SYNTHESIS OF BENZAZEPINE ALKALOIDS AND RELATED COMPOUNDS

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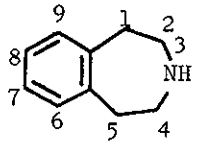
The various total synthesis and synthetic approaches to the isopavine, cephalotaxine and rheadan alkaloids, which have a 1,2,4,5-tetrahydro-3H-benz[d]azepine system as the main framework, are described. This review also summarises the synthetic reactions of benz[d]azepine.

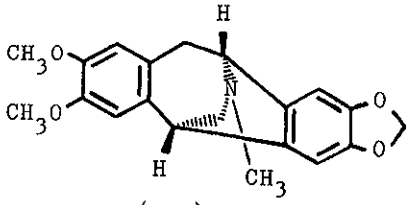
1. Introduction

The alkaloid having a 1,2,4,5-tetrahydro-3H-benz[d]azepine (1) as the main skeleton, which we have called "benzazepine alkaloids" in this article, are divided into three groups, isopavine, cephalotaxine and rheadan alkaloids, exemplified by amurensinine (2), harringtonine (3), and rhoeadine (4), respectively. These alkaloids would be derived biogenetically from 1-benzylisoquinoline (5) by oxidation and coupling as key reactions, and form groups in the isoquinoline bases.[1-3]

Chart 1



(1)



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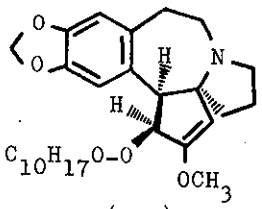

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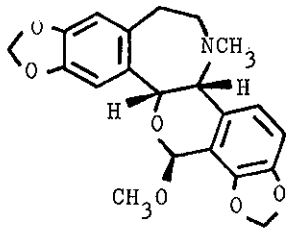

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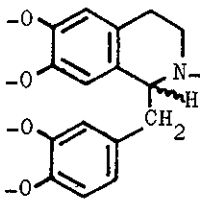
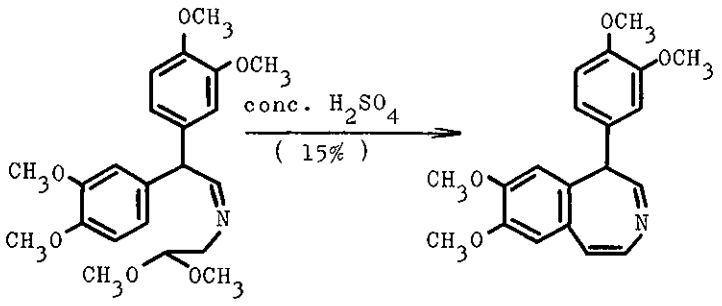


(5)

Chemistry of the benzazepine alkaloids such as structural determination and total synthesis has progressed greatly only during the past 20 years, although the benzazepine alkaloids and synthetic reactions of the benzazepine system have had a long history in

organic chemistry. In 1837 Merck[4] found porphyroxine in opium, and Hesse[5] in 1865 reported the isolation of rhoeadine (4) from Papaver rhoeas.[3] In 1903, Fritsch[6] obtained 1H-benzazepine (7) in 15 % yield from the benzalaminoacetal (6) by treatment with concentrated sulphuric acid,[7] although this structure could not be confirmed at that time.

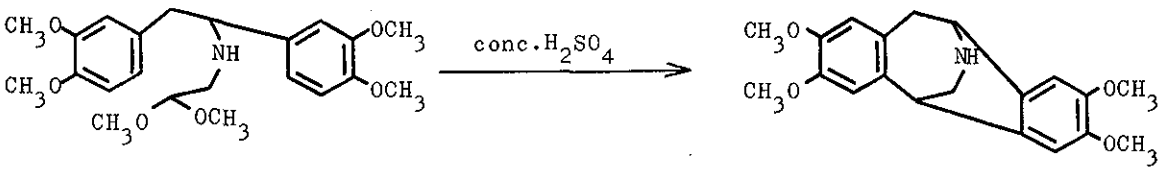
Chart 2



(6) (7)

Due to the complexity of the structure of rhoeadine and the low yield of Fritsch's product, benzazepine chemistry lays dormant for 50 years until Waldman[8] and Battersby,[9] independently, investigated the structure of the compound formed by the action of concentrated sulphuric acid on the aminoacetal (8) and correctly assigned the tetracyclic skeleton (9)to it. Battersby proposed that this structure be called "isopavine". This work then prompted advances in the structural determination and total synthesis of the isopavine alkaloids.

Chart 3



(8) (9)

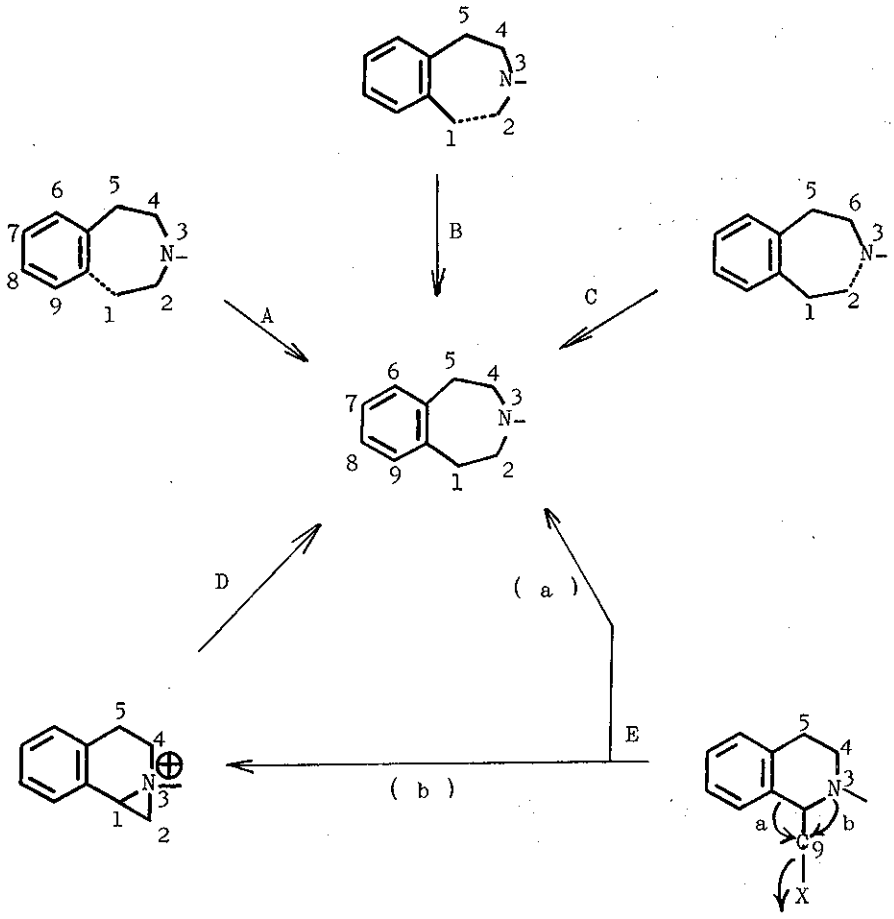
In 1960s, the improved methods of isolation by chromatography and structure determination by spectroscopy and X-ray analysis caused much progress in the chemistry of natural products, and the structure of harringtonine (3) and rhoeadine (4) having a rather complicated system was easily determined.

The structural assignment to these benzazepine alkaloids led to the development of new synthetic reactions in which the synthesis of a benzazepine was the key step in the total synthesis of these alkaloids. In this article, we will first discuss the general synthesis of the benz[d]azepine system and then the total synthesis or synthetic approach to the isopavine, cephalotaxine and rheadan alkaloids.

2. General Synthesis of Benz[d]azepine

The methods of synthesis of 1,2,4,5-tetrahydro-3H-benz[d]azepine can be divided into five patterns; the first (method A) consists in a cyclisation which makes a new linkage between C_1 and C_{9a}, the

Chart 4



second (method B) and the third (method C) are a bond formation between C_1 and C_2 or C_2 and N atoms, respectively, the fourth (method D) is a ring enlargement of the aziridinium salt derived from 3,4-dihydro-2-methylisoquinolinium salt, and the fifth (method E) is a molecular rearrangement of the phenyl group or the nitrogen atom to the C_9-position in 1-alkyl-1,2,3,4-tetrahydroisoquinoline.

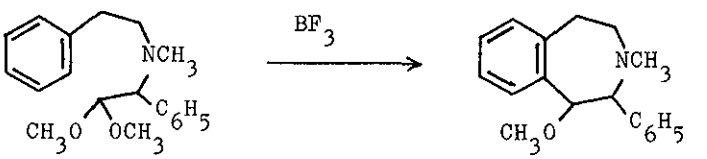
Method A

This method consists in the formation of a new linkage between C_1 and C_{9a} as shown in Chart 4 and is used widely in the synthesis of the 1,2,4,5-tetrahydro-3H-benz[d]azepine system and especially in total synthesis of the isopavine alkaloids.

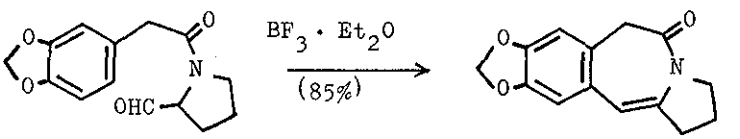
The most popular reaction is a cyclisation of the aminoacetal (10) using a Lewis acid to benzazepine (11),[10] which was first discovered by Fritsch[6] in 1903.

Similarly, the β-aminoaldehyde (12) was cyclised to the 1,2-

Chart 5



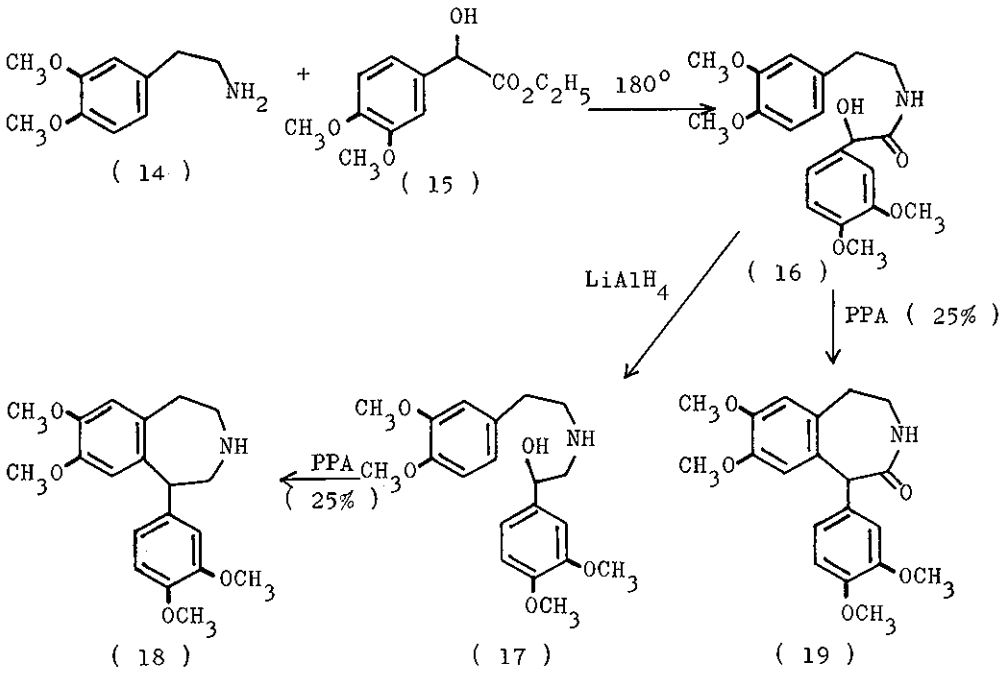
(10) (11)



(12) (13)

dihydro-3H-benz[d]azepine (13) in the presence of Lewis acid in good yield,[11] this step is a key reaction in a total synthesis of cephalotaxine described later.

Chart 6

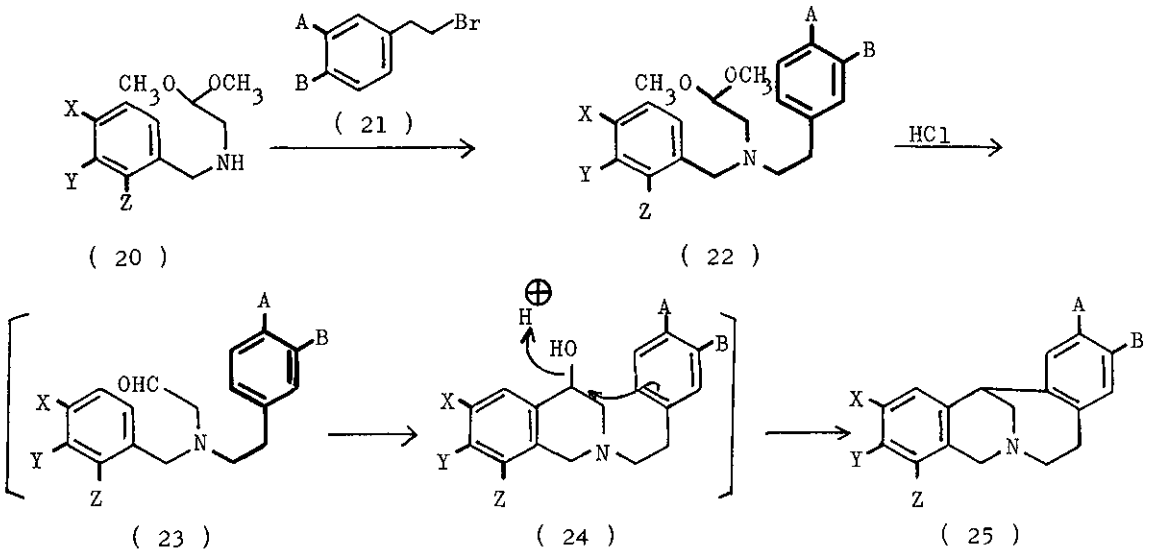


Condensation of homoveratrylamine (14) and homoveratryl mandelate (15) at 180° gave the amido alcohol (16), reduction of which yielded the N-(β-hydroxyethyl)phenethylamine (17) and then cyclisation with polyphosphoric acid gave the 1,2,4,5-tetrahydro-3H-benzazepine (18). A similar cyclisation of the amido alcohol (16) also furnished the benzazepine derivative (19).[12]

The substituted N-benzyl-N-phenylaminoacetals (22), prepared from the aminoacetals (20) and the phenethyl bromide (21), were converted into the doubly cyclised benzazepines (25) with concentrated hydrochloric acid at room temperature in good yield. This reaction can be explained by the fact that the aminoacetals (22) are hydrolysed very rapidly to the aldehydes (23) by concentrated hydrochloric acid at room temperature and that in a slower reaction the doubly cyclised products (25) are formed through the intermediate formation of the unstable 1,2,3,4-tetrahydro-4-hydroxy-2-phenethylisoquinoline (24) which however could not be isolated.[13,14]

This explanation is proved by the following experiments; thus, treatment of the 1,2,3,4-tetrahydro-4-hydroxy-2-phenethylisoquinoline (24a), prepared from the phenethyl bromide (21a) and the 1,2,3,4-tetrahydroisoquinoline (27) which in turn was obtained from the amino-acetal (26), with concentrated hydrochloric acid gave the benzazepine (25a), which was also obtained by acid treatment of the aldehyde (23a) synthesised from the N-benzylphenethylamine (28).[14] Hence, the formation of the benzazepine from N-benzyl-N-phenethylaminoacetal can be interpreted in terms of the initial formation of the 1,2,3,4-tetrahydro-4-hydroxyisoquinoline *via* N-benzyl-N-phenethylaminoaldehyde, followed by nucleophilic attack at C_4 by the dialkoxylated aromatic ring in the N-phenethyl residue as shown in Chart 7.

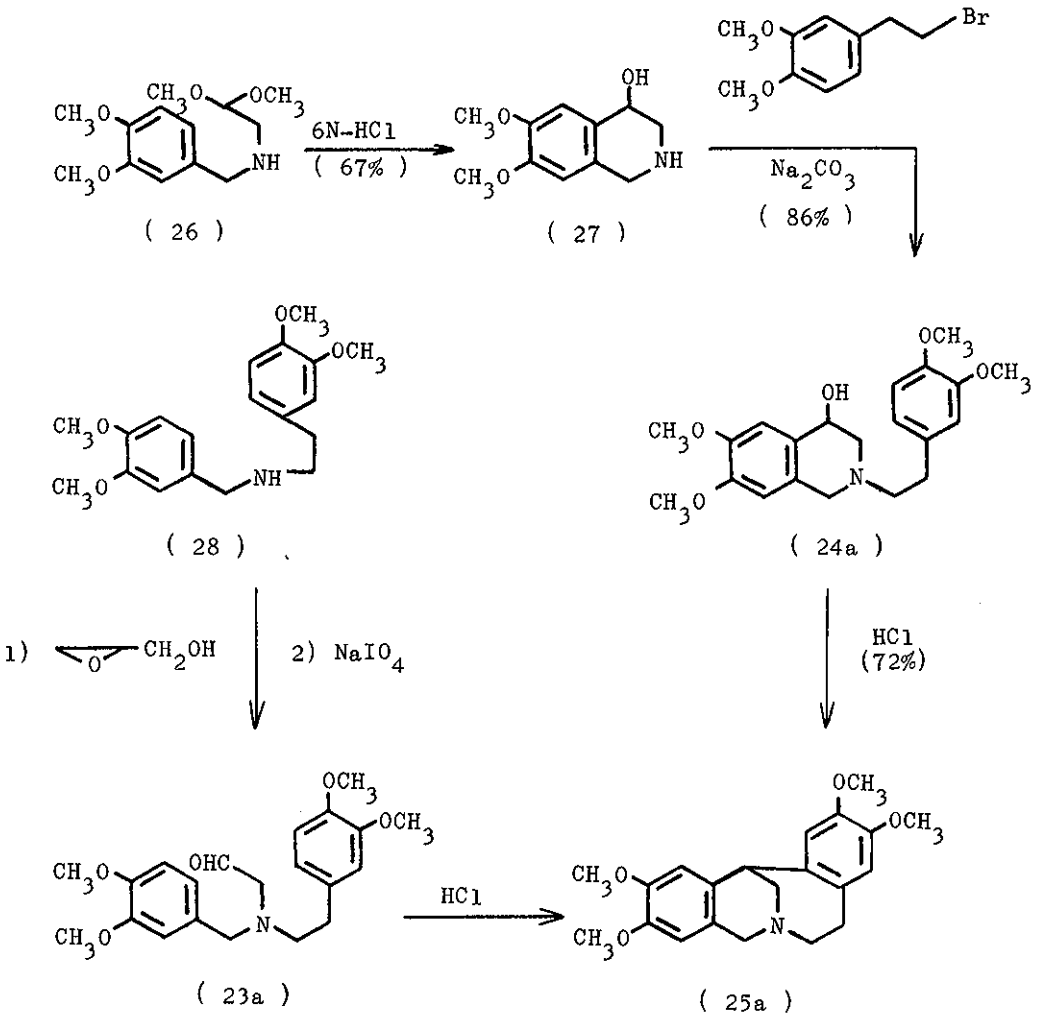
Chart 7



	X	Y	Z	A	B	Yield
a)	OMe	OMe	H	OMe	OMe	76%
b)	H	OMe	OMe	OMe	OMe	83
c)	H	OMe	OMe	$-OCH_2O-$		76
d)	OMe	H	H	OMe	OMe	50
e)	OMe	OMe	H	H	H	0

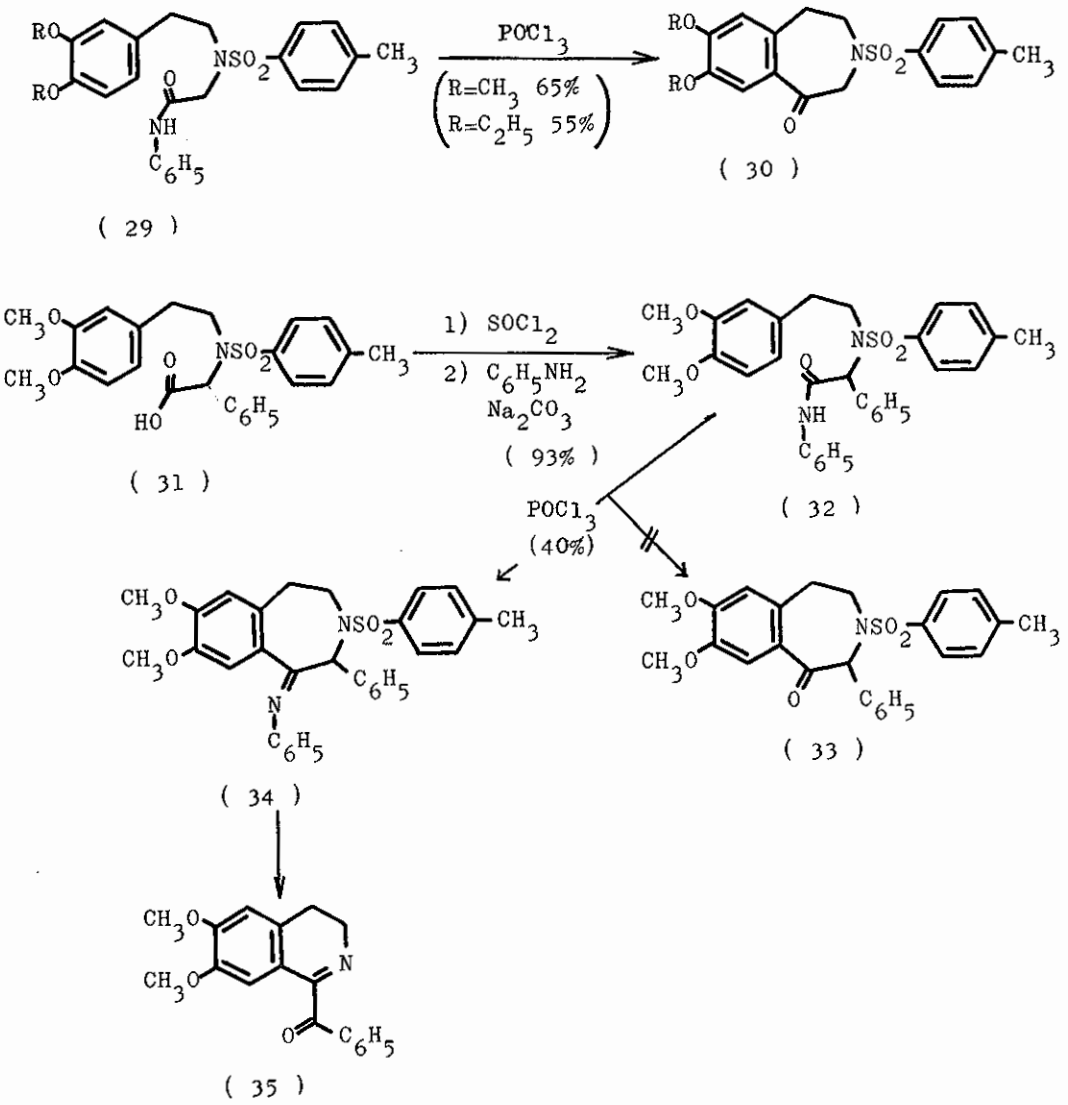
The same reaction has been widely applied to the total synthesis of isopavine alkaloids described later.

Chart 8



Gardent[15] in 1963 reported a synthesis (in moderate yield) of the benz[d]azepin-1-one (30), which has no phenyl group at C_2, by

Chart 9

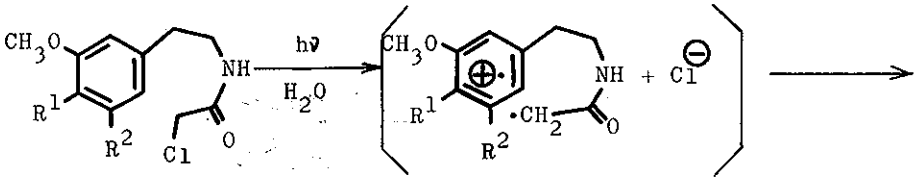

RO
RO
NSO2
CH3
O
NH
C6H5
(29)
POCl3
(R=CH3 65%
R=C2H5 55%)
(30)
CH3O
CH3O
HO
1) SOCl2
2) C6H5NH2
Na2CO3
(93%)
(31)
(32)
POCl3
(40%)
(33)
(34)
(35)

Bischler-Napieralski ring closure of the glycine anilide (29). Interestingly, partially hydrate phosphoryl chloride was used as the cyclisation reagent. However, this reaction could not be applied to a synthesis of 2-phenylbenz[d]azepine. Thus, when the phenylglycine anilide (32), prepared by amidation of the phenylglycine (31), was treated with hydrolysed phosphoryl chloride, no azepine (33) was formed; instead the 1-iminoazepine (34) was obtained in 40 % yield, which was then converted into 1-benzoyl-3,4-dihydroisoquinoline (35) by reaction with hydrochloric acid.[16]

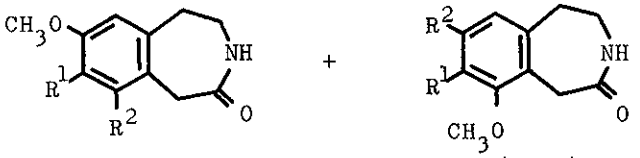
The synthesis of benz[d]azepines by photocyclisation has also been reported. Irradiation of an aqueous solution of N-chloroacetylphenethylamine (36a) with 2537Å light from a 60 W low pressure mercury lamp gave a separable mixture of the 1,2,4,5-tetrahydro-3H-3-benzazepin-2-ones (37a and 38a). The quantum yield for the formation of the benzazepinones suggests that this reaction involves an ionic process.[17] By this method, many benzazepinones have been synthesised,[17] which were then converted into the benzazepine by lithium aluminium hydride[18] or diborane reduction.[19]

Bernhard and Snieckus also reported a general synthesis of 2-dihydrobenzazepine (42) from the enamide (41) by photolysis. The

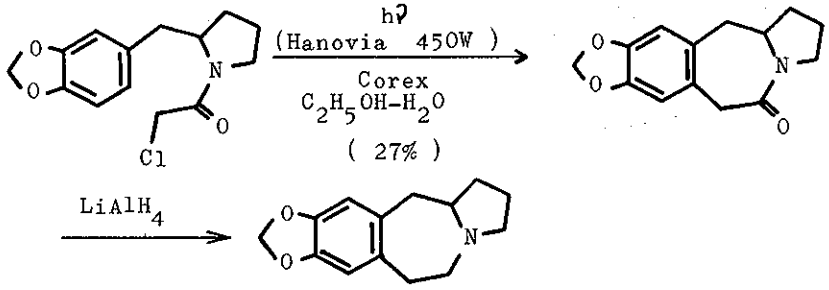
Chart 10



(36) a $R^1=R^2=H$
b $R^1=OCH_3$, $R^2=H$
c $R^1=R^2=OCH_3$



(37) (37)



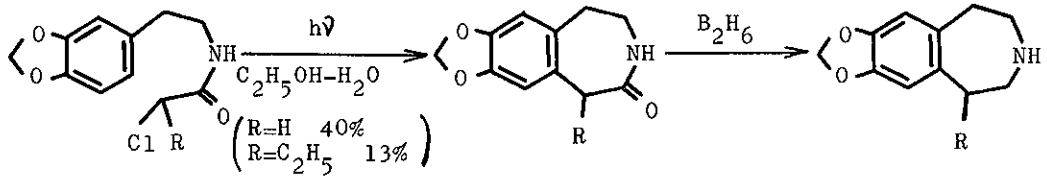
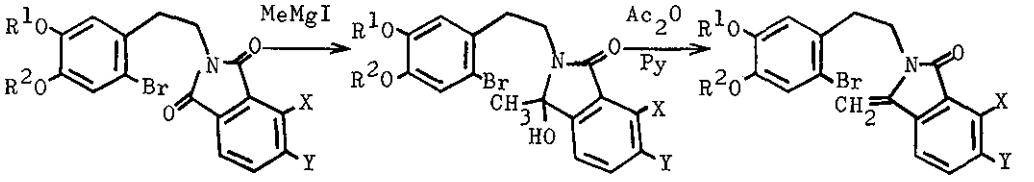
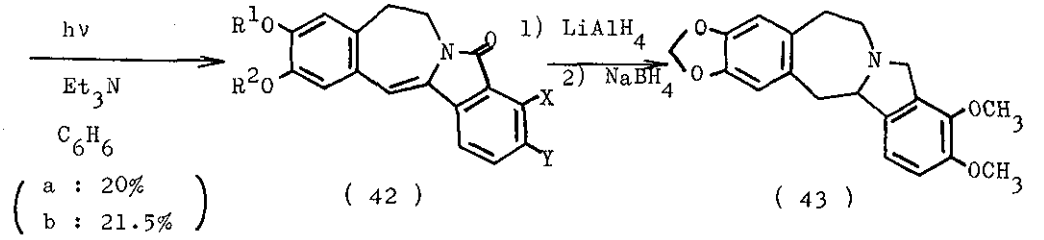


Chart 11



(40) (41)

(39) a $R^1=R^2=CH_3$, X=Y=H
b $R^1+R^2=CH_2$, X=Y=OCH_3



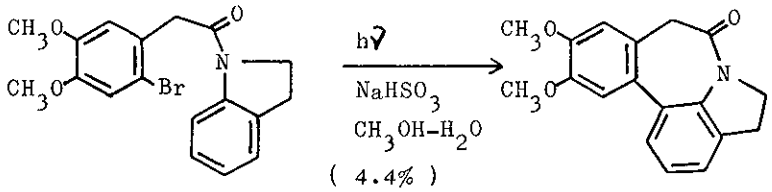
(a : 20%
b : 21.5%)

(42) (43)

starting material (41) was obtained by Grignard reaction of the imide (39) and dehydration of the resulting alcohol (40). Photolysis was carried out by irradiation with 2537Å light in benzene in the presence of triethylamine, and the product (42) was converted into Schöpf-Schweikert amine VI (43) by reduction.[20]

The dibenzoazepine system was synthesised by an application of the above enamide photocyclisation.[21] Thus, photolysis of the enamide type compound (44) with a 400 W high pressure mercury lamp in the presence of sodium hydrogen sulphite in aqueous methanol gave the dibenzoazepinone (45) corresponding to homolycorane in 4.4 % yield.[22]

Chart 12

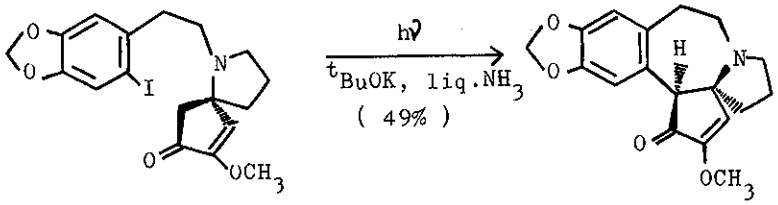


(44) (45)

Semmelhack[23] achieved an interesting photocyclisation to the benzazepine system by an intramolecular $S_{RN}1$ reaction mechanism. Irradiation of the aromatic iodide (46) having an active methylene group at an appropriate position with a Hanovia 450 W mercury lamp surrounded by a pyrex filter in liquid ammonia in the presence of potassium tert-butoxide afforded cephalotaxinone (47) in 94 % yield. The synthesis of the iodide (46) and the conversion of 47 into cephalotaxine will be discussed in a later section.

Semmelhack also converted the same iodide (46) into cephalotaxinone (47) by three other methods, the first was by benzyne reaction using tritylpotassium to obtain cephalotaxinone in 13 - 16 % yield,[24] the second by treatment with potassium amide in liquid ammonia or sodium-potassium alloy in 45 % yield,[23] and the third by reaction of bis(1,5-cyclooctadienyl)nickel at 25° with the anion derived from 46 with trityllithium in 25 - 30 % yield.[23]

Chart 13



(46) (47)

Method B

The second method for the synthesis of benz[d]azepine is a bond formation between C_1 and C_2, and only one example has been reported by Shamma.[25] Intramolecular aldol-like cyclisation of the formyl ester (48) with potassium tert-butoxide in dimethyl sulphoxide followed by lactonisation gave the thermodynamically less stable trans B/D fused rheadan type compound (49) in 56 % yield.

Chart 14

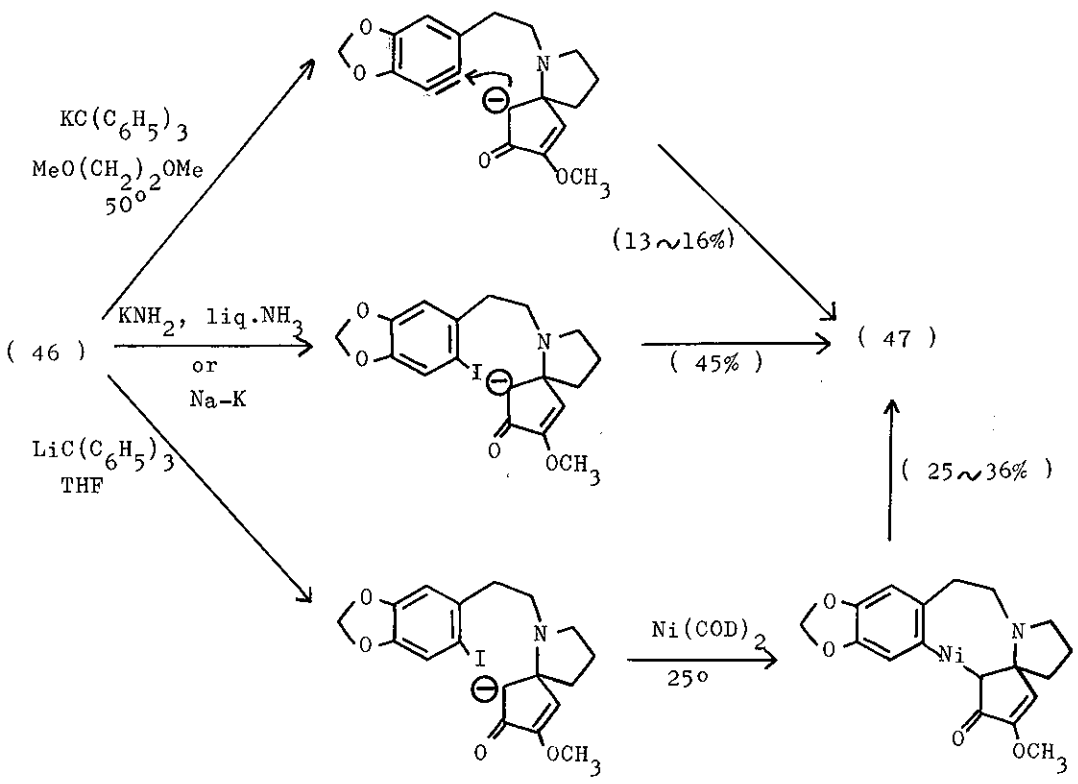
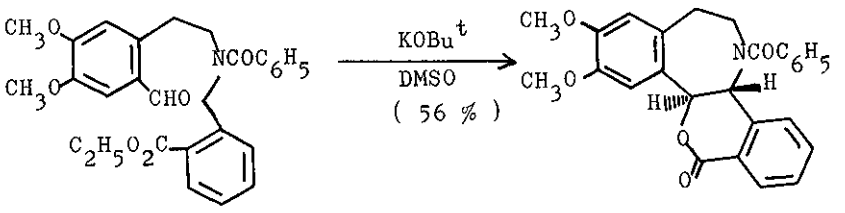

KC(C6H5)3
MeO(CH2)2OMe
50°
KNH2, liq.NH3
or
Na-K
LiC(C6H5)3
THF
(46)
(47)
(45%)
(13∼16%)
(25∼36%)
Ni(COD)2
25°
OCH3
Ni

Chart 15



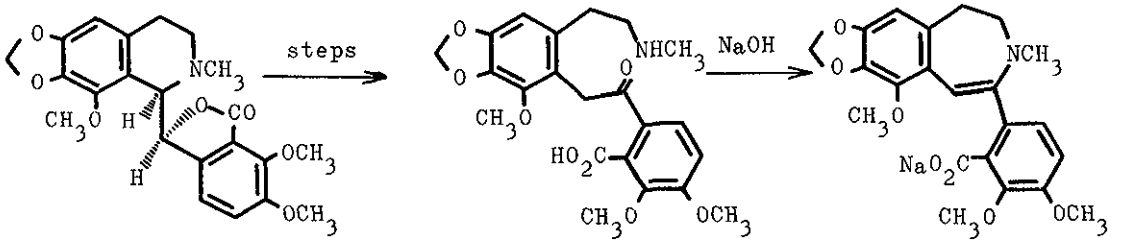
(48) (49)

Method C

The third method is a C_2-N bond formation by condensation of the amino group with the carbonyl or ester function, and this has been applied to the total synthesis of the rheadan alkaloids.

Nornarceine (51) derived from naturally occurring (-)-α-narcotine (50) was heated in 2 N sodium hydroxide to give the 1,2-dihydro-3H-benz[d]azepine (52) in 84 % yield;[26,27] this reaction has been used in a total synthesis of rhoeadine by Brossi[28,29] as described later.

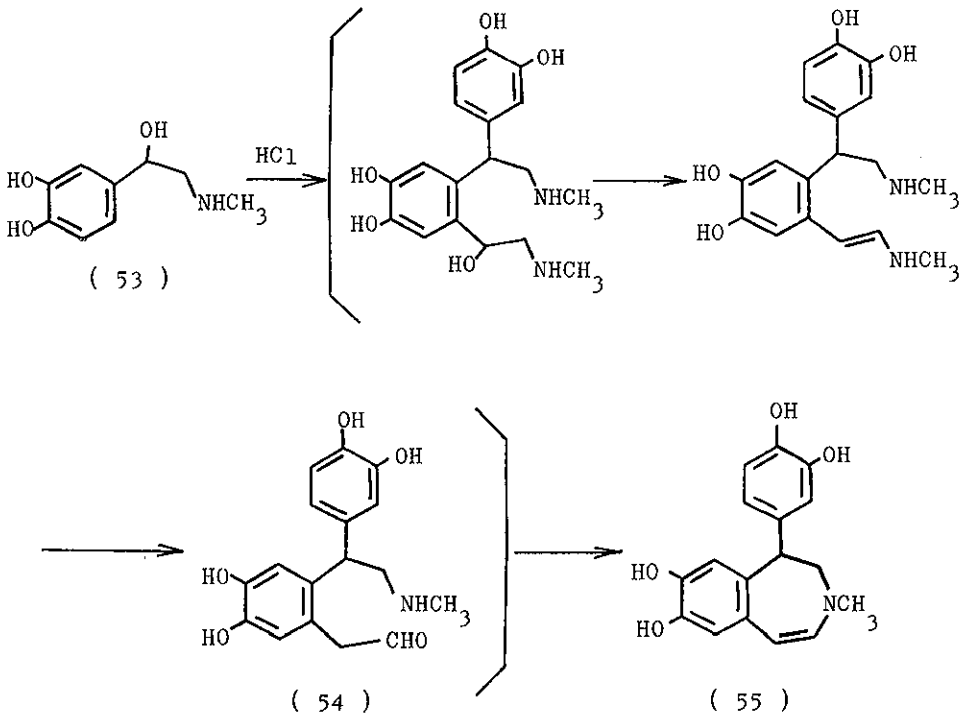
Chart 16



(50) (51) (52)

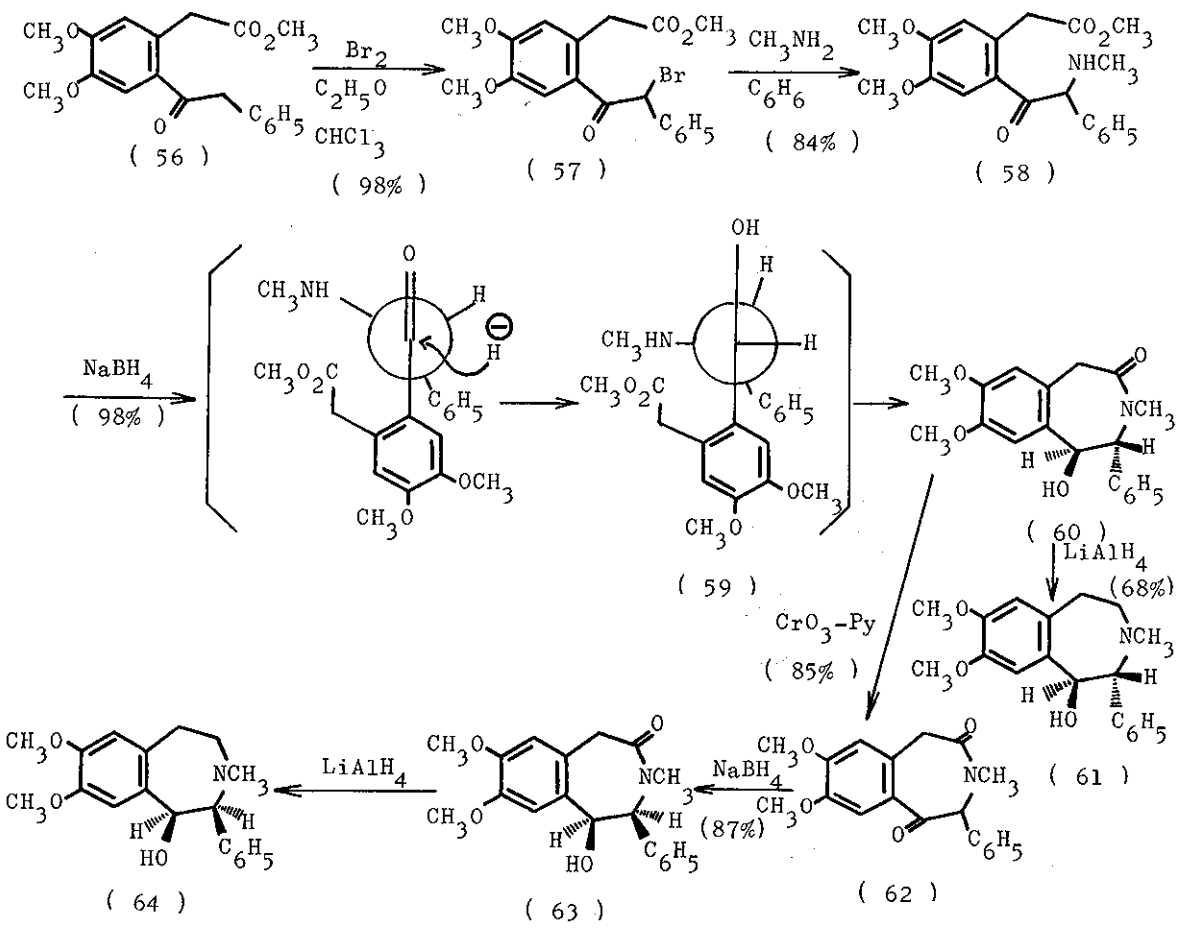
Acid treatment of adrenaline (53) with N hydrochloric acid at 37° for 5 days gave, together with other products, the 1,2-dihydro-3H-benz[d]azepine (55) isolated as the tetraacetate. In this reaction the aminoaldehyde (54) was suggested as a possible intermediate.[30]

Chart 17



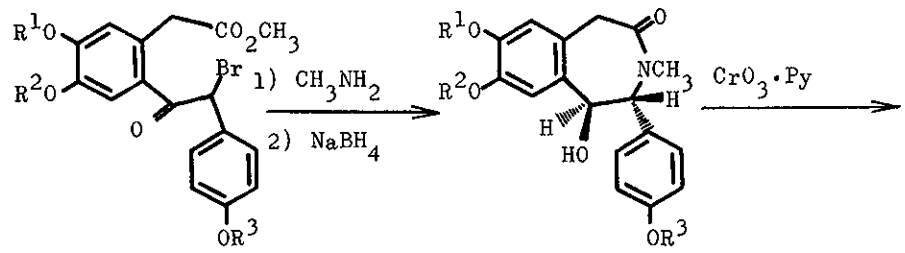
Intramolecular amidation of the amino ester (58) gave the benzazepine (60) from which the trans- and cis-isomers of 1,2,4,5-tetrahydro-7,8-dimethoxy-3-methyl-2-phenyl-3H-benzazepin-1-ol were synthesised stereospecifically by Inubushi.[16] Thus, the amino ester (58), which was obtained by an amination of the bromo ester (57) derived in turn from the keto ester (56), was heated in acetic acid to give the azepine (62) in poor yield. But treatment of 58 with sodium borohydride in methanol afforded the alcohol (59), which was immediately stereospecifically cyclised in 98 % yield to the benzazepine (60) having the hydrogens at C_1 and C_2 in the trans position. Lithium aluminium hydride reduction of 60 gave trans-2-phenylbenzazepin-1-ol (61). On the other hand, oxidation of 60 with chromium trioxide and pyridine, followed by sodium borohydride reduction of the resulting ketoazepine (62) afforded benzazepin-1-ol (63) which on lithium aluminium hydride reduction yielded cis-2-phenylbenzazepin-1-ol (64). The stereospecific reduction of 58 to 59 can be rationalised by Cram's rule. Thus, the reagent preferentially approaches the carbonyl group from the side of the smallest group-H, and the resulting alcohol is cyclised to give 60 which has the hydrogens at C_1 and C_2 in the trans position orientation.

Chart 18

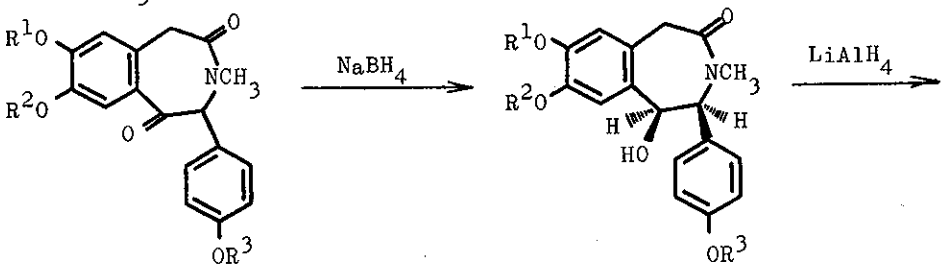


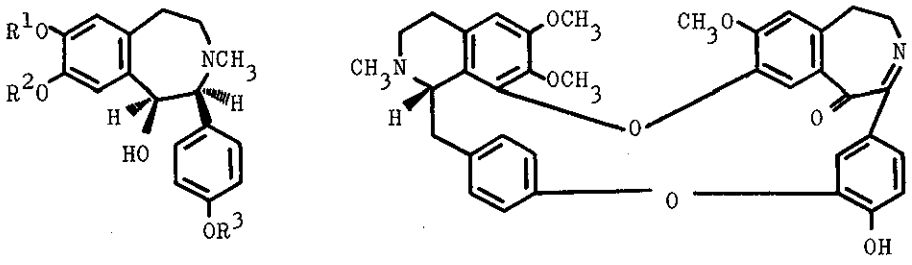
This stereospecific synthesis of 2-phenylbenzazepin-1-ol was applied for the structural determination of a bisbenzylisoquinoline alkaloids, stepinonine (65), by the same authors.[31,32] The sequence is shown in Chart 19.

Chart 19



$R^1=R^2=CH_3$, $R^3=C_2H_5$
$R^1=R^3=CH_3$, $R^2=C_2H_5$
$R^1=C_2H_5$, $R^2=R^3=CH_3$
$R^1=R^2=R^3=CH_3$





(65)

Method D

The fourth method consists in formation of the benzazepine by reaction of 3,4-dihydroisoquinoline with diazoalkane through an intermediate, 1aH-azirino[2,3a]isoquinoline derivative. The typical reaction is reported by Bernhard and Snieckus as follows.[19] Reaction of 3,4-dihydro-2-methyl-6,7-methylenedioxyisoquinolinium perchlorate (hydrastinine) (67), prepared from N-formylhomopiperonylamine (66) by standard method, with an excess of ethereal diazomethane in benzyl alcohol led to the aziridinium salt (68)[33,34] in addition to the aziridinoazepine (69). The ring expansion reaction of this salt (68) under mild solvolytic conditions gave the 1-substituted 1,2,4,5-tetrahydro-3H-benz[d]azepine derivatives. Thus, heating the aziridinium salt (68) with absolute methanol for 2 hr afforded the 1-methoxybenzazepine (70) in 19 % yield, which was easily converted into the benzazepine (71) by hydrogenolysis on 5 % palladium-barium sulphate. Similarly, treatment of 68 with boiling water gave the 1-hydroxybenzazepine (72) in 22 % yield. Moreover, reduction of the second aziridinium salt (69) with lithium aluminium hydride furnished in 20 % yield the 2-methylbenzazepine (73) by a S_N2 like ring opening.

In a related sequence, Göber and Engelhardt[35] reported that treatment of hydrastinine (67) and cotarnine (74) with phenyldiazomethane in methanol at room temperature gave the 1-methoxy-2-phenylbenzazepines (75) and (76), in 30 % yield, respectively.[36] Although the stereochemistry of the substituents was not recorded, these compounds probably have the cis-configuration based on the coupling constant of the C_1- and C_2-protons in the n.m.r. spectrum.

Chart 20

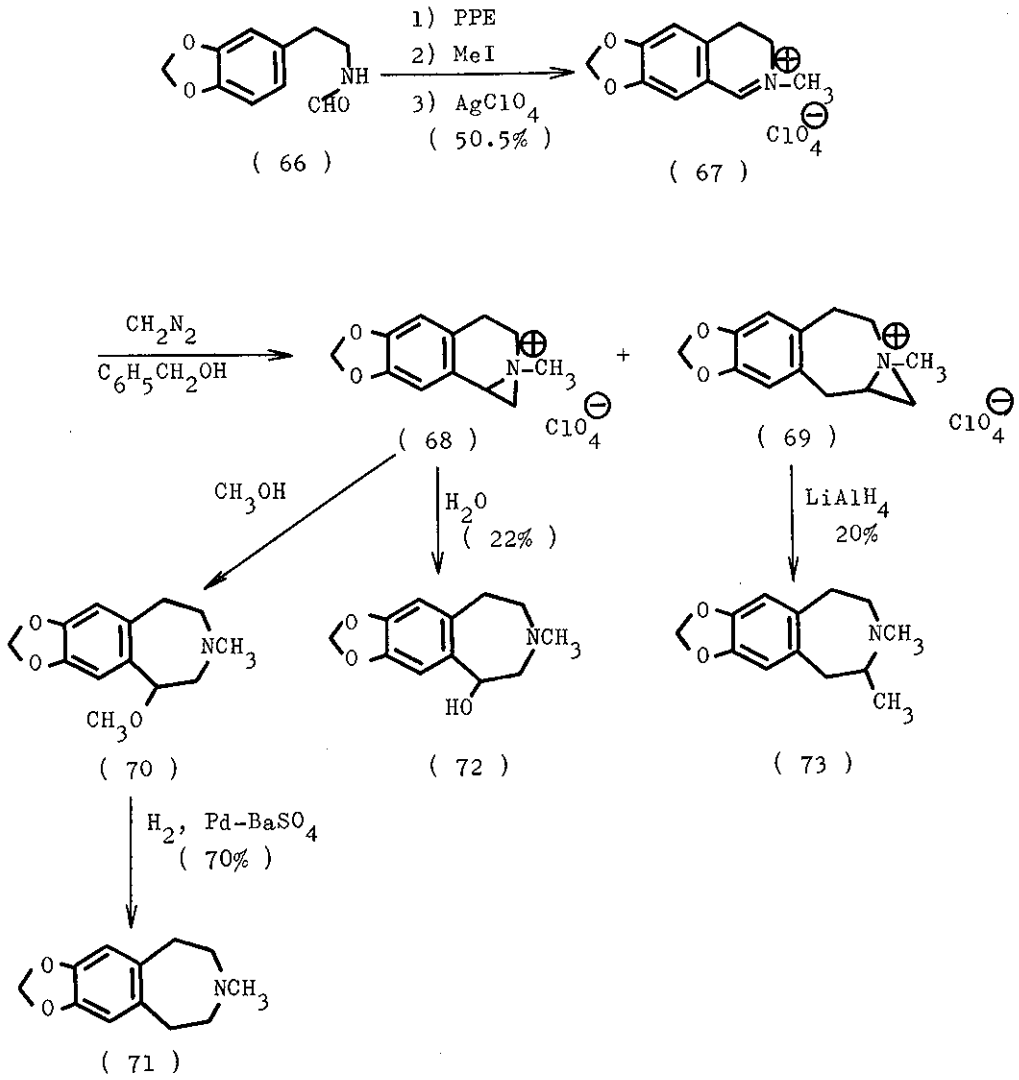
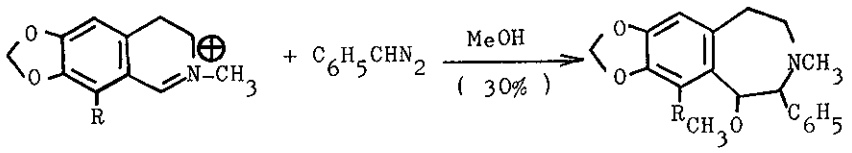

1) PPE
2) MeI
3) AgClO4
(50.5%)
NH
CHO
N-CH3
ClO4
(66)
(67)
CH2N2
C6H5CH2OH
(68)
(69)
CH3OH
H2O
(22%)
LiAlH4
20%
NCH3
CH3O
HO
CH3
(70)
(72)
(73)
H2, Pd-BaSO4
(70%)
(71)

Chart 21



(67) R=H

(74) R=OCH_3

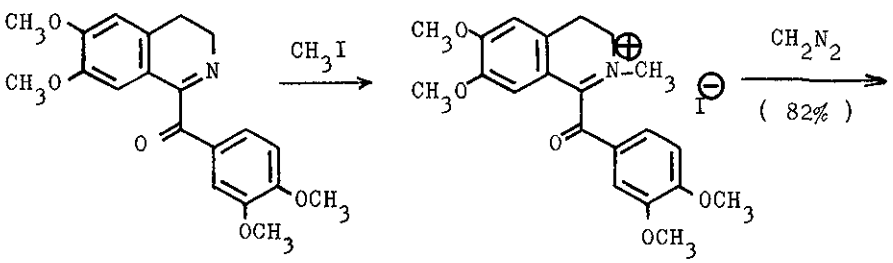
(75) R=H

(76) R=OCH_3

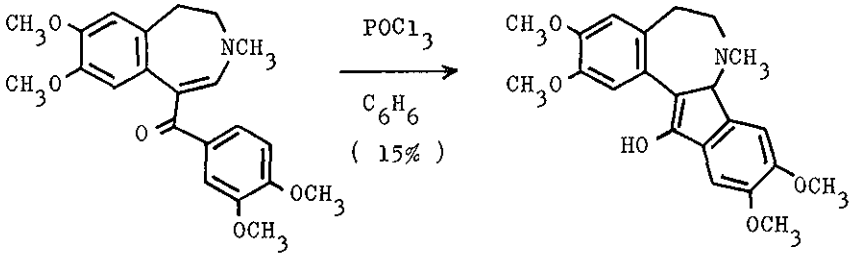
Kametani[37] synthesised the indenobenzazepine (80) which was a key intermediate for the preparation of a rheadan ring system, by application of this method. Treatment of the 1-benzoyl-3,4-dihydro-2-methylisoquinolinium iodide (78), obtained from 3,4-dihydropapaveraldine (77) and methyl iodide, with an excess of ethereal diazomethane in methanol at 0° and then leaving it overnight gave the 5-benzyoyl-1,2-dihydrobenzazepine (79) in 82 % yield. Cyclisation of this product with phosphoryl chloride in boiling benzene furnished the indenobenzazepine (80).

Dimethyloxosulphonium methylide is also available instead of

Chart 22



(77) (78)



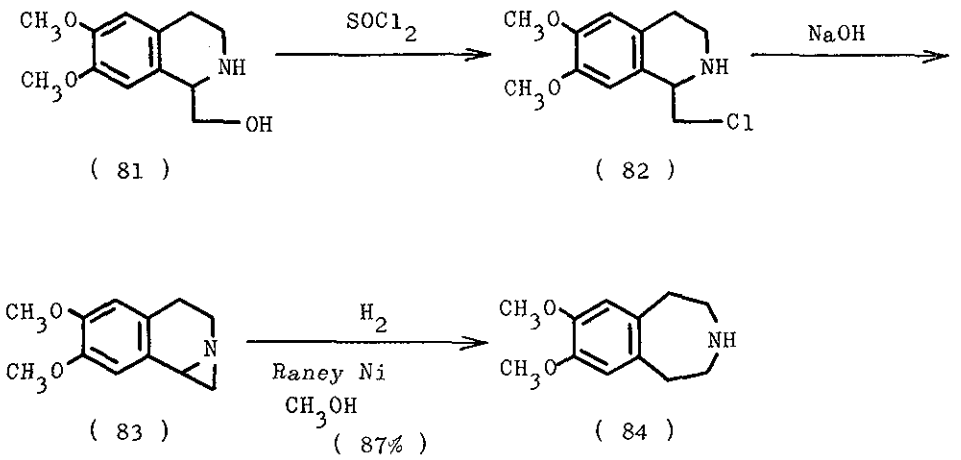
(79) (80)

diazomethane. Treatment of the 1-benzoyl-3,4-dihydro-2-methylisoquinolinium iodide (78) with dimethyloxosulphonium methylide in dimethyl sulphoxide at room temperature for 16 hr gave in poor yield the same benzazepine (79).[38]

Moreover, an isopavine alkaloid was also synthesised by this ring expansion method as described later.

All the examples discussed above have used quaternary ammonium salts as starting materials. However, Kobor and Koczke[39] reported a benzazepine synthesis by reductive ring opening of a tertiary aziridine derivative. Thus, treatment of calycotomine (81) with thionyl chloride, followed by alkaline treatment of the chloride (82), led to the aziridine (83). Reductive ring expansion of this with hydrogen and Raney-nickel in methanol generated in 87 % yield the benzazepine (84), which has no substituent on nitrogen.

Chart 23



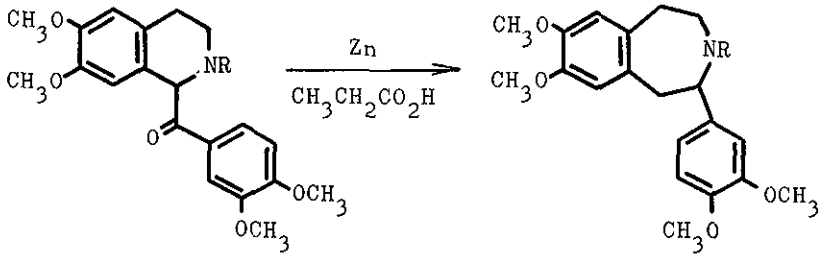
(81) (82) (83) (87%) (84)

The fifth method is an application of ring expansion by molecular rearrangement and is similar to the fourth method on the grounds of reaction mechanism in that both involve an aziridine intermediate.[40]

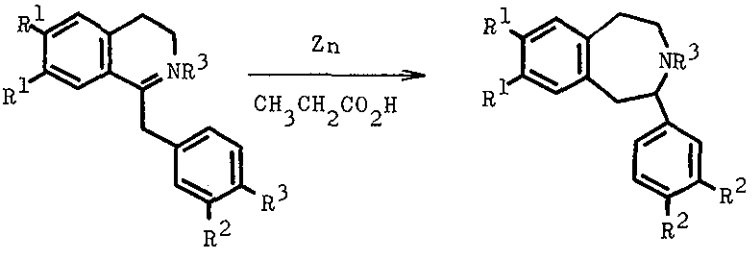
When tetrahydropapaveraldine type compound (85) was treated with zinc and propionic acid, 2-phenylbenzazepine (86) was isolated. Similarly, 1-benzoyl-3,4-dihydro-2-methylisoquinolinium salts (87) were reduced with zinc in propionic acid to give the 2-phenylbenz-

azepines (88), but the 1-benzoyl-3,4-dihydroisoquinolines were reduced without rearrangement under the same conditions to the 1,2,3,4-tetrahydroisoquinolines.[41]

Chart 24



(85) R=CH_3 or C_2H_5 (86) R=CH_3 or C_2H_5



(87) (88)

R^1=R^2=H, R^3=CH_3

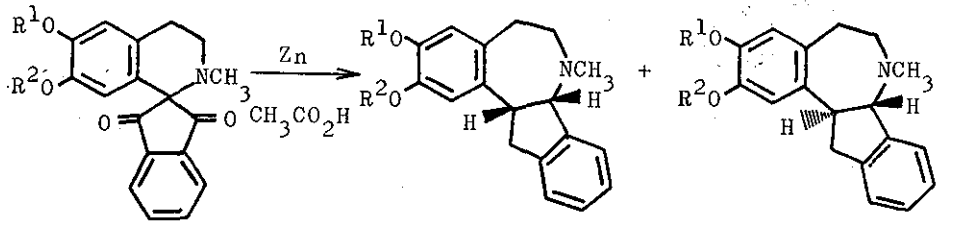
R^1=R^2=OCH_3, R^3=CH_3

R^1=R^2=OCH_3, R^3=C_2H_5

R^1=OCH_3, R^2=H, R^3=CH_3

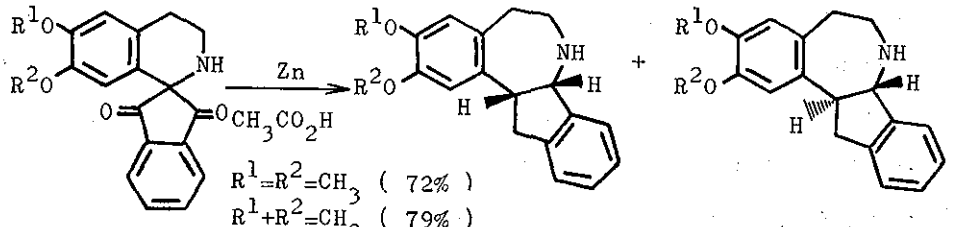
In a related sequence it was found that treatment of the diketo-spiroisoquinolines (89) with zinc in refluxing acetic acid for 1.5 hr gave a mixture of the cis- and trans-indanoazepines (90 and 91) in ratio of 1 : 3 in good yield, whose separation succeeded only partially.[42] In this reaction the secondary amines (92) were transformed into the cis - and trans- benzazepines (93) and (94) in a ratio of 1 : 3, whose fact was different from Gardent's work described above.

Chart 25



(89) $R^1=R^2=CH_3$ (73%)
$R^1+R^2=CH_2$ (85%)

(90) (91)



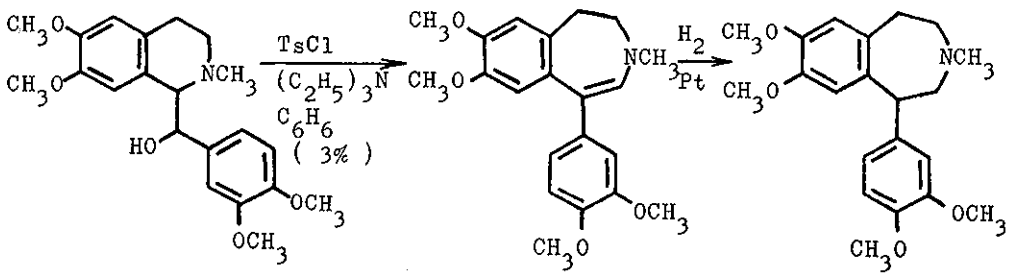
$R^1=R^2=CH_3$ (72%)
$R^1+R^2=CH_2$ (79%)

(92) (93) (94)

Furthermore, heating β-hydroxylaudanosine (95) with p-toluene-sulphonyl chloride and triethylamine in benzene for 6 hr generated 1-phenylbenzazepine (96) in poor yield by skeletal rearrangement. In this reaction the 1,2-dihydrobenzazepine was formed by rearrange-

ment of the aromatic ring to the β-position, and no aziridinium intermediate could participate in rearrangement. Hydrogenation of this product (96) on platinum gave the tetrahydrobenzazepine (97).[12]

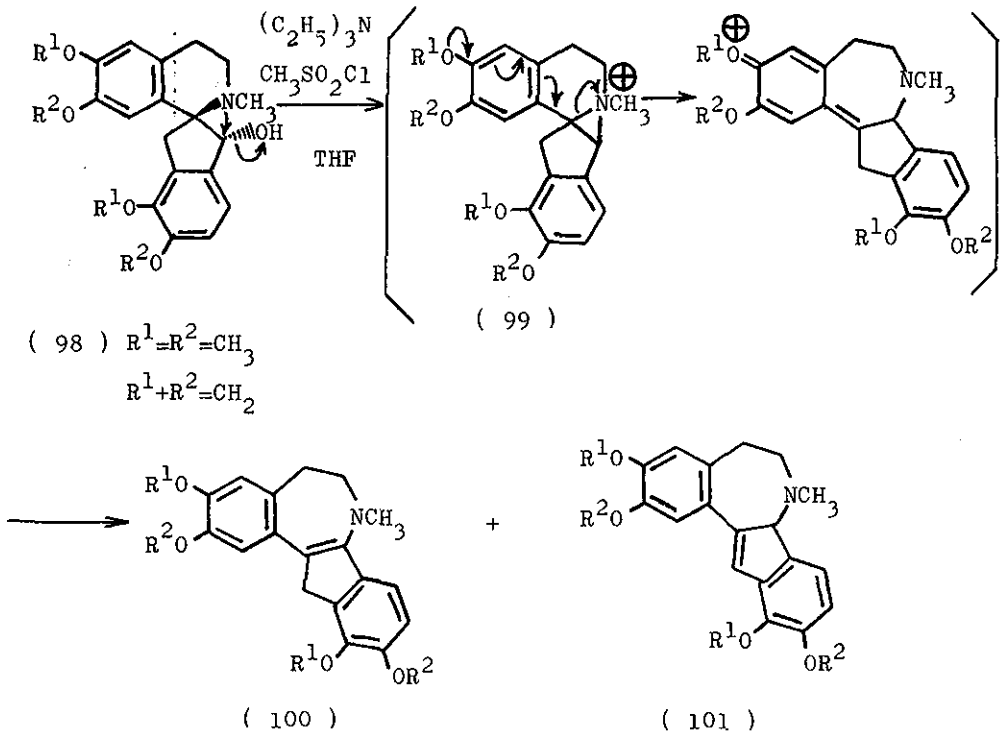
Chart 26



(95) (96) (97)

Irie[43,44] reported the construction of the benzazepine skeleton from a benzylic spiroisoquinoline, which had a β-aminoalcohol system, by skeletal rearrangement involving an aziridinium ion. When the trans-β-aminoalcohol (98) was treated with methanesulphonyl chloride in triethylamine and tetrahydrofuran at 0°, a molecular rearrangement occurred with formation of two isomeric benzazepines, (100) and (101), in a 1 : 10 ratio, which could be separated. The former base (100) was stable, but the latter (101) was unstable and converted into the former base (100) on alumina chromatography. Shamma[40] proposed that this reaction could proceed logically through the intermediacy of the aziridinium ion (99). The indenoazepines (101) were converted into the rheadan alkaloids, rhoeadine and alpinigenine by Irie.[44]

Chart 27



(98) $R^1=R^2=CH_3$
$R^1+R^2=CH_2$

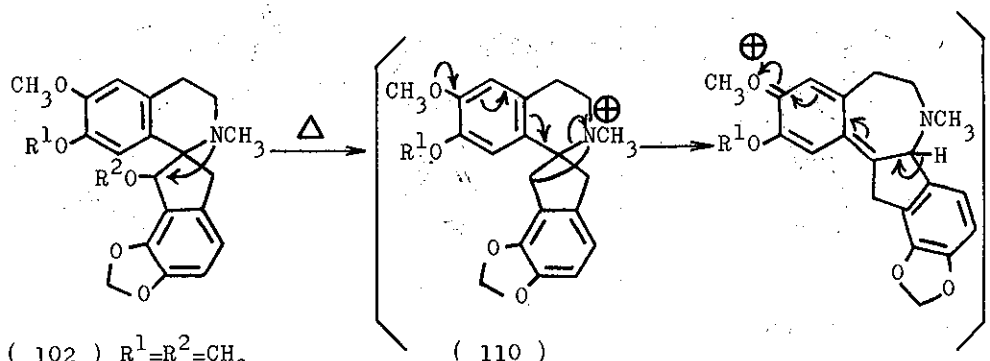
(99)

(100)

(101)

In 1971 and 1972, Mollov[45,46] reported that pyrolysis of ochotensine type alkaloids, fumaritirine (102), fumaritridine (103), fumarophycine (104), and O-methylfumarophycine (105) furnished the benzazepines (106 - 107), whose structures were characterised mainly by i.r. and n.m.r. spectroscopy. However, Shamma[40] suggested the products to have structures (108 - 109) by reaction mechanism through aziridinium intermediates (110) as indicated in Chart 28.

Chart 28



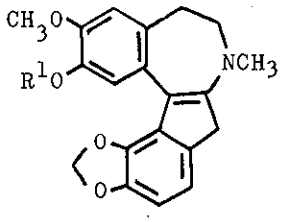
(102) $R^1=R^2=CH_3$

(103) $R^1=H$, $R^2=CH_3$

(104) $R^1=H$, $R^2=COCH_3$

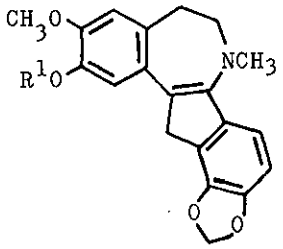
(105) $R^1=CH_3$, $R^2=COCH_3$

(110)



(106) $R^1=CH_3$

(107) $R^1=H$

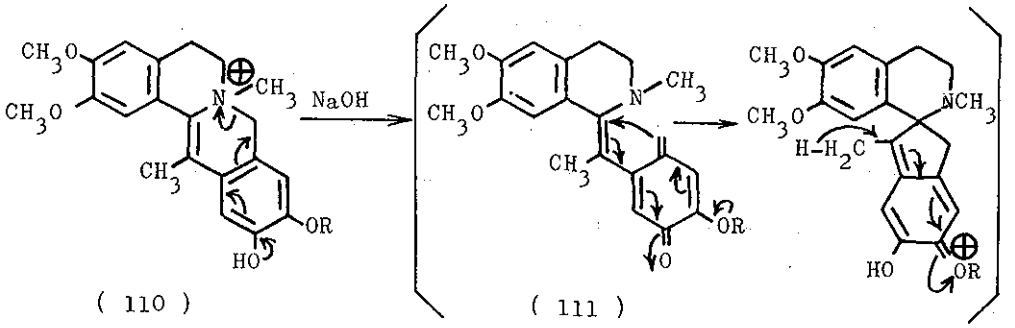


(108) $R^1=CH_3$

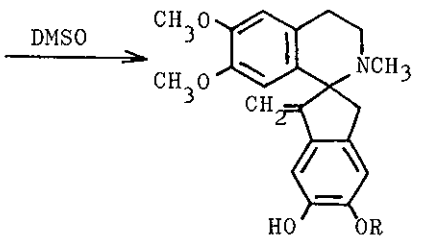
(109) $R^1=H$

On the basis of biogenetic analysis of spirobenzylisoquinoline alkaloids,[40,47,48] Shamma treated the 7,13-dimethylprotoberberinium salts (110) having phenolic hydroxyl group on ring D with sodium hydroxide in dimethyl sulphoxide and obtained the phenolic spirobenzylisoquinolines (112) via the quinone methide (111).

Chart 29



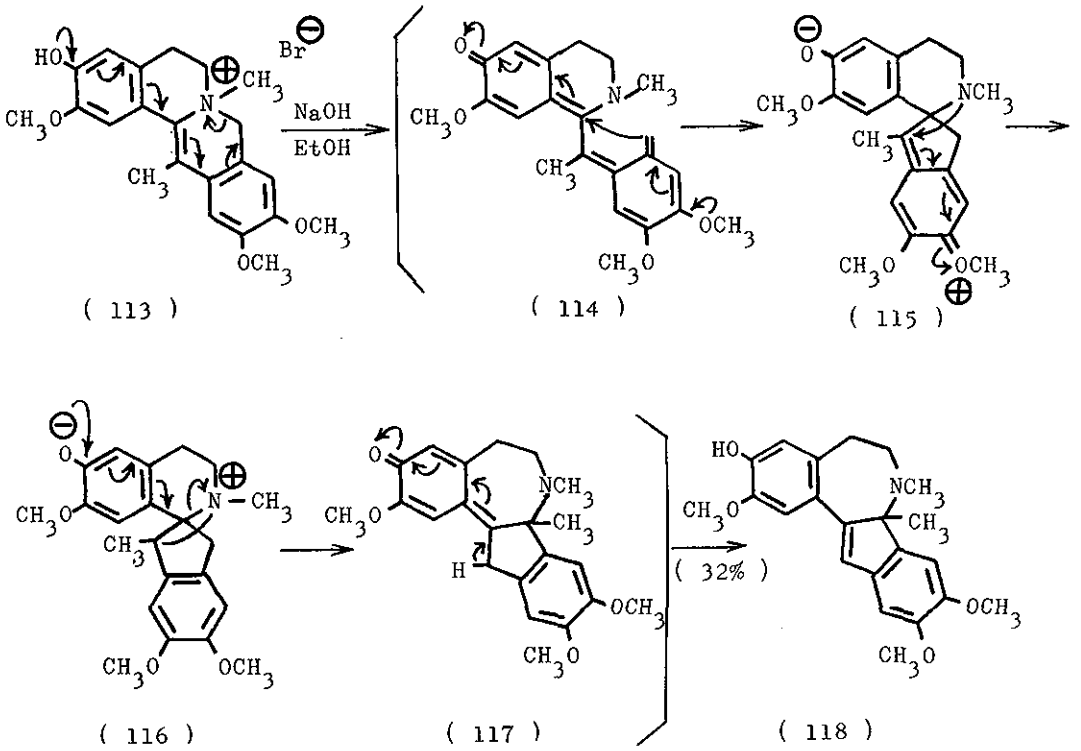
(110) (111)



(112)

On the other hand, base treatment of the protoberberine having a phenolic hydroxyl group at A ring proceeded in a different way to form the indenobenzazepine.[40,49] Thus, base-catalysed rearrangement of the 3-hydroxy-7,13-dimethyldihydroprotoberberinium salt (113) with sodium hydroxide in boiling ethanol for 90 hr yielded in 32 % yield the indenobenzazepine (118). In this reaction sequence, cyclisation of the quinone methide (114) led to the spirobenzylisoquinoline intermediate (115) which has a net positive charge spread between rings C and D. This charge-induced formation of the aziridinium ion (116) could readily be transformed into the product (118) via the p-quinone (117). It is interesting that the rearrangement stops at the spirobenzylisoquinoline stage when a phenolic function is present in ring D.

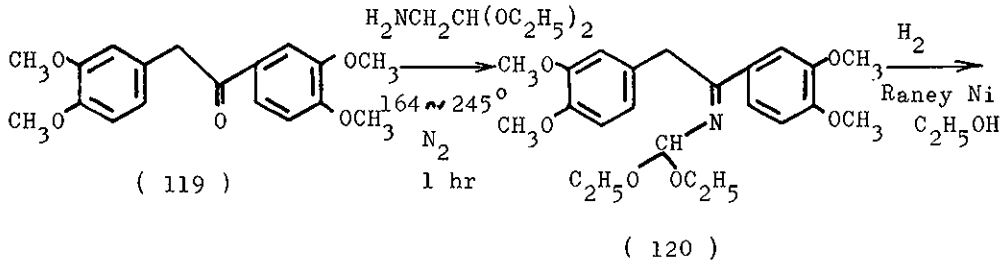
Chart 30



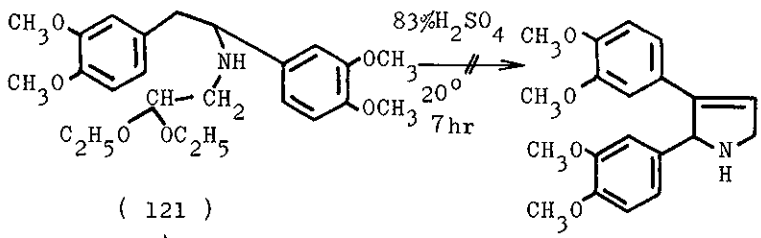
3. Total Syntheses of Isopavine Alkaloids

The isopavine system had been synthesised independently by Waldmann[8] and Battersby[9] before isopavine alkaloids were found in nature. Thus, Guthrie and his coworkers[50] in 1955 reported that the reaction of the benzylaminoacetal (121) with 83 % sulphuric acid at 20° for 7 hr gave the 2,3-dihydropyrrole derivative (122). The starting material (121) was synthesised by a usual way from the benzyl phenyl ketone (119) via the benzalaminoacetal (120).

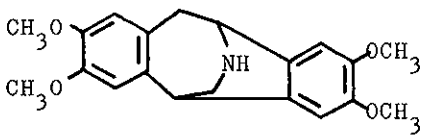
Chart 31



(119) (120)



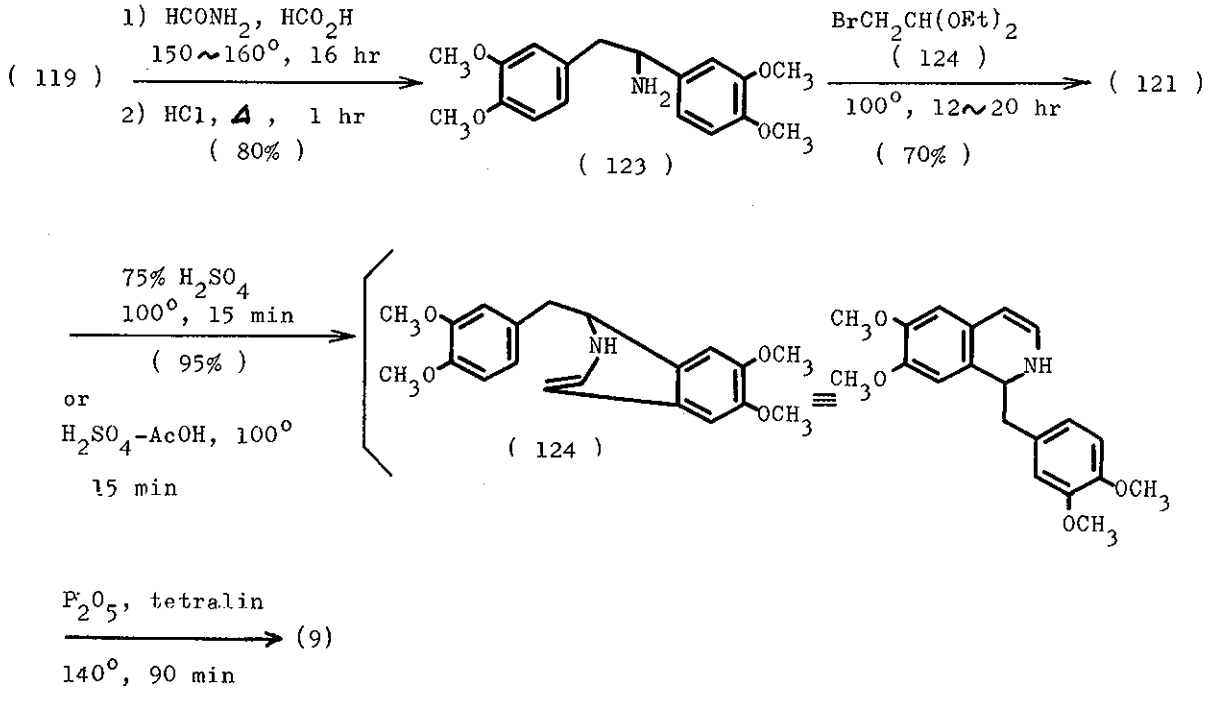
(121) (122)



(9)

Later, Waldmann and Chwala[8] reinvestigated Guthrie's work to present the correct structure (9) formed by double cyclisation. They synthesised the aminoacetal (121) by reaction of the bromoacetal with α-phenylphenethylamine (123) obtained from 119 by Leuckart reaction and treated 121 with 75 % sulphuric acid at 100° for 15 min. The structure was determined by oxidative degradation with potassium permanganate and Hofmann degradation. They also suggested that the intermediate could be the 1,2-dihydroisoquinoline derivative (124).

Chart 32

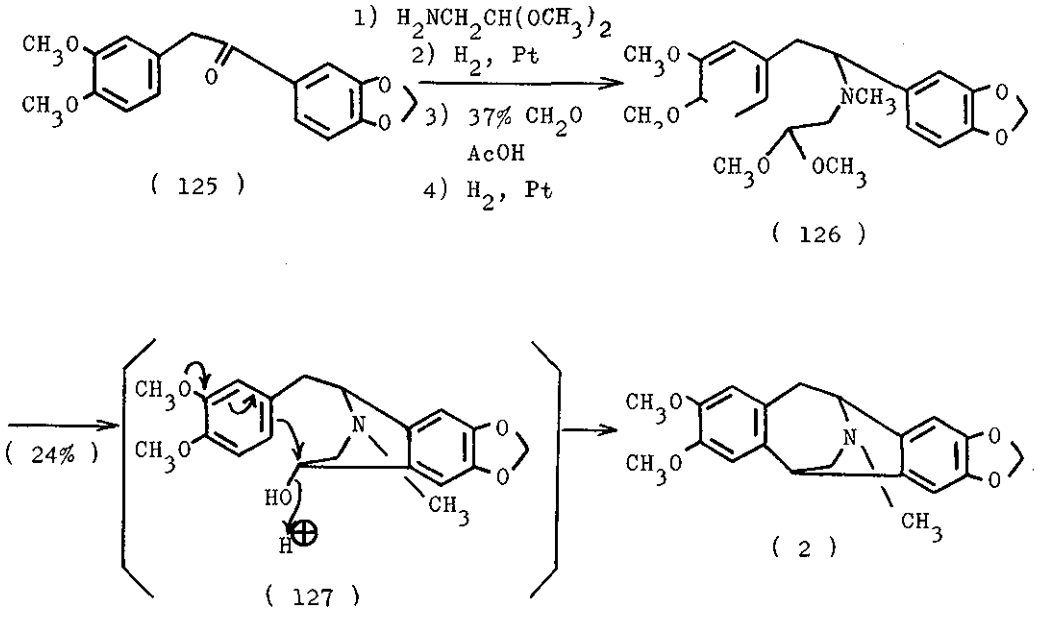


Shortly afterwards Battersby[9] also reported that Guthrie's product must have structure 9 based on chemical degradation and u.v. spectroscopy, and he proposed that this system be called "isopavine" on account of its similarity to the pavine structure.

This isopavine synthesis developed by Waldmann and Battersby has provided a standard method for the total synthesis of the isopavine type of alkaloids.

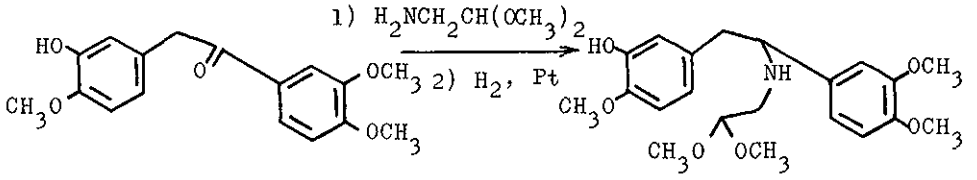
The first application of this method was a total synthesis of amurensinine (2) by Brown and his coworkers.[13,51] The aminoacetal (126), prepared from the benzyl phenyl ketone (125) as shown in Chart 33, was treated with concentrated hydrochloric acid at room temperature for 5 days to give amurensinine (2) in 24 % yield. In this double cyclisation, they suggested that the intermediate must be the 1,2,3,4-tetrahydro-4-hydroxyisoquinoline (127). Since N-dimethoxybenzyl-4-hydroxyisoquinoline (22) are readily cyclised in acid to the azepine derivatives (25) shown in Chart 7 and the aminoacetal (126) is converted in acid to amurensinine (2), they suggested that isopavine alkaloids arise from 1-benzyl-1,2,3,4-tetrahydro-4-hydroxyisoquinolines.

Chart 33

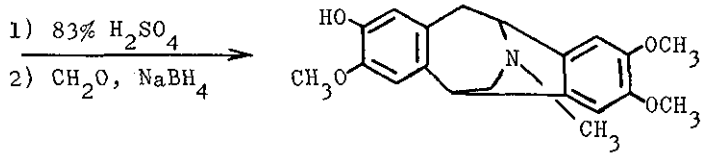


Similarly, Kupchan and Yoshitake[52] obtained thalisopavine (129) by treatment of aminoacetal (128) with 83 % sulphuric acid with exclusion of carbon dioxide at room temperature for 7 hr and then N-methylation of the product with formalin and sodium borohydride, and thus confirmed the position of the phenolic hydroxyl group in this alkaloid.

Chart 34



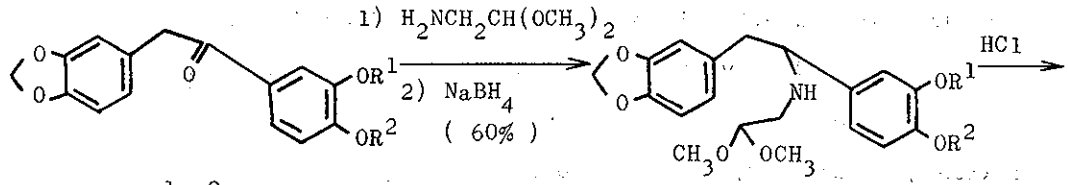
(128)



(129)

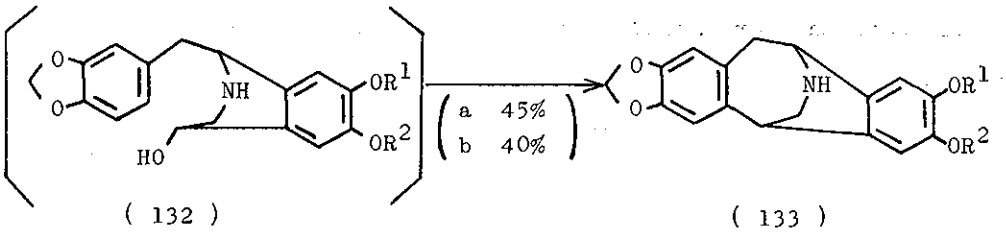
Reframidine (134) and reframine (135) have been also synthesised by the same method.[53] Thus, condensation of the ketones (130) with aminoacetaldehyde dimethyl acetal, followed by reduction with sodium borohydride gave the aminoacetals (131), which on treatment with concentrated hdyrochloric acid in ethanol for 5 days underwent double cyclisation in 40 - 45 % yield via the 1-benzyl-1,2,3,4-tetrahydro-4-hydroxyisoquinoline (132). N-Methylation of the products (133) completed the synthesis of reframidine (134) and reframine (135).

Chart 35



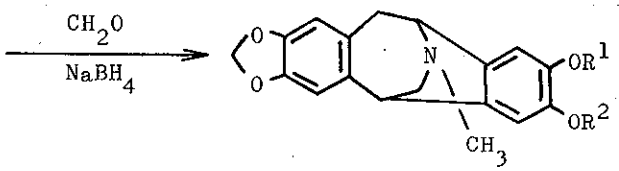
(130) a $R^1+R^2=CH_2$
b $R^1=R^2=CH_3$

(131)



(132)

(133)

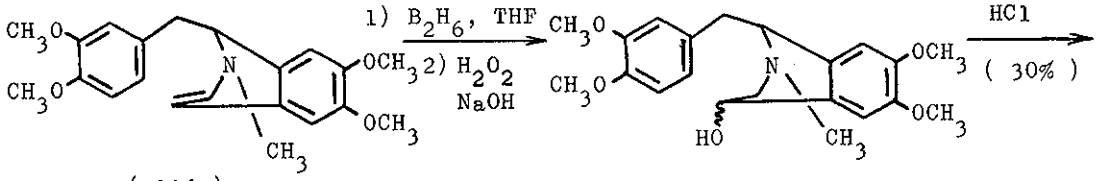


(134) $R^1+R^2=CH_2$

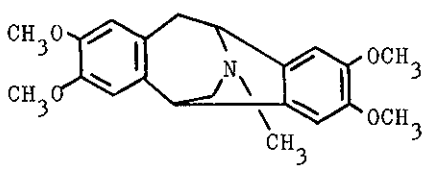
(135) $R^1=R^2=CH_3$

As described above, the 1-benzyl-1,2,3,4-tetrahydro-4-hydroxy-isoquinolines seem to be intermediates in double cyclisation, and, later, in support of this view it has been found that 4-hydroxy-isoquinoline is converted into isopavine by acid as follows. Hydro-boration of the 1,2-dihydroisoquinoline (136) in tetrahydrofuran, followed by oxidation with 30 % hydrogen peroxide in 20 % sodium hydroxide gave the 1,2,3,4-tetrahydro-4-hydroxyisoquinoline (137) in 60 % yield, which was treated with concentrated hydrochloric acid for 5 days to afford isopavine, O-methylthalisopavine (138) in 30 % yield. Amurensine (139) was also synthesised by the same method, but in this case the corresponding 4-hydroxyisoquinoline could not be isolated.[54]

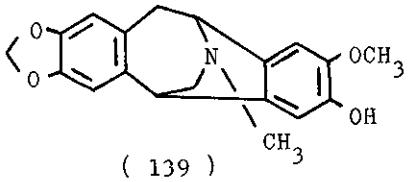
Chart 36



(136) (137)



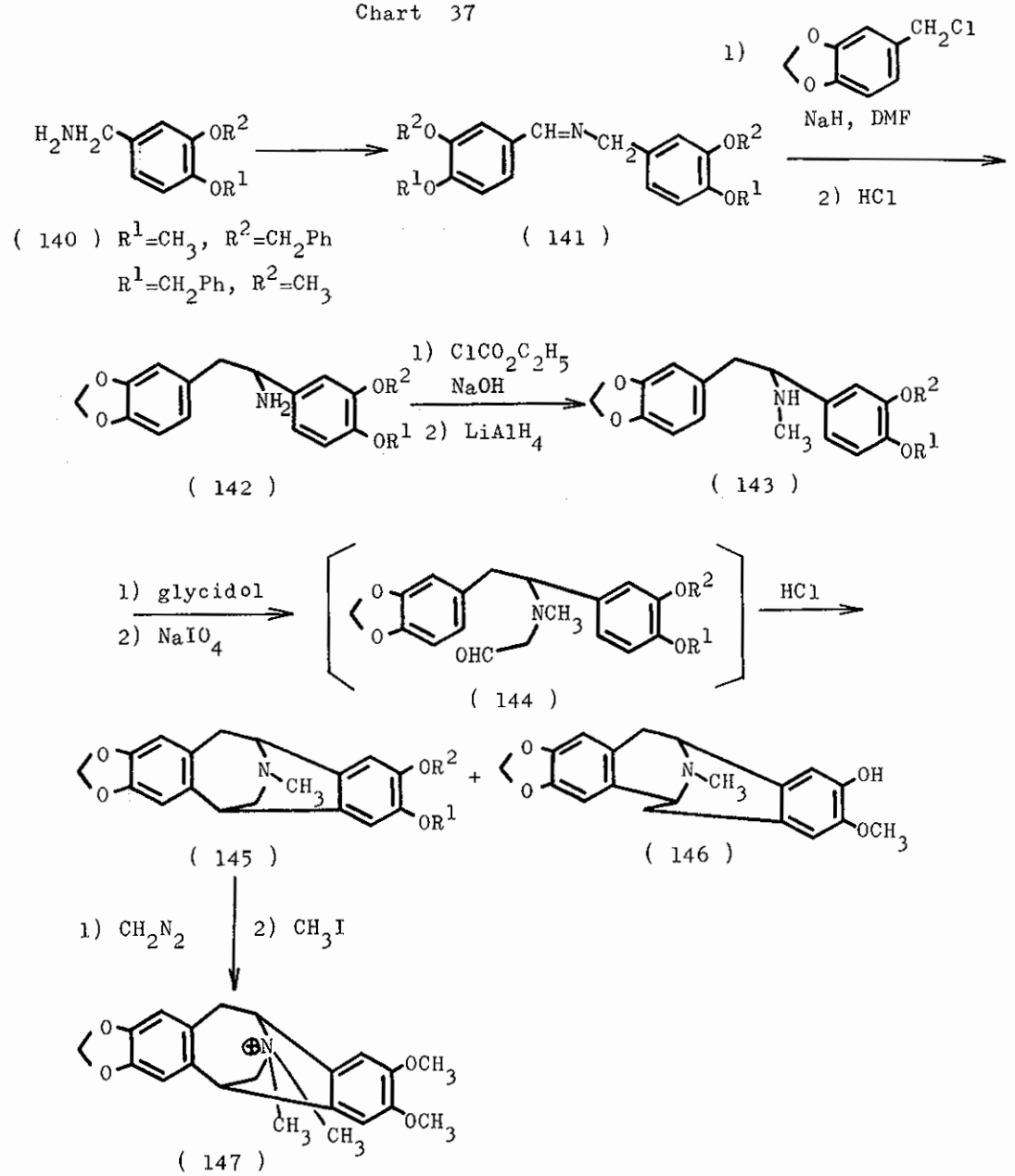
(138)



(139)

In 1974, Dyke and his coworkers[55] reported a modified synthesis of the aminoaldehyde and this was then converted by acid into iso-

Chart 37



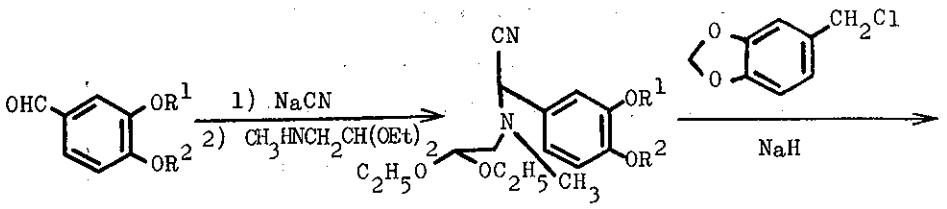
(140) R^1=CH_3, R^2=CH_2Ph
R^1=CH_2Ph, R^2=CH_3

(141) (142) (143) (144) (145) (146) (147)

pavine and pavine. The Schiff's bases (141) derived from the benzylamines (140) were condensed with piperonyl chloride to give the α-phenylphenethylamines (142), which on ethoxycarbonylation and reduction afforded the corresponding N-methylamine (143). Condensation of this with glycidol, followed by sodium periodate oxidation generated unstable aminoaldehydes (144), which, without isolation, were treated with concentrated hydrochloric acid in ethanol at room temperature for 16 hr and then at 100° for 24 hr to give the isopavines (145) and pavine (146) in 3.5 : 6 ratio. The isopavine was converted into reframine methiodide (147).

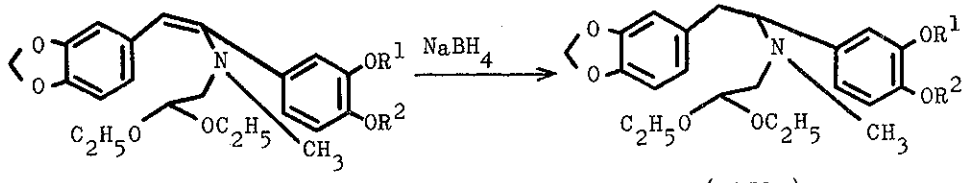
Moreover, the benzaldehydes (148) were converted into the cyanoaminoacetals (149), which were treated with piperonyl chloride, followed by reduction of the resulting benzylidene derivatives (150) to afford the aminoacetals (151). Cyclisation of 151 with 6 N hydrochloric acid at room temperature overnight and then heating for 6 hr gave isopavines (145) in 8 - 9 % overall yield from the benzaldehydes in addition to the pavines (146). In this double cyclisation, the intermediate 1-benzyl-1,2,3,4-tetrahydro-4-hydroxyisoquinolines (152) were formed in the initial cyclisation of the aminoacetals (151), and then a competition between nucleophilic substitution at C_4 by the 1-benzyl group leading to formation of isopavine (145) and dehydration to the 1,2-dihydroisoquinolines (153) occurs.[55] It has already been established that 1-benzyl-1,2-dihydroisoquinolines can undergo cyclisation to pavines under the conditions employed.[1,2]

Chart 38



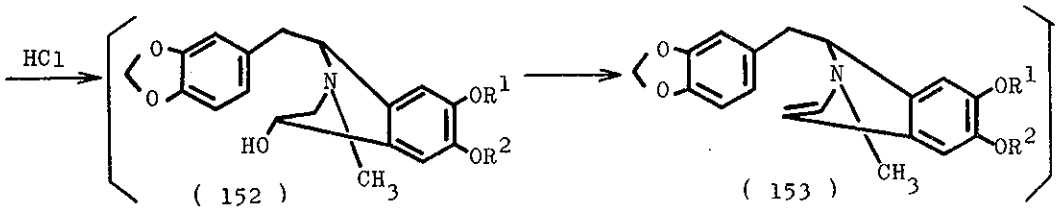
(148) R^1=CH_2Ph, R^2=CH_3
R^1=CH_3, R^2=CH_2Ph

(149)



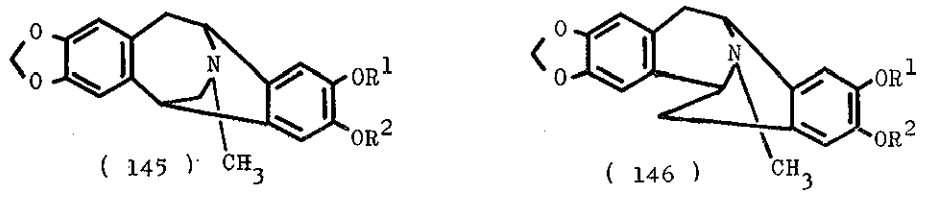
(150)

(151)



(152)

(153)

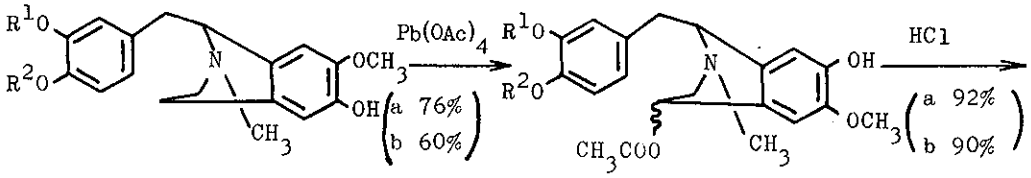


(145)

(146)

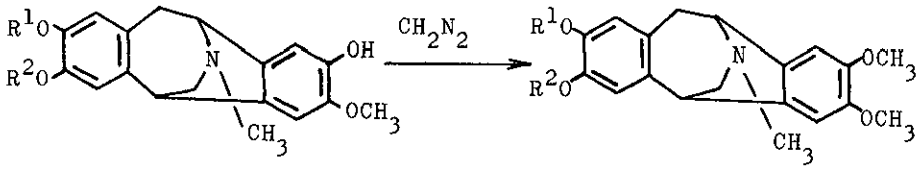
Umezawa and his co-workers[56] have accomplished a biogenetic type total synthesis of O-methylthalisopavine (138) and reframine (135) from the phenolic benzylisoquinolines (154). Thus, oxidation of the phenolic benzylisoquinolines (154) with lead tetraacetate in chloroform at 0° for a few min gave in good yield a diastereoisomeric mixture of 4-acetoxyisoquinolines (155), which were treated with concentrated hydrochlroic acid in ethanol at room temperature for 12 hr to afford the isopavines (156) in 90 - 92 % yield. Methylation of these isopavines gave O-methylthalisopavine (138) or reframine (135).

Chart 39



(154) a) $R^1=R^2=CH_3$
b) $R^1+R^2=CH_2$

(155)



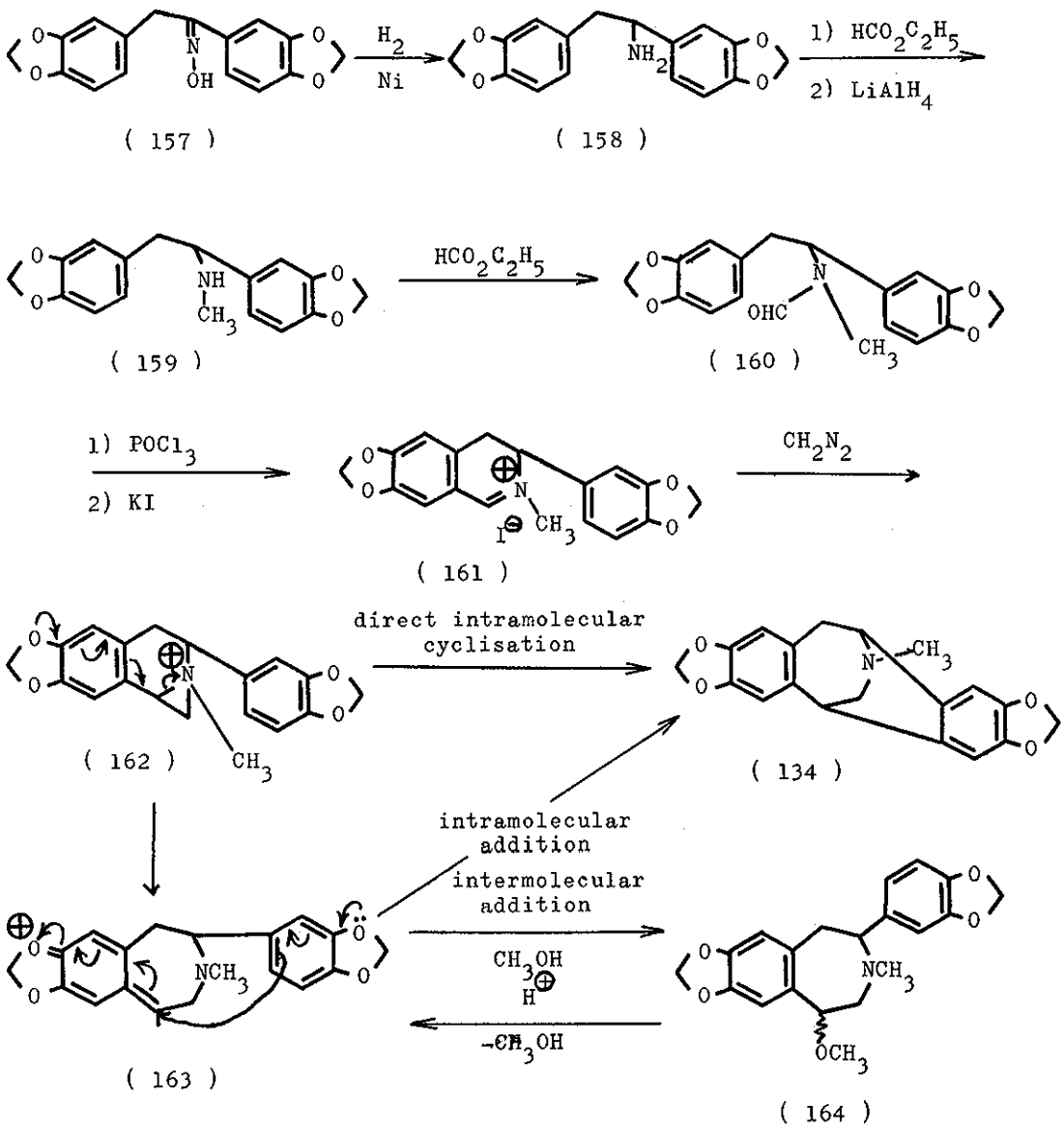
(156)

(135) $R^1+R^2=CH_2$
(138) $R^1=R^2=CH_3$

Kametani[57,58] in 1973 reported a new type of isopavine synthesis by a one-step ring opening and ring closure involving intramolecular attack by the electron-rich alkoxyphenyl group. This method is an application of the ring-expansion method through an aziridinium intermediate.

Deoxypiperoin oxime (157) was reduced with Raney-nickel and the resulting amine (158) was converted into the N-methylamine (159), whose N-formyl derivative (160) was subjected to Bischler-Napieralski reaction to give the 3,4-dihdyroisoquinolinium iodide (161). Treatment of this salt with diazomethane in methylene chloride at 0^{o} overnight afforded an amorphous product, possibly the crude aziridinium iodide (162), which was reacted with 1 % methanolic hydrochloric acid under reflux for 5 hr to form the benzazepine (164) in 20 % yield. This product was treated with 6N hydrochloric acid at room temperature for 1 week to give in 35 % yield reframidine (134). Moreover, the crude aziridinium salt (162) was converted directly into reframidine (134) by reaction with 6N hydrochloric acid in 20 % yield. Although there was no evidence for the formation of the azepine (164), the ready conversion into the isopavine (134) suggests that the aziridinium ring was not attacked intramolecularly by the 3-(alkoxyphenyl) group, but that the 6-oxygen atom on the isoquinoline ring was involved in forming a transient quinonoid intermediate (163), which was then attacked either intramolecularly by the 3-(alkoxyphenyl) group or intermolecularly by a methoxy-group, depending on the reaction conditions.

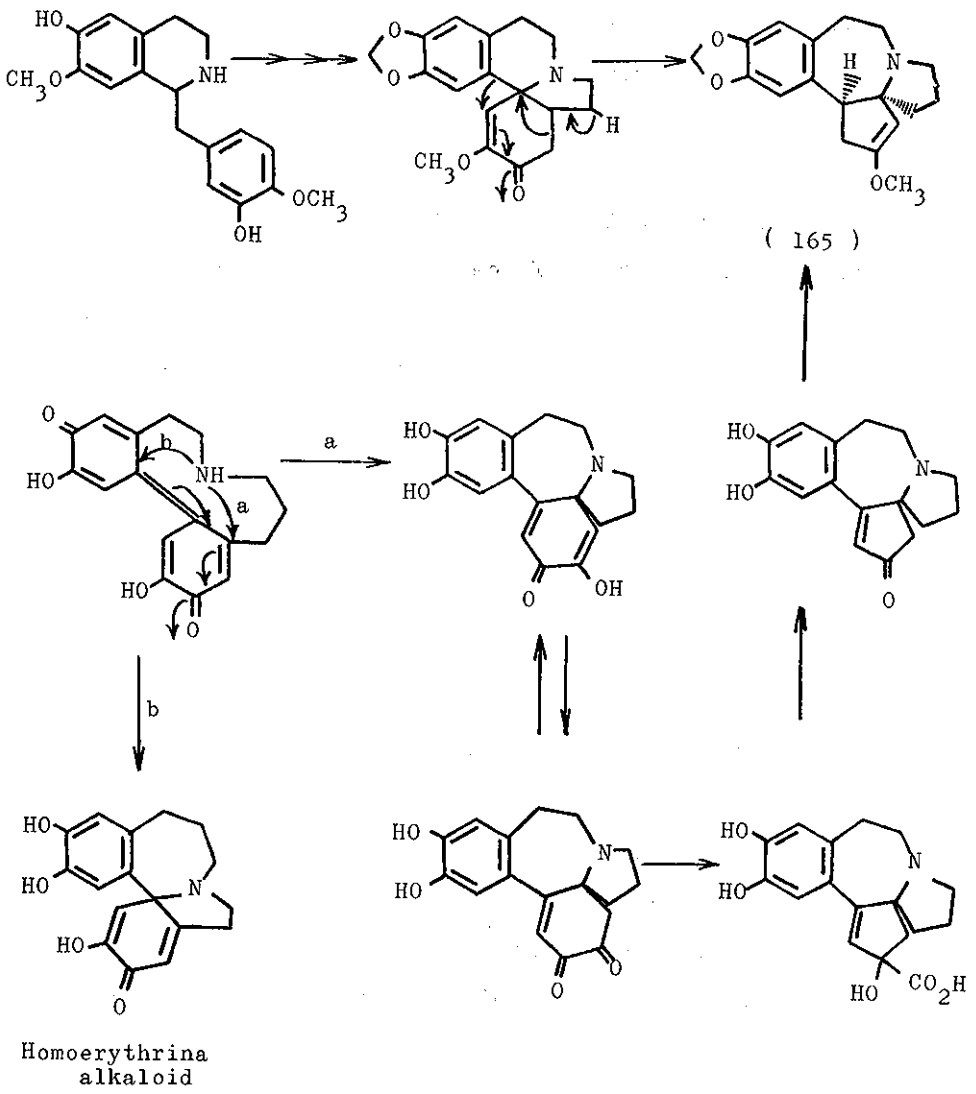
Chart 40


H2
Ni
1) HCO2C2H5
2) LiAlH4
(157)
(158)
HCO2C2H5
(159)
(160)
1) POCl3
2) KI
(161)
CH2N2
direct intramolecular
cyclisation
(162)
(134)
intramolecular
addition
intermolecular
addition
CH3OH
H⊕
-CH3OH
(163)
(164)

4. Total Synthesis of Cephalotaxine Alkaloids

Cephalotaxine (165) is the parent member of the Cephalotaxus group of alkaloids such as harringtonine (3),[1] some of which have shown significant inhibitory activity against experimental lymphoid

Chart 41



Homoerythrina alkaloid

leukemia in mice at relatively low dosage levels. Structural elucidation by a combination of chemical and X-ray crystallographic studies has shown cephalotaxine to have the modified erythrina structure (165), and a biogenetic scheme for the formation of cephalotaxine (165) from the Erythrina precursor has been proposed. However, the co-occurrence of Homoerythrina and Cephalotaxus alkaloids makes it most attractive to propose that both types of alkaloids are derived from a common precursor.[59]

In 1972, cephalotaxine (165) was synthesised by two different routes.[11,24] In the first total synthesis,[11] the key benzazepine (14) was synthesised by Lewis acid treatment of the β-aminoaldehyde (13), prepared by condensation of the phenylacetic acid chloride (166) with 2-hydroxymethylpyrrolidine (167), oxidation of the resulting amino alcohol (168), and reduction of which with lithium aluminium hydride yielded the enamine (169). The key enamine (169) was converted into the α-diketone (172) through the α-ketoacetate (170) and the α-keto alcohol (171). The α-diketone (172) was also obtained in one step by reaction of the enamine (169) with ethoxycarbonylpyruvate. Treatment of the α-diketone (172) with magnesium methoxide completed a spiro carbocyclic ring annelation to give desmethylcephalotaxinone (173), which has been found in Cephalotaxus harrangtonia. This product was subjected to trans-acetalisation to afford cephalotaxinone (174), reduction of which occurred stereospecifically to give cephalotaxine (165).

The second synthesis of cephalotaxine (165) involves a convergent preparation based on the two fragments, p-nitrobenzenesulphonate ester of 2-(2-chloro-4,5-methylenedioxyphenyl)ethyl alcohol and 1-aza-

7-methoxyspiro[4.4]non-6-en-8-one (178), which are related to the two sections of cephalotaxinone, as dissected in representation (174) in Chart 42

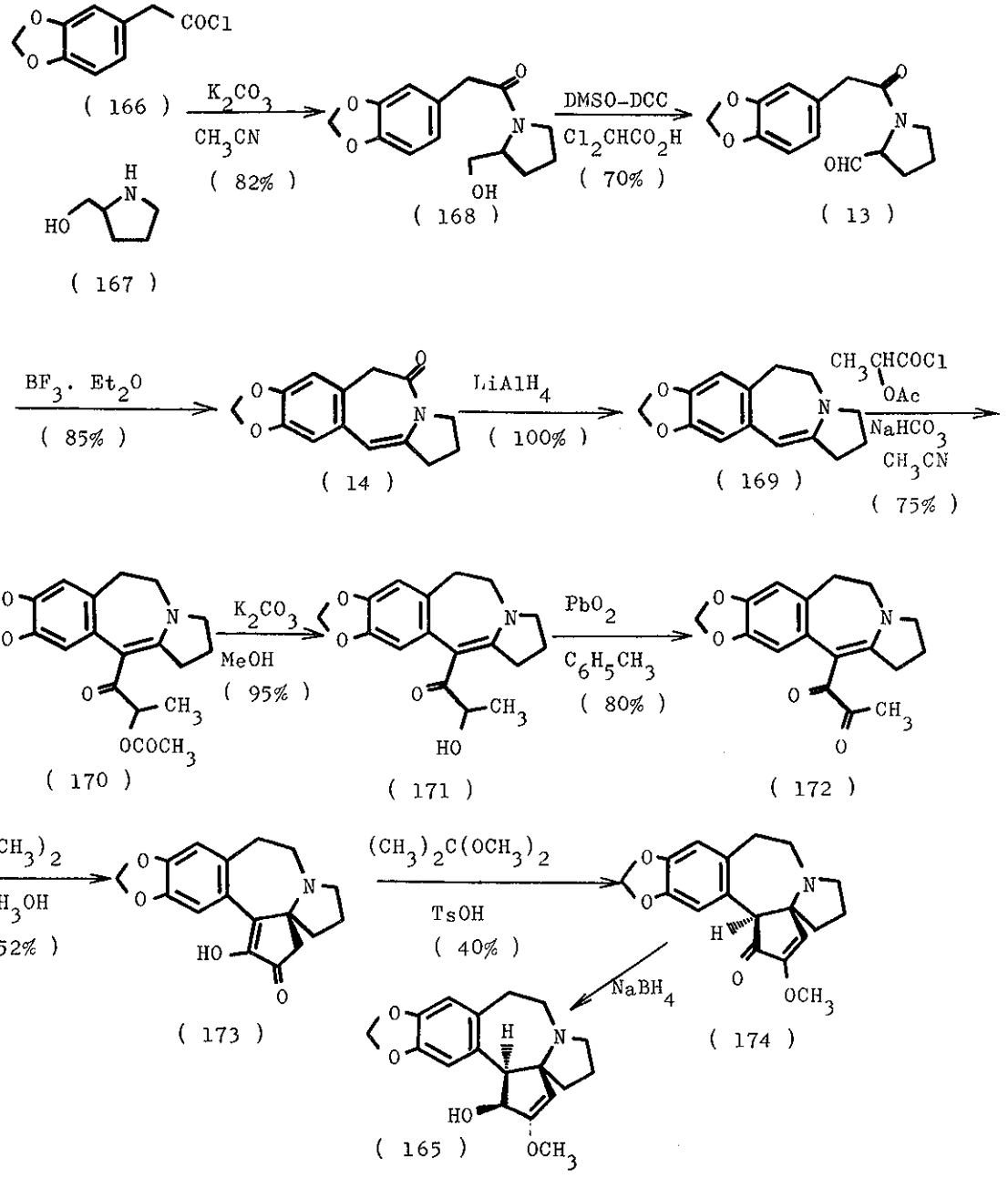
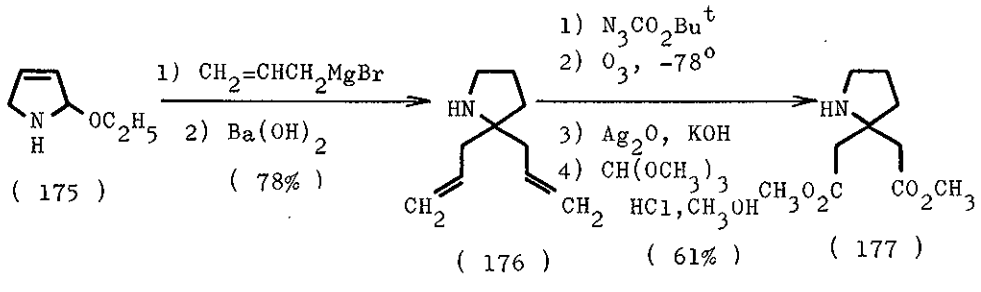
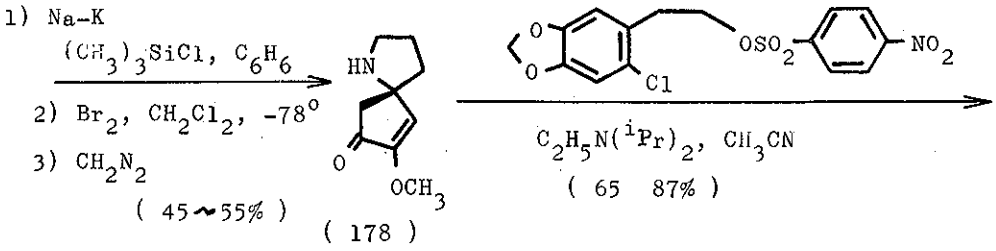


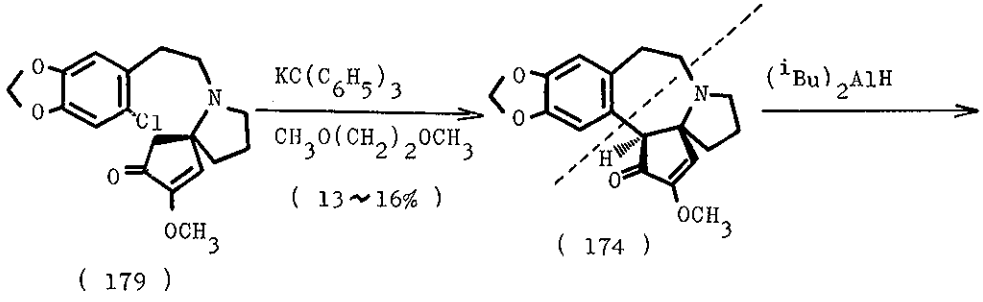
Chart 43



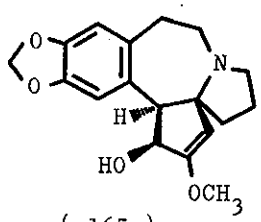
(175) (176) (177)



(178)



(179) (174)



(165)

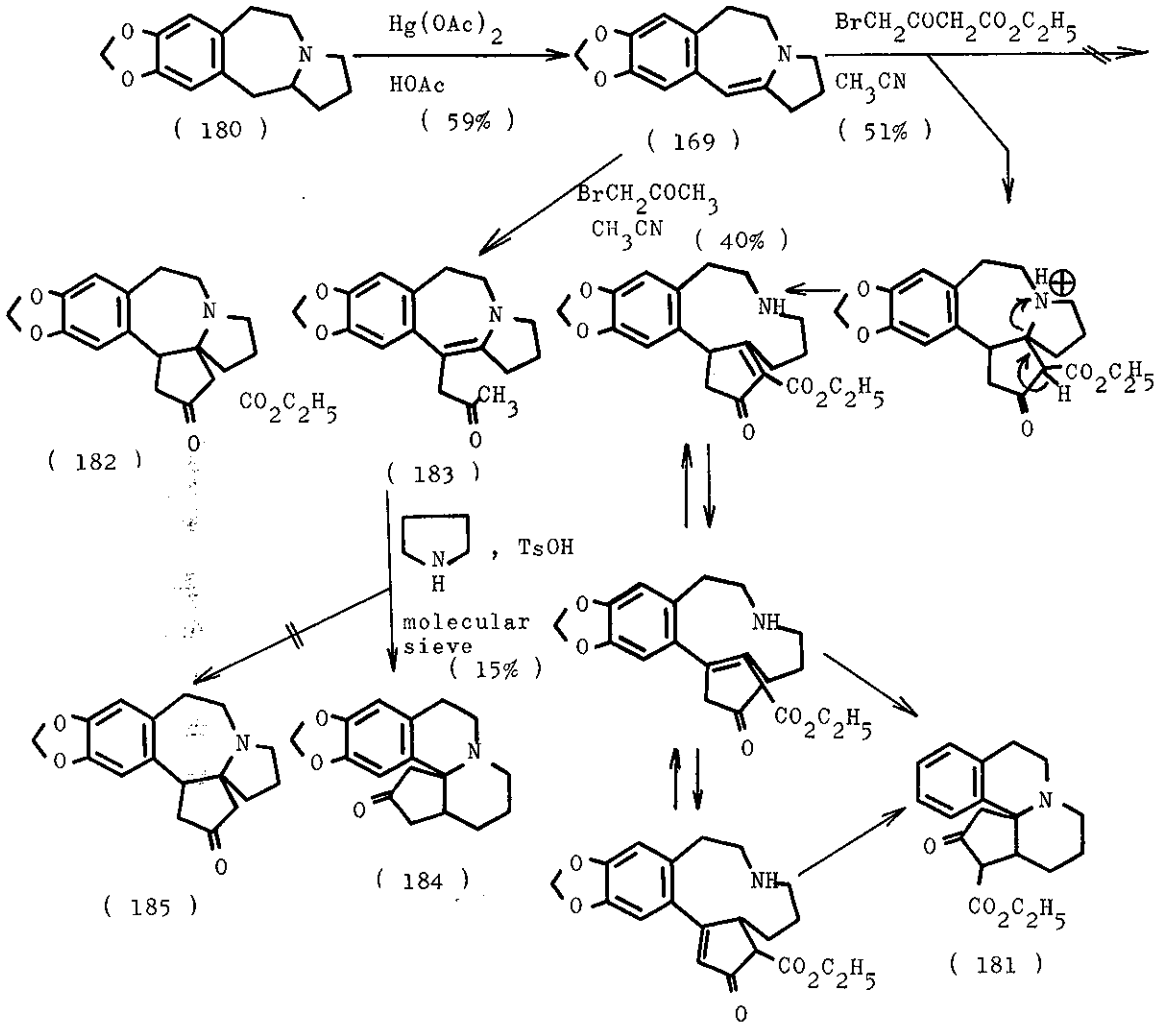
Chart 43. Grignard reaction of 2-ethoxy-2,5-dihydropyrrole (175) gave 2,2-diallylpyrrolidine (176), which was converted into the diester (177). Acyloin condensation of 177 in the presence of trimethylsilyl chloride, followed by hydrolysis and O-methylation, gave the heterospirocyclic compound (178). Condensation of the spiro compound (178) with the sulfonate in the presence of ethyl diisopropylamine afforded the N-phenethylspiro derivative (179), which was subjected to conditions favourable for the generation of a benzyne intermediate with tritylpotassium to give cephalotaxinone (174). Reduction of this product with diisobutylaluminium hydride afforded cephalotaxine (165).[24] The cyclisation of 179 to cephalotaxinone (174) was also achieved by other methods[23] described earlier (shown in Chart 13 and 14).

A third approach to cephalotaxine unfortunately ended in failure as a result of an intriguing rearrangement in the final stages of the synthetic sequence.[18] The benz[d]azepine (180) which was synthesised as shown in Chart 10, was converted into the enamine (169) by dehydrogenation with mercuric acetate. The enamine was treated with γ-bromoacetoacetate to give the γ-ketoester (181) rather than the desired product (182). The ketone (183) derived from the enamine (169) and bromoacetone also afforded the same type of rearrangement product (184), but not the cephalotaxine skeleton (185), reasonable mechanism for the rearrangement is shown in Chart 44.

5. Total Synthesis of Rheadan Alkaloids

The rheadan alkaloids, found only in the Papaveraceae species, are characterised by the presence of a benzazepine and a cyclic

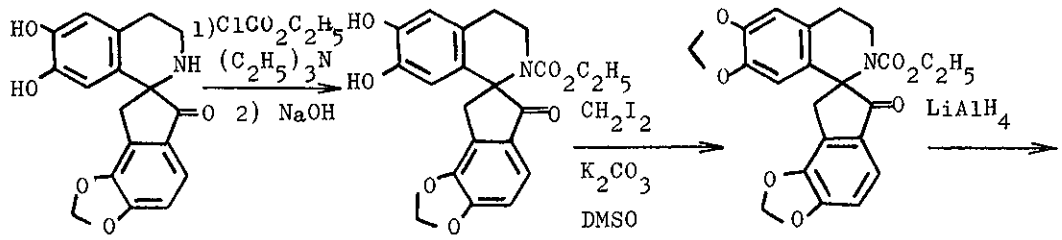
Chart 44


Hg(OAc)2
HOAc
(59%)
BrCH2COCH2CO2C2H5
CH3CN
(51%)
BrCH2COCH3
CH3CN
(40%)
, TsOH
molecular sieve
(15%)
(180)
(169)
(182)
(183)
(185)
(184)
(181)

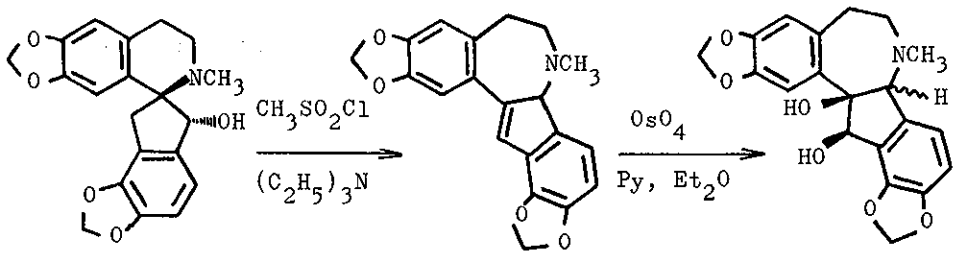
acetal or hemiacetal system. The structural determination of rhoeadine was carried out by Hofmann degradation. On the basis of a study of the i.r., u.v., n.m.r. and mass spectra of rhoeadine and its degradation products, rhoeadine is assigned structure (4).[1,2]

The first total synthesis of rhoeadine was reported by Irie in 1970,[43,44] in which the key reaction was an enlargement of the isoquinoline ring in a benzylic spiroisoquinoline to the benzazepine ring system by a Wagner-Meerwein rearrangement involving an aziridinium ion (see Chart 27). The spirobenzylisoquinoline (186) was transformed into the nonphenolic urethane (188) via phenolic urethane (187). Reduction of this product gave stereospecifically the trans-amino alcohol (98), which on Wagner-Meerwein rearrangement with mesyl chloride and triethylamine at 0° afforded a mixture of benzazepines (100) and (101). The free base of the latter (101) was unstable and was converted into the former base (100) in alumina chromatography. The benzazepine (101) was treated

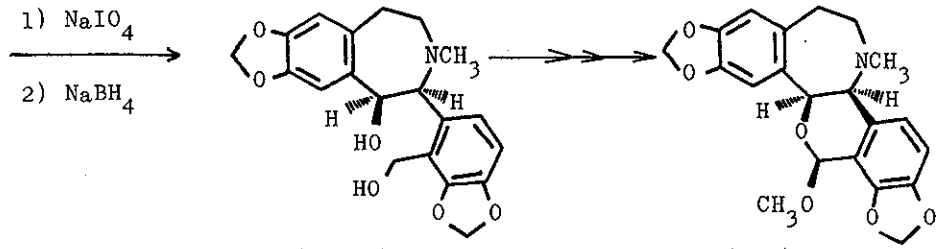
Chart 45



(186) (187) (188)



(98) (101) (189)

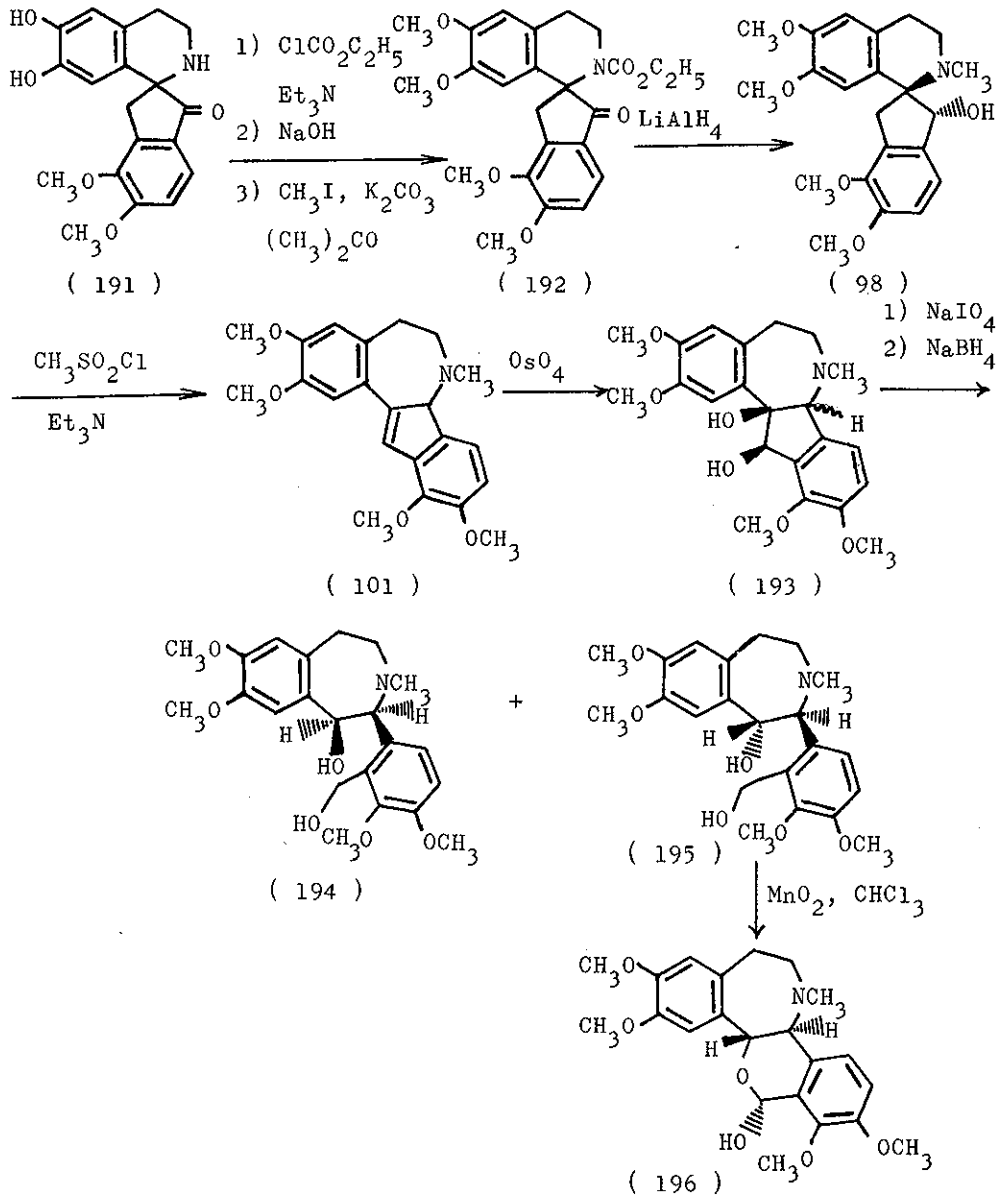


(190) (4)

with osmium tetroxide, and the resulting diol (189), presumably cis-oriented in view of the properties of the reagent, was transformed into (±)-rhoeageninediol (190) by periodate oxidation and sodium borohydride reduction. Since rhoeageninediol had been previously converted into rhoeadine (4), the total synthesis had been formally completed. The ring enlargement of the isoquinoline (98) to the benzazepines (100) and (101) proceeds through the probable intermediacy of an aziridinium ion as shown in Chart 27.

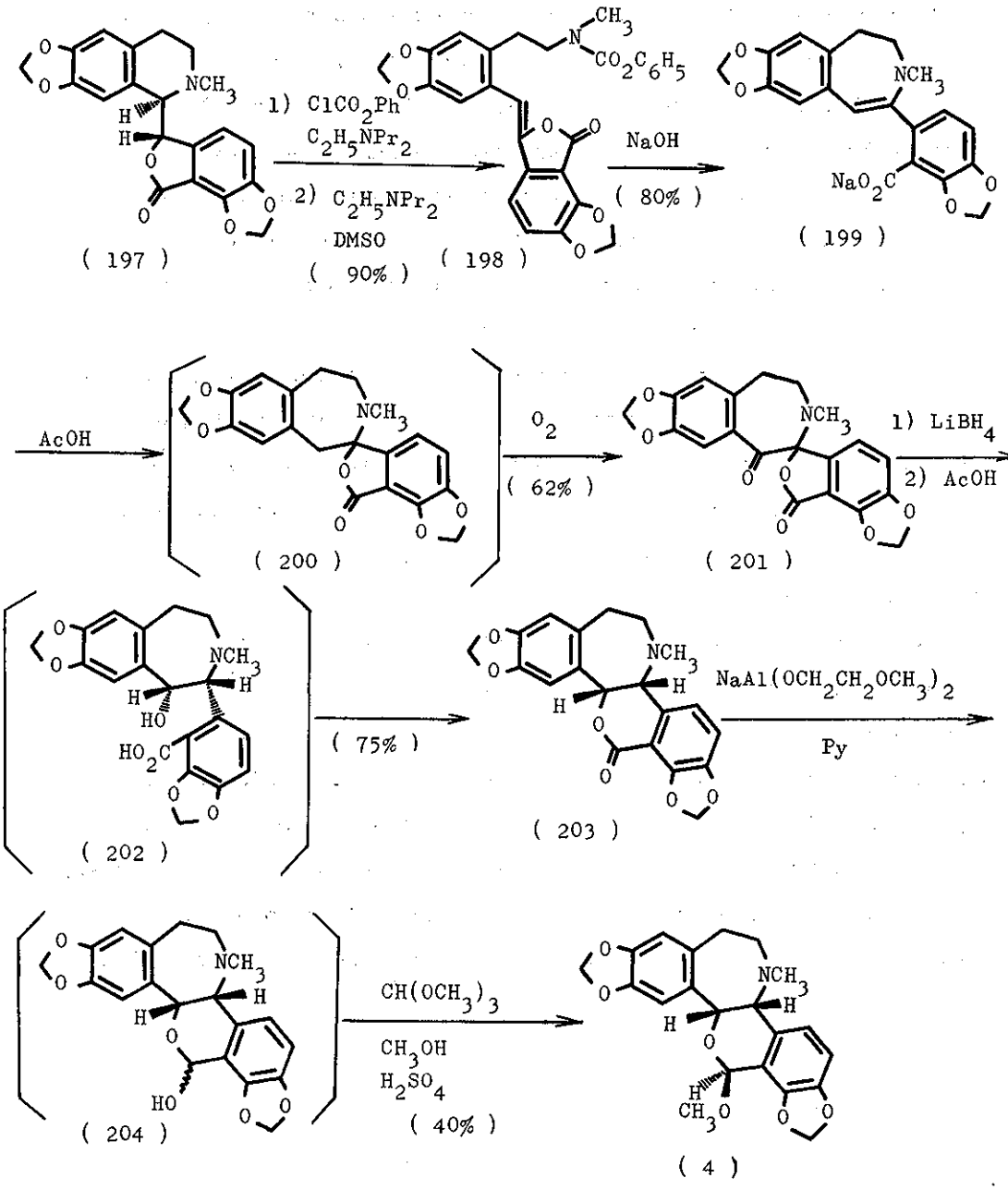
Irie[44] also reported the total synthesis of alpinigenine (196) by the same route. Thus, the second spirobenzylisoquinoline (191) was transformed into urethane (192), reduction of which gave the aminoalcohol (98). Wagner-Meerwein rearrangement of 98 by the same method afforded a mixture of benzazepines (100) and (101) in a 1 : 2 ratio as shown in Chart 27. The latter azepine (101) was oxidised with osmium tetroxide to give the glycol (193), which was treated with sodium periodate and then sodium borohydride to furnish a separable mixture of (±)-epialpinigeninediol (194) and (±)-alpinigeninediol (195) in a 5 : 1 ratio. The latter diol (195) was also obtained in 40 % yield from the glycol (193) by treatment with lithium perhydro-9b-boraphenalenylhydride in tetrahydrofuran at 0°. Manganase dioxide oxidation of (±)-alpinigeninediol (195) gave (±)-alpinigenine (196).

Chart 46


1) ClCO2C2H5
Et3N
2) NaOH
3) CH3I, K2CO3
(CH3)2CO
LiAlH4
CH3SO2Cl
Et3N
OsO4
1) NaIO4
2) NaBH4
MnO2, CHCl3
(191)
(192)
(98)
(101)
(193)
(194)
(195)
(196)

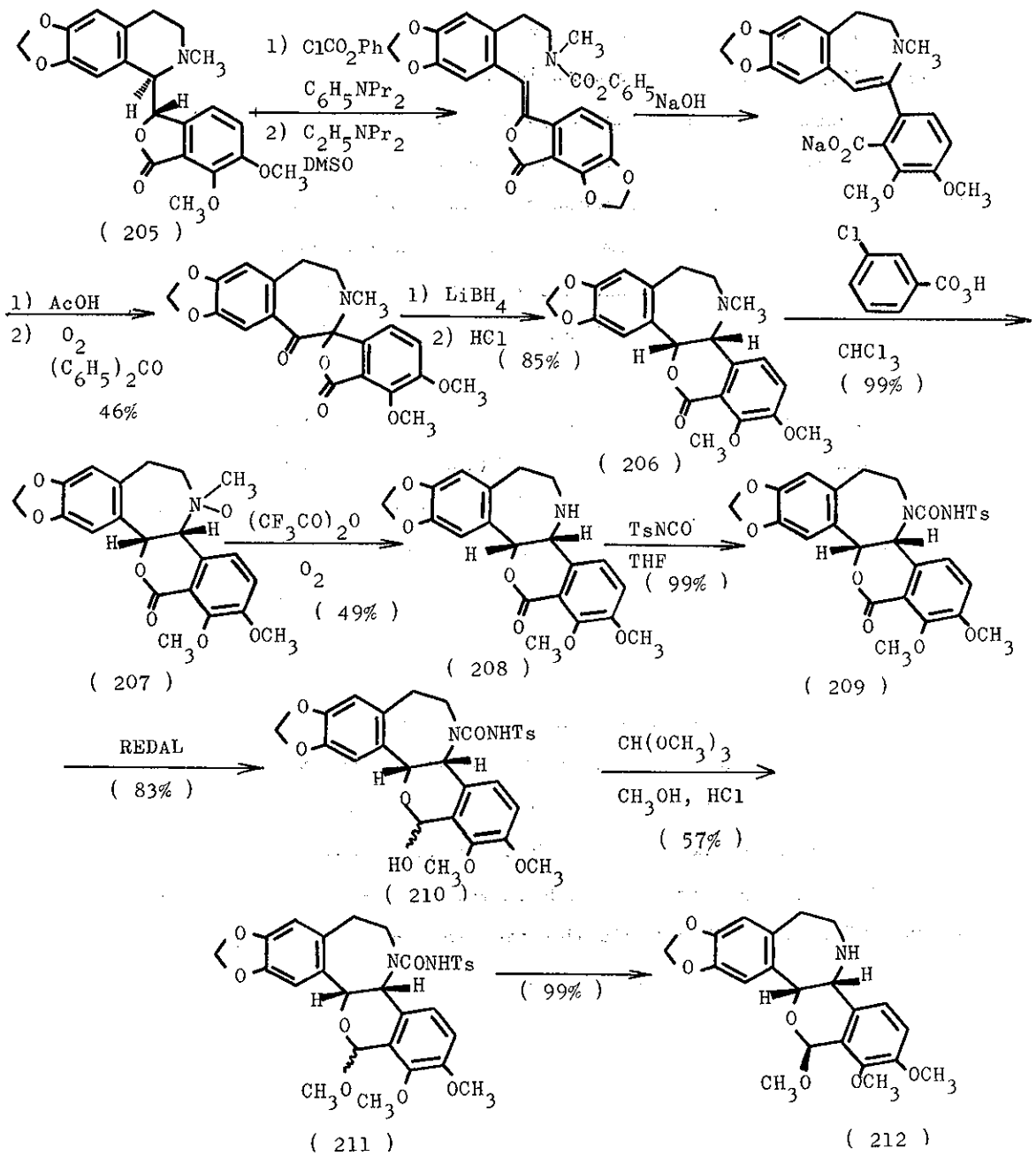
The second total synthesis of rhoeadine (4) has been achieved by Klötzer in 1971[28,29] based on model experiments for the preparation of benzazepines from the phthalide alkaloids, (-)-α-narcotine and (-)-β-hydrastine. Thus, reaction of (-)-bicuculline (197) with phenyl chloroformate and diisopropylethylamine, followed by dehydrohalogenation with a mixture of dimethyl sulphoxide and diisopropylethylamine yielded the urethane (198) in 90 % yield, which was treated with 2N sodium hydroxide under a current of nitrogen to afford in 80 % yield the dihydrobenzazepine sodium salt (199). Acidification of an aqueous solution of 199 with acetic acid effected cyclisation to the spirolactone (200) which was not isolated but dissolved in ethanol and readily oxidised by air to provide the keto-lactone (201) in 62 % yield. Reduction of this product with lithium borohydride followed by acidification with acetic acid afforded via the transient cis-hydroxy acid (202), the cis-lactone, (±)-oxyrhoeagenine (203) in 75 % yield. Resolution of (±)-oxyrhoeagenine with (+)-10-camphorsulphonic acid provided (-)-oxyrhoeagenine. Treatment of the mother liquors with (-)-10-camphorsulphonic acid yielded (+)-oxyrhoeagenine. Partial reduction of a pyridine solution of (+)-oxyrhoeagenine with sodium bis-(2-methoxyethoxy)aluminium hydride yielded a mixture of anomeric lactols (204), which were etherified in methanol with trimethyl orthoformate catalysed by sulphuric acid to give (+)-rhoeadine (4) in 40 % yield.

Chart 47


1) ClCO2Ph
C2H5NPr2
2) C2H5NPr2
DMSO
(90%)
NaOH
(80%)
AcOH
O2
(62%)
1) LiBH4
2) AcOH
(75%)
NaAl(OCH2CH2OCH3)2
Py
CH(OCH3)3
CH3OH
H2SO4
(40%)
(197)
(198)
(199)
(200)
(201)
(202)
(203)
(204)
(4)

Moreover, Klötzer[60] reported the synthesis of the papaverrubine

Chart 48



type of rheadan alkaloids (212) by a modification of the above method. The oxyrheadan (206), prepared from (-)-hydrastine (205) in the usual way as shown in Chart 48, was transformed into the N-oxide (207) with m-chloroperbenzoic acid, which was treated with trifluoroacetic anhydride and oxygen in chloroform to give the N-demethyloxyrheadan (208). This was converted into the urethane derivative (209) which was reduced to the hemiacetal (210). Trans-methylation of 209 with trimethyl orthoformate in methanol in the presence of hydrochloric acid and removal of the protecting group of the resulting acetal (211) gave the papaverrubine type compound (212).

The third synthesis of a rheadan alkaloid was reported by Manske,[61] who synthesised the benzazepine (100) (which has already been prepared by Irie[44]) by an alternative route[61,62] and converted it into the keto-lactone corresponding to Klötzer's compound (201) by photo-oxidation. Thus, N-acetylphenethylamine (213) was converted into the 2-cyanomethyl derivative (214), which was condensed with 2,3-dimethoxybenzaldehyde, followed by hydrolysis, to give amido-carboxylic acid (215). Friedel-Crafts cyclisation of 215 afforded the indanone (216), which was treated with ethanolic potassium hydroxide to provide in 62 % yield the benzazepine (100). The oxidation of 100 with oxygen in the presence of triton-B in pyridine gave the enamino-ketone (217) in 79 % yield, which on Rose Bengal sensitised photooxi-dation afforded in 37 % yield the keto-lactone (218). This was converted into cis-alpinine (219) by Klötzer's method.

Chart 49

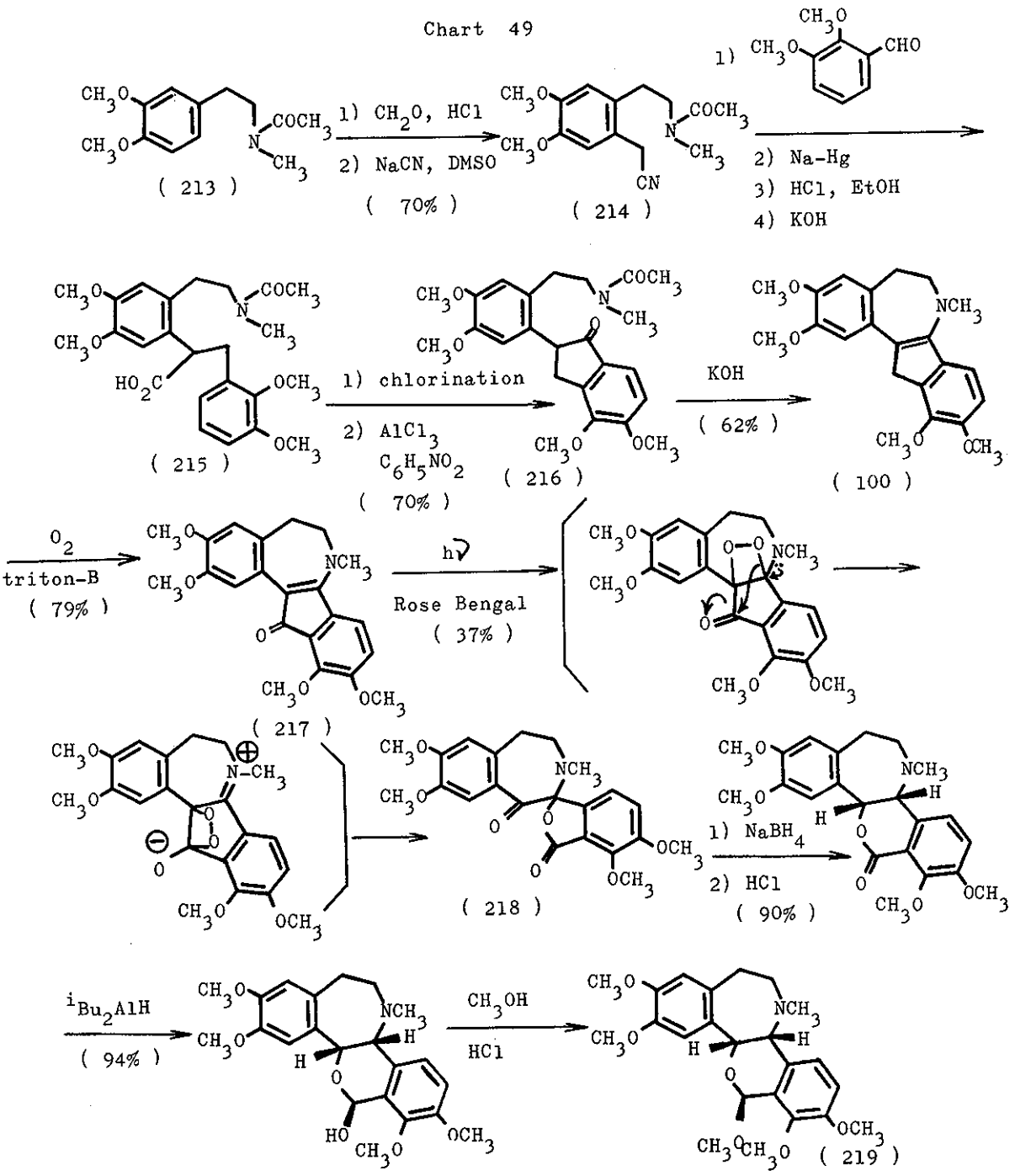
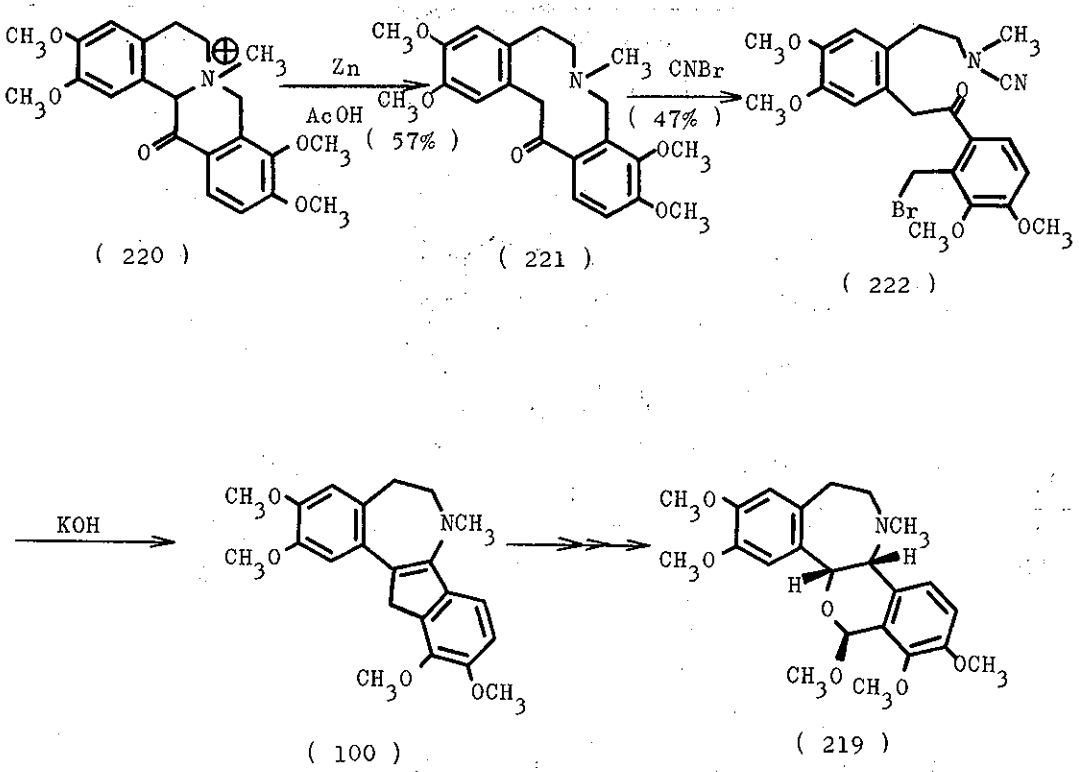

(213)
1) CH_2O, HCl
2) NaCN, DMSO
(70%)
(214)
1)
2) Na-Hg
3) HCl, EtOH
4) KOH
(215)
1) chlorination
2) $AlCl_3$
$C_6H_5NO_2$
(70%)
(216)
KOH
(62%)
(100)
O_2
triton-B
(79%)
(217)
h
Rose Bengal
(37%)
(218)
1) $NaBH_4$
2) HCl
(90%)
$^iBu_2AlH$
(94%)
CH_3OH
HCl
(219)

Chart 50



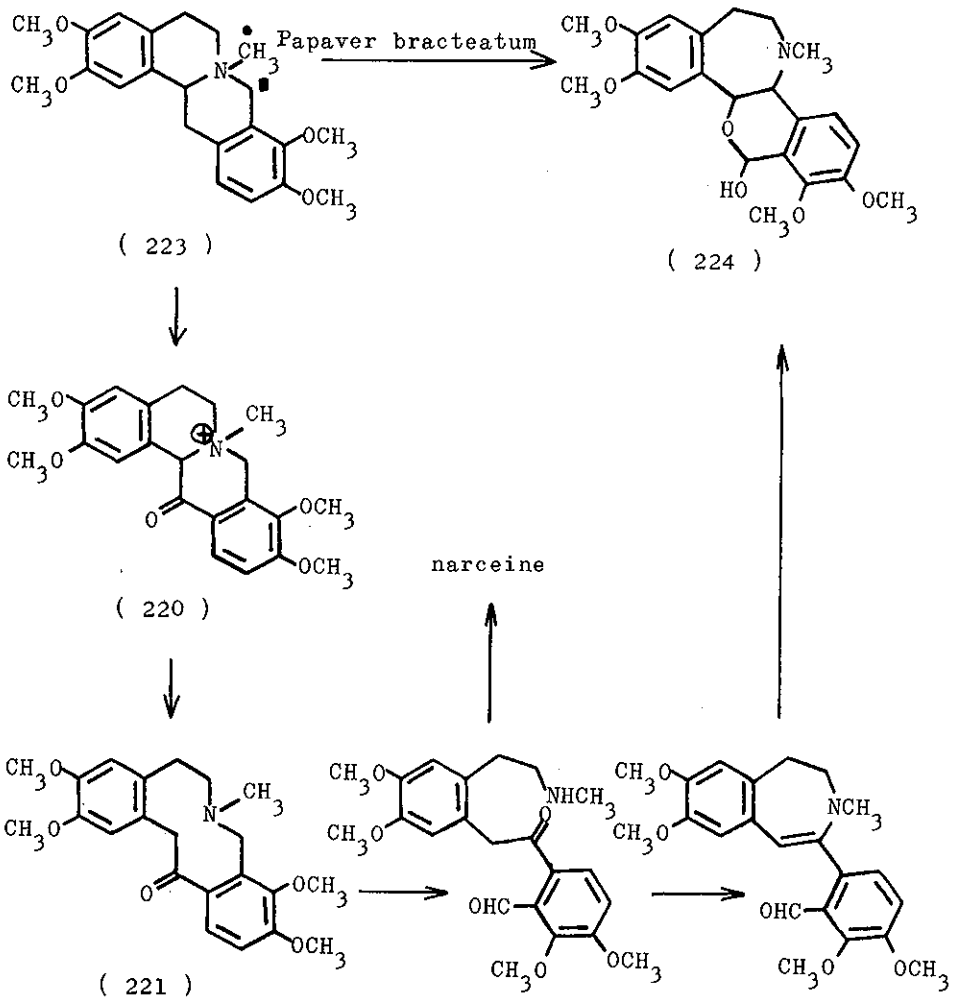
(220) (221) (222)

(100) (219)

Shortly afterwards, Manske[63] obtained the key intermediate (100) by other methods; 13-ketotetrahydropalmatine methosalt (220) was treated with zinc and 30 % acetic acid to give in 57 % yield the ring opened compound (221), which was subjected to von Braun reaction to form the narceine equivalent (222). Alkaline treatment of this afforded the benzazepine (100), which has been converted into cis-alpinine (219).

Based on the above experiments and the fact that alpinigenine (224) is biosynthesised from N-methyltetrahydropalmatine (223),[64] Manske proposed a new biogenesis of alpinigenine (224) from tetrahydropalmatine via 13-ketoprotoberberine (220) as shown in Chart 51.[63]

Chart 51



(223) (224) (220) (221)

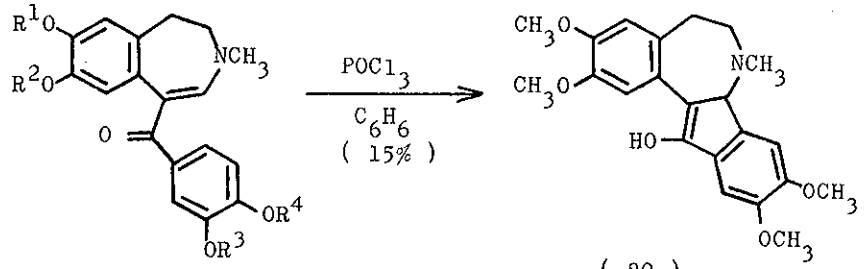
As described above, the benzazepine derivatives (100) and (101) first synthesised by Irie[43,44] are key intermediates for the synthesis of the rheadan alkaloids, and later, many syntheses of benzazepines have been reported. Shamma[40,49] described that base catalysed rearrangment of the dihydroprotoberberine salt (113) yielded the dibenzocyclopent[b]azepine (118) by the mechanism indicated in Chart 30. The rearrangement stops at the spirobenzylisoquinoline stage when a phenolic function is present in the bottom ring.

Fumaritirine (102), fumaritridine (103), and fumarophycine (104) were converted into the benzazepines (108) and (109), respectively, by pyrolysis as shown in Chart 28.[40,45,46] The diketospirobenzylisoquinolines (89) and (92) are transformed into cis- (90 and 93) and trans-fused indanobenzazepines (91 and 94), respectively, in a 1 : 3 ratio by treatment with zinc and acetic acid as shown in Chart 25.[42]

The 1-benzoyl-4,5-dihydro-3H-benzazepine (79) was cyclised to the hydroxyindenobenzazepine (80) in 15 % yield by treatment with phosphoryl chloride in boiling benzene,[37] however, the same reaction in boiling toluene gave the chloroindenobenzazepine (225), which was reduced with sodium borohydride in methanol in the presence of sodium hydroxide to afford the indenobenzazepine (226).[65-67]

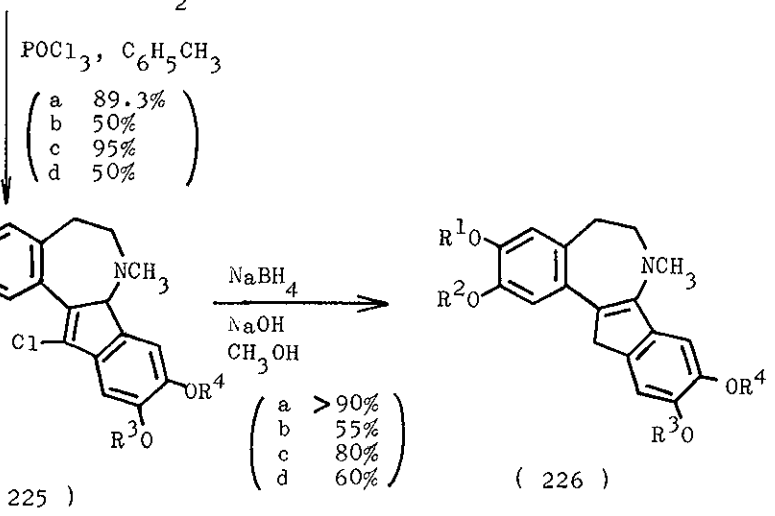
Trans-Oxyrheadans were obtained by Shamma.[25] 2-Benzyl-3,4-dihydroisoquinoline (227) was treated with benzoyl chloride and sodium

Chart 52



(79) a) $R^1=R^2=R^3=R^4=CH_3$
b) $R^1=R^2=CH_3$, $R^3+R^4=CH_2$
c) $R^1+R^2=CH_2$, $R^3=R^4=CH_3$
d) $R^1+R^2=R^3+R^4=CH_2$

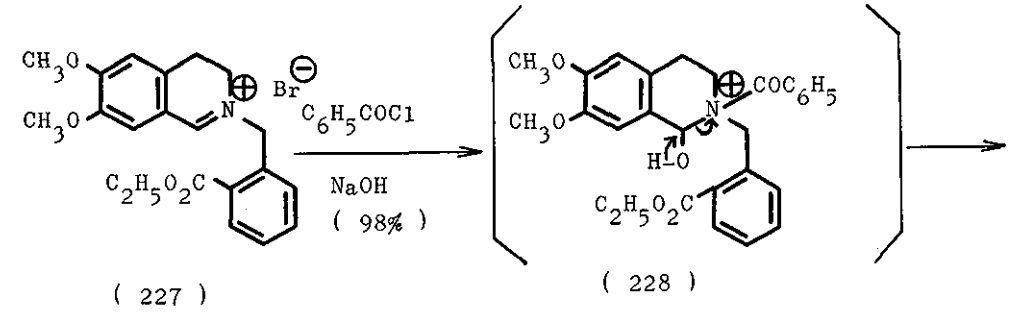
(80)



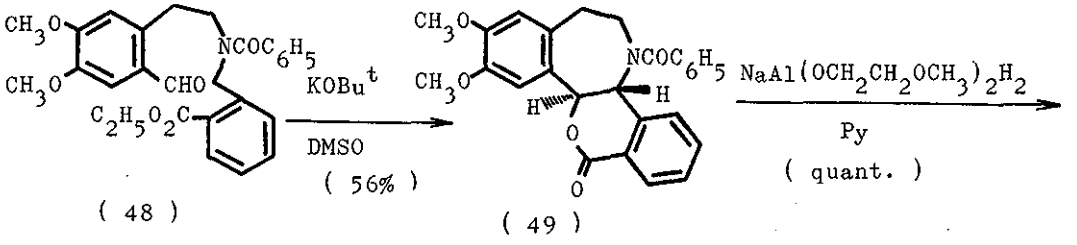
(225)

(226)

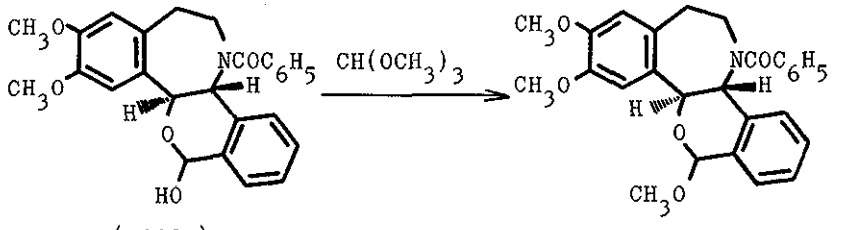
Chart 53



(227) (228)



(48) (49)

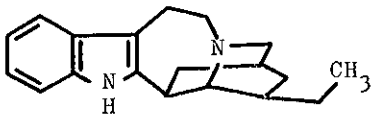


(229) (230)

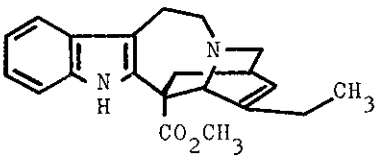
hydroxide to give the amide aldehyde (48) through the probable intermediate of the N-benzoylated pseudo-base (228), which was subjected to an intramolecular aldol-like cyclisation with potassium tert-butoxide and dimethyl sulphoxide, followed by lactonisation to afford the trans-fused oxyrheadan (49) in 56 % yield. Selective reduction of the lactone ring, followed by acetalisation of the resulting hemiacetal (229) gave trans-rheadan (230). This method is a new route to the thermodynamically less stable trans-fused rheadan.

In this account, we have described recent advances in the synthesis of benz[d]azepines and in the total synthesis of isopavine, cephalotaxine, and rheadan alkaloids which have a 1,2,4,5-tetrahydro-3H-benz[d]benzazepine system as the main skeleton. Modification of these synthetic methods could provide a new route for the total synthesis of some indole alkaloids, like ibogamine (231) or cepharanthine (232).

Chart 54



(231)



(232)

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