THE CHEMISTRY OF THE ACRIDIZINIUM ION

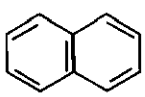
Sayeed-Din Saraf

Chemistry Department, Kuwait University, Kuwait

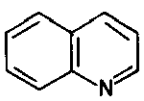
This paper reviews the various methods for the preparation of the acridizinium ion. One of the most successful method involved the use of cyclic acetal 2-(1,3-dioxolan-2-yl)pyridine (9), since the resulting intermediate obtained on treatment with benzyl bromide or substituted benzyl bromides are well suited for cyclisation in hot polyphosphoric acid. Acridizinium benzologs have also been prepared by replacement of the benzyl halides by naphthyl or phenanthrylmethyl halides or the pyridine carboxaldehyde by isoquinoline 1- or 3-carboxaldehydes. The properties, such as, oxidation, reduction, reaction with bases and electrophilic reagents are all discussed in detail.

The occurrence of aromatic compounds formally related to the classical aromatic hydrocarbons by the replacement of a CH by N has long been recognised. The structural relationship of quinoline (2) to naphthalene (1) was understood nearly hundred years ago[1], while the relationship of isoquinoline[2] was recognised a few years later.

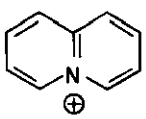
The quinolizinium ion (3) represents the nitrogen analog of naphthalene in which the



1



2



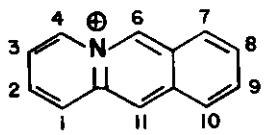
3

nitrogen atom occurs at a bridgehead position. In contrast to quinoline and isoquinoline, the other two simple nitrogen analogs of naphthalene, the chemistry of the quinolizinium ion has been little studied and knowledge regarding this ion has been gained almost entirely from investigations of alkaloids containing this nucleus as part of a fairly complex structure. Among the

alkaloids the quinolizinium nucleus probably occurs most widely as its dihydro derivative. For example, the dibenzoquinolizinium ion is the parent structure for the various berberine alkaloids[3-6], palmatin[7], columbamine[8], jatrorrhizine[9], coplisine[10], worenine[11], dehydrocorydaline and dehydrophthalic trifoline[12,13].

Despite the continuing attention devoted to simple aromatic systems, the first synthesis of the quinolizinium ion (3) was not announced until 1954[14,15], and this date may be regarded as the beginning of the systematic study of the quinolizinium ion and its benzologs[16].

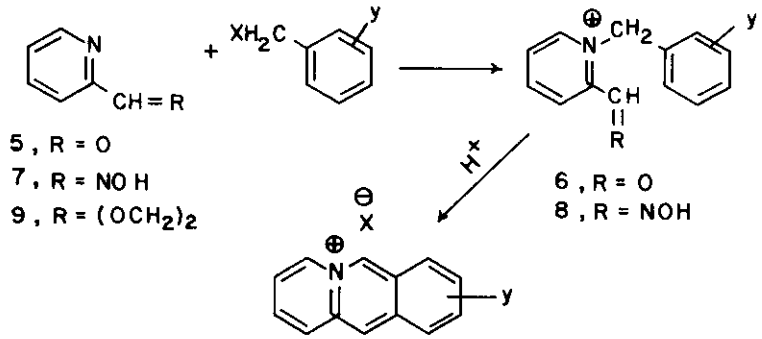
As regards the nomenclature, the tricyclic system is described as benzolog of quinolizinium ion or azonialog[17] of anthracene and has also been given the trivial name "Acridizinium Ion". The chemical abstract numbering for the system is given below (4)[18].



In the azonia arene nomenclature, the numbering is that of the parent hydrocarbon (4,a-azoniaanthracene)[19].

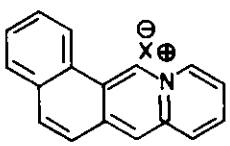
SYNTHESES

The first method for the preparation of the acridizinium ion involved the reaction between commercially available benzyl bromide or a substituted benzyl bromide and pyridine-2-aldehyde (5). The crude salt (6) thus obtained cyclised in boiling hydrobrimic acid to afford benzo(b)-quinolizinium derivatives[16,20]. Due to the unstable nature of the aldehyde, a more stable derivative picolinic aldoxime (7) offered the advantages of greater stability and ease of quarternisation and in addition the intermediate salt 8 was more easily purified and cyclised more rapidly than the aldehyde salt 6[21]. To overcome the resulting low yields in such cyclisations, a number of derivatives related to the oxime (7) were examined[22]. Use of semicarbazone (5,R=$NNHCONH_2$), thiosemicarbazone (5,R=$NNHCSNH_2$) and phenylhydrazone (5,R=$NNHC_6H_5$) did not produce any better results. The best results were obtained by condensing cyclic acetal, 2(1,3-dioxalan-2-yl)-pyridine (9) with benzyl halides particularly those containing a deactivating substituent[23]. Hydrobromic acid as cyclising agent gave the highest yield as compared to polyphosphoric acid, hydrogen fluoride or sulphuric acid.

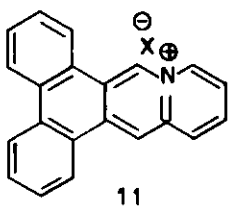


The results are summarized in Table I.

Substituting 1-bromomethylnaphthalene or 9-bromophenanthrene for benzyl halide in 6,benz-(h)acridizinium bromide (10) and dibenz(h,j)acridizinium bromide (11) were obtained in good yields[24].



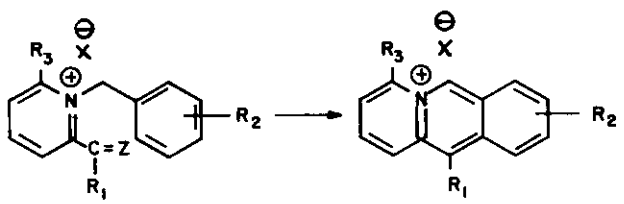
10



11

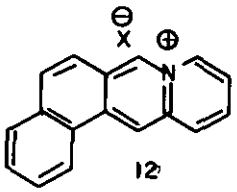
On the other hand, 2-bromomethylnaphthalene with pyridine-2-aldehyde afforded a salt, which on cyclisation was believed to have yielded benz[j]acridizinium bromide (12), the structure of

TABLE 1



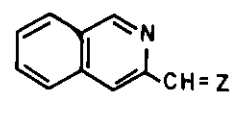
R_1	R_2	R_3	Z	Cyclising agent	Yield %	Ref.
H	H	H	NOH	HBr	89	21
H	H	H	O	HBr	60	21
H	H	H	$(OCH_2)_2$	HBr	95	22
H	H	H	$(OCH_2)_2$	HF	65	22
H	H	H	$(OCH_2)_2$	H_2SO_4	40	22
H	H	H	$(OCH_2)_2$	PPA	77	22
H	9-CH_3	H	NOH	HBr	92.5	21
H	9-CH_3	H	O	HBr	55	16,21
CH_3	H	H	NOH	HBr	21	21
CH_3	H	H	O	HBr	0.3	21
CH_3	H	H	$(OCH_2)_2$	PPA	35	22
CH_3	9-CH_3	H	NOH	HBr	40	21
CH_3	8-OH	H	NOH	HBr	99	21
H	H	CH_3	$(OCH_2)_2$	HBr	9	22
H	11-CH_3	H	O	HF	3	25
H	7-CH_3	H	O	HBr	45.7	16
H	H	H	$NNHCONH_2$	HBr	47	22
H	7-C_6H_5	H	NOH	HBr	89	50
H	9-C_6H_5	H	NOH	HBr	71	50
H	9-Iso-propyl	H	$(OCH_2)_2$	HBr	51	82
H	Benzo(h)		NOH	HBr	85	21
H	Benzo(h)		O	HBr	52	21

which was deduced from its ultraviolet spectrum[24].

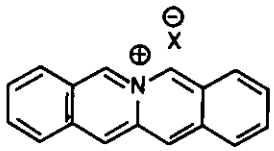


12

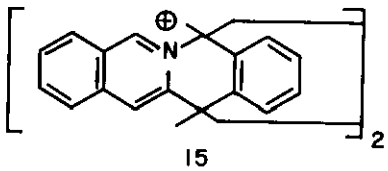
Substituting isoquiniline-3-carboxyaldehyde (13) for picoline aldoxime in 6 followed by cyclisation did not yield the expected product 14, but instead afforded a dimer (15). However, use of its oxime (16) afforded the corresponding benz(b)acridizinium salt (14) in 23% yield [25].



13, Z = O
16, Z = NOH



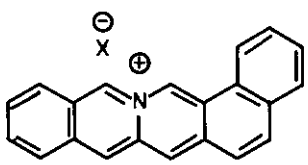
14



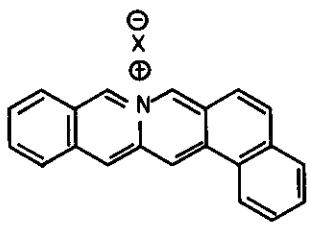
15

The formation of the dimer (15) was attributed to the low reactivity of the quaternary salt , which required longer refluxing time for cyclisation as compared to the oxime, which required about 10 minutes.

In a similar reaction, dibenz [b,h]- and dibenz[b,j]acridizinium bromides (17 and 18) were prepared from the corresponding salts prepared from 1-bromomethyl or 2-bromomethylnaphthalene and isoquinoline carboxyaldehyde in 43 and 66% yields, respectively [26].

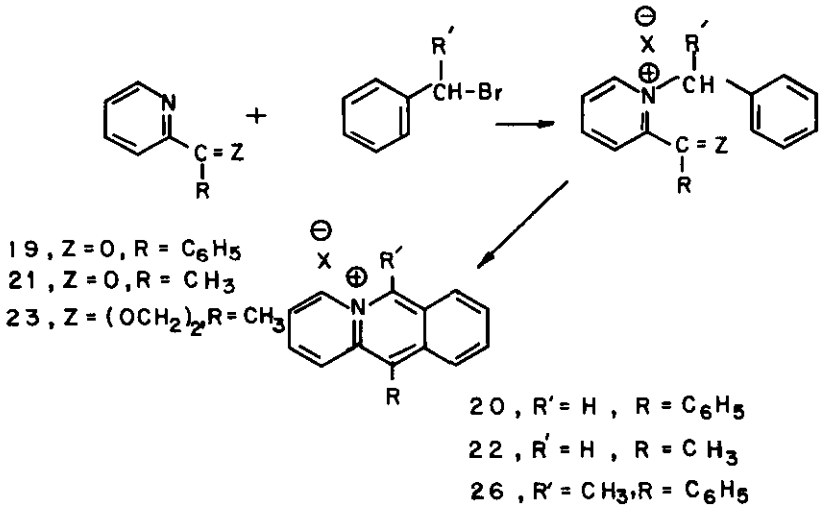


17



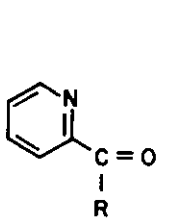
18

An alkyl or aryl group may be introduced into the meso positions of the acridizinium ion, generally with better success in the 11-position than in the 6-position. Quaternisation of a variety of benzyl halides with 2-benzoyl pyridine (19) followed by cyclisation with hydrogen fluoride afforded 11-phenylacridizinium ion (20) in 89.5% yield [27].

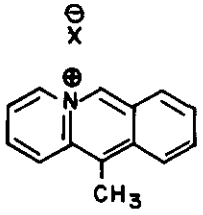


Under comparable conditions, 2-acetylpyridine (21) afforded a poor yield of 22 (3%), but use of cyclic ketal (23) improved the yield to 35% [27]. In a similar manner, 6-methyl and 6-propyl acridizinium salts were prepared from the quaternary salts (24 and 25) using hydrobromic acid as the cyclising agent [28].

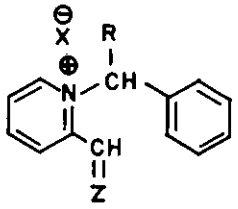
Of the five benzoyl pyridinium salts (25a) studied, the quaternary salt derived from p methoxybenzyl bromide failed to cyclise under the usual conditions, probably because the positions available are unactivated and meta to a methoxyl group.



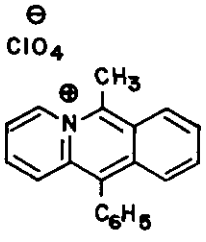
21, R = CH3



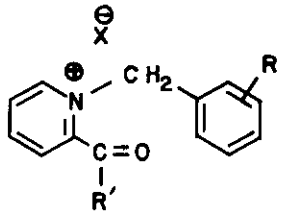
22



23, Z = (OCH2)2
24, Z = (OCH2)2, R = CH3
25, Z = (OCH2)2, R = Propyl



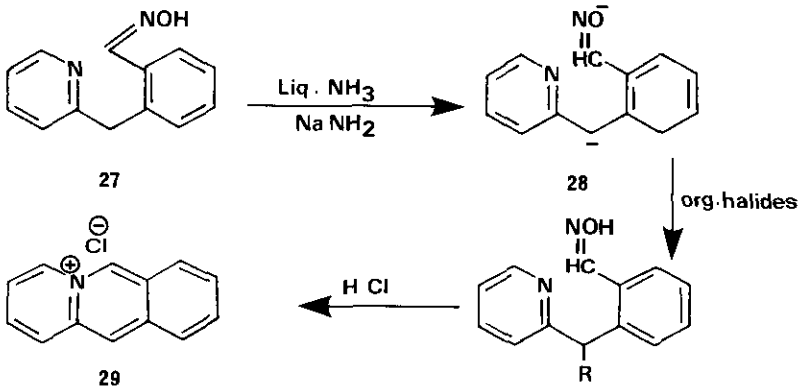
26



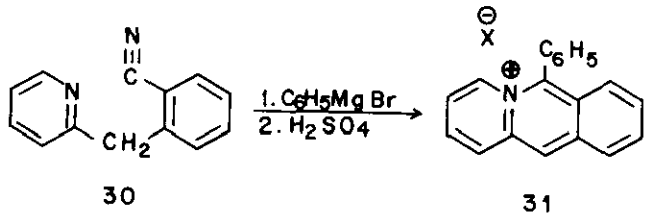
25a, R' = C6H5

Quaternisation of 2-benzoylpyridine with 1-phenylethyl bromide followed by cyclisation of the crude salt gave a low yield (8%) of 6-methyl-11-phenylacridizinium perchlorate (26) [27].

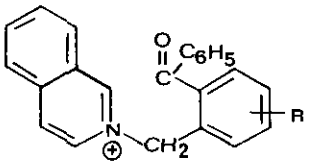
11-Alkyl substituted acridizinium compounds were also prepared from 2-(o-hydroxyiminomethyl)benzylpyridine (27) via the dianion (28). Addition of organic halides followed by cyclisation with boiling hydrochloric acid afforded 29 [29].



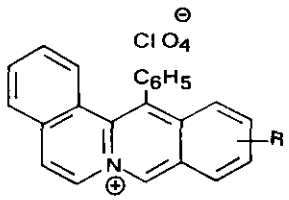
The 6-phenylacridizinium ion has been obtained by a route which is of theoretical interest only [30]. o-(2-Pyridylmethyl)benzonitrile (30) was treated with an excess of phenylmagnesium bromide, and after suitable hydrolysis to the crude ketone, was cyclised in concentrated sulphuric acid to yield 31.



Extension of this procedure lead to the synthesis of benzacridizinium derivatives with a substituent in the central nucleus. Cyclisation of the quaternary salt (32) with polyphosphoric acid afforded 7-phenylbenz(h)acridizinium perchlorate (33) in 90% yield. Only a single highly activated 1-benzoyl-2-benzylisoquinolinium salt (34) was found to cyclise in liquid hydrogen fluoride [31].



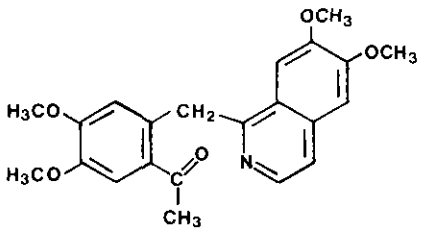
34, R=H



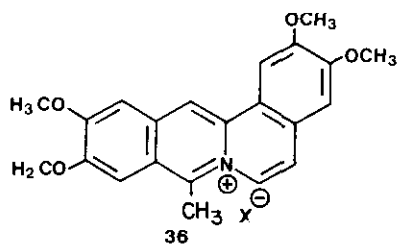
35, R=10-OCH_3

With a methoxy group at para position to the expected ring closure, cyclisation was greatly facilitated and in fact a 91% yield of the 10-methoxy-13-phenylbenzacridizinium perchlorate (35) was obtained.

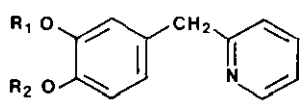
Coralyn (36) was prepared via acetopapaverine (37) by the acetylative cyclisation of papaverine [32,33]. This suggested that 2-(3,4-dialkoxybenzyl)pyridine might be made to undergo a similar acylative cyclisation. Thus cyclisation of alkoxybenzylpyridine derivatives (38) at 100° in sulphuric acid in the presence of an appropriate anhydride afforded the corresponding



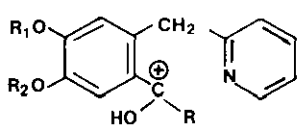
37



36



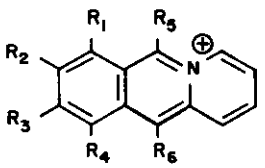
38



39

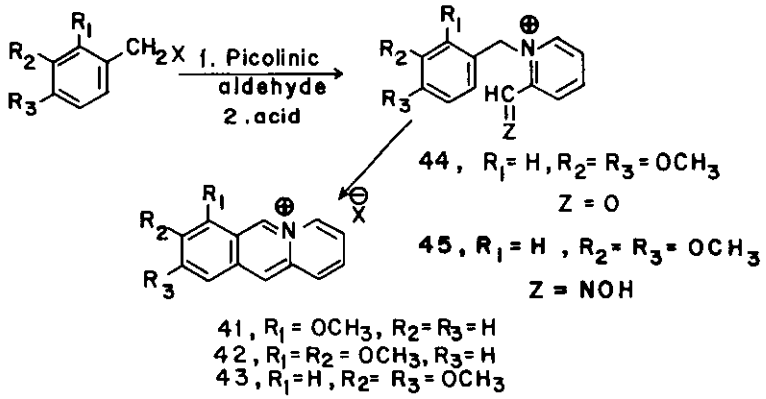
quinolizinium derivatives [34]. This type of synthesis can be regarded not only as the prototype of the Woodward synthesis [35-38] of quinolizinium derivatives, but also a further example

of aromatic cyclodehydration [39], one involving electrophilic attack on aromatic nitrogen rather than the usual carbon via the conjugate acid (39). The results are summerised in Table II.



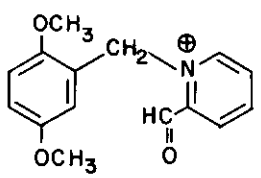
R_1	R_2	R_3	R_4	R_5	R_6	Cyclising agent	Yield %	Ref.
H	H	H	H	H	C_6H_5	HF	77	26
H	H	OCH_3	H	H	C_6H_5	HF	41	26
H	CH_3	H	H	H	C_6H_5	HF	34	26
H	H	H	CH_3	H	C_6H_5	HF	53	26
H	H	H	H	CH_3	CH_3	HF	8.6	26
H	OCH_3	OCH_3	H	CH_3	H	H_2SO_4/acetic anhydride	31	34
H	OC_2H_5	OC_2H_5	H	CH_3	H	H_2SO_4/propionic anhydride	74	34
H	—$(CH_2O)_2$—		H	CH_3	H	H_2SO_4/acetic anhydride	25	34
H	H	H	H	CH_3	H	HBr	11	28
H	H	H	H	H	C_6H_5	HBr	71	28
—$(CH_2O)_2$—		H	H	H	H	HCl	31	40
H	—$(CH_2O)_2$—		H	H	H	HCl	42	40
OCH_3	OCH_3	H	H	H	H	HCl	75	46

Extension of the same general method to the synthesis of alkoxyl derivatives of the acridizinium ion leads to the preparation of 8-methoxy, 7,8- and 8,9-dimethoxyacridizinium salts (41,42,43) [40]. Hydrochloric acid was found to bring about the cyclisation in good yields and without any ether cleavage, as was the case when hydrobromic acid was used as the cyclising agent.

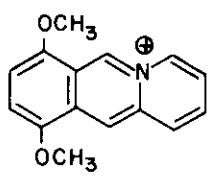


Contrary to Bradshers findings [40], Watthey and coworkers [41] have reported that cyclisation of the pyridinium salt 44 or 45 with concentrated hydrochloric acid at 100° did not only give an impure product but also led to the ether cleavage. However, they succeeded in cyclising the quaternary salt with hydrobromic acid at 75° over a period of 5 minutes. Their results are in agreement to those of Kupchan, et al. [42].

Bradsher and Barker [43] have reported their failure in the isolation of any pure product from the cyclisation of the quaternary salt 46 and instead, have isolated a mixture of 47 and one molecule of hydroxylamine hydrobrimide.

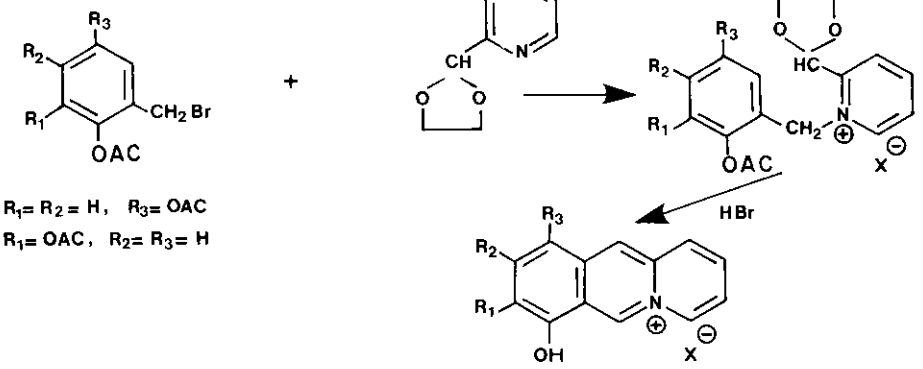


46



47

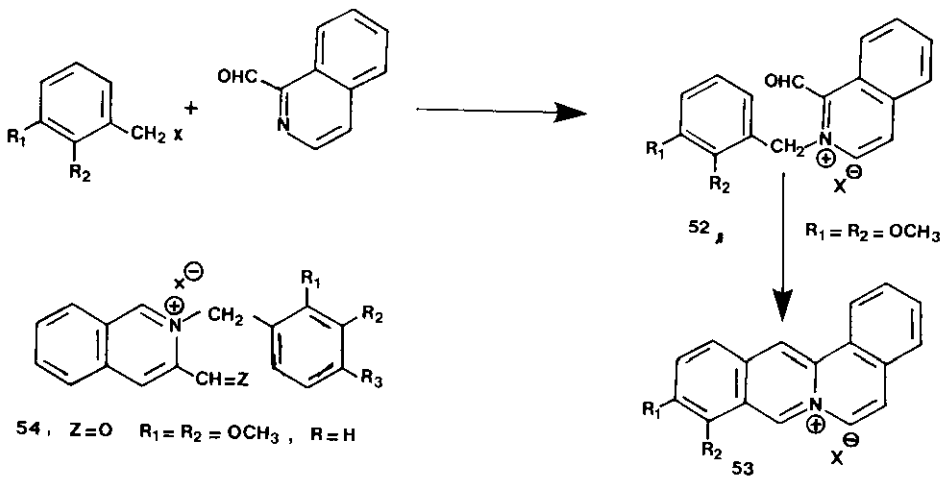
Fields and co-workers [44] have converted bromomethylhydroquinone diacetates (48 and 49) into the corresponding hydroxyacridizinium derivatives (50 and 51) by cyclisation of the pyridinium salts in boiling hydrobrimic acid or with a 15-32% hydrogen bromide-acetic acid mixture.



48, $R_1 = R_2 = H$, $R_3 = OAC$
49, $R_1 = OAC$, $R_2 = R_3 = H$

50, $R_1 = R_2 = H$, $R_3 = OH$
51, $R_1 = OH$, $R_2 = R_3 = H$

Condensation of 1-isoquinoline aldehyde with alkoxybenzyl halides followed by cyclisation of the crude salt (52) with hydrochloric acid resulted in the formation of an expected benz [a]-acridizinium chloride (53) in 52% yield [45]. It was also observed that even 2-benzyl-3-formyl-isoquinolinium salt (54) could be cyclised, if the benzyl group contains substituents, which



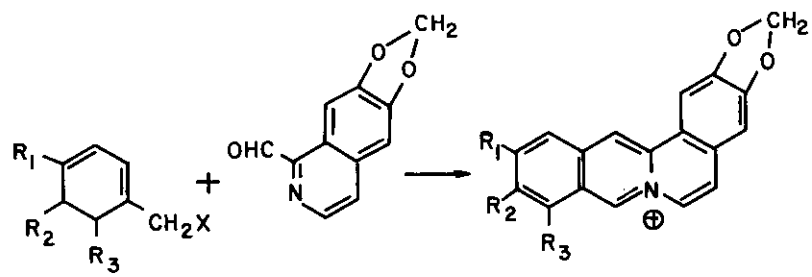
54, Z=O $R_1 = R_2 = OCH_3$, R=H

52, $R_1 = R_2 = OCH_3$

53

sufficinetly enhance the rate of cyclisation. Thus alkoxybenzologs of 54(Z=O), on heating with hydrochloric acid for 5-15 minutes afforded the corresponding alkoxybenz[b]acridizinium salts [26]. The salt (53) might be regarded as the parent substance of all the photoberberine alkaloid and could be referred as a dehydroprotoberberinium salt. By the use of alkoxybenzyl halides, several alkoxybenzyl[a]acridizinium salts were synthesised. The results are summarised in Table III.

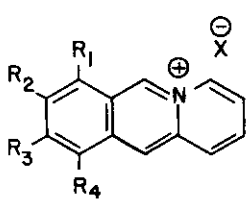
The dehydroberberinium salt (55) was prepared from the quaternary salt obtained from 6,7-methylenedioxyisoquinoline-1-aldehyde (56) and substituted benzyl halides. Cyclisation of the quaternary salt with hydrochloric acid afforded dehydroberberinium chloride (55) in 30% yield. Use of the corresponding oxime in the formation of the quaternary salt followed by cyclisation with polyphosphoric acid increased the yield to 67% [46].



56

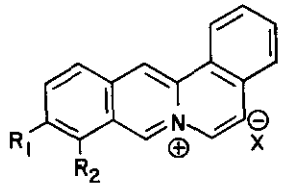
55, $R_1 = H$, $R_2 = R_3 = OCH_3$

TABLE III



	R_1	R_2	R_3	R_4	Cyclising agent	Yield %	Ref.
A	H	OCH_3	H	H	HCl	44	62
	H	OH	H	H	HBr	37	40
	OCH_3	OCH_3	H	H	HBr	75	40
	O—CH_2— O		H	H	HCl	42	40
	H	O—CH_2— O		H	HCl	31	40
	H	OCH_3	OCH_3	CH_3	HBr	62	41
	OCH_3	H	H	OCH_3	HBr	72	41

	R_1	R_2	R_3	Cyclising agent		Yield	Ref.
B	H	OCH_3	H		HBr	76	26
	OCH_3	OCH_3	H	HCl	HCl	29	26
	H	OCH_3	OCH_3		HCl	74	26
	H	O—CH_2—O—			HCl	39	26

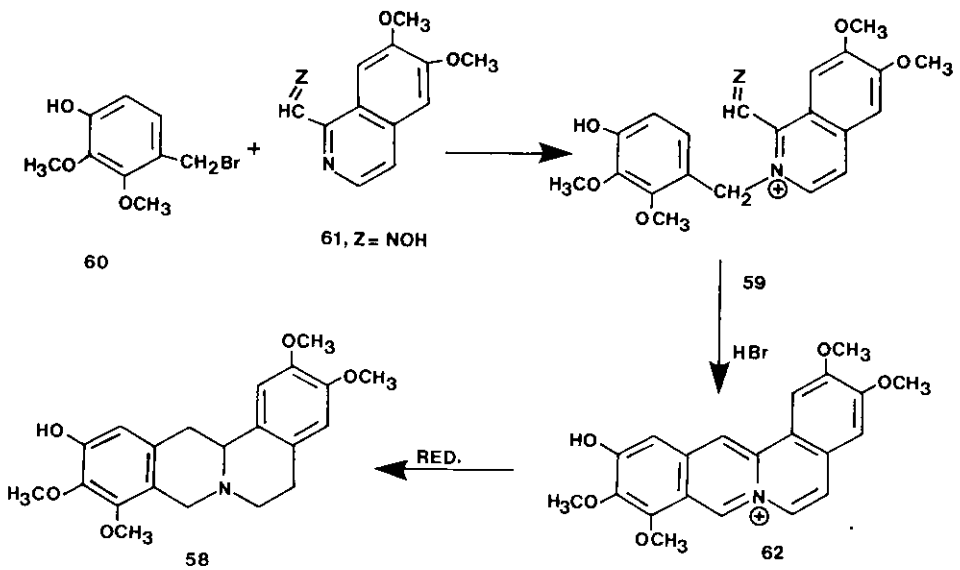


	R_1	R_2	Cyclising agent	Yield %	Ref.
C	H	H	HCl	52	45
	OCH_3	H	HCl	78	45
	OCH_3	OCH_3	HCl	53[a]	45
	O—CH_2— O		HCl	66[b]	45

a = yield reported is that of the perchlorate.

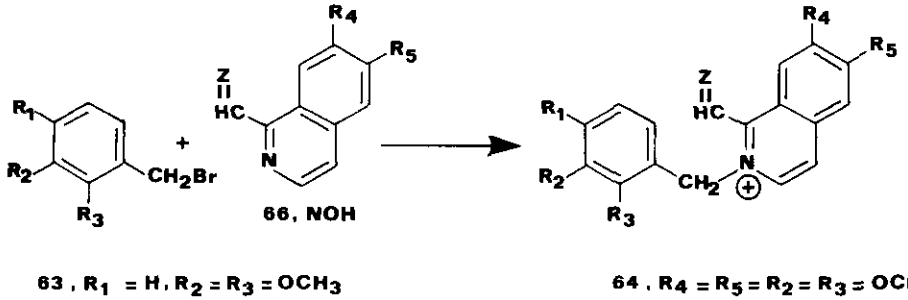
b = crystallised from the cyclisation mixture as the chloride.

Extension of this procedure led Bradsher and his co-workers [47] to the establishment of the structure of an alkaloid, stepharotine (58). Hydrobromic acid cyclisation of the quaternary salt (59) prepared from 2,3-dimethoxy-4-hydroxybenzyl bromide (60) and 6,7-dimethoxyisoquinoline-1-carboxyldoxime (61) afforded 11-hydroxy-2,3,9,10-tetramethoxybenz[a]acridizinium bromide (62), which on reduction over Adams catalyst gave (±) 11-hydroxy-2,3,9,10-tetramethoxy-5,6,13a-tetrahydro-8-dibenzo[a,g]quinolizine (58).



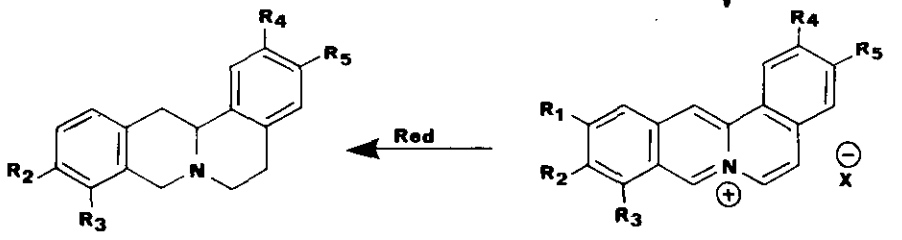
Quaternisation of the same aldehyde (61, z=0) with 2,3-dimethoxybenzyl bromide (63) in acetonitrile followed by cyclisation of the crude salt (64) with boiling hydrochloric acid resulted in the formation of the dehydropalmatine and was isolated as bromide (65) in 30% yield [48]. The yield was raised to 80% by using the oxime 66 in the presence of dimethyl formamide for quaternisation followed by cyclisation. Reduction of 65 over Adams catalvst yielded (±)-tetrahydropalmatine (66[a]) as hydrobromide. In a similar reaction dehydroepiber-

berinium chloride (65a) and other derivatives were prepared. The results are summarised in Table IV.



63, R_1 = H, $R_2 = R_3 = OCH_3$ **66**, NOH

64, $R_4 = R_5 = R_2 = R_3 = OCH_3$, R_1=H



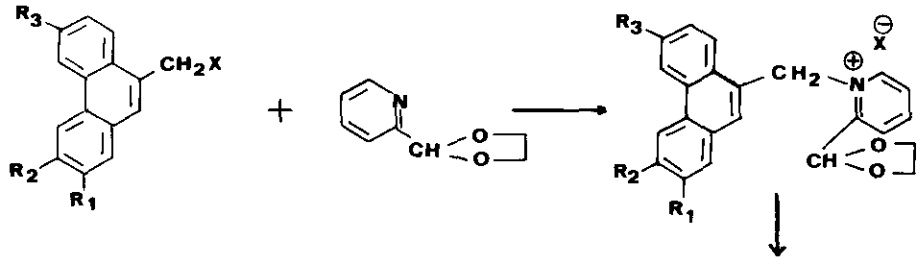
66a, R_1 = H, $R_2 = R_3 = R_4 = OCH_3$

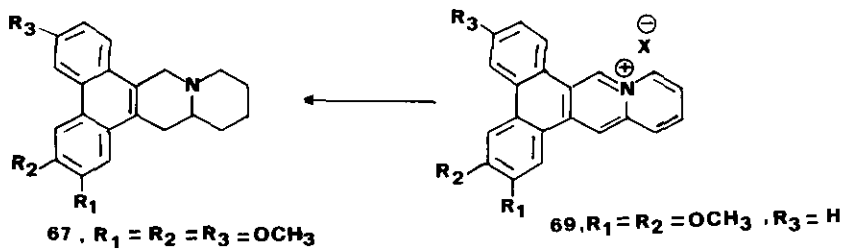
65, R_1= H, $R_2 = R_3 = R_4 = R_5 = OCH_3$

65 a, R_1=H, $R_2 = R_3 = OCH_2O$, $R_4 = R_5 = OCH_3$

Synthesis of some of the analogs of cryptopleurine (67) was carried out by quaternisation of 2,3-dimethoxy-9-bromomethylphenanthrene (68) with 2-(1,3-dioxalan-2-yl)pyridine followed by cyclisation of the crude salt with hydrobromic acid. The resulting product, 2,3-dimethoxydibenzo [h,j]acridizinium bromide (69) was isolated in quantitative yield. [49,50]

In a similar reaction 6-methoxy and 2,3,6-trimethoxydibenz[h,j] acridizinium salts were prepared and isolated as perchlorates.

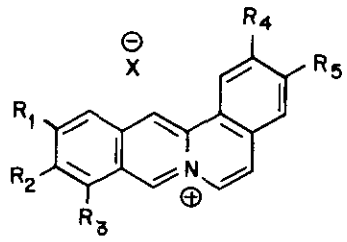




67 , $R_1 = R_2 = R_3 = OCH_3$ 69, $R_1 = R_2 = OCH_3$, $R_3 = H$

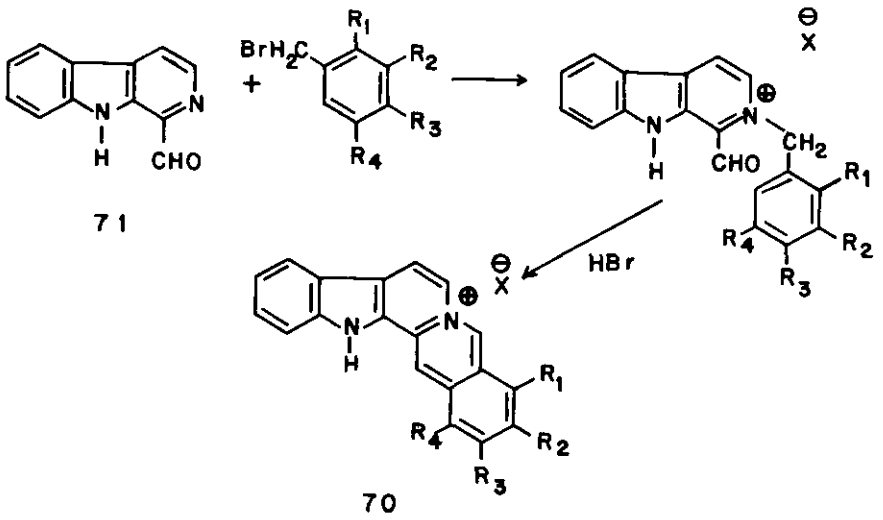
Bradsher and Umans [51] synthesised indolo(2,3-a)acridizinium bromide (70) which is considered as the parent system of the yohimbine, reserpine and alstoniline alkaloids. This was carried out by quaternisation of the pyridoindole carboxyaldehyde (71) with benzyl bromide in dimethyl formamide followed by cyclisation of the crude salt with polyphosphoric acid at 120° for 24 hours. Its structure was further confirmed by synthesising its 8,9-methyl derivative from

TABLE IV



R_1	R_2	R_3	R_4	R_5	Z	Cyclising agent	Yield %	Ref.
H	OCH_3	OCH_3	O—CH_2—O		O	HCl	30	46
H	OCH_3	OCH_3	O—CH_2—O		NOH	HCl	67	46
O—CH_2—O		H	O—CH_2—O		O	HCl	66	46
H	OCH_3	OCH_3	OCH_3	OCH_3	O	HCl	30	47
H	OCH_3	OCH_3	OCH_3	OCH_3	NOH	HCl	80	47
O—CH_2—O		H	H	H	NOH	HCl	100	47
H	O—CH_2—O		O—CH_2—O		NOH	HCl	85	47
OCH_3	OCH_3	H	O—CH_2—O		NOH	HCl	-	46[a]

a = as perchlorate.



1-methyl-2-(3-isoquinolyl)-indole and bromoacetone[52]. The results are summarised in Table 5.

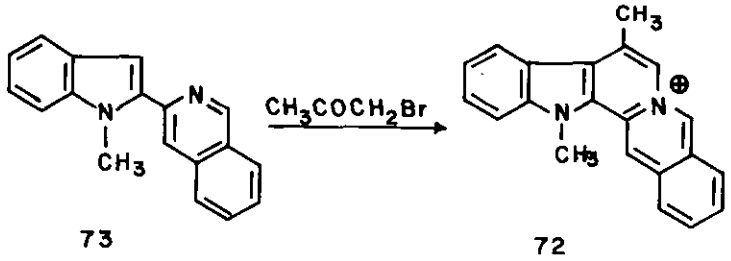
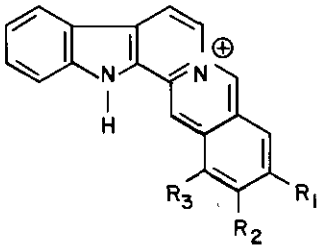


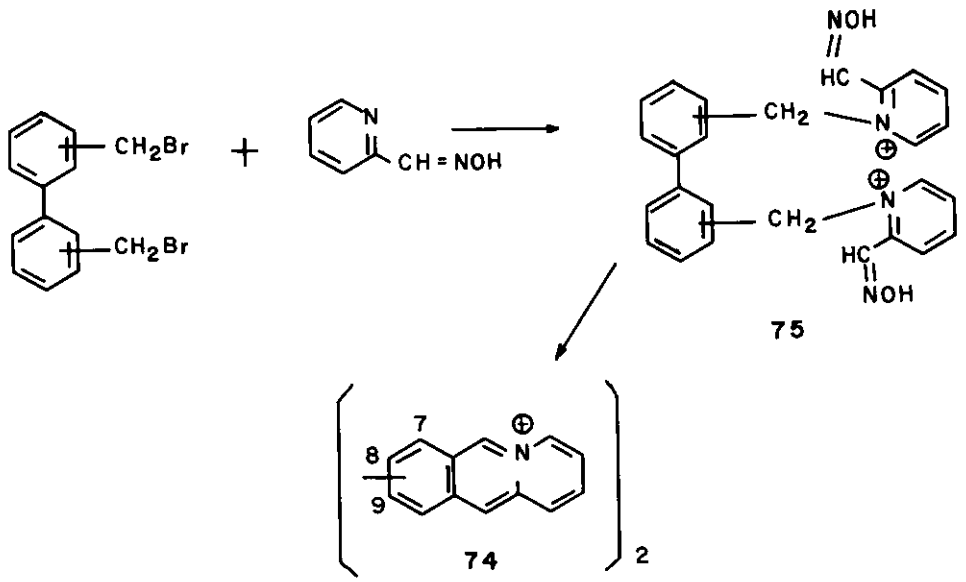
TABLE V



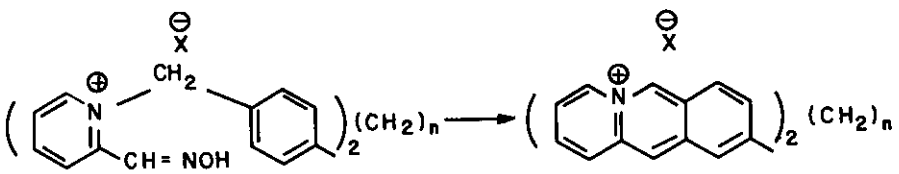
R_1	R_2	R_3	Cyclising agent	yield %	Ref.
H	H	H	PPA	72	50
OCH_3	H	H	HCl	80	50
H	OCH_3	OCH_3	HCl	81	50

The interest in the pharmacology of bis-quaternary nitrogen system with regard to their application as hypotensive, ganglionic and neuromuscular blocking agents[54,55] suggested the

possibility of synthesising some bis-acridizinium compounds (74). Cyclisation of the quaternary salt (75) with boiling hydrobromic acid resulted in the formation of 7,7'-bis(acridizinium brimide). Similarly 8,8'-bis and 9,9'-bis(acridizinium bromides) were prepared in good yields [56].



From 4,4'-bis(bromomethyl)diphenylmethane and 4,4'-bis(bromomethyl)bibenzyl via the quaternary salts 76 and 77,9,9'-methylenebis(acridizinium bromide) (78) and 9,9'-ethylenebis (acridizinium bromide) (79) were obtained in reasonable yields.

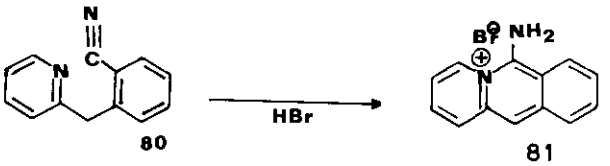


76 , n = 1
77 , n = 2

78 , n = 1
79 , n = 2

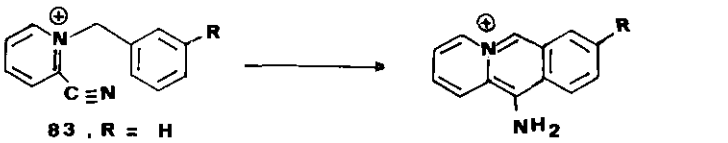
Aminoacridizinium Salts.

The first report of the successful preparation of 6-aminoacridizinium bromide was that of Bradsher and Sherer [57], who found that cyclisation of 2-(2-pyridylmethyl)benzonitrile (80) with hydrobromic acid yielded 6-aminoacridizinium bromide (81). This synthesis suggested that 11-aminoacridizinium derivatives (82) might be obtained by acid catalysed cyclisation of 1-benzyl-2-cyanopyridinium salts (83 and 83a). The best result were obtained by using concentrated sulphuric acid at 100° for cyclisation. Use of hydrogen chloride resulted in the cleavage of the



80 81

quaternary salt (82) yielding 2-picolinamide hydrochloride. Introduction of a methoxyl group para

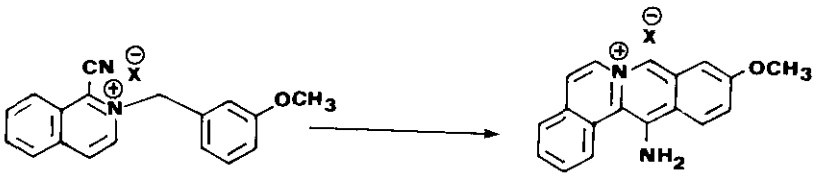


83 , R = H
83a , R = OCH_3

82 , R = OCH_3 or H

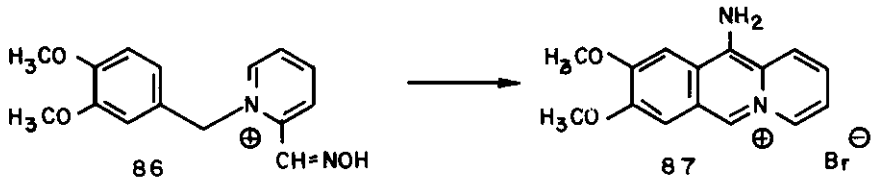
to the position of expected cyclisation (83) resulted in an improved yield (70%). The method however, failed to yield the benzologs of 83 from the cyclisation of 1-α or 1-β-naphthyl-2-cyanopyridinium salts [58].

In a similar reaction cyclisation of the quaternary salt (84, $X=BF_4$) prepared from 1-cyanoisoquinoline and m-methoxybenzyl bromide with 100% phosphoric acid at 130° afforded 10-methoxy-13-aminobenz(a)acridizinium tetrafluoroborate (85) in 88% yield [58].



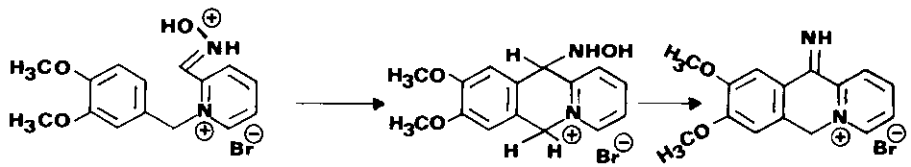
84 85

Watthey et al [41] in contradicting the results of Bradsher and co-workers [21] have reported that the cyclisation of 86 by hydrobromic acid did not afford the corresponding benz(b)quinolizinium bromide but gave a product which was shown to have the structure corresponding to 8,9-dimethoxy-11-aminoacridizinium bromide (87).



86 87

The proposed mechanism suggested the protonation of the oxime followed by cyclisation to yield an intermediate (88), which then dehydrates to the imine (89) a tautomer of 87. Such transformations are also involved in Semmler-Wolf aromatizations [59,60] in general and presumably in the acid promoted conversion of 3,5-dimethylcyclohexanone oxime to 3,5-xylylamine [61].



88 89

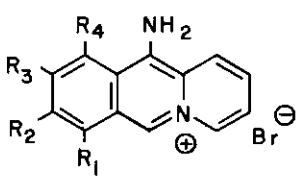
It was concluded that those substances which cyclise to give only the amino derivatives have a methoxy group para to the site of the cyclisation flanked by a methoxy group and a hydrogen atom, and those which gave little or no amino compound react more slowly enabling oxime hydrolysis to occur. The results are summarised in Table VI.

Quinones

Bradsher and Barker [62] have reported that the reaction of 2-bromomethyl-1,4-dimethoxynaphthalene (90) with picolinaldoxime (92) afforded a 99% yield of the quaternary salt (91), which on cyclisation followed by ether cleavage and oxidation resulted in the formation of a monoxime (93). This monoxime on boiling for 48 hours with a mixture of glacial acetic acid and 48% hydrobromic acid afforded 6a-azonianaphthacene quinone (94) in low yield.

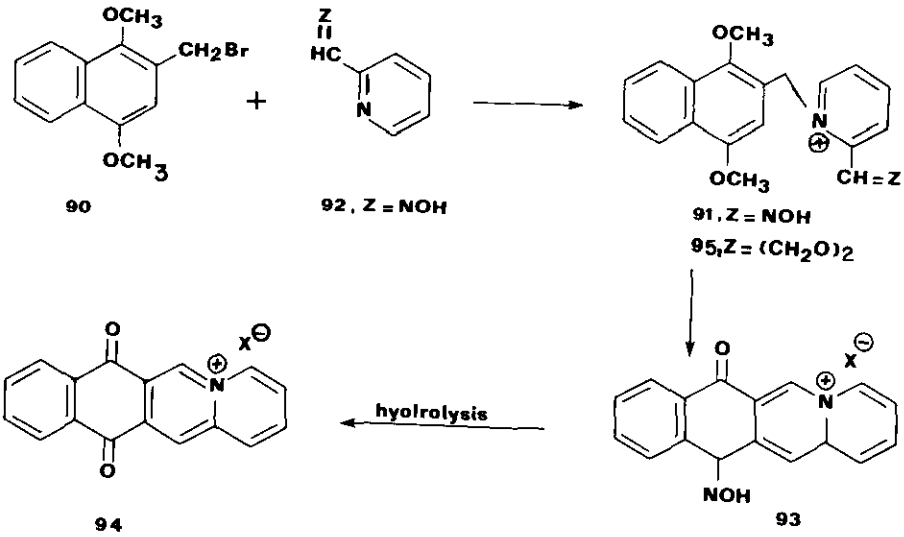
Use of 2-(1,3-dioxalan-2-yl)pyridine instead of the oxime gave the quaternary salt (95)

TABLE VI

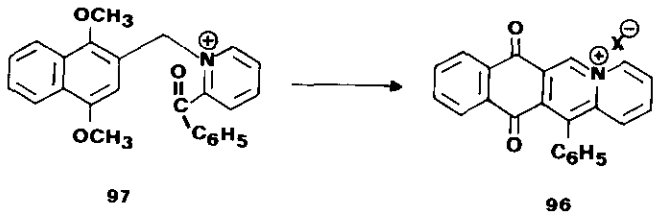


R_1	R_2	R_3	R_4	Cyclising agent	Yield %	Ref.
OCH_3	OCH_3	H	H	HBr	66	41
H	OCH_3	OCH_3	OCH_3	HBr	70	41
OCH_3	OCH_3	OCH_3	H	H_2SO_4	35	58
H	H	OCH_3	H	H_2SO_4	70	58

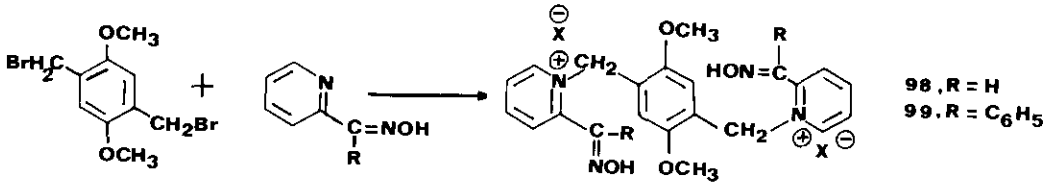
which cyclised to yield 93 directly in an overall yiled of 63%. Its 11-phenyl derivative (96)

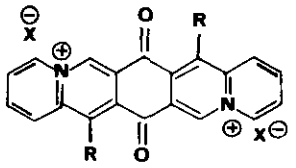


was synthesised from the quaternary salt (97) in an overall yield of 74%. Similarly the diquar-



ternary salts (98,99) were cyclised on heating for 24 hours at 100° in 48% hydrobromic acid in the presence of air to yield 100 and 101 in 71 and 50% yield respectively [43].



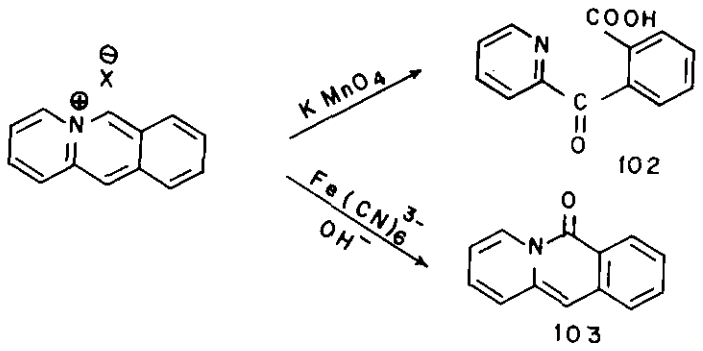


100, R = H
101, R = C_6H_5

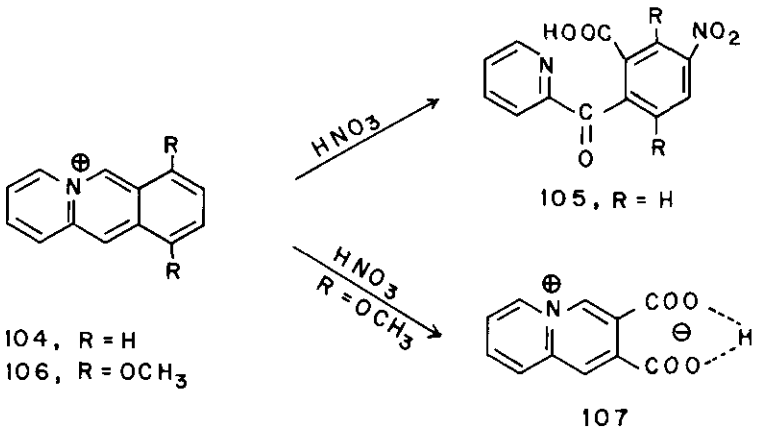
Reactions

Acridizinium salts are yellow, giving a fluorescent solutions in water or polar solvents and such solutions have an ultraviolet absorption spectrum reminiscent of that of anthracene [16], *except for a general shift to longer wave lengths and an intensified absorption at longer wave* lengths. Acridizinium salts appear to be stable provided they are shielded from light.

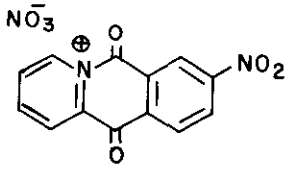
Oxidation of the acridinium ion can occur in several ways. With permanganate 2-(2-carboxybenzoyl)pyridine (102) and not phthalic acid as reported earlier [16] was isolated in 30% yield [63]. On the other hand, alkaline ferricyanide gave a 9% yield of 6H-benzo[b]quinoline-6-one (103) [64].



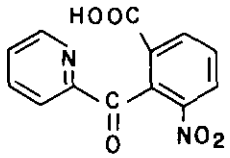
Heating acridizinium bromide (104) with 12M nitric acid at 100° for 3 hours resulted in the formation of 2-(2-carboxy-4-nitrobenzoyl)pyridine (105), while a similar oxidation carried out on 7,10-dimethoxyacridizinium ion (106) afforded the betaine (107) of 2,3-dicarboxyquinolizinium hydroxide [65]. The oxidation of 104 may be considered to be similar to that of the *attack of nitric acid on anthracene to yield anthraquinone. The intermediate acylammonium salt* (108) would be expected to hydrolyse rapidly to the keto acid (104, R=H). Later work [63], however, had shown that treatment of the acridizinium ion with a mixture of nitric acid and



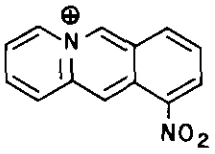
sulphuric acid at -5° resulted in the formation of a mononitroacridizinium salt which on oxida-



tion with concentrated nitric acid at 100° afforded 2-(2-carboxynitrobenzoyl)pyridine (109), which on decarboxylation, yielded 2-(2-nitrobenzoyl)pyridine, confirming that the original nitration product was the 10-nitro derivative (110). It was concluded that oxidation must precede nitration or else the product would be 110 and therefore 102 cannot be an intermediate as it has been recovered unchanged when subjected to the conditions of the oxidative nitration.

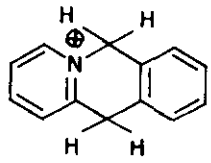


109

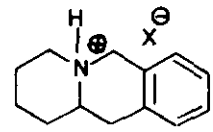


110

The reduction of the acridizinium nucleus can be made to occur stepwise. With a palladium catalyst, the reduction may be interrupted after the addition of one mole of hydrogen, affording 6,11-dihydroacridizinium ion (111). With a substituent at 6- and 11-positions, reduction over a palladium catalyst likewise afforded a 6,11-dihydro derivative. With a platinum catalyst both rings common to the nitrogen atom are reduced, affording benzo[b]octahydroquinolizinium salt

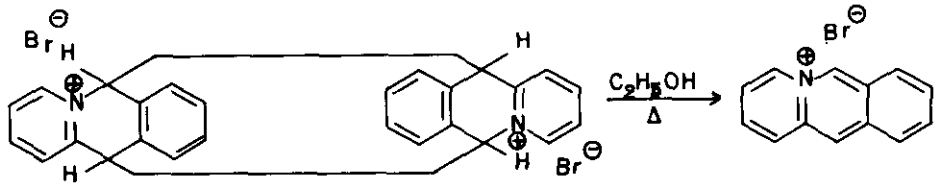


111



112

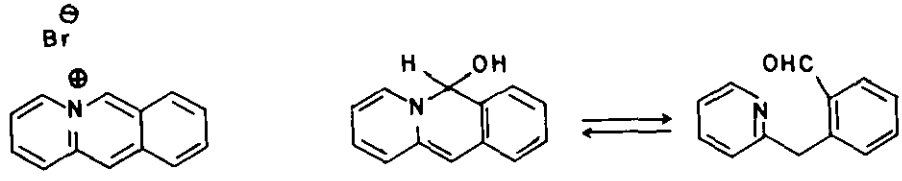
(112) [16]. The same compound (112) was obtained, when sodium borohydride was used as a reducing agent [67]. The acridizinium ion was found to be more sensitive to light than is anthracene, but like it, is beleived to undergo photodimerisation through the meso positions [68]. The photodimer (113) when refluxed for 24 hours with 48% hydrobromic acid remained unchanged, but refluxing it in 95% ethanol solution for 18 hours afforded acridizinium bromide in 82% yield.



113

Action of Bases

The acridizinium ion is quite stable in acid solution but is sensitive to attack by bases. It has been reported [57,38,69] that addition of base to an aqueous solution of acridizinium ion leads to the precipitation of a red or brown powder, which could not be recrystallised and was shown to be a mixture of the pseudo base (114) and the aldehyde (115). The structure of 115 was established by the formation of an oxime or a semicarbazone, which on refluxing for

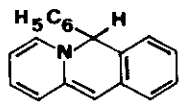


114 115

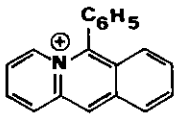
1 hour in hydrobromic acid, was converted to acridizinium bromide in 91% yield.

It has also been reported [57] that acridizinium bromide on treatment with phenylmagnesium bromide resulted in the formation of a dihydro base (116), which on refluxing with ethanolic

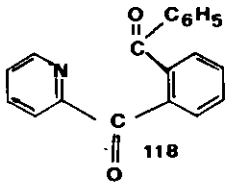
picric acid yielded the picrate of the base 116 and not the picrate of the aromatic quaternary salt (117) as reported earlier [69]. The structure of 117 was further established by the oxidation of 116 to 118 and by an independent synthesis of the diketone, 2-(2-picolinyl)benzophenone.



116

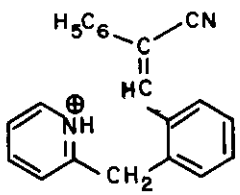


117

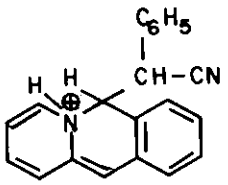


118

Condensation of phenylacetonitrile with acridizinium bromide in the presence of base[57,70] resulted in the formation of 2-(2-(α-cyanostyryl)benzyl)pyridine (120) and not 121 as was reported earlier. This seems possible only, if one assumes that the formylbenzylpyridine (115) was an intermediate in the condensation reaction.



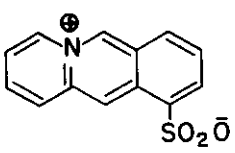
120



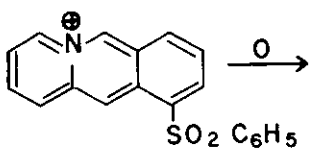
121

Sulphonation

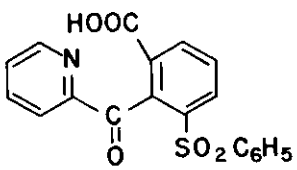
Fozard and Jones [70,71] have demonstrated that in the presence of an activating group, the quinolizinium ion does appear to undergo electrophilic substitution. When acridizinium bromide was dissolved in 20% fuming sulphuric acid, a sulphobetaine (122) was obtained in 82% yield [72]. Oxidation with nitric acid of its phenyl sulphone derivative (123) gave a keto acid (124), the structure of which was established by an independent synthesis showing thereby, that sulphonation has occurred at the 10-position [72]. The formation of 122 was rationalised on the basis that the 10-position is an α rather than a β position, and unlike the position 7 is not a position which bears a positive charge in the resonance hybrid.



122



123

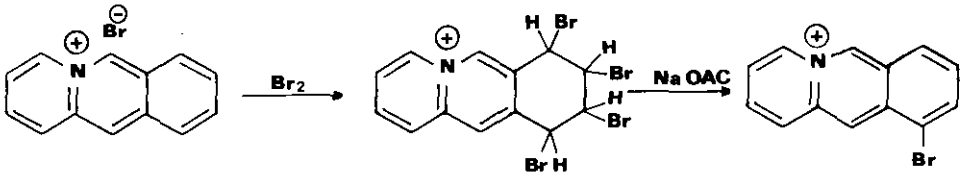


124

Halogenation

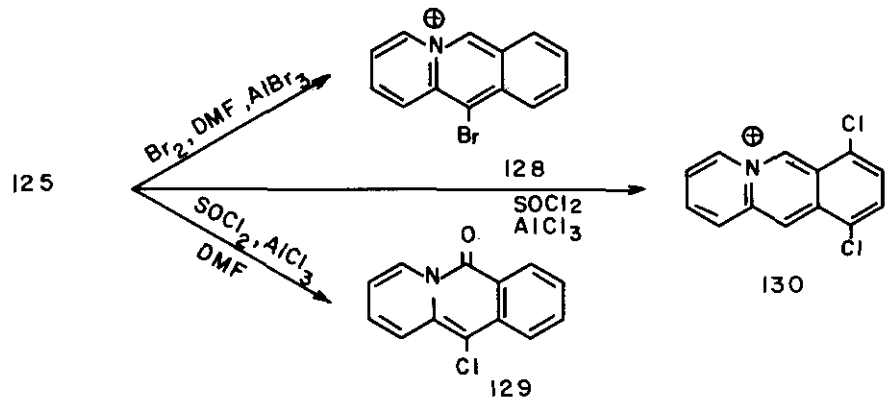
The mechanism of halogenation of the acridizinium ion appears less clear. Addition of

bromine to the acridizinium ion (125) in the absence of the solvent resulted in the formation of an addition compound (126) in which bromine was supposed to have added to the 7,8,9 and 10 positions [73] . This is in agreement to the addition of bromine to the terminal ring of 9.10-dichloroanthracene [74] . The new cation 126 reverts back to the



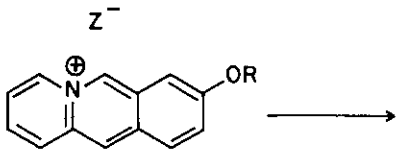
125 126 127

acridizinium ion on heating, and on treatment with sodium acetate afforded 10-bromoacridizinium ion (127) . Bromination in the presence of aluminium bromide and dimethylformamide yielded the 11-bromo derviative (128) , while from the chlorination with sulphuryl chloride, 11-chloro-6 H-benzo[b]quinolizine-6-one (129) was isolated.

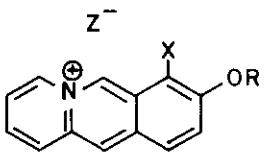


It appears most likely that, under the experimental conditions, the acridizinium nucleus like that of anthracene [75] was chlorinated in the meso positions affording the 6,11-dichloro-acridizinium cation, which then undergoes nucleophilic attack by water at the active 6-position, yielding the chlorobenzoquininlizine-6-one (129) . Halogenation by sulphuryl chloride in the absence of dimethylformamide afforded 7, 10-dichloroacridizinium ion (130) , the structure of which was established by an independent synthesis. Halogenation of the acridizinium ion containing an activating substituent was shown to yield a mono derivative. Thus bromination of 8-hydroxyacridizinium bromide (131) in acetic acid afforded 7-bromo-8-hydroxyacridizinium bromide (132). . Using sulphuryl chloride in dimethylformamide, 8-methoxyacridizinium chloride

(133) gave the corresponding 7-chloro derivative in 60% yield [76] .



131, R = H, Z = Br
133, R = CH_3, Z = Cl

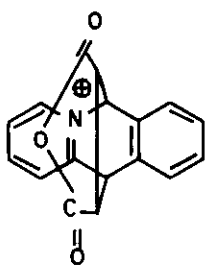


132, R = H, X = Br
134, R = H, X = Cl, Z = Pic

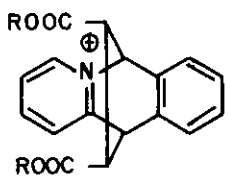
Transannular Addition of Dienophiles

The observation that acridizinium bromide undergoes photodimerisation [68] suggested that it might also resemble anthracene [77-79] , in functioning as the diene component in the Diels-Alder reaction. In fact it had been shown that acridizinium ion adds up substituted ethylenes across the meso positions of the nucleus. The first example involved the addition of the common dienophiles, maleic anhydride, maleate and fumerarate esters [80] . Later work with the cyclo-addition reactions included, acrylonitrile, ketene acetals [81] arylmaleimides [91] and norbornene derivatives [92] . The results are summerised in Table VII. All these reactions are unique example of Diels-Alder reaction in which the "diene" component bore a positive charge.

Addition of maleic anhydride to acridizinium bromide in acetic acid afforded an adduct (134) which on hydrolysis with perchloric acid followed by esterfication of the hydrolysed product (135) resulted in the formation of cis dimethyl ester (136) . The anti configuration with respect to the benzene ring, since the infrared and nmr spectra

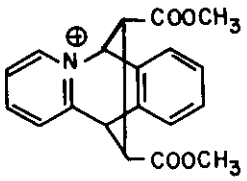


134

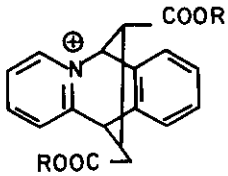


135, R = H
136, R = CH_3

showed proximity of one of the carbomethoxy groups to the quarternary nitrogen atom [82] . With methyl maleate, an adduct 137 was isolated in 43% yield and was designated syn configuration. In this reaction a rearranged product (138) was also obtained in 13% yield. It is most likely



137

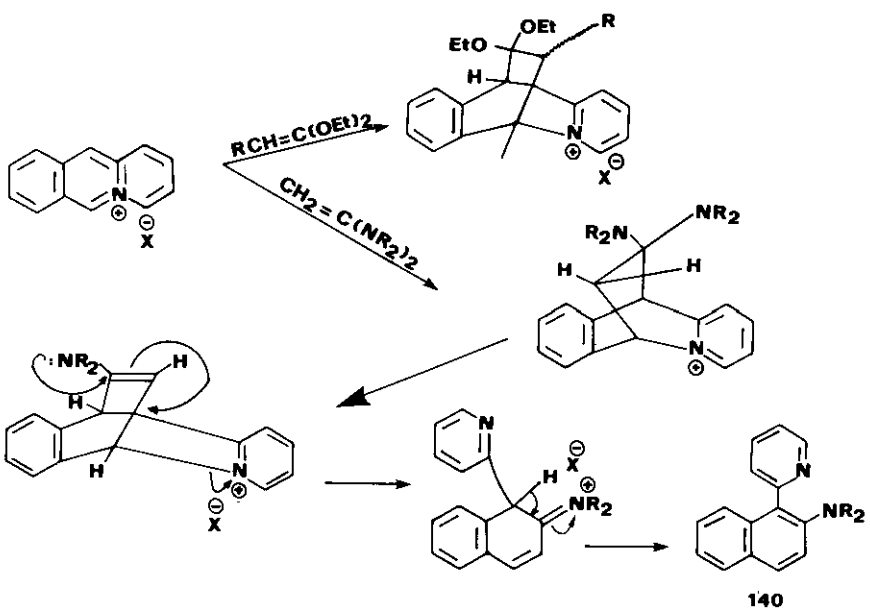


138, R = CH_3

139, R = C_2H_5

that the addition of maleate esters took place as a two step reaction and the carbonium ion first formed rotates through 180^{o} before cyclisation. It was also shown that the release of hydrogen bromide during the reaction has no bearing on the course of the reaction [84]. Diethyl maleate, on the other hand gave almost exclusively a trans product (139) identical with that obtained when diethyl fumerate was used as the ethylenic reactant. The increased rate of addition of fumerate was attributed to the steric rather than electronic effect, otherwise the order of reactivity should be reversed in going from a classical to an inverse electron demand type of 1,4-cyclo-addition.

Fields, Regan and Dignan [81] have reported that ketene acetals react rapidly and stereoselectively by Diels-Alder addition with a variety of types of azoniapolycyclic aromatic compounds (Table VII). Without exception the cycloaddition gave the positional isomers with the alkoxy



140

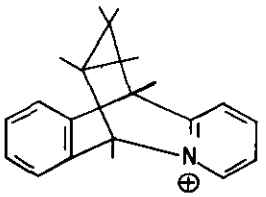
141, NR_2 = morpholino

groups nonadjacent to the quaternary nitrogen as a mixture, where possible, of two geometrical forms in which the R group resides either syn or anti to the quaternary nitrogen.

It was also shown that the reaction of 1,1-dimorpholino ethylene with the acridizinium bromide gave 2-morpholino-1-(2-pyridyl)naphthalene (140) probably resulting from an elimination reaction involving enamine (141) as an intermediate [81]. When the ketene acetal adducts (142) were subjected to acid hydrolysis, cleavage occurred with the formation of 9,10-dihydro-12-oxo-4a-azonia-9,10-ethanoanthracenes (143) as an intermediate product and depending on the nature of the R group at C-11, 143 proved to be more or less labile to acidic as well as basic reagents.

Table VII

Adducts of Acridizinium Ion and Dienophiles



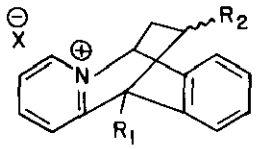
Dienophile	Reaction solvent	Conditions Temp.	Hr.	Yield %	Ref.
$CH_2=CH_2$	A	70	18	93	81
$CH_2=CHC_2H_5$	A	70	66	66	81
$CH_2=CHCH=CH_2$	A	70	18	93	81
$CH_2=CHCH_2OH$	B	100	18	77	81
$CH_2=CHCN$	D	70	48	68	81
$CH_2=CHC_6H_5$	B	100	2.5	93	81
$CH_2=C(CH_3)-C(CH_3)=CH_2$	B	100	1.5	66	81
$CH_2C(OEt)_2$	C	25	0.1	92	81
$BrCH=C(OEt)_2$	C	70	2	100	81
$CH_3CH=C(OEt)_2$	C	25	0.1	93	81
$C_6H_5CH=C(OEt)_2$	C	70	0.1	100	81
$C_6H_5CH=CHN(Et)_2$	C	25	0.1	91	81
Cyclopentadiene	D	25	1.5	94	81
Cyclopentene	D	60	96	76	81
Maleic anhydride	E	100	13	87	80
Diethyl maleate	E	95	48	65	80

Table VII continued.....

Diethyl fumerate	E	105	10	54	80
Dimethyl maleate	E	100	72	60	82
Dimethyl fumerate	E	100	24	96	82

Reaction media: A = methanol in autoclave; B = nitromethane ;
C = acetonitrile; D = acetonitrile-methanol(3:1 by volume); E =acetic acid

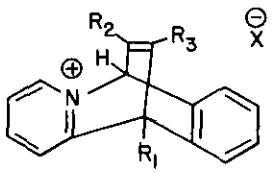
B. Addition of Vinyl derivatives to Acridizinium Bromide salts.



Vinyl derivative	R_1	R_2	Temp. Hr.	Time	Method	Yiled	Ref.
OEt	H	OEt	20	72	A	91	86
OEt	Ph	OEt	20	72	A	33	86
OBu	H	OBu	82	12	B	64	86
OAc	H	OAc	65	72	A	89	86
N-carbazyl	H	N-carbazyl	20	15	B	68	86
1-pyrr.	H	1-pyrrolidin-2-one	20	12	B	50	86

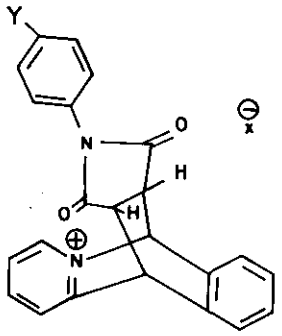
A = Fluoroborate salts were prepared by adding fluoroboric acid to the known bromide: B = *addition of fluoroboric acid instead of perchloric acid in the* isolation of the cation from polyphosphoric acid cyclisation mixtures.

C. Products of the Reaction of Some Acridizinium Fluoroborates with Derivatives of Acetylene at 135-140^0



R_1	R_2	R_3	Time Hr.	yield %	Ref.
Me	H	Ph	0.75	62	86
Ph	H	Ph	0.75	50	86
Me	$COOCH_3$	$COOCH_3$	0.10	93	86
Ph	$COOCH_3$	$COOCH_3$	0.175	30	86
Me	Ph	Ph	40	85	86
Ph	Ph	Ph	239	40	86

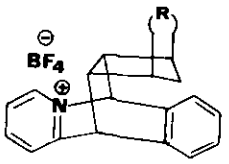
D. Cycloaddition products of Acridizinium Slats with N-Arylmaleimides



X	Y	Method	Yield %	Ref.
ClO_4	H	A	95	91
Br	H	A	90	91
Br	H	B	75	91
ClO_4	Me	B	70	91
Br	Me	B	70	91
ClO_4	Cl	A	90	91
Br	Cl	A	90	91
Br	Cl	B	75	91
ClO_4	OMe	A	90	91
Br	OMe	A	90	91
Br	OMe	B	90	91
ClO_4	$N(Me)_3$	A	60	91

A = Acridizinium salt was heated in acetic acid suspension at 100^{o} with an excess of maleimide, the time being about 20 hours for perchlorate and 2 hours for bromides
B = The molten reactants were heated at 160-170^{o} for 15 min.

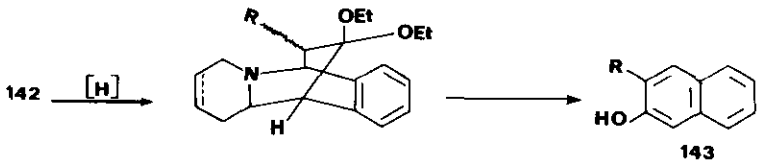
E. Addition of endo 5,6-substituted Norbornenes to Acridizinium Fluoroborates



Substituent ring R	Time	Temp.	Configuration syn: anti	Yield	Ref.
None	24	82[a]	60:40	82	92
$(CH_2)_3$	48	82[a]	85:15	42	92
CONHCO	72	82[a]	100:0	62	92
$CON(CH_3)CO$	120	82[a]	100:0	99	92
COOCO	96	120[p]	100:0	25	92
CH_2OCH_2	24	82[a]	100:0	53	92
$CH_2NH_2^+CH_2$	96	120[p]	70:30	22	92

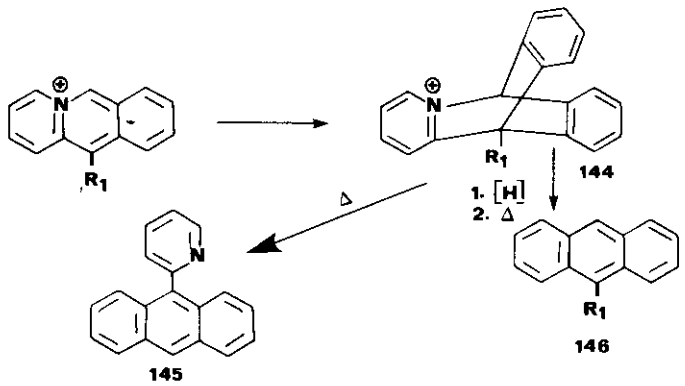
a = Refluxing acetonitrile ; p = Sealed tube.

More significant applications of the reaction products of the acridizinium ion with alkenes have been made by Field et al.[100-103] According to the authors if the cycloadduct 142 is reduced, the product when hydrolysed and heated loses unidentified amine products affording the nitrogen free naphthol (143).

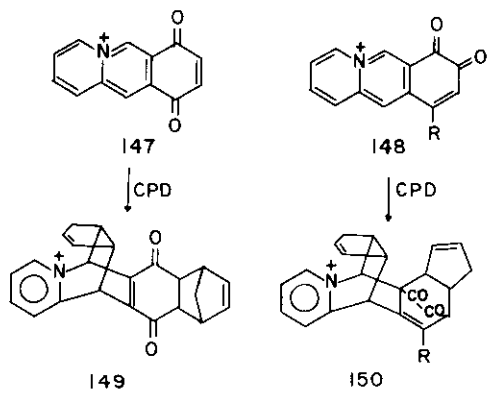


Another important observation by Field et al [102] was that the acridizinium ion (29) will undergo cycloaddition with benzyne, affording azoniatriptycene (144) in good yield. The presence of a phenyl group at position II (29,R_1=Ph) did not interfere with the cycloaddition nor did a variety of substituents on ring C. Field et al [102] have further shown that thermolysis of the adduct (144) afforded 9-(2-pyridyl)anthracene derivatives (145), while the second involves thermolysis of the reduction product of (144) affording anthracene derivatives (146) in excellent

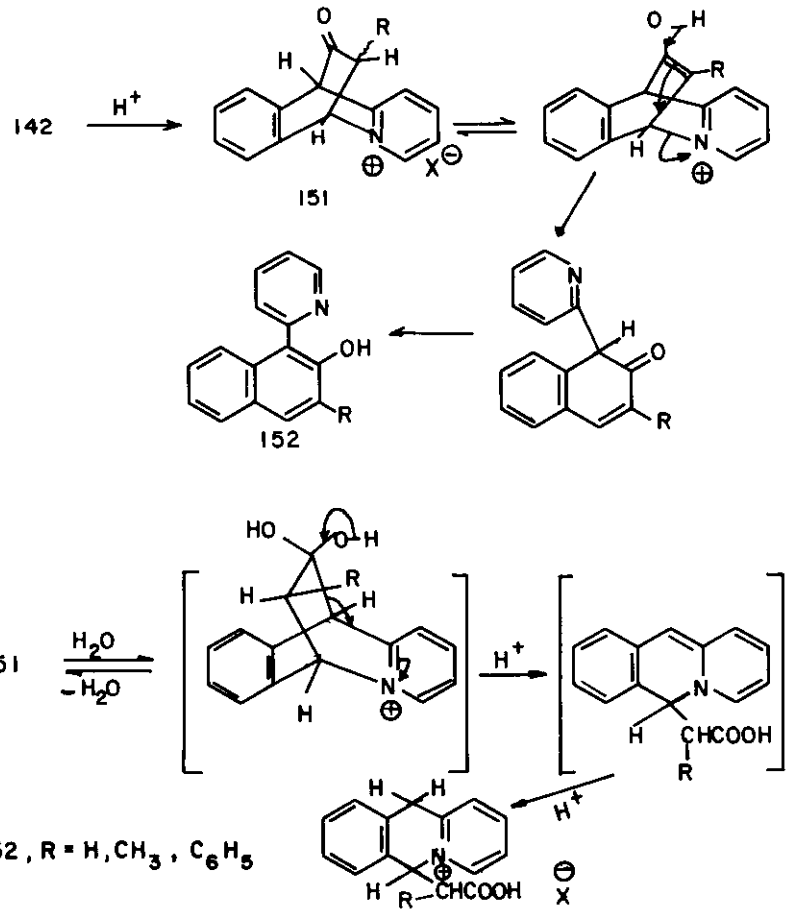
yield [103].



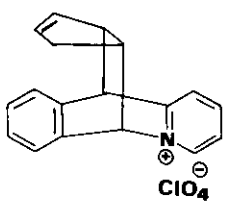
Field and Miller [104] have shown that cycloaddition occurred across the meso position of quinone derivatives (147) and (148) with excess cyclopentadiene but in both instances there was a second addition involving the quinone ring yielding what were believed to be 149 and 150 respectively.



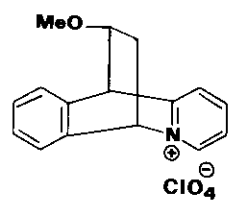
Bradsher and Day [85] have reported that in the cycloaddition of alkyl vinyl ethers and cyclopentadiene to the acridizinium ion, extreme stereoselectivity was observed. The product (153 and 154) obtained were shown to have syn configuration with respect to the phenylene ring [86]. These results are in agreement to those observed with the cycloaddition reactions of 2,3-dimethylisoquinolinium ion [87-89]. The results were distinctly different types of fragmentation to yield 1-(2-pyridyl)2-naphthols (151) and/or 9,10-(carboxymethyl)-4a-azoniaanthracene salts (152), the latter being the major product [84].



Contraary to the results obtained by Field et al.[81], Bradsher and Burnham [86] have reported

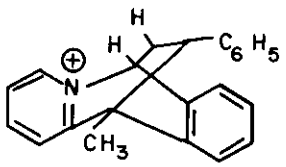


154

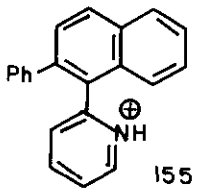


153

that the cycloaddition of less electron deficient acetylene derivatives could be made to succeed at higher temperatures. Although with phenyl acetylene, acridizinium ion yielded a rearranged product (155) similar to the one reported by Fields et al.[86] in the cycloaddition of dimorpholino-ethylene, but 11-methylacridizinium ion afforded the normal adduct (156) without any rearrangement thus demonstrating, that phenyl acetylene adds to 11-methylacridizinium ion with the same regio-specificity [90] as does styrene.

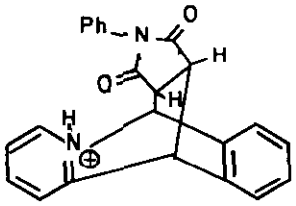


156

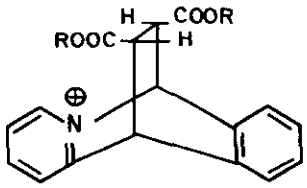


155

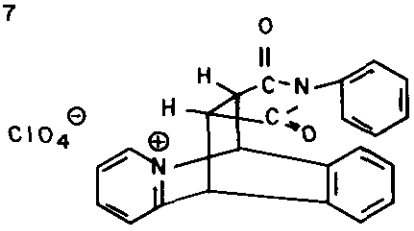
To find out any possible alteration in the stereochemistry of the cycloaddition of N-aryl-maleimides to the acridizinium ion by changing the polarity of the N-aryl group. Bradsher and Harvan [91] have observed that cycloaddition occurs stereospecifically anti with regard to the benzenoid nucleus. The maleimide adduct (157) on heating with 48% hydrobromic acid yielded a trans-diacid (158) whereas pyrolysis afforded the derivative of N-aryl-1-(2-pyridyl)naphthalene-2,3-dicarboximide (159).



157

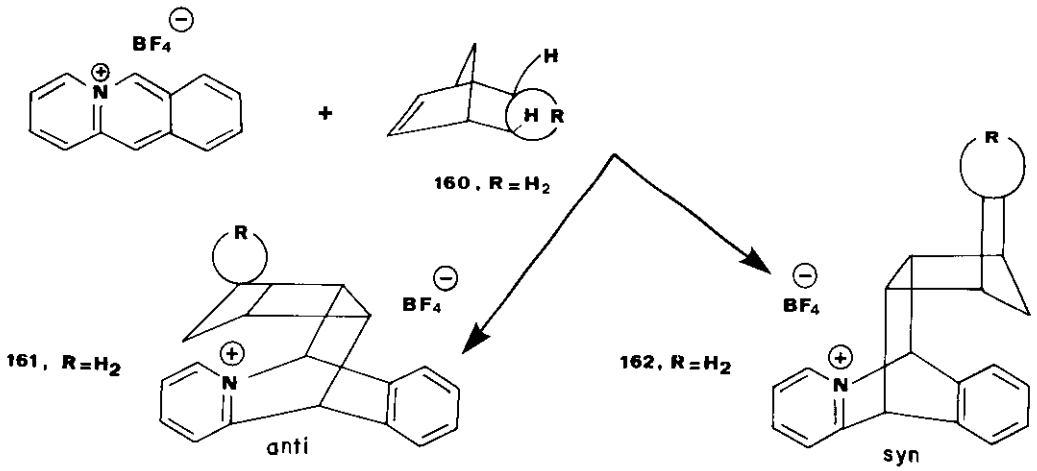


158

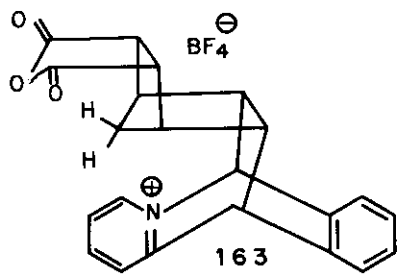


159

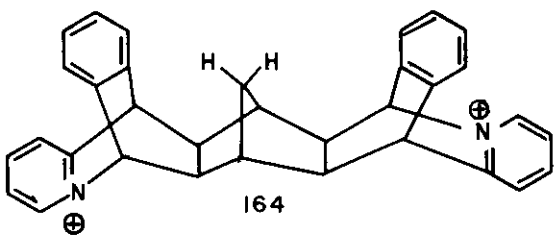
Addition of the acridizinium ion to norbornene (160) gave an exo addition proudct (161) and (162). Norbornene derivatives which had an endo ring attached at position 5 and 6 gave predominantly syn addition with respect to benzenoid ring, the highest yields were obtained, when hetro atom was in the ring. This stereoselectivity has been attributed to the attraction of the unshared electrons available on the central atom of the endo ring to the positive charge of the acridizinium nitrogen. Norborene-exo-5,6-dicarboxylic anhydride on the other hand gave a



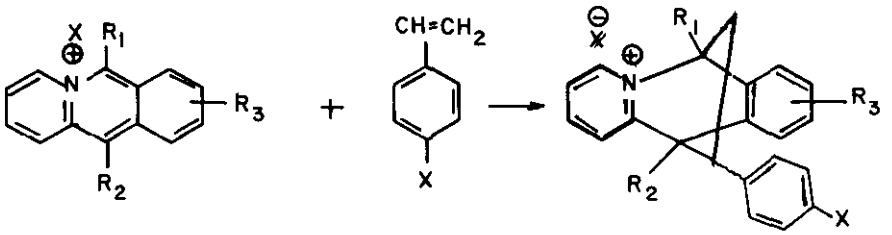
mixture from which a pure anti adduct (163) was isolated in an overall yield of 15%.



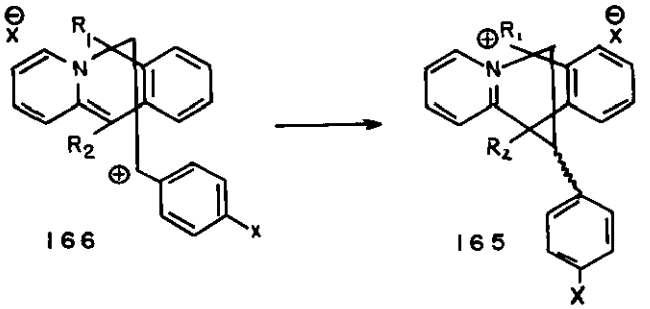
Addition of two moles of acridizinium ion to norbornadiene afforded the syn, syn diadduct (164) in 15% yield [92].



The classical paper of Sauer and Wiest [93] concerning the existence of Diels-Alder reactions with inverse electron demand first made it possible to understand, how a cation could function as a "diene". Acridizinium ion does not undergo cycloaddition with the electron deficient tetracyanoethylene but does react with the electron rich styrene. Synthetic [81] and kinetic [83] evidence has shown beyond doubt that the ion functions as the electron deficient species. Rates of addition of para substituted styrene to the acridizinium ion follows the inverse electron demand pattern, p-nitrostyrene being slowest and p-methoxystyrene being fastest in the series.

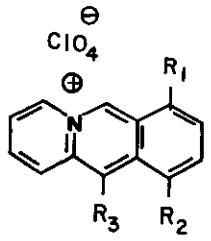


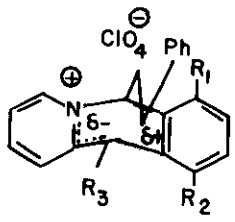
The formation of an adduct (165) was rationalised by suggesting the formation of a benzylic carbonium ion (166) as an intermediate which could then cyclise by attack of the electrons at position 11, suggesting further that the reaction occurs through a regiospecific reaction [83].

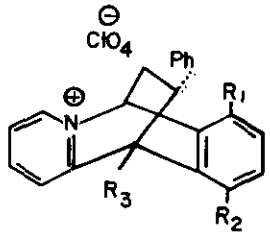


166 165

With a substituent at position 9 in the acridizinium ion where by resonance effects could not be readily transmitted to position 6, while steric effects would be minimized, the rate of addition of styrene was shown to be accelerated by electron withdrawing substituents and the rates afforded a significant Hammett plot [94]. It was also explained that the 9-substituents affected the cycloaddition rate by altering the availability of the positive charge at position 6 of the acridizinium ion. On the other hand, acrylonitrile was shown to be somewhat less responsive to polar influences than styrene, but reacted by the same mechanism involving an electrophilic attack upon the alkene by the positively charged 6-position of the acridizinium nucleus. The introduction of a methyl group at 6-position of the acridizinium ion was shown to slow the reaction significantly. On the other hand introduction of a methyl group at position II produced over a 13 fold increase in the rate of cycloaddition with styrene [84]. This must be due to the fact that the methyl at position II is under strain as the result of peri interaction with adjacent hydrogens and that this strain is relieved when the methyl group moves out of plane during cycloaddition (167) [89]. For further proof of this explanation rate of cycloaddition with 7,10,11-trimethylacridizinium ion was studied and it was found that the rate of cycloaddition with styrene [96] was more than ten times that of the 11-methyl derivative and this result was taken as a direct evidence of steric acceleration [97] rather than electronic in origin [98]. Similar results were obtained with anthracene derivatives [99], where the introduction of methyl groups into both of the meso positions of anthra-







167

a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = H$, $R_3 = Me$
c, $R_1 = R_2 = R_3 = Me$

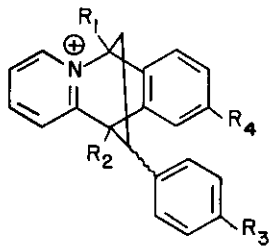
cene resulted in a 218-fold acceleration of the rate of cycloaddition with maleic anhydride, while methoxyl groups at the same positions resulted in decrease in rate. It has also been clarified that the decrease in rate is not due to the impaired coplanarity but more likely due to the greater effective size of the methyl group, which is actually more responsible for the rapid rate of cycloaddition for 9,10-dimethylanthracene. The rates of cycloaddition of various dienophiles are given in Table VIII.

The presence of a methyl group at position II of the acridizinium ion causes an enhancement in the rate of cycloaddition, but similar enhancement in the rate at the other meso position is not seen, which has now been attributed to the electron deficiency, which is reponsible for an entropy effect large enough to overwhelm any steric acceleration expected from the relief of a peri strain [104]. Arrhenius activation energy measurements have further shown, that the energy of activation for the formation of the styrene cycloadduct from 6-methylacridizinium ion was actually lower by I.I.K cal/mol than that for the similar reaction of the acridizinium ion. Similarly large negative entropy activation (-37.6 eu) for a methyl group at position 6 in comparison with a less important entropy factor (- 34.7 eu) for a methyl group at position II supports the evidence *concerning the importance of position 6 in the rate determining step of cycloaddition of acridizi*nium salts.

As regards the mechanism of cationic polar cycloaddition spectroscopic evidence has indicated that the acridizinium ion form charge transfer complexes with donor molecules. Analysis of the second order rate constant for the cycloaddition of N-vinylcarbazole with the acridizinium ion has also shown a decrease in the rate constant with increased concentration of N-vinylcarbazole. These data have been interpreted as evidence of a charge transfer complex in the reaction mixture. The differences in the energies of activation for reaction via the regiosomeric and stereomeric transition states must in most cases arise from differences in the polar influences lying along the reaction pathway which must include the initial frontier orbital interaction [105].

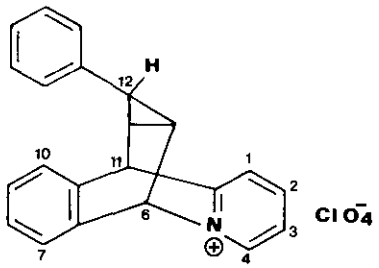
TABLE VIII

Rate of Cycloaddition of Styrene to Acridizinium Perchlorate

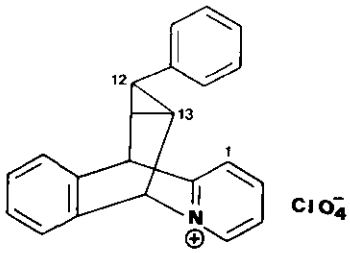


R_1	R_2	R_3	R_4	Rate K, $min^{-1}x10^{-3}$	Ref.
H	H	OCH_3	H	18 ± 1	83
CH_3	H	OCH_3	H	5.7 ± 0.2	83
H	CH_3	OCH_3	H	180 ± 10	83
CH_3	CH_3	OCH_3	H	93 ± 6	83
H	H	CH_3	H	8.1 ± 0.2	83
CH_3	H	CH_3	H	3.2 ± 0.2	83
H	CH_3	CH_3	H	94 ± 2	83
CH_3	CH_3	CH_3	H	57 ± 4	83
H	H	H	H	5.0 ± 0.1	83
CH_3	H	H	H	2.5 ± 0.2	83
H	CH_3	H	H	68 ± 3	83
CH_3	CH_3	H	H	43 ± 1	83
H	H	NO_2	H	2.3 ± 0.3	83
CH_3	H	NO_2	H	1.8 ± 0.3	83
H	CH_3	NO_2	H	36 ± 5	83
CH_3	CH_3	NO_2	H	30 ± 2	83
H	H	H	Me	2.0 ± 0.1	94
H	H	H	$CH(Me)_2$	2.8 ± 0.1	94
H	H	H	H	5.0 ± 0.2	94
H	H	H	F	5.4 ± 0.2	94
H	H	H	I	10.6 ± 0.6	94
H	H	H	Cl	10.1 ± 0.5	94
H	H	H	Br	11.2 ± 0.8	94
H	H	H	COOH	18.1 ± 0.7	94
H	H	H	COOMe	24.7 ± 1.0	94
H	H	H	NO_2	105 ± 0.5	94

NMR studies of a large number of adducts obtained from the acridizinium ion, Field et al [81] concluded that both syn and anti addition products has occurred in every case. However separation of syn and anti addition products had never been achieved. Bradsher and Westermann [106] were the first to achieve such separation in case of styrene adduct (168 and 169) by fractional crystallisation using I-butanol as a solvent.



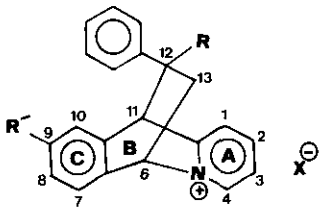
168, Syn isomer, m.p. 245-47°



169, anti isomer, m.p. 203-204°

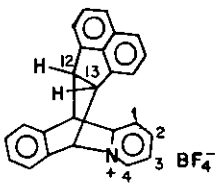
Syn isomer (168) which was least soluble was found to be the major one. NMR studies of these two isomers showed the signals for two aromatic protons at an unusually high field δ 6.5-6.8. These shielded aromatic protons were attributed to the phenyl group at position 12 atop the bridge and results from the two ortho hydrogens sweeping through the π cloud of the phenylene or the pyridinium ring. Another signal useful for distinguishing stereoisomers was the C-4 signal which occurs downfield and is easily identified and measured. In the anti isomer (162), C-12 phenyl group is positioned correctly to shield the 13-b proton and this shielding edge of the phenyl group is directed towards the pyridinium ring. This contribution is significant in that the C-4 hydrogen in the anti isomer is centered at δ 9.20, whereas the corresponding syn absorbance occurs at δ 9.7. Some of these differences in the NMR spectra have been used in identifying the syn and anti adducts in case of p-methoxystyreneacridizinium adducts on the basis of their ABMXY patterns, making it possible to assign to the anti isomer the methoxy signal occurring at the lower field. On a similar basis an adduct obtained from p-methylstyrene and the acridizinium ion revealed that the methyl group at lower field was that of the anti isomer, whereas in an adduct of α-methylstyrene and acridizinium ion, the C-12 methyl group was positioned above the pyridinium ring (170). Its signal appeared at a lower field than that of a stereoisomer in which the methyl group was over a phenylene ring. Integration of the signals showed that 64% of the methylstyrene adduct had the phenyl

170 R=H; R=Me
171 R=Me; R=H



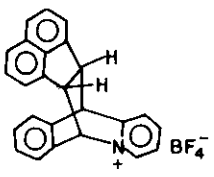
group in the syn position (170).

With an adduct of styrene and 9-methylacridizinium ion, two distinct methyl resonances were observed. The higher intensity one was identified due to the syn isomer (172) as this isomer can produce the maximum shielding. With the syn isomer, this shielding is magnified when the aryl group is constrained in a rigid configuration as in case of acenaphthalene adduct (173 and 174) in which case C-4 proton signal for the anti isomer (173) appeared at τ 8.35 compared to the high



173

m.p 272 – 274°



174

m.p 304 – 304·5°

melting syn isomer (174) with the value for the C-4 proton at τ 9.13.

These differences in NMR spectra have been utilised in determining the isomeric composition of about 25 unseparated mixtures.

BIBLOGRAPHY

1. A Baeyer, Ann., 155, 321, 1870
2. S. Hoogeworf and W.A. Van Dorp, Rec. Trav. Chim., 5, 305, 1886
3. W.H. Perkin Jr., J. Chem.Soc., 113, 492, 1918
4. W.H. Perkin Jr., and J.H. Ray, J.Chem.Soc., 127, 740, 1925.
5. R.D. Haworth, W.H. Perkin and J.Rankin, J.Chem.Soc., 125, 1686, 1924.
6. J.S. Buck and W.H. Perkin Jr.,J.Chem.Soc., 125, 1675, 1924.
7. R.D. Haworth, J.B. Koepfil and W.H. Perkin Jr., J.Chem.Soc., 548, 1927.
8. E.Spath and E. Mosettig, Ber., 60, 383, 1927.
9. E. Spath and E. Mosettig, Ber., 58, 2133, 1925.
10. E. Spath and K.Posega, Ber., 62, 1029, 1929.
11. T.A. Henry, The Plant Alkaloids, "4th Eidtion, Blakiston Co., Philadelphia, Penna, 1949,p 344.
12. J.B. Koepfil and W.H. Perkin Jr., J.Chem.Soc., 2989, 1928.
13. R.F. Manske, Can.J.Research, 218, 111, 1943.
14. R.B. Woodward and W.M. Mclamore, J.Am. Chem. Soc., 71, 379, 1949.
15. V. Boekelheide and W.G. Gall, J.Am. Chem. Soc., 76, 1832, 1954.
16. C.K. Bradsher and L.E. Beavers, J. Am. Chem. Soc., 77, 4812, 1955.
17. R.E. Doolittle and C.K. Bradsher, J. Heterocyclic Chem., 2, 399, 1965.
18. Chem. Abstr., 50, 366, 1956.
19. Report of the IUPAC Nomenclature Committee, J. Am.Chem.Soc., 82, 5572, 1960.
20. C.K. Bradsher and L.E. Beavers, Chem. and Ind., 1394, 1954.
21. C.K. Bradsher, T.W.G. Solomons and F.R. Vaughan, J. Org.Chem., 25, 757, 1960
22. C.K. Bradsher and J.C. Parham, J. Org. Chem., 28, 83, 1963.
23. C.K. Bradsher and J.C. Parham, J. Heterocyclic Chem., 1, 30, 1964.
24. C.K. Bradsher and L.E. Beavers, J.Am.Chem.Soc., 78, 2459, 1956
25. C.K. Bradsher and T.W.G. Solomons, J.Am.Chem.Soc., 82, 1808, 1960.
26. C.K. Bradsher and T.W.G. Solomons, J.Org. Chem., 25, 191, 1960.
27. C.K. Bradsher and T.W.G. Solomons, J.Am.Chem. Soc., 81, 2550, 1959.
28. C.K. Bradsher and J.C. Parham, J. Heterocyclic Chem., 1, 121, 1964.
29. C.K. Bradsher and J.C. Parham, J. Heterocyclic Chem., 8, 157, 1971.
30. C.K. Bradsher and J.P. Sherer, J. Org.Chem., 32, 733, 1967.
31. C.K. Bradsher and T.W.G. Solomons, J.Org.Chem., 24, 589, 1959.
32. W. Schneider and K. Schroeter, Ber., 53 B, 1459, 1920.
33. W. Schneider and K. Schroeter, Ber., 54B, 2021, 1921.

34. C.K. Bradsher and J.H. Jones, J.Org. Chem., 25, 293, 1960.

35. R.B. Woodward and B. Witkop, J. Org.Chem., 14, 397, 1949.

36. A. Richards and T.S. Stevens, Chem. and Ind., 905, 1954.

37. R.B. Woodward and W.M. Mclamore, J.Org. Chem., 14, 379, 1949.

38. A. Richards and T.S. Stevens, J. Chem.Soc., 3067, 1958.

39. C.K. Bradsher, Chem., Revs., 38, 447, 1946.

40. C.K. Bradsher and J.H. Jones, J.Am. Chem. Soc., 79, 6033, 1957.

41. J.W.H. Watthey, K.J. Doebel H.F. Vakay and A.L. Lopano, J.Org. Chem., 38, 4170, 1973.

42. S.M. Kupchan, G.R. Flouret and C.A. Matuszak, J.Org. Chem., 31, 1707, 1965.

43. C.K. Bradsher and M.W. Barker, J.Org. Chem., 29, 61, 1964.

44. D.L. Fields, J.B. Miller and D.D. Reynolds, J.Org. Chem., 30, 252, 1965.

45. C.K. Bradsher and J.H. Jones, J.Org.Chem., 23, 430, 1958.

46. C.K. Bradsher and N.L. Dutta, J.Am. Chem. Soc., 82, 1145, 1960.

47. Wolfgand Augstein and C.K. Bradsher, J.Org. Chem., 34, 1349, 1969.

48. C.K. Bradsher and N.L. Dutta, J.Org. Chem., 26, 2231, 1961.

49. C.K. Bradsher and R.B. Desai, Recueil, 83, 593, 1964.

50. C.K. Bradsher and H. Berger, J.Am. Chem.Soc., 80, 930, 1958.

51. C.K. Bradsher and J.H. Umans, J.Org. Chem., 28, 3070, 1963.

52. C.K. Bradsher and E.F. Litzinger Jr., J. Org. Chem., 29, 3584, 1964.

53. C.K. Bradsher and N.L. Yarrington, J.Org. Chem., 28, 78, 1963.

54. A.P. Gray, W.L. Archer, E.E. Spinner and C.J. Cavaihto, J.Am.Chem.Soc., 72, 3805, 1972.

55. A.P. Phillips, J. Am.Chem. Soc., 79, 575, 1957.

56. C.K. Bradsher and N.L. Yarrington, J.Org. Chem., 28, 78, 1963.

57. C. K. Bradsher and J.P. Sherer, J. Org. Chem., 32, 733, 1967.

58. C.K. Bradsher and L.S. Davies, J.Org. Chem., 38, 4167, 1973.

59. A.R. Collicut and G. Jones, J.Chem.Soc., 4101, 1960.

60. M.V. Bhatt, Experientia, 13, 70, 1957.

61. L. Wolff, Justice Liebigs Ann. Chem., 322, 351, 1902.

62. C.K. Bradsher and M.W. Barker, J.Org. Chem., 28, 1669, 1963.

63. C.K. Bradsher, L.L. Braun, J.D. Turner and G.L. Walker, J.Org.Chem., 39, 1157, 1974.

64. L.A. Paquette, Chem. and Ind., 1292, 1962.

65. C.K. Bradsher and M.W. Barker, J.Org. Chem., 29, 452, 1964.

66. L.L. Braun and C.K. Bradsher, J.Org.Chem., 33, 1296, 1968.

67. C.K. Bradsher and N.L. Yarrington, J.Org.Chem., 25, 294, 1960.

68. C.K. Bradsher and L.E. Beavers, J.Org.Chem., 22, 1740, 1957.

69. C.K. Bradsher and N.L. Yarrington, J. Am.Chem.Soc., 81, 1938, 1959.

70. A. Fozard and G. Jones, J. Chem. Soc., 2203, 1963.

71. A. Fozard and G. Jones, J.Chem.Soc., 2760, 3030, 1964.

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

73. C.K. Bradsher and J.D. Turner, J. Org. Chem., 32, 1169, 1976.

74. K.H. Meyer and K. Zahn, Ann., 296, 166, 1913.

75. E. Barnett, J.W. Cook and H.H. Grainger, J. Chem.Soc., 121, 2059, 1922.

76. C.K. Bradsher and R.C. Coreley, J. Org. Chem., 28, 1396, 1962.

77. O. Diels and K. Alder, Ann., 486, 191, 1913.

78. W.E. Bachmann and M.C. Kloetzel, J. Am. Chem. Soc., 60, 481, 1938.

79. E. Clar, Ber., 64, 2194, 1913.

80. C.K. Bradsher and T.W.G. Solomons, J. Am.Chem. Soc., 80, 933, 1958.

81. D.L. Fields and T.H. Regan and J.C. Dignan, J.Org. Chem., 33, 390, 1968.

82. C.K. Bradsher and J.A. Stone, J. Org. Chem., 33, 519, 1968.

83. C.K. Bradsher and J.A. Stone, J. Org. Chem., 34, 1700, 1968.

84. D.L. Fields and T.H. Regan, J.Org. Chem., 35, 1870, 1970.

85. C.K. Bradsher and F.H. Day, J. Heterocyclic Chem., 10, 1031, 1973.

86. W.S. Burnham and C.K. Bradsher, J. Org.Chem., 37, 355, 1973.

87. C.K. Bradsher, F.H. Day, A.T. Mcphail and Pui Suen Wong, J.Chem. Soc., Chem. Comm., 156,1973.

88. C.K. Bradsher, C.R. Miles, N.A. Porter and I.J. Westerman, Tetrahedron Lett., 4969, 1972.

89. C.K. Bradsher, F.H. Day, A.T. Mcphail and Pui Suen Wong, Tetrahedron Lett., 4205, 1971.

90. A. Hassner, J. Am. Chem. Soc., 90, 216, 1968.

91. C.K. Bradsher and D.L. Haravan, J. Org. Chem., 36, 3778, 1971.

92. M.E. Parham, M.G. Frazer and C.K. Bradsher, J.Org. Chem., 37, 358, 1972.

93. J. Sauer and H. Wiest. Angew. Chem., 74, 353, 1962.

94. J. Westermann and C.K. Bradsher, J. Org. Chem., 36, 969, 1962.

95. T.G. Wallis, N.A. Porter and C.K. Bradsher, J.Org. Chem., 38, 2917, 1973.

96. C.K. Bradsher, N.A. Porter and T.G. Wallis, J.Org. Chem., 39, 1172, 1973.

97. J.H. Bennett and T. Okamotos, J. Am. Chem.Sco., 78, 5363, 1956.

98. C.K. Bradsher, Advan. Heterocycl. Chem., 16, 289, 1973.

99. J. Sauer, D. Lang and A. Mielert, Angew. Chem., Int.English Edition, I, 268, 1962.

100. D.L. Fields and T.H. Regan, J. Org.Chem., 36, 2986, 1976.

101. D.L. Fields and T.H. Regan, J.Org. Chem., 36, 2991, 1971.

102. D.L. Fields, T.H. Regan and R.E. Graves, J. Org. Chem., 36, 2995, 1971.

103. D.L. Fields, J. Org. Chem., 36, 3002, 1971.

104. C.K. Bradsher, T.G. Wallis, I.J. Westermann and N.A. Porter, J. Am. Chem. Soc., 99, 2588, 1977.

105. C.K. Bradsher, G.L.B. Carlson, N.A. Porter, I.J. Westermann and T.G. Wallis, J.Org. Chem., 43, 822, 1978.

106. I.J. Westermann and C.K. Bradsher, J. Org. Chem., 44, 727, 1979.

Received, 21st June, 1980