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

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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 existance of a hetro atom in a higher valence state. Simple and familiar examples of such systems are the pyrilium (1,X=O) and thiapyrillium (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

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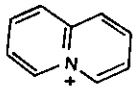

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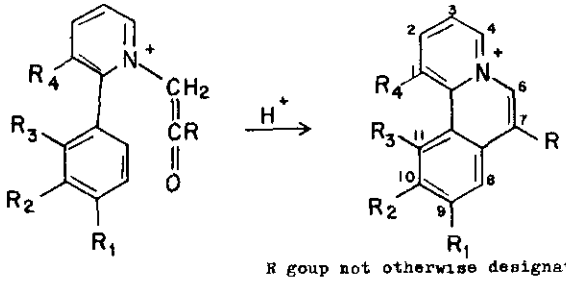
quinolizinium nucleus (2) [1-6]. The even smaller group of wholly aromatic quinolizinium salts consisted of a few complex compounds, which, with the exception of the tetracarbomethoxyquinolizinium derivatives of Diels and Alder were tetracyclic in nature.

Of the three benzologs of the quinolizinium ion, only the readily available acridizinium cation has been studied in detail and has been reviewed recently [7].

Bradsher et al. [8-10] 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 [11] 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 [12-14]. 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 goup not otherwise designated are hydrogen

10, R = CH_3

11, R = C_6H_5

12, R = R_1 = CH_3

13, R = R_2 = CH_3

14, R = R_3 = CH_3

15, R = CH_3, R_2 = OCH_3

16. R = CH_3, R_4 = OH

3, R = CH_3

4, R = C_6H_5

5, R = R_1 = CH_3

6. R = R_2 = CH_3

7, R = R_3 = CH_3

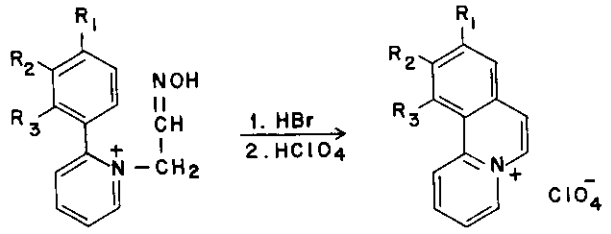
8, R = CH_3, R_2 = OCH_3

9, R = CH_3, R_4 = 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 [15]. 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_3 = CH_3)[12] 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 phenanthridizinium derivatives (17-20) in reasonable yields [14]. The low yield of 11-methyl-



17, $R_1=R_2=R_3=H$

18, $R_1=CH_3$, $R_2=R_3$ H

19, $R_2=CH_3$, $R_1=R_3=H$

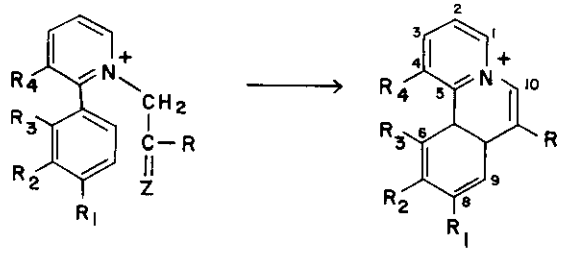
20, $R_3=CH_3$, $R_1=R_2=H$

phenanthridizinium perchlorate (20) is apparently due to steric inhibition and as comparable to that of 7,11-dimethyl analog (9%) reported previously [12].

The results are summerised in Table I.

Diels and co-workers [17,18] were the first reseach workers to prepare tetracarbomethoxy-phenanthridizinium salts, but the method was too complicated and is not suitable for the preparation of simple analogs.

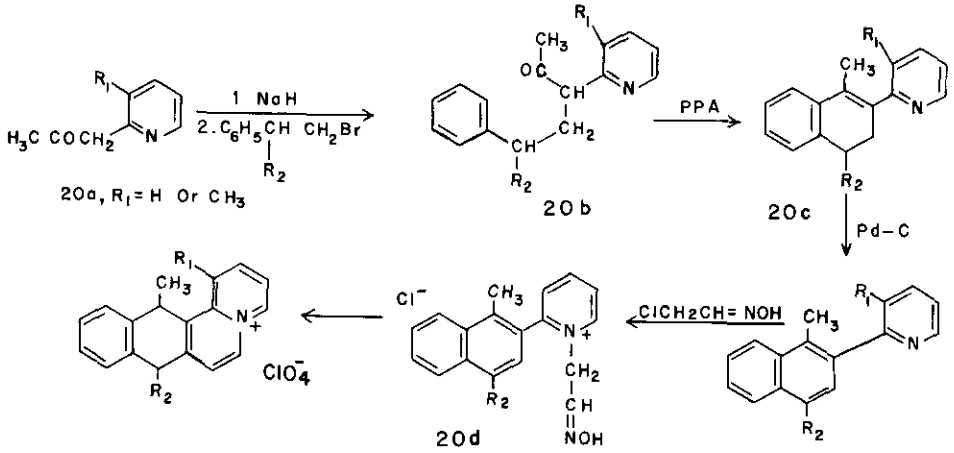
TABLE I



Compound number.	R_1	R_2	R_3	R_4	R	Z	Cyclising agent	Yield %	Time	Ref.
1.	H	H	H	H	C_6H_5	O	HBr	42	14 days	13
2.	H	H	H	H	CH_3	O	HBr	75	51 hr.	13
3.	CH_3	H	H	H	CH_3	O	HBr	71	50.5 hr	12

4.	H	CH_3	H	H	C_6H_5	O	HBr	64	66 hr.	12
5.	H	H	CH_3	H	CH_3	O	HBr	9	50.5 hr.	12
6.	H	OCH_3	H	H	CH_3	O	HBr	50	0.05 hr.	12
7.	H	H	H	OH	CH_3	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_3	H	H	H	NOH	HBr	61	24 hr.	14
11.	H	H	CH_3	H	H	NOH	HBr	12	65 hr.	14

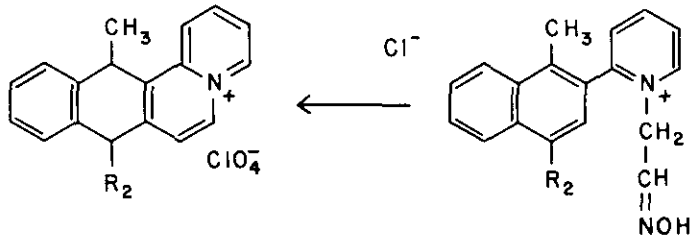
This method was extended to the synthesis of naphtho[2,3-a]quinolizinium salts. Alkylation of the methylene group of 2-acetonyl- or 3-methyl-2-acetonylpyridine (20a) by 2-phenyl-1-bromopropane in the presence o sodium hydride resulted in the formation of ketone (20b). Cyclisation of the ketone with polyphosphoric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



naphtho 2,3-a quinolizinium perchlorates [32].

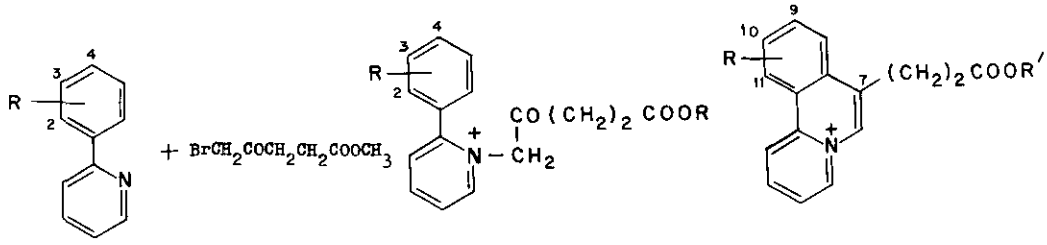
The results are summerised in Table II.

TABLE II



Compound number	R_1	R_2	X	Yield %
1.	H	H	ClO_4	76
2.	H	CH_3	ClO_4	82
3.	CH_3	H	ClO_4	48

Bradsher and Yarrington [16] introduced a carbonyl function into the phenanthridizinium nucleus by quarternisation of 2-phenylpyridine with methyl δ-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) [12].A methyl group in the ortho position of the phenyl ring (21, R CH_3) 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). Esterfication of the new acids (24-26) in absolute methanol or ethanol occurred in good yield.

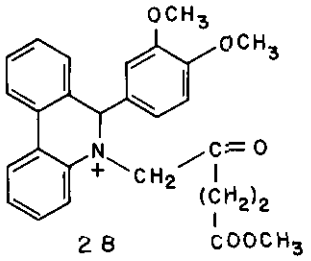


21, R = 2-CH_3

22, R' = CH_3, R = H
23, R' = H, R = CH_3

24, R = R H
25, R' = H, R = 9-CH_3
26, R' = H, R = 10-CH_3

On the other hand, quarternary salt obtained from 2-(1-naphthyl)pyridine and δ-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-α-bromolevulinate on heating with hydrochloric acid underwent a cleavage rather than cyclisation.



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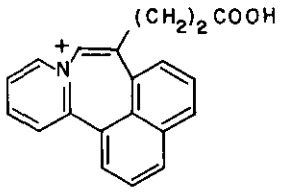

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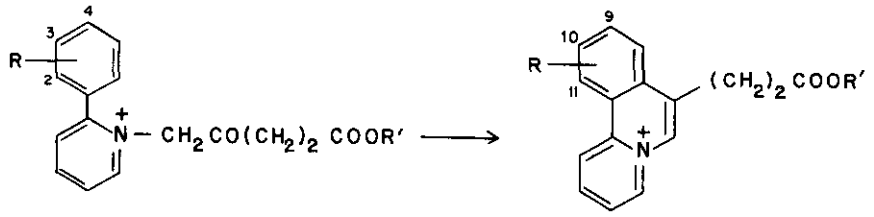
The spectral data showed the compound to have the structure of 6-(3,4-dimethoxyphenyl)-phenanthridizine hydrochloride.

The results are summerised in Table III.

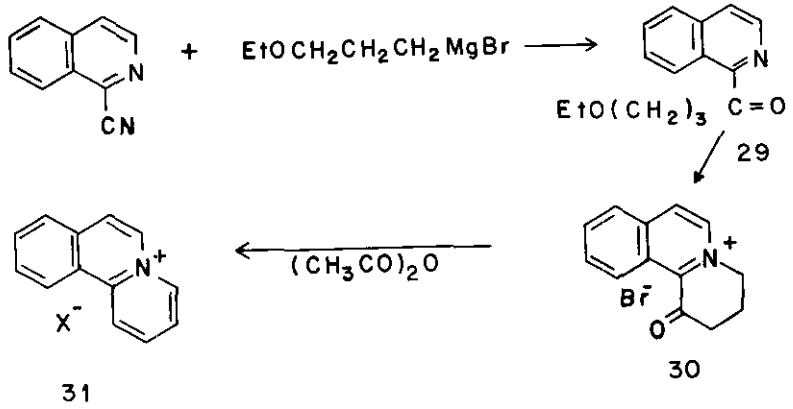
TABLE III



Compound number	R′	R	Yield %	Cyclising agent	Time days
1.	H	H	34.5	HBr	16
2.	H	9-CH_3	54	HBr	6
3.	H	10-CH_3	45	HBr	6
4.	H	11-CH_3	a	HBr	15

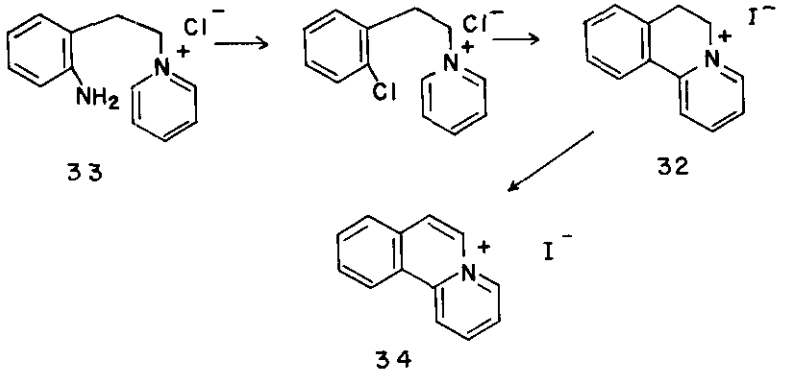
a) Starting material was recovered in 39 % yield without getting any cyclised product.

Glover and Jones [19] synthesised phenanthridizinium salt by reacting 1-cyanoisoquinoline 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) [19].



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

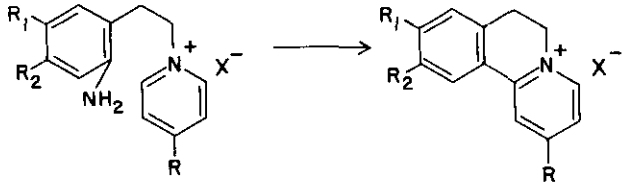
Scheme 1



2-aminophenethylpyridinium salts and following the above procedure,a number of 6,7-dihydrobenzo(a)quinolizinium salts were prepared [21] .

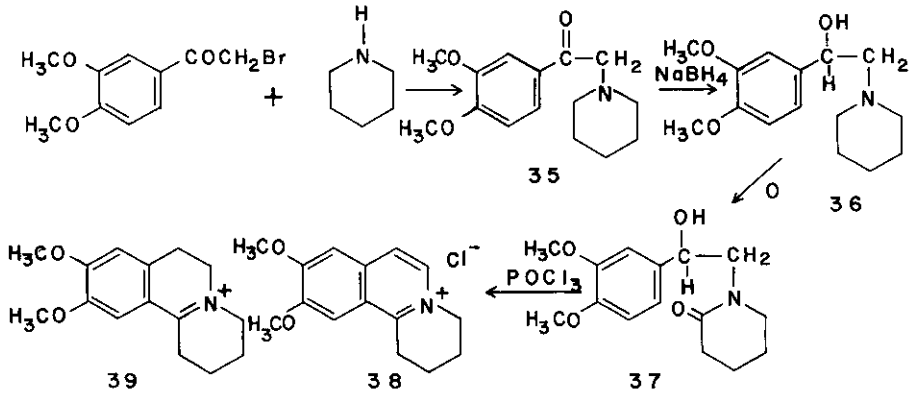
The results are summerised in table IV.

TABLE IV



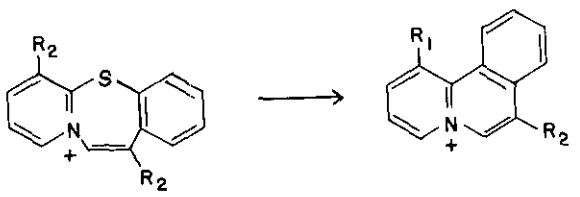
Compound number	R_1	R_2	R	X	Ref.
1.	O — CH_2 — O		H	I	21
2.	O — CH_2 — O		H	Cl	21
3.	OMe	OMe	H	Cl	21
4.	OMe	OMe	CH_3	Cl	21
5.	OMe	OMe	CH_3	I	21
6.	OMe	OMe	H	I	21
7.	O — CH_2 — O		H	Br	21

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



$NaBH_4$ 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).[22] .

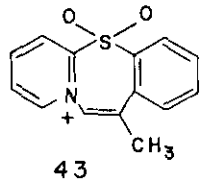
Another route to the phenanthridizinium ion is the ring contraction of pyrido-[2,1-b] benzo-[f]-1,3-thiazepinium perchlorates (39,40).[23] When these substances are treated with hydrogen peroxide and acetic acid,dethionylation occurs affording phenanthridizinium salts (41,42).



39, $R_1 = R_2 = H$ 41, $R_1 = R_2 = H$

40, $R_1 = R_2 = CH_3$ 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.



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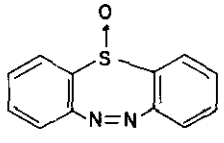
In a similar experiment, substituted phenanthridizinium salts were prepared in 24-40 % yields. It was also demonstrated that the first step in the oxidation process is the formation of a sulfoxide, which on heating first at 56° and then at 100° for two hours gave the desired products in resonable yields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

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



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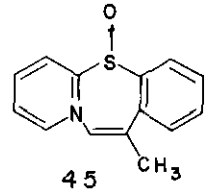

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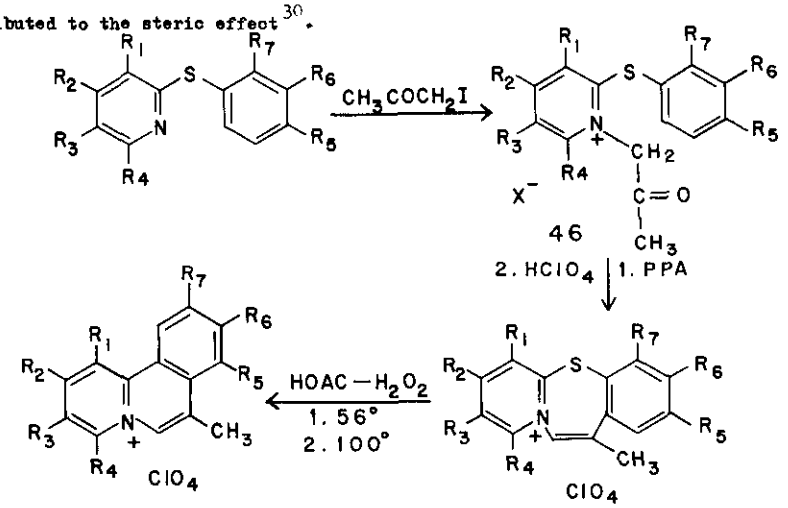
the intermediate (45) proposed in the present study, on heating would undergo sulphur extrusion. A sulfoxide intermediate has also been proposed [29] to explain at least one other example of sulphur extrusion brought about by the action of acetic acid and hydrogen peroxide.

To study further the effect of substituents on the sulphur extrusion reaction , cyclisation of the quarternary iodides (46) gave the corresponding phenanthridizinium perohlorates (47) in 23 to 37 % yields [25] . 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 [30].



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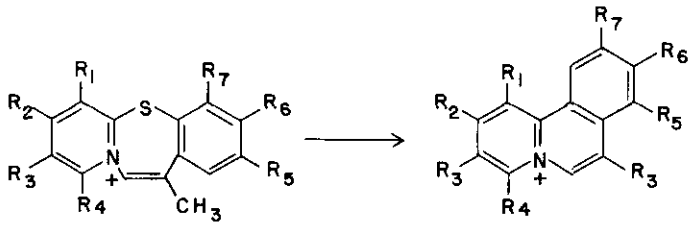
48 , $R_1 = CH_3$, $R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H$

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

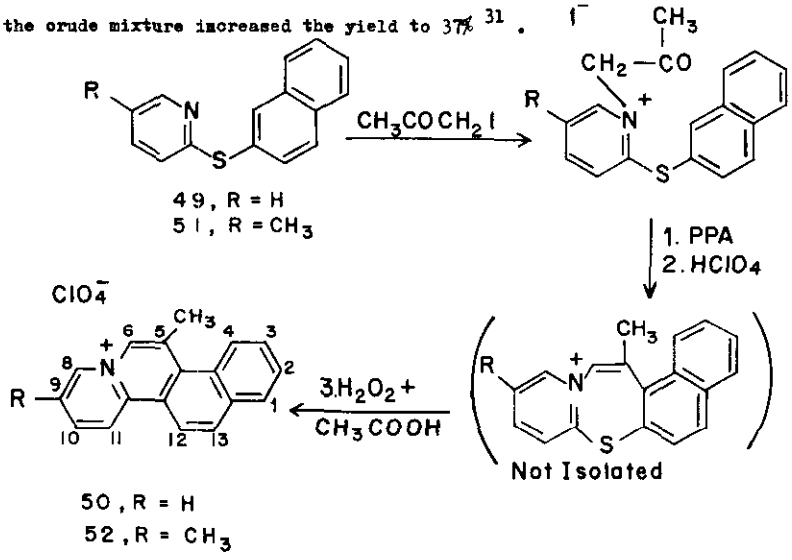
The results are summerised in Table V.

TABLE V



Compound number	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Time,hr. 56°	Time,hr. 100°	Yield%	Ref.
1.	H	H	H	H	H	H	H	12	10	38 ;63	23,24
2.	H	H	H	H	H	H	CH_3	3.5	10	31 ;45	24,23
3.	H	H	H	H	H	CH_3	H	12	10	47	24
4.	H	H	H	H	H	OCH_3	H	3	3	40	24
5.	CH_3	H	H	H	H	H	H	12	12	0	25
6.	H	CH_3	H	H	H	H	H	12	12	29	25
7.	H	CH_3	H	H	H	H	CH_3	12	8	23	25
8	H	CH_3	H	H	H	CH_3	H	12	8	37	25
9.	H	H	CH_3	H	H	H	H	12	12	24	25
10.	H	H	H	CH_3	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)phenanthridizinium perchlorate (50) was isolated in 9% yield.Addition of acetic acid and hydrogen peroxide to the crude mixture increased the yield to 37% [31].



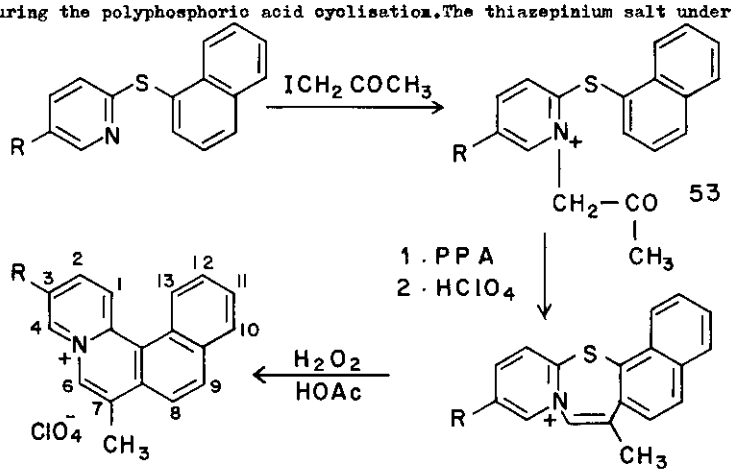
49, R = H
51, R = CH_3

50, R = H
52, R = CH_3

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

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

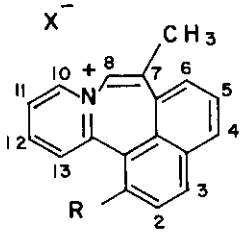
trusion during the polyphosphoric acid cyclisation.The thiazepinium salt underwent oxidative



55 , R = H

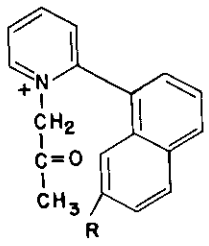
56, R = CH_3

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



58 , R = H, X = ClO_4

59, R = CH_3, X = ClO_4

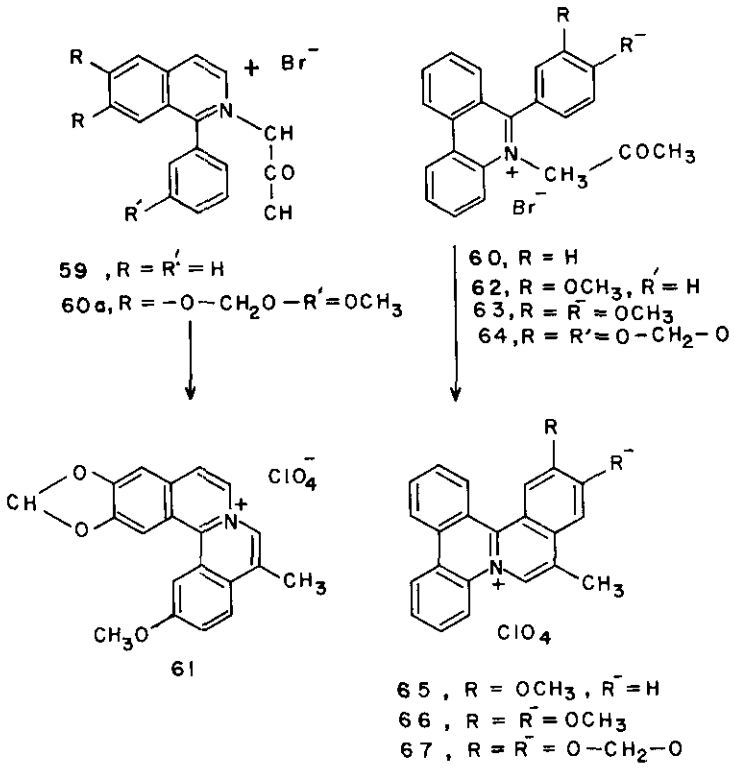


57, H, CH_3

perchlorate parallelling the reaction of the 2-phenylpyridinium series , but, later on it was shown that the product from 57 and related 2-(α-naphthyl)pyridinium ketones are benzo(l,m)morphanthridizinium derivatives (58,59) [30,31] resulting from ring closure at the more reactive α-position (C-8 in the naphthalene ring)[13,31].

Bradsher and Beavers have reported their faliure to cyclise 1-phenyl-2-acetonylisoquinolinium bromide (59) and 5-acetonyl-6-phenanthridinium bromides (60) [32a]. It was assumed that the faliure of 59 to cyclise arose from the overlapping of the hydrogen atom at position 8

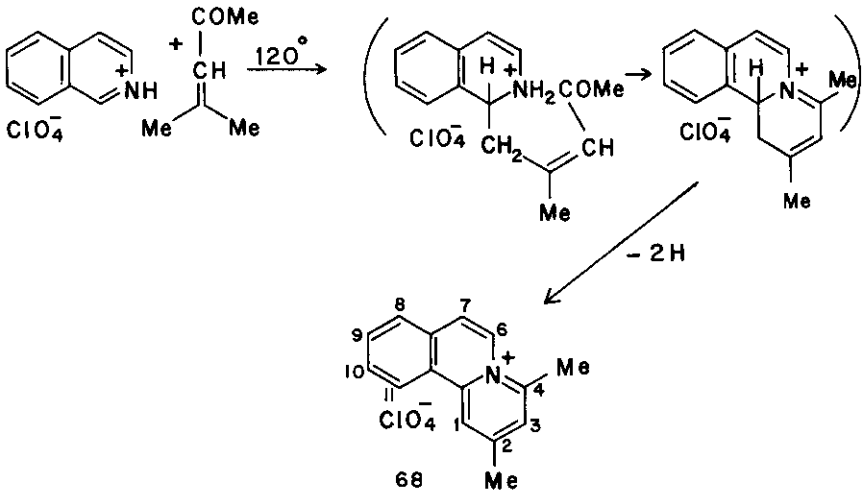
of the isoquinoline ring with thoes of the ortho positions of the phenyl ring since this would



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 quarternary salts (62-64),cyclisation in hydrochloric acid afforded 55-70% of the expected 11-methyldibenzo[a,c] phenanthridizinium salts(65-67) [33a] .

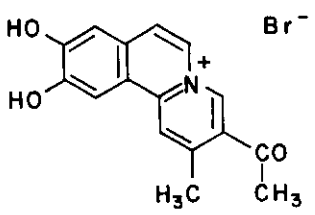
Chapman [33] has reported that heating isoquinolinium perchlorate with mesityl oxide for several hours at 120° afforded benzo(a)quinolizinium salt (68) in 35% yield.Its formation is believed to involve the addition of one of the isopropylidine methyl groups to the activated double bond of the isoquinolinium 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 β-position.

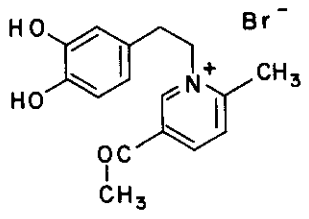


68

Teuber and Laudien [34] 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 quarternary 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 quarternary salts in 23 -82 % yields[35,36 37].



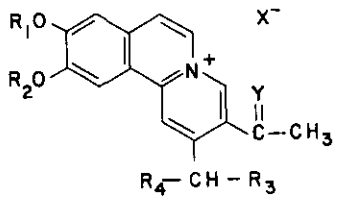
71



72

The results are summerised in Table VI.

TABLE VI



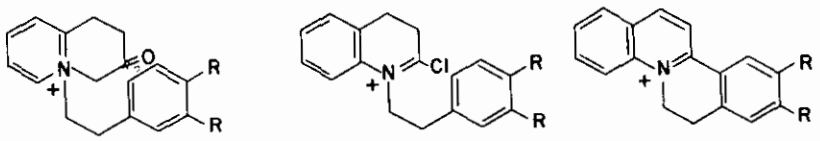
Compound number	R_1	R_2	R_3	R_4	Y	Yield %	Ref.
1.	H	H	H	H	H_2	70	35
2.	CH_3	CH_3	H	H	H_2	82	35
3.	CH_3	CH_3	$CH_2CH=CH_2$	$CH_2CH=CH_2$	H_2	80	35
4.	CH_3	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	H_2	23	35
5.	CH_3	CH_3	H	naphthyl-CH_2	H_2	23	35
6.	$CH_2CH=CH_2$	$CH_2CH=CH_2$	$CH_2CH=CH_2$	$CH_2CH=CH_2$	O	14	35
7.	$C_6H_5CH_2$	$C_6H_5CH_2$	H	$C_6H_5CH_2$	O	53	35
8.	H	CH_3	H	H	O	23	36
9.	CH_3	H	H	H	O	28	36
10.	CH_3	CH_3	H	H	O	25	37
11.	$CH_2CH=CH_2$	$CH_2CH=CH_2$	H	H	H_2	55	37
12.	CH_3	$COCH_3$	H	H	O	14	37
13.	CH_3CO	CH_3CO	H	H	O	55	37
14.	COC_6H_5	H	H	H	O	51	37

Hexahydroquinolizinium salts (73–75) have also been synthesised by cyclising *N*-*β*-arylethylpiperidone (76–79) with phosphoryl chloride [38]. However, the parent piperidone (76) failed to cyclise with phosphoryl chloride, but when cyclised with polyphosphoric acid, a small amount of the quarternary salt (73) was isolated. This is in direct disagreement to the findings of Sugasawa et al.[39], who has reported the isolation of 73 from 76 on cyclisation with phosphoryl chloride. In a similar cyclisation of 1-*β*-phenethylcarbostyril (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.

76, R = H
78, R = OCH_3
79, RR = CH_2O_2

73, R = H
74, R = OCH_3
75, RR = CH_2O_2

From 80, Sugasawa et al.[40] have claimed to have isolated 84, which has now been shown



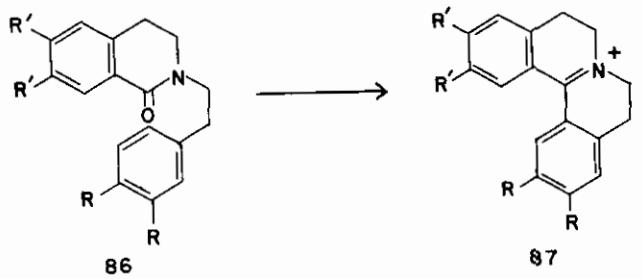
80, RR = CH_2O_2
83, R = H

81, RR = CH_2O_2
85, R = H

82, RR = CH_2O_2
84, R = H

to have the structure 85 [38].

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

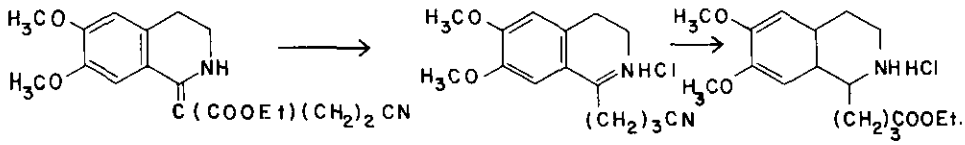


86

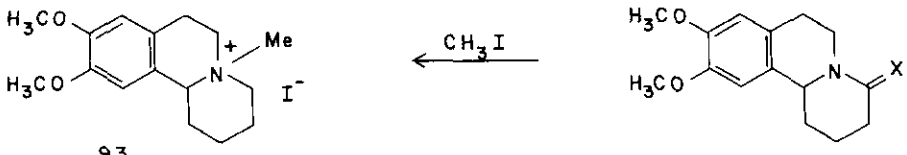
87

phosphoryl chloride at 130° gave the corresponding dibenzo [a,h] quinolizinium salt (87)[38].

Another route for the preparation of hexahydrobenzo(a)quinolizinium iodide [41] 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



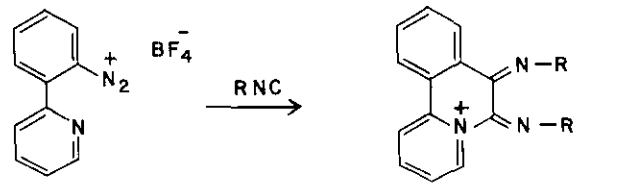
88 89 90



93 91, X = O 92, X = H_2

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).

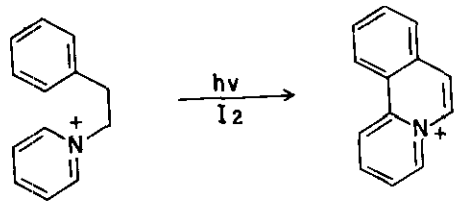
Addition of cyclohexylnitrile to 2-(α-pyridyl)benzene diazonium tetrafluoroborate (94) afforded 6,7-bis(cyclohexylimino)-6,7-dihydrobenzo(a)quinolizinium tetrafluoroborate (95) in



94 95, R = Cyclohexyl

70 % yield.[40]

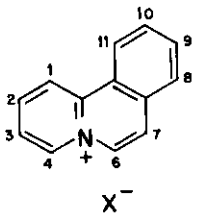
The most convinient method for the synthesis of phenanthridizinium derivatives involved the irradiation of styrylpyridinium salts (96) [41,42]. Best results were obtained by irradiating a well stirred ethanolic solution of styryl salts (96) containing some iodine. Subs-



39

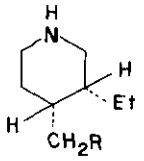
tituted phenanthridizinium salts were also prepared with substituents in either of the rings.While this is but one of the several attempts made to extend the photocyclisation observed with stlbenes[43] to the synthesis of hetrocyclic system [44] ,it is believed to be the first such instance involving a quarternary salt.The results are summerised in Table VII.

TABLE VII

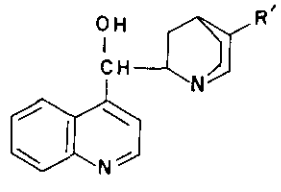


Compound number	Substituent	Yield %
1.	H	60
2.	1,3-$(Me)_2$	47
3.	1,3-$(ph)_2$	50
4.	8-Me	56
5.	10-Me	66
6.	8-OBz	43
7.	10-Cl	60
8.	8,9-$(OBz)_2$	25
9.	8,10-$(OBz)_2$	50

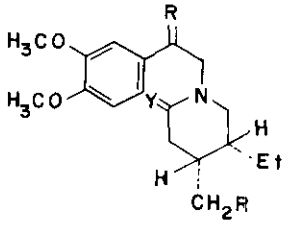
The number of alkaliods containing the benzo(a)quinolizine system such as emetine[43] psychotrine [44] protoemetine [45] O-methylpsychotrine,lubulosine[46] and ankorine[47] have been synthesised.A general synthesis of these alkaiods [48] involves the treatment of an ester(97) prepared from cinchomine (98) with 3,4-dimethoxyphenacyl bromide followed by reduction with sodium borohydride in ethanol yielded a diasteromeric mixture of 99.Oxidation of 99 with mercuric acetate-(ethylenedinitrilo)tetraacetic acid followed by hydrogenolysis of the resulting lactam alcohols(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=ClO_4)



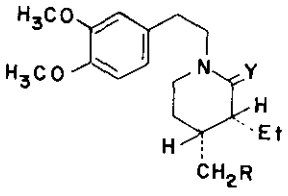
97



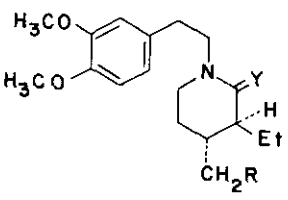
98, R = H Or Me ; R′ = Vinyl Or Ethyl



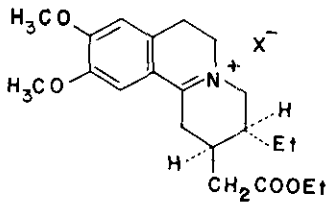
99, R = COOEt ; Y = H_2, Z = H, OH
100, R = COOEt ; Y = O ; Z = H_2



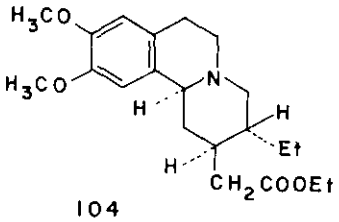
101, R = COOEt ; Y = O



102



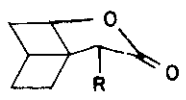
103, X = I
103, X = ClO_4



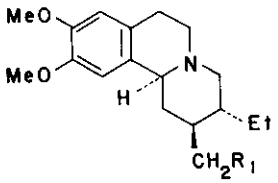
104

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

The emetine precursor[49] 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_1 = CH_2OH, COOMe).

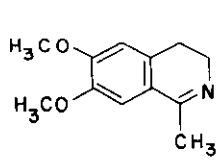


105, R = Et, allyl

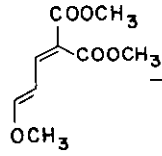


106, R_1 = CH_2OH, COOMe

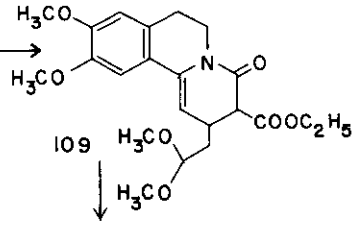
Kametani et al.[50] have synthesised emetine by reacting 3,4-dihydro-6,7-dimethoxy-1-methyl isoquinoline (107) [51] with dimethyl-3-methoxyallylidene malonate (108) at room temperature



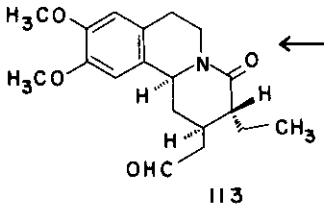
107



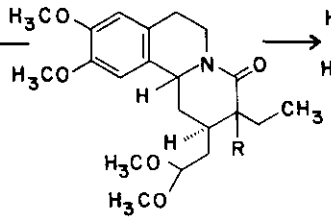
108



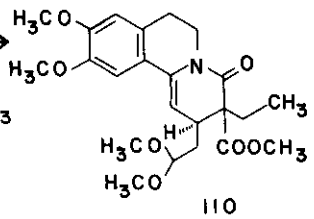
109



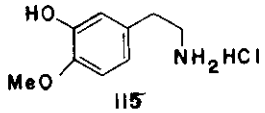
113



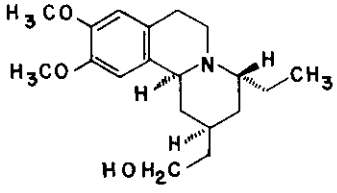
111, R = $COOCH_3$
112, R = COOH



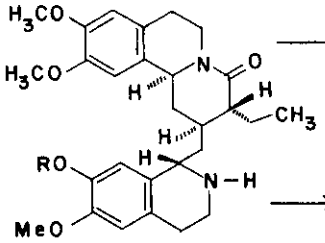
110



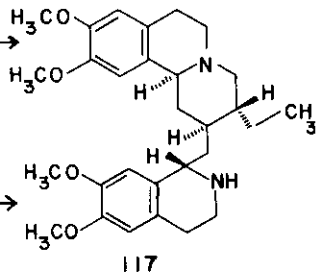
115



114



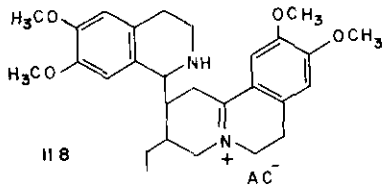
116, R = H
116a, R = CH_3



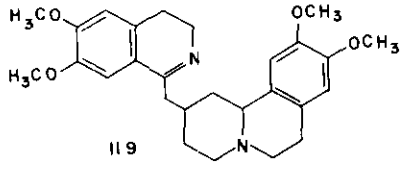
117

followed by refluxing, gave 2,3,6,7-tetrahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(ββ-dimethoxyethyl)benzo(a)quinolizine-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 (±) 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 (±)emetine (117).

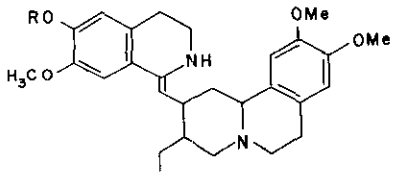
Didehydroemetine , was one of the products isolated in the photochemical and thermochemical decomposition of emetine [52] which, was designated by structure(118) [53, 54]. Its mass spectrum,



118



119

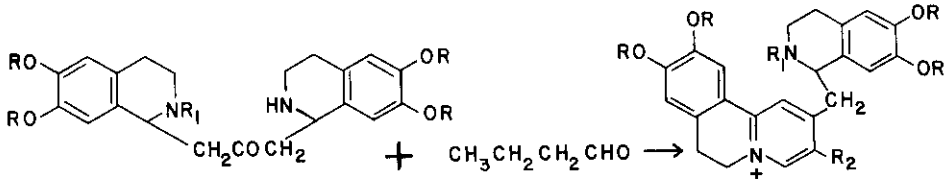


120 , R = Me
121 , R = H

however, did not resemble to the proposed structur, 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 isoemetine were

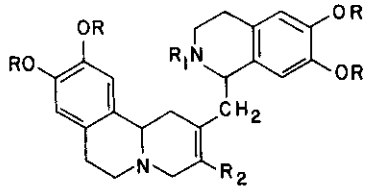
isolated [55-57] .Since emetine and isoemetine are stereoisomeric at C-1, the double bond in O-methylpsychotrine must be located here. As a consequence, O-methylpsychotrine has to be represented by 120 and psychotrine by 121. Deutrium exchange experiments have comfirmed that the two compounds, didehydroemetine 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



122, R_1 = Bz, R = CH_3

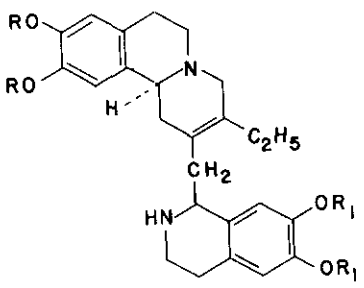
123, R = CH_3, R_2 = Et, R_1 = Bz



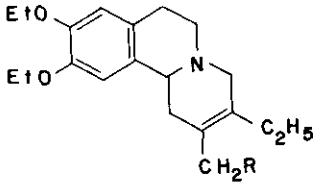
123a, R = CH_3, R_1 = Bz, R_2 = Et

(123) was isolated in 71 % yield. Reduction with sodium borohydride gave a mixture of N-benzoyl-2,3-dihydroisoemetine 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 [59] .The resulting benzoquinolizinone was treated with P-diethoxy-P-methylacetate phosphone followed by photoisomerising the methoxycarbanylmethylene-hexahydrobenzoquinolizine (124) . Reduction gave an aldehyde, which on treatment with 3-hydroxy--4-ethoxyphenethylamine hydrochloride and diazoethane afforded emetine derivative (125).

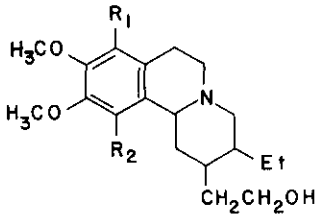


125, R = R_1 = Et



124, R = COOMe

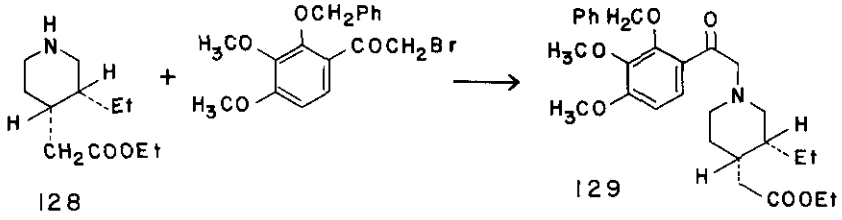
Ankorine is another alkaloid structurally related to emetine [60,61], which, has been assigned the plane structure (126) largely on the basis of physical measurements [62]. However neither the precise location of the phenolic hydroxyl group nor the stereochemistry was established at that time. The recent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



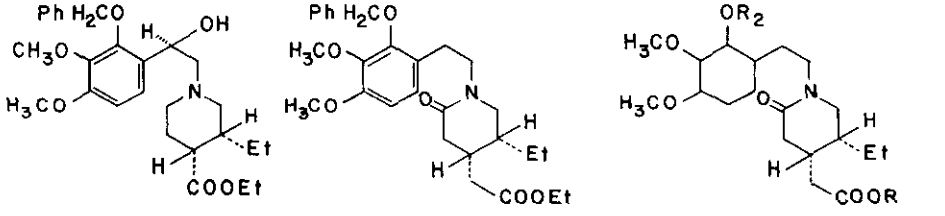
126, R_1 = H, R_2 = OH
127, R_1 = OH, R_2 = H

be placed at an alternative position (127). Fujii et al. [64,65] have established the absolute configuration of ankorine by synthesis, which involves the condensation of an optically active ester (128) [66,67] 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-(ethylenedinitrilo)tetraacetic acid [68,69] 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

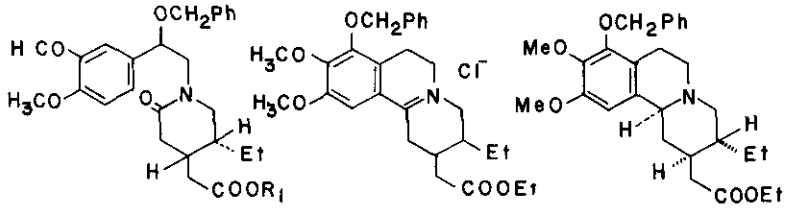
followed by heating the lactamacid at 180° for 80 minutes gave a mixture of trans (133) and cis isomer (134). Esterfication of the mixture followed by cyclisation with phosphoryl chloride in benzene gave a mixture of trans and cis esters (135). Catalytic hydrogenation of the



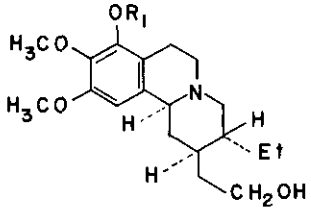
128 129



130 131 132, $R_1 = C_2H_5$; $R_2 = PhCH_2$
134, $R_1 = H$; $R_2 = PhCH_2$



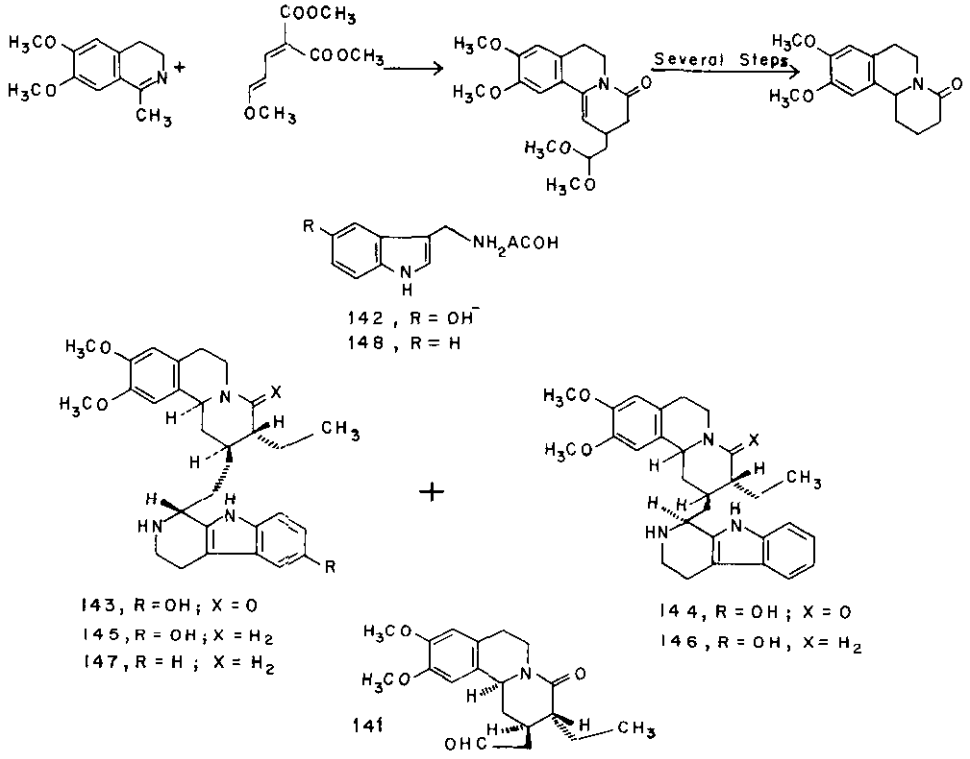
133, R = H 135 136



137, $R = CH_2Ph$
138, $R_1 = H$

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 [70]. 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)



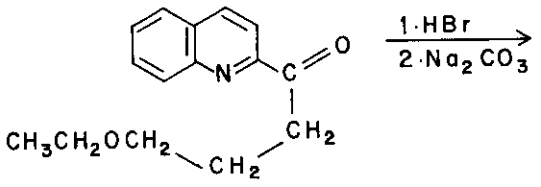
so formed was converted to 141 , which on codensation with seritonen (142) followed by reduction of the isomeric mixture (143, 144) with sodium bis(2-methoxyethoxy)aluminium hydride in pyridine afforded (±) tubulosine (145) and (±) isotubulosine (146) .

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

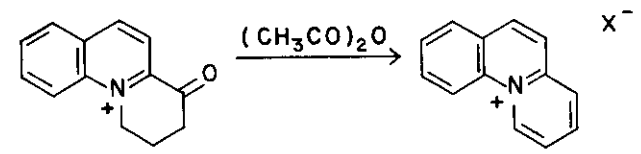
Similarly (±) deoxytubulosine (147) was prepared from 141 and tryptamine (148).

Synthesis of Benzo(c)quinolizinium Salts

The first synthesis of the benzo(c)quinolizinium ion was accomplished by Glover and Jones [19] 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-ethoxypropyl-magnesium 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



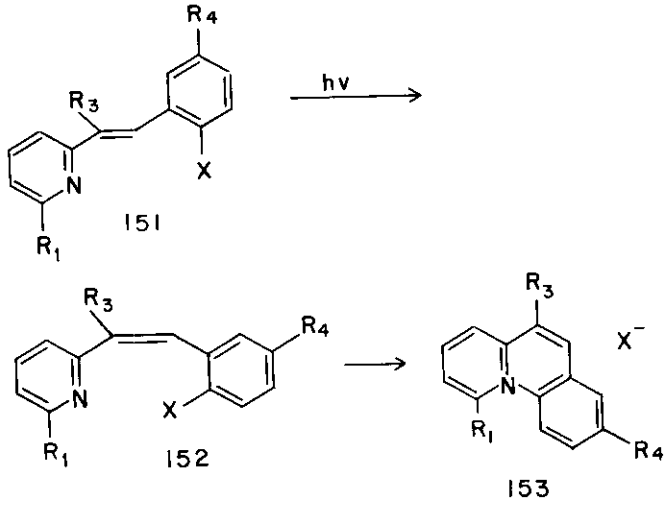
149



X⁻ 150 150a

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

A new general synthesis has been devised [71,72] 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 α-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 ($R_1 = CH_3$) in which case steric hindrance is believed to be responsible for the faliure of the internal quaternisation reaction. Usually the internal quarternisation reaction yielded reusable trans stilbazoles as byproducts.The participation of an aryl halide in a quarternisation reaction is believed [73] to be due in large measure to the



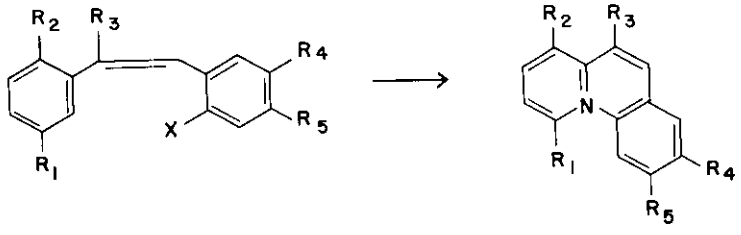
halogen by the electron withdrawal of the pyridyl group communicated through the conjugated system.

Irradiation of the benzene solution (151, $R_4 = NO_2$) failed to give the expected isomer, but instead 8-nitrobenzo(c)quinolizinium chloride was isolated in 70 % yield.

Heating stilbazole at 240^0 for 6 hours and eliminating the irradiation step resulted in the formation of pure benzo(c)quinolizinium 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-α-phenylstilbazole (151, $R_3 = C_6H_5$) failed to effect the cyclisation.

The results are summerised in Table VIII.

TABLE VIII



Compound number	R_1	R_2	R_3	R_4	R_5	X	Method	Temp.	Yield %
1	H	H	H	H	H	Cl	A	170	50 [b,c]
	H	H	H	H	H	ClO_4	B	240	54 [d]
	H	H	H	H	H	Br	B	240	50 [e,f]
2.	H	H	H	NO_2	H	Cl	A	25	80 [b,i,g]
	H	H	H	NO_2	H	ClO_4 [h]	...	..	d
3.	H	CH_3	H	NO_2	H	Cl	A	25	80 [b,i,g]
4.	H	CH_3	H	H	H	Cl	A	165	69 [b,c]
5.	H	H	H	H	Cl	ClO_4	A	170	70 [b,c]
	H	H	H	H	Cl	Cl	B	240	60 [d]
6.	H	CH_3	H	H	Cl	Cl	A	155	77 [b]
7.	H	H	CH_3	H	H	Cl	A	210	55 [b,i]
	H	H	CH_3	H	H	ClO_4 [h]	...	..	g
8.	H	H	C_6H_5	H	H	Cl	A	200	50 [b,c]
	H	H	C_6H_5	H	H	ClO_4	C	140	2 [d]
9.	H	H	$COOC_2H_5$	H	H	ClO_4	C	140	20 [i]

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°. 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° for one hour.

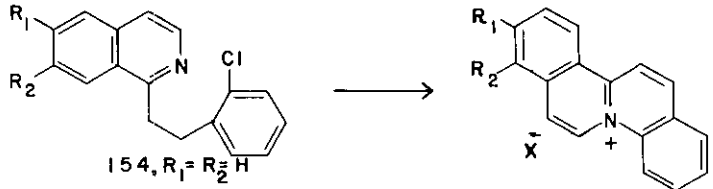
B. Stilbazole and iodine heated at 240° for 6 hours.

C. Cyclisation carried out in refluxing acetic anhydride

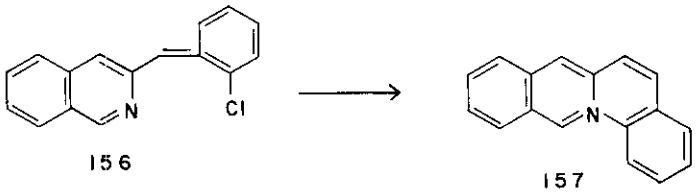
This method has been applied to the preparation of tetracyclic system in the hope, that, it would enable to synthesise the aza steriods and azonia helicenes [73].

2-Chloro-1-styrylisoquinoline (154) was readily prepared in good yield by condensation of 1-methylisoquinoline with 2-chlorobenzaldehyde.[74] The product, 1-(2-chloro)styrylisoquinoline on cyclisation at 200° 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 quarternary salt (155) suggests that the styrylisoquinoline is in the cis form. However, 6,7-dimethoxyisoquiniline-2-chloro-1-styrylisoquinoline (154, $R_1 = R_2 = OCH_3$) was not cyclised simply by heating, but on irradiation in benzene followed by heating at 165° gave

the dimethoxy salt (155, $R_1 = R_2 = OCH_3$; $X = ClO_4$). On the other hand 2-chloro-3-styrylisoquinoline (156) gave hardly 1% of the cyclised product (157). The faliure of 156 to undergo



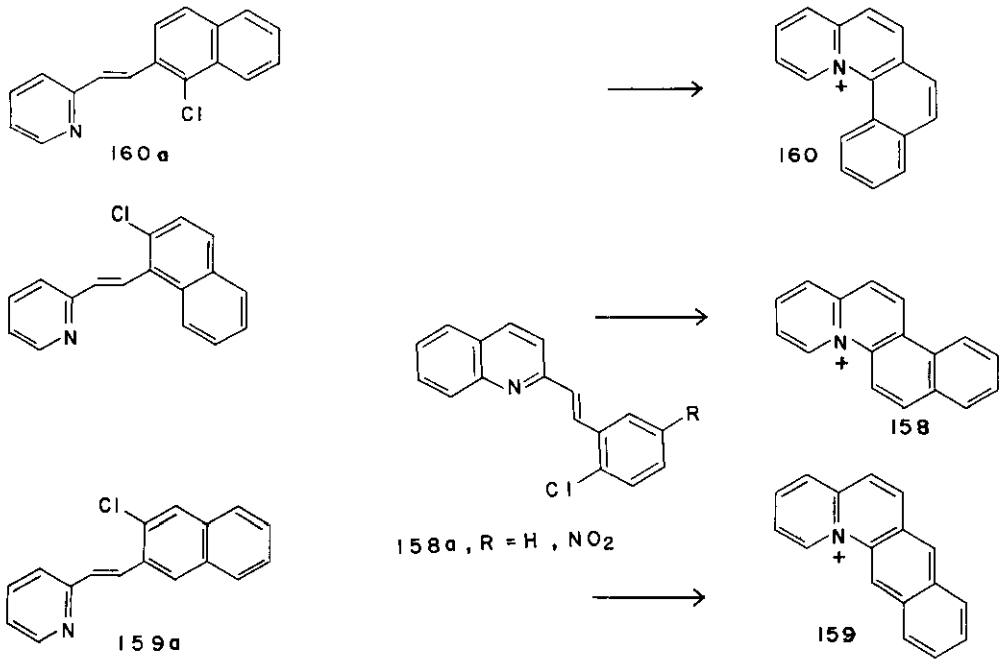
154, $R_1 = R_2 = H$ 155, $R_1 = R_2 = H$



156 157

cyclisation has demonstratrated that the internal quarternisation is not solely the consequence of favourable geometery, 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 quarternisation of the crude β-(1-Chloro-2-naphth-



160a 160

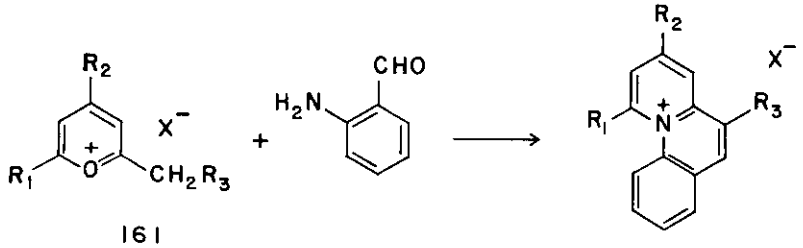
158a, R = H, NO_2 158

159a 159

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_2) 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 quarternary salt involves the condensation of trisubstituted pyrillium salts (161) with o-aminobenzaldehyde in acetic acid [75].The reaction mixture was heated under nitrogen and the products were isolated in the range of 46-73 %.

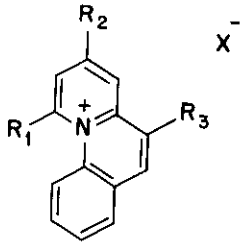


161

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

The results are summerised in Table IX .

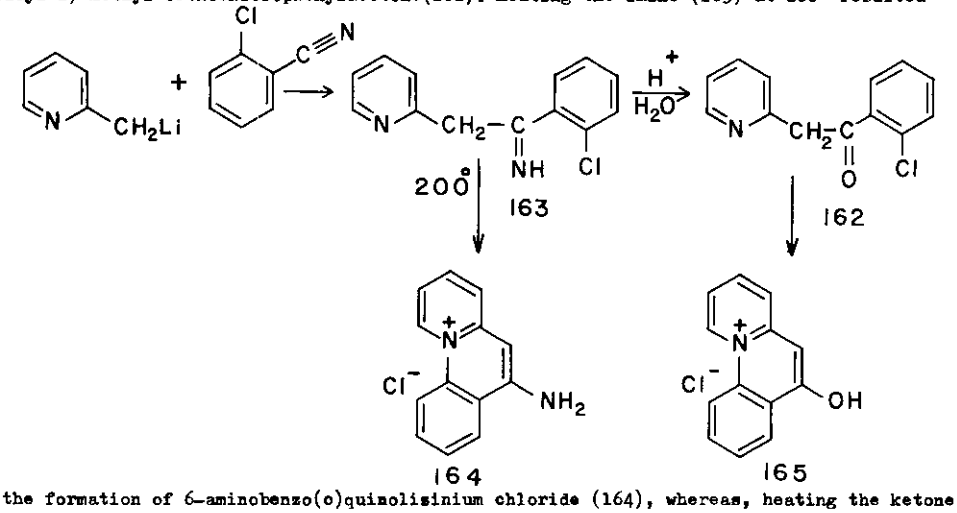
TABLE IX



Compound number	R_1	R_2	R_3	X	Yield %
1.	C_6H_5	C_6H_5	H	BF_4	64
2.	C_6H_5	C_6H_5	H	Br	43
3.	C_6H_5	C_6H_5	H	I	51
4.	CH_3	C_6H_5	H	BF_4	71
5.	CH_3	$C(CH_3)_3$	H	BF_4	48
6.	C_6H_5	C_6H_5	CH_3	BF_4	73

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

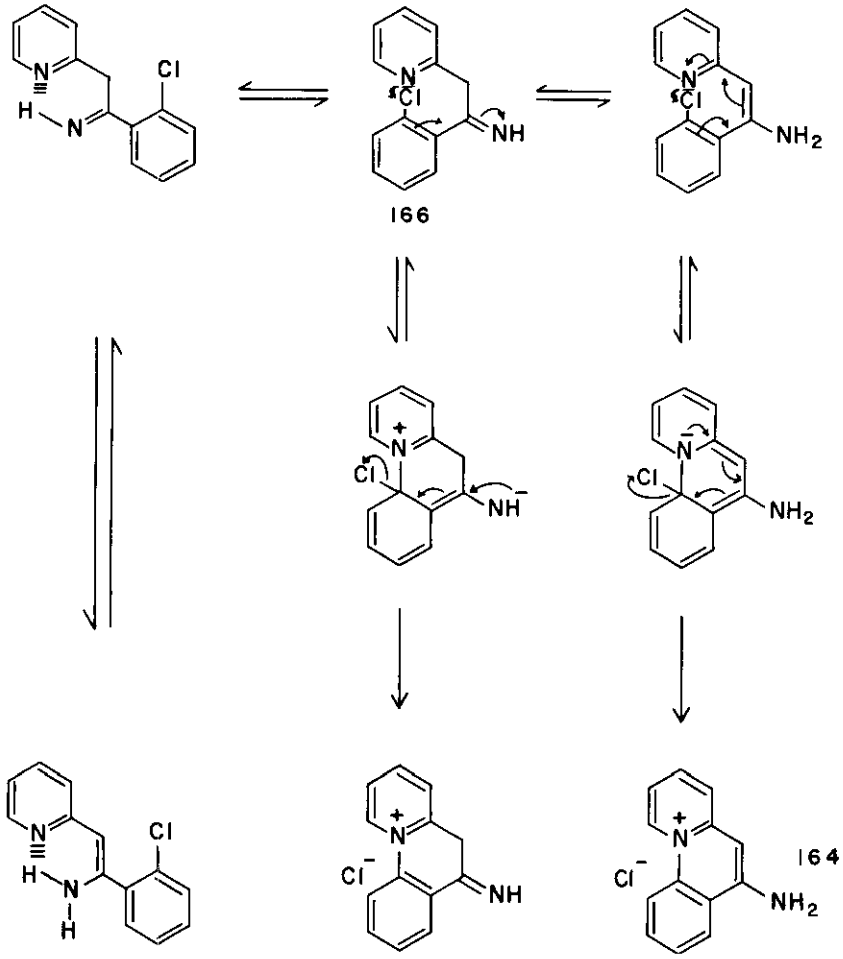
pyridyl-2)-methyl orthochlorophenylacetone(162). Heating the imine (163) at 200° resulted



in the formation of 6-aminobenzo(c)quinolizinium chloride (164), whereas, heating the ketone (162) resulted in the formation of 6-hydroxybenzo(c)quinolizinium chloride (165) [76].

The formation of 164 was rationalised by Scheme 3.

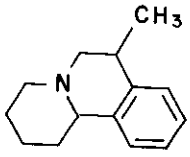
Scheme 3



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

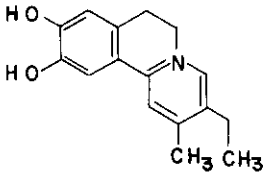
The initial paper [8] on the subject of the 7-substituted benzo(a)quinolizinium analogs reported, that the 7-methyl derivative could be reduced catalytically presumably to a methylbenzoquinolizidine derivative (167),whereas on oxidation with potassium permanganate phthalic acid was isolated.



HBr

167

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).[37].



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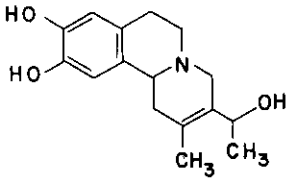

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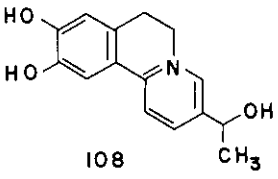
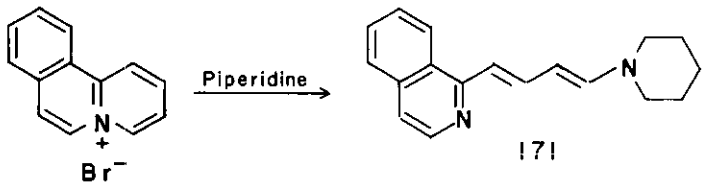


108

168

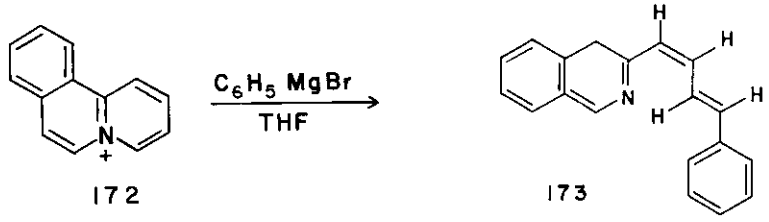
Richard and Steven[77] have reported that on standing in ammonia solution, 7-phenylbenzo(a)-quinolizinium ion was converted to a pseudo base .

It has also been reported [78] 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)]-isoquinoline (171) was isolated in 76 % yield.



171

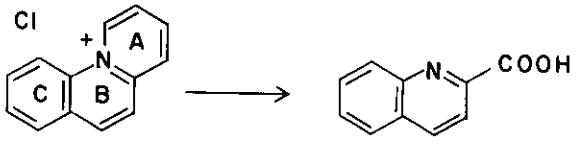
It has been reported [82] that treatment of the quarternary salt (172) with phenylmagnesium bromide in tetrahydrofuran also resulted in the ring opening yielding 173 as the only product.



172 173

Reactions of Benzo(c)quinolizinium Ion

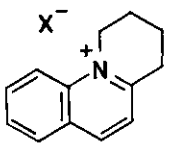
Fozard et al. [79] have reported that oxidation of benzo(c)quinolizinium chloride in boiling potassium permanganate afforded a poor yield of quinoline-2-carboxylic acid (174) formed by



174

the destruction of ring A.

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



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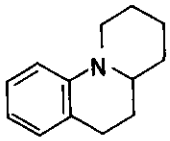

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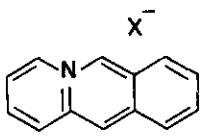
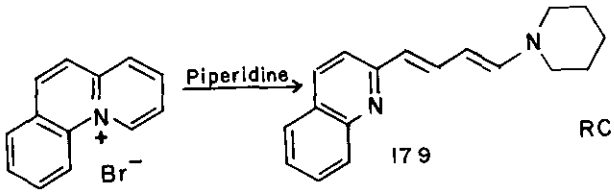


177

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 [80,81]. This bahaviour 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[82] with benzo(c)quinolizinium ion was shown to give hydroxybutyronitrile(178) in 22 % yield, whereas, on heating its alcoholic



179

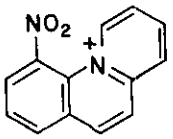
$RCH_2CH(OH)-CH_2-CN$

178, R = 2-Quinolyl

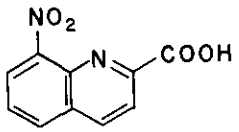
solution with piperidine for 20 minutes, the ring opening product 2-[4-piperidino-butadiene-(1,3)-yl-(1)]-quinoline (179) was isolated in quantitative yield [83].

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 [83]. Further catalytic reduction of the nitration product (180)

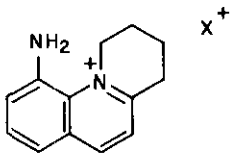


180

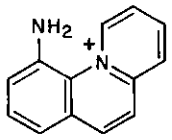


181

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



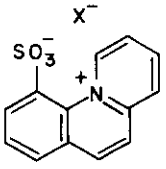
182



183

reduced resulting in the formation of an amine (183) in 69 % yield [82].

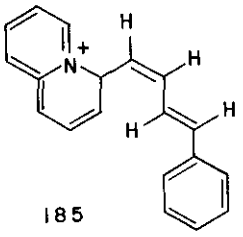
Sulphonation occurs in the more remote ring C at position 10 affording betaine (184)



184

in 69 % yield. This reaction is similar to the one with the acridizinium series.[82]

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



185

nary salt (172) afforded the ring opening product (185) [78] .

REFERENCES

1. W. Schneider and K. Schroeter, Chem.Ber., 528, 1495, 1920
2. O.Diel and K.Alder, Ann. Chem., 505, 103, 1933
3. S Sugasawa and K. Kakemi, Chem. Ber., 71, 1860 1935
4. R.B.Woodward and B.Wiktop,J.Am.Chem.Soc., 71, 379, 1949
5. R.B.Woodward and W.M.Melamore,J.Am.Chem.Soc., 71 194, 1949
6. R. Schwyzer,Helv. Chim.Acta, 35, 867, 1960
7. S.D.Saraf, Hetrocycles, 12, 2047, 1980
8. C.K.Bradsher and L.E.Beavers, J.Am.Chem.Soc., 77, 4812, 1955
9. C.K.Bradsher, Chem. Rev., 38, 477, 1946
10. C.K.Bradsher and L.E.Beavers, Chem Ind., 1394, 1954
11. R.M.Acheson ang G.A.Taylor, J.Chem.Soc., 1691, 1960
12. C.K.Bradsher and K.B.Moser, J.Am.Chem.Soc., 81,1940, 1959
13. C.K.Bradsher and L.A.Beavers, J.Am.Chem.Soc., 77, 453, 1955
14. R.W.L.Kimber and J.C.Parham, J org. Chem., 28 , 3205, 1963
15. F.C.Brown and P.H.Leaks, J.Am . Chem.Soc., 79, 1471, 1957
16. C.K.Bradsher and L.Yarrington, J.Org.Chem., 28, 81, 1963
17. O.Diels and K.Alder, Ann. Chem., 498, 16, 1932
18. O.Diels and J.Harms, Ann.Chem., 525, 73, 1936
19. E.E.Glover and G.Jones, J.Chem.Soc., 3021, 1958
20. S.Akaboshi and T.Kato, Yakugaku, Zasshi, 83, 1067, 1963
21. S.Akaboshi and T.Kato, Chem.Pharm.Bull., 11, 1446, 1963
22. F.Tozo,Y.Shigeyuki, Chem. Pharm. Bull. 20 ,1451, 1972
23. C.K.Bradsher and D.F.Lohr Jr., J.Org. Chem., 31, 978, 1966
24. C.K.Bradsher and J.W.McDonald, J.Org. Chem., 27, 4475, 1962
25. C.K.Bradsher and J.W.McDonald, J.Org.Chem., 27, 4478, 1962
26. H.H.Szmant and L.M.Alfonso, J.Am.Chem.Soc., 78, 1064, 1956
27. H.H.Szmant and L.M.Alfonso, J.Am.Chem.Soc., 79, 205, 1957
28. H.H.Szmant, "Organic Sulphur Compounds Vol. L,N.Kharasch Ed. Pergamon Press,New York, N.Y. 1961, page 163
29. R.H.B.Galt, J.D.Loudon and A.D.B.sloan, J. Chem. Soc., 1589, 1958
30. C.K.Bradsher,L.D.Quin and J.W.McDonald, J.Org. Chem., 26, 4944, 1961
31. C.K.Bradsher and J.W.McDonald, J.Org. Chem., 27, 4482, 1962
32. C.K.Bradsher and R.E.Dolittle, Tetrahedron Letters, 2, 399, 1965

32a. C.K.Bradsher and L.E.Beavers, J.Am.Chem.Soc., 78, 2159, 1956

33a. C.K.Bradsher and K.B.Moser, J.Org. Chem., 24, 592, 1959

33. D.D.Chapman, J. Chem. Soc., Commu. 489, 1975

34. H.J.Teuber and D. Laudien, Angew. Chem. Int.Ed., 3, 507, 1964

35. H.J.Teuber and K.D. Schroder, Chem. Ber., 102, 1779, 1969

36. H.J.Teuber and Hans-C-Jochum, Chem.Ber., 100, 2930, 1967

37. H.J.Teuber and D.Laudien, Chem. Ber., 100, 35, 1967

38. D.W.Brown, S.F.Dyke, M.Sainsbury and W.G.D.Lugton, Tetrahedron, 26, 4985,1970

39. S.Sugasawa and S.A.Kanoshi, Chem. Pharm. Bull 7, 609, 1959

40. R.R.Schmidt and H.Vatter,Tetrahedron Letters, 22, 1925, 1971

41. R.E.Dolittle and C.K.Bradsher,Chem.Ind., 127, 1965

42. R.E.Dolittle and C.K.Bradsher, J.Org. Chem., 31, 2616, 1966

43. H.T.Openshaw and N.Whittaker, J.Chem.Soc., 1461, 1963

44. S. Teital and A.Brossi, J.Am.Chem.Soc., 88, 4068, 1966

45.C.Szantay,C. Toko, and P.Kolonits,J.Org., Chem., 31, 1447,1966

46.A.R.Battersby and B.J.T.Harper, J.Chem.Soc., 1748, 1959

47. T.Fujii,S.Yoshifuji and K.Yamada, Tetrahedron Letters, 19, 1527, 1975

48. T.Fujii and S.Yoshifuji,Tetrahedron Letters, 10, 731, 1975

49. T.Sellchi, H.Susumi,T.Mikoto,T.Yoko and T. Yuki, Kagobutsu Toronkai Koen Yoshishu, 21, 50, 1978

50. T.Kametani,Y.Suzuki,H.Terasawa and M.Ihara,J.Chem.Soc., Perkin I, 1211, 1979

51. E.Spath, Chem. Ber., 71, 113, 1938

52. C.Schuij, G.M.J.Beijersbergen van Henegouwen and K.W.Gerritsma,J.Chem.Soc., Perkin I, 970, 1979

53. H.Auterhoff and W.Jacobi, Arch.Pharm., 294, 591, 1961

54.W.Jacobi,Ph.D. Thesis,University of Braunschweig,1961

55. H.Dietz, Ph.D. Thesis,Uinversity of Wurzburg

56. H.Auterhoff,K.Merz, Arch. Pharm, 291, 326, 1958

57.K.Merz, Ph.D.Thesis, University of Tubingen, 1959

58. Merok E.,A-G, Brit 1122,212, 1968

59.S.Caaba,R.Janos,J.Istvan,U.S.Patent 4133812,1979

60.H.T.Openshaw "Chemistry of the Alkaloids" S.W.Pelletier Ed.,Van Nostran,Reinhold Co., New York,N.Y. 1970, Chapter 9

61. A.Brossi, S.Teitel and G.V.Parry "The Alkaloids" Vol XIII,A.H.Manske Ed.Academic Press New York,N.Y. 1971,Chapter 3

62. A.R.Battersby, R.S.Kapit, D.S.Shakuni,S.P.Popli,J.R.Merchant and S.S.lager, Tetrahedron Letters, 1965, 1966

63.C.Szatay,E.Szentiramay and L.Szabo, Tetrahedron Letters, 42, 3725, 1974

64. T. Fujii,S.Yoshifuji and K. Yamaka, Tetrahedron Letters, 19, 1527,1975

65. T.Fujii and S.Y.Yoshifuji,Tetrahedron Letters,24, 1965,1975

66. V.Prelog and E.Zalan,Helv.Chem. Acta, 27, 535, 1944

67. V.Prelog and E.Zalan, Helv. Chim. Acta, 27, 545, 1944

68. W.Solomon " Chemistry of Alkaloids " S.W.Pelletier Ed.,1970,Chapter 11

69. T.Fujii and S.Yoshifuji.Chem.Pharm.Bull(Tokyo), 20, 1451, 1972

70. T.Kametani, Y. Suzuki and M.Ihara, Can.J.Chem., 57, 1679, 1979

71. A.Fozard and C.K.Bradsher, Chem.Commun.,288,1965

72. A.Fozard and C.K.Bradsher, J.Org.Chem., 31, 2346, 1966

73. A.Fozard and C.K.Bradsher, J.Org. Chem., 31, 3683, 1966

74. W.B.Mills and L.B.Smith, J.Chem.Soc,, 2724,1922

75. K.Dimoroth and H.Odenwalder,Tetrahedron Letters, 533, 1971

76. J.M.Vierfond,Y.Metty,R.Joubin and M.Miocque,Hetrocyclic Chem., 16, 735, 1978

77. A.Richardson and T.S.Stevens, J.Chem.Soc., 3067, 1958

78. M.Tetsuo, K.Yoichi and T.Ryusi,Chem.Pharm.Bull. 26, 2334,1978

79. A.Fozard, L.Davies and C.K.Bradsher,J.Chem.Soc., 318, 1938

80. G.R.Clemo, J.C.Cook and R.Raper, J.Chem.Soc., 1318, 1938

81. G.Jones and J.Wood, Tetrahedron, 21, 2529, 1965

82. C.K.Bradsher and J.D.Turner, J.Org.Chem., 31, 565, 1966

83. D.Morter and P.Krohka, Ann. Chem., 744, 65, 1971

Received, 24th September, 1980