Sapindales, this order also includes the family Rutaceae. The relationship of the family Rutaceae to the family Meliaceae is illustrated in Scheme 3. This close relationship is supported by a chemical link composed of a number of triterpenes and their derivatives⁹ and by a rare combination of a chromone alkaloid and limonoid in Harrisonia abyssinica (Simaroubaceae)¹⁴, Spathelia sorbifolia (Rutaceae)¹⁰⁰, and very recently in Dysoxylum binectariferum (Meliaceae)^{101,102}. The close relationship between



Scheme 3

the families Meliaceae and Rutaceae, and the presence of the homoerythrina alkaloids in the genera Dysoxylum and Phelline tend to support Bentham's classification of the genus Phelline under the family Rutaceae.

1.3 Scope of the Thesis

This thesis focusses mainly on the homoaporphine and the homoproaporphine alkaloids. These have not been reviewed since Kametani's treatment of them in 1973⁵. Although there have been no recent reviews on the simple 1-phenethylisoquinoline, bisphenethylisoquinoline, homomorphinane, and dibenz[d,f]azecine groups of alkaloids, to date, there are but a few representatives in these groups and there are few studies involving them. The colchicine and the cephalotaxine groups of alkaloids, being found to have significant biological activities, have been more extensively

studied compared to the other groups. As such, they are better treated as separate topics and thus, are not included in Table 1. Furthermore, these two alkaloid groups,^{1,2,103,104,186,187} as well as the homoerythrina group¹ have been reviewed previously and are not treated further in detail in this thesis.

2. C-HOMOAPORPHINE ALKALOIDS

2.1 Occurrence, Isolation and Detection Procedures

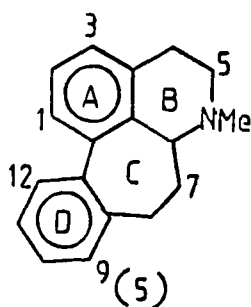
As mentioned in Chapter 1, the homoaporphine and homoproaporphine alkaloids have been isolated only within the plant subfamily Wurmbaeoideae (Liliaceae).¹⁸⁴ These alkaloids were found^{6,27} to co-occur with other 1-phenethylisoquinoline-derived alkaloids. Preliminary separations⁹⁸ on the crude extracts involved the isolation of the neutral phenolic components which were mainly composed of the tropolonic alkaloids, from the basic components composed of some tropolonic as well as non-tropolonic alkaloids. The basic extracts were subjected^{15,98} to paper- and thin layer chromatography and detected with UV light, Dragendorff, sulfuric acid, Oberlin-Zeisel, iodoplatinate, and antimony chloride reagents. Like the colchicine group (tropolonic group), the non-tropolonic group of alkaloids gave a wide range of colors with iodoplatinate and with sulfuric acid reagents. The components of interest were isolated¹⁵ mainly by preparative tlc and by column chromatography on alumina and on silica gel. The alkaloids detected were identified⁹⁷ as of the tropolonic or the non-tropolonic type mainly by their ultraviolet spectra. The R_f values and the color of the tlc spots were also especially useful in identifying the components which had been previously isolated and identified.

2.2 Structure and Spectroscopic Properties

2.2.1 The Structure of C-Homoaporphine Alkaloids

The C-17 tetracyclic carbon skeleton (5) of the homoaporphine alkaloids is based on the simple 1-phenethylisoquinoline structure. Compared to the aporphine skeleton, homoaporphines have an extra carbon in ring C. Rings A and D which are always aromatic, are in a twisted biphenyl configuration. Carbons 1,2,10, 11, and 12 are generally substituted with either hydroxy or methoxy groups. The nitrogen is generally methyl-substituted. Unlike the aporphine alkaloids, no C₃-substituted homoaporphines have been isolated.

Most work on structure elucidation of this group of alkaloids relies heavily on physical methods such as ultraviolet, infrared, nuclear magnetic resonance and mass spectroscopy. This is backed up by biogenetic arguments and by chemical transformations to known compounds. Degradative approaches to structure elucidation are ruled out generally by sample size limitations.



2.2.2 Infrared and Ultraviolet Spectroscopy; Circular Dichroism and Optical Rotatory Dispersion

The infrared spectra of these compounds mainly identifies the presence of the hydroxy groups and the carbon-carbon double

bonds of the aromatic system. The ultraviolet spectra remain valuable tools in the preliminary identification of the structure of this group of compounds. Three characteristic bands are usually observed. The first and the second primary aromatic bands are centred³⁶ at 258 and 218 nm, respectively, and the third, a secondary aromatic band, at 290 nm. A change in the substitution pattern does not greatly shift the wavelength of the absorption maxima (Table 3). A bathochromic shift observed³⁶ in alkali solution is indicative of a phenolic hydroxy substituent.

The sign of the Cotton effects of the biphenyl systems associated with ultraviolet circular dichroism (C.D.) or its complement, the optical rotatory dispersion (O.R.D.) was established¹⁰⁵ to be dependent on the absolute sense of twist, hence, the absolute configuration of the system. Brossi¹⁰⁷ and his co-workers studied the C.D. and O.R.D. curves of R-(-)-multifloramine (13) and S-(+)-multifloramine (13) prepared from resolved starting materials. The Cotton effects of these compounds were in complete agreement with the generalizations made by Mislow,¹⁰⁵ Bunnenberg¹⁰⁶ and their co-workers. These generalizations were based on the Cotton effects of some biaryl systems of known absolute configuration. Thus, R-(-)-multifloramine gave three characteristic peaks (Figure 1). Both the two long wavelength aromatic peaks have positive signs and are centered at about 305 and 275 nm. The third peak, centered at a wavelength below 250 nm is generally at a higher amplitude and of opposite sign relative to the other two.

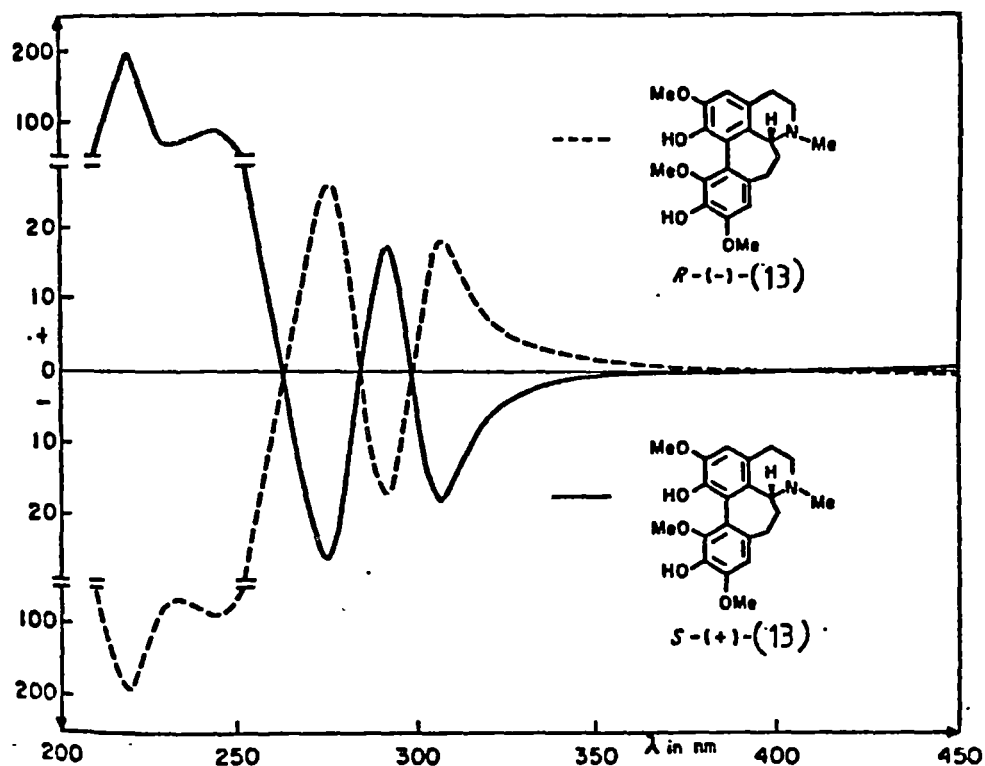


Figure 1
O.R.D. Curves of R-(-)-Multifloramine (13)
and S-(+)-Multifloramine (13)

2.2.3 Nuclear Magnetic Resonance Spectra

Proton magnetic resonance spectroscopy remains an excellent tool in identifying the nature and possible position of the substituents in the aromatic centres of the homoaporphine alkaloids. It distinguishes a methoxy group at C_1 and C_{12} from those at C_2 , C_{10} , or C_{11} , where the methoxy substituent at C_1 and C_{12} is consistently found upfield (δ 3.48-3.67; Table 3). The upfield shift is due to the shielding effects of rings A and D. The aromatic protons at C_3 and C_9 are generally indistinguishable (δ 6.5-6.8) while the proton signal at C_{12} is always found downfield (δ 6.8-7.5). This downfield shift is also observed in

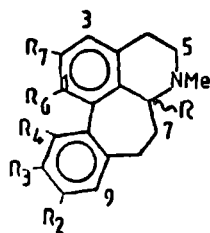


TABLE 3
U.V. DATA AND ^1H N.M.R. CHEMICAL SHIFTS OF SOME HOMOAPORPHINES AND THEIR DERIVATIVES

	SUBSTITUENTS						U.V. DATA				¹ H N.M.R. CHEMICAL SHIFTS (δ)							REF
	R	R ₂	R ₃	R ₄	R ₆	R ₇	λ _{max} (nm)				1-OMe	12-OMe	3,9-H	N-Me	2,10,11-OMe	11,12-H		
a	--H	OH	OMe	OMe	OH	OMe	218	260	291		3.67	6.69	6.60	2.20	3.80	3.80	144	
b	H	OMe	OMe	OH	OH	OMe	221	259	289 298			6.95	6.71	2.80	4.13	4.13 4.13	28	
c	--H	OMe	OMe	OH	OMe	OMe		258	287	3.5		6.64	6.37	2.33	3.82	3.82 3.82	66	
d	H	OMe	OH	OMe	OH	OMe	216	257	293		3.58	6.70	6.65	2.40	3.92	3.92	58	
e	--H	OMe	OMe	OMe	OMe	OMe	218	258	295	3.48	3.56	6.45	6.58	2.35	3.81	3.83 3.83	67	
f	--H	OMe	OMe	OMe	OH	OMe	221	260	293		3.59	6.59	6.56	2.36	3.86	3.83 3.83	35,56	
g	--H	OMe	H	H	OH	OMe		260	290			6.59	6.80	2.39	3.81	3.86 7.95,6.83	59,119	
h	--H	OH	OMe	H	OH	OMe		264	293			6.64	6.66	2.31	3.71	3.78 7.01	133	
i	--H	OMe	OH	H	OH	OMe						6.63	6.78			6.88	33	
j	--H	OMe	OMe	OH	OMe	OH				3.5		6.60	6.62	2.38	3.82	3.80	64	
k	--H	-OCH ₂ O-		H	OH	OMe						6.62	6.75	2.39	3.88		7.04 133	
l	--H	OMe	OMe	H	OH	OMe						6.48	6.48	2.37	3.78	3.78 3.81 7.12	58	
m	--H	OH	OMe	OH	OH	OMe						6.64	6.66		3.78	3.71 7.01	133	
n	--H	OMe	OH	H	OMe	OMe				3.43		6.66	6.72	2.34	3.84	3.86 7.00	133	
o	--H	OH	OMe	OH	OMe	OMe				3.40		6.67	6.74		3.80	3.85 7.08	133	
p	--H	OMe	OH	OMe	OMe	OMe				3.46	3.48	6.53	6.68	2.38	3.82	3.87	133	

the corresponding C_{11} proton of the aporphine alkaloids.

2.2.4 Mass Spectroscopy

The main fragmentation patterns^{64,108} of the homoaporphine alkaloids involve the loss of a methylenimine fragment ($CH_2=NCH_3$) by retro Diels-Alder fission of the B-ring, the loss of C_1 substituent, and cleavage of the C-ring. The substituent in C_1 is readily lost irrespective of whether it is a hydroxy or a methoxy substituent as it eases the strain on the twisted biphenyl system. Table 4 gives the relative abundances of the fragment ions⁶⁴ of the homoaporphine alkaloids (S)-floramultine (14), szovitsamine (15), O-methylkreysigine (16), and the homoaporphine derivative O,O-diacetyl-(S)-floramultine (17). Scheme 4 illustrates the fragmentation of (S)-floramultine. (14).

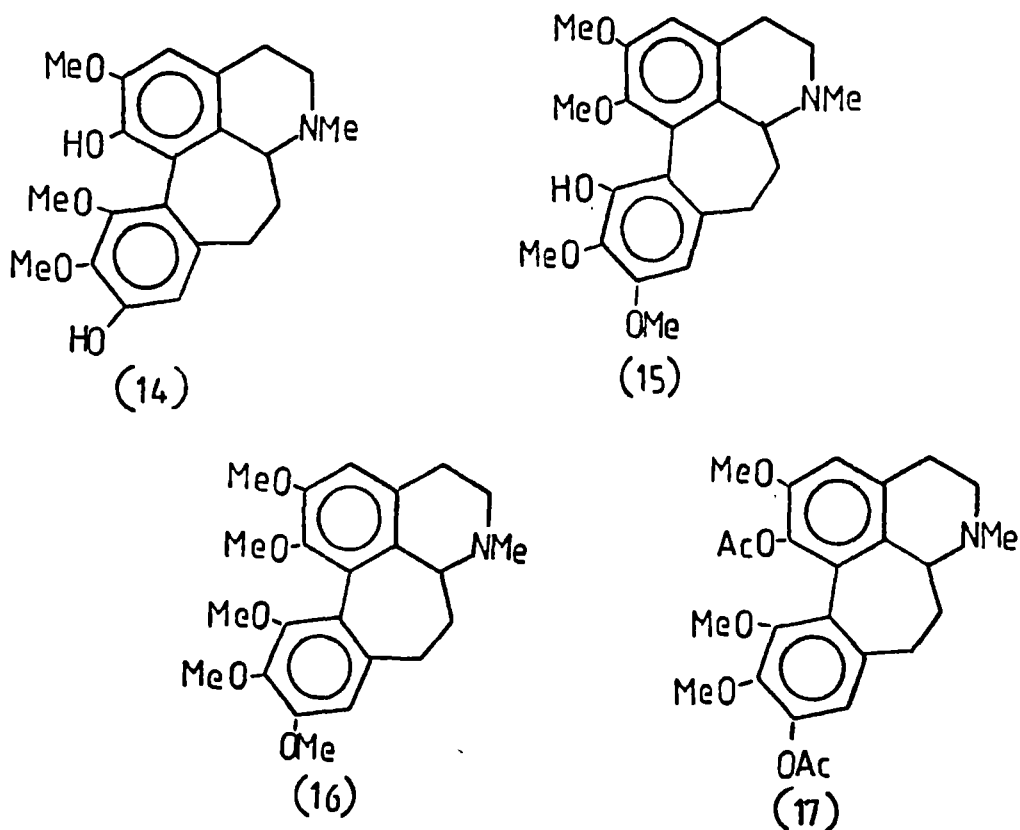
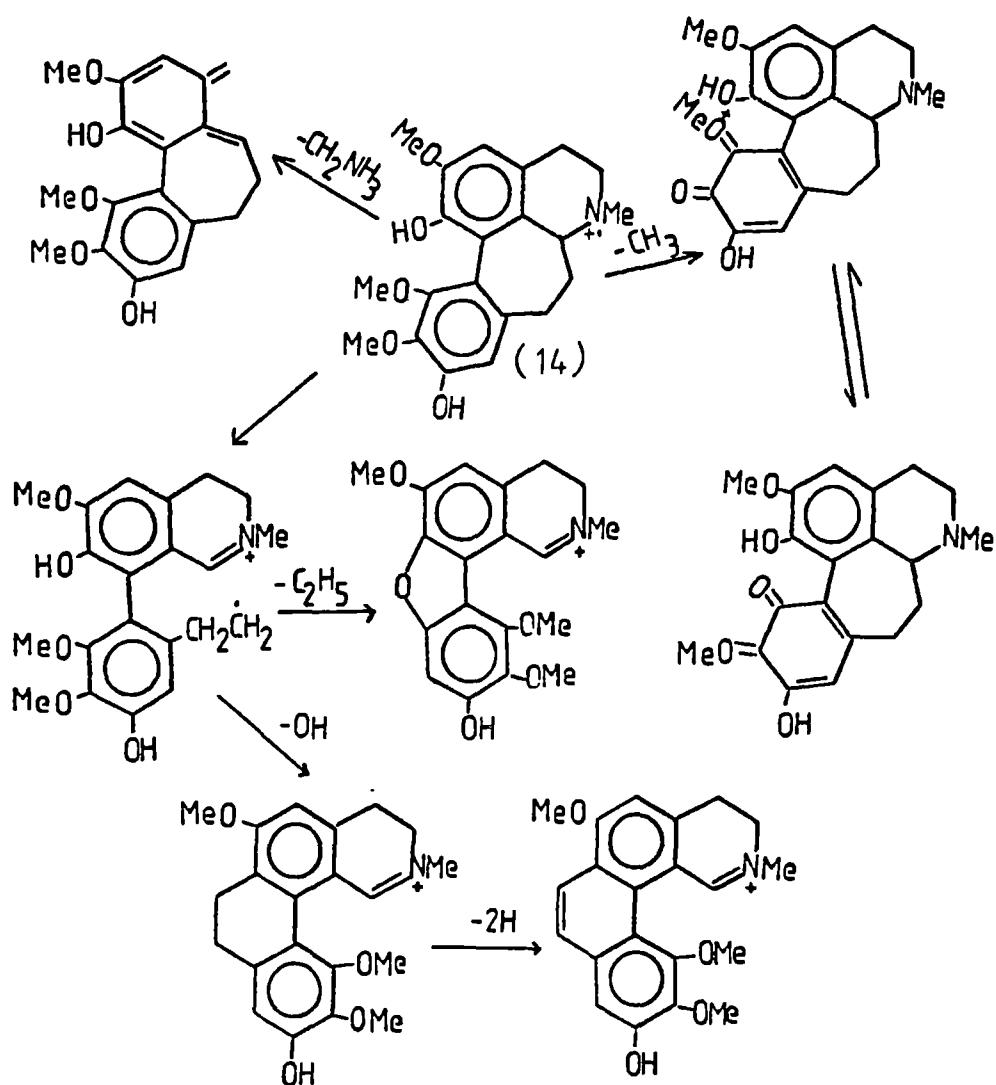


TABLE 4
RELATIVE ABUNDANCES OF THE FRAGMENT IONS
OF HOMOAPORPHINES (14), (15), (16), and (17)

Fragment Lost	Fragment	Percentage Abundances			
		(14)	(15)	(16)	(17)
	M^+	55	33	23	11
H	M-1	21	05	04	02
CH_3	M-15	35	15	17	03
OH	M-17	100	06	-	03
2H, OH	M-19	04	-	-	-
C_2H_5	M-29	17	07	10	-
OCH_3	M-31	25	100	100	-
H_2O , CH_3	M-33	15	04	-	-
CH_2NCH_3	M-43	05	03	02	20



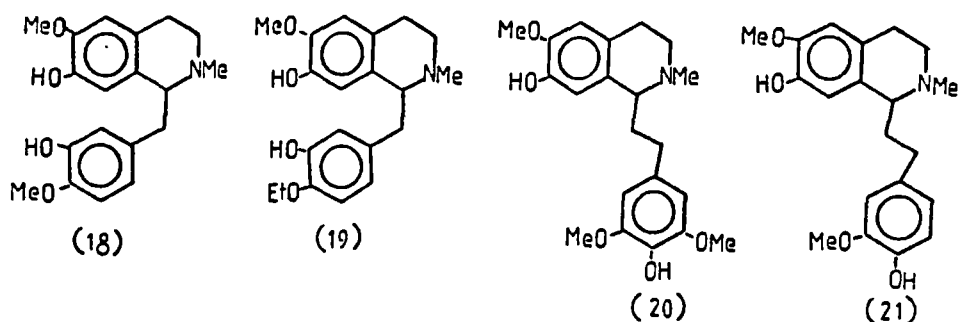
Scheme 4

2.3 Synthesis of the C-Homoaporphines

2.3.1 Phenolic Oxidation

Phenolic oxidative coupling, a key reaction in the biosynthesis of the isoquinoline alkaloids, has always been presumed¹⁰⁹ to proceed by way of radical pairing. In the 1-phenethylisoquinoline as well as in the 1-benzylisoquinoline series, the actual mechanism of this reaction has not been clearly

understood. Recently, Hewgill and Pass conducted esr experiments on 1-benzylisoquinoline¹¹⁰ and on 1-phenethylisoquinoline¹¹¹ alkaloids aimed at detecting radical intermediates in the oxidation process. Whereas each of reticuline (18) and phenethylisoquinoline (20) upon oxidation with potassium ferricyanide, were expected to form two radicals being diphenolic, esr data showed radicals in ring C only. In benzylisoquinoline (19), where the C₄-methoxy group of (18) was substituted with an ethoxy group, two radicals were observed in equal proportions. Homoorientaline (21) on the other hand, showed no radical formation at all.

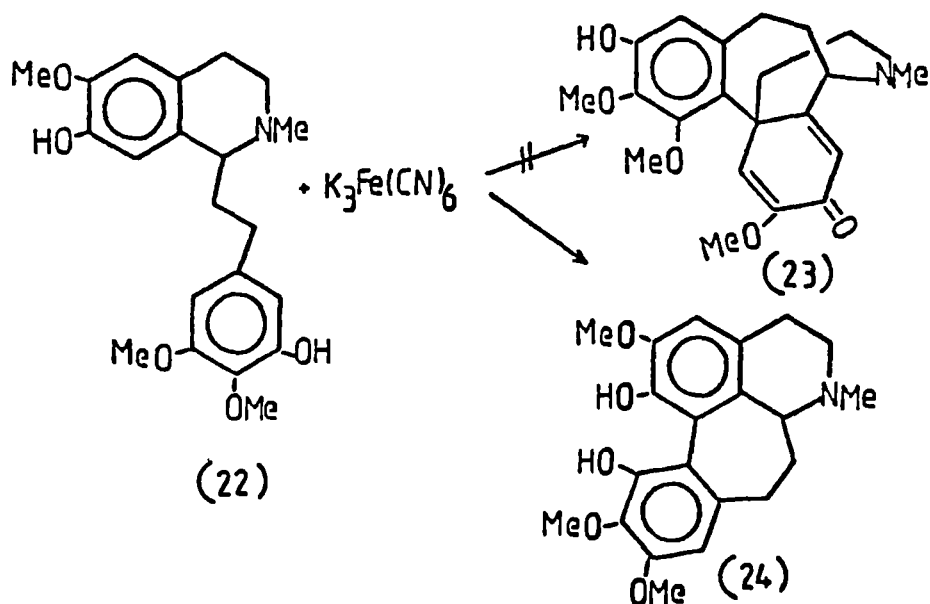


No clear cut interpretations of these results have been made; however, they offered possible explanations. If the radical intermediate was detected only in the C-ring, it might be that ring C is more easily oxidized than ring A, or perhaps, ring C radicals are more stable. Otherwise, some other processes such as an intermolecular or intramolecular transfer of unoxidized phenolic hydrogen atoms to the radical formed may have taken place. Still another possibility is that the oxidation of the A-ring is a slow step compared to that of ring C such that once ring A is oxidized it quickly pairs up with the ring C radical. There is also a slim chance that the equipment used was not sensitive enough to detect the radical intermediate in ring A.

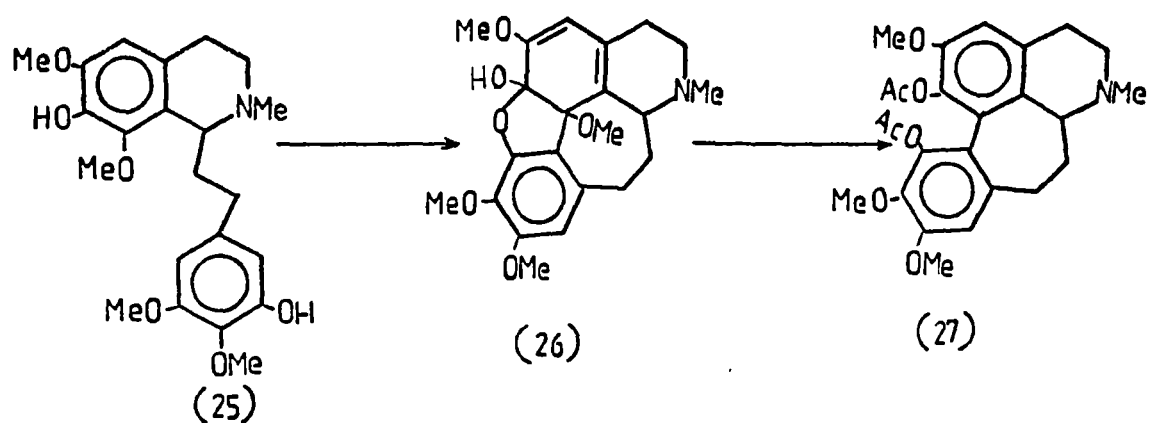
2.3.1.1 Diphenolic Intramolecular Coupling

2.3.1.1.1 Direct Oxidative Coupling

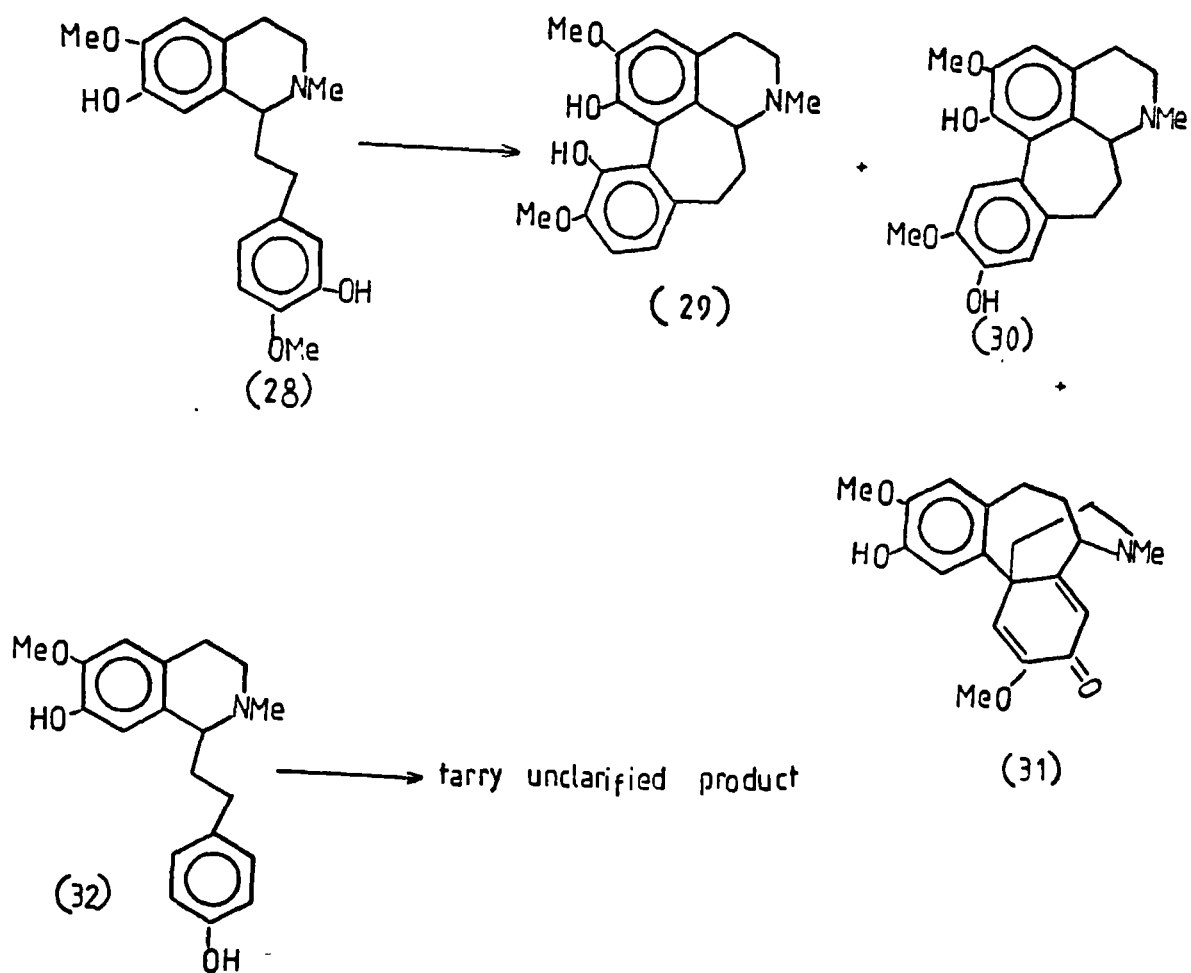
Many syntheses of this type have been reviewed⁵ by Kametani and Koizumi. One-electron oxidizing agents such as ferric chloride, potassium ferricyanide and vanadium oxytrifluoride were used in these syntheses. The first work in this area was reported⁹⁰ by Battersby. Autumnaline (22) was oxidized to form the ortho-ortho coupling product (24). The expected colchicine intermediate (23) was not isolated (Scheme 5). The addition of a methoxy group at C₈ of (22) to form (25) and its subsequent oxidation with potassium ferricyanide gave rise to a homoaporphine-type product (26) with a hemiacetal bridge (Scheme 6). No homoaporphine with this type of bridge has so far been isolated from plant sources. Treatment of (26) with isopropenylacetate-p-toluene sulfonic acid afforded the homoaporphine (27).



Scheme 5



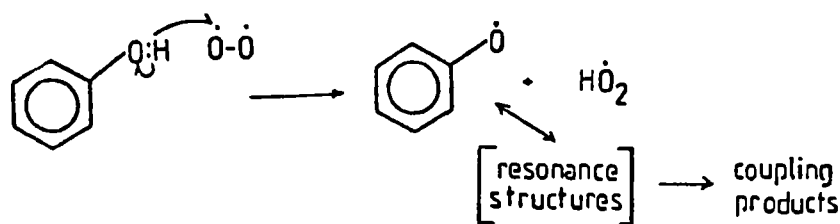
Scheme 6



Scheme 7

Kametani also studied^{112,113} the phenolic oxidative coupling of the 1-phenethylisoquinoline alkaloids using a mixture of cuprous chloride and oxygen in pyridine. The choice of this oxidizing system was based on the known phenolic oxidation enzymes laccase and tyrosinase. These two enzymes contain copper ion and use up oxygen for oxidation. Thus, the oxidation of (28) gave the ortho-ortho (29), ortho-para (30), and para-para (31) coupled products, each in very low yield (Scheme 7).

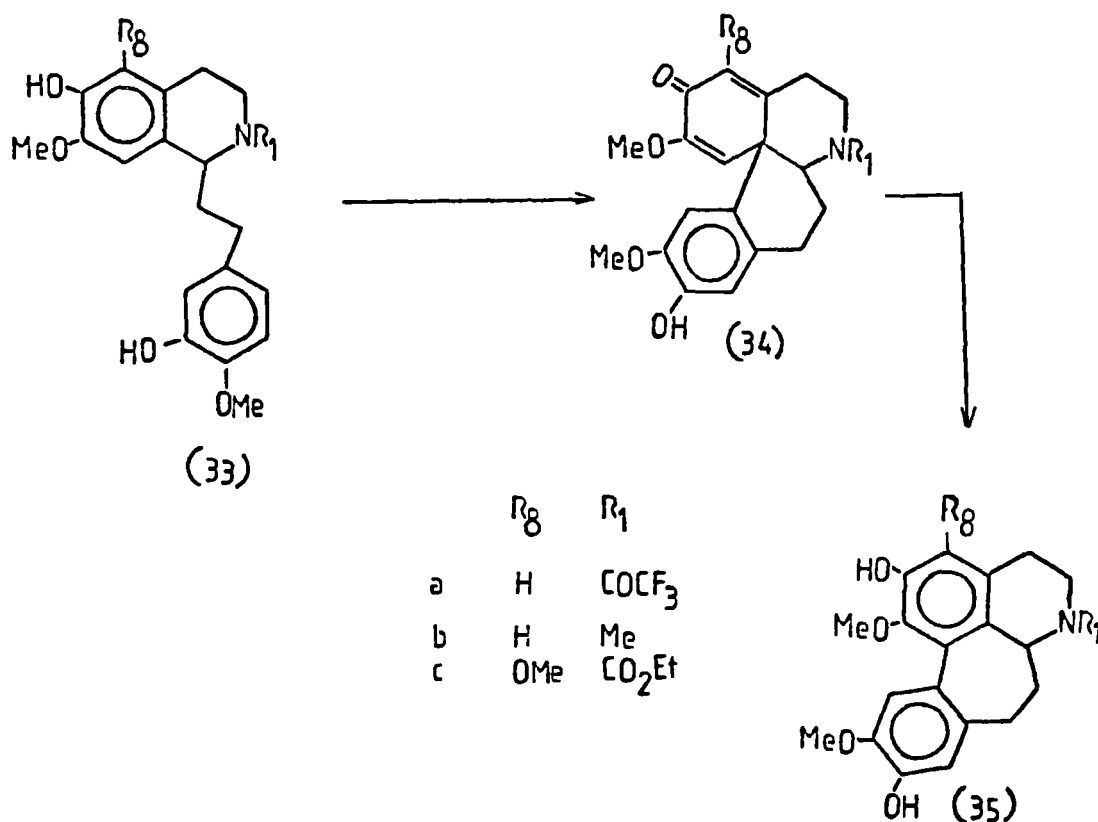
It has been presumed that for this coupling reaction to form a homoaporphine-type product, an O-methoxyphenol moiety must be present in both rings A and C. This generalization was deduced from the oxidation of (32) which formed a dimer of (32) instead of a homoaporphine. In this type of reaction, dimethylformamide proved to be a poor substitute for pyridine while cuprous bromide was just as effective as cuprous chloride. There are two possible mechanisms for this reaction. One, where phenol reacts with the activated molecular oxygen without changing the oxidation state of the cuprous ion. This mimics the tyrosinase enzyme action (Scheme 8). The second resembles the enzyme laccase. In this case, the cuprous ion mediates an electron transfer passing on electrons from the phenolic oxygen to molecular oxygen. Potassium superoxide proved to be a good substitute for molecular oxygen.



Scheme 8

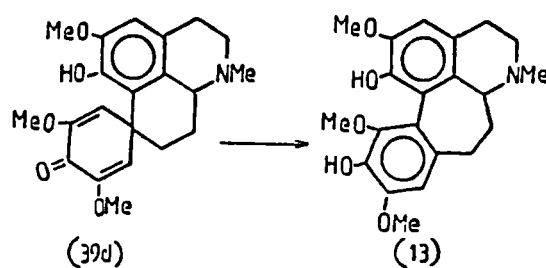
2.3.1.1.2 Via Homoproerythrinadienone

The only diphenolic oxidation which led to the formation of homoproerythrinadienone was reported¹¹⁴ by Marino and Samanen. The phenethylisoquinoline (33a) was oxidized with vanadium oxytrichloride to form the homoproerythrinadienone (34a), a proposed key intermediate^{114,136} in the biosynthesis of homoerythrina alkaloids (Scheme 9). Upon treatment of (34a) with boron trifluoride in ether, it underwent a dienone-phenol rearrangement giving rise to the homoaporphine alkaloid (35a). Under the same reaction conditions, (33b) and (33c) were also transformed to the homoproerythrinadienones (34b) and (34c), respectively. However unlike (34b), (34c) did not rearrange to a homoaporphine.



2.3.1.1.3 Via Homoproaporphine

Many of the homoaporphine alkaloids have been synthesized through the intermediacy of homoproaporphines. Homoproaporphines which are formed by ortho-para intramolecular coupling of 1-phenethylisoquinoline derivatives, are smoothly rearranged to homoaporphine in the presence of an acid. Battersby,⁵⁵ Kametani,^{34,58,119} and Brossi¹⁰⁷ contributed to this area of synthesis. The synthesis of multifloramine (13) from the dienone (39d), which was independently reported by Kametani⁵ and Brossi¹⁰⁷ was also carried out by Battersby¹²⁰ (Scheme 10). This was to determine and confirm the structures of the homoaporphines floramultine and kreysigine. Other more recent studies involving this type of synthesis are mentioned in other sections of this thesis.

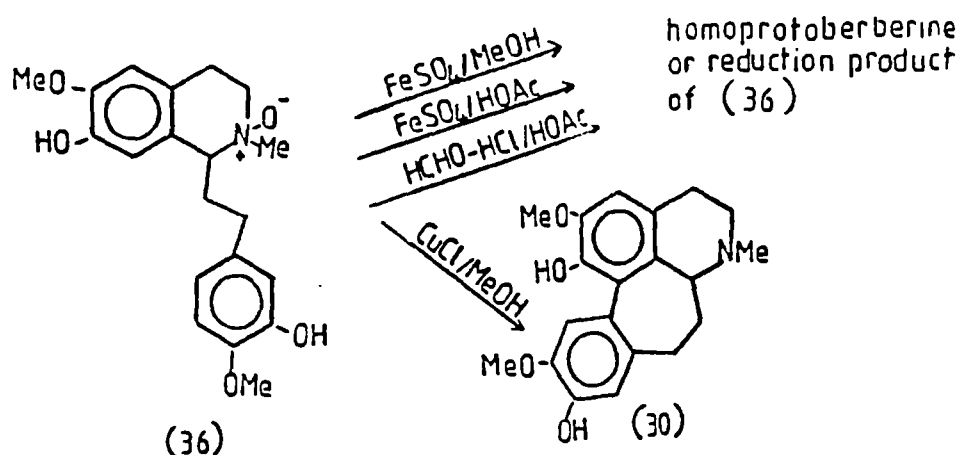


Scheme 10

2.3.1.1.4 Oxidation of 1-Phenethylisoquinoline N-Oxide

This is an extension¹²² of Kametani's successful cyclization of 1-benzylisoquinoline N-oxides to form protoberberine, aporphine and proaporphine-type alkaloids. The type of cyclization products formed were found to be dependent on the nature of the oxidizing system (Scheme 11). Thus, a homoaporphine was formed¹¹⁵ only with cuprous chloride in methanol as the oxidizing system. The oxidation of (36) gave the homoaporphine (30) as the sole product. The yield however was comparatively low, that is, 10.2%,

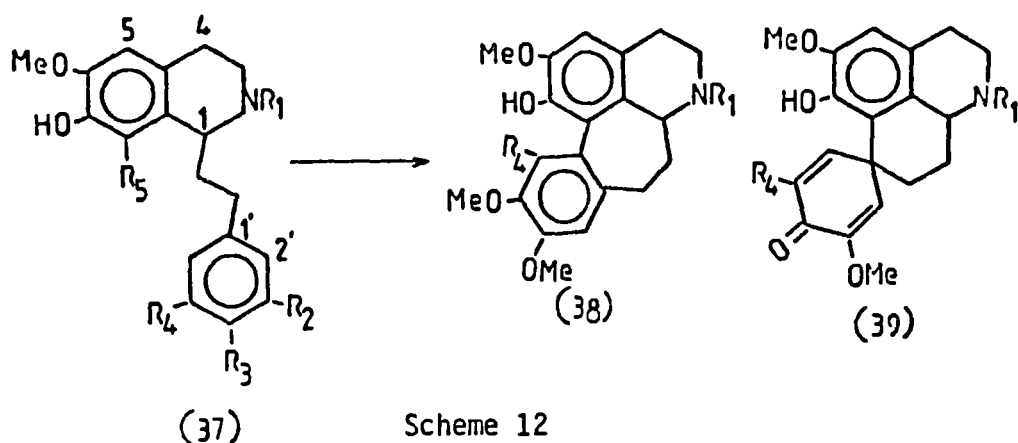
whereas the corresponding aporphine yield was 61%. The formation of the copper complex which should lead to an ortho-ortho coupling product was presumed to be difficult in the 1-phenethylisoquinoline series compared to the benzylisoquinoline series since the expected product was not formed.



Scheme 11

2.3.1.2 Monophenolic Oxidative Coupling

Kupchan reported¹¹⁶ the oxidation of some monophenolic 1-benzylisoquinoline- and 1-phenethylisoquinoline derivatives using vanadium oxytrifluoride as oxidizing agent. This method was found to efficiently transform the 1-benzylisoquinolines to aporphine- and morphinandienone-type products. In contrast, the 1-phenethylisoquinolines (37a-d) gave homoaporphines (38a-d) and homoproaporphines (39a-d) as products (Scheme 12). No homomorphinandienone-type product was formed. It must however be noted that in an earlier work by Schwartz¹¹⁷, the oxidation of (37c) using two-electron oxidizing agent thallium(III)trifluoroacetate afforded a homomorphinandienone as the sole product.



Compared with diphenolic oxidation, this method gave a relatively higher yield of the homoporphine and the homoproaporphine products. Much more, the relative yield of the homoporphines is higher as compared to the homoproaporphines if R_1 of (37) is a trifluoroacetyl group and is reversed when R_1 is a methyl group (Table 5). It has been suggested that there are two modes of cyclization reaction taking place simultaneously. One is obviously a direct coupling between C_8 and C_6 , to form the homoporphine skeleton and a C_8 and C_1 , coupling leading to the formation of a homoproaporphine. At room temperature and in acid medium, all the homoproaporphines easily rearranged to homoporphines.

TABLE 5

Homoporphine and Homoproaporphine Yields of (37)

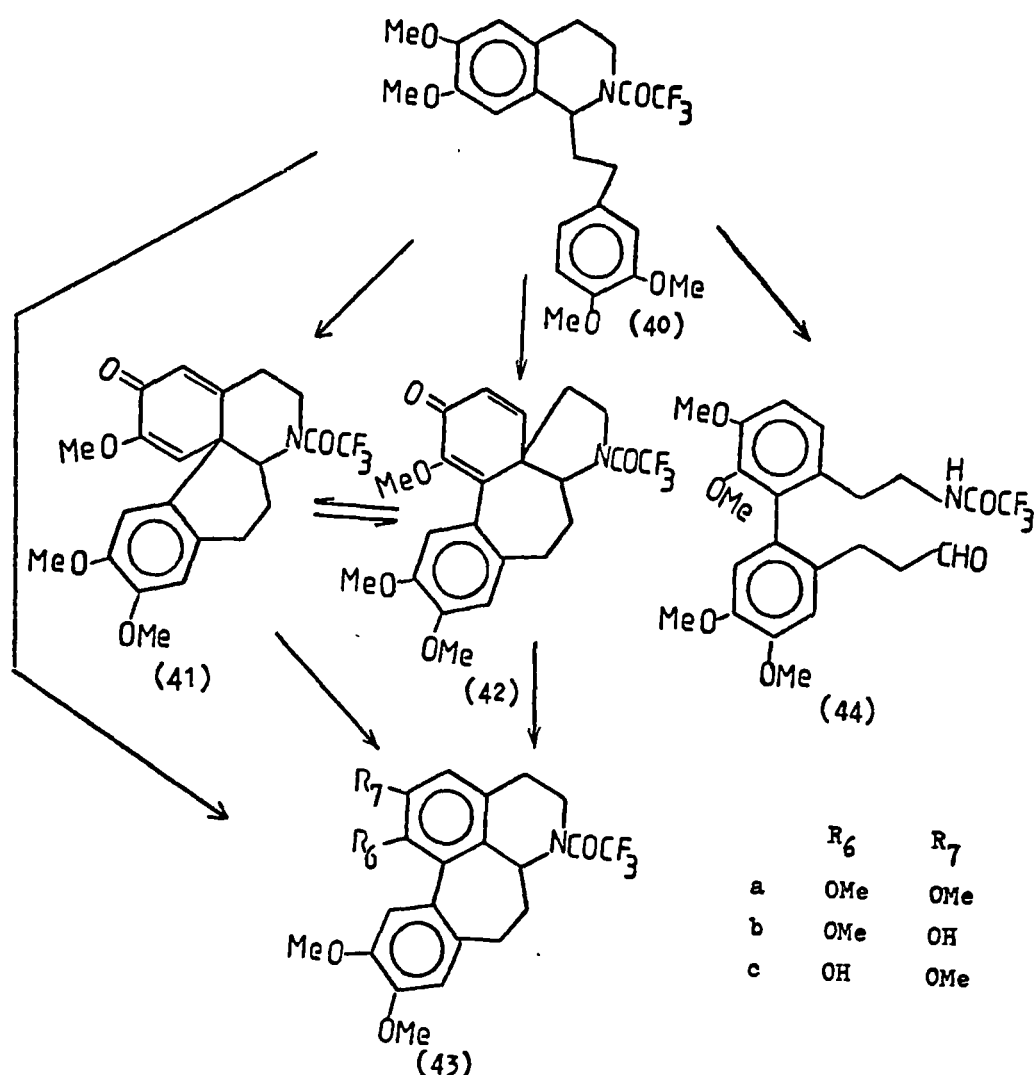
($R_2=R_3=OMe$; $R_5=H$)

R_1	R_4	Percentage Yield			
a	$COCF_3$	H	(38a) 40%	(39a) 18%	
b	Me	H	(38b) 14%	(39b) 42%	
c	$COCF_3$	OMe	(38c) 46%	(39c) 04%	
d	Me	OMe	(38d) 16%	(39d) 54%	

2.3.2 Non-phenolic Oxidation

In the oxidation of some 1-benzylisoquinoline alkaloids using vanadium oxytrifluoride, Kupchan obtained¹¹⁸ two kinds of products, the aporphine and the neospirinedienone-type. The formation of the aporphines was known to proceed by way of morphinandienone intermediates. This intermediate is then transformed to a neospirinedienone thence, to an aporphine. Under the same reaction conditions (Scheme 13), the 1-phenethylisoquinoline (40) was oxidized⁶⁹ to a homoaporphine (43a), a homoproerythrinadienone (41), a homoneospirinedienone (42), and an aldehyde (44). In boron trifluoride etherate, (41) and (42) rearranged to homoaporphines (43b) and (43c) respectively, whereas proerythrinadienones were known¹²³ to rearrange to a neospirinedienone. In contrast to the reaction pathway for aporphine formation, the formation of the homoaporphine system was proven to proceed via a homoproerythrinadienone intermediate instead of a homomorphinandienone. The homoproerythrinadienone intermediate was then transformed to a homoneospirinedienone and thence to a homoaporphine. The yield of homoaporphine in this synthesis was increased by increasing the reaction time to allow the intermediates to rearrange to homoaporphine.

The electrooxidation¹²⁴ of a non-phenolic 1-phenethylisoquinoline compound such as (40) did not form any carbon-carbon cyclized products.



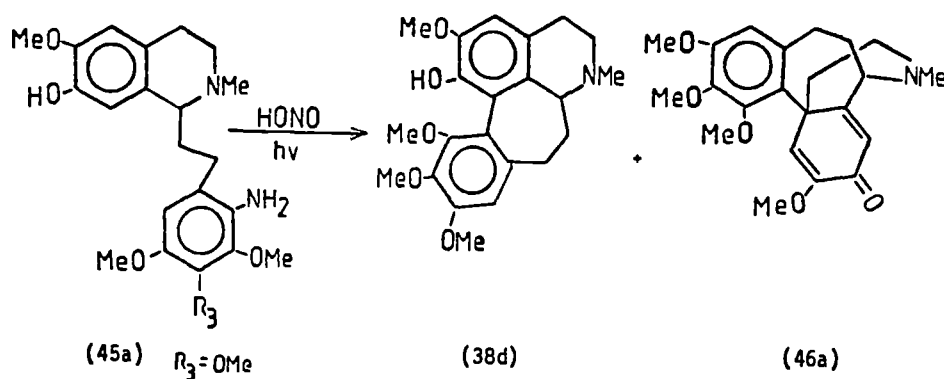
Scheme 13

2.3.3 Direct Cyclization

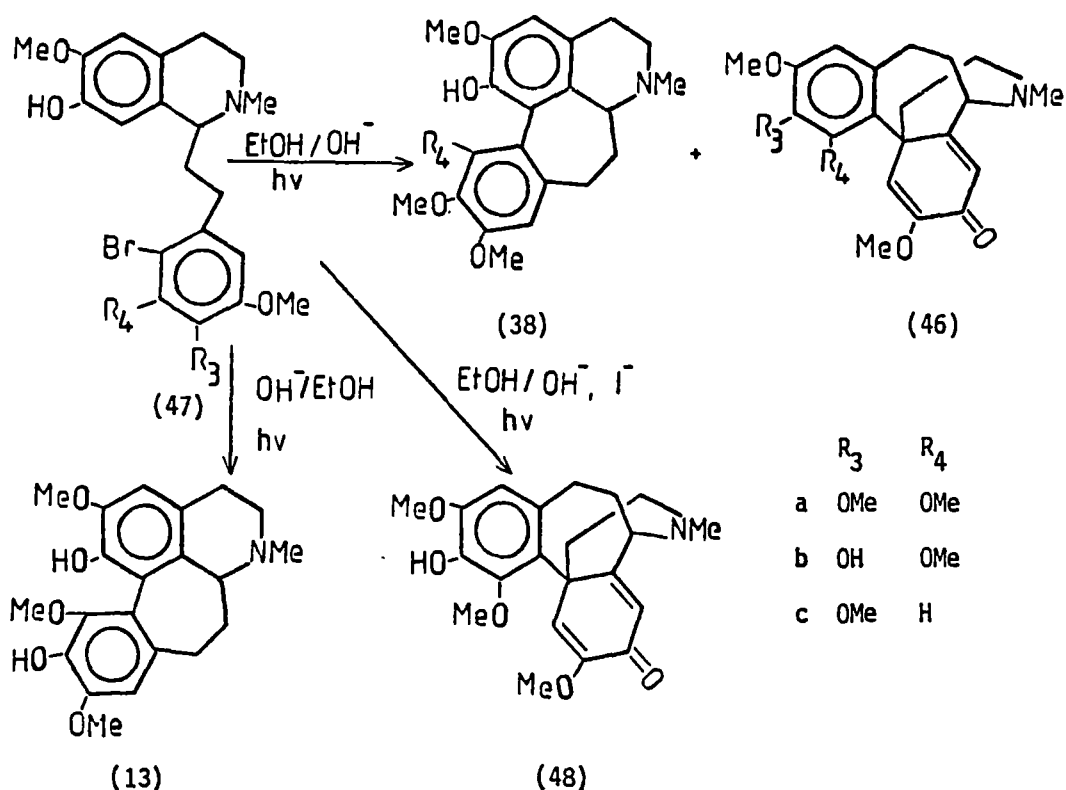
2.3.3.1 Photolytic Cyclization

Although the usual Pschorr reactions, that is, those possibly involving aromatic nucleophilic attack on a cation, have been successfully applied in the synthesis of the aporphines,¹²⁵ morphines and homomorphinanes¹²⁶, no homoaporphine alkaloids could be obtained using this method. Kametani's group developed¹²⁶ in their laboratory a reaction involving a radical

intermediate instead of a cation by irradiation of a diazonium salt to bring about homolysis of the carbon-nitrogen bond. This reaction, which they named a Photo-Pschorr reaction,¹²⁸ afforded aporphines in higher yields and was successfully applied¹²⁶ to the synthesis of homoaporphines. All the photolytic synthesis including the photolysis of bromophenethylisoquinolines to form homoaporphines have been reported and reviewed⁵ by Kametani. There has been no report related to this since the last review. Some representative examples of these reactions are given in Scheme 14 and 15. The photo-Pschorr reaction of the diazonium salt of (45a) gave¹²⁶ a mixture of a homoaporphine (38d) and a homomorphinan-dienone (46a) (Scheme 14). On the other hand, homoaporphines (38d) and (38b) and homomorphinanes (46a) and (46c) were formed¹¹⁹ from the photolysis of the bromophenethylisoquinoline (47a) and (47c) in alkaline medium (Scheme 15). The conversion of the phenethylisoquinoline (47b) to either a homoaporphine (13) or a homomorphinane (48) shows¹²⁹ the dependence of the product on the reaction medium. That is, in the presence of iodide, only (48) is formed. In its absence, a homoaporphine (13) is the sole product.



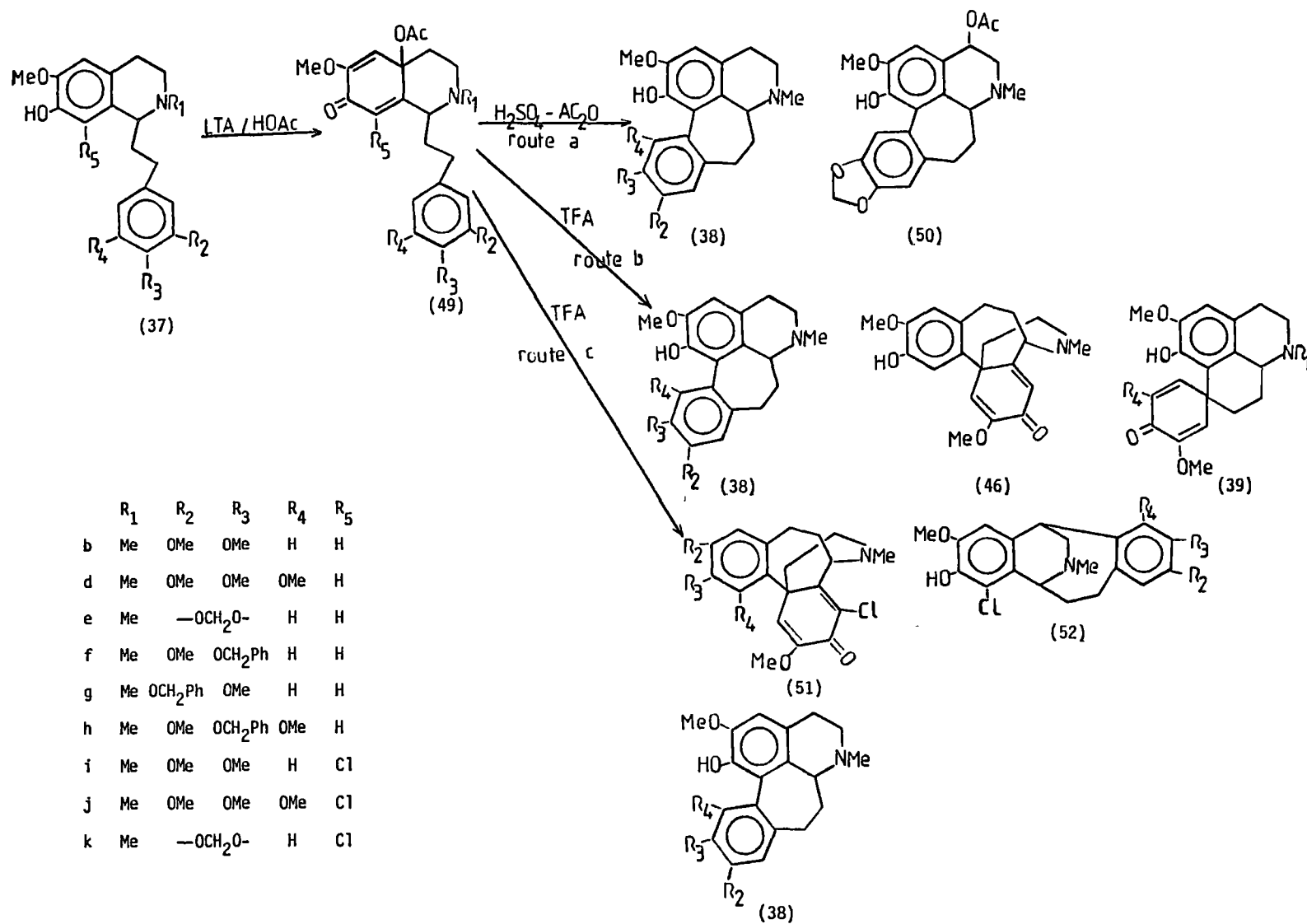
Scheme 14



Scheme 15

2.3.3.2 Via Quinol Acetates

The conversion of a phenol to *p*-quinol acetate has been applied to the benzyloisoquinoline¹²⁸ and 1-phenethylisoquinoline alkaloids^{127,130,131,132,133,135} by Hoshino, Hara and their co-workers. A summary of the results of their work on the 1-phenethylisoquinolines is given in Scheme 16 and in Tables 6 and 7. The initial conversion of the *p*-quinol acetates (49b), (49d) and (49e) using sulfuric acid-acetic anhydride reagent^{127,130,131} gave only the homoaporphine products (38b), (38d), and (38e) respectively (Scheme 16, route a). However, (49e) afforded a second homoaporphine product (50). It was presumed that homomorphinane and homoproaporphine-type products were also formed but have



Scheme 16

TABLE 6

PERCENTAGE YIELDS OF THE CYCLIZATION PRODUCTS OF THE QUINOL ACETATES (49b,d,e,f,g and h)

Activating Groups at ring C	% Yield of (38)		% Yield of (46)		% Yield of (39)	
	LTA ^a	LTA-TFA ^a	LTA	LTA-TFA	LTA	LTA-TFA
b 2-OMe	44.2		3.3	16.0	6.9	31
d 3-OMe	35.2	7.5	23.1	26.0	31.3	15
e 1-OCH ₂ O-	55.0	19.0	-	-	-	-
f 1-OMe 1-OCH ₂ Ph	39.3		6.1	14.0	15.5	18
g 1-OMe 1-OCH ₂ Ph	29.6		0.3	5.0	11.4	16
h 2-OMe 1-OCH ₂ Ph	27.3	10.0	12.2	13.0	15.9	10

^a oxidizing system

TABLE 7
PERCENTAGE YIELDS OF THE CYCLIZATION
PRODUCTS OF THE QUINOL ACETATES (49i,j and k)

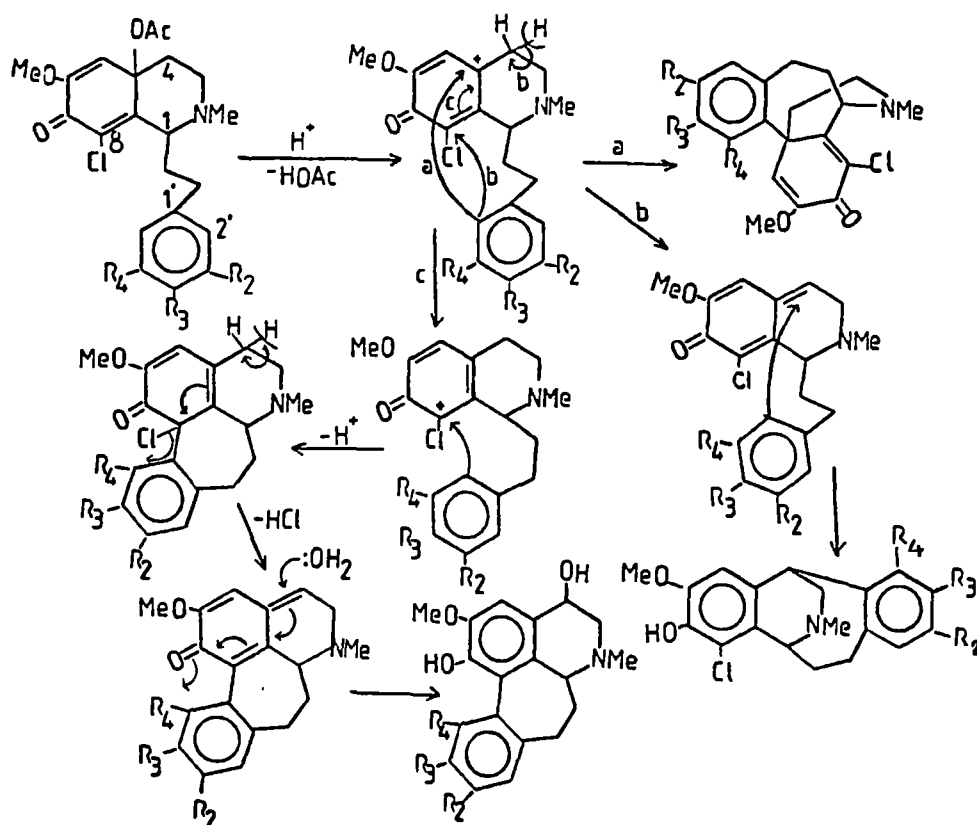
Activating Groups at ring C		% Yield		
		(38)	(51)	(52)
i	2-OMe	30	18	17
j	3-OMe	0	31	9
k	1-OCH ₂ O-	17	11	16

rearranged to a homoaporphine in the presence of a relatively strong acid. Thus with trifluoroacetic acid, (49b), (49d), (49f), (49g) and (49h) gave rise^{132,133} to three types of products: a homoaporphine (38), a homomorphinane (46), and a homoproaporphine (39), (Scheme 16, route b). The yields of (46) and (39) were however very low. Under the same reaction conditions, *p*-quinol acetate (49e), with a methylenedioxy substituent in ring C, formed the homoaporphine (38e) as the sole product. The low yields of (46) and (39) suggested that they may have rearranged to the homoaporphine skeleton. This theory was supported by the fact that the yield of (46) was increased by oxidizing (49) with lead tetraacetate-trifluoroacetic acid reagent¹³³, the homoaporphine yield decreased considerably (Table 6).

In Table 6, one can see that a favorable ring closure to a homoaporphine (C₈-C₆), a homomorphinane (C₁₀-C₆), and a homoproaporphine (C₈-C₁) is dependent on the nature of the activating group in ring C. The ring closure to a homoaporphine is most

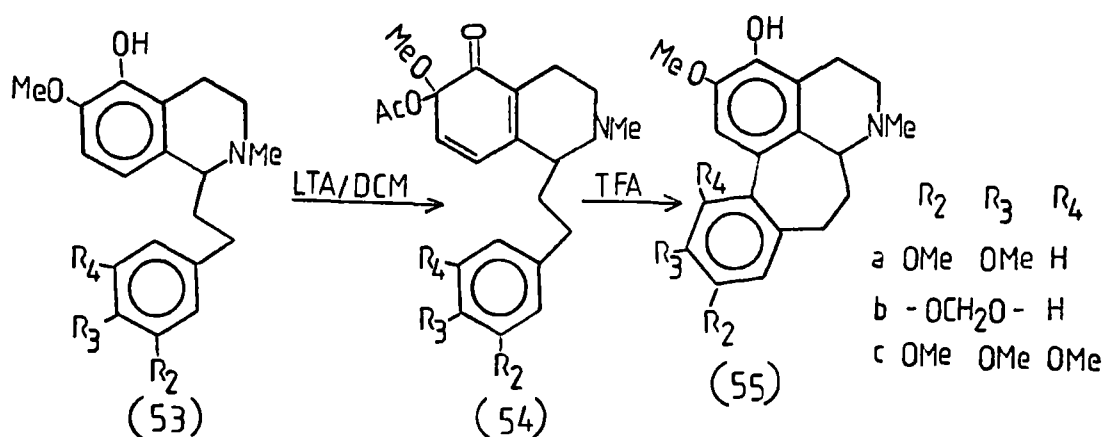
favoured with the methylenedioxy group as the substituent, where despite the use of a weaker acid, no product other than a homoaporphine was formed.

Since in the earlier work on the *p*-quinol acetates of the 1-phenethylisoquinolines only homoaporphines were formed where homomorphinanes and homoisopavines (C_4 - C_6 , ring closure) were also expected, Hara carried out¹³⁴ the reaction with C_8 blocked with a chlorine atom to minimize ring closure competition at C_8 . Thus, treatment of (49i), (49j) and (49k) with trifluoroacetic acid afforded the homomorphinane (51), homoisopavine (52) along with the homoaporphine-type products (38) (Scheme 16, route C; Table 7). Scheme 17 illustrates the suggested mechanisms for the reaction.



Scheme 17

Very recently, Hara reported¹³⁵ a successful preparation of the first 3-hydroxyhomoaporphines (55a), (55b), and (55c) from the *o*-quinol acetates (54a), (54b), and (54c) in very high yields, 91, 87, and 90 percent respectively (Scheme 18). In contrast to the trifluoroacetic acid treatment of *p*-quinol acetates, *o*-quinol acetates, produced from (53) by oxidation with lead tetraacetate, formed only one kind of product, (55).



Scheme 18

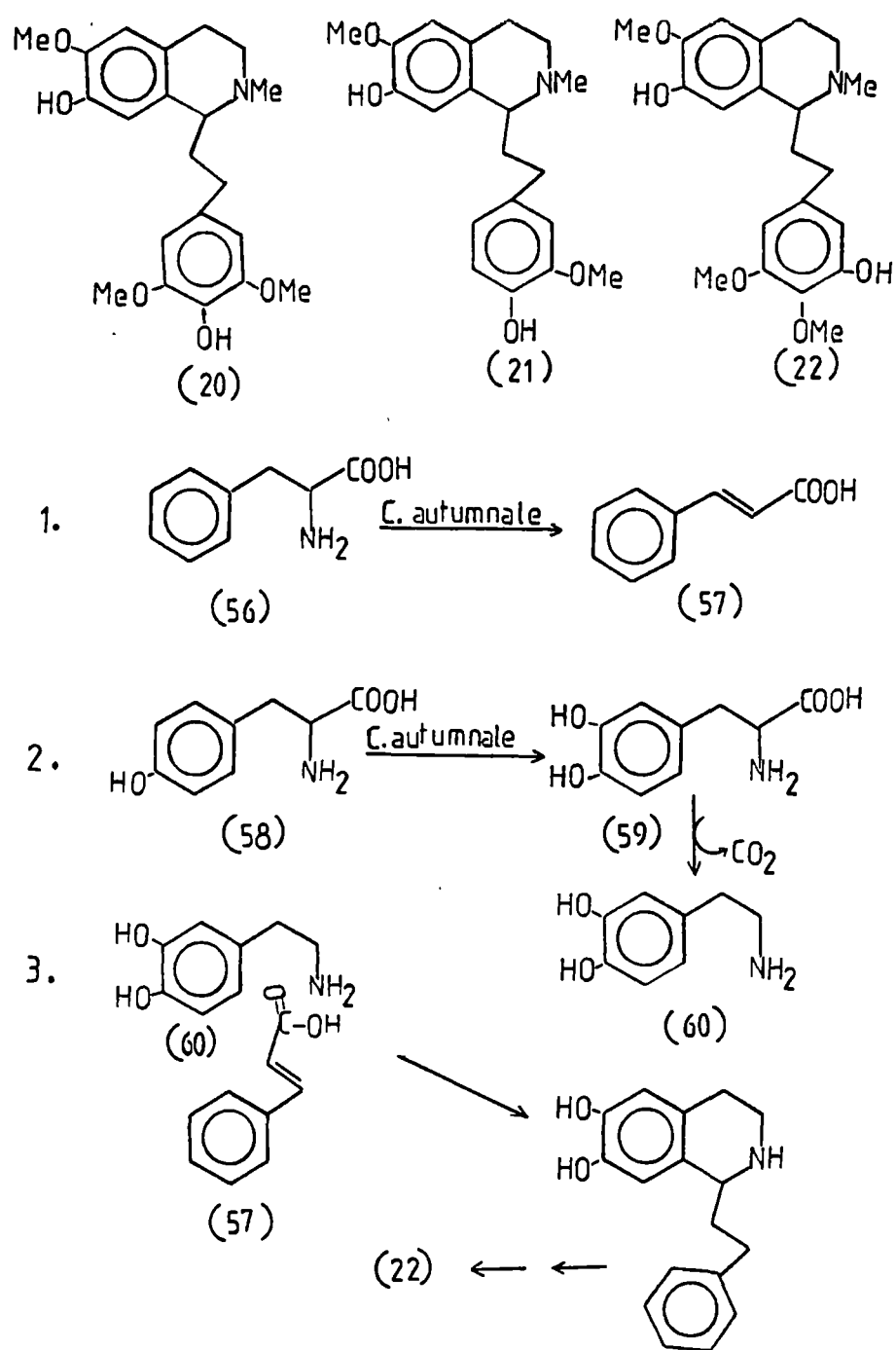
2.4 Biosynthesis of Homoaporphines

Battersby's biogenetic scheme for the homoaporphine alkaloids was designed¹³⁷ mainly by comparison with the biosynthetic pathway of the analogous benzylisoquinoline alkaloids. That is, the homoaporphines may be biosynthesized by direct oxidative coupling or by way of a homoproaporphine intermediate. This latter possibility is backed up by the co-existence⁹⁰ of the homoaporphines kreysigine, multifloramine, and floramultine with a homoproaporphine, kreysiginone, in Kreysigia multiflora, and from known experimental results.^{55,90} To obtain this biosynthetic information, Battersby administered¹³⁷ the ¹⁴C-labelled diphenolic 1-phenethylisoquinolines (20), (21), and (22) to Kreysigia

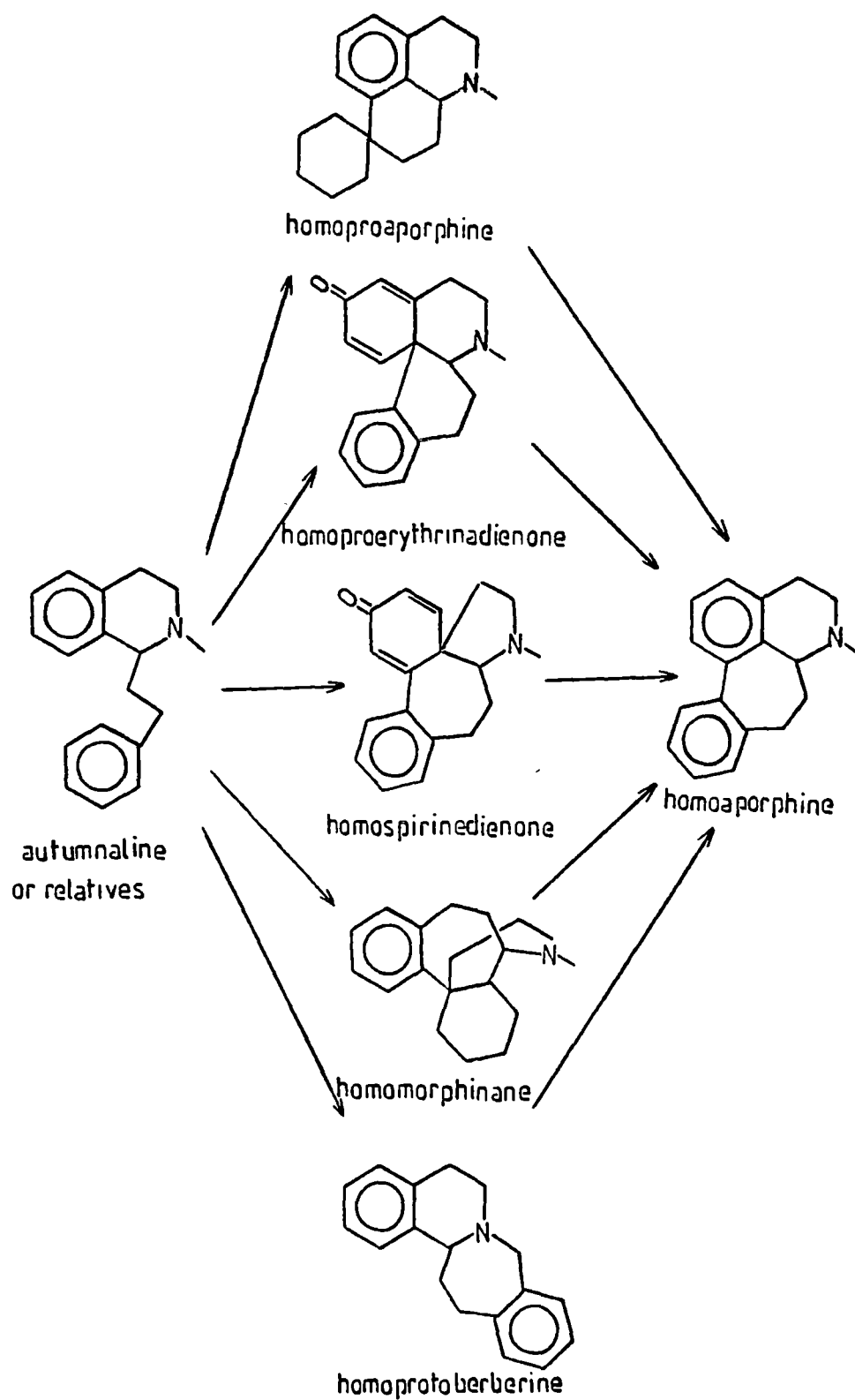
multiflora shoots. After allowing two weeks for incorporation, the alkaloids were extracted, purified, methylated and analyzed by chemical degradation. The percentage incorporation for each of (20), (21), and (22) was found to be 0.04, 0.21, and 1.6 percent respectively. The highest incorporation of autumnaline (22) supported in turn a direct coupling biosynthetic pathway. The alkaloid (21) was presumed to be incorporated by way of autumnaline as in the biosynthesis¹³⁸ of colchicine.

Autumnaline in turn is biosynthesized^{139,140,149} presumably from tyrosine (58) and phenylalanine (56) by way of dopamine (60) and cinnamic acid (57) (Scheme 19). Recently, Makosza established¹⁴¹ that an aldehyde and not an acid condenses with dopamine to form (S)-norlaudanisine. Picking up from this point, Herbert and Kragg also established¹⁴¹ that autumnaline is derived from cinnamic acid by way of cinnamaldehyde.

Although the same alkaloid may occur in different plant species, the biochemical reactions which lead to its formation are not necessarily the same. That other biosynthetic routes to homoporphines such as routes a,b,c,d, and e (Scheme 20) exist, is quite certain. The dienone intermediates such as the homoproaporphines and the homoproerythrinadienones in routes a and b, are analogous^{42,128,142} to those in the established routes to the aporphine alkaloids. That is, they undergo dienone-phenol or dienol-benzene rearrangement to form the homoaporphine skeleton. The possibility of route a is strongly supported by a number of diphenolic as well as monophenolic oxidative coupling experiments on 1-phenethylisoquinoline systems (Section 2.3). On the other hand, the homoproerythrinadienone intermediate was observed only



Scheme 19



Scheme 20

in diphenolic¹¹⁴ and in a non-phenolic¹⁴³ oxidative coupling experiments. In the same non-phenolic experiment, a homoneo-spirinedienone-type intermediate, the proposed intermediate in route c, was presumed to rearrange to a homoproerythrinadienone thence to a homoaporphine.

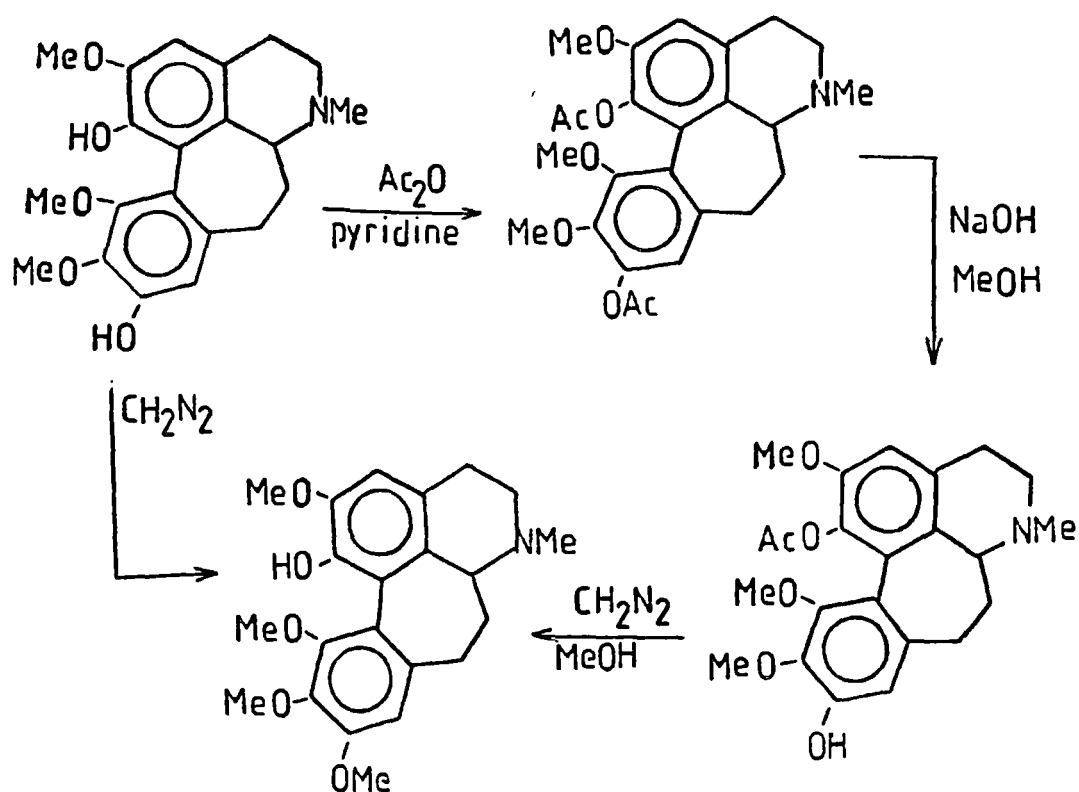
The results of Hara's experiments¹³³ on *p*-quinol acetates suggest that a homopromorphinan system can also rearrange to a homoaporphine-type product, thus there is a possibility that this rearrangement can also take place in plants. There has been no experimental results to support the conversion of a homoprotoberberine to a homoaporphine skeleton. Its protoberberine analogues have however been proposed¹²⁸ as possible precursors to the aporphine alkaloids. The homoprotoberberine possibility, together with the other proposed homoaporphine biosynthetic pathways all need further exploration and study.

2.5 Chemical and Physiological Properties

There have been no reports on the chemical behaviour of the homoaporphine alkaloids except those involved in the preparation of homoaporphine derivatives to confirm a proposed structure. Reactions undertaken^{52,120} include O-methylation, O-acetylation, O-demethylation and O-deacetylation. Scheme 20¹ shows some of these transformations in the case of floramultine (14) to Kreysigine (38d) directly or by way of (17) and (61). The direct transformation of (14) to (38d) shows a selective methylation in favour of the less hindered hydroxy group.

No study has been reported on the physiological activity of the homoaporphine alkaloids. It would however be of interest

to evaluate their activity as their structures are very closely related to those of the aporphine alkaloids. The latter class of alkaloids is known^{42,59,128} for their wide range of physiological activities, for example, thalicarpine and many other aporphines are known to exhibit antifungal or antibacterial activities. Apomorphine has emetic as well as hypnotic properties. A mild sedative, diuretic, and antiparasitic activity from boldine and an anti-tussive effect of glaucine have been established. An anti-parkinsonian activity is associated with some aporphines such as oliveroline.

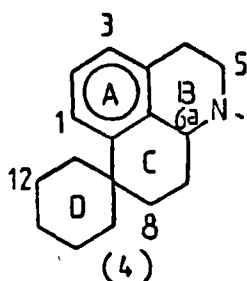
Scheme 20¹

3. C-HOMOPROAPORPHINE ALKALOIDS

3.1 Structure and Spectroscopic Properties

3.1.1 The Structure of C-Homoproaporphines

Like the C-homoaporphines, the C-homoproaporphine alkaloids have a C-17 tetracyclic skeleton (4) based on a C_8-C_1 , coupling of a 1-phenethylisoquinoline alkaloid.



Different types of homoproaporphines arise mainly from the nature of the substituents attached and the oxidation state of ring D. Three types of homoproaporphines may be identified based on ring D. Those in which ring D is a cyclohexadienone, a cyclohexenone, or a cyclohexanol system. Ring D cannot be aromatic. In systems with cyclohexadienone ring, the substituents in the dienone ring can be oriented cis- or trans- position to the hydrogen atom at C_{6a} . If the D-ring is a cyclohexenone, the double bond as well as the substituents on them are oriented either as cis- or trans- to C_{6a} hydrogen.

In all types of C-homoproaporphines, C_{6a} and the spiro centre C_{8a} assume either an S or an R configuration. Carbons 1 and 2 are always substituted with methoxy or hydroxy groups. Substitution may also be observed in carbons 9,10,11,12, and 13. Carbon 11 is generally ketonic or alcoholic. The nitrogen atom in ring B is generally tertiary, with a methyl substituent.

Some quaternary homoproaporphines exist however (Table 1 Part D). Two homoproaporphines, regelinone (75a) and isoregelinone (75b) possessing a carbonyl functional group in the C-ring have been isolated (Scheme 24, page 70).

In cases where C_1 is hydroxyl-substituted, and in the presence of a double bond at C_{12} and C_{13} , a cyclic hemiacetal may be formed; further transformation to a cyclic methyl acetal may also occur.

3.1.2 Ultraviolet and Infrared Spectra

The ultraviolet absorption peaks³⁶ of the C-homoproaporphines are very similar to those of the proaporphine alkaloids. Two primary aromatic bands centred at 235 nm and at 215 nm, and a secondary aromatic band at 285 nm, are generally observed. The absorption band of the dienone chromophore of ring D generally coincides with the first aromatic band at 235 nm. These three bands may be shifted depending on the degree of saturation and the character of the substituents in ring D. In a cyclohexadienone system, the absence or the presence of methoxyl substituents beta to the carbonyl carbon does not in general shift the absorption band. However, a methoxy substituent alpha to the carbonyl carbon brings about a bathochromic shift in the dienone band (235 nm). This shift is even greater when both the carbon atoms alpha to the carbonyl carbon are methoxyl-substituted.

When ring D is a cyclohexanone, the bands at 235 and 285 nm are prominent. The presence of a methoxy substituent does not in any way affect the absorption bands. For the cyclohexanol system, the aromatic band is shifted hypsochromically. The

disappearance of the dienone band at 235 nm is notable (Table 9).

The i.r. spectra of this class of compounds identify the presence of the unsaturated centers, hydroxyl groups, secondary amines, and carbonyl groups.

3.1.3 Circular Dichroism, Optical Rotatory Dispersion and X-ray Structural Studies

As mentioned in Section 2.2.2, the sign of the Cotton effect of a compound is a good measure of its absolute configuration. The simple isoquinoline alkaloid derivative with a chiral centre at C_1 are known to exhibit¹⁴⁵ two characteristic Cotton effects at approximately 240 and 280 nm. The sign of the two Cotton effects of the R-series is negative and is reversed for the S-series. This holds true^{59,149} for the 1-phenethylisoquinoline compounds. However, Snatzke and Wollenberg found¹⁴⁷ that for the proaporphine alkaloids, the sign of the Cotton effect is not only a function of the absolute configuration at C_1 but also of the character of the spirane ring. Kametani noted⁵⁸ the same in the 1-phenethylisoquinoline system and the homoproaporphines with a cyclohexadienone ring. While (C_1R)-isoquinoline (32) gave two negative Cotton effects, the sign of the second Cotton effect (230 nm) of the oxidation product of (32), the homoproaporphine (62), was inverted and shifted bathochromically from 230 to 264 nm (Figure 2). The sign of the first Cotton effect was not changed but was shifted from 280 to 300 nm.

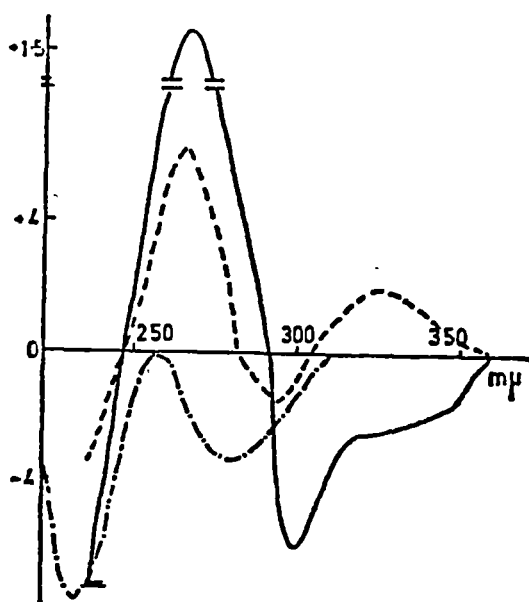
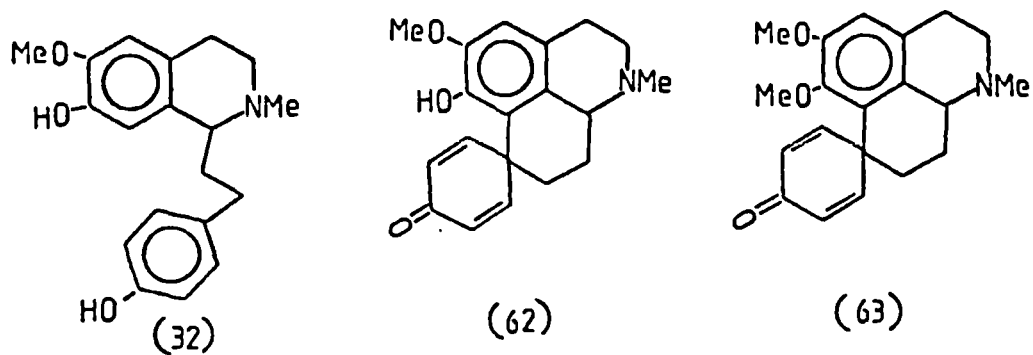


Figure 2. C.d. Curves for Solutions in Dioxan of (62) (____), (63) (-----), and (32) (____.)

A third Cotton effect was observed at 325 nm. This was attributed to the $n \rightarrow \pi^*$ transitions of the dienone carbonyl chromophore. The sign of this Cotton effect was found to be dependent on the conformation of ring D. Figure 3 shows three possible conformations of ring D. From the n.m.r. studies, conformation c was ruled out. Conformations a and b are such that the carbonyl oxygen is oriented closer to the C_1 substituent by folding. Between the two conformations, conformation b satisfies the observed negative Cotton effect at 325 nm. That is,

by proximity, the C₁-hydroxyl group interacts with the double bond in ring D bringing about a decrease in the electron density at the double bond, thus the negative sign. This was confirmed by the inversion of the sign of the Cotton effect at 325 nm in the isoquinoline (63). In this case, the interaction of the C₁-methoxyl group with the double bond in ring D favours an increase in the double bond electron density.

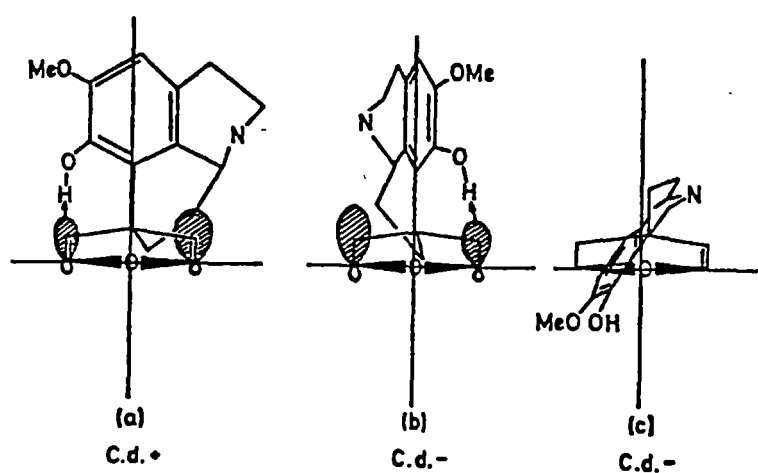


Figure 3. Possible Conformations of (62)

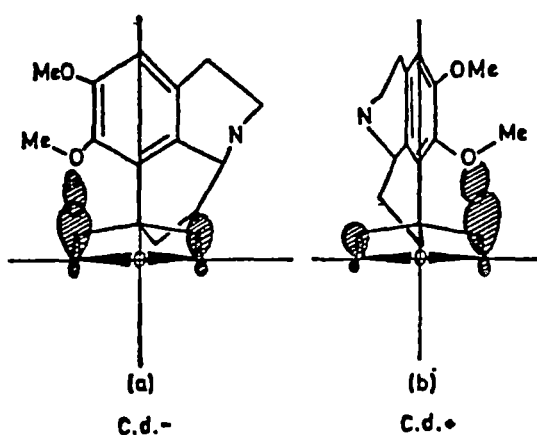


Figure 4. Possible Conformations of (63)

The absolute configuration of $C_{6a}R-C_{8a}S-(-)$ -bulbocodine (69b) was deduced⁵⁷ by comparison with the cotton effects of the proaporphine linearisine (65) (Figure 5). However, x-ray structural study on 11,12-dehydroglaziovine, a system with a cyclohexenone D-ring like bulbocodine (69b) and linearisine (65), showed that its absolute configuration is opposite to the configuration derived from its c.d. data which was interpreted in a similar approach as in the interpretation of the c.d. data of linearisine. Consequently, the absolute configuration assignment for bulbocodine need to be reconsidered. The absolute configuration of some of the reduced homoproaporphines such as $C_{6a}R-C_{8a}S-(-)$ -kesselringine (70b)^{49,145} (Figure 6) were deduced by comparison with the c.d. data of some reduced aporphines.

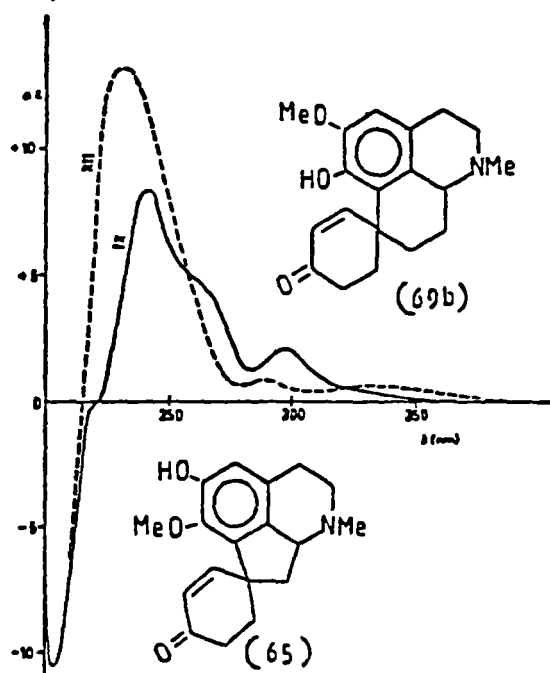


Figure 5. C.d. Curves in Ethanol of $(-)$ -Bulbocodine (69b)(____) and $(+)$ -linearisin (65) (----)

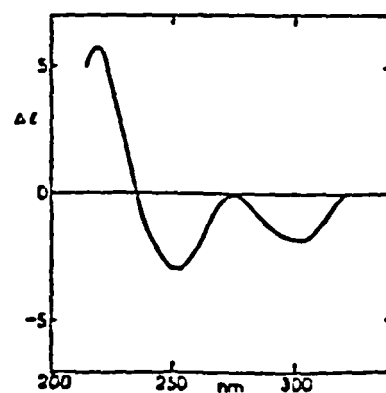
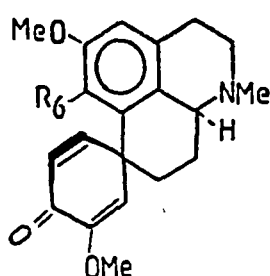


Figure 6. C.d. Curve of Kesselringine (70b) in Ethanol

Thus far, the x-ray crystallographic method of analysis presents a more reliable picture of the absolute configuration of a compound. However, the only homoproaporphine derivative analyzed^{132,133} using this method was the diastereomer (76b) of kreysiginone, as its application requires special techniques. The crystal data of the methiodide of (66) is given in Table 8 and its ORTEP diagram in Figure 7.



(76b) $R_6 = \text{OH}$

(66) $R_6 = \text{OAc}$

Table 8

X-ray Crystallographic Data of the Methiodide of (66)

compound: $\text{C}_{23}\text{H}_{28}\text{NO}_5\text{I}$	
mol. wt.: 525.38	$a=20.435(10) \text{ \AA}$
m.p.: 255.256°C	$b=11.899(5) \text{ \AA}$
crystal pattern: monoclinic	$c=21.379(10) \text{ \AA}$
space group: C_2/C	$\beta=113.741(1)^\circ$
$z=8$	$U=4758 \text{ \AA}^3$
$D_x=1.467 \text{ g cm}^{-3}$	final $R=0.05$ for 2852 reflections

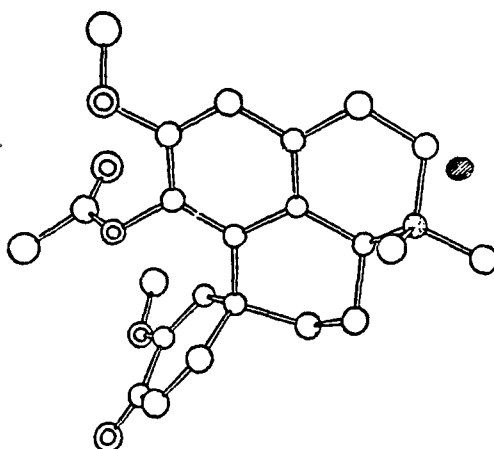


Figure 7. ORTEP diagram of (66)

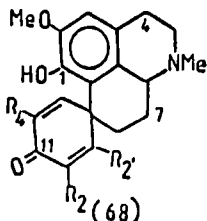
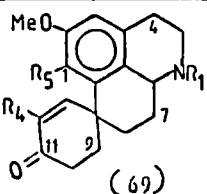
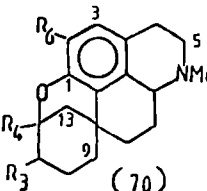
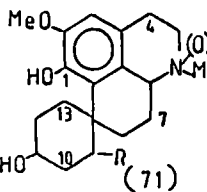
3.1.4 Nuclear Magnetic Resonance

The ^1H n.m.r. spectra of the homoproaporphines are very much similar^{42,59} to those of the proaporphines. The proton signals of the aromatic methoxy, aliphatic methoxy, N-methyl, olefinic and aromatic groups are indistinguishable for both classes of alkaloids (Table 9). Like the proaporphine alkaloids with a dienone system, the protons beta to the keto group in the spirane ring are always found at a lower field than the alpha protons. Likewise, the C_{13} protons are found at a lower field relative to the C_9 protons, reflecting the relative stereochemistry of the spirane ring. As in the other isoquinoline systems, a nuclear Overhauser effect is also observed between the C_2 -methoxy and the C_3 protons.

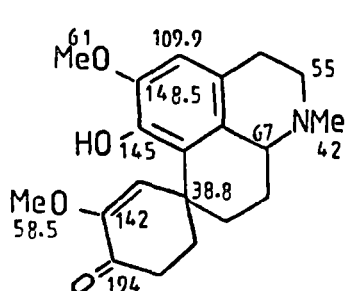
The ^{13}C n.m.r. spectra of luteidine⁴⁰ (69d), regeline⁴⁸ (70a), and regecoline¹⁵⁶ (72) have been determined. The signals such as those of C_3 (110-114 ppm), C_5 (53-55 ppm), N-methyl (42-60 ppm) and the methoxyl carbons (55-60 ppm) are also indistinguishable from those of the proaporphines^{148,189}. However,

Table 9

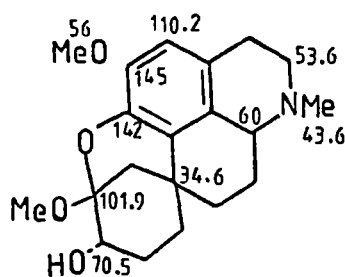
U.V. Data and ^1H N.m.r. Chemical Shifts (δ) of Some Homoproaporphines and their Derivatives

 (68)	SUBSTITUENTS			U.V. DATA		¹ H NMR (δ)								REF.	
	R ²	R ₂	R ₃	λ _{max} (nm)		N-Me	C ₂ -OMe	C ₁₀ , C ₁₂ -OMe	C ₃ -H	C ₉ -H	C ₁₂ -H	C ₁₃ -H			
	a	H	OMe	H	243	286	2.45	3.76	3.54	6.52	5.95	6.28	6.83	34,36	
	b	H	OMe	H	244	289	2.41	3.74	3.59	6.51	5.77	6.20	6.96	34,90	
	c	H	OMe	OMe	-	-	2.40	3.71	3.57, 3.50	6.46	5.78	-	6.46	58	
	d	OMe	H	H	235	285	2.40	3.75		6.51	-	5.46	6.11	152	
	e	H	H	H	235	290	2.45	3.80		6.56	6.95	6.70	7.2	150,151	
 (69)		R ₁	R ₄	R ₅											
	a	2Me	H	OH	210	285	2.56, 2.90	3.97		6.34		5.81	6.82	38	
	b	Me	H	OH	232	285	2.38	3.78		6.45		5.85	6.82	35,36,37	
	c	Me	H	OMe	227	276 288	2.34	3.75		6.48		-	-	39,91	
	d	Me	OMe	OH	228	272	2.37	3.78	3.51	6.46			5.79	40	
 (70)		R ₃	R ₄	R ₆											
	a	-- OH	OMe	OMe	216	225 290	2.36	3.74	3.34	6.42				48	
	b	-- OH	OMe	OH		231 293	2.37		3.38	6.51				50	
	c	-- OH	OMe	OH	210	285	2.35		3.25	6.47				8	
	d	OH	OMe	OMe		243 293	2.36	3.74	3.32	6.44				51	
	e	- OH	- OH	OH	219	290	3.1			6.40				52	
	f	- OH	- OH	OMe	218	290	2.32	3.73		6.40				53	
	g	OH	-- OH	OMe	216	290		3.80		6.50				54	
 (71)		n	R												
	a	O	OMe			2.42	3.82	3.22						152	
	b	1	H	216	290	3.40	3.80		6.50					44	
	c	O	H	216	287	2.34	3.75		6.48					43	

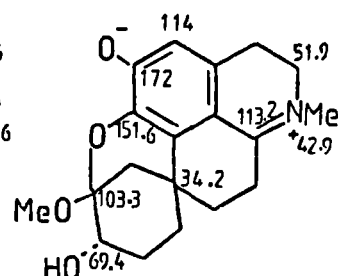
the signal at the spiro centre is found at a lower field for the proaporphines (46-53 ppm) relative to those of the homoproaporphines (34-39 ppm).



(69d)



(70a)



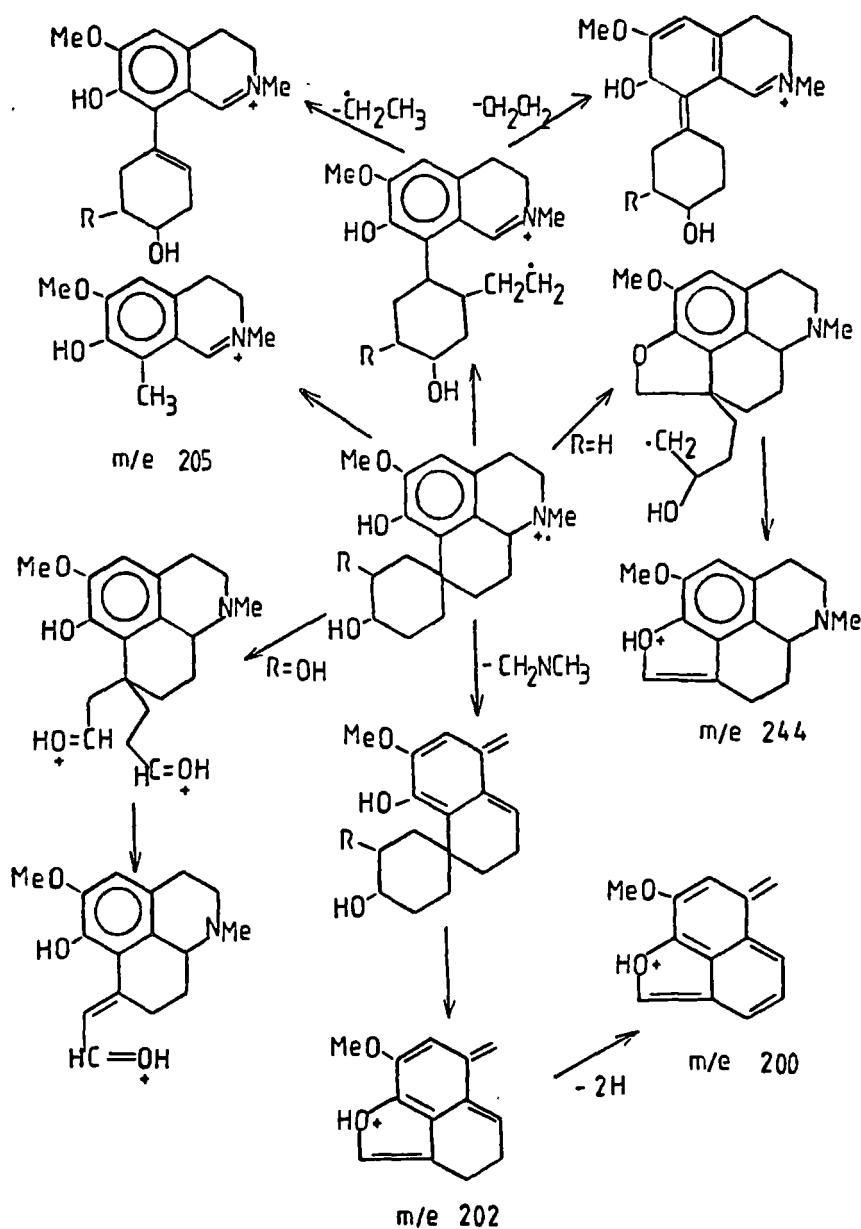
(72)

3.1.5 Mass Spectroscopy

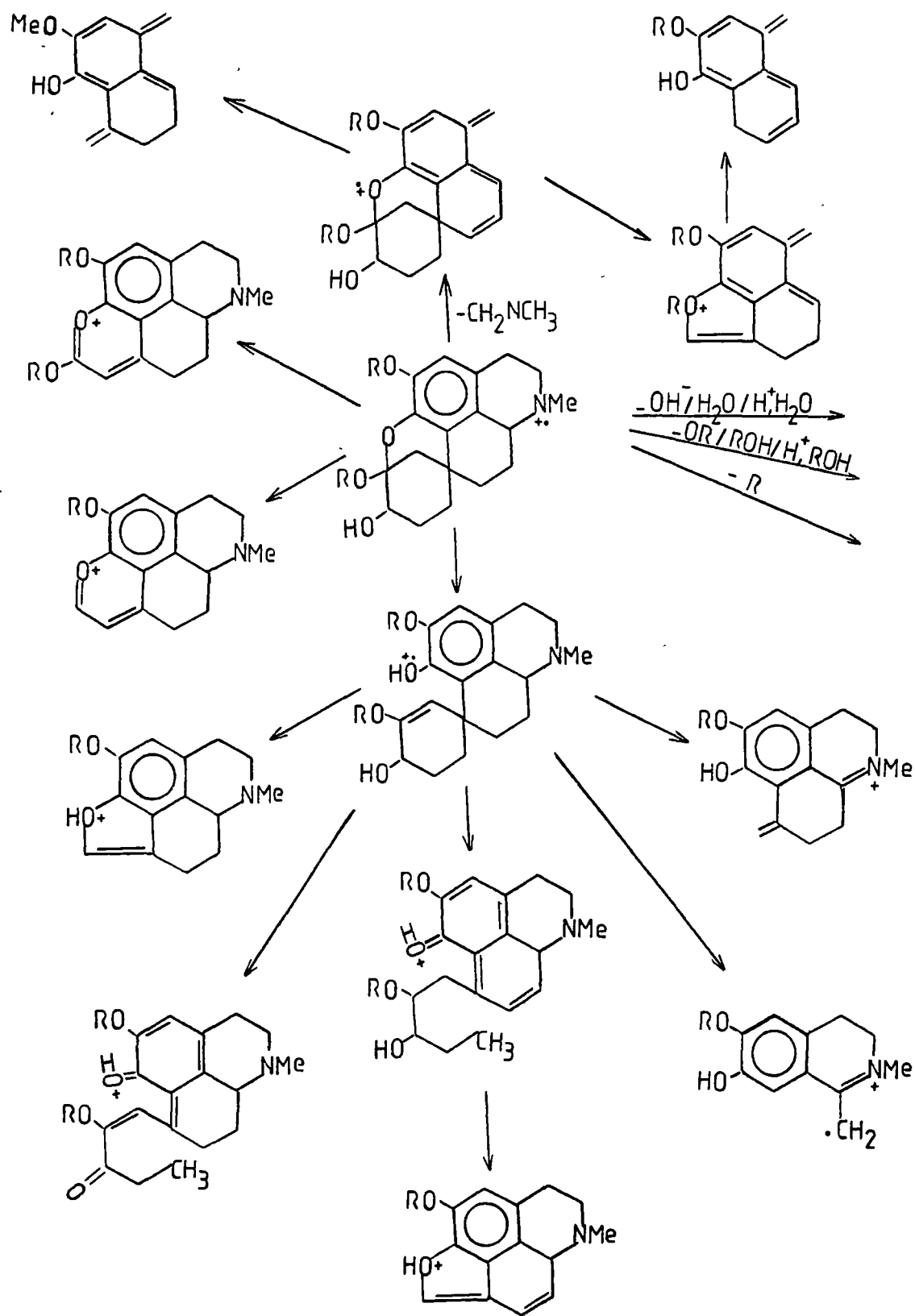
One of the principal modes of fission of the homoproaporphine alkaloids is the loss of a hydrogen atom ($M^{+} - 1$) to form a carbon-nitrogen double bond. This generally constitutes the base peak of the spectrum and distinguishes this class of alkaloids from the proaporphine series. That is, with most of the proaporphines¹⁵³, the molecular ion forms the base peak. This $M^{+} - 1$ base peak is not observed in the homoproaporphines when ring B is oxidized.

The loss of a methyl-methyleneimine moiety ($CH_2=NCH_3$) also characterizes the mass spectra of the homoproaporphines. The secondary fragmentations largely vary according to the character of the spirane ring. That is, the degree of saturation, the type of substituents and the stereochemistry of the molecule. Thus, like the proaporphine alkaloids¹⁵³, a series of small peaks is observed in the higher mass range of the spectrum due to the

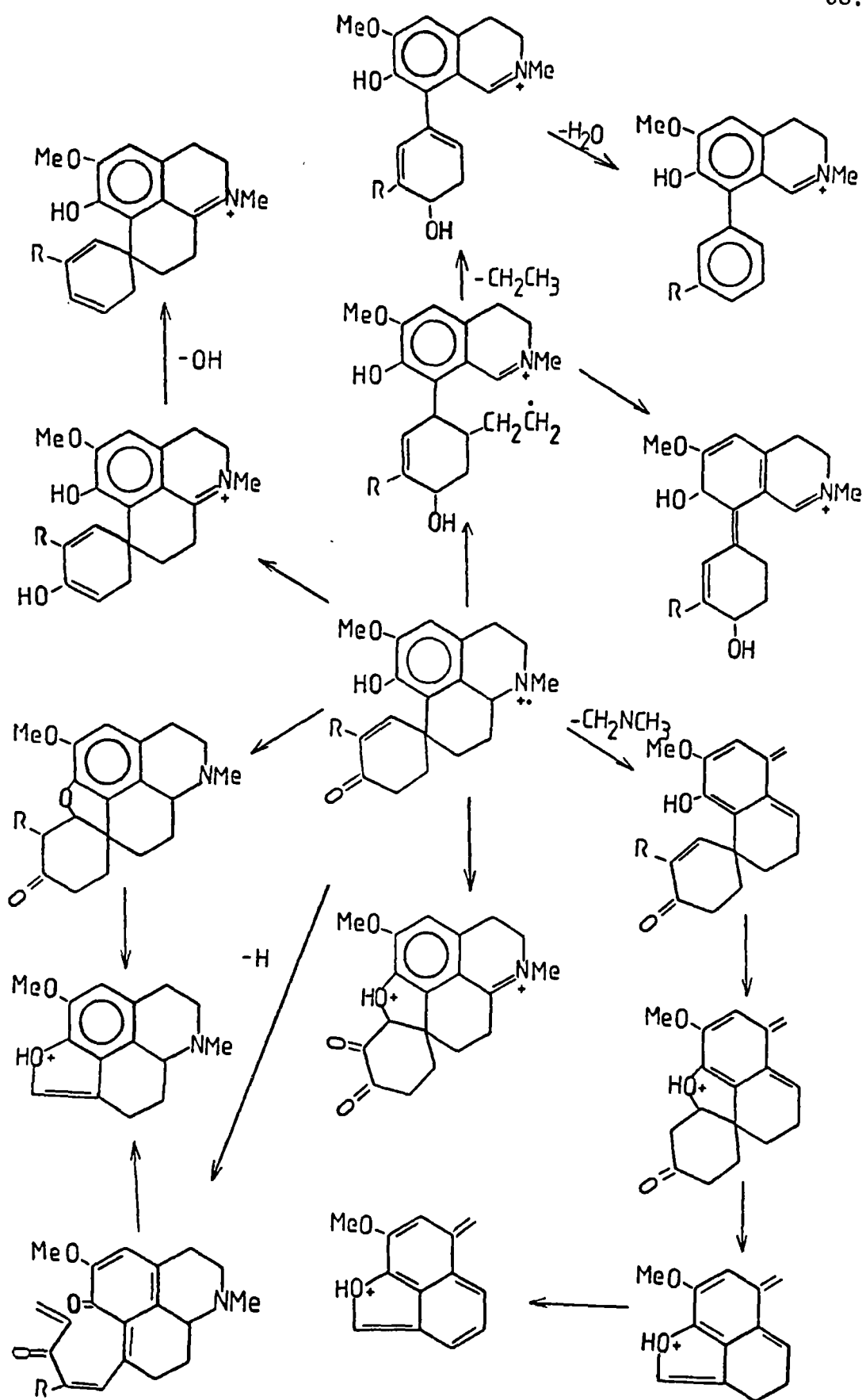
degradation of the spirane ring. These fragmentations are accompanied by the loss of fragments like hydroxyl, water, methyl, methoxyl and methanol and, in the presence of a ketonic functional group, a carbon monoxide moiety. Schemes 21, 22, and 23 illustrate^{49,108,154,155} the fragmentation of some of the homoproaporphines with different skeletal modifications. The degradation pattern of the homoproaporphines with a cyclohexadienone ring has been described⁵ in Kametani's review.



Scheme 21



Scheme 22

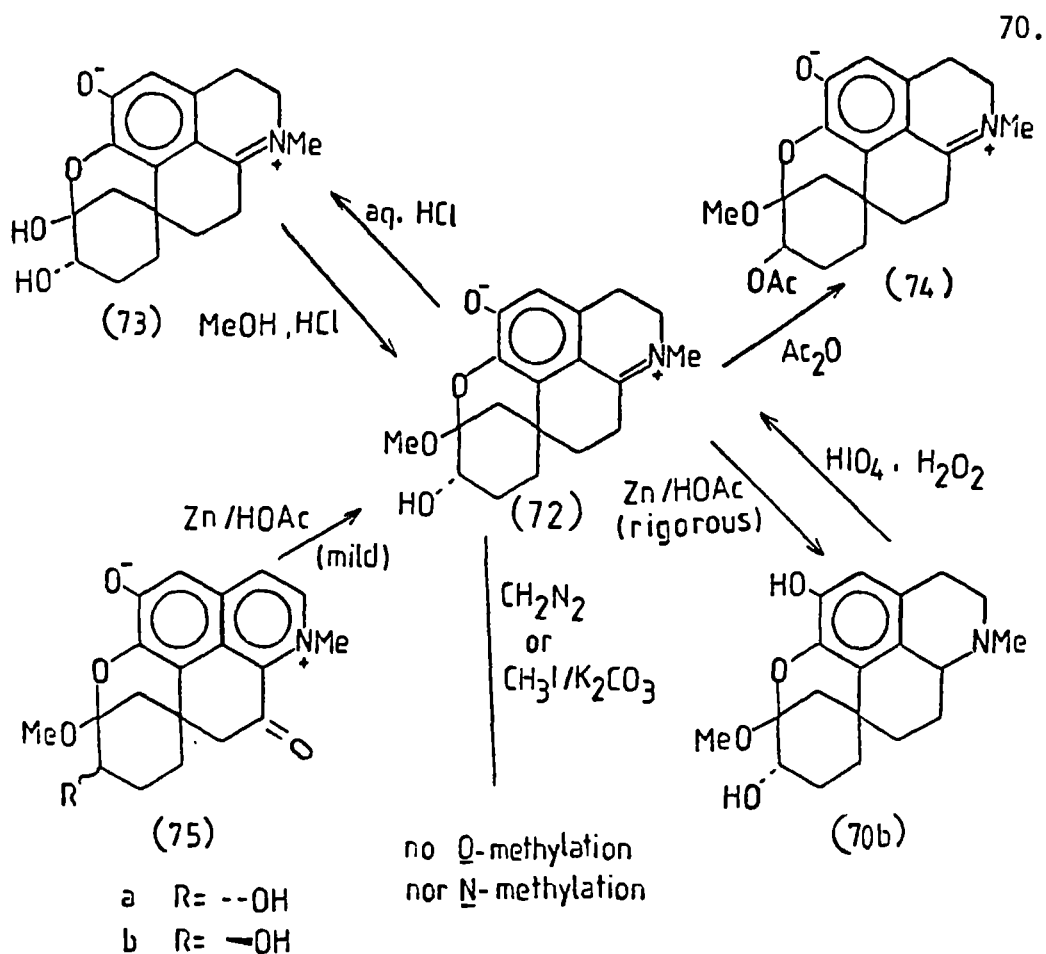


Scheme 23

3.1.6 The Structure of Regecoline

The alkaloid regecoline (72), isolated from the phenolic base extract of Colchicum kesselringii, has recently been characterized.¹⁵⁶ The ultraviolet spectrum of this base showed maximum wavelengths at 253, 312, and 355 nm suggesting a more extensive conjugation of the π system. From the infrared spectrum, a hydroxyl group, an aromatic system and a C=N group were identified at 3500, 1600, and 1638 cm^{-1} respectively. The ^1H n.m.r. spectrum revealed a non-aromatic methoxyl group at δ 3.43 and a quaternary N-methyl group at δ 3.59. The methoxy signal was differentiated from the N-methyl signal by comparison with the ^1H n.m.r. signal of the product of the hydrolysis, (73), of regecoline (Scheme 24). The aromatic proton signal at δ 6.84 (H_3) and the non-aromatic proton signal at δ 4.25 (H_{11}) are very similar to those of kesselringine (70b), regelinone (75a) and regelamine (70f).

The mass spectral data is also indicative of an oxidized ring B, as the molecular ion ($\text{M}^{+\cdot}$ 329) formed the base peak (94%), instead of the characteristic $\text{M}^{+\cdot}-1$ base peak of the homoproaporphines. The observed higher mass range fragments m/e 314 ($\text{M}^{+\cdot}-15$), 310 ($\text{M}^{+\cdot}-19$), 298 ($\text{M}^{+\cdot}-31$), 296 ($\text{M}^{+\cdot}-33$), 270 ($\text{M}^{+\cdot}-59$) and 228 further support a homoproaporphine skeleton. The ^{13}C n.m.r. data compared very closely with that of regeline (70a) except for the signal at 113 ppm, which was assigned to the olefinic C_{6a} .



Scheme 24

The proposed structure (72) was confirmed by chemical transformations (Scheme 24). The lack of reactivity of regecoline (72) towards the reagents diazomethane and methyl iodide confirmed that nitrogen is indeed in a quaternary state, and that no aromatic hydroxyl group is present in the molecule.

3.2 Synthesis of the C-Homoproorphines

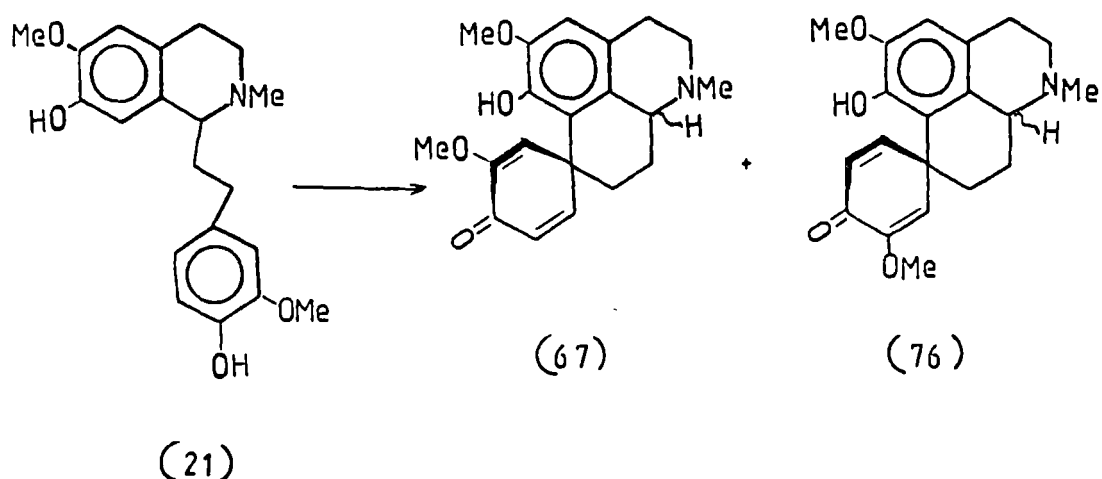
3.2.1 Phenolic Oxidation

3.2.1.1 Diphenolic Oxidation

Most of the methods employed in the synthesis of the homoporphines also apply to the synthesis of the homoproorphines. Based on the results of some studies described in the last review⁵ and in this section, it appears that under the same reaction

conditions, the nature of the substituents on the nitrogen and on the C-ring of the 1-phenethylisoquinoline precursor, greatly influences the type of the coupling product. An ortho- or para-hydroxyl substituent in the C-ring generally favours the formation of a homoproaporphine-type product. A variation in the substitution pattern in the A-ring does not seem to alter this preference.

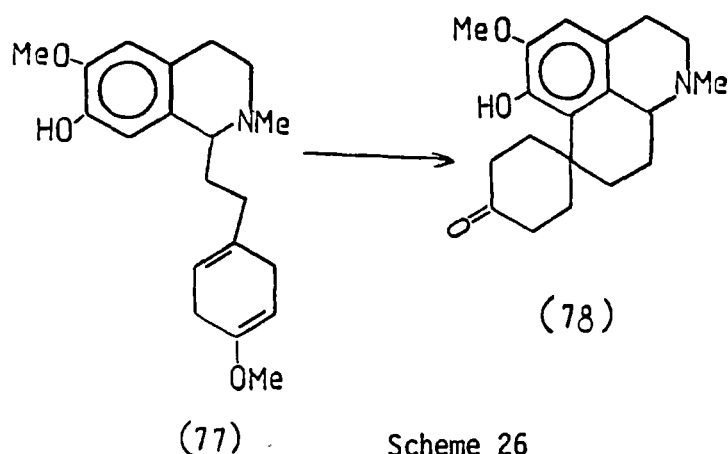
The first homoproaporphine system was synthesized independently by Battersby⁹⁰ and by Kametani⁵ even before an alkaloid of this type was isolated from plant sources. Both groups identified the homoproaporphine diastereomers (67) and (76) as the oxidation products of (21), using the one-electron oxidizing agents, ferric chloride and potassium ferricyanide (Scheme 25). The use of cuprous chloride and molecular oxygen in pyridine¹¹² to oxidize the hydrochloride salt of (21) also gave the products (67) and (76). Likewise, the oxidation of the N-oxide of (21) with cuprous chloride in methanol¹²² afforded the same products along with the reduced N-oxide, (21).



Scheme 25

3.2.1.2 Monophenolic Oxidation

The oxidation of the phenethylisoquinoline (77) to a homoproaporphine system (78) has been reported¹⁵⁸ (Scheme 26). Scheme 12 (Section 2.3.1.2) illustrates the formation of the homoaporphine (39) from the oxidation of some 1-phenethylisoquinolines using vanadium oxytrifluoride. It must be noted that the monophenolic oxidation products (39a) and (39b) exist¹¹⁶ in only one isomeric form whereas the diphenolic oxidations (Section 3.2.1.1) afforded two diastereomers.



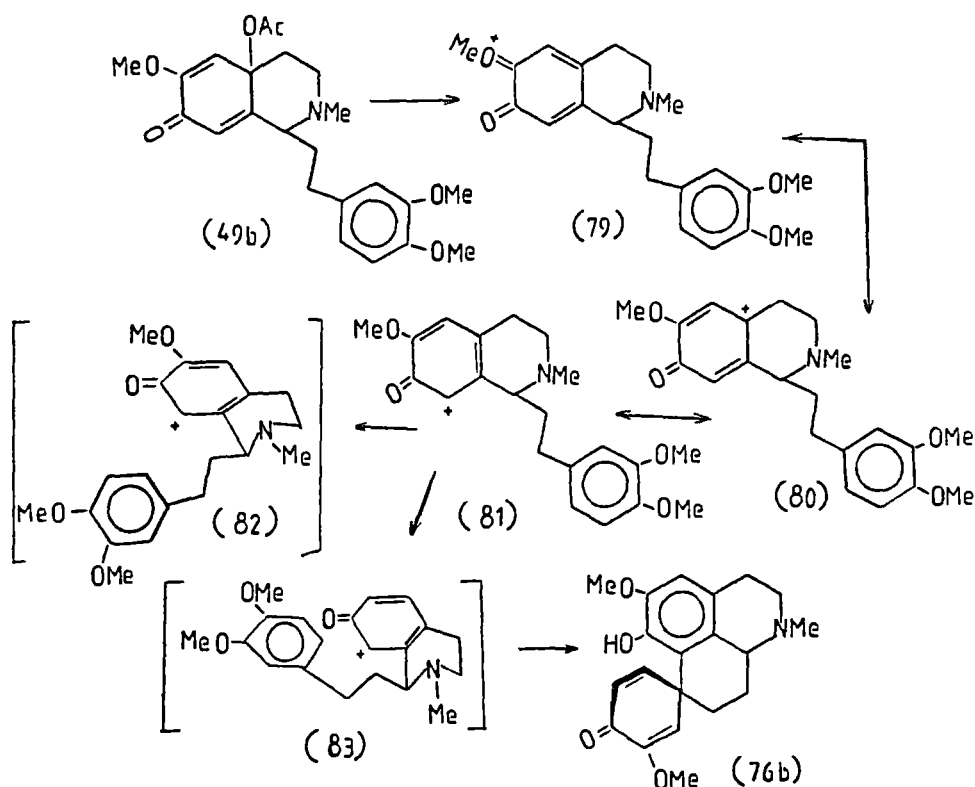
Scheme 26

3.2.2 Direct Cyclization

3.2.2.1 Via P-Quinol Acetates

This method of synthesis has been described in Section 2.3.3.2, where the cyclized products formed were of the homomorphinandienone, homoaporphine, homoisopavine and the homoproaporphine-type. Again, unlike the diphenolic methods of oxidation, the homoproaporphine product (39b) obtained¹³² existed in only one diastereomeric form as confirmed by x-ray crystallographic analysis (Section 3.1.3). The suggested mechanism of this stereospecific cyclization is illustrated in Scheme 27. It has

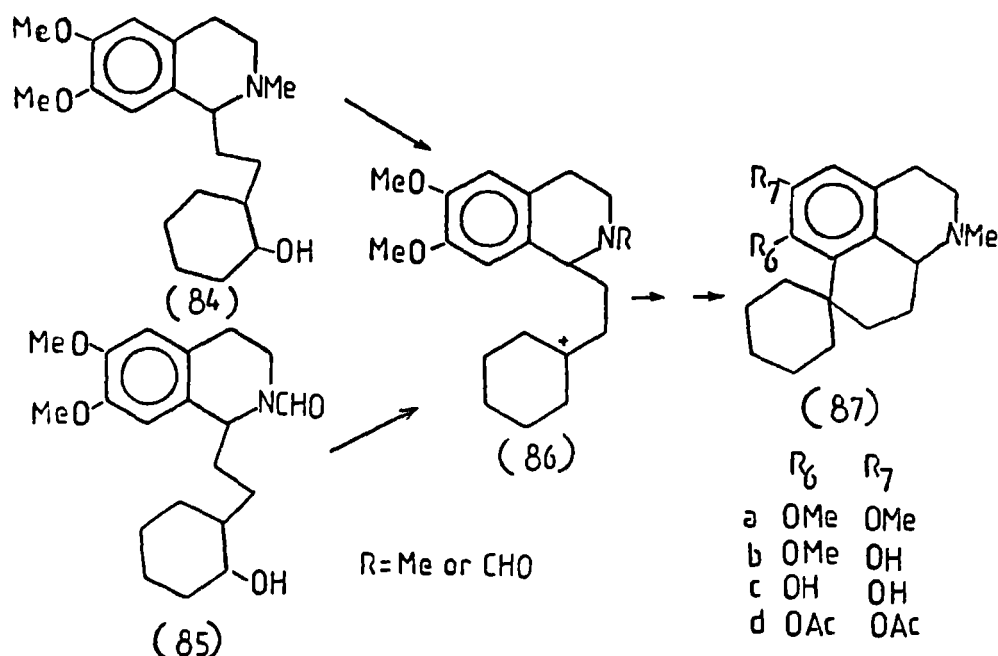
been presumed that the C₆-methoxy group in (49b), assists in the removal of the acetoxy group to form the intermediates (79), (80), and (81). The intermediate (81) in turn can exist in two possible transition states (82) and (83). In this case, a beta attack based on the energetically favoured chair-shaped transition state (83) gives the product (76b), the diastereomer of kreysiginone.



Scheme 27

3.2.2.2 Via Acid Hydrolysis

Treatment of the 1-phenethylisoquinolines (84) and (85) with polyphosphoric acid¹⁵⁷ proceeded by way of a carbocation intermediate (86) to form the reduced homoproaporphine (87) (Scheme 28). The O-demethylation and O-acetylation of (87a) afforded the products (87b), (87c), and (87d).

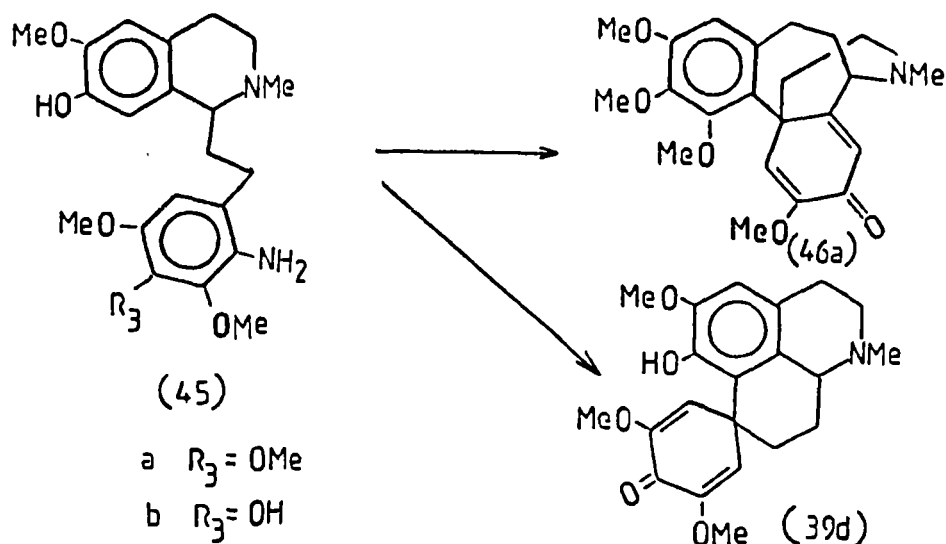


Scheme 28

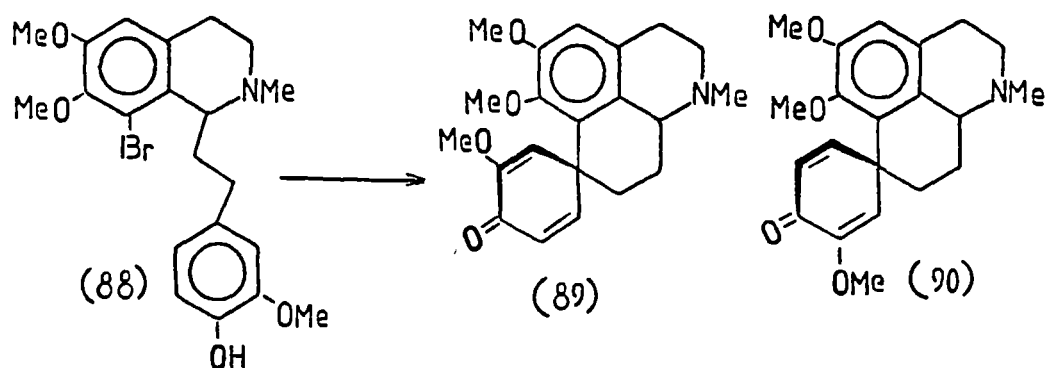
3.2.2.3 Photolytic Cyclization

The photolysis¹⁵⁹ of the diazonium salt of the 1-phenethylisoquinoline (45b) afforded the homoproaporphine (39a) as the sole product (Scheme 29). Under the same reaction conditions, the diazonium salt of (45a) gave a homomorphinandienone-type product (46a). It was deduced from these results that the presence of a hydroxyl substituent in the C-ring played an important role in the ring closure to a homoproaporphine as in the case of the diphenolic oxidation-type reaction.

Homoproaporphines may also be obtained by photolytic cyclodehydrobromination. Thus, irradiation¹⁶⁰ of (88) gave the diastereomeric homoproaporphines (89) and (90) under alkaline conditions (Scheme 30). No further studies in this area of synthesis have been reported since the last review.⁵



Scheme 29



Scheme 30

3.3 Biosynthesis

No tracer studies have actually been conducted to determine the biosynthetic route or routes to the homoproaporphine formation in vitro. However experimental results (Section 3.2) strongly suggest a direct intramolecular coupling of autumnaline or its derivatives, to a homoproaporphine system. Oxygenation could take place at an early stage as on autumnaline, or at a later stage, that is, after the homoproaporphine skeleton has been formed. Like the proaporphine series, and based on the available chemical data, no other possible route to a

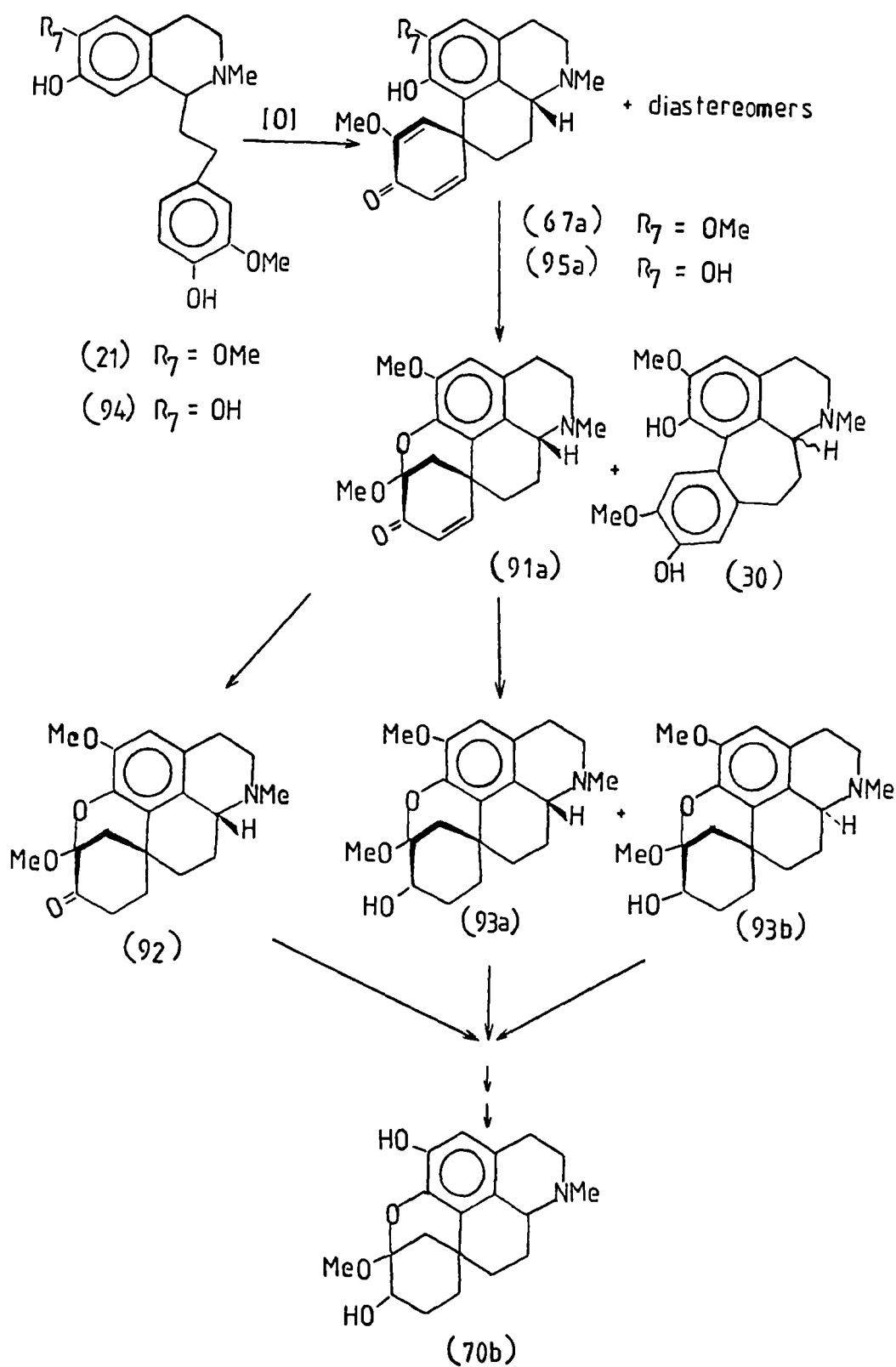
homoproaporphine-type alkaloid could be envisioned.

Two possible routes to the biosynthesis of the reduced homoproaporphine kesselringine (70b) were suggested and reported^{77,162,164} by Kametani (Scheme 31). The first^{77,162} was an extension of their earlier studies^{119,161} on the homoproaporphine kreysiginone (67). When the epimer of kreysiginone (67a) was treated with an acid, a homoproaporphine (91a) was formed along with a homoaporphine (30). The catalytic hydrogenation of (91a) in the presence of palladium on charcoal gave the cyclohexanone (92) as the product, whereas, with Adams' catalyst, two cyclohexanols (93a) and (93b) were formed. Subsequent changes in the oxygenation pattern of any of (92), (93a), or (93b) could lead to the formation of kesselringine (70b). The second route involved the 1-phenethylisoquinoline system (94) as a key intermediate. The oxidation product (95a) of (94) may undergo a series of biochemical reactions parallel to that of kreysiginone (67a) to form (70b).

3.4 Chemical and Physiological Properties

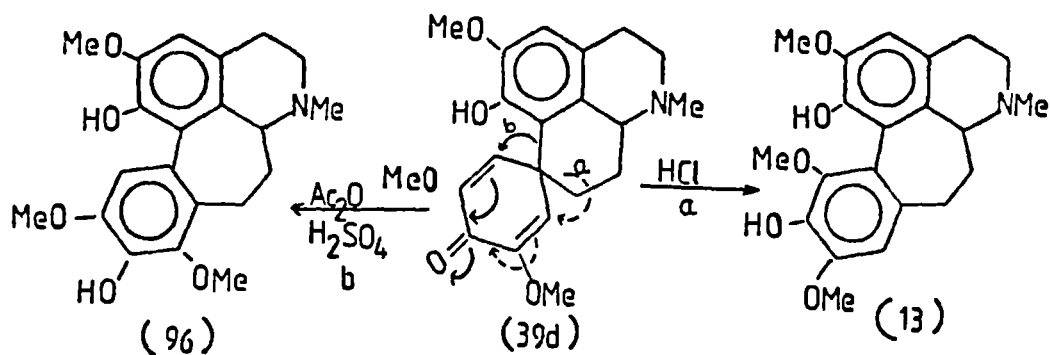
3.4.1 Reactions with Acids

In general, under acid conditions, homoproaporphines undergo a dienone-phenol or dienol-benzene rearrangement to form a homoaporphine-type product (Section 2.3.1.1.2). Two modes by which a dienone-phenol rearrangement can take place¹²⁰ are illustrated in Scheme 32. In the conversion of (39d) to (96), the A-ring migrates from C_{8a} to C₁₃ (route b). The O-acetylation of C₁ decreases the migratory aptitude of the aryl group favouring the migration of the ethylene group to C₉ to form

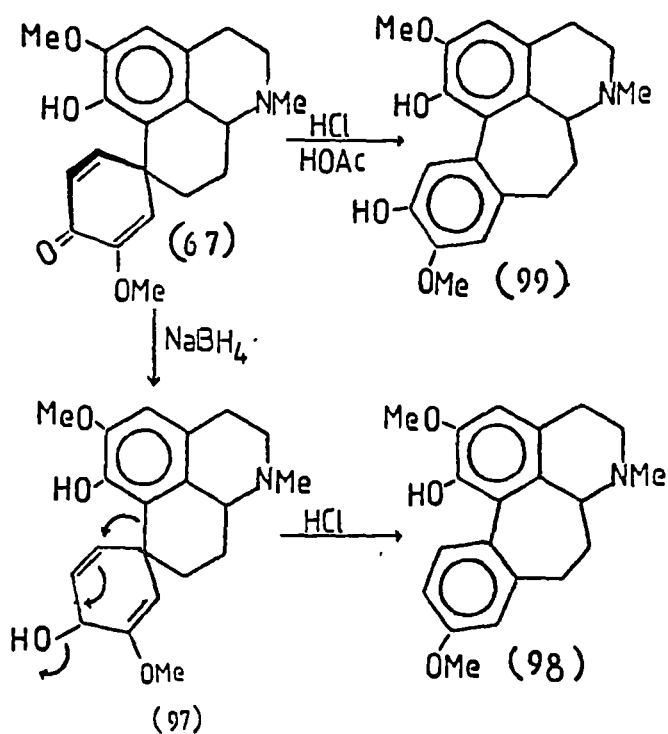


Scheme 31

the homoaporphine (13) (route a). The homoproaporphinols, such as (97) form¹¹⁹ a homoaporphine (98) by dienol-benzene rearrangement (Scheme 33).



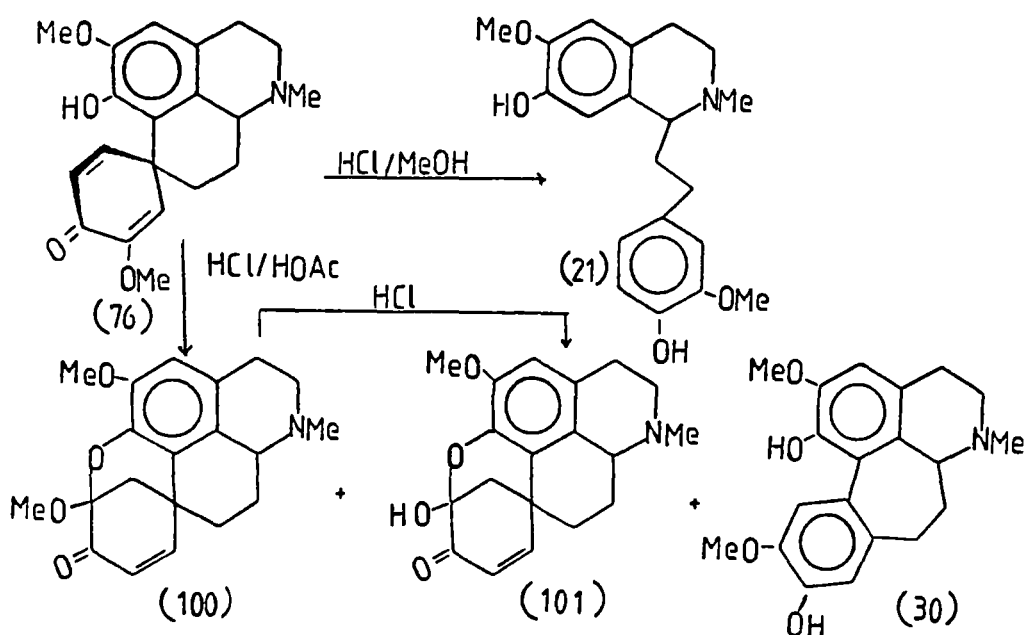
Scheme 32



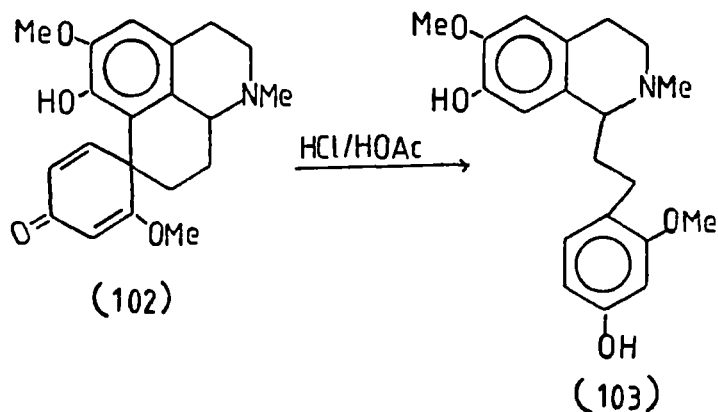
Scheme 33

Not all acid treatment of the homoproaporphines will however proceed to form a homoaporphine system. The reactivity is also a function of the conformation of the system. When the diastereoisomer (76) of (+)-kreysiginone (67) was treated with an

acid¹¹⁹ it rearranged to a homoaporphine (99) (Scheme 33) whereas (67) proceeded⁹⁹ to form a ketal (100) by enol-ether addition, along with the hydrolyzed and rearrangement products (101) and (30), respectively (Scheme 34). For the more rigid systems like (99), acid treatment simply hydrolyzed it to form (101). A homoproaporphine may also ring open in the presence of an acid as in the conversion of (76) to (21),⁹⁹ (Scheme 34), and (102) to (103)¹⁵² (Scheme 35).



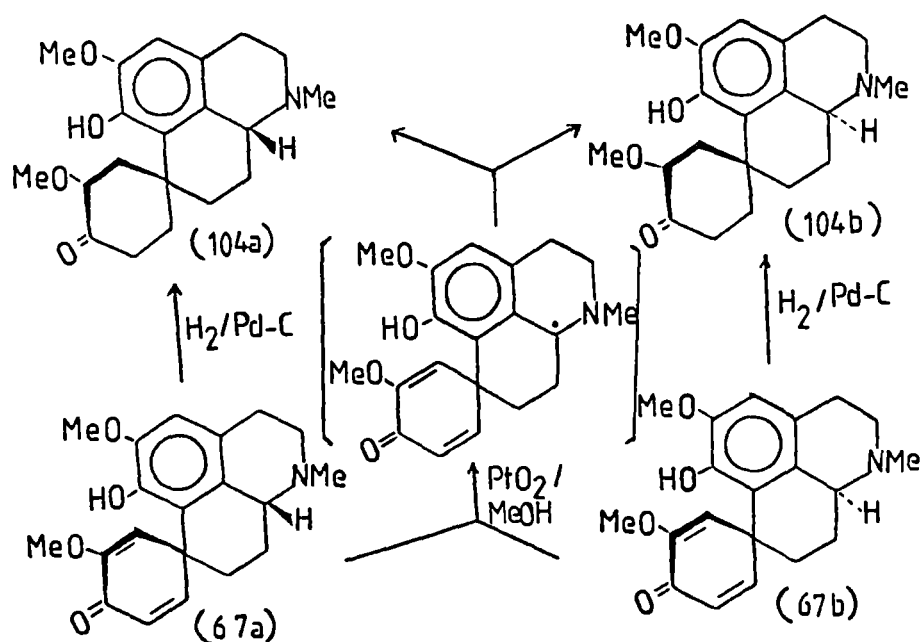
Scheme 34



Scheme 35

3.4.2 Epimerization Reactions

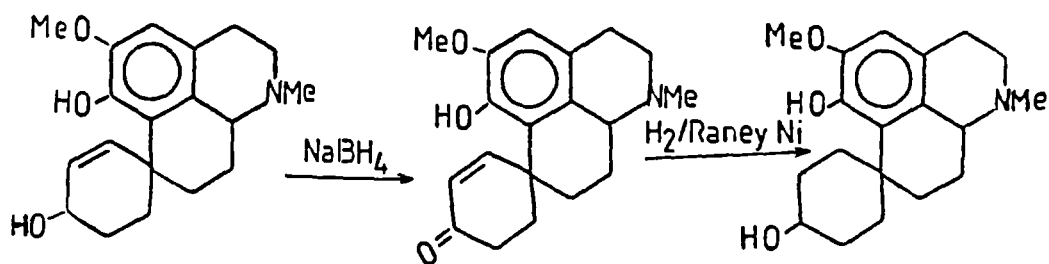
The chiral center of a homoproaporphine at C_{6a} is relatively stable¹⁶³ to the usual acid or base reagents. The catalytic reduction¹⁶¹ of (+)-kreysiginone (67) was the first case of a C_{6a} -epimerization in the homoproaporphine alkaloids (Scheme 36). Each of (67a) and (67b) afforded a racemic mixture of (104a) and (104b) when treated with Adams catalyst. Contrary to these results, the catalytic hydrogenation of each of (67a) and (67b) with palladium on charcoal did not bring about an epimerization at C_{6a} (Scheme 36). The epimerization reaction must be such that the dienones (67a) and (67b) were absorbed on the platinum oxide catalyst, and that H_{6a} was consequently cleaved homolytically to form a radical intermediate. This then could give rise to the epimers. A second case of the epimerization reaction at C_{6a} is illustrated in Scheme 31 (Section 3.3).



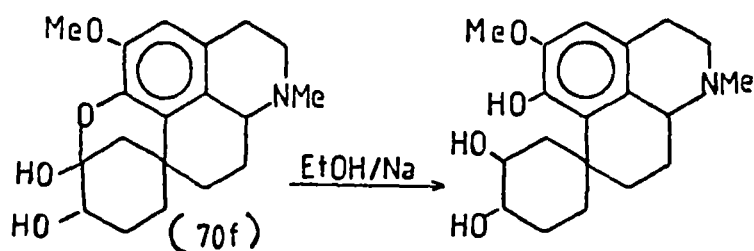
Scheme 36

3.4.3 Oxidation-Reduction Reactions

Oxidation and reduction processes have been applied to some homoproaporphines. This mainly involved the oxidation or reduction of the B- and the D-rings. In Section 3.4.2 a stereospecific and a stereoselective reduction of (+)-kreysiginone has been described. A mild and rigorous reduction of the B-ring of regecoline (72), regelinone (75), and kesselringine (70b), using zinc in acetic acid, and the oxidation of the B-ring of kesselringine (70b) using periodic acid and hydrogen peroxide have been illustrated in Scheme 24 (Section 3.1.6). In other cases, sodium borohydride^{53,119,152,163} (Scheme 33,37) and Raney nickel⁵³ (Scheme 37) were used to carry out the reduction of the D-ring of some homoproaporphines. A ketal ring system as in regelamine (70f) was ring opened⁵³ by reduction with sodium metal (Scheme 38).



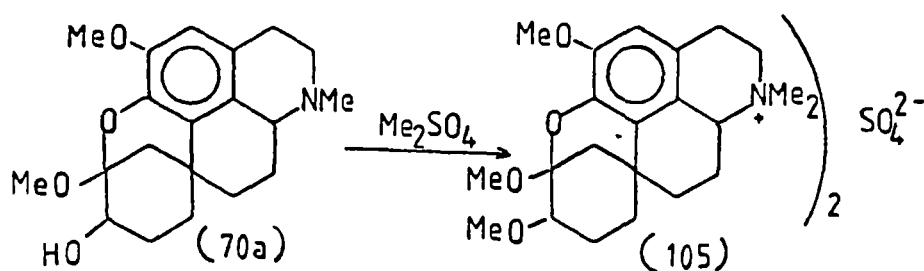
Scheme 37



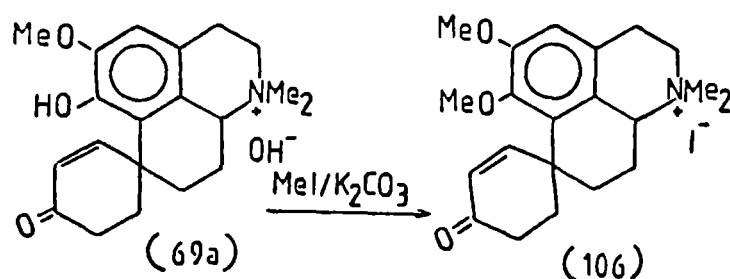
Scheme 38

3.4.4 O-Alkylation, N-Alkylation and O-Dealkylation Reactions

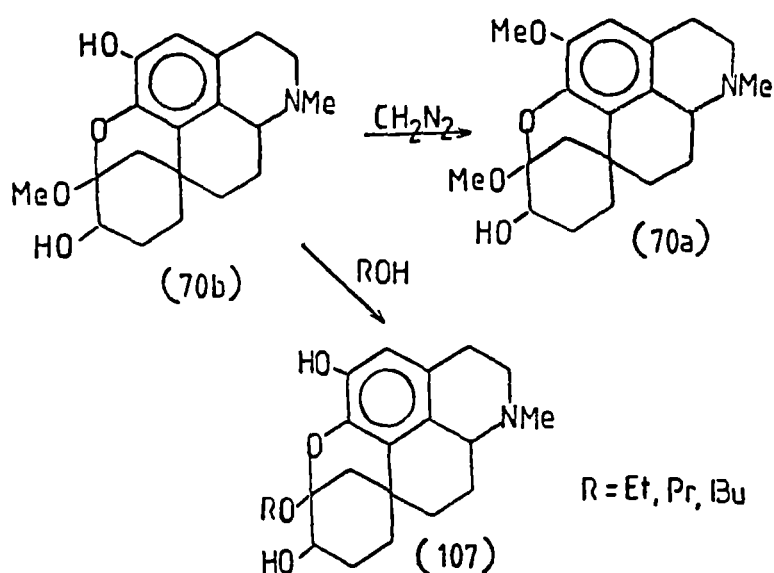
The presence of a tertiary nitrogen, as well as aromatic and aliphatic hydroxyl groups in the homoproaporphines allows the formation of N- and O-alkyl derivatives which are useful in elucidating structure. The reaction of regeline (70a) with dimethyl sulfate gave rise⁴⁸ to the N- and O-methylated product (105) (Scheme 39). Jolantine (69a) afforded³⁸ an O-methylated product, (106), with methyl iodide (Scheme 40). The O-methyl derivative (70a) of kesselringine was formed⁴⁹ from the reaction of kesselringine with diazomethane implying the presence of only one aromatic hydroxyl group (Scheme 41). Kesselringine also underwent⁵⁰ transesterification with some alcohols (R=Et, Pr, Bu) giving rise to the derivatives of (107) (Scheme 41). The O-demethylation of some homoproaporphines by hydrolysis with hydrochloric acid is illustrated in Schemes 24 and 34, Sections 3.1.6 and 3.4.1 respectively.



Scheme 39



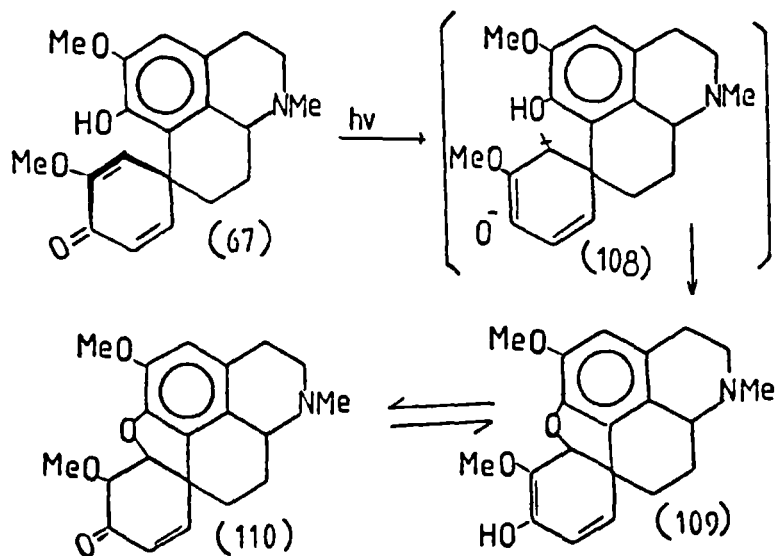
Scheme 40



Scheme 41

3.4.5 Photolytic Reaction

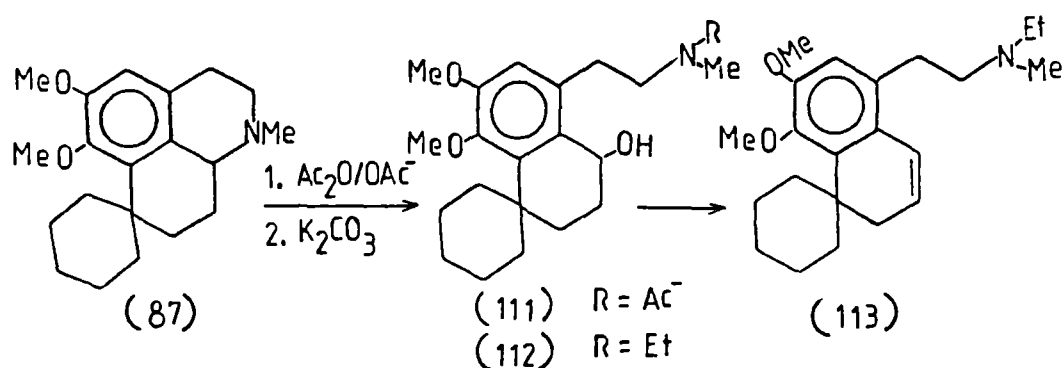
The irradiation¹⁶⁷ of kreysiginone (67) in the absence of an acid gave a product with an ether bridge. Presumably, the irradiation caused an electron distribution in the dienone moiety as in (108). An intramolecular 1,4-Michael-type addition in (108) could give rise to (109) which exists in equilibrium with its tautomer (110) (Scheme 42).



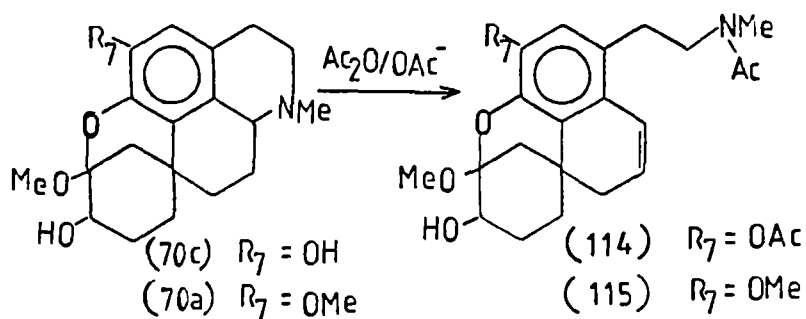
Scheme 42

3.4.6 Ring Cleavage

The N-acetylation¹⁵⁷ of (87) with acetic anhydride brought about a B-ring opening to form (111) which was consequently reduced with lithium aluminum hydride to give the product (112) (Scheme 43). Dehydration of (112) afforded the product (113). Similar results were obtained when luteine¹⁶⁵ (70c) and regeline⁴⁸ (70a) were treated with acetic anhydride (Scheme 44). Luteine was also O-acetylated as in (114).



Scheme 43



Scheme 44

3.4.7 Physiological Properties

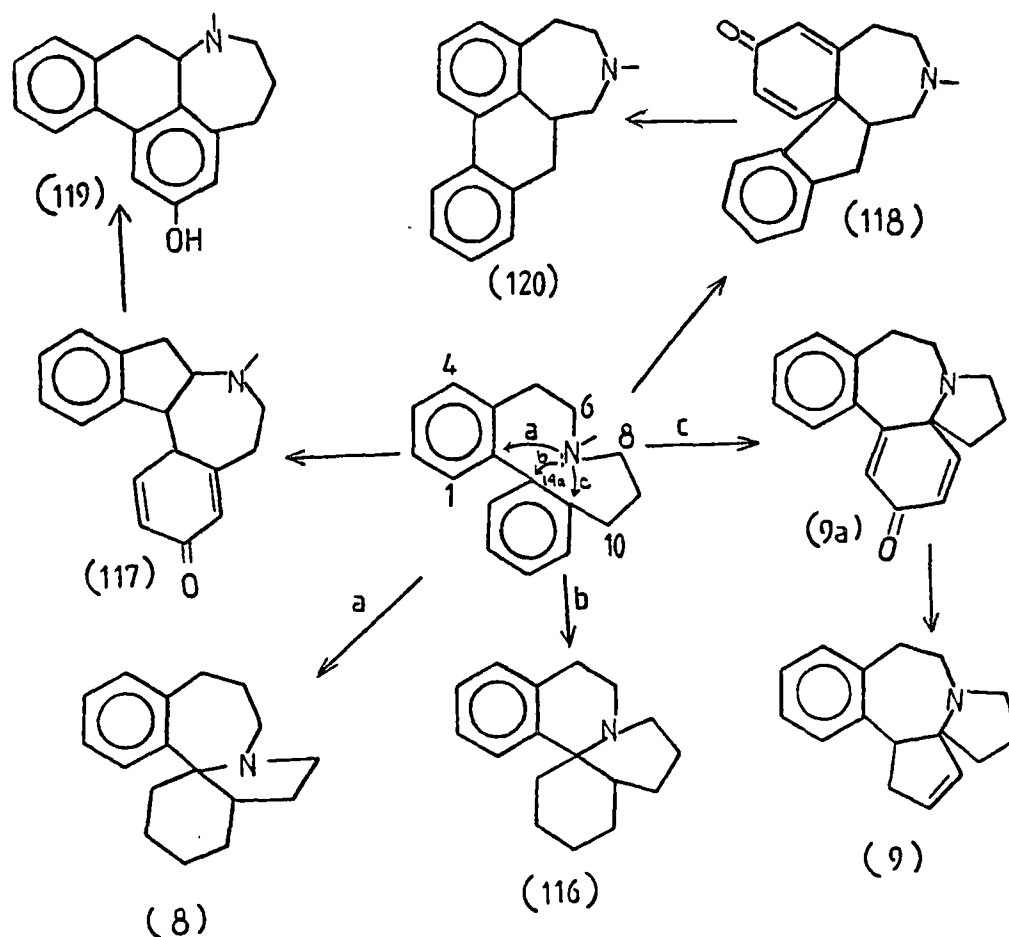
Work in this area has been reported^{168,169} by Kametani. The first report¹⁶⁸ mentioned the homoproaporphines being useful as drugs acting on the central nervous system. The second report¹⁶⁹ identified some homoproaporphine systems as possessing analgesic and sedative properties.

4. HYPOTHETICAL PHENETHYLISOQUINOLINE-DERIVED ALKALOIDS

4.1 Possible Skeletons

Most of the phenethylisoquinoline-derived alkaloids which have been isolated from a limited number of plant sources are analogous to the benzyloisoquinoline-derived alkaloids in structure and in biogenesis (Section 1.1). Their isolation supports the fact that although the seven to ten-membered ring systems are generally less favoured in vitro, plant systems are capable of overcoming this limitation. Considering this, and the diversity of the benzyloisoquinoline series of alkaloids isolated from a wide range of plant species, one can reasonably anticipate the isolation of some new alkaloids based on the phenethylisoquinoline precursors. These new skeletons may be homologous to some benzyloisoquinoline alkaloids or entirely new ones as unique colchicine and cephalotaxine-type skeletons have been isolated (Section 1.1). These skeletons may arise from oxidation and condensation processes, which are enhanced in the phenethylisoquinoline series compared with the benzyloisoquinoline series of alkaloids as the additional carbon in the aliphatic bridge induces more pronounced deformations, hence increased transannular interactions. This is exemplified in the dibenz[d,f]azecine skeleton (7) (Scheme 45). These condensation processes may involve an intramolecular Michael-type addition of a nitrogen atom to an aromatic centre as in the formation of the B-homoerythrina skeleton (8) (route a) and cephalotaxine-type precursor (9a), which undergoes ring contraction to form the cephalotaxine skeleton (9). Both the B-homoerythrina and the cephalotaxine alkaloids have already been synthesized and

isolated⁹³ from plants (Table 1). The same reaction is involved in the formation of a D-homoerythrina (116) skeleton (route b) which was synthesized by Marino and Samanen¹³⁶ but has not yet been isolated naturally.

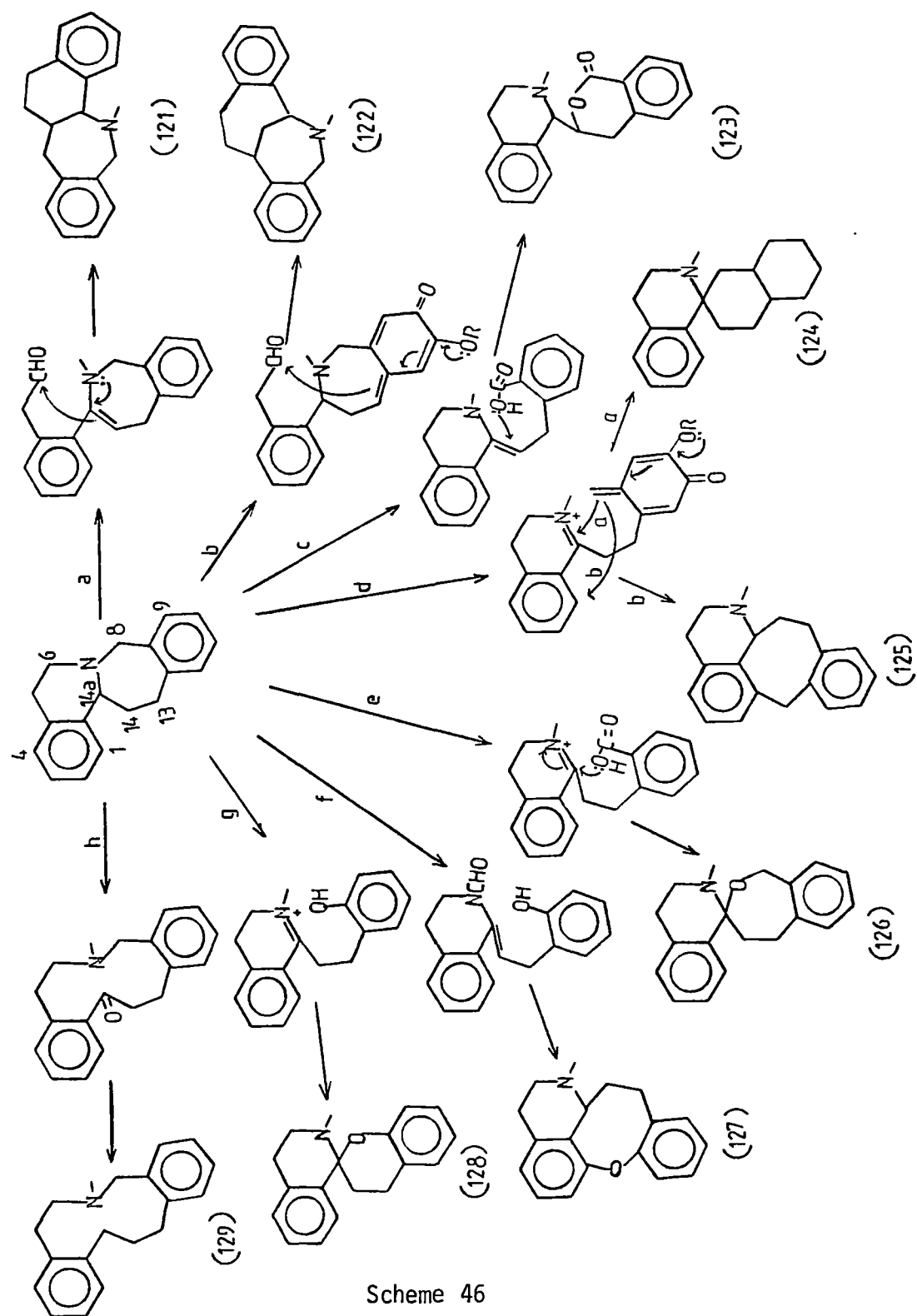


Scheme 45

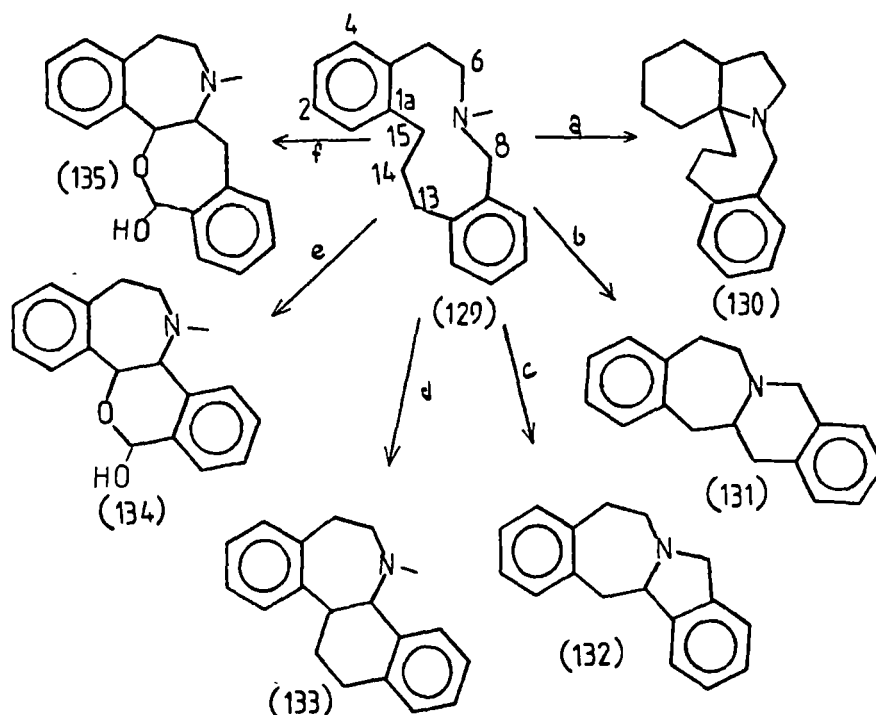
In other cases, the aliphatic centres of the B- and the C-rings may be oxidized to an olefinic or carbonyl carbon. This could lead to different modes of intramolecular nucleophilic addition reactions. Thus, the skeletons (117) and (118) may be formed by a hydroxy or methoxy-assisted nucleophilic addition of

the aromatic carbon, C_{14a} , to the olefinic carbon, C_6 or C_9 , respectively. Both (117) and (118) may rearrange to (119) and (120) skeletons.

As the protopine and the berbine-type alkaloids are important precursors in the biosynthesis of a wide variety of benzylisoquinoline alkaloids^{59,170}, it is also highly probable that homoprotoberberines (Scheme 46) and homoprotopines (Scheme 47) may play the same role in the phenethylisoquinoline series of alkaloids. Alkaloids possessing a homobenzophenanthridine skeleton, (121) or (122), may be biosynthesized by the oxidative cleavage of the C_6 -N bond of (10), and a subsequent C_6 - C_{14} (route a) or C_6 - C_{13} (route b) ring closure (Scheme 46). The cleavage of the N- C_8 bond of (10) may give rise to a number of new skeletons. A homophthalideisoquinoline skeleton (123) may be formed from the condensation of C_{14} with oxygen atom of the oxidized C_8 (route c). A C_8 - C_{14a} ring closure may also take place to form a spirophenethylisoquinoline-type product (124) (route d). Otherwise, a hydroxy or methoxy-assisted nucleophilic addition of C_{14a} to the olefinic C_8 may give rise to the skeleton (125). An alkaloid with the skeleton (126) may be formed from the condensation of a C_8 -oxygen with C_{14a} (route e). As it is possible that protoberberines may serve as precursors in the biosynthesis of the cularine alkaloids,¹⁷¹ the cularine homologue (127) may also be biosynthesized from a homoprotoberberine precursor (10) (route f). A C_{8a} -oxygen may also condense with C_{14a} to form the more stable skeleton (128) (route g). The homoprotopine-type alkaloid (129) may be formed from the oxidative cleavage of the N- C_{14a} bond of (10) (route h).



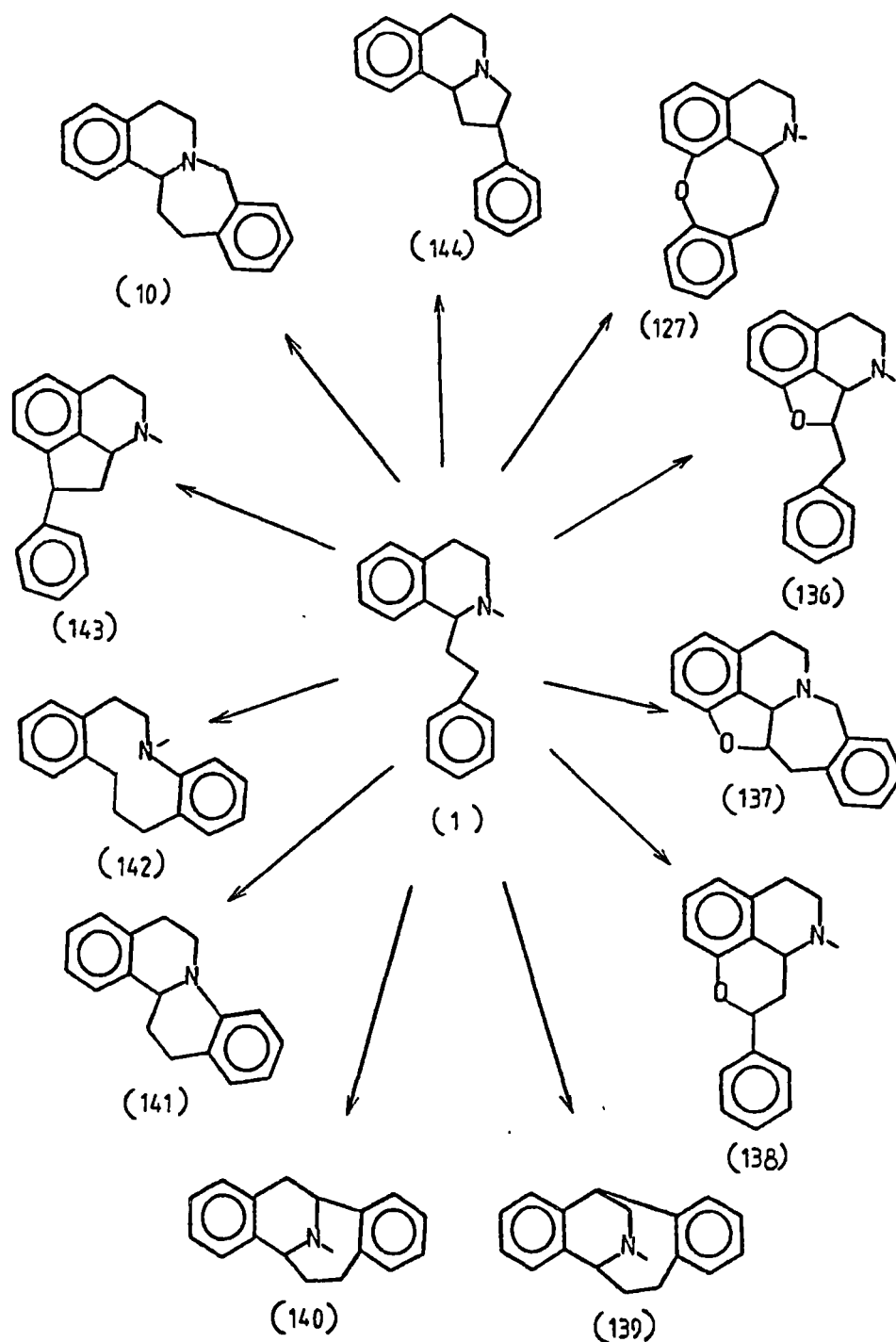
Scheme 46



Scheme 47

Likewise, alkaloids derived from a homoprotopine precursor (129) may also be isolated (Scheme 47). The nitrogen atom may interact with carbons 1a, 13, 14, or 15 to bring about the formation of some new phenethylisoquinoline skeletons such as (130) (route a), the homologue of the isoindolobenzazepine (131) (route b), and the skeleton (132) (route c). A homoindano-benzazepine skeleton (133) may be derived from the condensation of carbons 8 and 15 (route d). The oxidative cleavage of the N-C₈ bond of (129) may afford two types of products. The nucleophilic addition of the nitrogen atom to the olefinic C₁₃, and the subsequent condensation of the C₈ carboxylate oxygen with C₁₄ may give rise to a B-homorhoadine (134) (route e). When the nitrogen atom interacts with C₁₄ instead of C₁₃, a C-homorhoadine-type product (135) may be formed (route f).

More new phenethylisoquinoline-derived skeletons may arise directly or indirectly from a 1-phenethylisoquinoline precursor (1) (Scheme 48). The phenolic oxidation of a



Scheme 48

2'-hydroxy derivative of (1) may result in the formation of a homocularine skeleton (127). The same skeleton may be derived from the oxidation of a C-homoaporphine. If the hydroxy group is instead found at C₈, and where the alpha carbon of (1) is oxidized, (136), a quettamine¹⁷⁸ homologue may be obtained, which can be further modified to (137) by Mannich-type

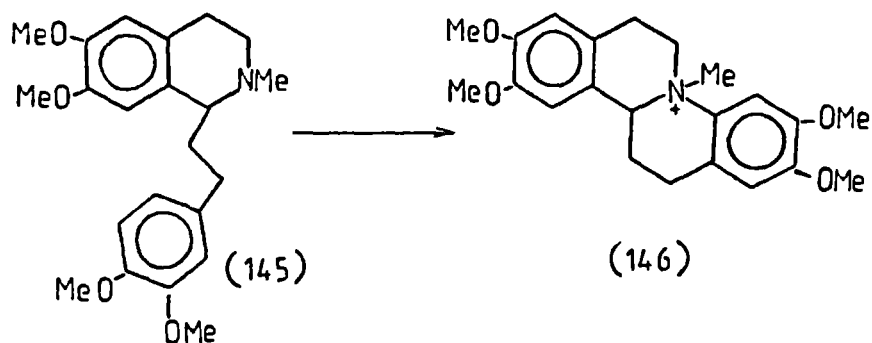
condensation. The 8-hydroxy derivative of (1) may also condense to (138). Other new alkaloids which may be biosynthesized from the oxidation of (1) are the homoisopavine (139), homopavine (140), C-homodibenzopyrrocoline (141) which can ring open to form the dibenzazecine (142), and homoazafluoranthene (143). As mentioned in Section 1.1, a homoprotoberberine (10) may be derived from (1) by Mannich-type condensation. In like manner, an alkaloid possessing a skeleton like (144) may also be formed.

4.2 Synthesis

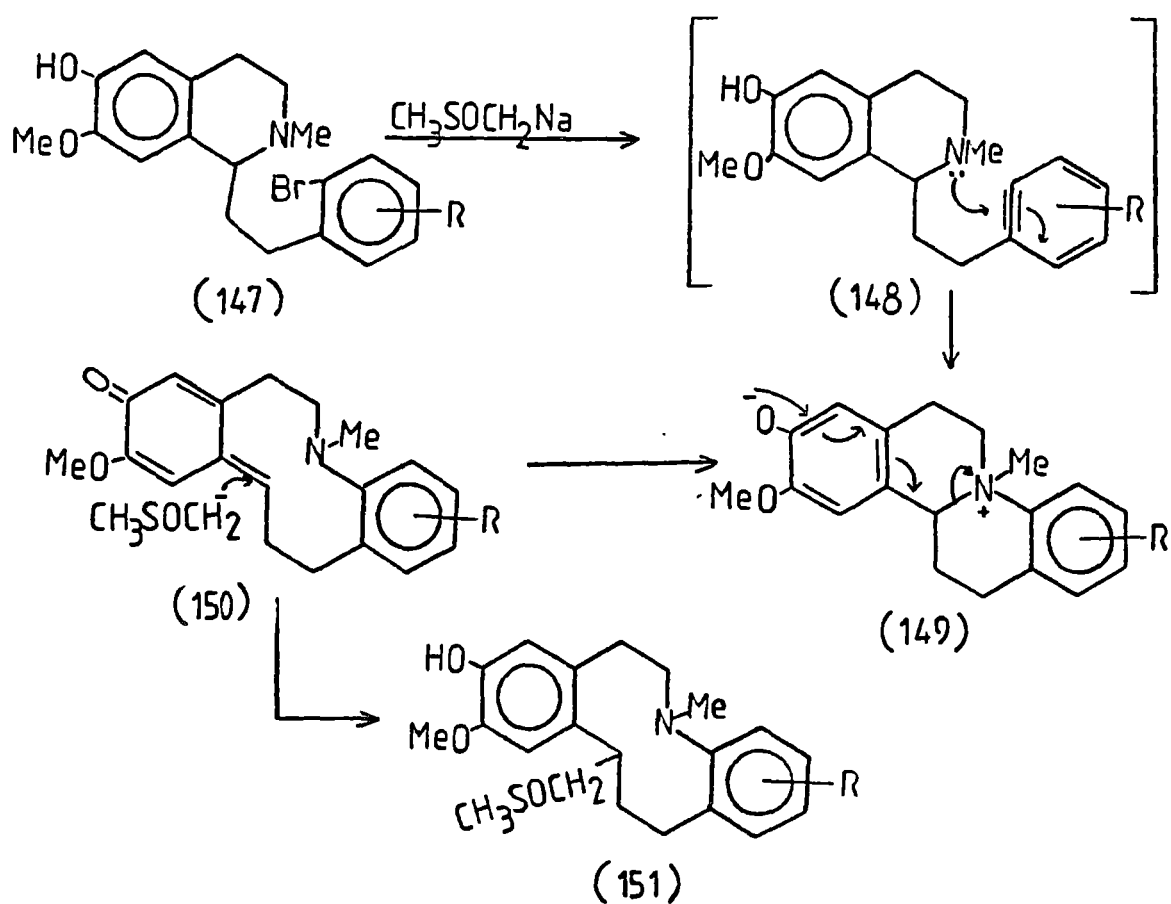
The last review⁵ on the phenethylisoquinoline alkaloids described the synthesis of a homocularine system (82) via the Ullmann method of ether synthesis, and that of a homoprotoberberine derivative. The latter was synthesized by Mannich condensation,¹⁸⁰ by homophthalideisoquinoline,¹⁸⁰ and by Dieckmann¹⁸⁰ approaches. Recently Kametani reported¹¹⁵ the synthesis of some homoprotoberberine derivatives by the phenolic oxidation of some 1-phenethylisoquinoline-N-oxide systems (Scheme 11). The homoisopavine-type system (145) was synthesized by the acid treatment of some p-quinol acetates (Scheme 15, Section 2.3.3.2).

A homodibenzopyrrocoline system (146) was obtained¹²⁴ from the electrooxidative coupling of the phenethylisoquinoline derivative (145) (Scheme 49). The peaks of the cyclic voltammogram of (145) were interpreted as being due to the removal of an electron from each of the aryl moiety and from the nitrogen atom, thus facilitating the nitrogen-carbon coupling. This skeleton type was also obtained¹⁷² from (147) by way of a C-ring benzyne intermediate (148) (Scheme 50). The quaternary homodibenzo-

pyrrocoline product (149) underwent a ring opening, and further elaboration afforded the dibenz[b,g]azecine derivative (151).



Scheme 49

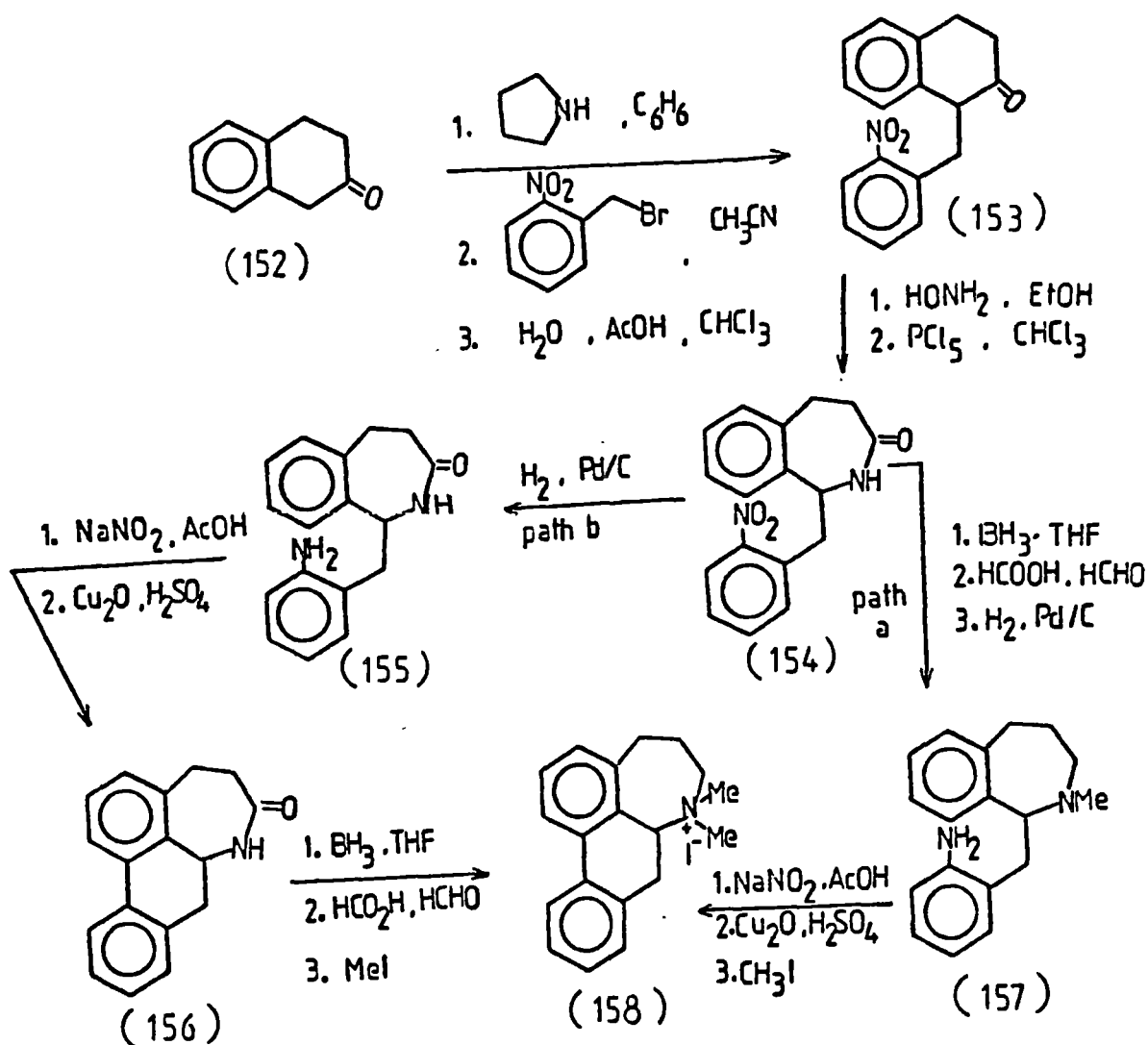


Scheme 50

A short and relatively efficient method of synthesis of a B-homologue of an aporphine, aimed at exploring the structure-activity relationships of some benzyloquinoline related systems has been reported¹⁷³ by Jensen and Woods (Scheme 51). The key precursor, a B-homo-1-benzyloquinoline (154) was synthesized from a tetralone (152) by way of (153). The B-ring of (153) was enlarged by a sterically controlled Beckmann rearrangement. The key step in this synthesis was the cyclization of the key precursor (154) by the classical Pschorr method. Two different paths in the formation of (158), involving identical chemistry but in different sequences were explored. Path b proved to be of higher yield than route a. The success of path b was attributed to the functionality of the B-ring. That is, in the amino lactam state (155) C₁, is more proximate to C₁ than in (157).

This approach is an improvement to the method reported¹⁷⁴ by Berney and Schuh who employed the Schmidt rearrangement reaction to enlarge the B-ring of (153) affording a 25-47% yield of (154), whereas, the Beckmann rearrangement of (153) gave 93% of (154). The overall high efficiency of this approach to B-homoaporphine synthesis may also be attributed to the fact that the usual side reactions associated with the classical Pschorr reaction were in a way circumvented by the proper order of the reaction steps. The 78% yield of (156) from (155) is unusually high for a classical Pschorr reaction. It may still be possible to attain a higher yield by exploring other methods of cyclization. This may call for a modification of the Pschorr reaction such as the use of freshly prepared copper metal, or the application of other known cyclization methods such as

cyclization by way of quinol acetates, a relatively high yielding process.

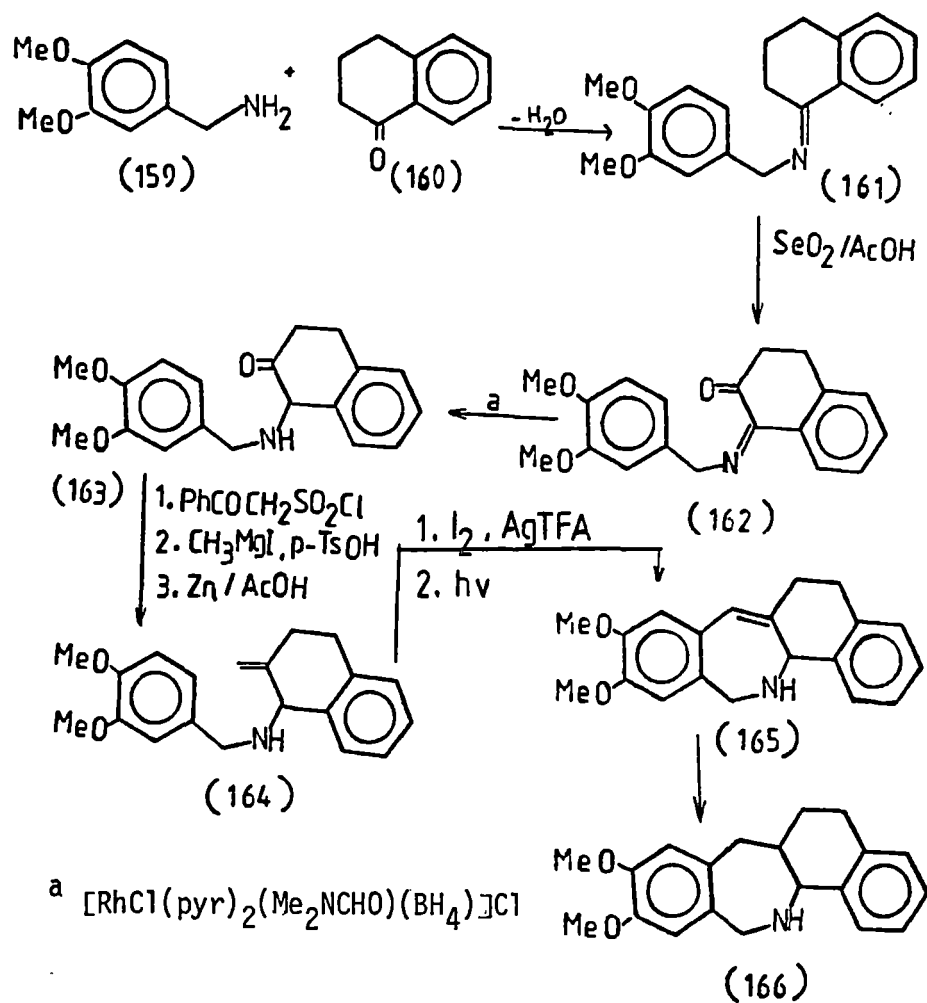


Scheme 51

4.3 Proposed Synthesis of B-Homobenzophenanthridines

The proposed synthesis of this group of compounds may be aimed at producing some samples for structure-activity relationship studies, at the same time, this may serve to explore a possible route to the formation of the enlarged ring system of the

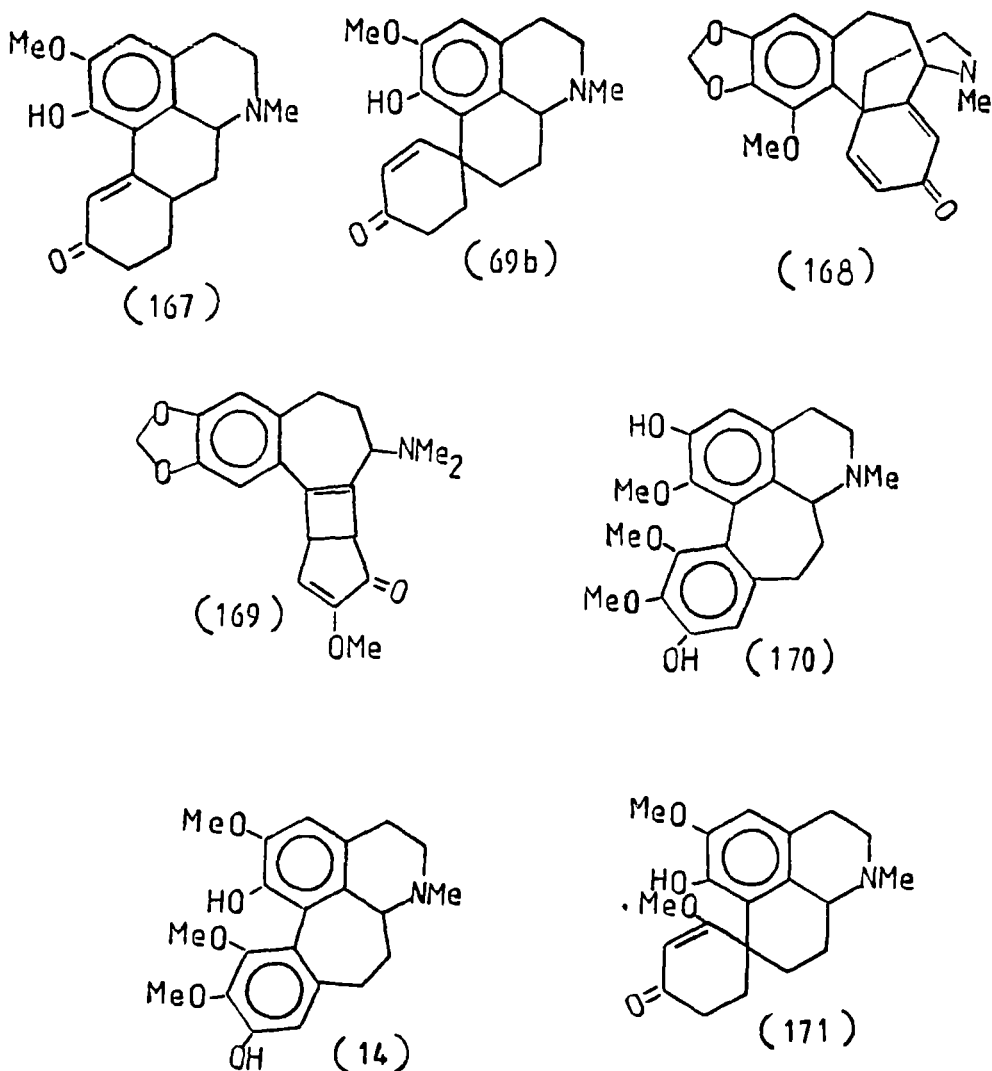
isoquinolines. The analysis of the target molecule (166) suggested the building up of the seven-membered B-ring to join together the A-ring with the C- and D-rings. The reaction of tetralone (160) with (159) to form the stable Schiff's base (161) is a straight forward reaction and would be expected to give a good yield (Scheme 52). The additional carbon atom to compose the seventh atom in the B-ring may be introduced by the functionalization of the carbon atom alpha to the imine double bond. Although this is not a well established reaction the increasing application of metal compounds in oxidation processes offers a wide range of possibilities. Thus, allylic oxidation of (161) may be achieved by using selenium oxide.¹⁷⁹ The use of other metal compounds as the oxidizing system, and the refunctionalization of the nitrogen atom prior to oxidation may also be considered. The product (162) may then be reduced with a rhodium borohydride complex.¹⁹⁰ The reaction of (163) with Grignard reagent would give the desired functionality as in (164). The final phase of the synthetic scheme would be the cyclisation of the iodine derivative of (164) by irradiation. The target molecule (166) may finally be obtained by the reduction of (165).

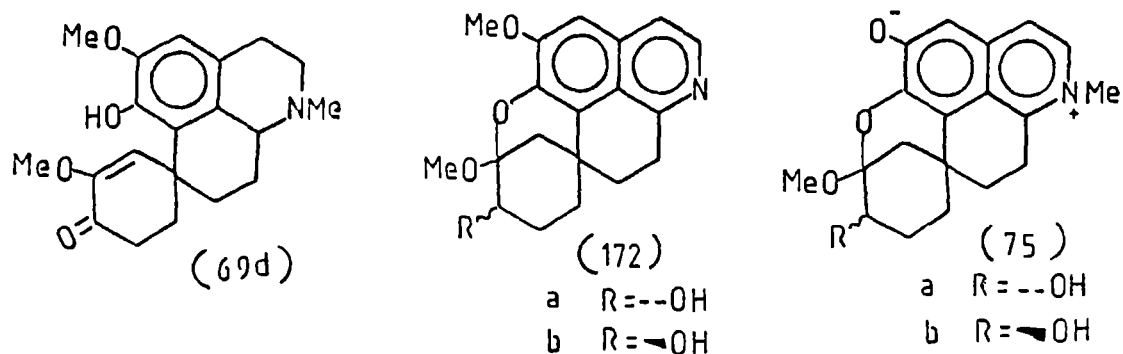


Scheme 52

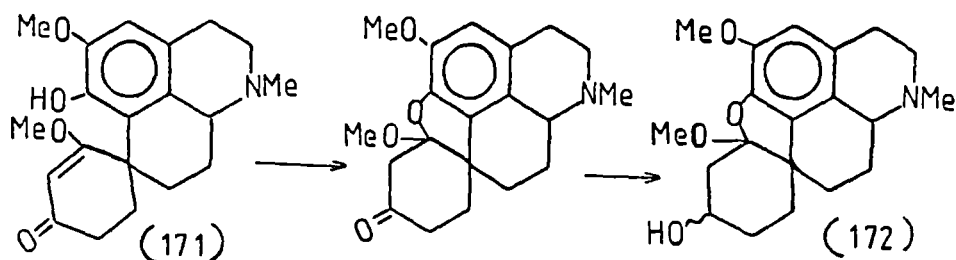
5. REVISED STRUCTURES

The structure of yolantamine which appeared in Chemical Abstracts¹⁷⁵ and in Santavy's paper¹⁷⁰ as (167), actually has the structure (69b). The alkaloid AM-3 which was formerly assigned²⁷ the structure of a homomorphinan base (168) was identified²⁵ as N-deacetyl-N-demethyl-lumino-cornigerine (169). Merenderine which was previously identified⁵² as (170) has now been modified⁶³ to (14). This is identical with the alkaloid bechuanine which in turn was identified⁶¹ as an enantiomer of (R)-floramultine.





In the light of the mass spectral studies on several homoaporphine systems, the structure of luteidine (69d) was revised¹⁰⁸ from an isomeric structure⁹⁰ (171). It is therefore suggested that the structure of luteicine (172) (Scheme 53) be re-examined as its assigned structure was confirmed⁴⁵ by chemical transformations based on the uncorrected structure of luteidine (171). Recently the structure of regelinone⁴⁶ (172a) and isoregelinone⁴⁷ (172b) were revised¹⁶⁶ to (75a) and (75b) respectively. The new structures were supported by n.m.r. data and by chemical transformations.



Scheme 53

REFERENCES

1. Huang, L., and Xue, Z., in "The Alkaloids: Chemistry and Pharmacology:", Vol. 23, Brossi, A. (ed.), (Academic Press: New York 1984), p. 157.
2. Capraro, H., and Brossi, A., in "The Alkaloids: Chemistry and Pharmacology", Vol. 23, Brossi, A. (ed.), (Academic Press: New York 1984), p. 1.
3. Battersby, A.R., *Chem. Commun.*, 1965, 415.
4. Sepulveda-Boza, S., Friedrichs, E., Puff, H., and Breitmaier, E., *Planta Medica*, 1983, 49, 32.
5. Kametani, T., and Koizumi, M., in "The Alkaloids: Chemistry and Pharmacology", Vol. 14, Manske, R.H.F. and Holmes, H.L. (eds.), (Academic Press: New York 1973), p.265.
6. Santavy, F., *Pharmazie*, 1982, 37, 56; Santavy, F., *Acta Univ. Palacki. Olomuc., Fac. Med.*, 1983, 104, 97.
7. Hutchinson, J., "The Families of Flowering Plants", Second ed., (Clarendon Press: Oxford 1959).
8. Potesilova, H., Alcaraz, C., and Santavy, F., *Collect. Czech. Chem. Commun.*, 1969, 34, 2128.
9. Seigler, D.S., in "The Alkaloids: Chemistry and Pharmacology", Vol. 16, Manske, R.H.F. and Holmes, H.L. (eds.), (Academic Press: New York 1977), p. 1.
10. Langlois, N., Das, B.C., Potier, P., and Lacombe, L., *Bull. Soc. Chim. Fr.*, 1970, 10, 3535.
11. Manske, R.H.F., in "The Alkaloids: Chemistry and Pharmacology", Vol. 14, Manske, R.H.F. and Holmes, H.L. (eds.), (Academic Press: New York 1976), p. 550.

12. Gershenzon, J., and Mabry, T.J., *Nord. J. Bot.*, 1983, 3, 5.
13. Taylor, D.A.H., *Annu. Proc. Phytochem. Soc. Eur.*, 1983, 22, 353.
14. Okorie, D., *Phytochemistry* 1982, 21, 2424.
15. Potesilova, H., El-Hamidi, A., and Santavy, F., *Collect. Czech. Chem. Commun.*, 1969, 34, 3540.
16. Gasic, O., Potesilova, H., and Santavy, F., *Planta Med.*, 1976, 30, 75.
17. Potesilova, H., Hruban, L., and Santavy, F., *Collect. Czech. Chem. Commun.*, 1976, 41, 3146.
18. Gasic, O., and Popovic, M., *Planta Med.*, 1977, 32, 368.
19. Aladesanmi, A.J., Kelley, C.J., and Leary, J., *Journal of Natural Products*, 1983, 46, 127.
20. Battersby, A.R., Herbert, R.B., and Santavy, F., *Chem. Commun.*, 1965, 17, 415.
21. Usmanov, A.M., Yusupov, M.K., and Aslanov, Kh.A., *Khim. Priro. Soedin.*, 1977, 422.
22. Battersby, A.R., Herbert, R.B., Pijewska, L., and Santavy, F., *Chem. Commun.*, 1965, 11, 228.
23. Battersby, A.R., Herbert, R.B., Pijewska, L., and Santavy, F., *J. Chem. Soc. Perkin I*, 1972, 1736.
24. Kametani, T., Satoh, Y., and Fukumoto, K., *J. Chem. Soc. Perkin I*, 1972, 2160.
25. Potesilova, H., Sedmera, P., Guenard, D., and Simanek, V., *Planta Med.*, 1985, 344.
26. Mukamed'yarova, N.L., Yusupov, M.K., Aslanov, Kh.A., and Sadykov, A.S., *Khim. Priro. Soedin.*, 1975, 11, 758.
27. Santavy, F., *Heterocycles*, 1981, 15, 1505.
28. Battersby, A.R., Ramage, R., Cameron, A.F., and Hannaway, C., *J. Chem. Soc. (C)*, 1971, 3524.

29. Yusupov, M.K., Aslanov, Kh.A., and Dinh Thi Ngo, *Khim. Priir. Soedin.*, 1975, 11, 271.
30. Hart, N.K., Johns, S.R., Lamberton, J.A., and Saunders, J.K., *Tetrahedron Letters*, 1968, 24, 2891.
31. Battersby, A.R., Munro, M.H.G., Bradbury, R.B., and Santavy, F., *Chem. Commun.*, 1968, 695.
32. Badger, G.M., and Bradbury, R.B., *J. Chem. Soc.*, 1960, 445.
33. Potesilova, H., Dvorackova, S., and Preininger, V., *Planta Med.*, 1985, 72.
34. Kametani, T., Satoh, F., Yagi, H., and Fukumoto, K., *J. Org. Chem.*, 1968, 33, 690.
35. Moza, B.K., Potesilova, H., and Santavy, F., *Acta Univ. Palacki. Olomuc., Fac. Med.*, 1962, 153.
36. Dvorackova, S., Hruban, L., Preininger, V., and Santavy, F., *Heterocycles*, 1975, 3, 575.
37. Yusupov, M.K., Abdullaeva, D.A., Aslanov, Kh.A., and Sadykov, A.S., *Dokl. Akad. Nauk. SSSR*, 1973, 208, 1123.
38. Turdikulov, Kh., Nguyen Van Dau, and Yusupov, M.K., *Khim. Priir. Soedin.*, 1976, 555.
39. Turdikulov, Kh., Yusupov, M.K., Aslanov, Kh.A., and Sadykov, A.S., *Khim. Priir. Soedin.*, 1974, 810.
40. Mukhamed'yarova, N.L., Levkovich, M.G., Aslanov, Kh.A., and Sadykov, A.S., *Khim. Priir. Soedin.*, 1976, 354.
41. Abdullaeva, D.A., Yusupov, M.K., Kasimov, A.K., Nguyen Van Dau, and Aslanov, Kh.A., *Khim. Priir. Soedin.*, 1976, 121.
42. Shamma, M., and Moniot, J.L., 'Isoquinoline Alkaloids Research: 1972-1977', (Plenum Press: New York 1978).
43. Yusupov, M.K., Trozyan, A.A., and Aslanov, Kh.A., *Khim. Priir. Soedin.*, 1975, 11, 808.

44. Chommadov, B., Yusupov, M.K., and Aslanov, Kh.A., *Khim. Prir. Soedin.*, 1985, 407.
45. Yusupov, M.K., Mukhamed'yarova, N.L., and Aslanov, Kh.A., *Khim. Prir. Soedin.*, 1976, 359.
46. Yusupov, M.K., Usmanov, A.M., Kasimov, A.K., and Turdikulov, Kh., *Khim. Prir. Soedin.*, 1977, 867.
47. Usmanov, A.M., and Yusupov, M.K., *Khim. Prir. Soedin.*, 1981, 195.
48. Abdullaeva, D.A., Yusupov, M.K., and Aslanov, Kh.A., *Khim. Prir. Soedin.*, 1976, 783.
49. Yusupov, M.K., Mukhamed'yarova, N.L., Sadykov, A.S., Dolejs, L., Sedmera, P., and Santavy, F., *Collect. Czech. Chem. Commun.*, 1977, 43, 1581.
50. Yusupov, M.K., and Sadykov, A.S., *Khim. Prir. Soedin.*, 1976, 350.
51. Yusupov, M.K., Chommadov, B., and Aslanov, Kh.A., *Khim. Prir. Soedin.*, 1985, 419.
52. Kasimov, A.K., Yusupov, M.K., Timbekov, E.Kh., and Aslanov, Kh.A., *Khim. Prir. Soedin.*, 1975, 11, 194.
53. Yusupov, M.K., Abdullaeva, D.A., Aslanov, Kh.A., and Sadykov, A.S., *Khim. Prir. Soedin.*, 1975, 11, 383.
54. Chommadov, B., Usmanov, A.M., and Yusupov, M.K., *Khim. Prir. Soedin.*, 1983, 790.
55. Battersby, A.R., Bradbury, R.B., Herbert, R.B., Munro, M.H.G., and Ramage, R., *Chem. Commun.*, 1967, 450.
56. Kametani, T., Satoh, Y., Shibuya, S., Koizumi, M., and Fukumoto, K., *J. Org. Chem.*, 1971, 36, 3733.
57. Santavy, F., Sedmera, P., Snatzke, G., and Reichstein, T., *Helv. Chim. Acta*, 1971, 54, 1084.

58. Kametani, T., Satoh, T., Yagi, H., and Fukumoto, K.,
J. Chem., Soc. (C), 1970, 382.
59. Shamma, M., 'The Isoquinoline Alkaloids: Chemistry and
Pharmacology', (Academic Press: New York 1972).
60. Beecham, A.F., Hart, N.K., Johns, S.R., and Lamberton, J.A.,
Aust. J. Chem., 1968, 21, 2829.
61. Santavy, F., and Hruban, L., *Collect. Czech. Chem. Commun.*,
1972, 1712.
62. Dvorackova, S., Sedmera, P., Potesilova, H., Santavy, F.,
and Simanek, V., *Collect. Czech. Chem. Commun.*, 1984, 49, 1536.
63. Trozyan, A.A., Yusupov, M.K., and Aslanov, Kh.A., *Khim. Priir.*
Soedin., 1975, 11, 527.
64. Kasimov, A.K., Timbekov, E.Kh., Yusupov, M.K., and
Aslanov, Kh.A., *Khim. Priir. Soedin.*, 1977, 230.
65. Yusupov, M.K., Aslanov, Kh.A., and Dinh Thi Ngo, *Khim. Priir.*
Soedin., 1975, 11, 431.
66. Yusupov, M.K., Dinh Thi Ngo, Aslanov, Kh.A., and
Sadykov, A.S., *Khim. Priir. Soedin.*, 1975, 11, 109.
67. Yusupov, M.K., Dinh Thi Ngo, and Aslanov, Kh.A., *Khim. Priir.*
Soedin., 1975, 11, 526.
68. Fitzgerald, J.S., Johns, S.R., Lamberton, J.A., and
Sioumis, A.A., *Aust. J. Chem.*, 1969, 22, 2187.
69. Johns, S.R., Kowala, C., Lamberton, J.A., Sioumis, A.A.,
and Wunderlich, J.A., *Chem. Commun.*, 1968, 1102.
70. Debourges, D., and Langlois, N., *J. Natural Products*, 1982,
45, 163.
71. Panichanun, S., and Bick, I.R.C., *Tetrahedron*, 1984, 40,
2677.

72. Langlois, N., Das, B.C., and Potier, P., *C.R. Acad. Sc., Ser C*, 1969, 269, 639.
73. Johns, S.R., Lamberton, J.A., and Sioumis, A.A., *Aust. J. Chem.*, 1969, 22, 2219.
74. Powell, R.G., *Phytochemistry*, 1972, 11, 1467.
75. Sioumis, A.A., *Aust. J. Chem.*, 1971, 24, 2737.
76. Langlois, N., Razafimbelo, J., Andriamialosa, R.Z., Pusset, J., and Chauviere, G., *Heterocycles*, 1984, 22, 2453.
77. Kametani, T., Fukumoto, K., and Satoh, F., *J. Heterocyclic Chem.*, 1975, 13, 29.
78. Panichanun, S., and Bick, I.R.C., *Tetrahedron*, 1984, 40, 2685.
79. Razafimbelo, J., Langlois, N., Chiaroni, A., and Riche, C., *C.R. Acad. Sc., Ser 2*, 1985, 301, 519.
80. Razafimbelo, J., Langlois, N., and Andriamialosa, R.Z., *C.R. Acad. Sc., Ser 2*, 1985, 300, 441.
81. Aladesanmi, A.J., Kelley, C.J., Leary, J.D., and Onan, K.D., *J. Chem. Research (S)*, 1984, 108.
82. Ma, G., and Sun, G., *J. Natural Products*, 1982, 45, 585.
83. Powell, R.G., Mikolajczak, K.L., Weisleder, D., and Smith, C.R., *Phytochemistry*, 1972, 11, 3317.
84. Chawla, A.S., and Jackson, A.H., *Natural Product Reports*, 1984, 1, 371.
85. Ma, G., Lu, C., Elsohly, H.N., Elsohly, M.A., and Turner, C.E., *Phytochemistry*, 1983, 22, 251.
86. Riche, C., *Acta. Cryst.*, 1974, 1386.
87. Seguineau, M., and Langlois, N., *Phytochemistry*, 1980, 19, 1279.

88. Mai, H.N., Langlois, N., Das, B.C., and Potier, P.,
C.R. Acad. Sc., Ser 2, 1970, 2154.
89. Langlois, N., *Tetrahedron Letters*, 1981, 22, 2263.
90. Battersby, A.R., McDonald, E., Munro, M.H.G., and Ramage, R.,
Chem. Commun., 1967, 934.
91. Raffauf, R., *Handbook of Alkaloids Containing Plants*,
(John Wiley and Sons: New York c1970).
92. Battersby, A.R., Herbert, R.B., McDonald, E., Ramage, R.,
and Clements, J.H., *Chem. Commun.*, 1966, 603.
93. Dyke, S.F., and Quessy, S.N., in "The Alkaloids: Chemistry
and Pharmacology", Vol. 13, Manske, R.H.F. and Holmes, H.L.
(eds.), (Academic Press: New York 1981), p. 1.
94. Santavy, F., *Collect. Czech. Chem. Commun.*, 1970, 35, 2857.
95. Thakur, R., Potesilova, H., and Santavy, F., *Planta Med.*,
1975, 28, 201.
96. Pijewska, L., Kaul, J.L., Joshi, R.K., and Santavy, F.,
Collect. Czech. Chem. Commun., 1967, 32, 158.
97. Vikova, M., Potesilova, H., Popovic, M., Valka, I., and
Santavy, F., *Acta Univ. Palacki, Olomuc.*, Fac. Med., 1981,
99, 115.
98. Potesilova, H., Hrbek, J., and Santavy, F., *Collect. Czech.
Chem. Commun.*, 1967, 32, 141.
99. Cronquist, A., "The Evolution and Classification of
Flowering Plants", (Nelson Press: London 1968).
100. Taylor, D., Warner, J., and Wright, J., *J. Chem. Soc.
Perkin I*, 1977, 397.
101. Vasudev, S., Shah, V., Dohadwalla, A., Mandrekar, S., and
De Souza, N., Ger. Offen. De 3, 329, 186 (1985).

102. Singh, S., Garg, H.S., and Khanna, N.M., *Phytochemistry*, 1976, 15, 2001.
103. Cook, J.W., and Loudon, J.D., in "The Alkaloids: Chemistry and Pharmacology", Vol. 2, Manske, R.H.F. and Holmes, H.L. (eds.), (Academic Press: New York 1952), p. 331.
104. Wildman, W.C., in "The Alkaloids: Chemistry and Pharmacology", Vol. 6, Manske, R.H.F. (ed.), (Academic Press: New York 1960), p. 247; Pursey, B., in "The Alkaloids: Chemistry and Pharmacology", Vol. 11, Manske, R.H.F. and Holmes, H.L. (eds.), (Academic Press: New York 1968), p. 407.
105. Mislow, K., Glass, M.A.W., O'Brien, R., Rutkin, P., Steinberg, D.H., Weiss, J., and Djerassi, C., *J. Am. Chem. Soc.*, 1962, 84, 1451.
106. Bunnenberg, E., Djerassi, C., Mislow, K., and Moskowitz, J., *J. Am. Chem. Soc.*, 1962, 84, 2823.
107. Brossi, A., O'Brien, J., and Teitel, S., *Helv. Chim. Acta*, 1969, 52, 678.
108. Timbekov, E.Kh., and Sadykov, A.S., *Khim. Priir. Soedin.*, 1985, 3.
109. Barton, D.H.R., *Chemistry in Britain*, 1967, 3, 330.
110. Hewgill, F.R., and Pass, M.C., *Aust. J. Chem.*, 1985, 38, 497.
111. Hewgill, F.R., and Pass, M.C., *Aust. J. Chem.*, 1985, 38, 615.
112. Kametani, T., Satoh, Y., Takemura, M., Ohta, Y., Ihara, M., and Fukumoto, K., *Heterocycles*, 1976, 5, 175.
113. Kametani, T., Ihara, M., Takemura, M., Satoh, Y., Terasawa, H., Ohta, Y., Fukumoto, K., and Takahashi, K., *J. Am. Chem. Soc.*, 1977, 99, 3805.

114. Marino, J.P., and Samanen, J.M., *Tetrahedron Letters*, 1973, 4553.
115. Kametani, T., Ihara, M., Takemura, M., and Satoh, Y., *Heterocycles*, 1980, 14, 817.
116. Kupchan, M.S., Dhingra, O.P., and Kim, C., *J. Org. Chem.*, 1976, 41, 4049.
117. Schwartz, M.A., Rose, B.F., and Visnuvajala, B., *J. Am. Chem. Soc.*, 1973, 95, 6862.
118. Kupchan, M.S., Liepa, A.J., Kameswaran, V., and Bryan, R.F., *J. Am. Chem. Soc.*, 1973, 95, 6862; Kupchan, M.S., Kameswaran, V., Lynn, J.T., Williams, D.K., and Liepa, A.J., *J. Am. Chem. Soc.*, 1975, 97, 5622.
119. Kametani, T., Satoh, F., Yagi, H., and Fukumoto, K., *J. Chem. Soc. (C)*, 1968, 1003; Kametani, T., Satoh, F., Yagi, H., and Fukumoto, K., *Chem. Commun.*, 1967, 1103.
120. Battersby, A.R., Bradbury, R.B., Herbert, R.B., Munro, M.H.G., and Ramage, R., *J. Chem. Soc. Perkin I*, 1974, 1394.
121. Kametani, T., Yagi, H., Fukumoto, K., and Satoh, F., *Chem. Pharm. Bull.*, 1968, 16, 2297.
122. Kametani, T., and Ihara, M., *J. Chem. Soc. Perkin I*, 1980, 629.
123. Kametani, T., Charubala, R., Ihara, M., Koizumi, M., Takahashi, K., and Fukumoto, K., *J. Chem. Soc. (C)*, 1971, 3915.
124. Najafi, A., and Sainsbury, M., *Heterocycles*, 1977, 6, 459.
125. Yang, N., Lenz, G., and Shani, A., *Tetrahedron Letters*, 1966, 2941.

126. Kametani, T., Koizumi, M., Shishido, K., and Fukumoto, K., *J. Chem. Soc. (C)*, 1971, 1923.
127. Hoshino, O., Toshioka, T., and Umezawa, B., *Chem. Commun.*, 1972, 740.
128. Kametani, T., and Honda, T., in "The Alkaloids: Chemistry and Pharmacology", Vol. 24, Brossi, A. (ed.), (Academic Press: New York 1985), p. 153; Murugesan, N., and Shamma, M., *Tetrahedron Letters*, 1979, 4521.
129. Kametani, T., and Koizumi, M., *J. Chem. Soc. (C)*, 1971, 3976.
130. Hoshino, O., Toshioka, T., Ohyama, K., and Umezawa, B., *Chem. Pharm. Bull.*, 1974, 22, 1307.
131. Hoshino, O., Hara, H., Serizaka, N., and Umezawa, B., *Chem. Pharm. Bull.*, 1975, 23, 2048.
132. Hara, H., Hoshino, O., and Umezawa, B., *Heterocycles*, 1977, 7, 307.
133. Hara, H., Hoshino, O., and Umezawa, B., *J. Chem. Soc. Perkin I*, 1979, 2657.
134. Hara, H., Hoshino, O., and Umezawa, B., *Heterocycles*, 1976, 5, 213.
135. Hara, H., Shinoki, H., Komatsu, T., Hoshino, O., and Umezawa, B., *Chem. Pharm. Bull.*, 1986, 34, 1924.
136. Marino, J.P., and Samanen, J.M., *J. Org. Chem.*, 1976, 41, 179.
137. Battersby, A.R., Bohler, P., Munro, M.H.G., and Ramage, R., *Chem. Commun.*, 1969, 1066; Battersby, A.R., Bohler, P., and Munro, M.H.G., *J. Chem. Soc. Perkin I*, 1974, 1399.
138. Battersby, A.R., Herbert, R.B., McDonald, E., Ramage, R., and Clements, J.H., *J. Chem. Soc. Perkin I*, 1972, 1741.

139. Battersby, A.R., Binks, R., Reynolds, J.J., and Yoewell, D.A., *J. Chem. Soc.*, 1964, 4257.
140. Battersby, A.R., McDonald, E., and Milner, J.A., *Tetrahedron Letters*, 1975, 3419.
141. Herbert, R.B., and Knagg, E., *Tetrahedron Letters*, 1986, 27, 1099.
142. Shamma, M., and Salgar, S., "Specialist Periodical Reports: The Alkaloids", Vol. 4 (Royal Society of Chemistry: London 1974), p.197.
143. Kupchan, M.S., Dhingra, O.P., Kim, C., and Kameswaran, J., *J. Org. Chem.*, 1976, 41, 4047.
144. Yusupov, M.K., Trozyan, A.A., Aslanov, Kh.A., and Sadykov, A.S., *Khim. Prir. Soedin.*, 1972, 777.
145. Grethe, G. (ed.), *Heterocyclic Compounds: Isoquinolines*, Vol. 38 part I, (John Wiley and Sons: New York 1981).
146. Rheiner, A., *Experientia*, 1964, 488.
147. Snatzke, G., and Wollenberg, G., *J. Chem. Soc. (C)*, 1966, 1681.
148. Shamma, M., and Hindenlang, D.M., "Carbon-13 Assignments of Amines and Alkaloids", (Plenum Press: New York 1972).
149. Leete, E., *Tetrahedron Letters*, 1965, 333.
150. Kametani, T., Fukumoto, K., Yagi, H., and Satoh, F., *Chem. Commun.*, 1967, 878.
151. Kametani, T., Yagi, H., Satoh, F., and Fukumoto, K., *J. Chem. Soc. (C)*, 1986, 271.
152. Kametani, T., and Satoh, F., *Chem. Pharm. Bull.*, 1969, 17, 814.
153. Dolejs, L., *Collect. Czech. Chem. Commun.*, 1974, 39, 571.

154. Kasimov, A.K., Timbekov, E.Kh., and Yusupov, M.K., *Teizisy Dokl. Sov.-Indiiskii Simp. Khim. Prir. Soedin.*, 1978, 36.
155. Timbekov, E.Kh., Kasimov, A.K., Abdullaeva, D.A., Yusupov, M.K., and Aslanov, Kh.A., *Khim. Prir. Soedin.*, 1976, 328.
156. Usmanov, A.M., Chommadov, B., Yusupov, M.K., and Aslanov, Kh.A., *Khim. Prir. Soedin.*, 1985, 248.
157. Schneider, F., and Bernauer, K., *Helv. Chim. Acta*, 1970, 53, 938.
158. Curran, W.V., *Chem. Commun.*, 1971, 478.
159. Kametani, T., Koizumi, M., and Fukumoto, K., *J. Org. Chem.*, 1971, 36, 3729.
160. Kametani, T., Sugahara, T., Sugi, H., Shibuya, S., and Fukumoto, K., *Chem. Commun.*, 1970, 724.
161. Kametani, T., Satoh, F., Fukumoto, K., Sugi, H., and Kigasawa, K., *Heterocycles*, 1973, 47.
162. Kametani, T., Fukumoto, K., Satoh, F., Kigasawa, K., and Sugi, H., *Heterocycles*, 1975, 3, 921.
163. Kametani, T., and Ihara, M., *Heterocycles*, 1976, 5, 649.
164. Kametani, T., Satoh, Y., and Fukumoto, K., *Chem. Pharm. Bull.*, 1977, 25, 922.
165. Mukhamed'yarova, N.L., Yusupov, M.K., Levkovich, M.L., and Aslanov, Kh.A., *Khim. Prir. Soedin.*, 1976, 801.
166. Usmanov, A.M., Chommadov, B., and Yusupov, M.K., *Khim. Prir. Soedin.*, 1985, 81 (*Chem. Abstr.*, 1985, 103, 71564t).
167. Harmon, R.E., and Jensen, B.L., *J. Heterocyclic Chem.*, 1970, 7, 1077.

168. Kametani, T., *Japan* 70, 19,062 (*Chem. Abstr.*, 1970, 73, 56291v).
169. Kametani, T., *Japan Kokai* 77, 48,697, (*Chem. Abstr.*, 1977, 87, 85164a).
170. Santavy, F., in "The Alkaloids: Chemistry and Pharmacology", Vol. 17, Manske, R.H.F. and Holmes, H.L. (eds.), (Academic Press: New York 1979), p. 385.
171. Firdous, S., Freyer, A.J., and Shamma, M., *J. Am. Chem. Soc.*, 1984, 106, 6099.
172. Kano, S., Ogawa, T., Yomatsu, T., Takahagi, Y., Komiyama, E., and Shibuya, S., *Heterocycles*, 1975, 3, 129.
173. Jensen, B.L., and Woods, M.A., *J. Heterocyclic Chem.*, 1979, 16, 1317.
174. Berney, D., and Schuh, K., *Helv. Chim. Acta.*, 1976, 59, 2059.
175. Yusupov, M.K., Abdullaeva, D.A., Aslanov, Kh.A., and Sadykov, A.S., *Dokl. Akad. Nauk SSSR*, 1973, 208, 1123 (*Chem. Abstr.*, 1973, 78, 136482b).
176. Yusupov, M.K., Abdullaeva, D.A., Aslanov, Kh.A., and Sadykov, A.S., *Dokl. Akad. Nauk SSSR*, 1973, 208, 1123 (*Chem. Abstr.*, 1973, 79, 79010r).
177. Parry, R.J., Chang, M.N.T., Schwab, J.M., and Foxman, B.M., *J. Am. Chem. Soc.*, 1980, 102, 1099.
178. Abu Zarga, M.H., Miana, G.A., and Shamma, M., *Tetrahedron Letters*, 1981, 22, 541.
179. Venien, F., and Mandrier, C., *C.R. Acad. Sc., C*, 1970, 270, 845.
180. Shamma, M., and Hillman, M., *Tetrahedron*, 1971, 27, 1363.

181. Battersby, A.R., Herbert, R.B., and Mo, L., *J. Chem. Soc. C*, 1967, 1739.
182. Fridrichsons, J., Mackay, M.F., and Mathieson, A.M., *Tetrahedron Letters*, 1968, 2887.
183. Yusupov, M.K., Abdullaeva, D.A., Kamaev, F.G., and Sadykov, A.S., *Dokl. Akad. Nauk. Uzb. SSSR*, 1976, 51.
184. Hegnauer, R., *Photochemistry*, 1986, 25, 1519.
185. Smith, C.R., Mikolajczak, K.L. and Powell, R.G., in "Anticancer Agents Based on Natural Product Models", Cassady, J.M. and Dourous, J.D. (eds.), (Academic Press: New York 1980), p.392.
186. Weinreb, S.M., and Semmelhack, M.F., *Accounts Chem. Res.*, 1975, 8, 158.
187. Kametani, T., and Fukumoto, K., *Heterocycles*, 1975, 3, 931.
188. Karle, I.L., in "The Alkaloids: Chemistry and Pharmacology", Vol. 22, Brossi, A. (ed.), (Academic Press: New York 1983), p. 51.
189. Hughes, D.W., and MacLean, D.B., in "The Alkaloids: Chemistry and Pharmacology", Vol. 18, Manske, R.H.F., and Rodrigo, R.G.A. (eds.), (Academic Press: New York 1981), p. 217.
190. Birch, A.J., and Williamson, D.H., in "Organic Reactions", Dauben, W.G. (ed-in-chief), (John Wiley: Sydney 1976), p. 27.