The Nature of the Addition of Dienophiles to the Acridizinium Ion[1]

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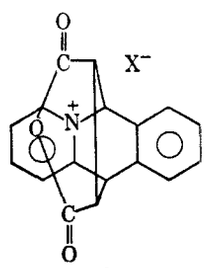
Since the methyl group or carbonyl group directly above a quarternary nitrogen atom is altered in a manner perceptible by the use of nmr and infrared spectra, it is now possible to assign the stereochemical structure of the adducts obtained by reaction of the acridizinium ion with maleic anhydride and with maleate and fumarate esters. The isomerization observed when maleate esters are allowed to react with the acridizinium ion is brought about by attack of acetic acid on the aromatic nucleus, releasing hydrogen bromide. A study of the rates of reaction of *para*-substituted styrenes shows this to be a Diels–Alder reaction exhibiting inverse electron demand.

It has been demonstrated[3] that the acridizinium[4] (benzo[*b*]quinolizinium) ion would undergo 1,4 cycloaddition with some common dienophiles. As was pointed out in the original publication, this was (and apparently remains) the unique example of a Diels–Alder reaction in which the "diene" component bears a positive charge. The continuing interest in 1,4 cycloadditions involving heterocyclic systems,[5] as well as unanswered questions concerning both the stereochemistry of the addition products and the cause of the rearrangements observed, prompted our reexamination of the reaction.



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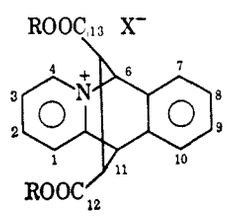
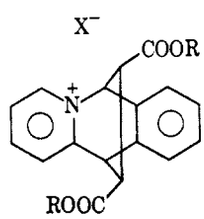


2, R = H
3, R = CH_3
4, R = C_2H_5

The conversion of the maleic anhydride adduct **1** into the diacid **2** and diesters **3** and **4** has been shown to occur without rearrangement. Nmr spectra of the dimethyl ester **3** in trifluoroacetic acid showed two three-proton singlets at τ 5.80 and 5.84. This slight, but we believe 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 the adjacent ester group.[6] More significantly the ir spectra of both the methyl and ethyl esters (**3** and **4**) show two absorptions in the carbonyl region at 1730 and 1760 cm^{-1}, explicable by the assumption that the attraction of the adjacent carbonyl oxygen for the quaternary nitrogen would have a bathochromic effect. On the basis of these two lines of physical evidence, plus one to be presented later, it is practically certain that the substituents at carbon atom 12 and 13 of the anhydride adduct **1** and the *cis* esters derived from it are *anti* with respect to the benzene ring.[7]

In the earlier paper[3] it was shown that the reaction of ethyl fumarate or ethyl maleate with acridizinium bromide yielded the same adduct which was assigned a *trans* structure (**7**). The adduct has been hydrolyzed, without rearrangement, to the corresponding dicarboxylic acid **5** which was esterified with methanol to yield the methyl ester **6**. The perchlorate salt of the



5, R = H
6, R = CH_3
7, R = C_2H_5

same methyl ester was obtained in 96% yield when methyl fumarate was allowed to react with acridizinium perchlorate. The methyl ester showed an eight-proton singlet at τ 6.15 arising from an overlap of the two methyls by protons at carbon atoms 12 and 13 and gave only a single absorption (at 1750 cm^{-1}) in the carbonyl stretching region of the ir spectrum. Whereas the structural evidence is less convincing than that in the case of the maleic anhydride adduct **1**, we feel that the correct assignment is as the *anti,syn*-12,13-dicarbomethoxy-6,11-dihydro-6,11-ethanoacridizinium salt since neither ester group gives evidence of being over the quaternary nitrogen atom.

In the original publication[3] it was suggested that, by analogy with the product from ethyl maleate, the adduct isolated in 10% yield from the reaction of methyl maleate with acridizinium bromide should be *trans*. When it was found that the cation obtained by the addition to the acridizinium ion of methyl fumarate was not identical with that from the methyl maleate, a restudy of the maleate addition was undertaken. The product obtained in 43% yield by the addition of methyl maleate to acridizinium perchlorate yields on acidification a dicarboxylic acid (**8**) which forms a cyclic anhydride when treated with acetic anhydride. This anhydride is isomeric but not identical with the maleic

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(2) NASA Trainee. This work was supported in part by Public Health Research Grant No. HE-02170 of the National Heart Institute of the National Institutes of Health.

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

(4) C. K. Bradsher and L. E. Beavers, *ibid.*, **77**, 4812 (1955).

(5) *E.g.*, S. B. Needleman and M. C. Chang Kuo, *Chem. Rev.*, **62**, 405 (1962); J. Hamer, Ed., "1,4-Cycloaddition Reactions," Academic Press Inc., New York, N. Y., 1967.

(6) Professor L. A. Paquette has pointed out to us (private communication) that the methyl protons are strongly deshielded by protonation of the ester function in the trifluoroacetic acid. It does not seem likely that the observed difference in chemical shift for the two ester methyl groups arises from differences in the extent of protonation, since nmr measurements of **3** in deuterium oxide (external standard) likewise show a small but significant difference in shift (τ 5.96 and 5.98). In the same solvent the *syn, syn*-dicarbomethoxy isomer **9** was too insoluble for measurement.

(7) Throughout the remainder of the paper the terms *syn* and *anti* will describe the relationship of substituents at positions 12 and 13 to the benzenoid ring.

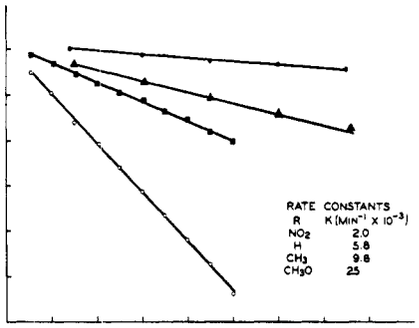
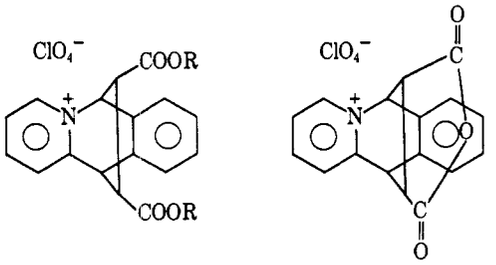


Figure 1.

anhydride adduct **1**. The obvious inference that the adduct obtained from methyl maleate is the *syn,syn*-12,13-dicarbomethoxy-6,11-dihydro-6,11-ethanoacridizinium (**9**) perchlorate was confirmed by the nmr



8, R = H
9, R = CH_3
10, R = C_2H_5

11

spectrum which showed an eight-proton singlet at τ 6.17 from overlap of the two methyls with protons at carbon atoms 12 and 13 while the ir spectrum showed only a single peak (at 1750 cm^{-1}) in the carbonyl stretching region.

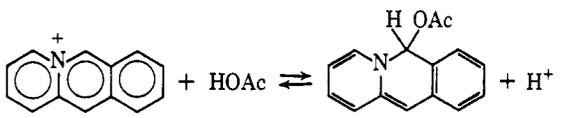
The only other pure product obtained from the reaction of dimethyl maleate with acridinium perchlorate was pure *anti,syn*-12,13-dicarbomethoxy-6,11-dihydroacridizinium (**6**) perchlorate, in 13% yield. This indicates that the rearrangement observed when ethyl maleate adds to the acridizinium ion also occurs, albeit to a lesser extent, when methyl maleate adds to an acridizinium salt.

The rearrangement of maleate esters during the cycloaddition reaction was puzzling. The conjecture made earlier[8] that the acetic acid used as a solvent in this reaction catalyzes the transformation of maleate to fumarate esters has been shown to be without foundation. No rearrangement of ethyl maleate to ethyl fumarate was detected by gas–liquid partition chromatography after the maleate ester had been heated in acetic acid for 11 hr in the presence of a quaternary salt, N-benzyl-2-bromopyridinium bromide. The possibility that ethyl maleate first underwent *cis* addition and that the *trans* product arose from a rearrangement of the adduct was examined by subjecting *anti,anti*-12,13-dicarbethoxy-6,11-dihydro-6,11-ethanoacridizinium (**4**) perchlorate and its *syn,syn* stereoisomer **10** to heating at 96° for 12 hr in acetic acid. In each case the starting material was recovered unchanged.

It now appeared clear that if the cycloaddition was not a two-step reaction the products obtained in apparent violation of the *cis* principle[8] must arise from the rearrangement of maleate to fumarate esters in the presence of the acridizinium ion. Since the usual procedure has been to employ an excess of the dienophile it was possible to interrupt the reaction at some stage and examine the condition of excess ester. When a 10 molar equiv of ethyl maleate was employed and the heating in acetic acid with acridizinium bromide was interrupted after 7.5 hr, the recovered ester was found by gas–liquid partition chromatography to be almost 100% pure ethyl fumarate.

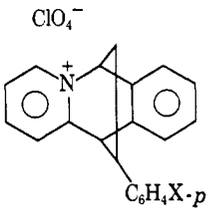
It seemed most likely that acridizinium bromide has a very much greater ability than 1-benzyl-2-bromopyridinium bromide to catalyze the rearrangement of maleate to fumarate esters simply because the acridizinium ion would much more easily undergo addition of acetic acid to the nucleus with liberation of a mineral acid which is the actual catalyst for the ester isomerization (Scheme I).

SCHEME I
ACETOLYSIS OF THE ACRIDIZINIUM ION



By distillation under reduced pressure of the acetic acid solvent from an acetic acid solution of acridizinium bromide, it has been possible to demonstrate that hydrogen bromide is present in the distillate and hence in the acridizinium ion solution. On the other hand, there is no evidence that acetate ion reacts to produce the specific organic product shown in Scheme I.

The addition of dienophiles to the positively charged acridizinium ion has become explicable as a consequence of the classical kinetic study by Sauer and Wiest[9] demonstrating the existence of Diels–Alder reactions with inverse electron demand. The acridizinium ion does not undergo cycloaddition with the electron-deficient tetracyanoethylene, but does react with the electron-rich styrene. The adduct from styrene (**12**) has the substituent at position 12.



12, X = H
13, X = CH_3
14, X = OCH_3
15, X = NO_2

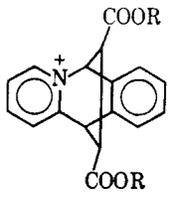
Since the adducts show very little absorption beyond 264 mμ in the ultraviolet it is possible to follow the disappearance of acridizinium ion from solution by measuring the disappearance of the strong absorption peak at 399 mμ. When the reaction is carried out using an excess of the dienophile, pseudo-first-order kinetics are observed. As may be seen in Figure 1 the reaction rate increases with increased electron release of the *para* substituent *p*-nitrostyrene reacting slowest and *p*-methoxystyrene fastest, an exact parallel to the observations of Sauer and Wiest.[9]

(8) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

(9) J. Sauer and H. Wiest, *ibid.*, **74**, 353 (1962).

TABLE I

12,13-DICARBOXY-6,11-DIHYDRO-6,11-ETHANOACRIDIZINIUM PERCHLORATES AND DERIVATIVES



Compd	R	Yield, %	Perchlorate mp, °C	λ_{max}, mμ (log ε) *anti,anti*	λ_{min}, mμ (log ε)	C=O stretch, cm^{-1}	Nmr (CF_3COOH), τ: Ester alkyl	Protons at positions: 6	11	12,13	Aromatic
2	H	66[a]	299.5–300.5[b]	263 (3.75)	241 (3.54)	1720		3.28	4.50	6.00 (s, 2)	0.70–2.48 (8)
3	CH_3	60[a]	249–250[b]	263 (3.76)	241 (3.49)	1730 1760	5.80 (s, 3) 5.84 (s, 3)	2.82 (s, 1)	4.10 (s, 1)	5.54 (s, 2)	0.33–2.22 (8)
4	C_2H_5	65[a]	262–263[b]	262 (3.78)	241 (3.51)	1730, 1760	8.77 (t, 3, J = 7 Hz) 8.85 (t, 3, J = 7 Hz)	3.30 (s, 1)	4.40 (s, 1)	6.03 (s, 2)[c]	0.83–2.67 (8)
1	H(An)[d]	87[e]	290–292[f]	263 (3.62)	24.15 (3.38)	1873 (w) 1786 1761 (w) 1718					
					anti,syn						
5	H	77[g]	244–246[h]	263 (3.70)	240 (3.47)	1710		2.60 (m, 1)	3.93 (m, 1)	5.33 (m, 1) 5.60 (m, 1)	0.08–2.14 (8)
6	CH_3	96[i]	226–227.5[h]	260 (3.71)	240 (3.46)	1750	6.15[j]	3.14 (s, 1)	4.42 (s, 1)	*j*	0.67–2.62 (8)
7	C_2H_5	85[k]	182.5–183.5[b]	263 (3.73)	242 (3.49)	1740	8.69 (t, 6, J = 7 Hz) 5.70 (q, 4, J = 7 Hz)	3.10 (s, 1)	4.38 (s, 1)	*l*	0.65–2.60 (8)
					syn,syn						
8	H	75[m]	253–255[h]	263 (3.70)	240 (3.50)	1720					
9	CH_3	43[n]	298–299	264 (3.60)	244 (3.38)	1750	6.17 (s, 8) 8.70 (t, 6, J = 7 Hz)	3.28 (s, 1)	4.58 (s, 1)	6.17	0.66–2.58 (8)
10	C_2H_5	75[o]	208.5–209.5[h]	262 (3.73)	242 (3.54)	1750 1760	5.73 (t, 4, J = 7 Hz)	3.25 (s, 1)	4.55 (s, 1)	6.18 (s, 2)	0.67–2.60 (8)
11	H(An)[d,p]		277–278[h]	264 (3.67)	241 (3.50)	1840					

[a] From the bromide of the anhydride **1** as the perchlorate salt. [b] Physical data (except nmr) for this compound from ref 3. [c] Signal overlapped by 5.64–6.10 (m, four, CH_3CH_2). [d] Cyclic anhydride. [e] By reaction of acridizinium bromide with maleic anhydride. [f] With decomposition. [g] By acid-catalyzed hydrolysis of the ethyl ester **7**. [h] New compound. [i] By reaction of methyl fumarate with acridizinium perchlorate. Methyl maleate afforded only a 13% yield of pure product **6**. [j] τ 5.80–6.15 (s, 8). It is believed that the sharp peak at 6.15 is due to the methyl groups, with an overlap of signals from protons at positions 12 and 13. [k] By reaction of ethyl fumarate with acridizinium perchlorate. Only a 76% yield was obtained when ethyl maleate was used. [l] In the range τ 5.40–6.25 there were signals superimposed upon the quartet at 5.70 accounting for two additional protons. [m] By hydrolysis of the methyl ester **9**. [n] By reaction of acridizinium perchlorate with methyl maleate. This is identical with the product obtained by reaction of acridizinium bromide with methyl maleate (followed by anion exchange) and by analogy erroneously assigned a *trans* structure.[3] [o] By transesterification of the methyl ester **9**. [p] By action of acetic anhydride on the dicarboxylic acid **8**. While the yield appeared good, the actual per cent is not available.

Since the stereochemistry of none of the acridizinium adducts was described in the earlier paper,[3] the physical constants of three dicarboxylic acids (**2**, **5**, **8**) and their esters and anhydrides are summarized in Table I.

Experimental Section

Except as noted all elemental analyses were carried out by the Janssen Pharmaceutica Research Laboratories, Beerse, Belgium. The melting points were taken in capillary tubes with a Thomas–Hoover melting point apparatus and the melting points of the analytical samples are corrected. All ultraviolet spectra of previously unreported compounds were determined in 95% ethanol solution using 1-cm quartz cells with a Beckman DB-G spectrophotometer. Infrared spectra were obtained with Perkin-Elmer Model 137 and 237 spectrophotometers using potassium bromide pellets. Nuclear magnetic resonance spectra were taken with a Varian A-60 spectrometer in trifluoroacetic acid solution using tetramethylsilane as a standard and the results are reported in τ units. Analysis of maleate and fumarate ester mixtures were carried out by using the F & M Model 402 chromatograph with a 4-ft column packed with 4% SE-30 and maintained at 110°. Identification of the esters was by the peak-matching technique.

***anti,anti*-12,13-Dicarboxy-6,11-dihydro-6,11-ethanoacridizinium Bromide (2, X = Br).**—The bromide of the *anti,anti*-dicarboxylic acid may be prepared in a manner analogous to the preparation of the perchlorate (2, X = ClO_4^-) except that hydrobromic acid is used. The analytical sample crystallized from acetone as colorless prisms, mp 247–249°.

Anal. Calcd for $C_{17}H_{14}BrNO_4$: C, 54.27; H, 3.75; N, 3.72. Found: C, 54.06; H, 3.69; N, 3.59.

***anti*-12,13,15,16-Tetrahydro[6,11:3′,4′]furanoacridizinium-13,15-dione Bromide (1, X = Br).**—The bromide salt of the *anti,anti* acid (1, X = Br) was heated for 1.5 hr at 100° with a solution containing one part acetic anhydride and nine parts, by volume, of acetic acid. Evaporation of the solvent under reduced pressure yielded the anhydride (**1**, X = Br), mp 244–246° (lit.[3] mp 244–246), and was identical with the adduct obtained when acridizinium bromide reacted with maleic anhydride.

Hydrolysis of *anti,anti*-12,13-Dicarbomethoxy- and 12,13-Dicarbethoxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorates (3 and 4, X = ClO_4).—The hydrolysis of the title salts to the corresponding acid (2, X = ClO_4^-) may be accomplished in good yield by refluxing for 16 hr in 4% hydrobromic acid.

Stability of *anti,anti*-12,13-Dicarbethoxy-6,11-dihydro-6,11-ethanoacridizinium (4) Perchlorate under Conditions of the Diels–Alder Reaction.—When the title compound was heated for 12 hr in acetic acid at 100° and the solvent removed under reduced pressure, the starting material was recovered unchanged.

***anti,syn*-12,13-Dicarboxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorate (5).**—*anti,syn*-12,13-Dicarbethoxy-6,11-dihydro-6,-11-ethanoacridizinium (**7**) perchlorate (1.5 g) prepared by the Diels–Alder reaction was hydrolyzed by refluxing for 16 hr in 100 ml of 4% hydrobromic acid. Concentration of the solution afforded 1.0 g (77%) of colorless needles, mp 244–246°.

Anal. Calcd for $C_{17}H_{14}ClNO_8$: C, 51.59; H, 3.57; N, 3.55. Found: C, 51.38; H, 3.65; N, 3.36.

A small sample of the acid was heated for 1.5 hr at 100° in 9:1 acetic acid–acetic anhydride. Upon removal of the solvents under reduced pressure the acid was recovered unchanged.

***anti,syn*-12,13-Dicarbomethoxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorate (6). A. By Esterification of the Acid (5).**—The perchlorate of the *anti,syn* acid **5** (1 g) was esterified

TABLE II

PREPARATION OF 12-ARYL-6,11-DIHYDRO-6,11-ETHANOACRIDIZINIUM PERCHLORATES (12–15)

Compd	p-XC6H4, X	Mp, °C	Yield, %	Nmr[a] C-11	J, Hz	Formula	Anal., %, calcd over found C	H	N
12	H	245–247[b]	55	4.83	3	$C_{21}H_{18}ClNO_4$	65.63	4.70	3.65
							65.24	4.87	3.62
13	CH_3[c]	213–216[d]	78	5.12	2	$C_{22}H_2ClNO_4$	66.33	5.03	3.52
							66.29	5.11	3.38
14	OCH_3[c]	171–173[d]	50	5.12	2	$C_{22}H_{20}ClNO_5$	63.77[e]	4.83	3.38
							63.70	4.89	3.38
15	NO_2	230–232[f]	60	4.78[g]		$C_{21}H_{17}ClN_2O_6$	58.88[e]	3.97	6.54
							58.75	3.99	6.68

[a] Nmr data are in τ units and measurements were made in trifluoroacetic acid using an internal standard; except as noted, a doublet was observed corresponding to a single proton. [b] λ_{max} 271 mμ (log ε 3.76), λ_{min} 244 mμ (log ε 3.51). [c] Acetonitrile was used instead of acetic acid as the solvent for the reaction. [d] Colorless needles from methanol–ethyl acetate. [e] Elemental analyses by Galbraith Laboratories, Inc., Knoxville, Tenn. [f] Colorless needles from ethanol–ether. [g] The blunt singlet could not be resolved into a doublet with our spectrometer. Despite the lack of this evidence, it is felt that the *p*-nitrophenyl group is at position 12 rather than 13.

by refluxing it for 4 hr in 2% methanolic hydrogen chloride. The product, obtained by concentration of the solution, crystallized from methanol as colorless needles, mp 226°.

B. By Cycloaddition.—A suspension of 2 g of acridizinium perchlorate in a solution of 4 g of methyl fumarate in 10 ml of acetic acid was mechanically stirred and heated on the steam bath for 24 hr. The resulting straw-colored solution was poured into 100 ml of dry ether. The precipitate was collected and washed with ether affording 2.9 g (96%) of a colorless powder, mp 213–216°. The analytical sample crystallized from methanol as colorless needles, mp 226–227.5°. Products obtained by procedures A and B were shown to be identical by infrared absorption and mixture melting point determinations.

Anal. Calcd for $C_{19}H_{18}ClNO_5$: C, 53.84; H, 4.28; N, 3.30. Found: C, 53.72; H, 4.35; N, 3.26.

Acid-catalyzed hydrolysis of this ester gave the corresponding acid **5**.

***syn,syn*-12,13-Dicarbomethoxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorate (9).**—A suspension of 1.5 g (0.00535 mole) of acridizinium perchlorate[10] in 3 ml of acetic acid containing 2.9 g (0.020 mole) of methyl maleate was mechanically stirred on a steam bath for 72 hr. The resulting light tan suspension was poured into 100 ml of dry ether and the precipitate collected and washed with ether. The product was 2.1 g of colorless powder, mp 178–190°. The powder was extracted with approximately 40 ml of hot absolute methanol filtering while hot. The residue was 1.0 g (43%) of the pure *syn,syn* isomer (**9**), mp 298–299°.[11] Concentration of the solution yielded 0.7 g of a mixture of salts, mp 225–255°, while concentration of the mother liquor to a volume of 5 ml afforded 0.3 g (13%) of the *anti,syn* isomer, mp 226–227°.

***syn,syn*-12,13-Dicarboxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorate (8).**—Just as in the case of the other esters, hydrolysis of the *syn,syn*-dicarbomethoxy **9** was accomplished in 4% hydrobromic acid to give a yield of 75%, mp 250–252°. The analytical sample crystallized from water as colorless needles, mp 253–255°.

Anal. Calcd for $C_{17}H_{14}ClNO_8$: C, 51.59; H, 3.57; N, 3.55. Found: C, 51.45; H, 4.19; N, 3.50.

The acid could be reesterified with methanolic hydrogen chloride to afford the original methyl ester **9**.

***syn*-12,13,15,16-Tetrahydro[6,11:3′,4′]furanoacridizinium-13,15-dione Perchlorate (11).**—A small amount of *syn,syn* acid **8** was dissolved in 9:1 glacial acetic acid–acetic anhydride and the mixture heated 1.5 hr at 100°. Concentration of the solution afforded a product which was recrystallized from acetic acid to which a small amount of acetic anhydride had been added, colorless needles, mp 277–278° dec.

Anal. Calcd for $C_{17}H_{12}ClNO_7$: C, 53.97; H, 3.17; N, 3.70. Found: C, 53.66; H, 3.23; N, 3.43.

A small quantity of the *syn*-anhydride **11** was dissolved in water and 1 drop of hydrobromic acid added. On cooling, colorless needles (mp 250–252°) separated, identified as the *syn,syn* acid **8** by comparison of infrared spectra.

(10) The perchlorate salt showed higher stability than the bromide salt, which became discolored and appeared to decompose on long heating.

(11) This substance was obtained earlier[3] in 10% yield and erroneously assigned a *trans* structure.

***anti*-6,11,12,15-Tetrahydro[6,11-*c*]furanoacridizinium-13,15-dione (1) Perchlorate.**—The named salt was prepared for comparison with the *syn* isomer by reaction of maleic anhydride with acridizinium perchlorate. The product crystallized from acetic acid containing a trace of acetic anhydride as colorless needles (mp 290–292° dec) in 85% yield.

Anal. Calcd for $C_{17}H_{12}ClNO_7$: C, 53.97; H, 3.17; N, 3.70. Found: C, 54.25; H, 3.38; N, 3.55.

***syn,syn*-12,13-Dicarbethoxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorate (10).**—This ester was obtained from the methyl ester **9** by transesterification in refluxing 10% ethanolic hydrogen chloride. The product crystallized from ethanol as colorless needles (mp 208–209.5°) to yield 0.4 g (75%).

Anal. Calcd for $C_{21}H_{22}ClNO_8$: C, 55.93; H, 4.92; N, 3.12. Found: C, 56.23; H, 4.85; N, 3.09.

A small quantity of the *syn,syn*-dicarbethoxy derivative **10** was heated for 12 hr in acetic acid under conditions used for the cycloaddition reaction. Removal of the solvent left the product unchanged, mp 208–209°.

Acid-catalyzed hydrolysis of the ethyl ester **10** afforded the *syn,syn* acid **8**.

12-Aryl-6,11-dihydro-6,11-ethanoacridizinium Perchlorates (12–15).[12]—The named compounds were prepared by the reaction at 100° of 1.5 g of acridizinium bromide and 10 ml of the appropriate styrene in 10 ml of acetic acid. After 10 hr the mixture was poured into water and extracted with ether. The aqueous layer was concentrated and 35% perchloric acid added. The resulting precipitate was collected and recrystallized from ethanol. The results have been summarized in Table II which appears above.

Molecular Compound of Acridizinium Perchlorate with Tetracyanoethylene.—Upon addition of 1 g of acridizinium perchlorate to a solution of 1.5 g of tetracyanoethylene in 50 ml of acetonitrile the solution turned dark red. After the mixture had refluxed for 0.5 hr it was allowed to cool, depositing orange prisms decomposing at 185–188° with the loss of the orange color followed by melting at 199.5–201° to yield 1.0 g (80%). The product had the composition expected if 2 moles of acridizinium perchlorate was associated with 1 of tetracyanoethylene. The uv spectrum (CH_3CN) showed characteristic acridizinium absorption plus additional maxima at 440 and 464 mμ.

Anal. Calcd for $C_{13}H_{10}ClNO_4 \cdot {}^1/_2C_6N_4$: C, 55.89; H, 2.91; N, 12.23. Found: C, 55.83; H, 3.17; N, 12.00.

Similar results were obtained if the heating was continued for 8 hr.

Attempted Isomerization of Ethyl Maleate in Acetic Acid in the Presence of 1-Benzyl-2-bromopyridinium Bromide.—A suspension of 0.6 g of the named salt in a solution of 8.0 g of ethyl maleate in 7.5 ml of acetic acid was heated for 11 hr on the steam bath. Ether and water were then added and the ethereal layer was washed with water and bicarbonate solution. Analysis of the dried (magnesium sulfate) solution showed that only ethyl maleate was present in the ester fraction.

(12) As may be seen from Table II, for three of the derivatives the nmr spectrum affords evidence that the aryl group is at position 12 rather than at position 13, since the proton at C-11 is split only into a doublet. While the evidence is less clear in the case of the *p*-nitrophenyl derivative (**15**) we feel that this likewise is a 12-substituted compound.

Recovery of Excess Ester from the Cycloaddition Reaction with Ethyl Maleate.—A cycloaddition reaction of 1.4 g of acridizinium bromide with 8.5 g of ethyl maleate in 8 ml of acetic acid at 100° was carried on in the usual way except that after 7.5 hr the reaction was interrupted and the excess ester fraction recovered as described in the preceding paragraph. Gas–liquid partition chromatographic analysis showed that ester recovered was essentially pure (>90%) ethyl fumarate.

Recovery of Hydrogen Bromide from an Acetic Acid Solution of Acridizinium Bromide.—Acridizinium bromide (3 g) was dissolved in 75 ml of acetic acid and the mixture heated on a steam bath for 3 hr. The flask was arranged for vacuum distillation under reduced pressure with dropwise addition of pure acetic acid to maintain the original volume. During the distillation the temperature of the solution was 88–89° under pressure used. The distillate was carefully redistilled at atmospheric pressure and was found to contain bromide ion as evidenced by formation of a pale yellow precipitate with acidified silver nitrate solution.

Reaction Rates of *p*-Substituted Styrenes with Acridizinium Chloride.—A 0.005 *M* solution of acridizinium chloride[13] was prepared by dissolving 1.168 g in enough acetic acid to make 100 ml of solution. To avoid photodimerization[14] the solution was stored in a stoppered flask made of nonactinic glass. Reactions were carried out in glass tubes maintained at a constant temperature (65°) by insertion in a methanol vapor bath.

For each run 1 ml (0.05 mmole) of the stock solution was withdrawn and placed in a 2-ml volumetric flask, 0.5 mmole of dienophile was added, and solution was made up to 20 ml by addition of dimethyl sulfoxide. The resulting mixture was placed in a reaction tube which was heated in the vapor bath. Samples of 100 μl were withdrawn by use of a syringe and diluted to 50 ml with water. The intensity of the 399-mμ peak of the acridizinium ion was used to measure the concentration.[15] Pseudo-first-order reaction rate plots were obtained for each of the styrenes. The curves shown in Figure 1 are each for a single run, but the rate constants shown are the average of three determinations.

Registry No.—1 perchlorate, 15314-07-5; 2 perchlorate, 15259-85-5; 2 bromide, 15285-87-7; 3 perchlorate, 15314-08-6; 4 perchlorate, 15350-48-8; 5 perchlorate, 15285-84-4; 6 perchlorate, 15259-86-6; 7 perchlorate, 15259-87-7; 8, 15259-88-8; 9, 15259-89-9; 10, 15285-85-5; 11, 15285-86-6; 12, 15259-90-2; 13, 15259-91-3; 14, 15259-92-4; 15, 15259-93-5; acridizinium perchlorate with tetracyanoethylene (2:1), 15281-69-3.

(13) C. K. Bradsher and J. D. Turner, *J. Org. Chem.*, **32**, 1169 (1967).

(14) C. K. Bradsher, L. E. Beavers, and J. H. Jones, *ibid.*, **22**, 1740 (1957).

(15) Earlier work in this laboratory by D. L. Kerbow [Ph.D. Dissertation, Duke University, Durham, N. C., 1966] has shown that solutions of acridizinium bromide obey Beer's law in the long-wavelength region.

Ring-Opening Alkylations of 1,1-Dialkyl-3-Substituted Azetidinium Cations. Substituent Entropy-Controlled Strained Ring–Chain Equilibria[1]

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1,1-Dialkyl-3-hydroxyazetidinium cations (1) alkylated a variety of active nucleophiles, including amines, alkoxides, mercaptides, halides, etc., reacting with ring opening. Failure to alkylate methanol indicated that the four-membered azetidinium cycle is less reactive than known aziridinium salts. The formation of 2,5-bis-(dialkylaminomethyl)dioxanes from 1 was rationalized in terms of a double alkylation *via* an azetidinium alkoxide zwitterion. Selective competitive alkylations were described. These cations (1) participate in reversible equilibria with 1-chloro-3-dialkylamino-2-propanols. Equilibrium constants in acetonitrile at 30–40° were determined directly for a series of systems and the thermodynamic quantities were calculated. The equilibria were controlled by substituent entropy, attributed to restrictive interactions between the groups in the 1 and 3 positions of the azetidinium cycle. A conformational equilibrium of the ring is also inferred.

The reactivity conferred on small cycles by ring strain and the effects of substituents on ring closure and ring scission are of current interest. The strained rings containing quaternary ammonium ring members are the three-membered aziridinium and the four-membered azetidinium ions. The studies of the former class by Leonard and his school[2a] and others[2b] have elegantly established the marked reactivity of these cations toward even weak nucleophiles. Thus nucleophilic reagents which react under SN2 conditions (alkoxides, mercaptides, cyanide, halides, amines, etc.) as well as such weak nucleophiles as methanol are alkylated under mild conditions with ring opening.

It is not clear that the lesser strain of the simpler azetidinium cycles acts to promote ring-opening alkylation. Although alkylations with bicyclic azetidinium halides have been described,[3] these cases involved bridgehead quaternary members, as did the dequaternization of certain bicyclic quinolizidinium ions.[4] There are a number of reported instances of reversal of the formation of simple azetidinium halides, *i.e.*, to give the precursor γ-halo amines,[5] but 1,1-diethylazetidinium ion has been reported not to react with cysteine under mild conditions.[6] Azetidinium ions have been advanced as intermediates to explain the formation of two isomers in reactions of substituted γ-halo amines.[7]

Our attention was directed to the 1,1-dialkyl-3-hydroxyazetidinium chlorides (1) by our interest in the spontaneous cyclization of 1-alkylamino-3-chloro-2-propanols to 1-alkyl-3-azetidinols.[8] A variety of 1 has been prepared from secondary amines and epichlorohydrin *via* 1-chloro-3-dialkylamino-2-propanols (2).[9]

(1) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(2) (a) N. J. Leonard, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **26**, 211 (1965); (b) for example, G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, *J. Org. Chem.*, **30**, 666 (1965), and C. F. Hammer and S. R. Heller, Abstracts, 150th NationalMeeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, p 65S.

(3) A. Ebnöther and E. Jucker, *Helv. Chem. Acta*, **47**, 745 (1964).

(4) G. Fodor, *J. Am. Chem. Soc.*, **88**, 1040 (1966).

(5) C. F. Gibbs and C. S. Marvel, *ibid.*, **57**, 1137 (1935); C. Mannich and G. Baumgarten, *Ber.*, **70B**, 210 (1937).

(6) M. Torigoe, *Pharm. Bull.* (Japan), **1**, 349 (1953); *Chem. Abstr.*, **49**, 11962 (1955).

(7) R. C. Elderfield and C. Ressler, *J. Am. Chem. Soc.*, **72**, 4059 (1950); W. B. Wheatley and L. C. Cheney, *ibid.*, **74**, 1359 (1952).

(8) V. R. Gaertner, *Tetrahedron Letters*, 4691 (1966); *J. Org. Chem.*, **32**, 2972 (1967).

(9) (a) L. Niemilowicz, *Monatsh. Chem.*, **15**, 118 (1894); (b) R. Rothstein and K. Binovic, *Compt. Rend.*, **236**, 1050 (1953); (c) E. Schneider, German Patent 1,111,638 (1961); (d) K. Ichikawa, *Yuki Gosei Kagaku Kyokai Shi*, **22**, 546 (1964); *Chem. Abstr.*, **61**, 7008 (1964).