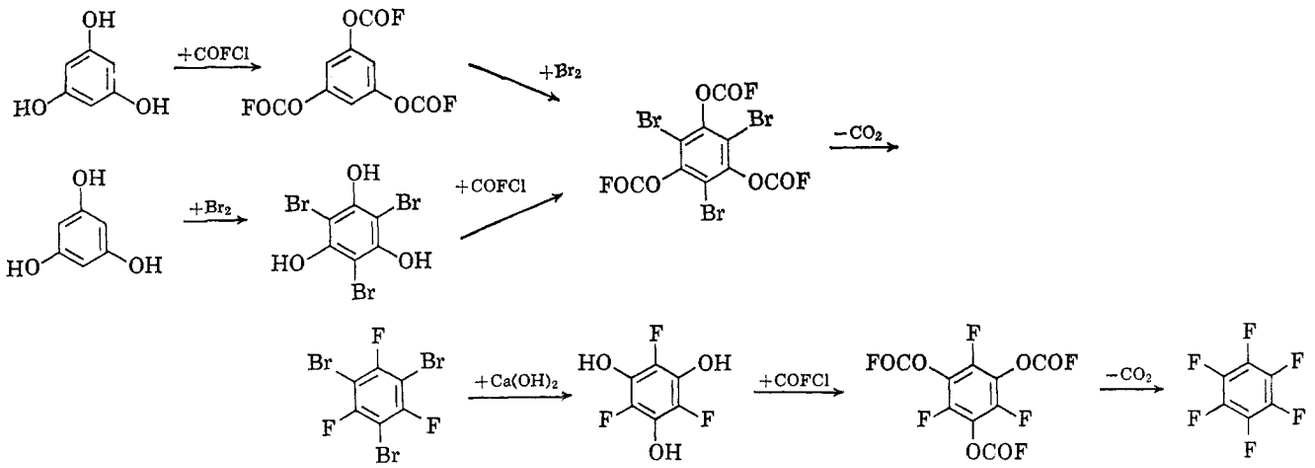
SCHEME III



toluene by vacuum distillation, a liquid residue (20.2 g, containing 94.5% of *m*-phenylene bisfluoroformate according to the gc ratios) was obtained and purified further by vacuum distillation. The properties of the compound are listed in Table I.

Preparation of 1,3,5-Phenenyl Trisfluoroformate.—Phloroglucinol (0.3 mole), toluene (150 ml) as a solvent, tributylamine (2 ml) as a catalyst, and COFCl (1.09 moles) underwent similar reaction for 15 hr at 80° in a 500-ml stainless steel lecture bottle. After removal of the volatile material, the solid residue was extracted with diethyl ether until the extract did not show any 1,3,5-phenenyl trisfluoroformate on the gas chromatograph. The product (52 g) was isolated from the diethyl ether solution and recrystallized from the same solvent. Its properties are listed in Table I.

Decarboxylation of the Aromatic Fluoroformates.—The same setup was used for all reactions. A stream of dry N_2, controlled by a flowmeter system, was passed through a small flask, containing the fluoroformate starting material. A fluoroformate vapor pressure of 100 mm was maintained by the external heating of the flask with an oil bath. The fluoroformate–nitrogen mixture was passed through an electrically heated quartz tube with Pt gauze as a filling. The products were quenched directly behind the exit of the tube by two cold traps, one at −78° and the other at −196°. The second trap was connected to a mercury blow-off. The reaction tube was automatically heated and its temperature was measured with a thermocouple on its outside wall. The inlet part of the setup between the fluoroformate container and the reaction tube was heated by three infrared lamps to prevent condensation of the starting material. The conversion of the starting material and the yields were determined by weighing of the used up starting material and of the collected products. The composition of the products was analyzed by gc. The compounds themselves were identified by infrared after gc separation. The results of all these reactions are summarized in Table II.

Hydrolysis of *o*-Bromofluorobenzene.—Distilled water (3 moles), *o*-bromofluorobenzene (0.05 mole), $Ca(OH)_2$ (0.05 mole), and CuO (10 mg) were placed into a 150-ml stainless steel cylinder, equipped with a pressure gauge and a valve. The cylinder was agitated for 4 hr at 230° with its contents under a pressure of 400 psi. The product was extracted with diethyl ether. The diethyl ether solution was dried with $MgSO_4$ and filtered, and the ether was removed under vacuum. According to gc analysis the residue consisted of 95.6% *o*-fluorophenol and 4.6% starting material. No *o*-bromophenol was detected.

Bromination of 1,3,5-Phenenyl Trisfluoroformate.—Bromine (25 ml) and 1,3,5-phenenyl trisfluoroformate (6.5 g) were refluxed and stirred for 3 days using a small amount of hydrogen-reduced iron as a catalyst. The bromine was removed by vacuum distillation and a dark brown oily residue remained. Elemental analysis and an infrared spectrum showed only partial bromination of the starting material.

Reaction between 1,3,5-Tribromophloroglucinol and COFCl.—Carbonyl chloride fluoride (0.5 mole), 1,3,5-tribromophloroglucinol (0.03 mole), tributylamine (1.5 ml) as a catalyst, and benzene (40 ml) as a solvent were placed into a 150-ml stainless steel lecture bottle and agitated at 100° for 20 hr. The volatile products were bled off, and the solvent was removed by vacuum distillation. A dark brown oily product was obtained, which according to its fluorine analysis (*Anal.* Calcd for 1,3,5-tribromophenenyl trisfluoroformate: F, 11.38. Found: F, 5.8.) and infrared spectrum was not the desired 1,3,5-tribromophenenyl trisfluoroformate. Attempts to isolate this compound out of the crude product were unsuccessful.

Resolution of a Racemic Substance by Ion-Exchange Chromatography[1a]

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An optically active, strong-base anion-exchange resin was prepared from L-(−)-N,N-dimethyl-α-phenethylamine and chloromethylated, cross-linked polystyrene. It was found possible to resolve partially the optical isomers of mandelic acid by the methods of frontal and displacement ion-exchange chromatography.

A number of reports appear in the literature describing the use of synthetic, optically active polymeric materials as sorbents for the chromatographic resolution of racemic substances. Grubhofer and Schleith[2] prepared a weak-base anion-exchange resin by incorporating quinine into a polymer. On passage of 0.036 *N* racemic mandelic acid in chloroform through this resin, the first fractions of the effluent after the breakthrough of mandelic acid contained 4, 7, 16, 26, 34,

(1) (a) Taken from the Ph.D. Thesis of J. A. L., 1965. (b) To whom inquiries should be sent: University of Michigan, Flint College, Flint, Mich. 48503.

(2) N. Grubhofer and L. Schleith, *Z. Physiol. Chem.*, **296**, 262 (1954).

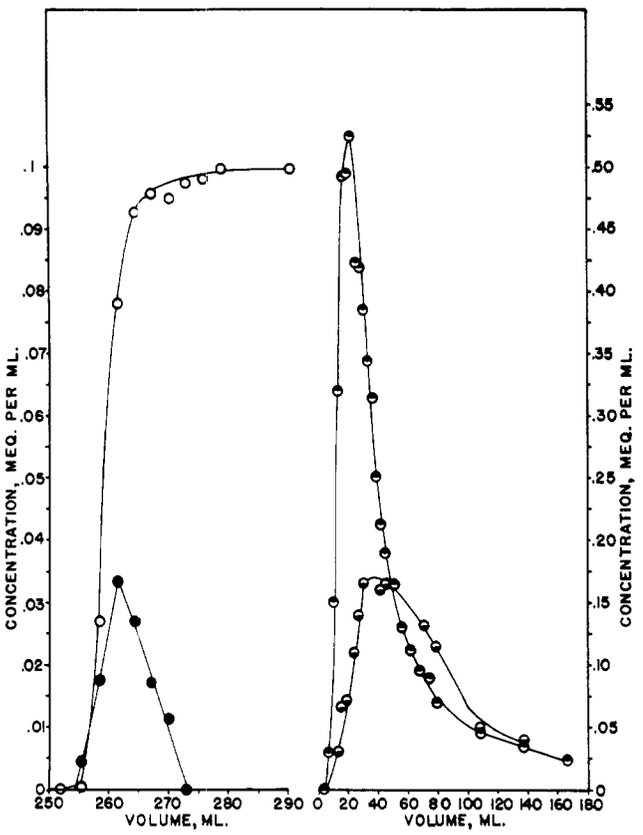

Figure 1.—Frontal analysis I: ○, concentration of mandelate in first half of frontal analysis, left-hand scale; ●, concentration × 10 of (+)-mandelate in first half of frontal analysis, left-hand scale; ◓, concentration of mandelate in second half of frontal analysis, right-hand scale; and ◒, concentration × 100 of (−)-mandelate in second half of frontal analysis, right-hand scale. For experimental conditions, see Table I.

and 43 μmoles of the (+) isomer with respective optical purities of 100, 70, 44, 34, 31, and 30%. Suda and Oda,[3] using a strong-base resin in which brucine had been incorporated, passed 0.053 *N* mandelic acid into their column and obtained effluent fractions containing 61, 90, and 190 μmoles of mandelic acid of 27, 9.6, and 5.1% optical purity, respectively. Roberts and Haigh[4] incorporated L-(−)-cysteine into a polymer and then passed 0.2 *N* racemic methionine through a column of this resin. The first 28-ml fraction of effluent after the breakthrough was optically inactive. Subsequent fractions contained the (+) isomer of methionine with optical purities of approximately 14, 8, 0, 16, 8, 22, 18, 18, 7, 19, and 0%. Losse, *et al.*,[5] prepared active ion-exchange resins by condensing (−)-tyrosine and formaldehyde with one of the following: chromotropic acid, resorcinol, or *m*-toluidine. By eluting 1-g samples of racemic amino acids through these resins with water or 0.1 *N* hydrochloric acid, they obtained samples of about 600 mg of the (+)-amino acid with optical purities between 21 and 53%.

An optically active resin may be sufficiently unstable so that its optically active constituent is released to the solution in appreciable quantity during a chromatographic resolution. This source of error can be ruled out if all the racemic substance applied to a column is recovered during an elution and if the polarimetric measurements indicate that both active isomers are recovered in equal amounts.

In the ion-exchange resins in all the cases cited,[2-5] the optically active carbon is next to the ion-exchange group. The desirability of this configuration was pointed out by Bunnett and Marks.[6] Further, with one exception,[4] the asymmetric carbon atoms are locked in a rigid structure in the resin. Such a configuration may exclude all but one direction of approach for racemic solute molecules to the ion-exchange site and to the asymmetric carbon. Hence, the sorbent may interact differently with the two isomers of a racemic solute since one may "fit" into the available space better than the other. If the groups about the active carbon are bulky, the directions of approach to the active site may be restricted.

In two cases,[2,3] the concentration of optically active carbon atoms in the resin was small, since a large active molecule was incorporated into an inactive polymer. It is probably highly desirable to have the concentration of active carbon atoms as large as possible.

Weak-Base Anion-Exchange Resin.—The first part of this investigation was an attempt to repeat the work of Tsuboyama and Yanagita,[7] who had treated chloromethylated cross-linked polystyrene (CMX) with active α-phenethylamine. These workers reported

$$-C_6H_4CH_2Cl + H_2NCHMe(C_6H_5) \longrightarrow -C_6H_4\overset{+}{C}H_2NH_2CHMe(C_6H_5)Cl^-$$

a partial resolution of mandelic acid with this resin. A repetition in this laboratory of the procedure of Tsuboyama and Yanagita produced a resin with a weak-base capacity of 1.90 mequiv/g of dry resin (free-amine form) and a strong-base capacity of 0.28 mequiv/g of dry resin (chloride form). All attempts in this laboratory to use this resin in chromatographic resolution ended in failure. The unexpected strong-base groups were formed by the reaction of the secondary nitrogen atom with two other chloromethyl groups to yield $(-C_6H_4CH_2)_3\overset{+}{N}CHMe(C_6H_5)$. This created additional cross-links and produced a resin through which mandelic acid or its anion could not readily diffuse.

Strong-Base Anion-Exchange Resins.—CMX was treated with excess N,N-dimethyl-α-phenethylamine to produce a resin with the group, $-C_6H_4CH_2\overset{+}{N}Me_2CHMe(C_6H_5)Cl^-$. Preliminary work with the racemic amine indicated that best results were obtained by performing the reaction at 100° for 2 hr. Lower temperatures produced smaller degrees of quaternization, *i.e.*, lower exchange capacities, while higher temperatures converted a significant part of the strong-base groups to weak-base groups, possibly by the following reaction.

$$-C_6H_4CH_2\overset{+}{N}Me_2CHMe(C_6H_5)Cl^- \longrightarrow -C_6H_4CH_2NMeCHMe(C_6H_5) + CH_3Cl$$

Two batches of optically active strong-base resin were prepared by the reaction between CMX and L-

(3) H. Suda and R. Oda, *Kanazawa Daigaku Kogakubu Kiyo*, **2**, 215 (1960).

(4) C. W. Roberts and D. H. Haigh, *J. Org. Chem.*, **27**, 3375 (1962).

(5) G. Losse, H. Jeschkeit, G. Fickert, and H. Rabe, *Z. Naturforsch.*, **17b**, 419 (1962).

(6) J. F. Bunnett and J. L. Marks, *J. Am. Chem. Soc.*, **74**, 5893 (1952).

(7) S. Tsuboyama and M. Yanagita, *Sci. Papers Inst. Phys. Chem. Res* (Tokyo), **53**, 245 (1959).

(−)-N,N-dimethyl-α-phenethylamine. Their strong-base capacities, 2.33 and 2.23 mequiv/g of dry resin (chloride form), agreed well with the analogous racemic resin. They had no detectable weak-base groups, and the sorption of water was 1.06 and 1.01 g/g of dry, chloride-form resin, respectively. It was calculated[1a] that 51 and 48% of the benzene rings, respectively, in these resins had been quaternized. Since the original CMX had chloromethyl groups on only 80% of the rings, the quaternization of these groups was 64 and 60% complete, respectively. The reaction probably occurred without racemization since the excess (−)-amine recovered after the synthesis of the active resin had the same specific rotation as the unused (−)-amine.

Evidence of the stability of the resins was found in the fact that the strong-base capacity of the active resins was not diminished by use in the chromatographic experiments.

Frontal Chromatography.—In three chromatographic experiments, solutions of racemic sodium mandelate were passed slowly into a column of the chloride-form, optically active resin. The mandelate ion displaced the chloride on the resin. The concentration of mandelate in the effluent reached the concentration of the influent mandelate shortly after the breakthrough point of the mandelate. The first fractions containing mandelate gave definite positive rotations. The passage of racemic mandelate into the column was continued until the effluent was also racemic. Then the interstitial mandelate was washed from the column with water, and the mandelate on the resin was displaced with sodium chloride or potassium nitrate. The first fractions containing mandelate that came from the column following the interstitial water had negative rotations. Although these experiments involve frontal chromatography in its strictest definition only up to the emergence of racemic mandelate, they are denoted here as frontal experiments to distinguish them from the later experiments in displacement chromatography.

The selectivity coefficient of the resin for the (−) isomer is $E = L(-)M(+)/L(+)M(-)$ where L denotes the number of milliequivalents of isomer [denoted by (+) or (−)] on the resin and M is the concentration of the indicated isomer in the interstitial solution. $M(+)$ equals $M(-)$ when the mandelate emerging from the column is racemic. The values of $L(+)$ and $L(-)$ are readily calculated by two simultaneous equations: $L(+) + L(-) = Q_T$ and $L(-) - L(+) = \Delta L$ where Q_T is the total exchange capacity of the column and ΔL is the excess in milliequivalents of (−)-mandelate over (+)-mandelate on the column at the point of emergence of racemic mandelate. These equations may be combined to yield

$$E = \frac{Q_T + \Delta L}{Q_T - \Delta L} \quad (1)$$

The data of three frontal chromatographic experiments are summarized in Table I. The discrepancy between the amounts of active (+) and (−) isomer found at the breakthrough of the mandelate and in the exchanged mandelate, respectively, of experiment I is probably due to a small error in the zero setting of the polarimeter. The rotations found in the several fractions were never greater than six times the probable error of reading the polarimeter (± 0.005°).

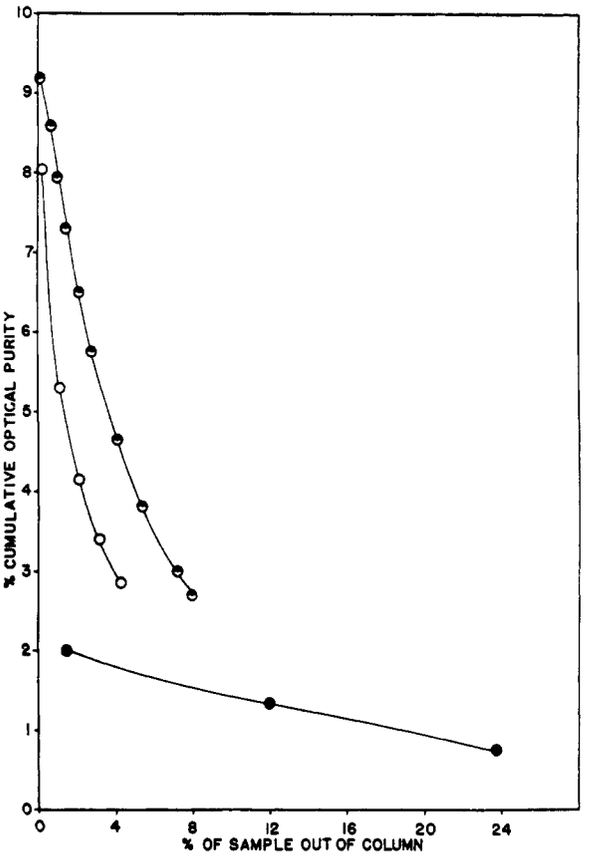

Figure 2.—Comparison of the three frontal experiments: O, frontal I; ●, frontal II; and ◓, frontal III.

TABLE I
SUMMARY OF FRONTAL CHROMATOGRAPHY EXPERIMENTS

	Expt I	Expt II	Expt III
Height of column, cm	48.5	45.5	189
Cross-sectional area, cm²	0.50	0.50	1.46
Q_T, mequiv	26.2	26.2	300
Sodium mandelate concn, N	0.10	1.0	0.10
Flow rate, cm/min	0.24	0.20	0.23
Displacing or eluting agent used	1.0 N NaCl	1.0 N KNO_3	...
ΔL, (+) isomer in effluent, mequiv[a]	0.032	0.047	0.65
ΔL, (−) isomer in effluent, mequiv[b]	0.12	0.059	...
E, based on (+) found	1.002	1.004	1.004
E, based on (−) found	1.009	1.005	...

[a] This is the total amount of the active (+) isomer found in the effluent up to the emergence of racemic mandelate. [b] This is the total amount of active (−) isomer found in the effluent in the second half of the experiment.

Figure 1 gives further detail on frontal experiment I. Figure 2 shows how the cumulative optical purity decreased with the quantity of mandelate that had emerged from the column. The term "cumulative optical purity" at any given point means the optical purity that would be found if all of the mandelate collected in the effluent up to this point were mixed and examined. It is readily calculated from the analysis of the individual fractions of the effluent. The abscissa in Figure 2 is the quantity of mandelate that has emerged from the column expressed as the percentage of the "sample" of racemic mandelate used in the experiment. Since the ion-exchange groups were com-

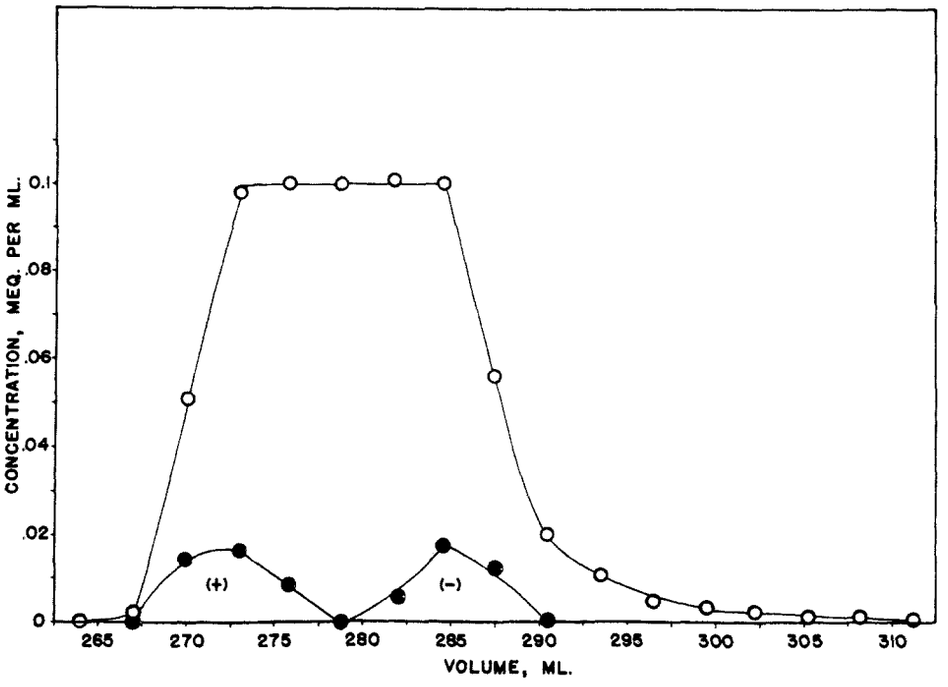

Figure 3.—Displacement analysis I: O, total mandelate concentration; and ●, ten times the concentration of active (+)- or active (−)-mandelate in a fraction.

pletely converted to the mandelate form, the "sample" is equal to the milliequivalents of column capacity.

Displacement Chromatography.—Nine partial resolutions of sodium mandelate were performed by displacement chromatography in which a sample of racemic sodium mandelate was added to a column of the chloride-form, optically active resin and then displaced by potassium nitrate. Figure 3 shows the course of one typical displacement analysis experiment. The mandelate concentration rose sharply to a plateau at the level of the normality of the displacing agent and then fell sharply to almost zero. The first fractions of mandelate had positive rotations, the latter negative.

In nine displacement experiments, the height of the column, H, was varied between 42 and 488 cm, the cross-sectional area between 0.27 and 0.50 cm^2, the total column capacity between 25 and 146 mequiv, the quantity of mandelate, S, between 1.0 and 20 mequiv, the ratio of the height of the mandelate band to the column height, H_b/H, between 0.013 and 0.51, the normality of the potassium nitrate between 0.020 and 0.10, and the flow rate between 0.38 and 0.54 cm/min. Except for two experiments where the value of H_b/H was greater than 0.20, the following relationships were found. The cumulative optical purity of the (+)-mandelate at any given percentage emergence of the mandelate sample (here defined as the amount of mandelate added to the column) was proportional to the square root of the column height. Equation 2 is valid with a standard deviation of 1.8.

$$\frac{\Delta L \times 10^4}{S\sqrt{H}} = 10.4 \qquad (2)$$

In the two displacement experiments with values of H_b/H equal to 0.31 and 0.51, the respective values of $\Delta L \times 10^4/S\sqrt{H}$ were 5.1 and 2.2.

By setting ΔL equal to $S/2$ and by making the assumption of dubious validity that eq 2 is applicable with column heights very much greater than those used in this investigation, it can be calculated that a complete resolution of mandelic acid would be achieved with a column 2.3 km in height. It is obvious that a complete resolution of mandelic acid by this method is impracticable. However, large quantities of mandelic acid can be partly resolved by using columns with lengths and/or cross-sectional areas larger than those used in this investigation.

Experimental Section

L-(−)-α-Phenethylamine.—The straightforward method of Theilacker and Winkler[8] was used to resolve this amine: $[\alpha]^{24}D$ −39.9° (neat), d^{24}_4 0.950 (lit.[8,9] $[\alpha]^{22}D$ −40.3°, $[\alpha]^{25}D$ −39.4°, d^{24}_4 0.950).

L-(−)-N,N-Dimethyl-α-phenethylamine was prepared by the procedure of Kursanov and Vitt[10] from the L-(−)-α-phenethylamine D-(+)-tartrate: $[\alpha]^{26}D$ −70.73° (neat), d^{26}_4 0.902 (lit.[10] $[\alpha]^{25}D$ −71.2°, d^{20}_4 0.903).

Optically Active Strong-Base Resin.—CMX (90 g, 2% cross-linked, 200–400 mesh) was mixed with 200 g of L-(−)-N,N-dimethyl-α-phenethylamine in a glass flask. The polymer was allowed to swell at room temperature for 1 hr. Then the mixture was stirred at 100° for 2 hr in a thermostated oil bath. The mixture was allowed to stand at room temperature for 24 hr and then filtered through a dry, sintered-glass funnel. The excess amine in the filtrate had $[\alpha]^{25}D$ −70.7°. The resin was washed with 500 ml of 1.0 N hydrochloric acid, 1 l. of ethanol, and 2 l. of deionized water. This washing cycle was repeated, and the final washing with water was continued until silver nitrate gave a negative test for chloride ion in the wash water.

Determination of Ion-Exchange Capacity.—A sample of about 2 g of the resin was stirred for 24 hr with an aqueous solution 0.04 N in sodium hydroxide and 1.0 N in sodium chloride to convert the strong-base groups to the chloride form and the weak-base groups (if any) to the free-amine form. The electrolytes were removed by washing with water, and the resin was dried *in vacuo* over silica gel. A 1-g sample of this dried

(8) W. Theilacker and H. G. Winkler, *Chem. Ber.*, **87**, 690 (1954).

(9) A. W. Ingersol, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 506.

(10) D. N. Kursanov and S. V. Vitt, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1397 (1950).

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]

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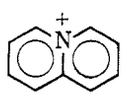
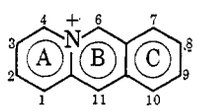
Received September 14, 1965

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.