

## THE CHEMISTRY OF THE BENZO(a)- AND BENZO(c)QUINOLIZINIUM IONS

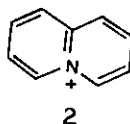
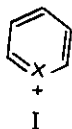
Sayeed-Ud-Din Saraf

Chemistry Department, University of Kuwait, KUWAIT

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This paper reviews the various synthetical methods for the preparation of the two angular benzologs of quinolizinium ions. The best method involves the irradiation of styrylpyridinium salts and stilbazoles for the preparation of benzo(a)- and benzo(c)quinolizinium salts respectively. Some of the alkaloids containing benzoquinolizine system are also reviewed. Various reactions of the two benzologs are also discussed.

The cationoid aromatics owe their aromaticity to the existence of a hetero atom in a higher valence state. Simple and familiar examples of such systems are the pyrilium (1, X=O) and thiapyrilium (1, X=S) salts in which a CH of the benzene ring is replaced by an oxonium or sulphonium linkage. The simplest aromatic system incorporating the ammonium nitrogen is the



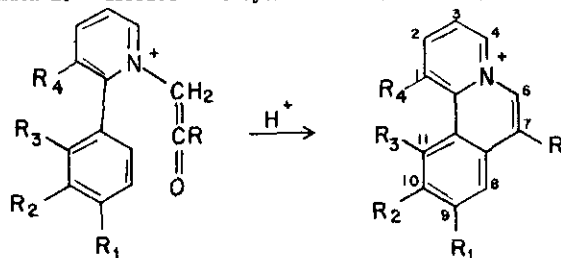
quinolizinium nucleus (2) <sup>1-6</sup>. The even smaller group of wholly aromatic quinolizinium salts consisted of a few complex compounds, which, with the exception of the tetracarbomethoxyquinolizinium derivatives of Diels and Alder were tetraacyclic in nature.

Of the three benzologs of the quinolizinium ion, only the readily available acridizinium cation has been studied in detail and has been reviewed recently <sup>7</sup>.

Bradsher et al. <sup>8-10</sup> have used their well known method of cyclodehydration to the synthesis of the two angular benzoquinolizine systems and it is our aim to review the work done by various research groups in this particular field.

#### Synthesis of the Benzo(a)quinolizinium System

The first general method <sup>11</sup> for the synthesis of simple phenanthridizinium derivatives (3-9) involved the quarternisation of 2-phenylpyridine or a derivative with an appropriate halocarbonyl derivative, after which the resulting salts (10-16) were usually cyclised in boiling hydrobromic acid <sup>12-14</sup>. The salt 14 formed by reaction of iodoacetone with 2-(2-tolyl)pyridine proved much more difficult to cyclise than did its isomer 12 and 13. The



R group not otherwise designated are hydrogen

10, R = CH<sub>3</sub>

11, R = C<sub>6</sub>H<sub>5</sub>

12, R = R<sub>1</sub> = CH<sub>3</sub>

13, R = R<sub>2</sub> = CH<sub>3</sub>

14, R = R<sub>3</sub> = CH<sub>3</sub>

15, R = CH<sub>3</sub>, R<sub>2</sub> = OCH<sub>3</sub>

16, R = CH<sub>3</sub>, R<sub>4</sub> = OH

3, R = CH<sub>3</sub>

4, R = C<sub>6</sub>H<sub>5</sub>

5, R = R<sub>1</sub> = CH<sub>3</sub>

6, R = R<sub>2</sub> = CH<sub>3</sub>

7, R = R<sub>3</sub> = CH<sub>3</sub>

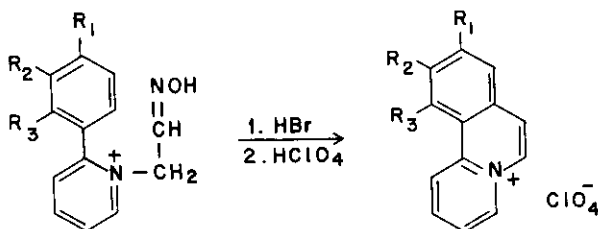
8, R = CH<sub>3</sub>, R<sub>2</sub> = OCH<sub>3</sub>

9, R = CH<sub>3</sub>, R<sub>4</sub> = OH

pyridinium salt (12) afforded only a 9% yield of 7,11-dimethylphenanthridizinium bromide (7) while under comparable conditions the salt 12 gave a 71% yield of 7,9-dimethylphenanthridizinium bromide (5). Cyclisation para to a methoxyl group gave a 50% yield of 8 in only 3 minutes <sup>15</sup>. This clearly indicates that the presence of a methyl group on the phenyl ring did not interfere with the cyclisation except when in the ortho position (14, R<sub>3</sub> = CH<sub>3</sub>) <sup>12</sup> in which case the low yield could be anticipated, because, ring A and C have

difficulty in attaining coplanarity. Surprisingly the presence of a free hydroxyl group even at one of the positions, where it is most likely to impede the achievement of coplanarity is without any harmful effect.

The use of chloroacetaldoxime as quarternising agent with 2-phenylpyridine yielded phenanthridisinium derivatives (17-20) in reasonable yields<sup>14</sup>. The low yield of 11-methyl-



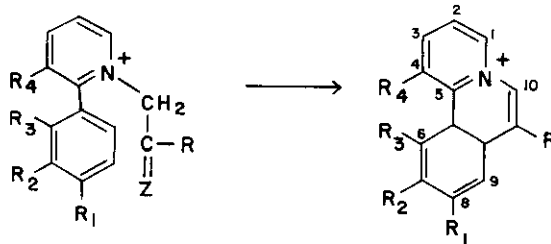
- 17, R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>=H  
 18, R<sub>1</sub>=CH<sub>3</sub>, R<sub>2</sub>=R<sub>3</sub>=H  
 19, R<sub>2</sub>=CH<sub>3</sub>, R<sub>1</sub>=R<sub>3</sub>=H  
 20, R<sub>3</sub>=CH<sub>3</sub>, R<sub>1</sub>=R<sub>2</sub>=H

phenanthridisinium perchlorate (20) is apparently due to steric inhibition and as comparable to that of 7,11-dimethyl analog (9%) reported previously<sup>12</sup>.

The results are summarised in Table I.

Diels and co-workers<sup>17,18</sup> were the first research workers to prepare tetracarboethoxy-phenanthridisinium salts, but the method was too complicated and is not suitable for the preparation of simple analogs.

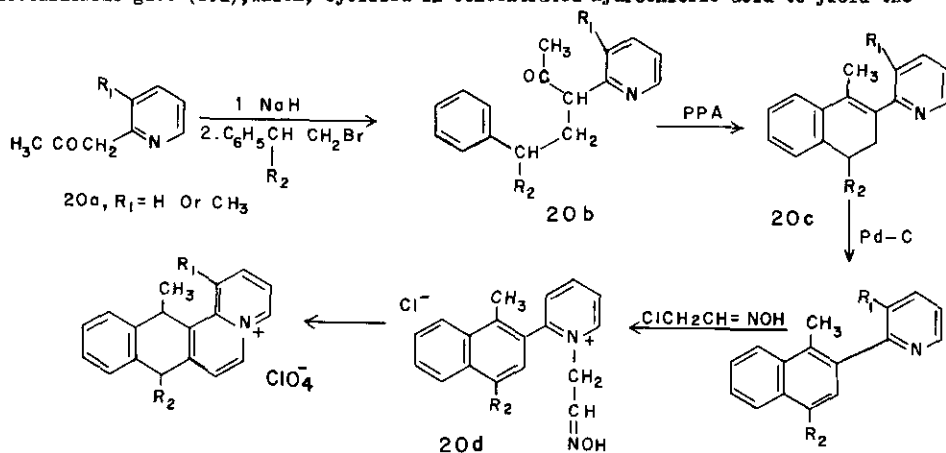
TABLE I



Compound number	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R	Z	Cyclising agent	Yield %	Time	Ref.
1.	H	H	H	H	C <sub>6</sub> H <sub>5</sub>	O	HBr	42	14 days	13
2.	H	H	H	H	CH <sub>3</sub>	O	HBr	75	51 hr.	13
3.	CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	O	HBr	71	50.5 hr	12

4.	H	CH <sub>3</sub>	H	H	C <sub>6</sub> H <sub>5</sub>	O	HBr	64	66 hr.	12
5.	H	H	CH <sub>3</sub>	H	CH <sub>3</sub>	O	HBr	9	50.5 hr.	12
6.	H	OCH <sub>3</sub>	H	H	CH <sub>3</sub>	O	HBr	50	0.05 hr.	12
7.	H	H	H	OH	CH <sub>3</sub>	O	HBr	85	50 hr.	12
8.	H	H	H	H	H	NOH	HBr	35	24 hr.	14
9.	H	H	H	H	H	NOH	HBr	45	24 hr.	14
10.	H	CH <sub>3</sub>	H	H	H	NOH	HBr	61	24 hr.	14
11.	H	H	CH <sub>3</sub>	H	H	NOH	HBr	12	65 hr.	14

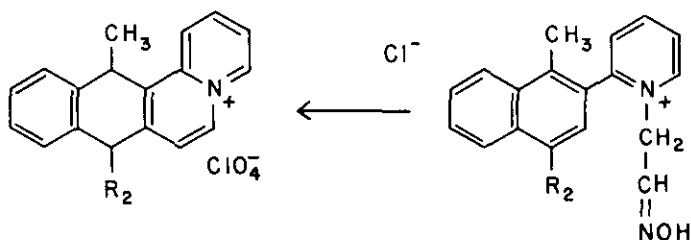
This method was extended to the synthesis of naphtho[2,3-a]quinolizinium salts. Alkylation of the methylene group of 2-acetyl- or 3-methyl-2-acetylpyridine (20a) by 2-phenyl-1-bromopropane in the presence of sodium hydride resulted in the formation of ketone (20b). Cyclisation of the ketone with polyphosphoric acid afforded 3,4-dihydronaphthalenes (20c). Dehydrogenation of 20c over palladium-charcoal followed by quaternisation with chloroacetaldoxime gave (20d), which, cyclised in concentrated hydrochloric acid to yield the



naphtho 2,3-a quinolizinium perchlorates <sup>32</sup>.

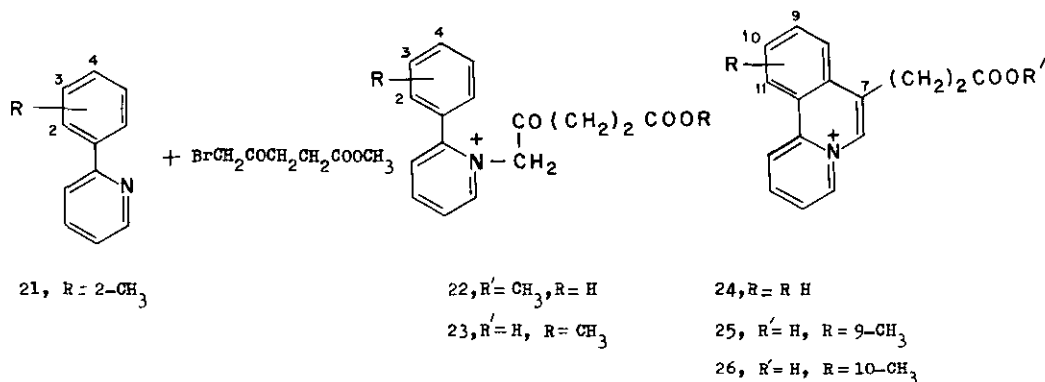
The results are summarised in Table II.

TABLE II

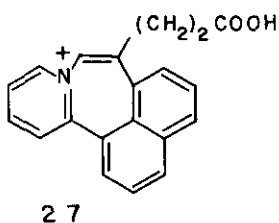
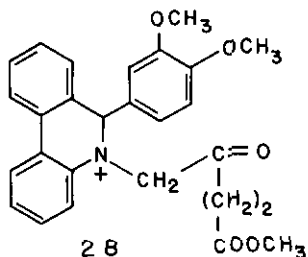


Compound number	R <sub>1</sub>	R <sub>2</sub>	X	Yield %
1.	H	H	ClO <sub>4</sub>	76
2.	H	CH <sub>3</sub>	ClO <sub>4</sub>	82
3.	CH <sub>3</sub>	H	ClO <sub>4</sub>	48

Bradsher and Yarrington<sup>16</sup> introduced a carbonyl function into the phenanthridinium nucleus by quarternisation of 2-phenylpyridine with methyl  $\delta$ -bromolevulinate. Cyclisation of the quarternary salts (22,23) in hydrobromic acid was slower (6-16 days) as compared to the cyclisation of 1-acetonyl-2-pyridinium salts (2-3 days)<sup>12</sup>. A methyl group in the ortho position of the phenyl ring (21, R = CH<sub>3</sub>) failed to give the cyclised product even after a reflux period of 15 days. This must be due to the fact that the methyl group at position 2 impedes the achievement of the coplanarity essential for cyclisation. However, in nearly all cyclisations, uncyclised keto acid (23) was recovered along with the cyclised product (24). Esterification of the new acids (24-26) in absolute methanol or ethanol occurred in good yield.



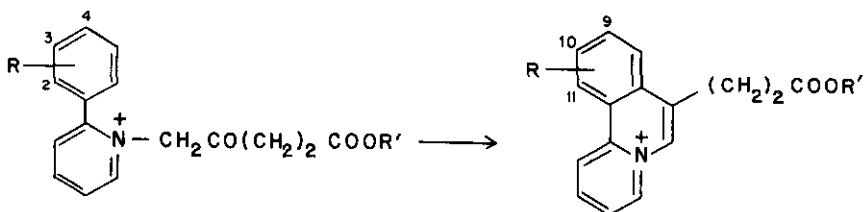
On the other hand, quarternary salt obtained from 2-(1-naphthyl)pyridine and  $\delta$ -bromolevulinate when cyclised gave a new compound (27) suggesting that cyclisation has occurred into the alpha position of the naphthalene ring to form a seven membered ring rather than into the beta position to form a six membered ring. On the other hand quarternisation product (28) obtained by reacting 6-(3,4-dimethoxyphenyl)phenanthridine with methyl- $\alpha$ -bromolevulinate on heating with hydrochloric acid underwent a cleavage rather than cyclisation.



The spectral data showed the compound to have the structure of 6-(3,4-dimethoxyphenyl)-phenanthridizine hydrochloride.

The results are summarised in Table III.

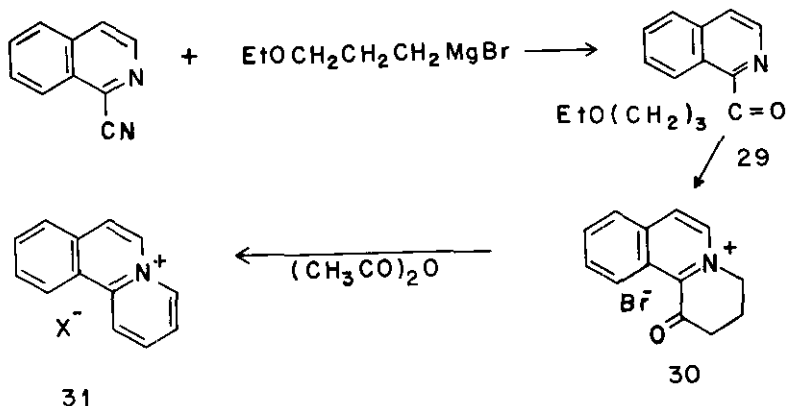
TABLE III



Compound number	R'	R	Yield %	Cyclising agent	Time days
1.	H	H	34.5	HBr	16
2.	H	9-CH <sub>3</sub>	54	HBr	6
3.	H	10-CH <sub>3</sub>	45	HBr	6
4.	H	11-CH <sub>3</sub>	a	HBr	15

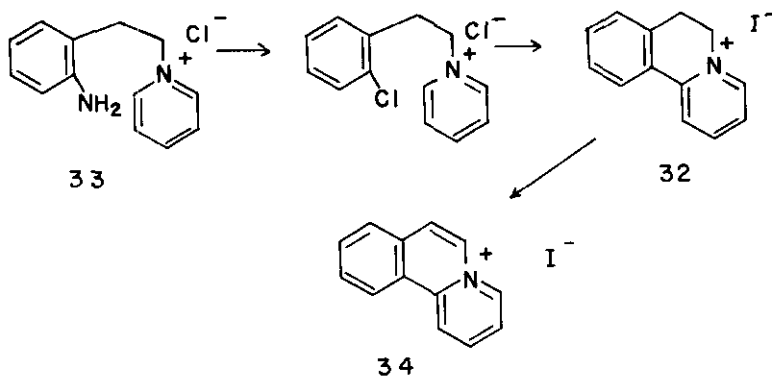
a) Starting material was recovered in 39 % yield without getting any cyclised product.

Glover and Jones<sup>19</sup> synthesised phenanthridizinium salt by reacting 1-cyanoisquinoline with 3-ethoxypropylmagnesium bromide and the ketone (29) thus obtained was cyclised to give the corresponding cyclic bromide (30), which was converted in boiling acetic anhydride into the phenanthridizinium salt (31)<sup>19</sup>.



Akaboshi and Kato<sup>20</sup> have synthesised 6,7-dihydrobenzo(a)quinolisinium iodide (32) by cyclising 2-aminophenethylpyridinium salt (33) using Pischorr reaction. (Scheme 1). Dehydrogenation of 32 with palladium-carbon at 260<sup>o</sup> for 5 minutes followed by extraction with ethanol and addition of potassium iodide afforded benzo(a)quinolizinium iodide (34). Using substituted

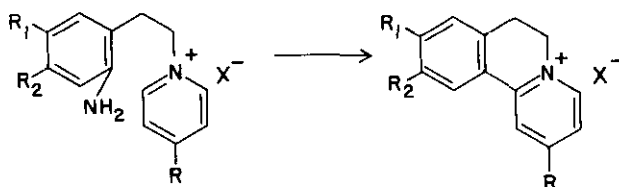
Scheme 1



2-aminophenethylpyridinium salts and following the above procedure, a number of 6,7-dihydrobenzo(a)quinolisinium salts were prepared<sup>21</sup>.

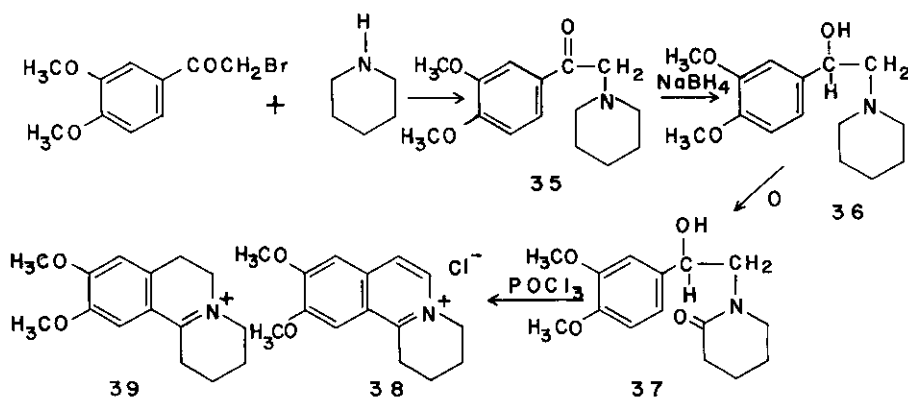
The results are summarised in table 1V.

TABLE IV



Compound number	R <sub>1</sub>	R <sub>2</sub>	R	X	Ref.
1.	O — CH <sub>2</sub> — O		H	I	21
2.	O — CH <sub>2</sub> — O		H	Cl	21
3.	OMe	OMe	H	Cl	21
4.	OMe	OMe	CH <sub>3</sub>	Cl	21
5.	OMe	OMe	CH <sub>3</sub>	I	21
6.	OMe	OMe	H	I	21
7.	O — CH <sub>2</sub> — O		H	Br	21

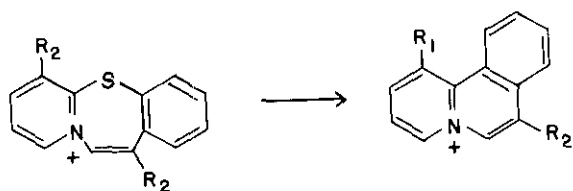
Another method for the preparation of phenanthridizinium system involved the reaction between 3,4-dimethoxyphenacyl bromide and piperidine. The resulting ketone (35) was reduced with



NaBH<sub>4</sub> to the corresponding alcohol (36). Oxidation of the amino alcohol furnished lactam alcohol (37), which on treatment with phosphoryl chloride gave tetrahydrobenzo(a)-quinolizinium chloride (38). On the other hand hydrogenolysis of 37 followed by ring closure gave hexahydrobenzo(a)quinolizinium salt (39).<sup>22</sup>

Another route to the phenanthridizinium ion is the ring contraction of pyrido-[2,1-b]benzo-[f]-1,3-thiazepinium perchlorates (39,40).<sup>23</sup> When these substances are treated with hydrogen peroxide and acetic acid, dethionylation occurs affording phenanthridizinium salts (41,42).





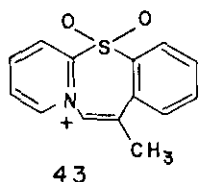
39,  $R_1 = R_2 = H$

40,  $R_1 = R_2 = CH_3$

41,  $R_1 = R_2 = H$

42,  $R_1 = R_2 = CH_3$

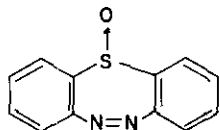
The possibility that a sulphone is an intermediate in the oxidative dethionylation of benzo f -1,3-thiazepinium salt (40) was excluded on the basis that 5,5-dioxo-12-methylpyrido-2,1-b benzo f -1,3-thiazepinium perchlorate (43) on heating with hydrogen peroxide and acetic acid under the usual conditions, was recovered unchanged.



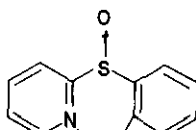
43

In a similar experiment, substituted phenanthridizinium salts were prepared in 24-40 % yields. It was also demonstrated that the first step in the oxidation process is the formation of a sulfoxide, which on heating first at 56° and then at 100° for two hours gave the desired products in reasonable yields 24,25.

The strongest support for sulfoxide hypothesis is found in the work of Szman and Alfonso 26-28 in which it was demonstrated that the sulfoxide of 2,5-diphenyldithiadene or dibenzo-1-thia-4,5-diaza-2,4,6-cycloheptatriene sulfoxide (44), a structure closely related to



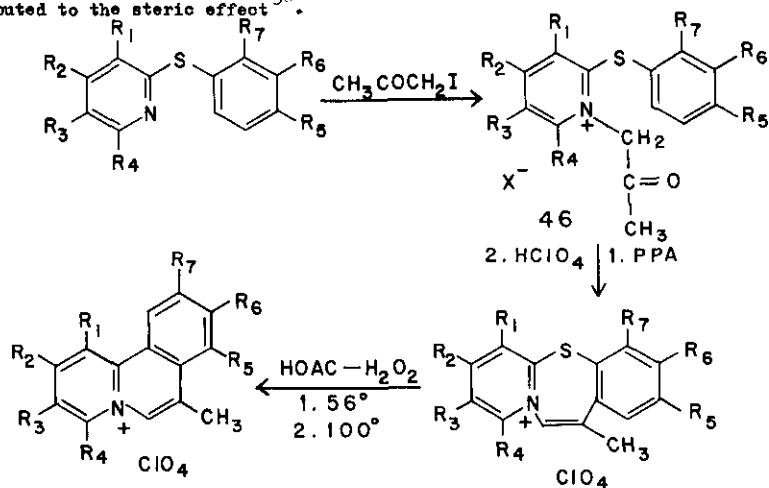
44



45

the intermediate (45) proposed in the present study, on heating would undergo sulphur extrusion. A sulfoxide intermediate has also been proposed<sup>29</sup> to explain at least one other example of sulphur extrusion brought about by the action of acetic acid and hydrogen peroxide.

To study further the effect of substituents on the sulphur extrusion reaction, cyclisation of the quarternary iodides (46) gave the corresponding phenanthridisinium perchlorates (47) in 23 to 37% yields<sup>25</sup>. The sulphide in which the nitrogen of the pyridine ring has two ortho substituents failed to form a quarternary salt even after six months, which has been attributed to the steric effect<sup>30</sup>.



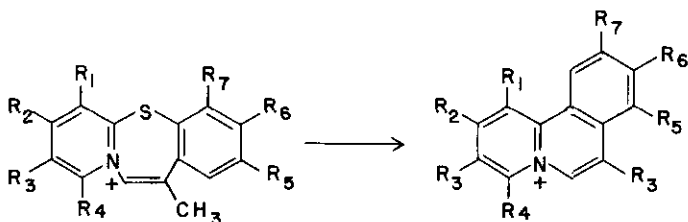
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48, R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = R<sub>5</sub> = R<sub>6</sub> = R<sub>7</sub> = H

Similarly 6,12-dimethylpyrido[2,1-b]-1,3-thiazepinium perchlorate (48) did not yield any sulphur extrusion product as it seems likely that electronic and steric factors may be operative in the failure of 48 to undergo sulphur extrusion<sup>25</sup>.

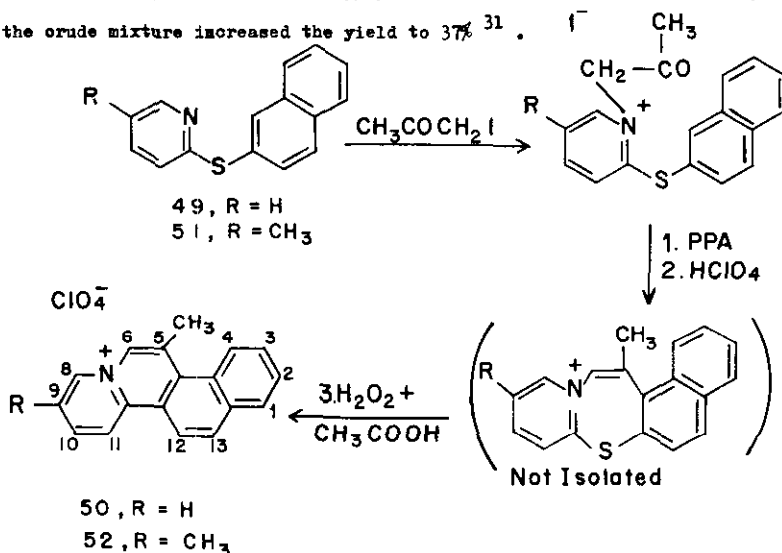
The results are summarised in Table V.

TABLE V



Compound number	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	Time, hr.		Yield%	Ref.
								56 <sup>0</sup>	100 <sup>0</sup>		
1.	H	H	H	H	H	H	H	12	10	38, 63	23, 24
2.	H	H	H	H	H	H	CH <sub>3</sub>	3.5	10	31, 45	24, 23
3.	H	H	H	H	H	CH <sub>3</sub>	H	12	10	47	24
4.	H	H	H	H	H	OCH <sub>3</sub>	H	3	3	40	24
5.	CH <sub>3</sub>	H	H	H	H	H	H	12	12	0	25
6.	H	CH <sub>3</sub>	H	H	H	H	H	12	12	29	25
7.	H	CH <sub>3</sub>	H	H	H	H	CH <sub>3</sub>	12	8	23	25
8.	H	CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	H	12	8	37	25
9.	H	H	CH <sub>3</sub>	H	H	H	H	12	12	24	25
10.	H	H	H	CH <sub>3</sub>	H	H	H				25
11.	H	H	H	H	t-Bu	H	H				25

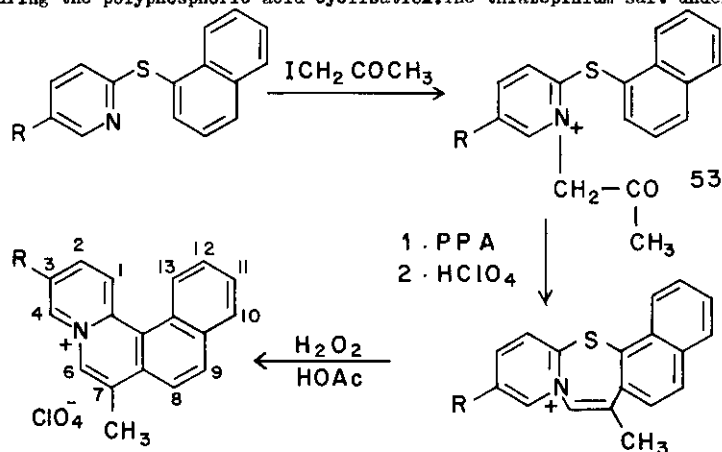
Quarternisation of 2-(2-naphthyl)thiopyridine (49) with iodoacetone followed by cyclisation with polyphosphoric acid gave an oily product, from which 5-methylbenzo(i)phenanthridinium perchlorate (50) was isolated in 9% yield. Addition of acetic acid and hydrogen peroxide to the crude mixture increased the yield to 37%<sup>31</sup>.



Starting with 5-methyl-2-(2-naphthyl)thiopyridine (51), 5,9-dimethylbenzo(i)phenanthridinium perchlorate (52) was isolated in 17% yield.

Starting with 1-naphthalenethiol, the synthesis proceeded in analogous fashion via the sulphide, the acetonil salt (53) and the thiazepinium salt. There was no evidence of sulphur ex-

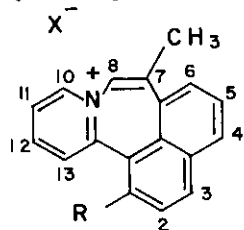
trusion during the polyphosphoric acid cyclisation. The thiazepinium salt underwent oxidative



55, R = H

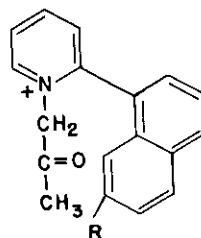
56, R = CH<sub>3</sub>

sulphur extrusion in the presence of hydrogen peroxide and acetic acid affording 7-methylbenzo(k)phenanthridinium perchlorate (55) in 60 % yield. Similarly, 3,7-dimethylbenzo(k)phenanthridinium perchlorate (56) was synthesised by sulphur extrusion route<sup>31</sup>. The cyclodehydration product of 57 was originally considered to be 7-methylbenzo(k)phenanthridinium



58, R = H, X = ClO<sub>4</sub>

59, R = CH<sub>3</sub>, X = ClO<sub>4</sub>

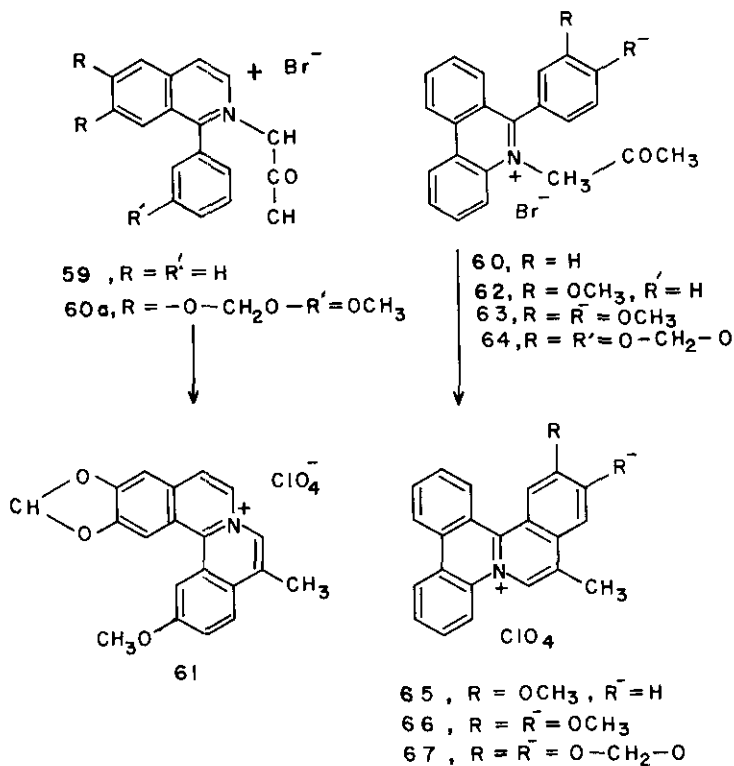


57, H, CH<sub>3</sub>

perchlorate paralleling the reaction of the 2-phenylpyridinium series, but, later on it was shown that the product from 57 and related 2-( $\alpha$ -naphthyl)pyridinium ketones are benzo(l,m)phenanthridinium derivatives (58,59)<sup>30,31</sup> resulting from ring closure at the more reactive  $\alpha$ -position (C-8 in the naphthalene ring)<sup>13,31</sup>.

Bradsher and Beavers have reported their failure to cyclise 1-phenyl-2-acetylisoquinoliniumbromide (59) and 5-acetoxy-6-phenanthridinium bromides (60)<sup>32a</sup>. It was assumed that the failure of 59 to cyclise arose from the overlapping of the hydrogen atom at position 8

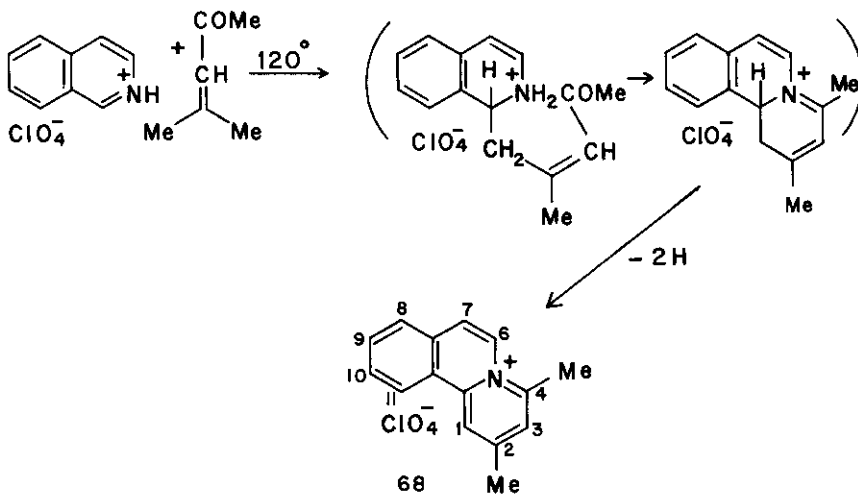
of the isoquinoline ring with those of the ortho positions of the phenyl ring since this would



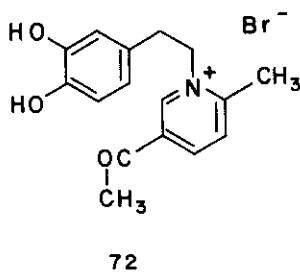
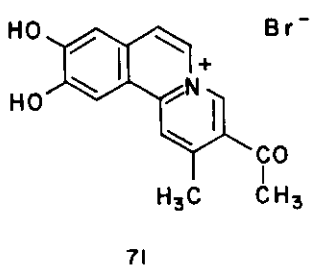
interfere with the achievement of the coplanarity necessary for ring closure. However, activation brought about by an electron donating groups at meta position of the phenyl ring in (60a) brought about the cyclisation with hydrochloric acid, affording the expected 2,3-methylenedioxy-12-methoxy-9-methylbenzo(a)phenanthridizinium perchlorate (61). From the quaternary salts (62-64), cyclisation in hydrochloric acid afforded 55-70% of the expected 11-methyl-dibenzo[a,c]phenanthridizinium salts (65-67) <sup>33a</sup>.

Chapman <sup>33</sup> has reported that heating isoquinolinium perchlorate with mesityl oxide for several hours at 120° afforded benzo(a)quinolizinium salt (68) in 35% yield. Its formation is believed to involve the addition of one of the isopropylidene methyl groups to the activated double bond of the isoquinolinium ring followed by ring closure between the nitrogen and the carbonyl group and spontaneous oxidative aromatisation as shown in scheme 2.

The reaction could be applied to a wide variety of unsaturated ketones, both open chain and cyclic as long as they contain at least one methyl substituent in the  $\beta$ -position.

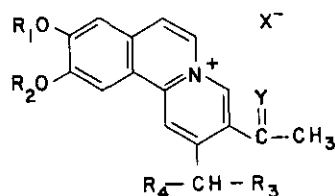


Teuber and Laudier<sup>34</sup> have reported that 3,4-dihydroxyphenethylamine reacts with two moles of either acetoacetaldehyde acetal or 1-methoxy-1-butene-3-one in hot glacial acetic acid to give a mixture of 40% benzo(a)quinolizinium salt (71) and 31% of the pyridinium salt (72). Using water as a solvent the quaternary salt (71) was obtained in 13% yield. Treatment of 71 with number of reagents in the presence of potassium iodide and potassium carbonate in acetone yielded substituted quaternary salts in 23-82% yields<sup>35,36,37</sup>.



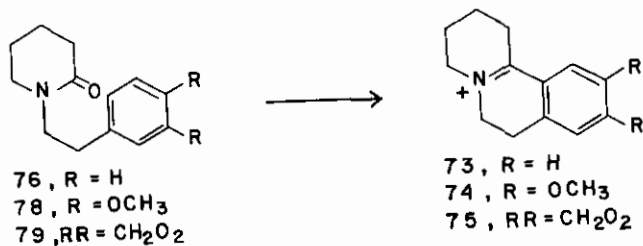
The results are summarized in Table VI.

TABLE VI

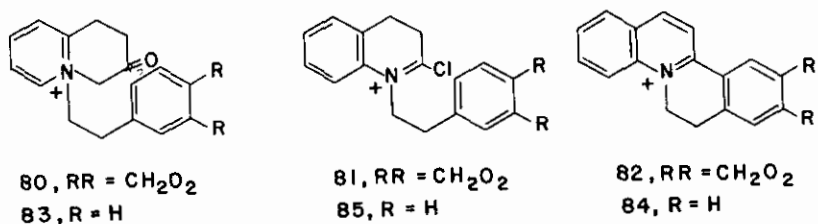


Compound number	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Y	Yield %	Ref.
1.	H	H	H	H	H <sub>2</sub>	70	35
2.	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H <sub>2</sub>	82	35
3.	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H <sub>2</sub>	80	35
4.	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H <sub>2</sub>	23	35
5.	CH <sub>3</sub>	CH <sub>3</sub>	H	CH <sub>2</sub> naphthyl-CH <sub>2</sub>	H <sub>2</sub>	23	35
6.	CH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	O	14	35
7.	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	H	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	O	53	35
8.	H	CH <sub>3</sub>	H	H	O	23	36
9.	CH <sub>3</sub>	H	H	H	O	28	36
10.	CH <sub>3</sub>	CH <sub>3</sub>	H	H	O	25	37
11.	CH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	H	H <sub>2</sub>	55	37
12.	CH <sub>3</sub>	COCH <sub>3</sub>	H	H	O	14	37
13.	CH <sub>3</sub> CO	CH <sub>3</sub> CO	H	H	O	55	37
14.	COC <sub>6</sub> H <sub>5</sub>	H	H	H	O	51	37

Hexahydroquinolizinium salts (73-75) have also been synthesised by cyclising *N*- $\beta$ -aryl-ethylpiperidone (76-79) with phosphoryl chloride<sup>38</sup>. However, the parent piperidone (76) failed to cyclise with phosphoryl chloride, but when cyclised with polyphosphoric acid, a small amount of the quaternary salt (73) was isolated. This is in direct disagreement to the findings of Sugawara et al.<sup>39</sup>, who has reported the isolation of 73 from 76 on cyclisation with phosphoryl chloride. In a similar cyclisation of 1- $\beta$ -phenethylcarbostyryl (80) with phosphoryl chloride, a mixture of two products (81,82) were isolated, from which 9,10-dimethylenedioxy-6,7-dihydrobenzo[*a,f*]quinolizinium salt (82) was isolated in 4% yield.

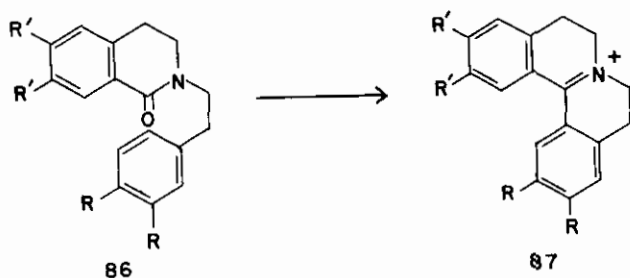


From 80, Sugasawa et al.<sup>40</sup> have claimed to have isolated 84, which has now been shown



to have the structure 85<sup>38</sup>.

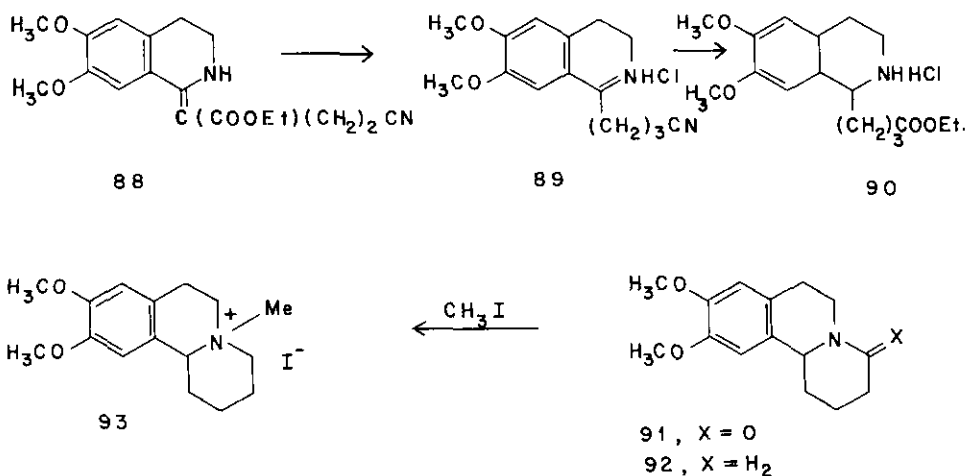
On the other hand, cyclisation of 2-β-phenethyl-3,4-dihydroisocarbostyryl (86) with



phosphoryl chloride at 130<sup>0</sup> gave the corresponding dibenzo [a,h]quinolizinium salt (87)<sup>38</sup>.

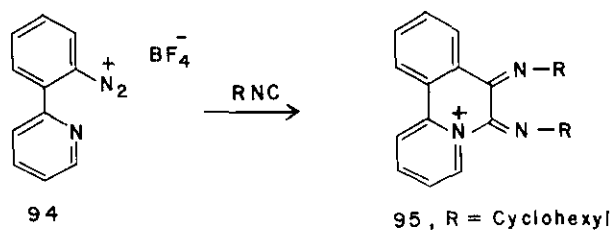
Another route for the preparation of hexahydrobenzo(a)quinolizinium iodide<sup>41</sup> involves the hydrolysis of an acrylonitrile adduct of 1-(ethoxycarbonylmethylene)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (88) at higher temperature. The hydrolysis product (89) was





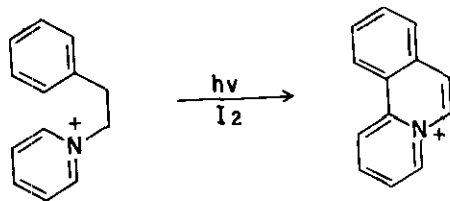
hydrogenated catalytically to (90). This cyclised in base to 91, which on reduction with lithium aluminium hydride was converted to (92). Addition of methyl iodide gave (93).

Addition of cyclohexylalitrile to 2-( $\alpha$ -pyridyl)benzene diazonium tetrafluoroborate (94) afforded 6,7-bis(cyclohexylimino)-6,7-dihydrobenzo(a)quinolizinium tetrafluoroborate (95) in



70% yield.<sup>40</sup>

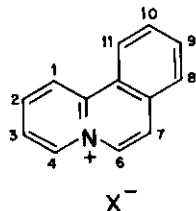
The most convenient method for the synthesis of phenanthridizinium derivatives involved the irradiation of styrylpyridinium salts (96)<sup>41,42</sup>. Best results were obtained by irradiating a well stirred ethanolic solution of styryl salts (96) containing some iodine. Sub-



39

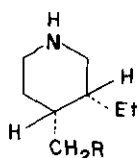
tituted phenanthridizinium salts were also prepared with substituents in either of the rings. While this is but one of the several attempts made to extend the photocyclisation observed with stilbenes<sup>43</sup> to the synthesis of heterocyclic system<sup>44</sup>, it is believed to be the first such instance involving a quaternary salt. The results are summarized in Table VII.

TABLE VII

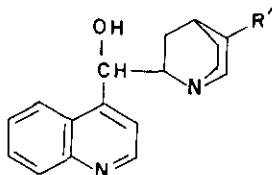


Compound number	Substituent	Yield %
1.	H	60
2.	1,3-(Me) <sub>2</sub>	47
3.	1,3-(ph) <sub>2</sub>	50
4.	8-Me	56
5.	10-Me	66
6.	8-OBz	43
7.	10-Cl	60
8.	8,9-(OBz) <sub>2</sub>	25
9.	8,10-(OBz) <sub>2</sub>	50

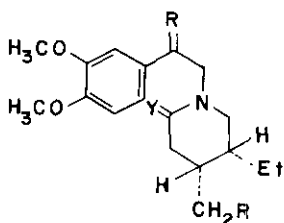
The number of alkaloids containing the benzo(a)quinolizine system such as emetine<sup>43</sup> psychotrine<sup>44</sup> protoemetine<sup>45</sup> O-methylpsychotrine, lubulosine<sup>46</sup> and ankorine<sup>47</sup> have been synthesised. A general synthesis of these alkaloids<sup>48</sup> involves the treatment of an ester (97) prepared from cincholine (98) with 3,4-dimethoxyphenacyl bromide followed by reduction with sodium borohydride in ethanol yielded a diastomeric mixture of 99. Oxidation of 99 with mercuric acetate-(ethylenedinitrilo)tetraacetic acid followed by hydrogenolysis of the resulting lactam alcohol (palladium-carbon, ethanol) gave 100, 101 and 102 in 44, 4 and 30% yields respectively. Cyclisation of 100 with phosphoryl chloride in toluene under reflux afforded (103, X=I) in 95% yield. Conversion of the iodide salt into (103, X=Cl<sub>4</sub>)



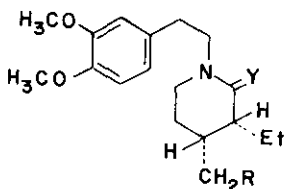
97



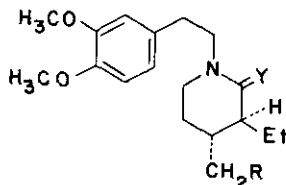
98, R = H Or Me ; R' = Vinyl Or Ethyl



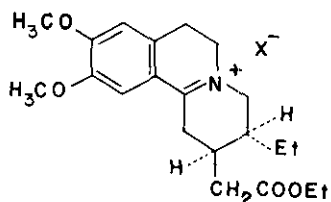
99, R = COOEt ; Y = H<sub>2</sub>, Z = H, OH  
100, R = COOEt ; Y = O ; Z = H<sub>2</sub>



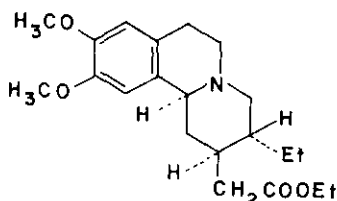
101, R = COOEt ; Y = O



102



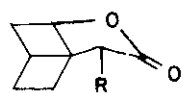
103, X = I  
103, X = ClO<sub>4</sub>



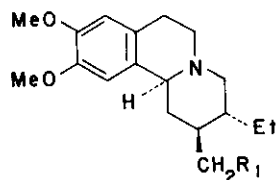
104

and subsequent catalytic hydrogenation produced 104, from which the base (-)-104 was obtained in 98% overall yield.

The emetine precursor<sup>49</sup> was also obtained from lactones (105) prepared from norbornylene via hydroboration and oxidation. The resulting norcamphor was oxidised by Bayer-Villiger method, followed by alkylation of the lactone (105, R = H) with ethyl bromide or allyl bromide to give protoemetinol (106, R<sub>1</sub> = CH<sub>2</sub>OH, COOMe).

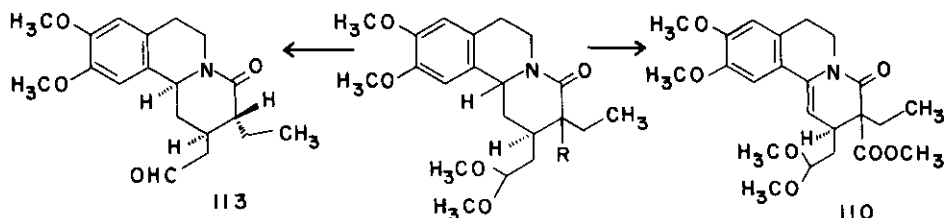
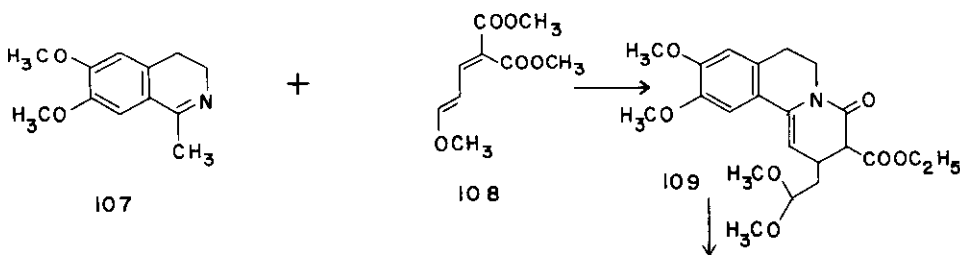


105, R = Et, allyl

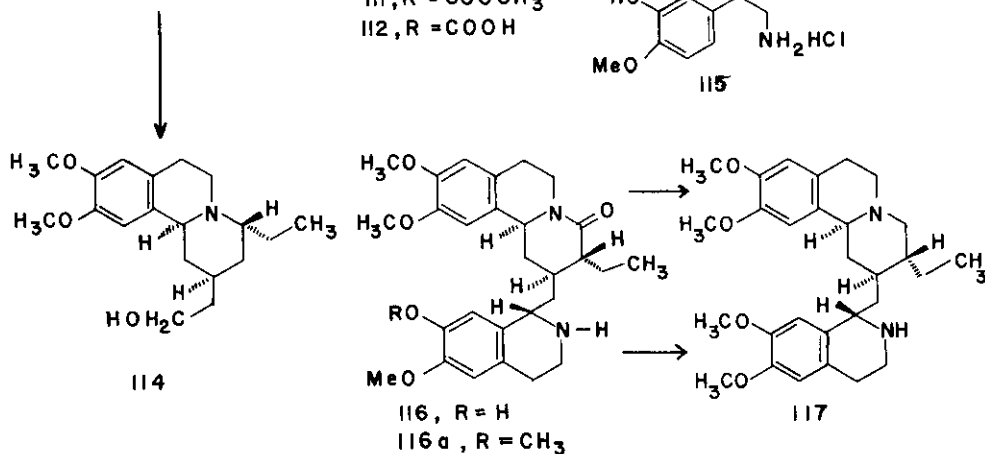
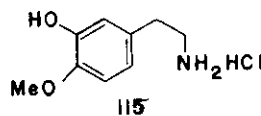


106, R<sub>1</sub> = CH<sub>2</sub>OH, COOMe

Kametani et al.<sup>50</sup> have synthesised emetine by reacting 3,4-dihydro-6,7-dimethoxy-1-methyl isoquinoline (107)<sup>51</sup> with dimethyl-3-methoxyallylidene malonate (108) at room temperature



111, R = COOCH<sub>3</sub>  
112, R = COOH

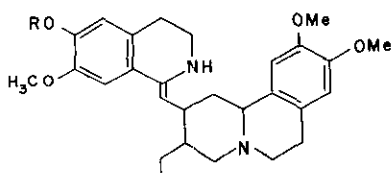
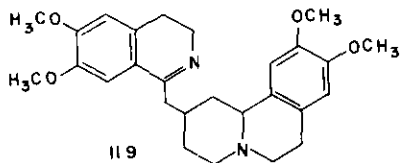
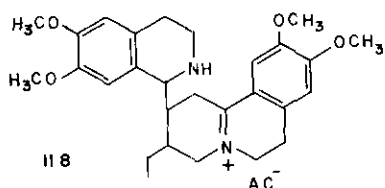


116, R = H  
116a, R = CH<sub>3</sub>

117

followed by refluxing, gave 2,3,6,7-tetrahydro-9,10-dimethoxy-3-methoxycarbonyl-2-( $\beta$ -dimethoxyethyl)benzo(a)quinolizina-4-one (109) in 88.5% yield. Treatment of 109 with ethyl iodide in the presence of sodium hydride gave 3-ethyl derivative (110), which, on reduction with Adams catalyst in methanol afforded the lactam (111). Hydrolysis of the lactam with potassium hydroxide in aqueous methanol gave the carboxylic acid (112). Decarboxylation followed by treatment with hydrochloric acid resulted in the formation of aldehyde (113). Reduction of the aldehyde with lithium aluminium hydride afforded ( $\pm$ ) dihydroprotoemetine (114) in 59% yield. Reaction of 113 with the phenolic base (115) in hot methanol-dilute hydrochloric acid gave 116 as the main product, which, after purification was treated with diazomethane to give (116a). This crude product (116a) was reduced with lithium aluminium hydride in hot ether-dioxane to yield ( $\pm$ )emetine (117).

Didehydroemetine, was one of the products isolated in the photochemical and thermochemical decomposition of emetine<sup>52</sup> which, was designated by structure (118)<sup>53, 54</sup>. Its mass spectrum,



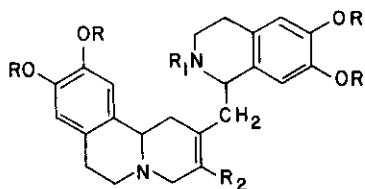
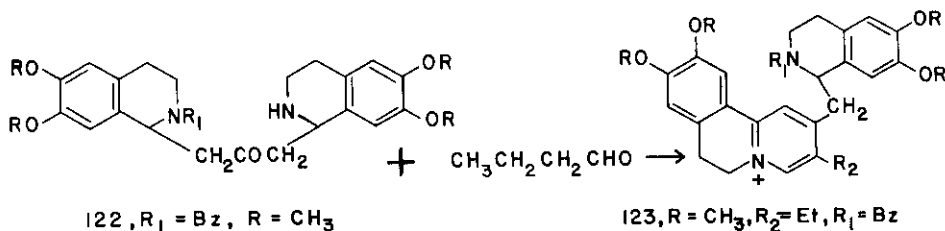
120, R = Me

121, R = H

however, did not resemble to the proposed structure, but rather that of O-methylpsychotrine, to which structure 119 was assigned. As the mass spectrum of didehydroemetine contains fragments at  $m/e$  274-272,  $m/e$  258 and 244, it shows that the extra double bond is not situated in the benzo(a)quinolizine moiety of the molecule. The fragments originating from the isoquinoline moiety of the molecule appear at the same position as those of O-methylpsychotrine. These facts support a structure for didehydroemetine as 119. The position of the double bond in O-methylpsychotrine was established by reduction, when emetine and isocetine were

isolated <sup>55-57</sup>. Since emetine and isometine are stereoisomeric at C-1, the double bond in O-methylpsychotrine must be located here. As a consequence, O-methylpsychotrine has to be represented by 120 and psychotrine by 121. Deutrium exchange experiments have confirmed that the two compounds, didehydroemetine and O-methylpsychotrine are tautomers and their correct structure is represented by 119 and 120 respectively.

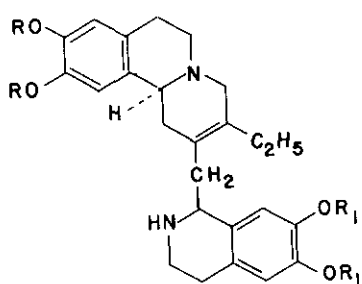
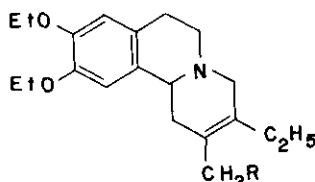
Another route to emetine derivatives involves the addition of butyraldehyde to a suspension of 122 under nitrogen atmosphere. The mixture was shaken for six hours followed by heating at 70° under nitrogen atmosphere. The product, 3-ethyl-2-(N-benzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolyl-1-methyl-9,10-dimethoxy,6,7-dihydrobenzo(a)quinolizinium perchlorate



123a, R = CH<sub>3</sub>, R<sub>1</sub> = Bz, R<sub>2</sub> = Et

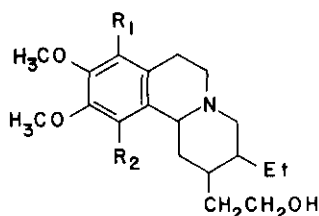
(123) was isolated in 71 % yield. Reduction with sodium borohydride gave a mixture of N-benzoyl-2,3-dihydroisometine perchlorate and N-benzoyl-2,3-dihydroemetine (123a). In a similar reaction, number of other derivatives were prepared.

Other emetine derivatives were prepared by cyclising 6,7-diethoxy-3,4-dihydroisoquinoline hydrochloride with 2-ethylvinyl acetate <sup>59</sup>. The resulting benzoquinolizisone was treated with P-diethoxy-P-methylacetate phosphane followed by photoisomerising the methoxy-carbonylmethylene-hexahydrobenzoquinolizine (124). Reduction gave an aldehyde, which on treatment with 3-hydroxy-4-ethoxyphenethylamine hydrochloride and diazoethane afforded emetine derivative (125).


 125, R = R<sub>1</sub> = Et


124, R = COOMe

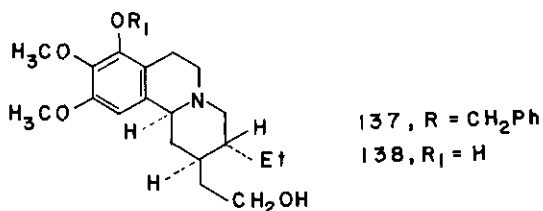
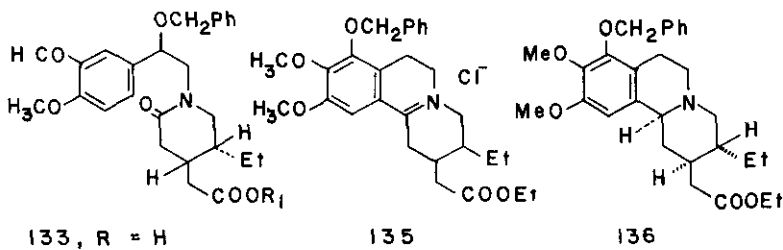
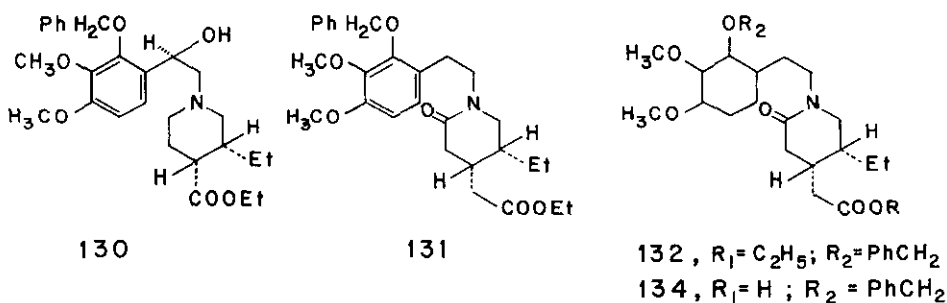
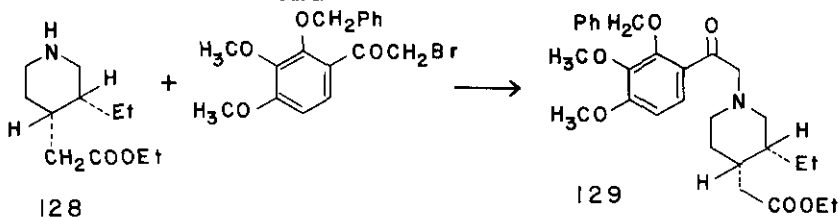
Ankorine is another alkaloid structurally related to emetine<sup>60,61</sup>, which, has been assigned the plane structure (126) largely on the basis of physical measurements<sup>62</sup>. However neither the precise location of the phenolic hydroxyl group nor the stereochemistry was established at that time. The recent communication of Santay et al.<sup>63</sup> of the synthesis of four possible racemic stereoisomers of ankorine suggested that the phenol function of ankorine must


 126, R<sub>1</sub> = H, R<sub>2</sub> = OH

 127, R<sub>1</sub> = OH, R<sub>2</sub> = H

be placed at an alternative position (127). Fujii et al.<sup>64,65</sup> have established the absolute configuration of ankorine by synthesis, which involves the condensation of an optically active ester (128)<sup>66,67</sup> with 2-benzoyloxy-3,4-dimethoxyphenacyl bromide at 60° for 6 hours. The ketone (129) thus obtained was reduced with sodium borohydride in ethanol at 0° to give a distereomeric mixture of amino alcohol (130). Oxidation of 130 with mercuric acetate-(ethyl-dinitrilo)tetraacetic acid<sup>68,69</sup> followed by purification gave 6-piperidone (131) as distereomeric mixture in 57% yield. Hydrogenolysis of the mixture 131 over palladium-carbon in ethanol gave lactamphenol which, was then benzylated to an ether (132). Hydrolysis of 132

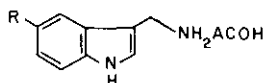
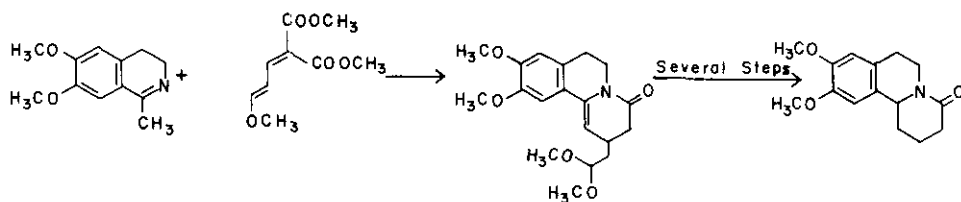
followed by heating the lactam acid at  $180^{\circ}$  for 80 minutes gave a mixture of *trans* (133) and *cis* isomer (134). Esterification of the mixture followed by cyclisation with phosphoryl chloride in benzene gave a mixture of *trans* and *cis* esters (135). Catalytic hydrogenation of the



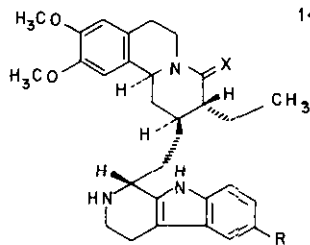
quarternary salt (135) furnished tricyclic ester (136), which on reduction with lithium aluminium hydride in refluxing ether afforded alcohol (137). Debenzylation of 137 by hydrogenolysis led to the ultimate compound (138) in 64% overall yield.



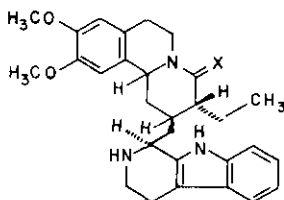
Tubulosine and deoxytubulosine are the other alkaloids containing the benzo(a)quinolizine system <sup>70</sup>. Synthesis of these alkaloids involve the condensation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (139) with dimethyl 3-methoxyallylidene malonate. The enamide (140)



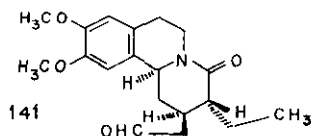
142, R = OH<sup>-</sup>  
148, R = H



143, R = OH; X = O  
145, R = OH; X = H<sub>2</sub>  
147, R = H; X = H<sub>2</sub>



144, R = OH; X = O  
146, R = OH; X = H<sub>2</sub>



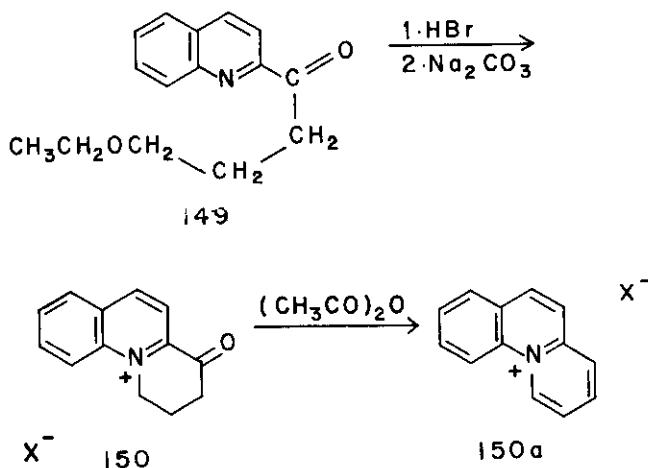
so formed was converted to 141, which on condensation with seritonen (142) followed by reduction of the isomeric mixture (143, 144) with sodium bis(2-methoxyethoxy)aluminium hydride in pyridine afforded (±) tubulosine (145) and (±) isotubulosine (146).

Isotubulosine was isolated as a minor product, as it could not be completely separated from tubulosine.

Similarly ( $\pm$ ) deoxytubulosine (147) was prepared from 141 and tryptamine (148).

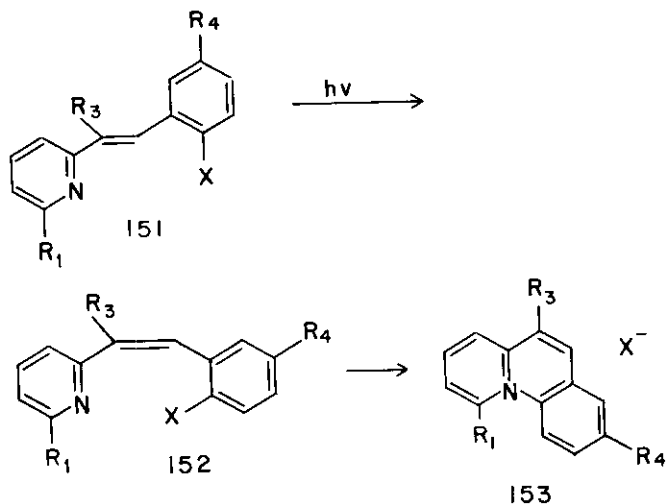
#### Synthesis of Benzo(c)quinolizinium Salts

The first synthesis of the benzo(c)quinolizinium ion was accomplished by Glover and Jones<sup>19</sup> using their general method for the synthesis of the quinolizinium ion and its benzologs. The ketone 149 formed by the reaction of 2-cyanoquinoline with 3-ethoxypropylmagnesium bromide with hydrobromic acid to cleave the alkoxyl group and the resulting halide was converted to the cyclic ketone (150). The Jones dehydration carried out on the



cyclic ketone led to the benzo(c)quinolizinium cation (150a)

A new general synthesis has been devised<sup>71,72</sup> which makes the benzo(c)quinolizinium ion as accessible as the benzo(b)quinolizinium ion. The stilbazole (151) formed by the condensation of 2-chlorobenzaldehyde with  $\alpha$ -picoline or a suitable derivative were irradiated in benzene solution and the mixture consisting largely of the cis isomer (152) was heated for one hour at 170°. The average conversion to benzo(c)quinolizinium salts (153) was 66% except when there was a methyl group at the 6-position of the pyridine group ( $R_1 = \text{CH}_3$ ) in which case steric hindrance is believed to be responsible for the failure of the internal quaternisation reaction. Usually the internal quaternisation reaction yielded reusable trans stilbazoles as byproducts. The participation of an aryl halide in a quaternisation reaction is believed<sup>73</sup> to be due in large measure to the



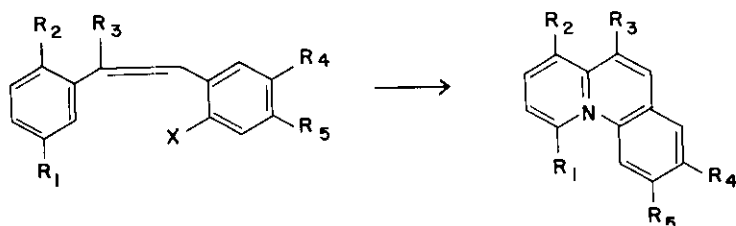
halogen by the electron withdrawal of the pyridyl group communicated through the conjugated system.

Irradiation of the benzene solution (151, R<sub>4</sub> = NO<sub>2</sub>) failed to give the expected isomer, but instead 8-nitrobenzo(c)quinolinizinium chloride was isolated in 70 % yield.

Heating stilbazole at 240° for 6 hours and eliminating the irradiation step resulted in the formation of pure benzo(c)quinolinizinium in 54 % yield. At lower temperatures, the yield was appreciably reduced while the use of higher temperatures caused considerable decomposition. On the other hand, heating the *trans*- $\alpha$ -phenylstilbazole (151, R<sub>3</sub> = C<sub>6</sub>H<sub>5</sub>) failed to effect the cyclization.

The results are summarised in Table VIII.

TABLE VIII



Compound number	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	X	Method	Temp.	Yield %
1	H	H	H	H	H	Cl	A	170	50 <sup>b,c</sup>
	H	H	H	H	H	ClO <sub>4</sub>	B	240	54 <sup>d</sup>
	H	H	H	H	H	Br	B	240	50 <sup>e,f</sup>
2.	H	H	H	NO <sub>2</sub>	H	Cl	A	25	80 <sup>b,i,g</sup>
	H	H	H	NO <sub>2</sub>	H	ClO <sub>4</sub> <sup>h</sup>	...	..	d
3.	H	CH <sub>3</sub>	H	NO <sub>2</sub>	H	Cl	A	25	80 <sup>b,i,g</sup>
4.	H	CH <sub>3</sub>	H	H	H	Cl	A	165	69 <sup>b,c</sup>
5.	H	H	H	H	Cl	ClO <sub>4</sub>	A	170	70 <sup>b,c</sup>
	H	H	H	H	Cl	Cl	B	240	60 <sup>d</sup>
6.	H	CH <sub>3</sub>	H	H	Cl	Cl	A	155	77 <sup>b</sup>
	H	H	CH <sub>3</sub>	H	H	Cl	A	210	55 <sup>b,i</sup>
7.	H	H	CH <sub>3</sub>	H	H	Cl	A	210	55 <sup>b,i</sup>
	H	H	CH <sub>3</sub>	H	H	ClO <sub>4</sub> <sup>h</sup>	...	..	g
8.	H	H	C <sub>6</sub> H <sub>5</sub>	H	H	Cl	A	200	50 <sup>b,c</sup>
	H	H	C <sub>6</sub> H <sub>5</sub>	H	H	ClO <sub>4</sub>	C	140	2 <sup>d</sup>
9.	H	H	COOC <sub>2</sub> H <sub>5</sub>	H	H	ClO <sub>4</sub>	C	140	20 <sup>i</sup>

a) Bases on *trans*-stilbazole initially used. b) Cyclisation carried out on unpurified *cis-trans* mixture. c) The irregular Cluster from ethanol-ethyl acetate. d) Tan needles from ethanol.

e) Lit. m.p. 188-89<sup>o</sup>. f) Prepared via the perbromide. g) Small tan needles from ethanol.

h) Prepared by addition of 25 % perchloric acid to the chloride. i) Allowed to stand for 48 hours after irradiation.

A. Irradiation of benzene solution followed by heating at 170<sup>o</sup> for one hour.

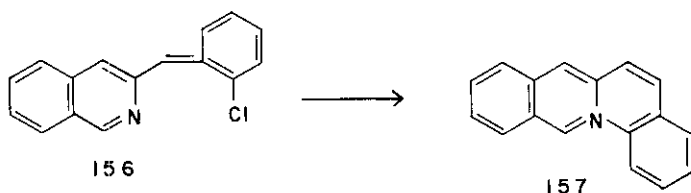
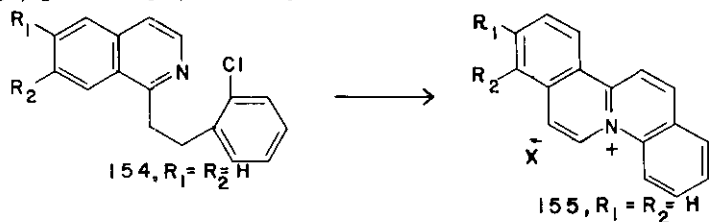
B. Stilbazole and iodine heated at 240<sup>o</sup> for 6 hours.

C. Cyclisation carried out in refluxing acetic anhydride

This method has been applied to the preparation of tetracyclic system in the hope, that, it would enable to synthesise the aza steroids and azonia helicenes<sup>73</sup>.

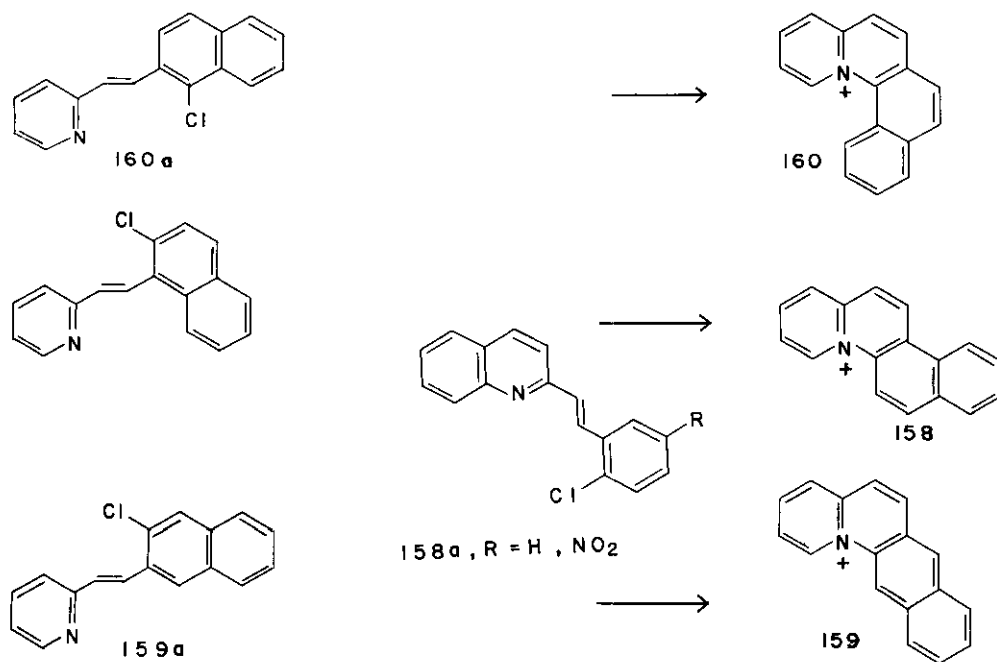
2-Chloro-1-styrylisoquinoline (154) was readily prepared in good yield by condensation of 1-methylisoquinoline with 2-chlorobenzaldehyde.<sup>74</sup> The product, 1-(2-chloro)styrylisoquinoline on cyclisation at 200<sup>o</sup> gave the quinolizinium salt (155) in 70 % yield with no previous irradiation. No change was observed in the ultraviolet spectrum of the isoquinoline (154), when a benzene solution was irradiated and this combined to the facile cyclisation to the quaternary salt (155) suggests that the styrylisoquinoline is in the *cis* form. However, 6,7-dimethoxyisoquinoline-2-chloro-1-styrylisoquinoline (154, R<sub>1</sub> = R<sub>2</sub> = OCH<sub>3</sub>) was not cyclised simply by heating, but on irradiation in benzene followed by heating at 165<sup>o</sup> gave

the dimethoxy salt (155,  $R_1 = R_2 = \text{OCH}_3$ ;  $X = \text{ClO}_4^-$ ). On the other hand 2-chloro-3-styrylisoquinoline (156) gave hardly 1% of the cyclised product (157). The failure of 156 to undergo



cyclisation has demonstrated that the internal quaternisation is not solely the consequence of favourable geometry, but, must depend heavily upon the shift of electrons from the halogen bearing carbon to the nitrogen atom via the conjugated system.

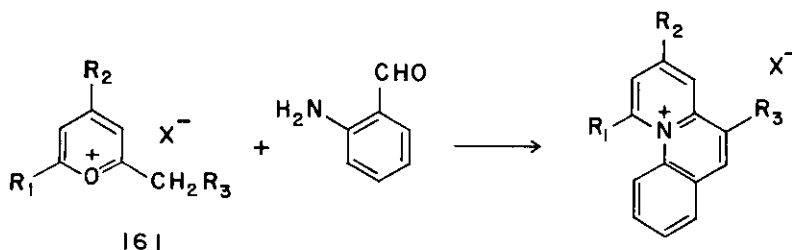
The other three tetracyclic systems (158-160) were all prepared by irradiating the appropriate chloronaphthyl-2-vinylpyridines and heating the crude *cis* and *trans* mixtures obtained on irradiation. It is significant that quaternisation of the crude  $\beta$ -(1-chloro-2-naphth-



yl)2-vinylpyridine (160a) conjugated through the bond between carbon atom 1 and 2 of the naphthalene nucleus gives a better yield (50 %) than that from the crude 3-chloro isomer (159a) conjugated through the bond of lower order between carbon atoms 2 and 3.

On the other hand *trans*-2-chloro-2-styrylquinoline (158a, R=H or NO<sub>2</sub>) showed no tendency to undergo cyclisation. This must be due to the fact that, isomerisation is always a competing reaction in these cycloquarternisations, it is obvious that in this case the weakly basic character of the quinoline nitrogen results in preferential isomerisation.

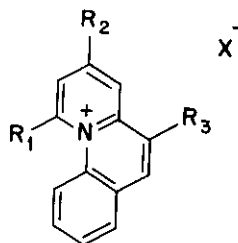
Another method for the synthesis of the quaternary salt involves the condensation of trisubstituted pyrrilium salts (161) with *o*-aminobenzaldehyde in acetic acid <sup>75</sup>. The reaction mixture was heated under nitrogen and the products were isolated in the range of 46-73 %.



However, this method failed to give 1-substituted benzo(o)quinolizinium salt.

The results are summarized in Table IX .

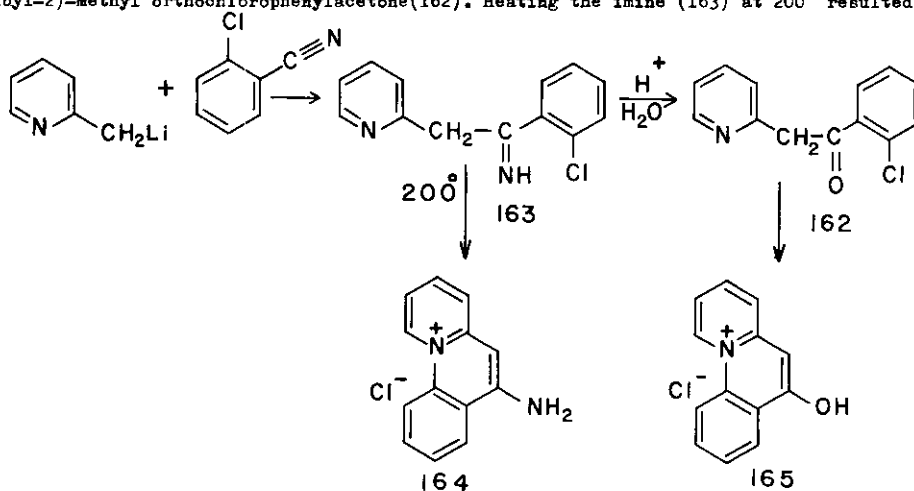
TABLE IX



Compound number	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X	Yield %
1.	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	BF <sub>4</sub> <sup>-</sup>	64
2.	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	Br <sup>-</sup>	43
3.	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	I <sup>-</sup>	51
4.	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	BF <sub>4</sub> <sup>-</sup>	71
5.	CH <sub>3</sub>	C(CH <sub>3</sub> ) <sub>3</sub>	H	BF <sub>4</sub> <sup>-</sup>	48
6.	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	BF <sub>4</sub> <sup>-</sup>	73

Another route to the benzo(o)quinolizinium salts involves the condensation of picolyl-2-lithium with *o*-chlorobenzonitrile. Hydrolysis of the imine resulted in the formation of

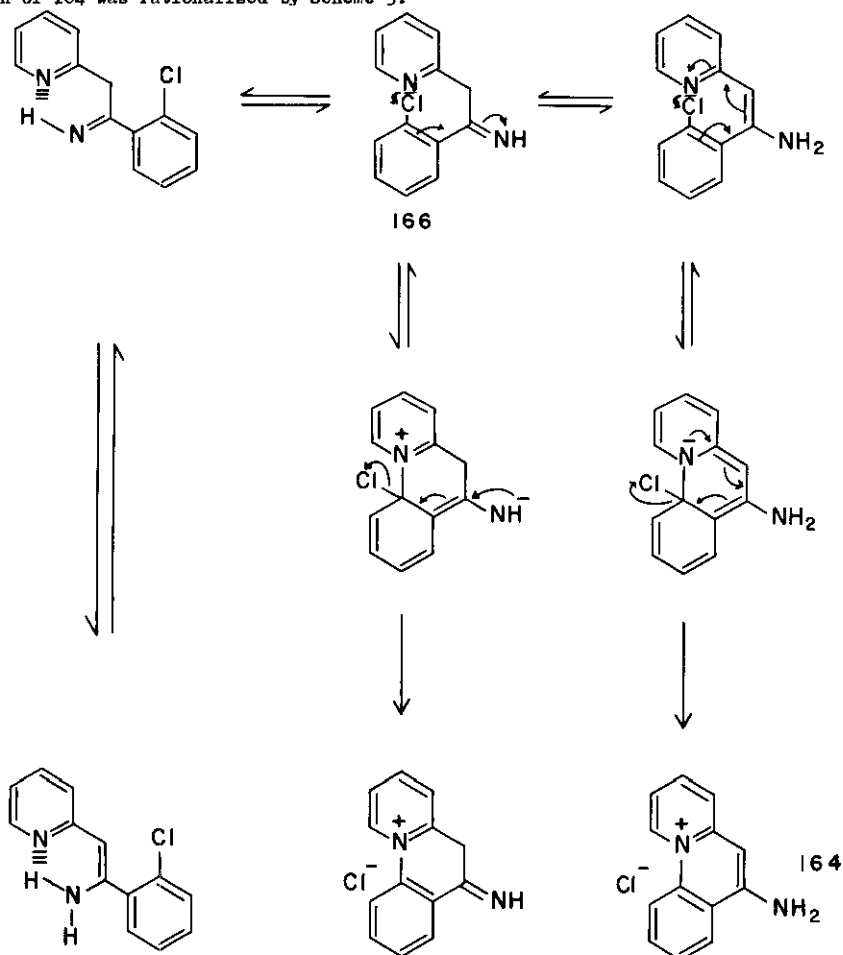
pyridyl-2)-methyl orthochlorophenylacetone(162). Heating the imine (163) at 200° resulted



in the formation of 6-amino-2-(2-methylpyridin-5-yl)quinolizinium chloride (164), whereas, heating the ketone (162) resulted in the formation of 6-hydroxy-2-(2-methylpyridin-5-yl)quinolizinium chloride (165) <sup>76</sup>.

The formation of 164 was rationalized by Scheme 3.

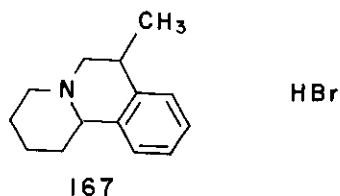
Scheme 3



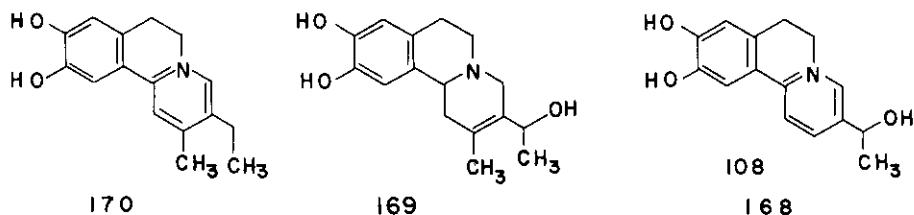
The mechanism suggests the ring closure of the imine (166) by an attack from the pyridinium nitrogen followed by the elimination of the halogen to give the ring closure product (164).

Reactions of Benzo(a)quinolizinium Ion

The initial paper<sup>8</sup> on the subject of the 7-substituted benzo(a)quinolizinium analogs reported, that the 7-methyl derivative could be reduced catalytically presumably to a methylbenzoquinolizidine derivative (167), whereas on oxidation with potassium permanganate phthalic acid was isolated.



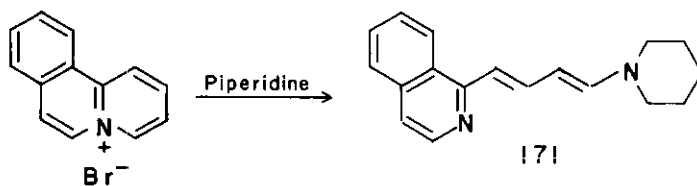
Reduction of 71 over platinum oxide resulted in the formation of corresponding alcohol (168), whereas with sodium borohydride, a tetrahydro derivative (169) was isolated in 32% yield. On the other hand Clemenson reduction yielded (170).<sup>37</sup>



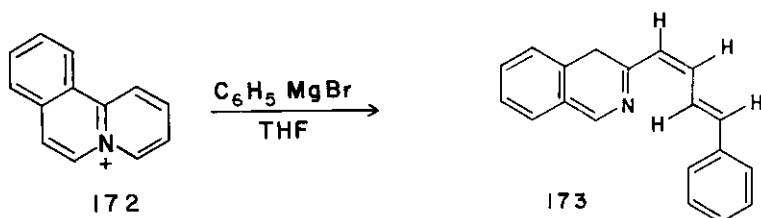
Richard and Steven<sup>77</sup> have reported that on standing in ammonia solution, 7-phenylbenzo(a)-quinolizinium ion was converted to a pseudo base.

It has also been reported<sup>78</sup> that heating an alcoholic solution of benzo(a)quinolizinium bromide with piperidine for 15 minutes, the ring opening product 1-[[4-piperidinobutadiene-(1,3)-yl-1]]-isocouinoline (171) was isolated in 76% yield.



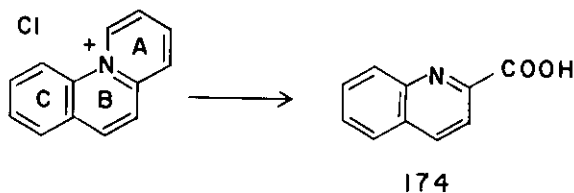


It has been reported<sup>82</sup> that treatment of the quaternary salt (172) with phenylmagnesium bromide in tetrahydrofuran also resulted in the ring opening yielding 173 as the only product.



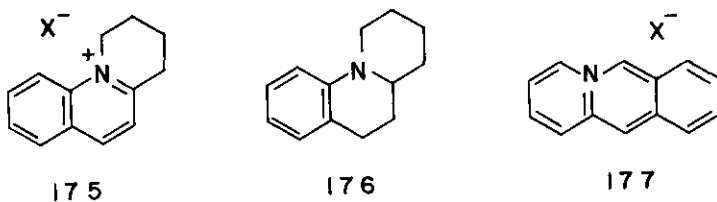
Reactions of Benzo(c)quinolinium Ion

Fozard et al.<sup>79</sup> have reported that oxidation of benzo(c)quinolinium chloride in boiling potassium permanganate afforded a poor yield of quinoline-2-carboxylic acid (174) formed by



the destruction of ring A.

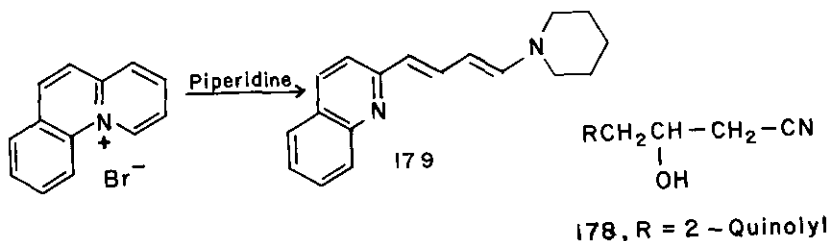
Hydrogenation of the quaternary salt (172) with palladium-carbon catalyst afforded 1,2,3,4-tetrahydrobenzo(c)quinolizinium chloride (175) showing that hydrogenation has



occurred exclusively in ring A, whereas, with platinum oxide both rings A and B were saturated yielding 176, a base prepared earlier by other routes<sup>80,81</sup>. This behaviour is in contrast to that of the acridizinium ion (177), which undergoes hydrogenation first in ring B then in ring A.

#### Action of Base

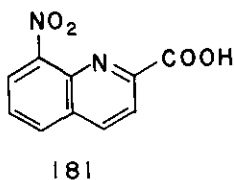
Reaction with sodium hydroxide-hydroxylamine mixture<sup>82</sup> with benzo(c)quinolizinium ion was shown to give hydroxybutyronitrile (178) in 22% yield, whereas, on heating its alcoholic



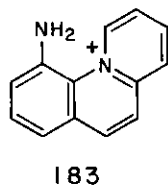
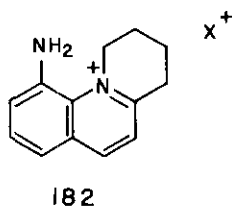
solution with piperidine for 20 minutes, the ring opening product 2-[4-piperidino-butadiene-(1,3)-yl-(1)]-quinoline (179) was isolated in quantitative yield<sup>83</sup>.

#### Action of Electrophilic Reagents

Nitration of benzo(c)quinolizinium ion afforded 10-nitrobenzo(c)quinolizinium perchlorate (180), the structure of which was further proved by oxidation, when 8-nitroquinoline-2-carboxylic acid (181) was isolated<sup>83</sup>. Further catalytic reduction of the nitration product (180)

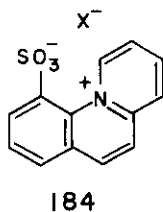


in the presence of platinum oxide resulted in the reduction of ring A as well as the nitro group affording 182, but in the presence of palladium-carbon, only the nitro group was



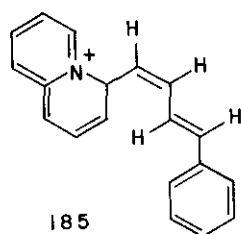
reduced resulting in the formation of an amine (183) in 69 % yield<sup>82</sup>.

Sulphonation occurs in the more remote ring C at position 10 affording betaine (184)



in 69 % yield. This reaction is similar to the one with the acridisinium series.<sup>82</sup>

It has also been reported that the reaction of phenylmagnesium bromide with the quarter-



nary salt (172) afforded the ring opening product (185) <sup>78</sup>.

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