resin was put on a sintered-glass filter and washed with 30-ml portions of 0.1 *N* potassium nitrate until the filtrate was free of chloride ion. The chloride in the combined washings was titrated with standard 0.1 *N* silver nitrate with 6 drops of 1 *M* potassium chromate as indicator. The strong-base capacity of the resin is equal to the quantity (milliequivalents) of silver nitrate used. Another 1-g sample of the dry resin was stirred for 144 hr in a closed container with 25.0 ml of standard 0.1 *N* hydrochloric acid. Then the mixture was filtered on a dry sintered-glass funnel. The hydrochloric acid in a 10.0-ml aliquot of the filtrate was determined by titration with standard sodium hydroxide. The weak-base capacity was calculated from these data.

Chromatography.—In the frontal experiments, racemic sodium mandelate was passed into the columns (Table I). Fractions (3 ml) of effluent were collected automatically and examined in a Beckman DU spectrophotometer at 2570 A and in a Rudolph Model 80 polarimeter with a 1-dm tube and a sodium-vapor lamp. From these data, the concentration of the sodium mandelate and its optical purity were calculated. The addition of racemic mandelate solution was stopped when the concentration of mandelate in the effluent was equal to that in the influent. At this point the effluent mandelate had no detectable rotation (Figure 1). The interstitial mandelate was washed out with deionized water. Then either 1.0 *N* sodium chloride or 1.0 *N* potassium nitrate was passed into the column. Fractions were collected and analyzed as before.

In the resolutions by displacement chromatography, a suitable quantity of a solution of racemic sodium mandelate was added to the column of the optically active strong-base resin in the chloride form. Then the mandelate was displaced by a solution of potassium nitrate. Fractions of effluent were collected and analyzed as described above. A correction for the absorbance by nitrate at 2570 A was applied to the fractions at the rear of the mandelate band since there was some overlapping of the mandelate and nitrate. The absorbance of nitrate at 3020 A was converted to the equivalent absorbance at 2570 A and subtracted from the absorbance of the fractions. Mandelate does not absorb at 3020 A.

Acknowledgment.—The authors wish to acknowledge the helpful comments and suggestions of Daniel Reichenberg. A fellowship from Johnson and Johnson and a donation of chloromethylated resin from the Dow Chemical Company are also gratefully acknowledged. This work was supported in large part by Grant GM-09687 from the National Institutes of Health.

Acridizinium Ion Chemistry. V.[1] Sulfonation[2]

C. K. BRADSHER AND J. D. TURNER

Department of Chemistry, Duke University, Durham, North Carolina

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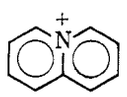
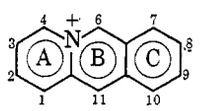
The first electrophilic substitution (sulfonation) of the parent acridizinium ion has been accomplished. The resulting sulfobetaine was converted to a sulfone which by oxidative scission of ring B afforded a keto acid. The ketone obtained by decarboxylation of the keto acid was synthesized and proved to be 2-picolinoylphenyl phenyl sulfone. It follows that the new sulfonation product is the betaine of 10-sulfoacridizinium hydroxide.

One might have predicted that the quinolizinium ion (I), a resonant aromatic cation, would be reluctant to undergo electrophilic substitution. There has been no report of such a substitution save in those derivatives having an activating group present.[3]



I



II

The acridizinium or benzo[*b*]quinolizinium ion (II) might be expected to be more reactive, but the only reported electrophilic substitutions were carried out on the 8-hydroxy and 8-methoxy derivatives.[4]

The present communication describes the first electrophilic substitution of the parent acridizinium cation. When acridizinium bromide was dissolved in 20% fuming sulfuric acid at room temperature and after 1 hr the mixture was poured into ether, a sulfobetaine was obtained in 82% yield. It appeared likely that ring C, being most remote from the positive nitrogen atom, would be the one attacked. Two isomeric betaines having the sulfo groups in ring C at positions 7[5] and 9[6] had been prepared earlier by indirect methods. It was not surprising that neither of these compounds was identical with the new direct sulfonation product since at least two of the structures contributing to the acridizinium ion resonance hybrid bear positive charges at positions 7 and 9.

One technique for identifying the position of substituents in ring C of the acridizinium nucleus involves catalytic reduction of rings A and B and subsequent observation of the infrared absorptions due to out-of-plane vibrations of the hydrogen atoms on ring C.[7] The reduction product of the new betaine, like the reduction product of the betaine of 7-sulfoacridizinium hydroxide, showed the typical absorption pattern (in the 680–860-cm^{-1} region) for three adjacent aromatic hydrogens. Unfortunately, the reduction product of the 9-substituted isomer (two adjacent aromatic hydrogens) showed an unexpectedly strong absorption at 705 cm^{-1}, raising a question concerning the validity in this series of structural assignments based upon absorptions in the 705–710-cm^{-1} region.

To facilitate the degradation of the sulfonation product (III) it was converted to a phenyl sulfone (V) *via* the sulfonyl chloride IV. Oxidation of the phenyl acridizinium sulfone (V) with nitric acid[1] led to a keto acid (VI), showing that the sulfo group could not be in ring B of the betaine. Decarboxylation of the keto acid

(1) For the preceding communication of this series, see C. K. Bradsher and M. W. Barker, *J. Org. Chem.*, **29**, 452 (1964).

(2) This investigation was supported by Public Health Service Research Grant No. H-2170 of the National Heart Institute.

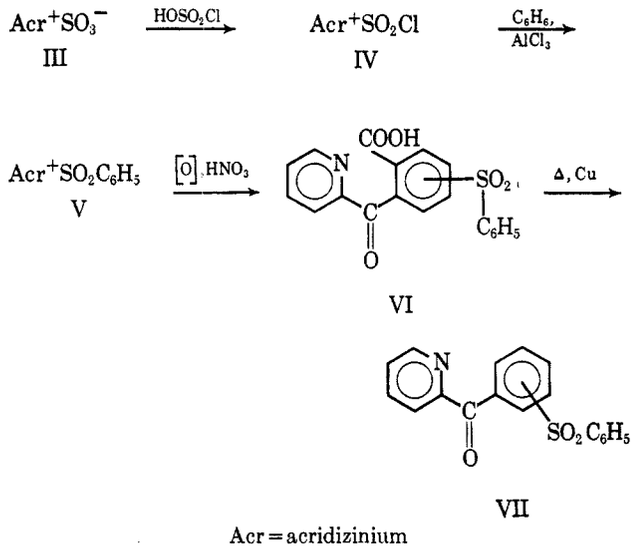
(3) A. Fozard and G. Jones, *J. Chem. Soc.*, 2203 (1963); 2760, 3030 (1964); P. A. Duke, A. Fozard, and G. Jones, *J. Org. Chem.*, **30**, 526 (1965); B. S. Thyagarayan and P. V. Gopalakrishnan, *Tetrahedron*, **20**, 1051 (1964).

(4) C. K. Bradsher and R. C. Corley, *J. Org. Chem.*, **28**, 1396 (1963).

(5) C. K. Bradsher, J. C. Parham, and J. D. Turner, *J. Heterocyclic Chem.*, **2**, 228 (1965).

(6) C. K. Bradsher and J. C. Parham, *ibid.*, **1**, 30 (1964).

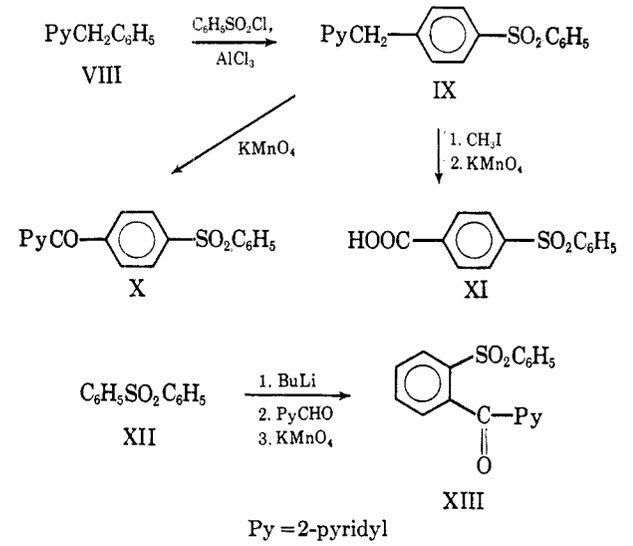
(7) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 64.



Acr = acridizinium

VI yielded a ketone (VII). Assuming only that the original betaine III was not sulfonated in ring A, it seemed certain that the ketone VII was 4-picolinoylphenyl or 2-picolinoylphenyl phenyl sulfone, both of which were unknown.

When 2-benzylpyridine (VIII) was allowed to react with benzenesulfonyl chloride under Friedel–Crafts conditions, the product isolated (as the picrate) proved to be 4-(2-pyridylmethyl)phenyl sulfone (IX). The structure of IX was demonstrated by quaternization of the pyridyl group, followed by oxidation. The product had the composition and melting point of the



Py = 2-pyridyl

known[8] 4-carboxyphenyl phenyl sulfone (XI). Direct oxidation of IX with permanganate yielded 4-picolinoylphenyl phenyl sulfone (X), which was not identical with the unidentified decarboxylation product (VII).

The 2-picolinoylphenyl phenyl sulfone (XIII) was made *via* the 2-lithiophenyl phenyl sulfone obtained by metalation of phenyl sulfone[9] with butyllithium. The 2-lithiophenyl phenyl sulfone was allowed to react with picolinaldehyde and the product was oxidized to 2-picolinoyldiphenyl sulfone (XIII). The new sulfone was identical in every respect with the unidentified decarboxylation product (VII) of the keto acid VI. It follows that the new sulfonation product is the betaine of 10-sulfoacridizinium hydroxide.

(8) H. Arnold and D. Vogelsang, German Patent 939,325 (1956); *Chem. Abstr.*, **52**, 14684*i* (1958).

(9) W. E. Truce and M. F. Amos, *J. Am. Chem. Soc.*, **73**, 3013 (1951).

Experimental Section

All elemental analyses were carried out by Janssen Pharmaceutica, Beerse, Belgium. Melting points were determined in capillaries using a Laboratory Devices Mel-Temp block. Except as noted, the ultraviolet absorption spectra were determined in 95% ethanol using a Cary Model 14 spectrophotometer.

Betaine of 10-Sulfoacridizinium Hydroxide (III).—One gram of acridizinium bromide was dissolved in 10 ml of 20% fuming sulfuric acid cooled in an ice bath. The solution was permitted to stand for 1 hr at room temperature and then poured slowly into cold dry ether, cooled in an ice bath. The precipitate was collected on a suction filter, washed with ether, and recrystallized from water, affording 0.84 g (82%) of a bright yellow microcrystalline solid: mp >400°; $\lambda_{max}^{H_2O}$ mμ (log ε), 200 sh (4.18), 228 sh (4.14), 236 (4.19), 254 sh (3.88), 330 sh (2.99), 353 (3.24), 376 (3.20), and 396 (3.13).

Anal. Calcd for $C_{13}H_9NO_3S \cdot {}^1/_3H_2O$: C, 58.71; H, 3.66; N, 5.27. Found: C, 58.75; H, 3.46; N, 5.40.

10-Sulfobenzo[*b*]quinolizidine.—To a suspension of 0.52 g of the betaine of 10-sulfoacridizinium hydroxide (III) in 100 ml of 95% ethanol, 0.05 g of platinum oxide was added. The mixture was stirred at room temperature for 24 hr under 1 atm of hydrogen. The solution was then filtered to remove the platinum and the filtrate was reduced in volume to about 30 ml. Ethyl acetate was added to the boiling solution and the mixture was allowed to stand at −15° to crystallize. Recrystallization of the product afforded 0.25 g (47%) of a colorless microcrystalline solid, mp 344–346°.

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 57.98; H, 6.59; N, 5.47.

7-Sulfobenzo[*b*]quinolizidine.—From the betaine of 7-sulfoacridizinium hydroxide,[5] the quinolizidine derivative was prepared in 58% yield as in the reduction of III, giving colorless microcrystals, mp 348–350°.

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.18; H, 6.41; N, 5.36.

9-Sulfobenzo[*b*]quinolizidine.—The title salt was obtained from the betaine of 9-sulfoacridizinium hydroxide[6] by the procedure described for the isomers, giving colorless microcrystals, mp 324–326°, in 41% yield.

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.24; H, 6.52; N, 5.32.

10-(Chlorosulfonyl)acridizinium (IV) Perchlorate.—One gram of the betaine of 10-sulfoacridizinium hydroxide (III) was dissolved in 10 ml of chlorosulfonic acid and heated on the steam bath for 1.5 hr. The solution was poured very slowly on 50 g of ice and the resulting water solution was filtered. To the filtrate, 35% perchloric acid was added and the mixture was allowed to stand for 3 hr at 0° before the product was collected. The product was recrystallized from dry acetone–ethyl acetate, affording 0.95 g (65%) of yellow crystals, mp 183° (explosion).

Anal. Calcd for $C_{13}H_9Cl_2NO_6S \cdot 0.25H_2O$: C, 40.80; H, 2.50; N, 3.66. Found: C, 40.68; H, 2.59; N, 3.57.

10-(Phenylsulfonyl)acridizinium (V) Bromide.—To a suspension of 3.5 g of 10-chlorosulfonylacridizinium (IV) perchlorate suspended in 50 ml of dry thiophene-free benzene, 3.0 g of anhydrous aluminum chloride was added, and the mixture (protected from moisture) was mechanically stirred for 2.5 hr. The benzene was decanted from the green gum which had formed. The gum was dissolved in methanol, and to the solution was added slowly a solution of 2 ml of liquid bromine in 6 ml of 48% hydrobromic acid, followed by slow addition of 200 ml of water. After the mixture had stood for 24 hr in the refrigerator, the tribromide salt was collected and then converted to the bromide salt by boiling in a mixture of equal parts of acetone and methanol. The resulting solution was concentrated and ethyl acetate was added to effect crystallization. The product was recrystallized from methanol–ethyl acetate as bright yellow needles, 2.25 g (61%), mp 266–267°.

Anal. Calcd for $C_{19}H_{14}BrNO_2S$: C, 57.00; H, 3.52; N, 3.49. Found: C, 56.85; H, 3.36; N, 3.69.

From the green gum remaining after the Friedel–Crafts reaction, the **perchlorate** can be recovered by crystallization from methanol–water. The product formed light green needles: mp 222–224°; λ_{max}, mμ (log ϵ), 237 (4.11), 255 sh (3.64), 360 (3.38), 382 (3.28), and 402 (3.06).

Anal. Calcd for $C_{19}H_{14}ClNO_6S \cdot 0.5H_2O$: C, 53.21; H, 3.53; N, 3.27. Found: C, 53.28; H, 3.42; N, 3.36.

2-(2-Picolinoyl)-3-carboxyphenyl Phenyl Sulfone (VI).—A solution of 0.8 g of 10-(benzenesulfonyl)acridizinium (V) bromide in 20 ml of 12 *M* nitric acid was heated on the steam bath for 4 hr. The nitric acid was removed on the steam bath under reduced pressure and the residue was recrystallized from ethanol–water. The product, 0.45 g of colorless needles, mp 209–210°, was insoluble in water but soluble in dilute sodium hydroxide solution.

Anal. Calcd for $C_{19}H_{13}NO_5S$: C, 68.12; H, 3.57; N, 3.81. Found: C, 68.12; H, 3.53; N, 4.08.

2-(2-Picolinoyl)phenyl Phenyl Sulfone (VII) by Decarboxylation of VI.—A mixture of 0.1 g of VI and 0.2 g of copper powder was heated in a sublimation apparatus for 3 hr at 200–220° under 3–4-mm pressure. The sublimate crystallized from ethanol to yield 0.053 g (60%) of microcrystalline needles, mp 177–178°.

Anal. Calcd for $C_{18}H_{13}NO_3S$: C, 66.87; H, 4.05; N, 4.33. Found: C, 66.65; H, 3.96; N, 4.37.

Picrate of 4-(2-Pyridylmethyl)phenyl Phenyl Sulfone (IX).—To a mechanically stirred mixture containing 19 g of anhydrous aluminum chloride in 20 ml of benzenesulfonyl chloride at 0°, 10 g of 2-benzylpyridine (VIII) was added over a period of 30 min. The solution was stirred at room temperature for 30 min, heated on the steam bath for 1 hr, and finally cooled in an ice bath, and the mixture was decomposed by slow addition of ice water. The mixture was made basic by the slow addition of 300 ml of 10% sodium hydroxide solution. The slurry was extracted with ether and the ether solution was dried (magnesium sulfate) and concentrated. Ethanolic picric acid precipitated 8.2 g of crude picrate which, on fractional recrystallization, yielded 3.2 g of long yellow needles, mp 192–193°.

Anal. Calcd for $C_{24}H_{18}N_4O_9S$: C, 53.53; H, 3.37; N, 10.41. Found: C, 53.58; H, 3.43; N, 10.57.

4-Carboxyphenyl Phenyl Sulfone (XI).—A suspension of 0.9 g of the picrate of 4-(2-pyridylmethyl)phenyl phenyl sulfone (IX) in 100 ml of 5% sodium hydroxide was heated for 30 min on the steam bath. The resulting solution was cooled in an ice bath and extracted with ether. The ethereal solution was dried and concentrated and the yellow residue was taken up in 4 ml of tetramethylene sulfone. Methyl iodide (3 ml) was added and the solution was allowed to stand for 3 days. Ethyl acetate (200 ml) was added and the mixture was allowed to stand at −15° for 14 hr. The ethyl acetate was decanted from the hygroscopic gum. To the gum, 75 ml of water, 25 ml of 10% sodium hydroxide solution, and 5.0 g of potassium permanganate were added, and the mixture was heated on the steam bath for 9 hr. The mixture was next filtered, acidified with concentrated hydrochloric acid, and extracted with ether. The solid residue remaining after evaporation of the ether was recrystallized from ethanol, affording 0.13 g (30%) of colorless plates, mp 273° (lit.[3] mp 273°).

Anal. Calcd for $C_{13}H_{10}O_4S$: C, 59.53; H, 3.84. Found: C, 59.40; H, 4.02.

4-(2-Picolinoyl)phenyl Phenyl Sulfone (X).—The conversion of 0.7 g of the picrate of 4-(2-pyridylmethyl)phenyl phenyl sulfone (IX) to the free base was carried out as described in the preceding experiment. The crude base remaining after evaporation of the ether was dissolved in 50 ml of 5% sulfuric acid. Over a period of 30 min, 3.0 g of potassium permanganate was added slowly in portions while the solution was heated on the steam bath. Heating was continued for an additional 4 hr and the solution was cooled, made basic with 10% sodium hydroxide solution, and extracted with ether. The ethereal solution was concentrated and the residue was crystallized from ethanol–water, giving 0.36 g (86%) of colorless plates, mp 98–99°.

Anal. Calcd for $C_{18}H_{13}NO_3S$: C, 66.87; H, 4.05; N, 4.33. Found: C, 66.96; H, 3.96; N, 4.47.

2-(2-Picolinoyl)phenyl Phenyl Sulfone (XIII) from Phenyl Sulfone (XII).—To a cold stirred suspension (ice bath) of 20 g of phenyl sulfone in 370 ml of dry ether under a dry nitrogen atmosphere, 60 ml of a 15% solution of butyllithium was added over a 0.5-hr period. The solution, which turned orange, was stirred for 2 hr in the ice bath and 1 hr after removal of the ice bath. The ice bath was replaced, and 12 g of 2-picolinaldehyde in 25 ml of dry ether was added slowly over a period of 20 min. The solution, which changed from orange to purple and finally to a cream color, was stirred for 30 min in an ice bath and for 1 hr at room temperature. To the reaction mixture 200 ml of 15% sulfuric acid was added, and the mixture was warmed to evaporate the ether. The hot aqueous solution was filtered, and the solution was stirred and heated ion the steam bath while 15 g of potassium permanganate was added slowly in small portions. Heating was continued for an additional 10 hr, and the mixture was made basic by addition of 10% sodium hydroxide solution and extracted with hot benzene. The dried benzene solution was concentrated, and the residue was crystallized from ethanol to give 12.4 g (42%) of colorless needles, mp 177–178°. This product was shown to be identical with the decarboxylation product (VII) of 2-(2-picolinoyl)-3-carboxyphenyl phenyl sulfone (VI) by mixture melting point and infrared spectra.