Nonbenzenoid Aromatic Systems. XIII.[1a] Certain Substituent Group Effects on the pK_a of 1-Azulenecarboxylic Acid

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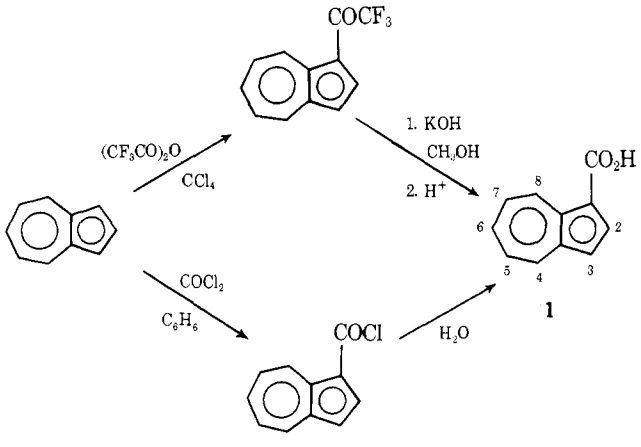
The synthesis of 2- (OCH_3, CH_3, Cl, Br, I, CN), 3- (OCH_3, CH_3, Br, $COCH_3$, CN, NO_2) and 6-substituted (OCH_3, CH_3, Br) 1-azulenecarboxylic acids (1) as well as 4-, 5- and 7-CH_3-1's are described. The thermodynamic pK_a's of these derivatives of 1 (except for 2-I-1 and 2-CN-1 owing to poor solubility) were determined in 50% (v/v) aqueous ethanol at 25.0 °C. The four substituent effects in the ortholike 2 position of 1 are correlated with σ_p^0 constants. Compared to related effects in *o*-$XC_6H_4CO_2H$ ionizations, a significant steric contribution to the ortho effect in the ortho-substituted benzoic acid derivatives is clearly established. The six substituent effects in 3-X-1 pK_a's show that the 3 position in 1 behaves intermediate between a benzene meta and para position. The variable behavior of substituent effects at the 3 position relative to the nature of the reaction center at C_1 is discussed. The limited 6-X-1 data set is in keeping with this position being a long-range paralike position. The individual methyl group effects at positions C_4–C_7 of the seven-membered ring are correlated with results of CNDO/2 calculations on 1 and its conjugate base. Although a small alternating effect is observed at C_4–C_7, the methyl group effects center around σ_p^0 behavior.

Hammett's choice of the dissociation of substituted benzoic acids in water at 25 °C as the standard reaction (ρ = 1.0) in developing his classic $\rho\sigma$ linear free energy relationship placed the study of substituent effects on aromatic carboxylic acid pK_a's at center stage in such correlation analyses.[2] As we approach the general question of how substituent effects are felt and transmitted from various nonequivalent positions to attached reaction centers in azulene, it was fitting and proper to initiate this general study by determining the effects of substituent groups on the pK_a's of the azulenecarboxylic acids.[3] The present paper will deal with certain substituent effects at the 2 (benzene ortholike), 3 (benzene metalike), and 6 positions (long-range benzene paralike) as well as the methyl group effects at the 2–7 positions on the pK_a of 1-azulenecarboxylic acid (1) in 50% (v/v) aqueous ethanol at 25 °C.

Synthesis of Substituted 1-Azuloic Acids. Two convenient methods are available for introducing the carboxylic acid group into the 1 position of azulene: (1) trifluoroacetylation of azulene using trifluoroacetic anhydride followed by base hydrolysis,[4] and (2) reaction of azulene with phosgene followed by hydrolysis.[5]



3-Substituted 1-Azuloic Acids (3-X-1). The acids 3-X-1 where X = Br, $COCH_3$, CN, and NO_2 were prepared by electrophilic substitution in the 3 position of methyl 1-azulenecarboxylate[4] followed by base hydrolysis to the respective acids. For the substituents X = CH_3O and CH_3, 1-methoxy-[1a] and 1-methylazulene[1a] were trifluoroacetylated. Base hydrolysis of 3-methyl-1-trifluoroacetylazulene gave 3-CH_3-1 while base hydrolysis of 3-methoxy-1-trifluoroacetylazulene led to extensive decomposition. However, 3-CH_3O-1 was prepared by treating 1-methoxyazulene with phosgene followed by hydrolysis.

2-Substituted 1-Azuloic Acids (2-X-1). Using Anderson's trifluoroacetylation procedure,[4] 2-methoxy-, 2-methyl-, 2-chloro, 2-bromo-, and 2-iodoazulenes[1a] were converted to the corresponding 2-X-1's. The synthesis of 2-CN-1 involved conversion of 2-I-1 to methyl 2-iodo-1-azulenecarboxylate (2) followed by reaction of 2 with cuprous cyanide in refluxing dimethylformamide (DMF). Hydrolysis of the methyl ester gave 2-CN-1.

6-Substituted 1-Azuloic Acids (6-X-1). 6-Methoxyazulene[1a] was allowed to react with phosgene and hydrolysis of the product acid chloride gave 6-CH_3O-1. Base hydrolysis of methyl 6-methyl-1-azulenecarboxylate[6] produced 6-CH_3-1.

6-Bromoazulene[1a] was converted to 6-Br-1 by reaction with phosgene and then hydrolysis. Since the sample of 6-Br-1 failed to give a satisfactory elemental analysis, it was converted to the methyl ester with diazomethane. Halogenodealkylation of methyl 6-bromo-1-azulenecarboxylate with lithium bromide in refluxing DMF afforded 6-Br-1 (46%) and 6-bromoazulene (39%). Here again a satisfactory elemental analysis was not obtained with 6-Br-1.

4-, 5-, and 7-Methyl-1-azuloic Acids. Trifluoroacetylation of 4-methylazulene[7] produced a single product identified as 1-trifluoroacetyl-4-methylazulene (3), on the basis of its NMR spectrum. The presence of the trifluoroacetyl group at C_1 has a marked anisotropic effect on the peri-C_8H if this proton is present; in the case of 3 this effect was apparent. Base hydrolysis of 3 gave 4-CH_3-1.

When a mixture of methyl 5- (4) and 7-methyl-1-azulenecarboxylates (5)[6] was chromatographed on Woelm alumina, the two isomers were separated. Each ester was then hydrolyzed to the corresponding acid. Their structural assignments are based on the NMR spectra of the methyl esters. In 4 the peri-C_8H is coupled to C_7H while in 5 this coupling is absent.

pK_a's of Substituted 1-Azuloic Acids. The thermodynamic pK_a's of the substituted 1-azuloic acids were determined in 50% (v/v) aqueous ethanol at 25 °C[3] and are listed in Table I. Even in this solvent the low solubilities of 2-CN-1 and 2-I-1 precluded their pK_a determinations.

Although the data sets for 2-X-1 and 6-X-1 are quite limited, the 3-X-1 data set contains a reasonable number of substituent groups and spread in their electronic responses to a reaction center. The present collection of pK_a data

Table I. pK_a's of Substituted 1-Azuloic Acids in 50% (v/v) Aqueous Ethanol at 25.00 ± 0.01 °C

Registry no.	Substituent in X-1	pK_a	ΔpK_a [pK_a (H) − pK_a (X)]
1201-25-8	H	6.992 ± 0.004[a]	0.000
58313-00-1	2-CH_3O	7.296 ± 0.004	−0.304
33447-31-3	2-CH_3	7.311 ± 0.006	−0.319
54798-17-3	2-Cl	6.422 ± 0.013	0.570
58313-01-2	2-Br	6.392 ± 0.008	0.600
58313-02-3	3-CH_3O	6.952 ± 0.006	0.040
58313-03-4	3-CH_3	7.092 ± 0.007	−0.100
58313-04-5	3-Br	6.528 ± 0.017	0.464
58313-05-6	3-CH_3CO	6.208 ± 0.014	0.784
58313-06-7	3-CN	5.898 ± 0.012	1.094
31802-33-2	3-NO_2	5.612 ± 0.011	1.380
10527-10-3	4-CH_3	7.096 ± 0.007	−0.104
58313-07-8	5-CH_3	7.192 ± 0.004	−0.200
58313-08-9	6-CH_3O	7.154 ± 0.010	−0.162
58313-09-0	6-CH_3	7.118 ± 0.003	−0.126
58313-10-3	6-Br	6.616 ± 0.023	0.376
58313-11-4	7-CH_3	7.171 ± 0.005	−0.179

[a] Standard deviations.

should minimally answer the question of how the 3 substituents interact with the reaction centers involved in the carboxylic acid–carboxylate anion equilibrium; that is, relative to the 1 position is the 3 position a "benzene metalike" position?

To answer this question, the pK_a data in Table I were treated by regression analysis and these results are listed in Table II. Our analysis began by treating each data set with the Yukawa–Tsuno–Sawada (YTS) relationship[8] treating each position as paralike in the expression $\Delta pK_a = \rho[\sigma_p^0 + r(\sigma_p^+ - \sigma_p^0)]$.[8]

It was immediately obvious from the results of the YTS correlations that from the small values of r, σ_p^0 constants correlated the limited 2-X-1 and 6-X-1 data sets. However, the value of $r = -0.18$ for the 3-X-1 data set indicated that less resonance than that present in σ_p^0 constants[8b] was involved in the interaction of the 3 substituents and the C_1 acid function. That σ_m and σ_m^0 constants appear to overcorrect this is shown in those correlations in Table II. Figure 1 shows the pK_a data plotted against σ_p^0 constants.

The reduced resonance effect by 3 substituents compared to that predicted by σ_p^0 constants is seen with *both* the 3-CH_3O-1[9] and 3-CH_3-1 acid pK_a's compared to the correlation line using 1 and the four 3-X-1's bearing electron-withdrawing groups. A further check on this point was carried out using the Swain–Lupton correlation, $\Delta pK_a = f\mathcal{F} + r\mathcal{R} + i$;[10] see Table III. The $\%\mathcal{R}$ (average relative importance of resonance) was 37 ± 4, which may be compared with 53% for σ_p, 22% for σ_m, 42% for σ_p^0, and 23% for σ_m^0.[10] Thus both the YTS and Swain–Lupton dual substituent approaches lead to the same conclusion that the 3 position in 3-X-1's behaves intermediate between a meta and para position in benzene derivatives.

Roberts et al.[12] reported $\rho = 1.46 \pm 0.05$ for *m*- and *p*-$XC_6H_4CO_2H$ ionization in 50% aqueous ethanol using Hammett σ constants. As we can see from the data for 3-X-1 and 6-X-1 pK_a's quite similar ρ values are obtained for the 1-azulenecarboxylic acid ionization using a somewhat different σ (σ_p^0) constant. Although this agreement in ρ values is excellent comparing the substituted benzoic acids with the combined 3-X-1's and 6-X-1's (last entry in Table II), there may be some doubt concerning the validity in the combination of these two data sets. This corroborates the position taken by Dewar et al.[13] and modified by Forsyth[14] in using the ρ value determined for benzene derivatives and "synthesizing" σ's for correlating substituent effects in other aryl units in related reaction processes.

Table II. Regression Analysis of Substituted 1-Azuloic Acids pK_a Data

Position (parameter)[a,g]	ρ	r[b]	C[c]	s[d]	F[e]	n[f]
2 (YTS)	2.15 ± 0.05	0.4	1.000	0.02	1232	5
3 (YTS)	1.68 ± 0.06	−0.18	0.998	0.04	586	7
6 (YTS)	1.22 ± 0.09	0.05	0.998	0.03	119	4
3 (σ_m)	1.93 ± 0.20		0.975	0.14	97	7
3 (σ_m^0)	1.87 ± 0.17		0.979	0.13	115	7
3 (σ_p^0)	1.52 ± 0.09		0.991	0.09	263	7
3 (σ_p^0), 6 (σ_p^0)	1.45 ± 0.07		0.989	0.09	350	10

[a] Position(s) and constant(s) used in correlation. Yukawa–Tsuno–Sawada identified as YTS. [b] The value of r in YTS equation. [c] Correlation coefficients. [d] Standard error of the estimate in pK_a units. [e] Critical value of the variance ratio test. [f] Number of points in data set; each uses X = H. [g] The sources for the substituent constants used in these analyses were σ_m (ref 10), σ_p (ref 10), σ_m^0 (ref 8b), and σ_p^0 (ref 8b with that for $COCH_3$ as 0.502[10]).

Table III. Swain–Lupton Correlation Results for Substituted 1- Azulenecarboxylic Acids

Substituent position	f[a]	r[a]	i[a]	$\%\mathcal{R}$[a]	C[b]	n[c]
2[d]	1.23 ± 0.02	1.61 ± 0.04	−0.01	45.0 ± 0.04	0.9997	5
3	1.01 ± 0.09	0.97 ± 0.16	0.04	37 ± 4	0.992	7
6[d]	0.71 ± 0.06	0.93 ± 0.10	0.02	45 ± 3	0.997	4

[a] Parameters calculated as per ref 10. [b] Correlation coefficient. [c] Number of points in data set; each uses X = H. [d] Data set does not include strong electron-withdrawing groups.

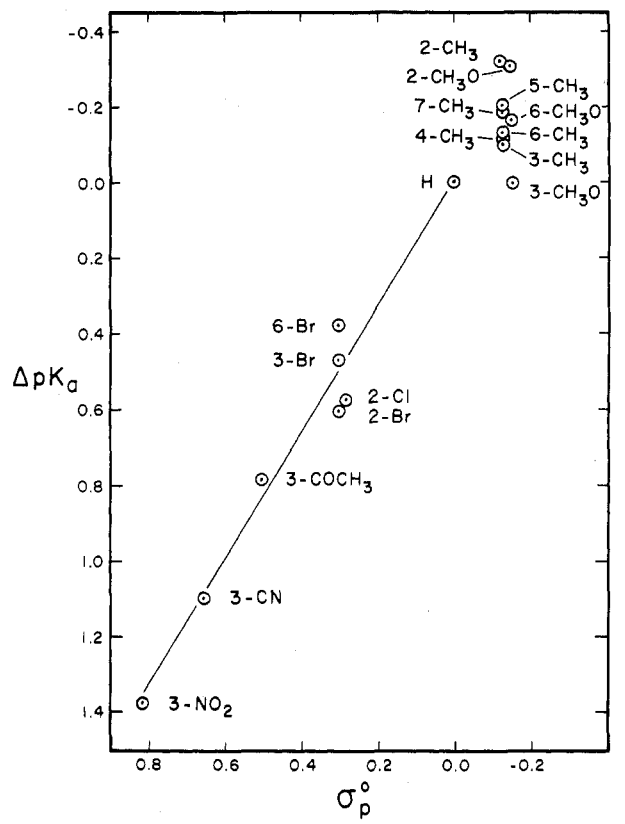


Figure 1. Plot of ΔpK_a's of X-1's against σ_p^0 constants. The line is that defined by electron-withdrawing 3-X-1's and 1.

Although the data sets of 2-X-1 and 6-X-1 are very limited we have applied the Swain–Lupton correlation[10] to

Table IV. Comparison of pK_a's of 2-X-1 and o-$XC_6H_4CO_2H$

	2-X-1		o-$XC_6H_4CO_2H$[17]	
H	pK_a[a]	ΔpK_a[c]	pK_a	ΔpK_a[c]
H	6.99		5.76[a,d] (4.20)[b]	
CH_3O	7.30	−0.31	5.83 (4.09)	−0.07[a,d] (0.11)[b]
CH_3	7.31	−0.32	5.78 (3.91)	−0.02 (0.29)
Cl	6.42	0.57	4.82 (2.94)	0.94 (1.26)
Br	6.39	0.60	4.73 (2.85)	1.03 (1.35)

[a] In 50% (v/v) aqueous ethanol at 25.0 °C. [b] In water at 25.00 °C.[17b] [c] pK_a (H) − pK_a (X). [d] Reference 17a.

them in an attempt to assess the sensitivities of these substituents to field and resonance effects. The resultant values are listed in Table III along with those of 3-X-1.

Comparing the empirical weighting factors f and r found for substituents at the 3 and 6 positions (Table III) we see that while these sensitivities to the resonance effect are the same, the sensitivity to the field effect is less at the 6 position. The latter was expected since the distance in azulene from the proton at C_1H to C_6 is 5.2 Å while the same distance (C_1H) to C_3 is 3.3 Å. This coupled with a poorer angle for charge–dipole interaction from C_6X to C_1H compared to C_3X (cos θ in the Kirkwood–Westheimer treatment of field effects)[15] leads to a reduced field effect by the 6 substituents.

The substituent effects by the 2 substituents in the pK_a's of 2-X-1 are interesting since they bear on the question of the ortho or proximity effect in ortho-substituted benzoic acid ionizations.[16] Table IV list the pK_a's of 2-X-1's and the corresponding o-$XC_6H_4CO_2H$'s[17] for comparison. We see that the change from water to 50% (v/v) aqueous ethanol has a parallel effect on the o-$XC_6H_4CO_2H$ ΔpK_a's. This was also observed by McCoy and Riecke[18] in the pK_a's of various o-alkylbenzoic acids in aqueous methanol.

As we change from o-$XC_6H_4CO_2H$ to 2-X-1 the distance between the X and CO_2H group increases owing to the geometric change involving a six-membered ring in o-$XC_6H_4CO_2H$ and a five-membered ring in 2-X-1. This change in geometry gave the large K_1/K_2 ratio of $10^{7.1}$ for 1,2-azulenedicarboxylic acid compared to 288 for this same ratio for phthalic acid.[3] In the cases of the CH_3O and CH_3 substituents especially, we find the *normal* effects of these substituents in 2-X-1 to be *acid weakening* which are almost negligible in the o-$XC_6H_4CO_2H$ series. Also, the substituent effects of o-Cl and o-Br on the pK_a of benzoic acid are larger in magnitude (greater acid-strengthening effect) than those found in 2-X-1's with X = Cl and Br. These latter differences are greater than those expected from the geometry changes in going from the six-membered ring of o-$XC_6H_4CO_2H$ to the five-membered ring of 2-X-1 using the field effect model with the same effective dielectric constant.[15]

We interpret this comparison as adequate evidence for a substantial contribution by *steric inhibition of resonance* to the overall effects in the ionization of o-$XC_6H_4CO_2H$'s realizing that factors such as steric inhibition of solvation and field and resonance effects are also operating.[18] The above data taken together with other recent reports[18,19] should satisfy even the most ardent critics of the presence of a significant contribution of steric inhibition of resonance in reactions of ortho-substituted benzoic acids.

The effect of the methyl group on the pK_a of 1 was determined at six of the seven nonequivalent ring positions (Table I and Figure 1). Omitting the 2-methyl effect due to the additional factors involved in the ortho effect, the remaining five methyl effects appear as roughly two groups

Table V. The CNDO/2 Regional Charges, q_r's, and Changes in Regional Charges, Δq_r's, Compared to Azulene for *syn*-1 and 1-Azulenecarboxylate Anion[20]

Ring position	q_r azulene	q_r *syn*-1	Δq_r[a] (*syn*-1)	q_r^- 1-$AzCO_2^-$	Δq_r^-[b] (1-$AzCO_2^-$)
3	5.084	5.081	0.00	5.119	−0.04
4	4.943	4.943	0.00	4.979	−0.04
5	5.025	5.007	+0.02	5.078	−0.05
6	4.942	4.940	0.00	4.978	−0.04
7	5.025	5.001	+0.02	5.069	−0.04

[a] $\Delta q_r = q_r$ (AzH) − q_r (*syn*-1). [b] $\Delta q_r^- = q_r$ (AzH) − q_r (1-Az-CO_2^-).

with the 3-, 4-, and 6-CH_3 effects being smaller than those found for the 5- and 7-CH_3 effects. In an attempt to understand these methyl substituent effects, we have modeled the reaction with CNDO/2 MO calculations[20] (*not structure minimized*) for the structures of 1 and its conjugate base. Calculations on *syn*- and *anti*-1 gave no significant changes in the ring position regional charges, q_r's,[21] except for the 2 position, where a small change (0.01) was noted. The geometry of the azulene ring selected was that used in ab initio calculations[22] taken from x-ray crystallographic studies.[23] The other bond lengths and angles[24] were as follows: C_1–C(O_2H), 1.48 Å; C=O, 1.24 Å: C(=O)–OH, 1.29 Å; C_1–C=O ∠, 122°; C_1–C(=O)–OH ∠, 118°; C–O in CO_2^-, 1.26 Å; O–C–O ∠ in CO_2^-, 126°. The q_r's and Δq_r's (compared to azulene, AzH) are listed in Table V for the five nonequivalent ring positions under consideration.

As expected, the carbonyl-ring interaction had only a small perturbing influence on the 3–7 ring positions; the predominant factor in the acid weakening of 1-azulenecarboxylic acid (pK_a 6.99) compared to benzoic acid (pK_a 5.80 in 50% H_2O–EtOH) was the large surplus of electron density at C_1 of the unsubstituted azulene system (AzH). What we do see in the Δq_r's in Table V is that electron density is lost from the 5 and 7 positions (also at the 2, 9, and 10 positions Δq_r's ~0.02, not shown in Table V) when we replace C_1H in AzH by C_1CO_2H. Since all of the Δq_r^-'s are more approximately equal, the major acid-weakening effects on the pK_a of 1 by the methyl substituent would be expected at the C_5 and C_7 ring positions, in agreement with the experimental results.[25]

We see that in the azulene nonequivalent ring positions relative to the $-CO_2H \rightleftarrows -CO_2^-$ reaction center at C_1, no truly meta position is found. While the methyl group effects at C_2–C_7 on the pK_a of 1 do show an alternating effect they center around σ_p^0 behavior. Qualitatively, we believe that this is the result of more efficient charge delocalization in the 1-azulyl group with a greater number of ring sites sharing the formal charge compared to that found in the isomeric, benzenoid 1- and 2-naphthoic acids.[26]

An interesting feature of our results to date is the variable nature of the substituent effects at C_3 in reactions of the 1-azulyl group. As we have pointed out in the present study, under the modest perturbing influence of 1 ionization the C_3 substituent effects are intermediate between meta- and paralike behavior. However, in k_Δ acetolysis of 3-substituted 2-(1-azulyl)ethyl tosylates[27] excellent correlation of the data (3-OCH_3 to 3-NO_2) with σ_p^0 constants is observed. While this is not expected when one considers only canonical resonance structures, it is predicted from molecular orbital approaches.

Experimental Section[28]

1-Trifluoroacetyl-2-methoxyazulene. To a solution of 130 mg (0.823 mmol) of 2-methoxyazulene[1a,30] in 20 ml of CCl_4 at room temperature was added 1 ml of $(CF_3CO)_2O$. The color changed

from blue to light red. After 5 min 100 ml of ether was added, and the organic solution was washed with five 50-ml portions of water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on alumina[29] and an orange band was eluted with 1:1 benzene–CH_2Cl_2. The resulting orange solid was recrystallized from CH_2Cl_2–hexane to give 175 mg (83%) of the product as light orange needles: mp 100–101 °C; NMR (CCl_4, internal Me_4Si): τ 0.45 (m, C_8H, 1), 1.7–2.65 (m, $C_{4,5,6,7}H$'s, 4), 3.38 (s, C_3H, 1), and 5.85 (s, OCH_3, 3)

Anal. Calcd for $C_{13}H_9F_3O_2$: C, 61.42; H, 3.56. Found: C, 61.50; H, 3.91.

2-Methoxy-1-azuloic Acid (2-CH_3O-1). A mixture of 40 mg (0.16 mmol) of 1-trifluoroacetyl-2-methoxyazulene and 400 mg of KOH in 5 ml of 50% aqueous ethanol was heated under reflux for 4 h. This solution was poured into water and extracted with CH_2Cl_2. The aqueous layer was acidified with dilute hydrochloric acid and the acid was extracted with CH_2Cl_2 which was dried (Na_2SO_4) and evaporated. The crude orange acid was recrystallized from $CHCl_3$–hexane giving 27 mg (85%) of orange crystals, mp 174–175 °C.

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.02; H, 5.00.

1-Trifluoroacetyl-2-methylazulene. 2-Methylazulene[1a,30] (110 mg, 0.78 mmol) was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina[29] where 1:1 benzene–CH_2Cl_2 eluted a red band leaving a large diffuse red band near the top of the column. The eluted band was evaporated and the solid recrystallized from hexane at −20 °C to give 60 mg (33%) of the desired product as red needles: mp 49–50 °C; NMR (CCl_4, internal Me_4Si) τ 0.70 (m, C_8H, 1), 1.5–2.8 (m, $C_{4,5,6,7}H$'s, 4), 2.90 (s, C_3H, 1), and 5.20 (s, CH_3, 3).

Anal. Calcd for $C_{13}H_9F_3O$: C, 65.55; H, 3.81. Found: C, 65.80; H, 3.56.

The apparent reason for the low yield of the product was hydrolysis on the alumina column.

2-Methyl-1-azuloic Acid (2-CH_3-1). Base hydrolysis of 60 mg (0.25 mmol) of 1-trifluoroacetyl-2-methylazulene as above and work-up afforded 25 mg (53%) of maroon crystals (recrystallized from ether–hexane), mp 180–190 °C dec.

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.50; H, 5.27.

1-Trifluoroacetyl-2-chloroazulene. The trifluoroacetylation of 780 mg (4.8 mmol) of 2-chloroazulene[30] was carried out as above. The product was chromatographed on deactivated (3% water) alumina.[29] CH_2Cl_2 developed a single, broad, violet band that was eluted with $CHCl_3$ to afford 1.240 g (100%) of the title compound. Crystallization from ethanol afforded large, red plates: mp 88.0–88.5 °C; ir (KBr) 6.12 μ (s, C=O); NMR ($CDCl_3$, internal Me_4Si) τ 0.43–0.77 (m, C_8H, 1), 1.50–1.85 (m, C_4H, 1), 1.87–2.67 (m, $C_{5,6,7}H$'s, 3), and 2.77 (s, C_3H, 1); λ_{max} (CH_2Cl_2) 275 nm (log ϵ 4.44), 323 (4.61), 376 (4.15) (sh), 392 (4.13) (sh), and 495 (2.95).

Anal. Calcd for $C_{12}H_6F_3ClO$: C, 55.72; H, 2.34. Found: C, 55.55; H, 2.46.

Methyl 2-Chloro-1-azulenecarboxylate. 1-Trifluoroacetyl-2-chloroazulene (1.90 g, 7.34 mmol) was base hydrolyzed as above to give 1.44 g (95%) of crude 2-chloroazuloic acid (2-Cl-1). To 1.590 g (7.7 mmol) of crude 2-Cl-1 in 500 ml of ethyl acetate was added an excess of an ethereal CH_2N_2 solution. This mixture was allowed to stand for 30 min, the solvent volume reduced, and the residue chromatographed on alumina.[29] Benzene eluted a narrow, yellow band that was not investigated, and a broad, red band that afforded 1.470 g (87%) of the title compound. CH_2Cl_2 eluted a narrow, yellow-orange band that was not investigated. Crystallization from ethanol afforded fine, red needles of the ester: mp 86.0–86.5 °C; ir (KBr) 5.92 (s, C=O) and 9.55 μ (s, C–O); NMR ($CDCl_3$, internal Me_4Si) τ 0.38–0.72 (m, C_8H, 1), 1.57–1.87 (m, C_4H, 1), 2.05–2.67 (m, $C_{5,6,7}H$'s, 3), 2.78 (s, C_3H, 1), and 6.02 (s, CO_2CH_3, 3); λ_{max} (CH_2Cl_2) 294 nm (log ϵ 4.72), 304 (4.77), 340 (3.81), 350 (3.84), 366 (3.51), 515 (2.72), 538 (2.70) (sh), and 590 (2.28) (sh).

Anal. Calcd for $C_{12}H_9O_2Cl$: C, 65.32; H, 4.11. Found: C, 65.62; H, 3.97.

2-Chloro-1-azuloic Acid (2-Cl-1). Methyl 2-chloro-1-azulenecarboxylate (130 mg, 0.58 mmol) was hydrolyzed with 400 mg of KOH in 8 ml of 80% aqueous ethanol heated under reflux for 30 min. Work-up gave 80 mg (39%) of 2-Cl-1 as maroon crystals which were recrystallized from $CHCl_3$–hexane as maroon needles, mp 235–237 °C dec (ready sublimation >170 °C).

Anal. Calcd for $C_{11}H_7O_2Cl$: C, 63.94; H, 3.41. Found: C, 63.61; H, 3.51.

1-Trifluoroacetyl-2-bromoazulene. 2-Bromoazulene[1a] (90 mg, 0.44 mmol) was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina.[29] Benzene eluted a violet band, that yielded 30 mg of unreacted 2-bromoazulene, and a red band that was not investigated. $CHCl_3$ developed a violet band that eluted as a red-colored solution, affording 50 mg (38%, 57% net) of the title compound that slowly crystallized upon standing: mp 77.0–78.0 °C; ir (KBr) 6.06 μ (s, C=O); NMR ($CDCl_3$, internal Me_4Si) τ 0.92 [d (J = 10 Hz), C_8H, 1], 1.63 [d (J = 10 Hz), C_4H, 1], 2.00–2.57 (m, $C_{5,6,7}H$'s, 3), and 2.65 (s, C_3H, 1); λ_{max} (cyclohexane) 270 nm (log ϵ 4.28), 276 (4.34), 315 (4.56), 325 (4.59), 352 (3.87), 513 (2.80), 540 (2.77), and 590 (2.35).

Anal. Calcd for $C_{12}H_6F_3BrO$: C, 47.55; H, 2.00. Found: C, 47.80; H, 2.23.

2-Bromo-1-azuloic Acid (2-Br-1). 1-Trifluoroacetyl-2-bromoazulene (40 mg, 0.13 mmol) was hydrolyzed with base as above. Work-up gave 20 mg (61%) of maroon crystals of 2-Br-1, mp 226–228 °C dec (ready sublimation >180 °C).

Anal. Calcd for $C_{11}H_7O_2Br$: C, 52.61; H, 2.81. Found: C, 52.51; H, 2.50.

1-Trifluoroacetyl-2-iodoazulene. 2-Iodoazulene[30] (280 mg, 1.11 mmol) was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina[29] where hexane eluted a violet band containing 50 mg of 2-iodoazulene. CH_2Cl_2 developed a violet-blue band that was eluted with ethanol which afforded 295 mg (76%, 93% net) of the title compound. Crystallization from hexane afforded red needles: mp 90.0–90.5 °C; ir (KBr) 6.05 μ (s, C=O); NMR (CCl_4, internal Me_4Si) τ 0.98–1.60 (m, C_8H, 1), 1.53–1.90 (m, C_4H, 1), and 1.93–2.75 (m, 4); λ_{max} (cyclohexane) 274 nm (log ϵ 4.23), 323 (4.50), 334 (4.50), 362 (3.93) (sh), 523 (2.78), and 552 (2.75) (sh).

Anal. Calcd for $C_{12}H_6F_3IO$: C, 41.17; H, 1.73. Found: C, 41.21; H, 1.79.

2-Iodo-1-azuloic Acid (2-I-1). 1-Trifluoroacetyl-2-iodoazulene (270 mg, 0.77 mmol) was hydrolyzed with base as above. After work-up, the combined ethereal extracts gave 230 mg (100%) of 2-I-1. Recrystallization from $CHCl_3$ afforded silky, violet needles: mp 210–212 °C dec; ir (KBr) 6.08 (s, C=O) and 8.10 μ (s); NMR (Me_2SO-d_6, internal Me_4Si)[33] τ 0.00–0.67 (m, C_8H, 1), 1.50–1.62 (m, C_4H, 1), and 1.75–2.62 (m, 4); λ_{max} (CH_2Cl_2) 295 nm (log ϵ 4.64), 306 (4.74), 316 (4.43) (sh), 350 (3.84) (sh), 364 (3.72) (sh), and 515 (2.83).

Anal. Calcd for $C_{11}H_7O_2I$: C, 44.32; H, 2.37. Found: C, 44.43; H, 2.58.

Methyl 2-Iodo-1-azulenecarboxylate (2). 2-Iodo-1-azuloic acid (100 mg, 0.34 mmol) in 100 ml of ether was treated with an excess of ethereal CH_2N_2. After standing for 10 min, the solvent volume was reduced and the residue was chromatographed on alumina[29] where CH_2Cl_2 eluted a single, lavender band that afforded 104 mg (98%) of the title compound. Crystallization from CCl_4 yielded lavender needles: mp 65.0–66.5 °C; ir (neat film) 5.88 (s, C=O) and 9.55 μ (s, C–O); NMR (CCl_4, internal Me_4Si) τ 0.28–0.58 (m, C_8H, 1), 1.63–1.92 (m, C_4H, 1), 2.03–2.90 (m, 4), and 6.07 (s, CO_2CH_3, 3); λ_{max} (cyclohexane) 304 nm (log ϵ 4.71), 317 (4.73), 346 (4.08), 363 (4.12), 532 (2.71), 565 (2.68), and 615 (2.30) (sh).

Anal. Calcd for $C_{12}H_9O_2I$: C, 46.18; H, 2.91. Found: C, 46.23; H, 2.98.

Methyl 2-Cyano-1-azulenecarboxylate. To 155 mg (0.495 mmol) of 2 in 10 ml of dry (distilled from BaO) DMF was added 67 mg (0.75 mmol) of CuCN. The mixture was heated at 140–150 °C for 3.5 h as the color gradually changed from red to blue. This mixture was cooled, diluted with 100 ml of benzene, and washed with six 100-ml portions of warm aqueous NaCN (prepared from 20 g of NaCN and 600 ml of warm water). The blue, benzene layer was washed with 100 ml of water and dried (Na_2SO_4), the solvent volume reduced, and the residue chromatographed on alumina.[29] Benzene-CH_2Cl_2 (1:1) eluted a narrow, violet band that afforded 20 mg of unreacted 2. Continued elution afforded a broad, blue band that yielded 82 mg (78%, 90% net) of the title compound. Crystallization afforded lavender needles: mp 172–174 °C; ir (KBr) 4.52 (m, C≡N), 5.92 (s, C=O), and 9.50 μ (s, C–O); NMR ($CDCl_3$, internal Me_4Si) τ 0.12–0.38 (m, C_8H, 1), 1.32–1.58 (m, C_4H, 1), 1.83–2.67 (m, 4), and 5.98 (s, CO_2CH_3, 3); λ_{max} (95% ethanol) 261 nm (log ϵ 4.18), 295 (4.72), 306 (4.82), 347 (4.03), 361 (3.75), 545 (2.96) (sh), and 568 (2.99).

Anal. Calcd for $C_{13}H_9O_2N$: C, 72.93; H, 4.29; N, 6.63. Found: C, 74.09; H, 4.22; N, 6.44.

2-Cyano-1-azuloic Acid (2-CN-1). To 83 mg (0.394 mmol) of methyl 2-cyano-1-azulenecarboxylate in 8 ml of ethanol was added 150 mg (2.68 mmol) of KOH in 2 ml of water. This mixture was heated under reflux for 15 min, diluted with 100 ml of water, and

extracted with 50 ml of ether to remove unreacted material. The aqueous portion was acidified with 10% hydrochloric acid and extracted with five 200-ml portions of ether. The combined ethereal extracts were washed with 500 ml of water and dried (Na_2SO_4), and the solvent volume reduced to yield 73 mg (95%) of the title compound. Crystallization from ethanol yielded violet needles: mp 293–294 °C; ir (KBr) 4.52 (m, C≡N) and 6.05 μ (s, C=O); NMR (Me_2SO-d_6, internal Me_4Si) τ −3.05 (broad s, CO_2H, 1), 0.12–0.42 (m, C_8H, 1), 1.00–1.37 (m, C_4H, 1), and 1.50–2.67 (m, 4); λ_{max} (95% ethanol) 261 nm (log ε 4.04), 294 (4.52), 306 (4.59), 347 (3.88), 360 (3.58), 545 (2.89) (sh), and 568 (2.90).

Anal. Calcd for $C_{12}H_7O_2N$: C, 73.09; H, 3.58. Found: C, 72.88; H, 3.81.

1-Trifluoroacetyl-3-methoxyazulene. 1-Methoxyazulene[1a] (75 mg, 0.50 mmol) was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina.[29] Benzene eluted a green band that yielded 125 mg (100%) of the title compound. Crystallization from hexane afforded long, dark-green needles: mp 92.0–92.5 °C; ir (KBr) 6.09 (s, C=O) and 9.44 μ (s, C–O); NMR (CCl_4, internal Me_4Si) τ 0.18–0.53 (m, C_8H, 1), 1.43–1.73 (m, C_4H, 1), 2.17–2.87 (m, 4), and 5.97 (s, OCH_3, 3); λ_{max} (cyclohexane) 282 nm (log ε 4.19), 313 (4.30), 319 (4.32), 327 (4.43), 423 (3.99), 450 (4.04), 576 (2.67), 610 (2.72), 623 (2.73), 657 (2.62), 682 (2.56), 735 (2.16), and 765 (2.00).

Anal. Calcd for $C_{13}H_9F_3O_2$: C, 61.42; H, 3.57. Found: C, 61.35; H, 3.47.

3-Methoxy-1-azuloic Acid (3-CH_3O-1). To a cool (ice bath) solution of 130 mg (0.82 mmol) of 1-methoxyazulene[1a] in 5 ml of dry benzene was added 1.0 ml of a 12.5% solution of $COCl_2$ in benzene for 5 min. This mixture was allowed to warm to room temperature and after 45 min 5 ml of water was added. Following 10 min of additional stirring, the mixture was diluted with 50 ml of water and 50 ml of ether. The layers were separated and the extraction repeated with two 50-ml portions of ether. The combined ethereal extracts were extracted with three 50-ml portions of 10% aqueous KOH, the ethereal layer discarded, and the aqueous portion washed with four 50-ml portions of $CHCl_3$ which removed a brown coloration. The blue-green aqueous portion was acidified with 10% hydrochloric acid and extracted with three 100-ml portions of ether. These combined ethereal extracts were washed with 150 ml of water and dried (Na_2SO_4), the solvent volume reduced, and the green residue chromatographed on silica gel with 3:1 CH_2Cl_2–ether. A narrow, green band eluted followed closely by a broad, blue band. The green band was not investigated and the broad, blue band afforded 48 mg (29%) of the title compound. Crystallization from 3:1 $CHCl_3$–hexane gave green needles: mp 201–202 °C; ir (KBr) 6.04 μ (s, C=O); NMR ($CDCl_3$, internal Me_4Si)[33] τ 0.35–0.65 (m, C_8H, 1), 1.42–1.68 (m, C_4H, 1), 2.15 (s, C_2H, 1), 2.23–3.00 (m, $C_{5,6,7}H$'s, 3), and 5.93 (s, OCH_3, 3); λ_{max} (CH_2Cl_2) 301 nm (log ε 4.46), 308 (4.46), 313 (4.53), 405 (3.89) (sh), and 620 (2.68).

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.14; H, 5.03.

Methyl 3-Methoxy-1-azulenecarboxylate. 3-CH_3O-1 (118 mg, 0.58 mmol) was esterified with CH_2N_2 as above. After work-up, the residue was chromatographed on alumina.[29] CH_2Cl_2 eluted a small, green band that was not investigated and a broad, blue band that afforded 75 mg (60%) of the title compound, as a green oil which crystallized from 1:1 hexane–CCl_4 to yield green rosettes: mp 62.0–62.5 °C; ir (neat film) 5.98 (s, C=O) and 9.79 μ (s, C–O); NMR (CCl_4, internal Me_4Si) τ 0.42–0.72 (m, C_8H, 1), 1.45–1.75 (m, C_4H, 1), 2.20–3.10 (m, $C_{2,5,6,7}H$'s, 4), 6.00 (s, OCH_3, 3), and 6.13 (s, CO_2CH_3, 3); λ_{max} (cyclohexane) 287 nm (log ε 4.39), 291 (4.50), 298 (4.61), 305 (4.57), 311 (4.67), 382 (3.96), 409 (4.07), 623 (2.59), 640 (2.62), 675 (2.54), 706 (2.54), and 755 (2.14).

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.60. Found: C, 71.96; H, 5.40.

1-Trifluoroacetyl-3-methylazulene. 1-Methylazulene[1a,4] was trifluoroacetylated as above. After work-up, the residue was chromatographed on alumina.[29] Benzene eluted a narrow green band that was not investigated, followed by a broad, brown-red band that afforded 278 mg (66%) of the title compound. Crystallization from hexane yielded long, brown plates: mp 96.0–96.5 °C; ir (KBr) 6.10 μ (s, C=O); NMR (CCl_4, internal Me_4Si) τ 0.17–0.50 (m, C_8H, 1), 1.59–1.80 (m, C_4H, 1), 1.83–2.75 (m, 4), and 7.42 (s, CH_3, 3); λ_{max} (cyclohexane) 272 nm (log ε 4.20), 298 (4.37), 309 (4.45), 316 (4.54), 392 (4.05), 415 (4.11), 553 (2.74), 596 (2.62), 632 (2.20), and 658 (2.11).

Anal. Calcd for $C_{13}H_9F_3O$: C, 65.54; H, 3.80. Found: C, 65.45; H, 3.70.

3-Methyl-1-azuloic Acid (3-CH_3-1). 1-Trifluoroacetyl-3-methylazulene (278 mg, 1.17 mmol) was hydrolyzed with base as above. After work-up, the solid residue was washed with five 10-ml portions of hexane which removed a yellow substance (not investigated). The remaining residue afforded 132 mg (60%) of the title compound. Crystallization from ether yielded long, fine, gray needles: mp 195–196 °C; ir (KBr) 6.10 (s), 7.00 (s), and 9.09 μ (s); NMR (Me_2SO-d_6, internal Me_4Si) τ −2.22 (broad s, CO_2H, 1), 0.32–0.62 (m, C_8H, 1), 1.32–1.65 (m, C_4H, 1), 1.82 (s, C_2H, 1), 2.00–2.72 (m, $C_{5,6,7}H$'s, 3), and 7.38 (s, CH_3, 3); λ_{max} (95% ethanol) 291 nm (log ε 4.64), 296 (4.63), 303 (4.72), 366 (3.91), 380 (3.99), 564 (2.63), and 665 (2.40) (sh).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.70; H, 5.67.

Methyl 3-Bromo-1-azulenecarboxylate. A mixture of 230 mg (0.12 mmol) of methyl 1-azulenecarboxylate[4] and 0.40 g of *N*-bromosuccinimide in 25 ml of benzene was stirred at room temperature for 20 min, then poured onto an alumina[29] column. A blue band eluted which solidified on solvent evaporation. Recrystallization from CH_2Cl_2–hexane at −30 °C gave 273 mg (83%) of the desired ester as blue crystals: mp 89–90 °C; NMR (CCl_4, internal Me_4Si) τ 0.42 (m, C_8H, 1), 1.4–2.8 (m, $C_{2,4,5,6,7}H$'s with C_2H as s at τ 1.73, 5), and 6.13 (s, CH_3, 3).

Anal. Calcd for $C_{12}H_9O_2Br$: C, 54.37; H, 3.42. Found: C, 54.10; H, 3.26.

Methyl 3-Acetyl-1-azulenecarboxylate. To a solution of 250 mg (1.34 mmol) of methyl 1-azulenecarboxylate[4] in 5 ml of acetic anhydride was added 0.3 ml of $SnCl_4$ in 50 ml of CH_2Cl_2. After work-up, the residue was chromatographed on alumina[29] where CH_2Cl eluted a deep-red band of the product. Recrystallization from CH_2Cl_2–hexane at −30 °C gave 180 mg (50%) of the desired ester: mp 120–121 °C; NMR (CCl_4, internal Me_4Si) τ −0.2 to 0.1 (m, $C_{4,8}H$'s, 2), 1.27 (s, C_2H, 1), 2.0–2.5 (m, $C_{5,6,7}H$'s, 3), 6.1 (s, CH_3, 3), and 7.39 (s, CH_3, 3).

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.80; H, 5.47.

Methyl 3-Cyano-1-azulenecarboxylate. To a cool (ice bath) solution of 250 mg (1.34 mmol) of methyl 1-azulenecarboxylate[4] and 1.45 g (13.4 mmol) of BrCN in 25 ml of ether was added dropwise 1.55 ml of $SnCl_4$. After stirring overnight at room temperature and work-up, the residue was chromatographed on alumina.[29] Benzene eluted a blue band containing 94 mg (25%) of methyl 3-bromo-1-azulenecarboxylate identical with that prepared above. CH_2Cl_2 eluted a red band containing 95 mg (34%) of the desired cyano ester: mp 141–142 °C; NMR (CCl_4, internal Me_4Si) τ 0.1–2.5 (m, $C_{2,4,5,6,7,8}H$'s with C_2H as s at τ 1.5, 6) and 6.08 (s, CH_3, 3).

Anal. Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29. Found: C, 73.95; H, 4.37.

Methyl 3-Nitro-1-azulenecarboxylate. To a solution of 290 mg (1.56 mmol) of methyl 1-azulenecarboxylate[4] in 15 ml of acetic anhydride was added 600 mg of $Cu(NO_3)_2$ in 25 ml of acetic anhydride over a 10-min period. After 15 min of stirring and work-up, the residue was chromatographed on alumina[29] with benzene. Benzene eluted a yellow band which may have been 1,3-dinitroazulene. CH_2Cl_2 eluted a red band containing the nitro ester. Recrystallization afforded 90 mg (25%) of the product: mp 145–147 °C; NMR ($CDCl_3$, internal Me_4Si) τ 0.0–0.4 (m, $C_{4,8}H$'s, 2), 1.24 (s, C_2H, 1), 1.6–2.5 (m, $C_{5,6,7}H$'s, 3), and 6.06 (s, CH_3, 3).

Anal. Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.73; H, 3.92; N, 5.83.

3-Bromo-, 3-Acetyl-, 3-Cyano-, and 3-Nitro-1-azuloic Acids. Each of the above esters was hydrolyzed with KOH in 50% aqueous methanol at room temperature for 3 h, then heated under reflux for 30 min. Extraction with ether removed any starting ester. Acidification and extraction of the desired acid into ether gave these compounds which were recrystallized from ether–hexane. 3-Br-1, mp 270 °C dec. Anal. Calcd for $C_{11}H_7BrO_2$: C, 52.62; H, 2.81. Found: C, 52.25; H, 2.65. 3-CH_3CO-1, mp 220–235 °C dec. Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 73.80; H, 4.86. 3-CN-1, mp 265–270 °C (sublimed). Anal. Calcd for $C_{12}H_7NO_2$: C, 73.09; H, 3.58; N, 7.10. Found: C, 73.00; H, 3.74; N, 7.24. 3-NO_2-1, mp 260–270 °C (sublimed). Anal. Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; H, 6.45. Found: C, 60.45; H, 3.02; N, 6.21.

1-Trifluoroacetyl-4-methylazulene. 4-Methylazulene[7] (164 mg, 1.15 mmol) was trifluoroacetylated as above. Work-up gave a crude product which exhibited only a single CH_3 resonance in the NMR spectrum. This was chromatographed on alumina[29] where 1:1 CH_2Cl_2–benzene eluted the major component identified as the 4-methyl isomer which was recrystallized from hexane: mp 73.0–73.5 °C; NMR (CCl_4, internal Me_4Si) τ 0.22–0.49 (m, C_8H, 1), 1.75–3.0 (m, $C_{2,3,5,6,7}H$'s, 5), and 7.15 (s, CH_3, 3).

Anal. Calcd for $C_{13}H_9F_3O$: C, 65.55; H, 3.81. Found: C, 65.60; H, 3.65.

4-Methyl-1-azuloic Acid (4-CH_3-1). 1-Trifluoroacetyl-4-methylazulene (60 mg, 0.25 mmol) was hydrolyzed with base as previously described. Work-up gave 40 mg of 4-CH_3-1 which was recrystallized from ether–hexane as purple crystals: mp 185–188 °C dec (lit.[31] mp 192–193 °C dec); NMR ($CDCl_3$, internal Me_4Si)[33] τ 0.15–0.30 (m, C_8H, 1), 1.55 (d, C_2H, 1), and 2.1–3.0 (m, $C_{3,5,6,7}H$'s, 4).

5- (5-CH_3-1) and 7-Methyl-1-azuloic Acids (7-CH_3-1). A mixture of methyl 5- and 7-methyl-1-azulenecarboxylates was available from the reaction series (1) formation of the Meisenheimer type complex by 6 addition of lithium dicyclohexylamide to 5-methylazulene, (2) carbonation, and (3) formation of the methyl esters of the carboxylic acids.[6] Chromatography of this mixture on Woelm neutral, activity 1 alumina effected separation into two distinct bands; band 1 was eluted with cyclohexane and band 2 was eluted with CH_2Cl_2.

Band 1 was identified as methyl 7-methyl-1-azulenecarboxylate (5) on the basis of its NMR spectrum (CCl_4, internal Me_4Si): τ 0.35 (broadened s with some coupling indicated, C_8H, 1), 1.60–3.0 ($C_{2,3,4,5,6}H$'s, 5), 6.15 (s, OCH_3, 3), and 7.21 (s, CH_3, 3).

Band 2 was identified as methyl 5-methyl-1-azulenecarboxylate (4) on the basis of its NMR spectrum (CCl_4, internal Me_4Si) τ 0.54 (d of d's, C_8H, 1), 1.60–3.0 ($C_{2,3,4,6,7}H$'s, 5), 6.17 (s, OCH_3, 3), and 7.25 (s, CH_3, 3).

Base hydrolysis of each of these esters in 50% aqueous methanol afforded their respective acids, 7-CH_3-1, mp 189–190 °C dec, and 5-CH_3-1, mp 192–193 °C dec, in >90% yield.

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: (7-CH_3-1) C, 77.12; H, 5.40; (5-CH_3-1) C, 77.42; H, 5.52.

6-Methoxy-1-azuloic Acid (6-CH_3O-1). 6-Methoxyazulene[1a] (132 mg, 0.84 mmol) was allowed to react with $COCl_2$ in benzene for 1 h at 0 °C by the method used in preparing 3-CH_3O-1. After work-up, 60 mg (36%, 73% net) of 6-CH_3O-1 was obtained. Crystallization from ether afforded orange plates: mp 194.5–195.0 °C; ir (KBr) 6.15 μ (s, C=O); NMR (Me_2SO-d_6, internal Me_4Si)[33] τ 0.25–0.73 (m, C_8H, 1), 1.40–1.75 (m, C_4H, 1), 1.93 [d (J = 4 Hz), C_2H, 1], 2.43–3.07 (m, $C_{3,5,6,7}H$'s, 4), and 5.95 (s, OCH_3, 3); λ_{max} (95% ethanol) 302 nm (log ϵ 4.65) (sh), 314 (4.72), 346 (3.92), 357 (3.90), 370 (3.63) (sh), and 485 (2.72).

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.00; H, 5.10.

6-Methyl-1-azuloic Acid (6-CH_3-1). A sample (110 mg) of methyl 6-methyl-1-azulenecarboxylate was available from the study that produced the mixture of methyl 5- and 7-methyl-1-azulenecarboxylates.[6] This sample was chromatographed on deactivated (10% H_2O) silica gel with benzene. The solvent was evaporated from the eluate and the ester was hydrolyzed with KOH in 50% aqueous methanol. Work-up gave the acid which was chromatographed on deactivated (10% H_2O) silica gel with 1:1 CH_2Cl_2–ether. The acid was recrystallized from ether–hexane, giving 65 mg of 6-CH_3-1 as deep red crystals, mp 206–208 °C dec.

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.31; H, 5.12.

Methyl 6-Bromo-1-azulenecarboxylate. 6-Bromoazulene[1a] (75 mg, 0.36 mmol) was allowed to react with $COCl_2$ in benzene at room temperature for 60 h as above. After work-up, 45 mg (50%, 100% net) of crude 6-Br-1 was obtained. This was dissolved in ether and treated with an excess of ethereal CH_2N_2. After work-up, the residue was chromatographed on alumina[29] with benzene. A violet band eluted, leaving behind a tightly held yellow band which was not investigated. The violet band afforded 115 mg (78%) of the title copound. Recrystallization from ether yielded flat, purple needles, with a sweet aroma: mp 101.2–102.0 °C; ir (KBr) 5.95 (s, C=O) and 9.60 μ (s, C–O); NMR ($CDCl_3$, internal Me_4Si) τ 0.48–0.88 (m, C_8H, 1), 1.57–2.58 (m, 4), 2.70 [d (J = 4 Hz), C_3H, 1], and 6.05 (s, CH_3, 3); λ_{max} (cyclohexane) 297 nm (log ϵ 4.81), 302 (4.28), 309 (4.89), 347 (3.79), 355 (3.88), 373 (3.85), 547 (2.58), 592 (2.50), and 650 (2.07).

Anal. Calcd for $C_{12}H_9O_2Br$: C, 54.36; H, 3.42. Found: 54.38; H, 3.47.

6-Bromo-1-azuloic Acid (6-Br-1). A 10-ml solution of DMF containing 3.0 g of lithium bromide hydrate and 2 g of crushed 2A molecular sieves under nitrogen was heated for 30 min under reflux and then 115 mg (0.435 mmol) of methyl 6-bromo-1-azulenecarboxylate in 5 ml of DMF was added dropwise. This solution was heated under reflux for 4 h, cooled, diluted with 200 ml of ether, and extracted with five 75-ml portions of 5% aqueous sodium bicarbonate. The combined aqueous layers were acidified with 10% hydrochloric acid and extracted with three 50-ml portions of ether. The combined ethereal layers were dried (Na_2SO_4) and the solvent volume reduced to yield 50 mg (46%) of 6-Br-1 which was recrystallized from THF, giving violet needles: mp 250–253 °C (sealed capillary); ir (KBr): 6.02 μ (s, C=O); NMR ($CDCl_3$, internal Me_4Si)[33] τ 0.17–0.47 (m, C_8H, 1), and 1.38–2.87 (m, 5); λ_{max} (95% ethanol) 295 nm (log ϵ 4.71), 306 (4.75), 345 (3.76), 354 (3.80), 371 (3.72), 543 (2.62), 590 (2.53) (sh), and 650 (2.00) (sh). The log ϵ values are calculated assuming 100% purity of the acid. Although several samples were prepared and submitted for elemental analysis, no satisfactory analysis was obtained. The reason for this is unknown.

The neutral ethereal portion of the reaction mixture was dried (Na_2SO_4), the solvent volume reduced, and the residue chromatographed on alumina.[29] Hexane–CH_2Cl_2 (1:1) eluted a blue band that yielded 35 mg (39%) of 6-bromoazulene. CH_2Cl_2 eluted a pink band that afforded 10 mg (9% recovery) of unreacted methyl 6-bromo-1-azulenecarboxylate.

Table VI. Thermodynamic pK_a's in Water at 25.00 ± 0.01 °C

Acid	This work	Lit.[32]
Benzoic	4.199	4.199 ± 0.004
Acetic	4.757 ± 0.002	4.757 ± 0.004
Pivalic	5.031 ± 0.003	5.032 ± 0.002
Succinic (pK_1)	4.189 ± 0.001	4.206 ± 0.003
Succinic (pK_2)	5.637 ± 0.002	5.639 ± 0.004

Determination of Dissociation Constants. The method used for determination of the dissociation constants of X-1's has been reported.[3] The method used zone defined benzoic acid as our primary standard to set the pH scale. The dissociation constants of several acids in water were then determined to evaluate the accuracy and precision of the method; these results are listed in Table VI. A probable reason for the small discrepancy in the pK_1 of succinic acid and the literature value is that we used reagent grade succinic acid while Wilcox and Leung[32] used zone refined material.

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Registry No.—2-I-1, 58313-12-5; 2-CN-1, 58313-13-6; **2**, 58342-98-6; **4**, 51381-35-2; **5**, 51381-36-3; 1-trifluoroacetyl-2-chloroazulene, 54798-15-1; 2-chloroazulene, 36044-31-2; methyl-2-chloro-1-azulenecarboxylate, 54798-16-2; 1-trifluoroacetyl-2-bromoazulene, 58313-14-7; 2-bromoazulene, 58312-57-5; 1-trifluoroacetyl-2-iodoazulene, 58313-15-8; 2-iodoazulene, 36044-41-4; methyl 2-cyano-1-azulenecarboxylate, 38287-28-4; 1-trifluoroacetyl-3-methoxyazulene, 41867-34-9; 1-methoxyazulene, 30264-97-2; methyl 3-methoxy-1-azulenecarboxylate, 58313-16-9; 1-trifluoroacetyl-3-methylazulene, 58313-17-0; 1-methylazulene, 769-31-3; methyl 3-bromo-1-azulenecarboxylate, 42081-17-4; methyl 1-azulenecarboxylate, 14659-03-1; methyl 3-acetyl-1-azulenecarboxylate, 58313-18-1; methyl 3-cyano-1-azulenecarboxylate, 38287-27-3; methyl 3-nitro-1-azulenecarboxylate, 41867-40-7; 1-trifluoroacetyl-4-methylazulene, 58313-19-2; 4-methylazulene, 17647-77-7; 5-methylazulene, 1654-55-3; 6-methoxyazulene, 35046-03-8; methyl 6-methyl-1-azulenecarboxylate, 51381-40-9; methyl 6-bromo-1-azulenecarboxylate, 58313-20-5; 6-bromoazulene, 35046-05-0; 2-methoxyazulene, 36044-37-8; 1-trifluoroacetyl-2-methoxyazulene, 58313-21-6; trifluoroacetic anhydride, 407-25-0; 1-trifluoroacetyl-2-methylazulene, 58313-22-7; 2-methylazulene, 769-86-8.

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An Efficient Synthesis of 1-β-D-Arabinofuranosylcytosine

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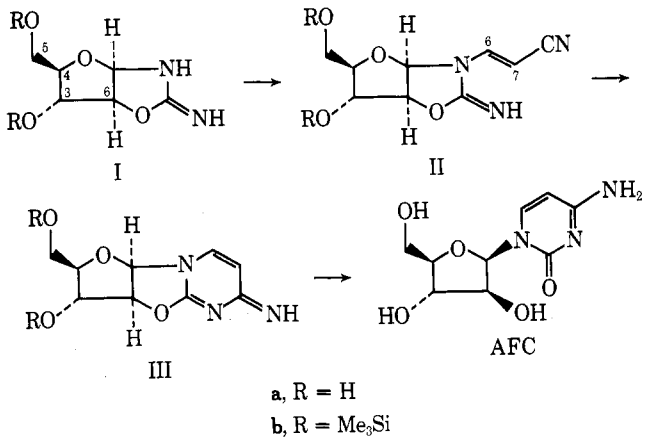
Isoxazole is treated with strong base at low temperature to form in high selectivity the cis enolate salt of cyanoacetaldehyde. Tosylation, followed by reaction with trimethylamine, furnishes *cis*-β-trimethylammoniumacrylonitrile tosylate in high yield. This product is treated with 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline to form the desired cis cyanovinyl adduct which is further converted to 1-β-D-arabinofuranosylcytosine.

Cytosine arabinoside (1-β-D-arabinofuranosylcytosine, AFC) has been proven effective in the treatment of acute leukemias. Additionally, *anhydro*-AFC is being investigated as an antitumor agent. Since increasing amounts of AFC are being used medicinally a low-cost synthesis of AFC has been pursued in this and other laboratories. Very recently Sanchez and co-workers[1] published an elegant method to prepare AFC. The reaction of D-arabinose with cyanamide to form 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (Ia) is followed by reaction of Ia with propiolonitrile to yield a cyanovinyl adduct which Sanchez formulates as the trans adduct IIa.



a, R = H
b, R = Me_3Si

Treatment of the cyanovinyl adduct with aqueous ammonia gave a high yield of AFC, presumably via 2,2′-anhydro-1-β-D-arabinofuranosylcytosine (IIIa). Our goal was to prepare AFC by a procedure that could ultimately be used in large-scale manufacture and by a procedure that allowed isolation of *anhydro*-AFC (III), if possible. Use of oxazoline I as an intermediate was favored since the oxazoline is of the correct configuration at C-1 of the arabinose moiety. Unfortunately the above process utilizes propiolonitrile, a compound that was judged too hazardous for large-scale synthesis. Our specific goal then became to find a substitute for the key reagent, propiolonitrile.

It was found that *cis*-β-trimethylammoniumacrylonitrile tosylate (IVc), a stable, white, crystalline solid, can be substituted for propiolonitrile in the synthesis. Reaction of IVc with oxazoline Ia was carried out best in DMF at 50 °C. Use of protic solvents such as water, methanol, or 2-propanol for the reaction gave only poor yields of AFC. However, dipolar aprotic solvents were effective, with DMF giving the highest yields. Addition of acetonitrile at the end of the reaction caused crystallization of a white solid isolated in 70–74% yield, which is assigned the acetonitrile solvate of 2,2′-*anhydro*-AFC tosylate salt (IIIa TsOH CH_3CN) by NMR comparison to authentic[1] 2,2′-*anhydro*-AFC hydrochloride. It is very likely that the *cis*-cyanovinyl adduct Va is generated as an intermediate which then cyclizes to IIIa in the presence of tosic acid.