PROTON MAGNETIC RESONANCE SPECTRA OF ACRIDIZINIUM ADDUCTS

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The structural determination of the acridizinium adducts using the technique of nuclear magnetic resonance has been discussed in detail.

The classical 4+2 Diels-Alder reaction involves the thermally allowed cycloaddition of an electron rich diene with an electron-deficient dienophile. In 1962 Sauer and Wiest[1] demonstrated the existance of a "Diels-Alder reaction with inverse electron demand", in which the electronic roles are exchanged with the former becoming the electrophile and the latter the nucleophile. However, the existance of an actual positive charge on the electrophilic species in cationic polar cycloaddition distinguishes it from the other types of cycloaddition and make it at best, a limiting case of the "Diels-Alder with inverse electron demand.

In particular, the formal + charge present in polar cycloaddition would be expected to influence the formation and geometry of intermediate charge-transfer complexes and the electrophilic character of the reaction with alkenes. These effects would naturally result in having an important influence upon the region and stereochemistry as well as the concertedness[2] of polar cycloaddition.

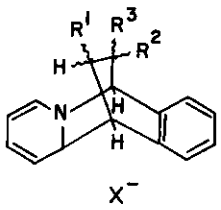
The acridizinium ion (1) used in the first polar cycloaddition reaction of a quaternary salt[3] has been used in the largest number of polar cycloaddition studies. This cation is particularly suitable for such a study since it is easily prepared, is stable and sufficiently reactive to react with many poorly nucleophilic alkenes. Fields et al.[4] have demonstrated that experiments carried out at different temperatures and in different solvents are adequate to prove the inverse electron demand character of the reaction. Thus ketene diethyl acetal, reacted in minutes at room temperature, while the strongly electrophilic alkene, tetracyanoethylene, failed to react under any conditions.

Fields et al.[4] have also shown that a variety of unsymmetrical alkenes (Table 1) added regiospecifically to the acridizinium nucleus, which was rationalised by the assumption that the more negatively polarised end of the alkene was preferentially attracted towards position 6, the previously demonstrated[5] center for nucleophilic attack on the acridizinium ring. At the same time, they reported the addition of acrylonitrile to yield a 12- rather than a 13-cyano adduct is the reverse of what would be expected

from the polarisation of the acryionitrile molecule.

ADDUCTS OF ACRIDIZINIUM ION AND DIENOPHILES

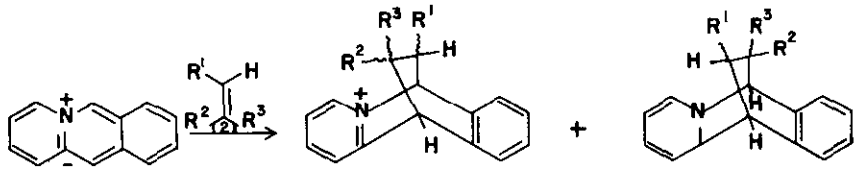
TABLE 1.



Adduct	R_1	R_2	R_3
3	H	Et	H
4	H	$CH = CH_2$	H
5	H	CH_2OH	H
6	H	CN	H
7	H	Ph	N-morpholino [6]
8	H	Ph	H
9	H	$C = CH_2$ CH_3	CH_3
10	H	OEt	OEt [7]
11	CH_3	OEt	OEt [8]
12	Br	OEt	OEt [9]
13	C_6H_5	OEt	OEt [10]

Elucidation of the structure of various cycloadducts by nuclear magnetic resonance is simplified by the strong deshielding effect of the positively charged nitrogen atom. In case of an adduct formed the dienophiles (Table 1) the distinguishing feature of the nmr spectra of the adducts are the reasonances of the bridgehead protons (at C-9 and C-10) and of the proton to nitrogen on the pyridine ring (at C-3). Considering the variety of bridgehead substituents, the chemical shift of these protons fall in a fairly narrow range: C-4H, 9.37 + 0.01 (range 9.27-9.64); C-9H, 5.49 + 0.21 (range 5.22 - 5.86), C-10H, 6.63 + 0.14 (range 6.40 -6.95). The multiplicities of these signals are

diagnostic in a straight forward manner for the occurrence of both geometrical and positional isomerism. Expect for a few cases where broadening obscured the line splitting, the multiplicitiesindicated the presence of syn-anti isomer with no evidence for the positional isomers (eq. 1). Thus adducts 3-9 are believed to be solely 12-mono, or 12,

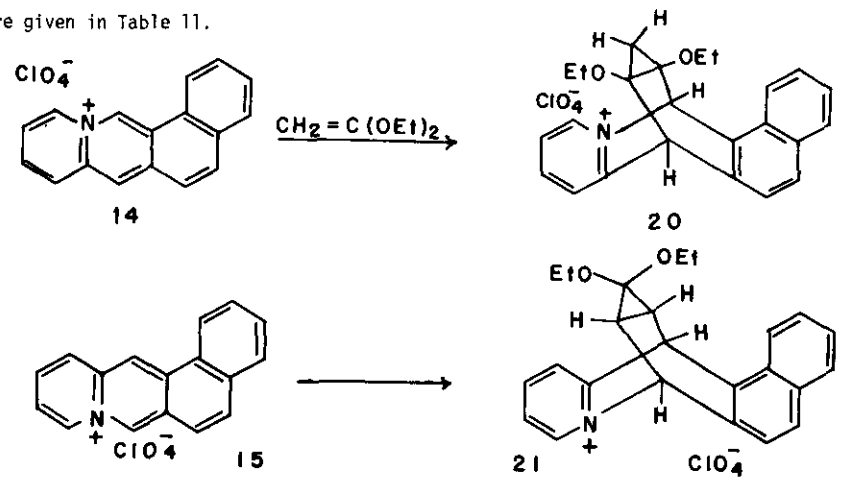


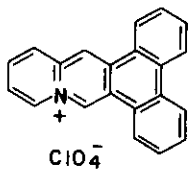
eq. I

12-disubstituted 9,10-dihydro-4a-azonia-9,10-ethanoanthracene salts, whereas the ketene acetal adducts, 10-13 are solely 12,12-diethoxy derivatives.

In one of the adduct (9), the nmr spectrum showed an absorption at δ 0.87 and 0.98 (s, of relative area 1:2) and at 1.80 and 1.83 (s, of similar but less easily measured relative areas). These are assigned to the 12-CH_3 and the allylic CH_3 respectively, the multiplicity arising from syn, anti isomerism. Two multiplets centred at 2.17 and 2.42 are assigned as the center strong peaks of the AB part of an ABX spectrum; the outer weak lines are obscured by the allylic CH_3 peaks on the one side and the residual DMSO-d_5 peaks on the other side. The total pattern represents the absorption of the bridge methylene (C-11) and the bridgehead proton at C-10. The vinyl = CH_2 absorption is a pair of broad singlets at 4.57 and 4.69. The C-9 bridgehead is a sharp singlet at 5.30. The aromatic protons absorb in a complex multiplet extending from 7.2 to 8.8, the pyridyl proton α to nitrogen appears as a complex multiplet centred at 9.3.

Cycloadducts obtained from 14-19 were produced from rapid stereospecific cycloaddtions of ketene diethyl acetal, each giving an adduct having the ethoxyl group, in a position nonadjacent to the quaternary nitrogen. Nmr analysis of the adducts (20-25) are given in Table 11.





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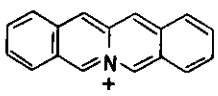

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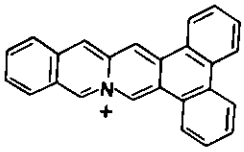

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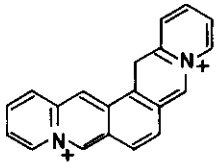

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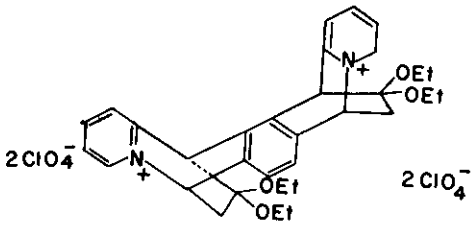

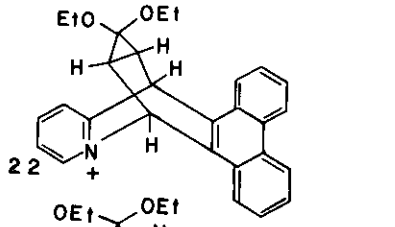

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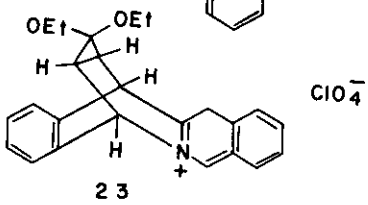

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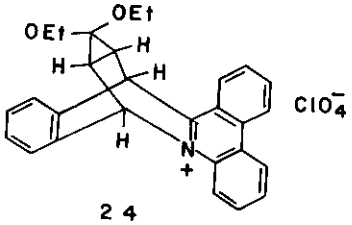

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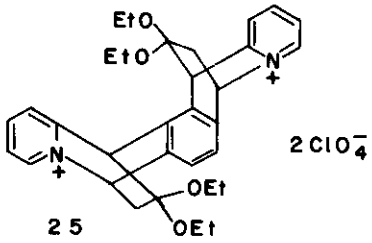

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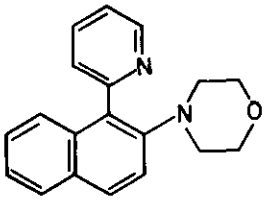
TABLE II

Compound number	Bridgehead proton δ, ppm (multiplicity) [a]
20	... [b], 6.00(s)
21	6.85(m), 6.53(s)
22	.... [b], 6.60(s)
23	6.70(m), 5.00(s)
24	6.80(m), 5.67(s)
25	6.63(m), 6.01(s)

a. The peaks described as m are, in most cases very broad singlet peaks, the broadening being ascribed to unresolved multiplicity. b. This signal is buried in the aromatic multiplet as indicated by area measurements.

The product isolated from 1,1-dimorpholinoethylene and acridizinium ion proved to be not a 1:1 adduct, but rather, the new 2-morpholino-1-(2-pyridyl)napthalene (26). Its nmr spectrum ($CDCl_3$) had a four proton A_2B_2 pattern centred at δ 3.13 (morpholino), a nine proton



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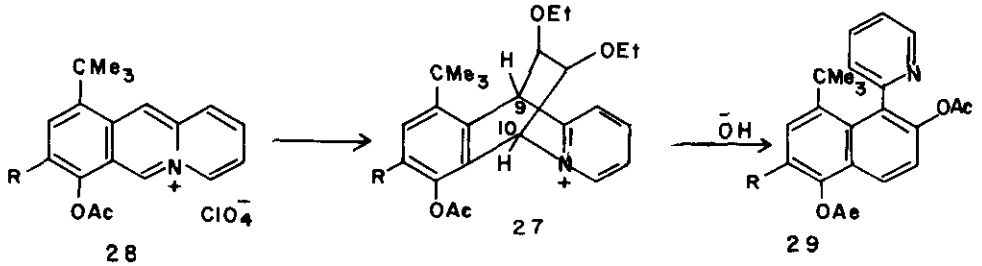
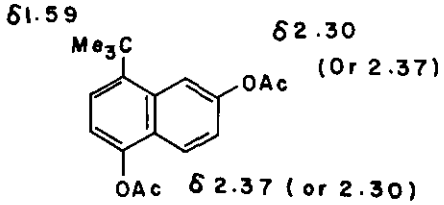
multiplet (aromatic) at δ 7.0-8.0, and the proton to nitrogen as a doublet of multiplet at 8.73.

In an adduct (27) obtained from ketene diethyl acetal and acridizinium salt (28), the stereochemistry of the addition was confirmed by nmr spectroscopy, based on the multiplicities of the bridgehead hydrogen i.e. H-9, a singlet at δ 6.05 and H-10 a broadened triplet at



δ 6.67 (DMSO- d_6)[11]. Mild hydrolysis of the adduct 27 yielded 29. The salient features of its nmr spectrum included two AB quartets (3,4 and 6,7-naphthalene protons) in the aromatic

region superimposed on the pyridyl proton absorptions and the usually high field positions for the tert-butyl and one of the two acetoxy-methyl signals (0.6 and 0.3 ppm) higher field respectively than those of the analogous model compound 30.



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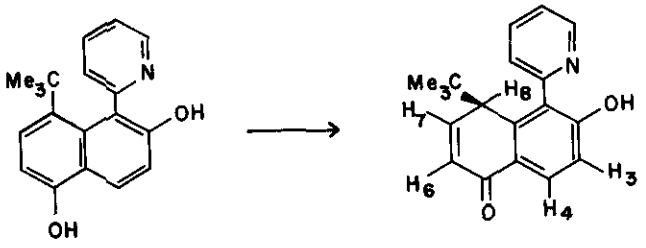
Such upfield shifts would result if the gross overcrowding is accomodated by bond angle deformations, so that the tert-butyl and pyridyl groups are bent away from one another above and below the naphthalene ring with the pyridine rotated further out of the plane to a degree that helps to minimize its interaction with the tert-butyl group as well as the two acetoxy groups. In this conformation, the tert-butyl group would lie outside the zone of maximum deshielding of the naphthalene, and both it and the 2-acetoxy group would reside in the shielding zone of the pyridine ring as well.

Low temperature nmr spectra of 29 was examined in the hope that the high degree of steric interference would lead to restricted rotation of the tertiary butyl groups, a phenomenon which has been observed in considerably less sterically crowded molecules [12-14] at -86°, the absorption of the tert-butyl group of 29 had broadened considerably (w 1/2 13 Hz compared to w 1/2 0.8 Hz for TMS at -100°) but was still symmetrical. That at least part of the broadening was due to restricted position of the tert-butyl group was indicated by the fact that the acetate methyls were broadened only approximately one third as much as the tert-butyl peak.

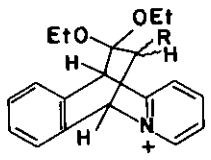
On the other hand, deacetylation without accompanying loss of tert-butyl substituent was easily achieved under basic conditions and from a reaction of 29 with methanolic potassium hydroxide, a crystilline product 31 was isolated. Most definitive evidence for its structure



31 32

was the spectral evidence derived from nmr measurements. The tert-butyl signal was observed as a sharp singlet at 0.55 ppm, a field position more in keeping with a tert-butyl group attached to an sp^3 than an sp^2 carbon. The remaining absorptions completely consistent for 31 were observed at δ 4.3(d, 1H,J=5.5 Hz, H_8), 6.47(d,1H, J=10 Hz,H_6), 7.03(d,1H,J=8.5Hz,H_3), 7.21 and 7.27(d of d, J = 5.5, 10 Hz, H_7), pyridyl proton multiplets at 7.50 and 7.85(2H,H_3 and H_4 protons). The coupling assignment for H_5, H_7 and H_8 were confirmed by double irradiation experiments. Coupling between H_8 and H_6 is so small as to be barely observable. It was this evidence which eliminated the structure 32 for the isolated compound.

Field and Regan[15] have also reported the formation of an adduct 33 from acridizinium perchlorate and ketene diethyl acetal. Treatment of the adduct with 6 N hydrochloric acid resulted in the formation of two products 34 and 35. The minor product proved to be a



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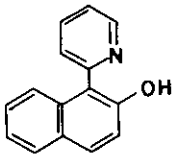

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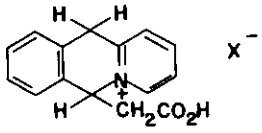

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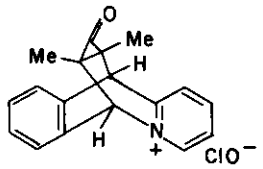
naphthol (34), which in nmr($CDCl_3$) consisted of a nine proton multiplet at δ 7.17-8.35(aromatic), one proton doublet of multiplets centred at 8.70(pyridyl H to N), and one exchangeable proton at δ 11.91 (-OH). The chemical shift of the hydroxyl proton is independant of concentration, indicative of molecular hydrogen bonding, which is consistent with the 1,2-substitution pattern assigned to 34.

The nmr (DMSO-d_6) of 35 displayed methylene proton to the carbonyl group and adjacent to the asymmetric center ($>CHCH_2COOH$) as four peaks centered at δ 4.68 representing the center strong peaks of the AB portion of an ABX pattern. The remaining absorptions appeared as a two proton singlet at δ 4.77 (α-picolinium methylene, a poorly resolved one proton triplet centered at δ 6.50 ($>CHCH_2COOH$), X part of ABX, a seven proton multiplet at δ 7.41 -8.80 (aromatic), and a one proton doublet of multiplets centred at δ 9.25 (pyridyl H to $\overset{+}{N}$).

Adduct 36 on the other hand on treatment with sodium methoxide resulted in the formation of an anhydro base (37), which on acidification with hydrochloric acid produced pyridinium salt (38).



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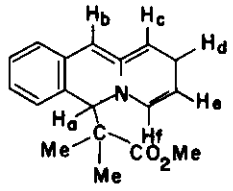

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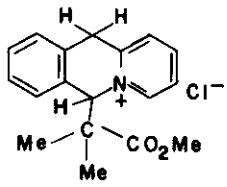

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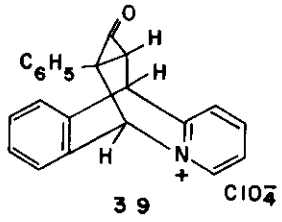
Nmr($CDCl_3$) of 37 displayed two methyl groups as singlet at δ 1.12 and 1.22, ester methyl as singlet at 3.65, H_a and H_b singlet at 5.13 and 5.17, H_f as doublet of multiplets at 6.50 and 4 aromatic protons as multiplet at 6.18-7.30. Similarly, the following value of the nmr spectra established the structure of 38.

δ 1.18 (s,6, gem-dimethyl), 3.63 (s, 3,ester methyl), 4,70 (broadened s, 2,C-9-methylene), 6.55 (s, 1, C-10 H), 7.38-8.79 (m, 7, aromatic H), and 9.25 (d,1, aromatic proton to $\overset{+}{N}$).

Cleavage of 39 with methanolic sodium methoxide also occurred rapidly at room temperature yielding an anhydro base 40 and naphthol 41 in 70 and 10% yeilds respectively.



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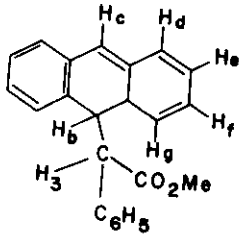

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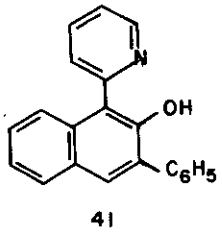

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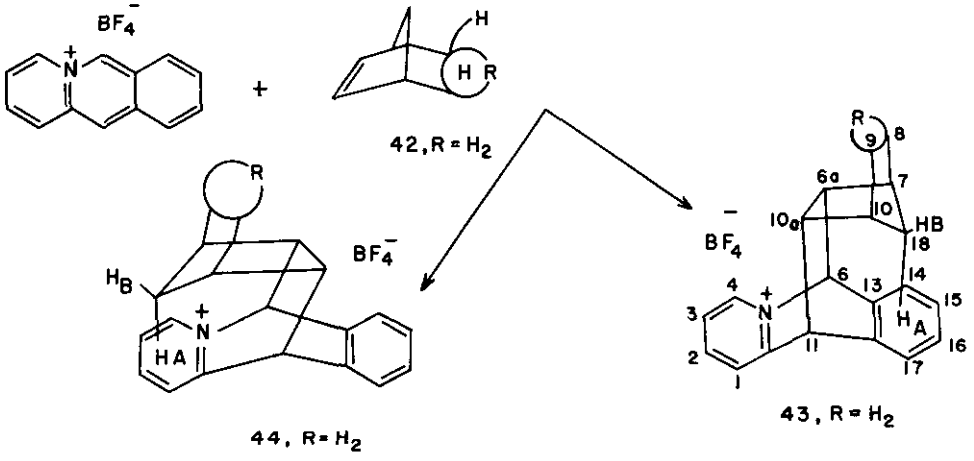
The nmr ($CDCl_3$) of 40 gave the following value [15].

δ 3.41 (s, 3, ester methyl), 4.25 (d, 1, J = 10 Hz, H_a) 4.73-5.00 (m, 1, H_f), 5.20 (broadened d, 1, J = 10 Hz, H_b), 5.35 (s, 1, H_c), 5.69-6.25 (m, 3, H_d, H_e, H_g) and 6.87-7.57 (m, 4, aromatic H).

Addition of acridizinium ion to norbornene (42) yields a mixture which, on the basis of nmr evidence,appears to contain only exo addition products. In the spectra of both components (43, 44) of the mixture, signals arising from one proton (H_A-18) of the proton methylene bridge appear at a magnetic field so high (above δ.00) as to be explicable only, if the protons were strongly shielded by diamagnetic ring currents of an aromatic ring[16].

In case of an adduct with cyclopentadiene [17], the H_A-18 signal at the highest field was a doublet at δ 0.85, which had approximately two-third of the area of the other H_A-18 doublet at δ -0.42. The assignment of the higher field doublet as anti (with respect to the benzenoid ring) was made by reducing the mixture of syn and anti (43, 44, R = H_2) catalytically. This would reduce the pyridinium ring only [18, 19] with the result that the strong shielding effect due to the ring current of the pyridinium ring would disappear, while due to the benzenoid ring would remain. The crude reduction product had lost the resonance at δ-0.85 (44, H_A-18) as well as another at δ 0.87(44, H_B-18). This made it possible to assign the isomer giving the signal at the highest field as the anti (44, R = H_2). In the syn isomer (43, R = H_2) protons on carbon 7 and 10 over the uncharged benzene ring are so similar in their environment that they have the same resonance and



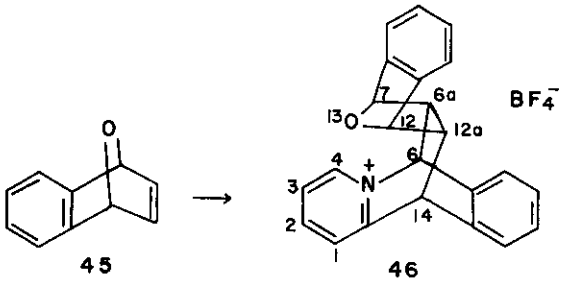
because the lack of coupling with protons 4 and 11 and with each other, appear to be magnetically equivalent. On the other hand bridgehead protons at 6a and 10a project towards the pyridinium ring and appear as quartets with different resonances, because of the different distances of the two protons from the positive charge.

The anti isomer 44 has bridgehead proton H -10 and H-7 over and at different distances from the quaternary nitrogen, and hence have resonance at different fields. On the other hand protons at 10a and 6a bridgehead positions are directed over the uncharged benzene ring and appear as a single singlet.

Using pure syn isomer, a doublet at δ 0.42 on irradiation resulted in the collapse of a doublet at δ 0.60 into a singlet. A similar collapse of the δ 0.42 doublet was observed when the signal at δ 0.60 was irradiated, indicating geminal coupling (J_{AB}=12Hz) of the 18_A and 18_B protons of the methylene group. Due to strong deshielding of bridgehead proton H-6, adjacent to nitrogen makes it easy to identify. With the syn isomer, irradiation of the signal at δ 6.30 due to H-6 caused the collapse of the quartet at δ 2.30 to a doublet identifying the signal for the proton at 6a. Irradiation of the other easily identifiable proton at position 11 caused a collapse of the quartet at δ 2.18 to a doublet and identified the signal due to the proton at 10a

Similar irradiation experiments with the anti isomer (44, R = H_2) revealed signals from H-6A and 10-HA as one singlet and those from H-7 and H-10 as singlets. It is significant that protons H-6 and H-11 are not coupled.

Addition of 1,4-dihydronaphthalene 14-endo-oxide (45) to the acridizinium nucleus resulted in the formation of an anti stereoisomer (46). Structural assignment of 46



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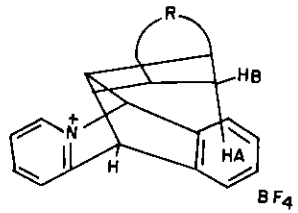
was based on the observation that the protons at 6a and 12a are equivalent (hence over the benzenoid ring) while those at C-7 and C-12 were not, indicating that one of the two was significantly closer to the positive charge on nitrogen and hence deshielded than the other. NMR results of the adducts are given in Table III.

In the cycloaddition product (47) obtained from N-arylmaleimides and the acridizinium ion, the nmr of the adduct (47) showed an expected doublet at approximately δ5.7 for the bridgehead proton at C-11 and 7.0 for the more strongly deshielded proton at C-6. Homonuclear spin decoupling studies with the N-(6-tolyl) derivatives (48) showed that irradiation of the signal at δ 7.0 caused the quartet at δ 4.6 to collapse to a doublet.

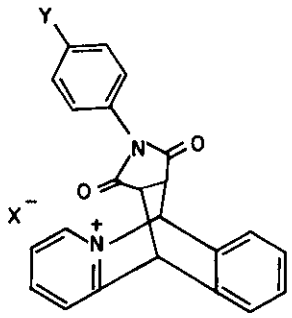


NMR DATA OF THE ADDUCTS FROM ACRIDIZINUM ION DIENOPHILES

Substituents ring R	Sample	H-18$_A$	H-18$_B$	H-10	H-7	H-10a	H-6a	H-11	H- 6
None	Syn	-0.82 (d)[a]	0.60 (d)[a]	8.27 (s)	2.18 (q)[g,h]	2.30 (q)[c,d]	2.30 (q)[c,d]	5.05 (d)[a]	6.30 (d)[d]
	Anti	-0.85 (d)[a]	0.87 (d)[a]	2.35 (s)	2.27 (s)	e	e	5.10 (s)	6.30 (s)
$(CH_2)_3$	Mixture	-0.32 (d)[a]	0.78 (d)[a]	e	e	e	e	5.03 (d)[f]	6.30 (d)[g]
CONHCO	Syn	-0.16 (d)[m]	1.10 (d)[a]	3.0 (m)	2.50 (q)[i,j]	2.50 (q)[i,j]	2.83 (q)[e,j]	5.20 (d)[i]	6.43 (d)[g]
$CON(CH_3)CO$	Syn	-0.10 (d)[a]	1.09 (d)[a]	e	e	2.27 (q)[g,h]	2.62 (q)[g,c]	5.20 (d)[b]	6.67 (d)[g]
COOCO	Syn	-0.05 (d)[a]	1.08 (d)[a]	2.97 (s)	2.97 (s)	2.30 (q)[l,m]	2.80 (q)[d,m]	5.20 (d)[b]	6.67 (d)[g]
CH_2OCH_2	Syn	-0.12 (d)[b]	0.94 (d)[b]	s	s	s	s	5.05 (d)[f]	6.30 (d)[g]
		-0.07 (d)[a]	1.10 (d)[b]	s	s	s	s	5.10 (d)[p]	6.37 (d)[e]
$CH_2NH_2CH_2$	Mixture	-0.53 (d)[q]	1.30(d)[b]	s	s	s	s	5.10 (d)[p]	6.37 (d)[o]

a. J_{AB} = 12 Hz. b. $J_{10a,11}$ = 3Hz. c. $J_{6,10a}$ = 10 Hz. d. $J_{6,6a}$ = 2Hz
e. Not clearly resolved. f. $J_{10a,11}$ = 3 Hz. l. $J_{10a,11}$ = 4 Hz.
g. $J_{6,6a}$ = 3Hz. o. J_{AB} = 12 Hz. i. $J_{10a,11}$ = 3 Hz. j
m. $J_{6a,10a}$ = 9 Hz. n. $J_{6a,6}$ = 2 Hz. q. $J_{6,6a}$ = 1 Hz
s. All data on this line is assigned to syn isomer. p. $J_{10a,11}$ = 1 Hz.

This allowed the assignment of the signal at δ 4.2 to be that of the proton at C-12 spin

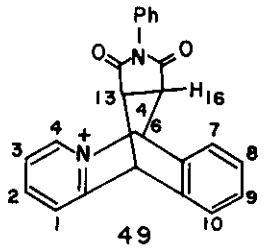


47, Y = H

48, Y = CH_3

coupled to C-11 (J = 3.5 Hz) and to C-16 (J = 7 Hz). The signal at δ 4.6 must arise from the C-16 protons, spin coupled to the proton, at C-6 and C-12.

Selective hydrogenation of 48 resulted in the formation of 49. The signal due to the

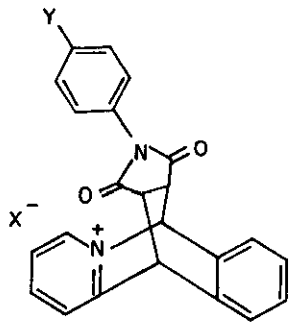


49

hydrogen at C-12 and C-16 remained virtually unchanged suggesting that they were over the intact benzene ring as represented in 49 rather than over the reduced pyridinium ring.

The nmr value of various such adducts are recorded in Table IV.

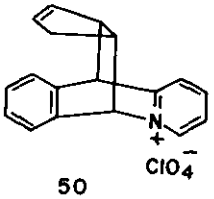
TABLE IV



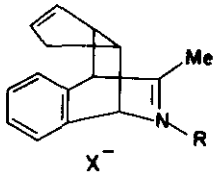
Y	Nmr(multiplicity)[a]				
	C-6	C-11	C-12	C-16	Others
H	7.75 (d)	5.75 (d)	4.27 (q)	4.73 (q)	
CH_3	7.00 (d)	5.77 (d)	4.20 (q)	4.60 (q)	2.34 (s)
Cl	7.00[b](d)	5.77 (d)	4.22 (q)	4.60 (q)	
OCH_3	7.00[b]	5.74 (d)	4.18 (q)	4.55 (q)	3.88
$N(Me)_3$	7.00[b]	5.74 (d)	4.20 (q)	4.60 (q)	3.66

a. Signals due to aromatic protons have been omitted. b. Overlapped signals.

Bradsher et al. [21] have reported that addition of cyclopentadiene to acridizinium ion gave a single isomer (50) as against the findings of Field et al. [4], who were unaware that the product 50 was a single geometrical isomer. The structure of the adduct was established by its nmr and by comparing the values of the protons to an adduct of dimethylisoquinolinium cyclopentadiene (51). Assignment of the resonance to the specific protons were made by spin decoupling experiments. Having close similarity in the coupling pattern and the chemical



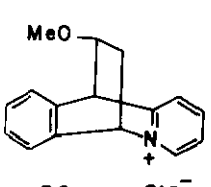
50



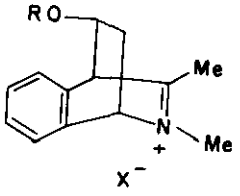
51

shift in 50 and 51, 50 was considered to be syn with respect to the phenylene ring (Table V).

Similarly, nmr spectra of the uncrystallised adduct revealed the presence of only a single geometrical isomer. Comparison of the nmr spectra (Table VI) of 52 with that of the adduct 53 of the known structure [22] obtained by reaction of methyl vinyl ether with 2, 3-dimethylisoquinolinium iodide, shows a remarkable similarity in the multiplicity and sequence of the signals consistent only with the assumption that the two compounds have similar stereochemistry.



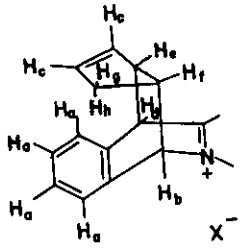
52 ClO_4^-



53

Teble V

Comparison of Chemical Shifts (δ) of Related Protons in Adduct of Cyclopentadiene with the Acridizinium Ion and the 2,3-Dimethylisoquinolinium Ion.

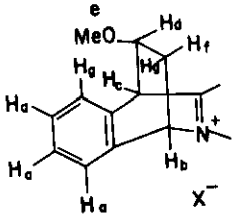


Acridizinium Adduct 50			Dimethylisoquinolinium Adduct 51	
Protons	Chemical Shift (δ) a	Multiplicity	Chemical Shift (δ)	Mulitplicity
a	7.48	m	7.44	m
b	6.17	d	5.50	d
c	5.43	s	5.30	s
d	5.08	d	4.87	d
e	3.62	m	3.62	m
f	3.32	m	3.38	m
g	2.65	m	2.48	m
h	2.07	m	1.97	m

a. All spectra were determined in trifluoroacetic acid.

Table VI

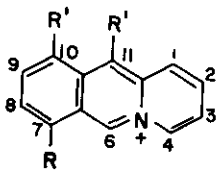
Comparison of Chemical Shifts (δ) of Related Protons in Adducts of Methyl Vinyl Ether with the Acridizinium Ion and the 2,3-Dimethylisoquinolinium Ion

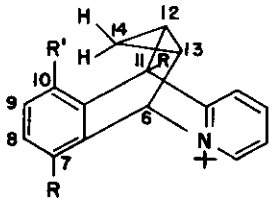


Protons	Chemical Shift δ, a	Multiplicity	Chemical Shift	Multiplicity
a	7.64	m	7.58	m
b	6.49	m	5.75	m
c	5.63	d	5.38	d
d	4.48	m	4.57	m
e	3.72	s	3.60	s
f	3.00	m	3.00	m
g	2.22	m	1.78	m

(a) All spectra were determined in trifluoroacetaic acid.

Cycloaddition of the acridizinium ion with cyclopropene resulted in the formation of an adduct 54 and its nmr indicated that it consisted of only a single racemate[23]. For each of the nonaromatic protons in the adduct 54, the ^{1}H NMR gives a clear signal which can be identified by decoupling experiments. Of the C-14 methylene protons the farthest



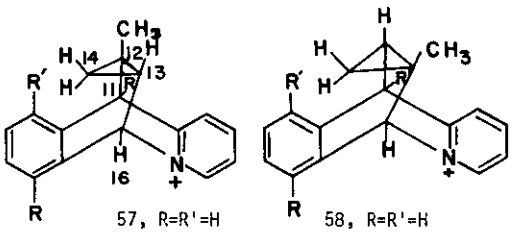


54, R' = R = H
55, R = Me; R' = H
56, R = R = Me

upfield (H_A) appears as a multiplet at δ 0.13, a chemical shift comparable to that shown by the methylene protons of norcarane[24]. The other C-14 proton (H_B) appears as a quartet at δ 0.96 suggesting a more strongly deshielded environment[25]. Selective reduction of adduct (54) moved the methylene signals (C-14 H_A and C-14 H_B to higher field appearing at δ -0.88 (multiplet) and 0.45 (quartet). This observation confirms the configuration of the adduct, having a cyclopropene ring in syn with respect to the phenylene ring. The adducts 55 and 56 also gave the evidence of only a single stereoisomers. In case of 55, selective reduction resulted in a shift of the H_A multiplet from δ 0.19 to 0.47 and the H_B quartet from δ 1.02 to 0.53, again giving the evidence that the methylene protons were over the phenylene ring.

The bridgehead protons at C-6 and C-11 acridizinium cycloadducts are easily distinguished by ^{1}HNMR and the regiochemistry of cycloaddition is usually discernible from the multiplicities of these protons[4]. Using 1-methylcyclopropene acridizinium adduct, the nmr revealed that it was a mixture of both regioisomers, the predominant product

(88%) being the 12-methyl derivative (57) and the minor (12%) being the 13-methyl isomer (58). The sharpness of the nmr signals, particularly those for the C-14 protons, again gave evidence for the presence of only a single stereochemical configuration. By analogy to the cyclopropene adducts, this product is likewise believed to have cyclopropane ring syn with respect to the phenylene ring.

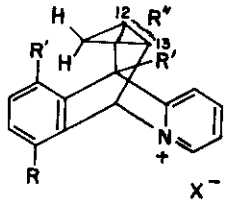


57, R=R'=H
59, R=Me; R'=H
61, R=R'=Me

58, R=R'=H
60, R=Me; R'=H
62, R=R'=Me

NMR results of various adducts are given in Table VII.

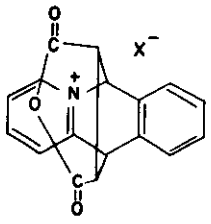
Table VII



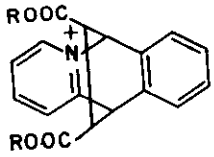
Compound	R	R'	R"	X	^{1}HNMR (TFA) of the Cycloadducts
54	H	H	H	BF_4	0.13 (m,1,C-14), 0.96 (q,1,C-14),1.95(m,1,C-12), 2.20(m,1, C-13), 5.14(d,1,C-11), 6.45(d,1,C-6), 7.52(bs,4,C-7 ,-8, -9,10), 7.86 (t,1,Py-H), 8.14(d,1,Py-H),8.46(t,1,Py-H).
55	CH_3	H	H	BF_4	0.19 (m,1,C-14), 1.02(q,1,C-11), 1.99(m,1,C-12), 2.33(m,1, C-13), 2.57(s,3,7-CH_3), 5.16(d,1,C-11), 6.79(d,1,C-6), 7.91(t,1,Py-H), 8.20(d,1,C-1), 8.53(t,1,Py-H),9.13(d,1,C-4).
56	CH_3	CH_3	H	BF_4	0.26(m,1,C-14), 0.96(q,1,C-14),1.63(m,1,C-12),2.33(m,1,C-13), 2.54,2.65(singlets, incompletely resolved, 9-,7-,10-,11-Me), 6.77(d,1,C-6), 7.28(bs,2,C-8,9), 7.99(t,1,C-4).
57,58	H	H	CH_3	PF_6	0.25(m,1,C-14), 0.83(t,1,C-14), 1.28(bs,3,12,13-CH_3), 1.85 (m,1,C-12,13), 4.88(s,0.88,C-11), 5.15(d, ,0.12,C-11), 6.19(s,0.12,Py-H), 8.25(d,1,Py-H),9.19(d,1,C-4).

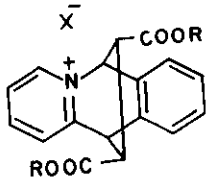
59,60	CH_3	H	CH_3	BF_4	0.33(m,1,C-14), 0.89(t,1,C-14), 1.33(bs,3,12,13-CH_3), 2.00 (m,1,C-12,-13), 2.59(s,3,7-CH_3), 5.02(s,0.9,C-11), 5.26(d, 0.1,C-11), 6.57(s,0.1,C-6), 6.91(d,0.9,C-6), 7.49(bs,3,C-8, -9,-10), 8.08(t,1,Py-H), 8.43(d,1,Py-H),9.36(d,1,C-4).
61,62	CH_3	CH_3	CH_3	BF_4	0.57(m,1,C-14), 0.82(t,1,C-14), 1.12(s,2.4,12-CH_3) 1,34(s, 0.6,13-CH_3), 1.92(m,1,C-12,13), 2.50, 2.65(2s, unresolved, 9,7,10,11-CH_3), 6.41(s,0.2,C-6), 6.74(d,0.8,C-6), 7.22(m,2, C-8,9), 7.99(t,1,Py-H), 8.30(d,1,Py-H),8.64(t,1,Py-H), 9.20(d,1,C-4).

The conversion of maleic anhydride adduct (63) into the diacid (64) and diesters (65,66) has been shown to occur without rearrangement[26]. Nmr spectra of the dimethyl ester (65) in trifluoroacetic acid showed two three proton singlets at τ 5.80 and 5.84. This slight but significant difference in deshielding can best be explained by assuming that a methyl group is over the quaternary nitrogen atom and is more strongly deshielded than the methyl of adjacent ester group. Paquette[27] on the other hand has pointed out that the methyl protons are strongly deshielded by protonation of the ester group in the trifluoroacetic acid. His claim has been rejected by Bradsher et al.[26] by showing that nmr measurements of 65 in deuterium oxide likewise show a small but significant difference in shift (τ5.96 and 5.98). Previous claim by Bradsher et al.[3] of isolating a trans adduct (69) from the reaction of ethyl maleate or ethyl fumarate with acridizinium bromide has now been shown by nmr spectra to be anti, syn, 12,13-dicarbomethoxy-6,11-dihydro-6,11-ethanoacridizinium salt. The methyl ester (68) showed an eight proton singlet at τ 6.15 arising from an overlap of the two methyls by protons at carbon



63



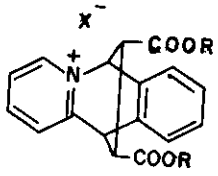


64, R = H 67, R = 7

65, R = CH_3 68, R = CH_3

66, R = C_2H_5 69, R = C_2H_5

atoms 12 and 13. Also the fact that neither ester group gave any evidence of being over



70, R = CH_3

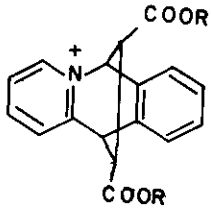
71, R = C_2H_5

the quaternary nitrogen atom.

It was also claimed that the product from the reaction of methyl maleate and acridizinium bromide was trans[3]. Nmr spectra has shown it to be syn,syn-12,13-dicarbomethoxy-6,11-dihydro-6,11-ethanoacridizinium (70) perchlorate. Its nmr spectrum showed an eight proton singlet at 6.17 from overlap of two methyls with protons of carbon atoms 12 and 13. Nmr data of the compounds are given in Table VIII.

TABLE VIII

12,13-dicarboxy-6,11-dihydro-6,11-ethanoacridizinium perchlorates and derivatives



Compound	R	Nmr (CF_3COOH),				
		Ester alkyl	6-H	11-H	12,13-H	Aromatic
64	H		3.28	4.50	6.00(s,2)	0.70-2.48(8)
65	CH_3	5.80(s,3)	2.82(s,1)	4.10(s,1)	5.54(s,2)	0.33-2.22(8)
		5.84(s,3)				
66	C_2H_5	8.77(t,3,J=7Hz)	3.30(s,1)	4.40(s,1)	6.03(s,2)	0.83-2.67(8)
		8.85(t,3,J=7Hz)				
67	H		2.60(m,1)	3.93(m,1)	5.33(m,1)	0.08-2.14(8)
68	CH_3	6.15	3.14(s,1)	4.42(s,1)	a	0.67-2.62(8)
69	C_2H_5	8.69(t,6,J=7Hz)	3.10(s,1)	4.38(s,1)	b	0.65-2.60(8)
		8.70(q,4,J=7Hz)				
70	CH_3	6.17(s,8)	3.28(s,1)	4.58(s,1)	6.17	0.66-2.58(8)
71	C_2H_5	8.70(t,6,J=7Hz)				
		5.73(t,4,J 7Hz)	3.25(s,1)	4.55(s,1)	6.18(s,2)	0.67-2.60(8)

a. δ 5.80-6.15(s,8), b. In the range δ 5.40-6.25

It was shown that the rate of cycloaddition of the 9-substituted acridizinium ion with styrene[28] and acrylonitrile[29] was related to the electron deficiency at position 6. Like the nmr spectrum of the other aromatic quaternary cations[30-32] that of the acridizinium ion shows the protons flanking the quaternary nitrogen to be strongly deshielded. Of these two strongly deshielded protons, that at position 6 gives resonance at the lower field, the chemical shift (10.6-11.0 ppm) varying with the nature of the 9-substituent. Measuring the nmr spectra at 39 ± 1°, chemical shifts of the proton at 6 were obtained at four concentrations in the range of 2.0-3.5 mol %. The standard deviation in δ varied from 0.08 to 0.26 Hz[33]. The data is recorded in Table IX.

Table IX

comparison of chemical shift data with σ_p and with the rate of addition of styrene to 9-substituted acridizinium perchlorates

R	(Hz)	(Hz)	σ_p	Kx10^3	min.$^{-1}$
CH_3	187.5	-5.9	-0.170[a]	2.0	0.1
i-Pr	188.0	-5.4	-0.51[a]	2.8	0.1
H	193.4	0.0	0.000	5.0	0.2
F	193.5	0.1	0.062[a]	5.4	0.2
Cl	194.5	1.1	0.227[a]	10.1	0.5
Br	194.1	0.7	0.232[a]	11.2	0.8
COOH	196.9	3.5	0.406[b]	18.1	0.7
NO_2	203.7	10.3	0.778[b]	105	5

a. D.H. McDaniel and H.C. Brown, J.Org.Chem., 23, 420, 1958.

b. H. Ven Bekkum, P.E. Verkade and B.M. Wepster, Recl. Chim. Pays-Bas, 78, 815, 1959.

A least squares plot of log K/k^o for the addition of styrene to 9-substituted acridizinium derivative vs $\Delta\delta^o$ (change in chemical shift R=H) is shown in Figure 1. The corelation factor of 0.98 is quite satisfactory. From the data, a significant corelation has been found with Hammett σ_p, a plot (Figure 2) of $\Delta\sigma^c$ vs σ_p gave a significant corelation of 0.97. This corelation of proton chemical shifts with Hammett substituent constants can be interpreted as arising from the polarisation of the C-H bond at position 6, which must in turn arise from the density of π electrons at the position[34,35]. The slope of the line (Figure 2) is 15.8 ± 1.3 Hz sigma.

While there has been an increasing number of attempts to relate the nmr of aromatic ring hydrogens to electron density at the carbon to which they are attached[36,37-41],

no one previously appears to have related the rate of cycloaddition of such systems to the

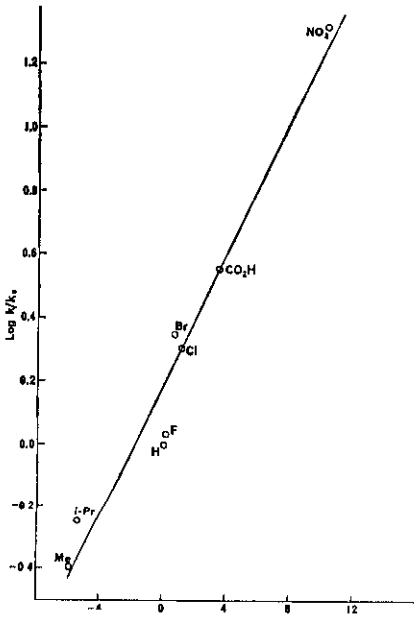


Fig. 1. Least square plot of log k/k^0 vs $\Delta\delta^o$

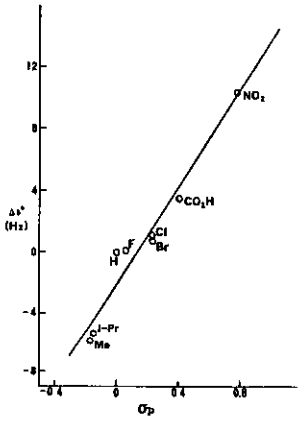
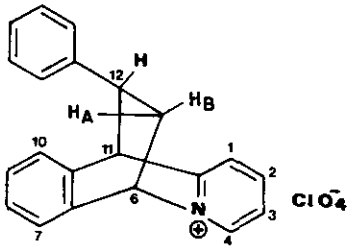


Fig.2. Least square plot of $\Delta\delta^o$ vs Hammet σ_p

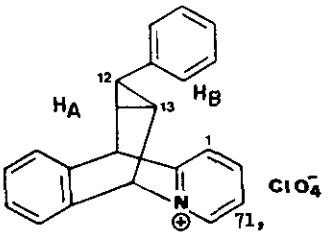
pmr of a proton at a carbon atom which would be involved in the creation of a new π bond. This corelation of chemical shift and cycloaddition rates will definitely prove important in the study of steric vs electronic effects in polar cycloaddition [42].

In the cycloaddition of styrene to the acridizinium ion, the distribution of the syn and anti forms in the product had not been determined and neither of the diastereomers has been obtained as a pure reacemate, Bradsher and Westermen [43] have separated the two racemates by fractional crystallisation. However, separation of the syn and the anti forms by this method is not usually a useful analytical method for the estimation of the proportion of each recemate present in the original mixture. Some of the differences in the nmr pattern of the two isomers have been utilized in determining the syn and the anti ratio in the various adducts. Thus in the nmr spectra of the two oure recemates (70, 71) obtained from styrene and acridizinium ion, signals for the aromatic protons appeared at an unusually high field, δ6.5-6.8. In agreement with the assignment by Field and Regan [44], these shielded aromatic protons were attributed to the phenyl group at position 12 aton the bridge and result from the two ortho hydrogens sweeping through the π cloud of the phenylene or pyridinium ring. Selective hydrogenation of the adduct mixture, the anti isomer (71) can be deprived of this type of shielding with the result that the ortho hydrogens give signals

in the usual aromatic range. In contrast, selective hydrogenation of the syn isomer (70), hardly any effect was noticed in the nmr signals generated by the ortho hydrogens, forming a basis for the assignment of this isomer as the syn isomer (70).



70, syn isomer



71, anti isomer

The assignment made for the two isomers were also consistent with those made, using other proportions of the ^{1}H NMR spectra. Although in each case the nonaromatic protons comprised an ABMXY spin system, several distinct differences were exhibited in the spectra of the two isomers. As may be seen in Figure 3 and 4, the syn adduct possessed a greater

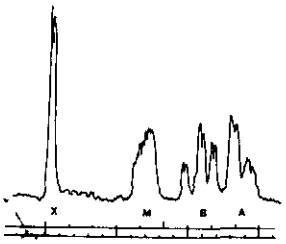


Figure 3. The ABMX portion of the ^{1}H NMR spectrum of the syn isomer

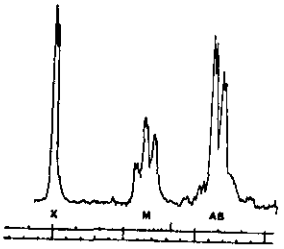


Figure 4. The ABMX portion of the ^{1}H NMR spectrum of the anti isomer

line separation in the AB portion than did the anti isomer.

The respective patterns of the isomers may be explained in terms of through-space proximity effects of the pyridinium ring as well as the phenyl group located at C-12. In the syn isomer (70) a small shielding contribution from the phenyl group at C-12 is dirceted on 13a, the bridge hydrogen cis to the ring. At the same time bridge proton 13b, nearest

the pyridinium ring, is being deshielded by the charge of the quaternary nitrogen resulting in a wide spacing of the AB protons (Figure 31). In the anti isomer, however, the opposite effects of the shielding by the bridge phenyl group and deshielding by the cationic charge operate on the same proton of 13b. The result of these off setting effects is a close spacing of the AB protons (Figure 4). The deshielding of the quaternary nitrogen is significant in the adduct obtained from the reaction of 1,1-diphenylethylene with the acridizinium ion, the patterns for protons 13a and 13b are separated by δ 0.43 in the ^{1}H NMR spectrum.

Likewise the near equivalence of the 13a and 13b protons in the anti adduct of styrene is reflected in the multiplicity of the C-12 proton, which appears (Figure 4) essentially as a triplet with minor splitting from the C-11 bridgehead proton, In the syn isomer (Figure 3), the C-12 signal appears as a complex multiplet.

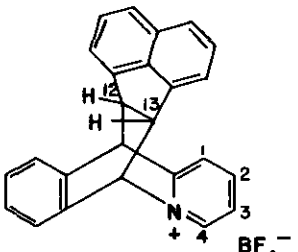
Another signal useful for distinguishing between the stereoisomers is the C-4 singlet which occurs farthest downfield and is easily identified and measured. When the C-12 phenyl group is positioned correctly to shield the 13b proton as in the anti isomer (71) the deshielding edge of the phenyl group is directed towards the pyridinium ring. This contribution is significant in that, the C-4 proton in the anti isomer is centred at 9.20. Whereas the corresponding syn absorbance occurs at δ 9.07. Since the values for the C-4 proton of the syn isomer agrees closely with that found in adducts lacking a bridge phenyl group, it appears reasonable to conclude that syn phenyl at position 12 does not perturb the C-4 resonance.

These differences in the ^{1}H NMR spectra have been utilised in the identification of syn and anti forms of p-methoxystyreneacridizinium adducts. In nmr, the methoxyl signals of the stereoisomers occur at slightly different field values. By comparison with the known styrene adducts these syn and anti adducts have been identified easily on the basis of their ABMYX spin patterns making it possible to assign to the anti isomer the methoxyl signal occurring at the lower field. A similar analysis of the stereomeric products obtained from p-methylstyrene and the acridizinium ion revealed that the methyl group at lower field was that of the anti isomer.

Catalytic reduction of the pyridinium ring deprives the anti isomer, but not the syn isomer of two shielded aromatic (ortho) protons. Calculations of the isomer ratio from the relative areas of the shielded vs the normal aromatic ^{1}HNMR resonances, can give the syn, anti ratio, but the method is applicable only to those adducts, which contain a phenyl group having at least one ortho hydrogen at position 12 and that, the system not be sub-

stituted in such a way that the signals from the ortho hydrogens are no longer clearly separated from those of the other aromatic hydrogens.

In case of acenaphthylene adducts (72,73) assignment of the anti isomer (73) was made by the observation that the C-4 proton signal appeared at δ 8.35 indicating that it was strongly deshielded (vis 72), whereas the syn isomer had an almost unperturbed value for the



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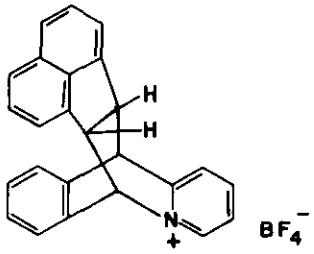
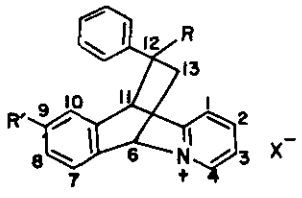


72

C-4 proton, δ 9.13. The validity of these assignments has been reenforced by the observation that the bridge protons at C-12 and C-13 are more nearly equivalent in the anti isomer than in the syn, since this is in agreement with an earlier observation [45].

When the adduct of styrene with 9-methylacridizinium ion was examined by nmr spectrocopy two distinct methyl resonances were observed. The one of higher intensity, also found at the higher field, was due to syn isomer (74), since this isomer can produce the maximum shielding.



74, R = H; R = CH_3
75, R = CH_3; R' = H

The use of acridizinium derivatives with methyl groups in ring C has proved a convinient means for the determination of the orientation of an aryl group at position 12 of an adduct (table X).

In the anti isomer, the effect of shielding by the aryl group at position 12 would be minimised, the signals from the 9-methyl group are all nearly the same. In marked contrast, the syn methyl resonances varied. The evidence of shielding increases with the size and

electron richness of the system. The shielding is magnified, when the aryl group is constrained in a rigid configuration as in the case of acenaphtylene adduct which must focus π cloud continuously on the methyl substituents.

Table X

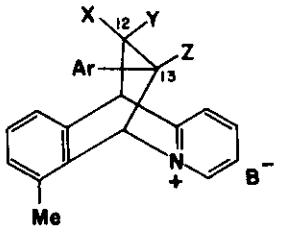
the ^{1}H nmr chemical shifts[a] for the 9-methyl group in acridizinium adducts and the isomeric compositions derived from the data

Alkene Addend	Anti-9-Me	Syn-9-Me	% Syn
9-Vinylcarbazole		2.06	100
Indene	2.45	2.10	80
Styrene	2.46	2.32	72
2-Vinylpyridine	2.52	2.45	50
Acenaphthylene	2.42	1.98	48

a. Chemical shifts are expressed in δ units and were taken in TFA.

In an adduct of 9-methylacridizinium ion with α-methoxystyrene the reaction mixture consisted of almost equal parts, syn and anti products, which are contrary to the fact that a methoxyl group should predominate in syn orientation. A possible clue to the lack of methoxyl group is provided by ^{13}C NMR studies carried out by Hatade et al.[46], which showed that introduction of an α-alkyl group into vinyl ethers resulted in stereo inhibition of resonance. It seems likely that an α-phenyl group would have a similar effect on resonance involving the methyl group of α-methoxystyrene (75).

A methyl group at positon 7 of the acridizinium ion has also been used as a digonstic tool in the study of adducts having an aryl group on the ethano bridge at position 13(76,77).



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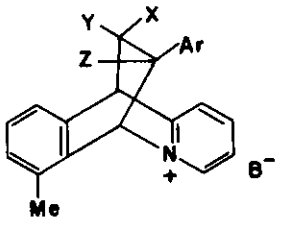

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An aryl group at position 13, if in the syn configuration (76) would shield the methyl group at position 7, while in the anti position (77), shielding effect would be minimal. An adduct of cis-β-methoxystyrene with 7-methylacridizinium tetrafluoroborate revealed in NMR, that 93% of the adduct had the syn configuration (76, X = OMe; Y =Z = H) Table XI).

The 7-methylacridizinium ion proved a useful substrate for studying the stereochmistry of trans-stilbene adducts. Results obtained with two trans-stilbene suggest that the tendency to add on the 12-anti-13-syn mode is predominant reflecting an unexplained pattern observed earlier [47, 48] in the addition of diethyl fumarate to the acridizinium ion.

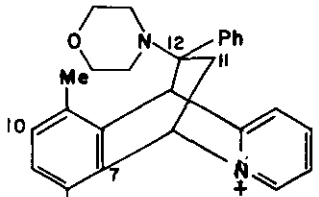
Table XI

THE ^{1}H NMR CHEMICAL SHIFTS FOR THE 7-METHYL GROUP IN SEVERAL ACRIDIZINIUM ADDUCTS AND THE ISOMERIC COMPOSITIONS ESTIMATED FROM THE DATA

	Chemical Shifts [a] δ ppm		
Alkene Addend	Anti-7-Me	Syn-7-Me	% Syn
cis-β-methoxystyrene	2.62	2.19	93
trans-stilbene	2.68	1.96	64
trans-4,4'-dimethoxystilbene	2.69	2.13	55

a. Chemical Shifts were measured in CF_3COOH.

When the adduct of 7,10-dimethylacridizinium ion was examined by NMR the two methyl signals at 2.52 and 2.46 were too close together for the phenyl group to have been syn



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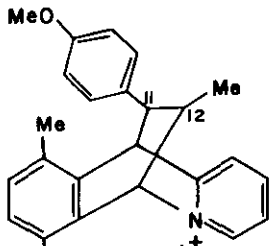

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and therefore the correct assignment is as the anti-phenyl isomer (78). In order to demonstrate that the 10-methyl group will respond to aryl shielding, the anethol adduct (79) showed a highly shielded methyl signals at δ 1.85 whereas the stereoisomer showed an "unperturbed" methyl signal at δ 2.63.

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