Acridizinium Ion Chemistry. VII.[1] Halogenation[2]

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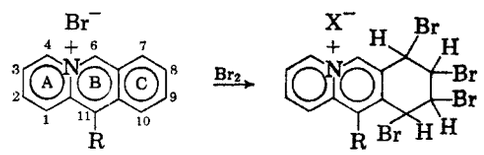
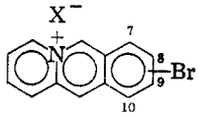
In the presence of an excess of bromine, the acridizinium cation adds bromine reversibly, presumably at positions 7, 8, 9, and 10. With sodium acetate, the addition compounds yields the 10-bromoacridizinium ion. With dimethylformamide as a solvent, and in the presence of the appropriate aluminum halide, bromination (with bromine) and chlorination (with sulfuryl chloride) occur in the central nucleus yielding, respectively, the 11-bromoacridizinium ion and 11-chloro-6H-benzo[*b*]quinolizin-6-one. Chlorination with a large excess of sulfuryl chloride as the solvent and aluminum chloride as a catalyst yields the 7,10-dichloroacridizinium ion.

In an earlier report[3] the first electrophilic substitution (sulfonation) of the parent acridizinium ion (I) was described. The present communication describes the behavior of the cation with halogenating agents.

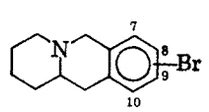


I, R = H
II, R = CH_3

III, R = H
IV, R = CH_3



V, 7-Br
VI, 8-Br
VII, 9-Br
VIII, 10-Br



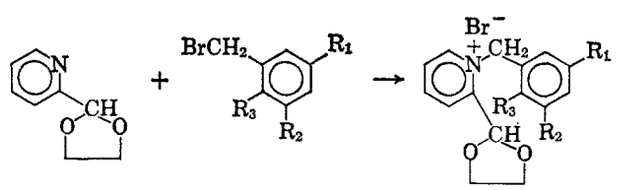
IX, 8-Br
X, 10-Br

Initial attempts to brominate the cation in glacial acetic acid using conventional catalysts (ferric chloride, zinc chloride) were unsuccessful, but, when the bromide salt (I) was dissolved in liquid bromine and permitted to stand for 15 hr at room temperature, a tetrabromo addition compound (III) was formed. The initial product (III, X = Br_3) appeared to have as the anion the tribromide ion which was converted to the bromide by the action of acetone–methanol.

Elemental analysis of the new bromide, as well as the perchlorate salt (III, X = ClO_4), gave results consistent with the assumption that the product was an addition product formed by addition of 2 moles of bromine. Further evidence that substitution had not occurred was that the new salt (III, X = Br), on heating, liberated bromine, regenerating the original acridizinium bromide (I). Similarly, 11-methylacridizinium bromide (II) was found to add to 2 moles of bromine to form a product which regenerated the starting material on heating.

While the evidence does not yet amount to a demonstration, it seems most likely that the addition compound has the four bromine atoms attached to ring C, paralleling the addition of bromine to the terminal ring of 9,10-dichloroanthracene.[4] The ultraviolet absorption spectrum of III is consistent with the assumption that the chromophore is a substituted quinolizinium[5] ion, and the nmr spectrum is explicable in terms of formula III.

When the tetrabromo compound (III) was treated with sodium acetate, it yielded a monobromoacridizinium bromide which was identical with neither of the known 7- or 9-bromoacridizinium[6] salts (V and VII). A possible method for the synthesis of the new compound in small yield appeared to be the cyclization of the quaternary salt (XIIa) formed by the reaction of



XI

XIIa, R_1 = Br; R_2 = R_3 = H (not isolated)
b, R_1 = R_2 = Cl; R_3 = H
c, R_1 = R_3 = Cl; R_2 = H

m-bromobenzyl bromide with 2-(1,3-dioxalan-2-yl)pyridine (XI). This synthesis is ambiguous in that cyclization could occur *ortho* or *para* to the ring bromine atom but on the basis of analogy,[7] it was expected that cyclization *para* to the bromine atom would predominate. Actually only a single bromoacridizinium bromide, presumed to be the 8-bromo (VI), was isolated. This product was not identical with the bromoacridizinium salt obtained by reaction of sodium acetate on the tetrabromide, tentatively considered the 10 isomer (VIII).

As a more rigorous proof of the structure assigned to the new bromoacridizinium salts, they were each reduced with sodium borohydride, and the resulting bases (IX and X) were converted to metho salts. The infrared spectrum of the reduction product of the original bromoacridizinium salt obtained from the tetrabromide (III) gave infrared absorptions characteristic of the out-of-plane vibrations of *three* adjacent aromatic hydrogens, excluding the possibility that the halogen was at position 8. In the same way, the reduction product of the bromoacridizinium salt obtained from *m*-bromobenzyl bromide (XII) was shown to have a maximum of *two* adjacent aromatic hydrogens, excluding the possibility that the halogen was at position 10. These observations definitely confirmed the correctness of our original assignments.

The fact that a bromine atom remains attached to position 10 when sodium acetate reacts with the addi-

(1) For the preceding communication of this series, see C. K. Bradsher and J. P. Sherer, *J. Org. Chem.*, **32**, 733 (1967).

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

(3) C. K. Bradsher and J. D. Turner, *J. Org. Chem.*, **31**, 565 (1966).

(4) K. H. Meyer and K. Zahn, *Ann.*, **396**, 166 (1913).

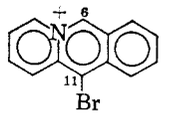
(5) E. E. Gover and G. Jones, *J. Chem. Soc.*, 3021 (1958).

(6) C. K. Bradsher, J. H. Parham, and J. P. Sherer, *J. Chem. Eng. Data*, **10**, 180 (1965).

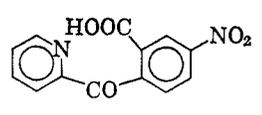
(7) *E.g.*, W. v. Miller and G. Rohde, *Ber.*, **23**, 1887 (1890); *cf.* W. Miersch, *ibid.*, **25**, 2109 (1892); F. Tyson, *J. Am. Chem. Soc.*, **61**, 183 (1939).

tion compound (III) is probably due to the greater acidity of the proton attached to the carbon at that position. Of the four carbon atoms making up ring C, carbon 10 is unique in being connected to a carbon bearing a partial positive charge. The removal of a proton at carbon 10 is probably followed by expulsion of a bromide ion and loss of a molecule of bromine to give the 10-bromoacridizinium salt (VIII).

When acridizinium bromide was dissolved in dry dimethylformamide containing aluminum bromide, heated to 100° and an excess of bromine was added a new monobromoacridizinium cation was produced. Oxidation of the product with nitric acid afforded the known[8] 2-(2-carboxy-4-nitrobenzoyl)pyridine (XIV),



XIII

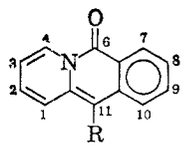


XIV

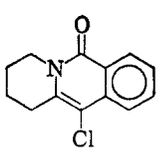
evidence that the bromine atom had been attached to ring B. Since a bromine atom at position 6 would be expected to undergo nucleophilic displacement with very great facility, the new cation has been assigned the formula of the 11-bromoacridizinium ion (XIII).

When the halogenation was carried out in dimethyl formamide essentially as described for the 11 bromination, but using an excess of sulfuryl chloride instead of bromine, and aluminum chloride instead of bromide as the catalyst, the product obtained by pouring the reaction mixture into water was a nonionic, water-insoluble compound. The infrared spectrum showed a characteristic amide carbonyl absorption band at 1665 cm^{-1}, but the compound was not acidic. Examination of the longer wavelength ultraviolet absorption in methanol revealed a single, broad absorption band at 392 mμ. A similar examination carried out in concentrated sulfuric acid solution revealed absorption bands at 385, 400, and 424 mμ, a pattern characteristic of the acridizinium system.[9] The sulfuric acid solution of the product when irradiated with ultraviolet light gave the bluish fluorescence characteristic of acridizinium compounds. Passage of hydrogen chloride through a benzene solution of the compound gave a hydrochloride which was very deliquescent and proved too unstable to purify.

The similarity in the properties of our compound to those of 4-quinolizone[10] suggested that our chlorination product was 11-chloro-6H-benzo[*b*]quinolizin-6-one (XV), the 11-chloro derivative of a compound (XVI)



XV, R = Cl
XVI, R = H

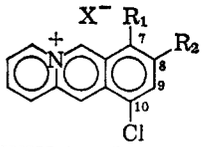


XVII

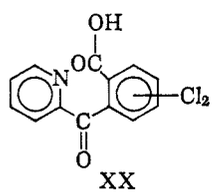
first described by Paquette.[11] Oxidation of XV with nitric acid afforded 2-(2-carboxy-4-nitrobenzoyl)pyridine (XIV), evidence that the chlorine atom is in a *meso* position. The tetrahydro derivative formed upon catalytic hydrogenation has been assigned structure XVII.

It appears most likely that, under the conditions used, the acridizinium nucleus, like that of anthracene,[12] chlorinates in the *meso* positions affording the 6,11-dichloroacridizinium cation and that this species undergoes nucleophilic attack by water at the active 6 position during the work-up procedure, yielding the chlorobenzoquinolizin-6-one (XV).

Preliminary attempts to bring about chlorination of acridizinium bromide in sulfuryl chloride in the presence of aluminum chloride resulted in bromination as well as chlorination, and acridizinium chloride was used in all later experiments. When acridizinium chloride and aluminum chloride were dissolved in an excess of sulfuryl chloride and the mixture was allowed to stand at room temperature for 20 hr, dichlorination of the cation occurred. Oxidation of the dichloroacridizinium bromide with nitric acid yielded a 2-(2′-carboxydichlorobenzoyl)pyridine (XX). Isolation of this oxidation product eliminated the possibility that either of the chlorine atoms was substituted on the central nucleus. Assuming that it was unlikely that substitution would occur on ring A, owing to the quaternary nitrogen atom, there existed six possible dichloroacridizinium cations to be considered. Of the six, two, the 8,9- or 7,9-dichloro, had been reported[6] and neither was identical with the chlorination product. Of the four remaining derivatives, two were selected as most promising for synthesis. These were the 8,10-dichloro (XVIII), in which neither of the halogens is



XVIII, R_1 = H; R_2 = Cl
XIX, R_1 = Cl; R_2 = H



XX

substituted on a carbon atom which (as the result of resonance) bears a partial positive charge, and the 7,10-dichloro (XIX), the product predicted from an addition–elimination process. The synthetic method was similar to that used in making 8-bromoacridizinium (VI) except that in the present instances the outcome of the cyclization step was unambiguous. The discovery that the dichlorination product is identical in all respects with the 7,10-dichloroacridizinium cation suggests that chlorine may add first forming a 7,8,9,10-tetrachloro derivative (analogous to III), followed by removal of the two most acidic protons, those at carbons 7 and 10, and the loss of two chloride ions. It would be interesting to explore the alternate possibility, that the 10-chloro derivative is first formed and undergoes simple electrophilic substitution to afford the 7,10 derivative, but this hypothesis can not be tested at the present time since the 10-chloro compound is unknown.

It is clear from our experiments that there is a distinct difference between halogenations of acridizinium ion carried out in the presence of dimethylformamide, which appear to involve simple electrophilic substitutions at the *meso* positions, and those in which dimethyl-

(8) C. K. Bradsher and M. W. Barker, *J. Org. Chem.*, **29**, 452 (1964).
(9) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).
(10) V. Boekelheide and J. P. Lodge, *ibid.*, **73**, 3681 (1951).
(11) L. A. Paquette, *Chem. Ind.* (London), 1292 (1962).
(12) E. Barnett, J. W. Cook, and H. H. Grainger, *J. Chem. Soc.*, **121**, 2059 (1922).

formamide is absent, which involve attack on the terminal nucleus (ring C), certainly by addition, in the case of bromination, and, possibly by addition–elimination, in the case of chlorination with sulfuryl chloride.

Experimental Section

The elemental analyses were by Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, Germany, or Dr. C. Janssen, Research Laboratorium, Beerse, Belgium. Melting points were taken in capillaries using a Laboratory Devices Mel-Temp apparatus. Unless otherwise noted all ultraviolet absorption spectra were observed in 95% ethanol solution using a Cary Model 14 spectrophotometer and 1-cm silica cells. Nmr spectra were recorded with a Varian A-60 spectrometer using tetramethylsilane as an external standard.

Acridizinium Bromide (I).—For the preparation of acridizinium bromide on a large scale, the most satisfactory route in terms of availability and stability of starting materials, as well as yield of product, is *via* preparation and cyclization of 1-benzyl-2-(1-hydroximinomethyl)pyridinium bromide.[13] Although it was not recognized at the time this method was first described, the initial cyclization product contains a double salt of acridizinium bromide and hydroxylamine hydrobromide.[14] The following procedure gives consistently high yields of acridizinium bromide free from hydroxylamine salts. Crude 1-benzyl-2-(1-hydroximinomethyl)pyridinium bromide was prepared by allowing a mixture of 24.4 g of picolinaldoxime, 30 ml of dimethylformamide, and 37.6 g of benzyl bromide to stand in the dark at room temperature for 27 hr followed by slurrying the mixture in ethyl acetate and collecting the solid. The solid was placed in 265 ml of 48% hydrobromic acid and the mixture was refluxed for 30 min. While the solution was still hot it was transferred to 3 l. of hot water and the solution was cooled to room temperature by addition of ice. To the resulting solution, a solution of 22 ml of bromine in 4 l. of water was added, with stirring, causing the precipitation of the tribromide salt of acridizinium cation. The salt was collected, washed with ice water, and partially dried on the filter by continuing the suction for 1 hr. The moist salt was transferred to 500 ml of 1:1 acetone–methanol and the mixture was heated and stirred to effect solution. Heating was continued until the volume had been reduced to about 300 ml and the product was crystallized by addition of ethyl acetate, yielding 43 g (83%) of yellow needles, mp 239–240° (lit.[9] 239–241°).

7,8,9,10-Tetrabromo-7,8,9,10-tetrahydroacridizinium Bromide (III).—One gram of acridizinium bromide (I) was dissolved in 3 ml of liquid bromine and the mixture was allowed to stand at room temperature for 15 hr. The solution was then poured into 200 ml of ethyl acetate and the resulting mixture was allowed to stand at −15° for 24 hr. An orange solid, evidently a tribromide salt, separated and was collected and washed with ethyl acetate. The orange product was dissolved in a boiling 19 mixture of methanol and acetone, the mixture was concentrated, and ethyl acetate was added. The product which separated slowly on standing was recrystallized from methanol–ethyl acetate, affording 1.2 g (52%) of light yellow, irregular needles, mp 118–120° (loses bromine).

Anal. Calcd for $C_{13}H_{10}Br_5N \cdot CH_3OH$: C, 27.48; H, 2.31; N, 2.29. Found: C, 27.58; H, 2.02; N, 2.65.

The **perchlorate** was prepared by addition of 35% perchloric acid to a warm, aqueous solution of the bromide, and crystallized from methanol–ethyl acetate as light yellow plates, mp 195–197° (loses bromine).

Anal. Calcd for $C_{13}H_{10}Br_4ClNO_4 \cdot CH_3OH$: C, 26.62; H, 2.23; N, 2.22. Found: C, 26.91; H, 1.83; N, 2.52.

The nmr spectrum determined with a solution in hexadeuteriodimethyl sulfoxide showed an A_2B_2 system with a two-proton doublet centered at δ 6.80 (J = 5.5 cps) and a two-proton doublet at 5.90 (J = 5.5 cps). Integration showed a ratio of six aromatic to four nonaromatic protons.

Acridizinium Bromide (I) from 7,8,9,10-Tetrabromo-7,8,9,10-tetrahydroacridizinium (III) Bromide.—A suspension of 0.7 g of the 7,8,9,10-tetrabromo-7,8,9,10-tetrahydroacridizinium (III) bromide in 25 ml of xylene containing 0.5 g of phenol was refluxed for 30 min and cooled to room temperature, and 100 ml of ethyl acetate was added. After the mixture had stood for 4 hr at −15° the organic solvent was decanted and the residue was recrystallized from methanol–ethyl acetate. The product was acridizinium bromide [0.25 g (83%), mp 240–242° (lit.[9] 239–240°)] and identity was confirmed by the infrared spectrum.

11-Methylacridizinium Bromide (II).—This salt was prepared from a solution of the known[15] perchlorate by precipitation of the tribromide salt with a solution of bromine in 48% hydrobromic acid. The tribromide was converted to the bromide in the usual way and crystallized from methanol–ethyl acetate, yielding yellow needles, mp 244–245°.

Anal. Calcd for $C_{14}H_{12}BrN \cdot 0.25H_2O$: C, 60.34; H, 4.52; N, 5.03. Found: C, 60.69; H, 4.22; N, 5.35.

7,8,9,10-Tetrabromo-7,8,9,10-tetrahydro-11-methylacridizinium (IV) Bromide.—The bromination of 11-methylacridizinium bromide (0.85 g) was carried out as in the case of the parent compound (I). The product (0.64 g, 35%) was obtained as a pale yellow, microcrystalline solid, mp 148–150°.

Anal. Calcd for $C_{14}H_{12}Br_5N$: C, 28.31; H, 2.04; N, 2.36. Found: C, 27.98; H, 2.10; N, 2.67.

11-Methylacridizinium Perchlorate from 7,8,9,10-Tetrabromo-7,8,9,10-tetrahydro-11-methylacridizinium (IV) Bromide.—The tetrabromo bromide (IV, 0.6 g) was heated in xylene essentially as in the case of the parent compound. The crude salt collected from the xylene was dissolved in water and converted to the perchlorate. The perchlorate was recrystallized from methanol–ethyl acetate to give 0.24 g (81%) of yellow plates, mp 242–244° (lit.[15] 243–244.5°).

10-Bromoacridizinium Bromide (VIII).—To a solution of 0.5 g of 7,8,9,10-tetrabromo-7,8,9,10-tetrahyroacridizinium bromide in 25 ml of water at room temperature, a solution of 1 g of sodium acetate in 15 ml of water was added and the mixture was allowed to stand for 15 hr at room temperature. The solution was filtered and the product was precipitated as the tribromide salt with the usual bromine-hydrobromic acid reagent. The tribromide was converted in the usual way to the bromide by use of methanol–acetone. The product was crystallized from methanol–ethyl acetate as yellow, irregular crystals, mp 250–252° (yield 0.22 g, 78%).

Anal. Calcd for $C_{13}H_9Br_2N$: C, 46.05; H, 2.68; N, 4.13. Found: C, 45.74; H, 2.90; N, 4.43.

The **picrate** was prepared in ethanol and recrystallized from the same solvent as a microcrystalline powder, mp 265–266°.

Anal. Calcd for $C_{19}H_{11}BrN_4O_7$: C, 46.83; H, 2.28; N, 11.50. Found: C, 47.11; H, 2.28; N, 11.42.

10-Bromobenzo[*b*]quinolizidine Methiodide (X).—To 0.25 g of 10-bromoacridizinium (VIII) bromide dissolved in 40 ml of water, a solution of 0.25 g of sodium borohydride in 25 ml of water was added slowly. The mixture was heated on the steam bath for 30 min with stirring. The red gum which separated was extracted with ether and the ether solution was dried (magnesium sulfate) and concentrated, and the residue was allowed to stand at room temperature for 3 hr with an excess of methyl iodide. The quaternary salt was crystallized from methanol as irregular needles, mp 244–245° (yield 0.17 g, 57%). The infrared spectrum showed an intense absorption at 760 and a peak of medium intensity at 695 cm^{-1}, indicating[16] the presence of three adjacent aromatic hydrogens.

Anal. Calcd for $C_{14}H_{19}BrIN \cdot 0.5H_2O$: C, 40.31; H, 4.83; N, 3.36. Found: C, 40.42; H, 4.75; N, 3.44.

8-Bromoacridizinium (VI) Bromide.—A solution of 2 g of 2-(1,3-dioxolan-2-yl)pyridine (XI)[15] and 3 g of *m*-bromobenzyl bromide in 2 ml of tetramethylenesulfone was permitted to stand at room temperature for 4 days. The quaternary salt (XIIa) was precipitated as a gum by addition of ethyl acetate and after the mixture had stood for 3 hr at −15°, the ethyl acetate was decanted. The residual gum was dissolved in 20 ml of concentrated sulfuric acid and the solution, after 2 hr at room temperature, was heated on the steam bath for 5 min. The mixture was cooled in an ice bath and poured into ice-cold, anhydrous ether. The ether was decanted and the residue was dissolved in water. To the water was added a solution containing three parts by volume of 48% hydrobromic acid to one of bromine. After the mixture had stood for 3 hr at about 0° the precipitate, presumably

(13) C. K. Bradsher, T. W. G. Solomons, and F. R. Vaughan, *J. Org. Chem.*, **25**, 757 (1960).

(14) For a description of the isolation and analysis of the double salt of 7,10-dimethoxyacridizinium hydrobromide and hydroxylamine hydrobromide, see C. K. Bradsher and M. W. Barker, *ibid.*, **29**, 61 (1964).

(15) C. K. Bradsher and J. C. Parham, *ibid.*, **28**, 83 (1963).

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1958, p 75.

the tribromide (VI, X = Br_3) was collected and suspended in a 1:1 mixture of methanol and acetone. The volume was reduced to about 50 ml and the product was crystallized by addition of ethyl acetate. The crude bromide was recrystallized from methanol–ethyl acetate to give 2.4 g (59%) of yellow, irregular needles, 233–235°.

Anal. Calcd for $C_{13}H_9Br_2N \cdot 0.5H_2O$: C, 44.86; H, 2.90; N, 4.03. Found: C, 45.08; H, 2.88; N, 4.15.

8-Bromobenzo[*b*]quinolizidine (IX) Methoperchlorate.—The reduction of 0.65 g of 8-bromoacridizinium (VI) bromide was carried out as in the case of the isomer VIII. The methiodide was prepared in the same way, but the quaternary salt was precipitated from aqueous solution as the perchlorate by addition of 35% perchloric acid. The methoperchlorate crystallized from methanol–ethyl acetate as buff-colored microcrystalline aggregates, mp 208–210° (yield 0.34 g, 58%). The infrared absorption spectrum showed an absorption band at 805 cm^{-1}, indicating the presence of two adjacent aromatic hydrogen atoms.[16]

Anal. Calcd for $C_{14}H_{19}BrClNO_4$: C, 44.17; H, 5.03; N, 3.68. Found: C, 44.17; H, 4.53; N, 3.66.

11-Bromoacridizinium (XIII) Bromide.—To a solution containing 3.4 g of acridizinium bromide and 3 g of anhydrous aluminum bromide in 20 ml of dry dimethylformamide, heated on a steam bath and mechanically stirred, 3 ml of bromine was added over the period of 1 hr. Heating was continued for 0.5 hr and the solution was cooled and poured slowly into 100 ml of ice water. The resulting precipitate, probably a tribromide salt (XIII, X = Br_3) was treated in the usual way with methanol–acetone. Recrystallization of the bromide from methanol–ethyl acetate gave 2.3 g (52%) of yellow, irregular, microcrystalline aggregates, mp 256–258°.

Anal. Calcd for $C_{13}H_9Br_2N \cdot 0.25CH_3COOC_2H_5$: C, 46.57; H, 3.07; N, 3.88. Found: C, 46.59; H, 2.82; N, 3.99.

The **perchlorate** crystallized from methanol–ethyl acetate as reddish, irregular needles, mp 168–169° (color change to yellow at 140°).

Anal. Calcd for $C_{13}H_9BrClNO_4$: C, 43.54; H, 2.53; N, 3.91. Found: C, 43.61; H, 2.56; N, 3.93.

Oxidation of 11-Bromoacridizinium (XIII) Bromide to 2-(2-Carboxy-4-nitrobenzoyl)pyridine (XIV).—A solution of 1.2 g of 11-bromoacridizinium bromide in 40 ml of 12 *M* nitric acid was heated for 4 hr on a steam bath. The nitric acid was removed with a rotary evaporator heated by a steam bath, and the residue was recrystallized from ethanol–water affording 0.21 g (22%) of cream-colored granules, mp 224–226° (lit.[6] mp 225–227°).

Anal. Calcd for $C_{13}H_8N_2O_5$: C, 57.36; H, 2.96; N, 10.29. Found: C, 57.68; H, 3.20; N, 9.95.

11-Chloro-6H-benzo[*b*]quinolizin-6-one (XV).—A solution of 2 g of anhydrous aluminum chloride and 5 g of acridizinium bromide in 30 ml of dry dimethylformamide was heated for 5 hr in a three-necked flask provided with stirrer, reflux condenser, and dropping funnel while 30 ml of sulfuryl chloride was added dropwise. The solution was cooled to room temperature and poured slowly into 150 ml of water. The resulting mixture was filtered and the usual bromine–hydrobromic acid mixture was added to the filtrate. The tribromide salt was treated in the usual way with acetone–methanol and on concentrating the solution a bright orange precipitate was obtained. Recrystallization of the precipitate from methanol gave 1.95 g (44%) of bright orange needles, mp 240–241°. The infrared absorption spectrum showed a peak at 1665 cm^{-1} assigned to an amide carbonyl.[17]

Anal. Calcd for $C_{13}H_8ClNO$: C, 67.98; H, 3.51; N, 6.10. Found: C, 67.72; H, 3.55; N, 6.04.

Oxidation of 11-Chlorobenzo[*b*]quinolizin-6-one (XV) to 2-(2-Carboxy-4-nitrobenzoyl)pyridine (XIV).—The oxidation of the chlorobenzoquinolizin-6-one (mV) with nitric acid was carried out in 12 *M* nitric acid essentially as described for 11-bromoacridizinium (XIII) bromide. The acid XIV was obtained in 50% yield [mp 224–226° (lit.[8] 225–227°)] and the identity of the product was demonstrated by direct comparison of infrared spectra.

Reduction of 11-Chlorobenzo[*b*]quinolizin-6-one (XV) to 1,2,3,4-Tetrahydro-11-chlorobenzo[*b*]quinolizin-6-one (XVII).—A suspension of 0.5 g of 11-chlorobenzo[*b*]quinolizin-6-one and 0.05 g of platinum oxide in 50 ml of ethanol was stirred under an atmosphere of hydrogen for 4 hr. The product crystallized from ethanol–water to give pale, cream-colored needles, mp 136–137° (yield 0.4 g, 79%). The infrared spectrum showed an amide carbonyl absorption[17] at 1640 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.83; H, 5.39; N, 5.91.

Acridizinium Chloride.—Five grams of acridizinium bromide was dissolved in a minimum quantity of water, excess 10% sodium hydroxide was added, and the resulting red precipitate was extracted with ether. The ether solution was washed with water, and then 75 ml of concentrated hydrochloric acid was added. The red color disappeared from the ether layer with the appearance of a yellow color in the aqueous phase. The ether and acid were evaporated in on a rotary evaporator (steam bath) under reduced pressure. The residue was crystallized from methanol–ethyl acetate yielding 2.4 g (58%) of yellow prisms, mp 206–208° dec.

Anal. Calcd for $C_{13}H_{10}ClN \cdot H_2O$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.65; H, 5.18; N, 6.04.

7,10-Dichloroacridizinium (XIX) Perchlorate, by Chlorination.—A solution containing 1.8 g of acridizinium chloride and 2 g of anhydrous aluminum chloride in 25 ml of sulfuryl chloride, protected from moisture, was allowed to stand at room temperature for 20 hr. The solution was poured on 200 g of ice and permitted to hydrolyze slowly. The resulting aqueous solution was filtered and 35% perhloric acid was added to the filtrate. The salt which precipitated was collected and recrystallized from methanol–ethyl acetate giving 2.3 g (77%) of yellow plates, mp 226–228°.

Anal. Calcd for $C_{13}H_8Cl_3NO_4$: C, 44.79; H, 2.31; N, 4.02. Found: C, 44.85; H, 2.26; N, 4.07.

The **bromide** was prepared by precipitation of the tribromide salt (XIX, X = Br_3) from an aqueous solution of the perchlorate followed conversion to the bromide in acetone. The product crystallized from methanol–ethyl acetate as yellow, granular crystals, mp >300° dec.

Anal. Calcd for $C_{13}H_8BrCl_2N$: C, 47.45; H, 2.44; N, 4.26. Found: C, 47.41; H, 2.38; N, 4.28.

2-(2′-Carboxy-3′,6′-dichlorobenzoyl)pyridine (XX).—One gram of 7,10-dichloroacridizinium (XIX) bromide was dissolved in 40 ml of 12 *M* nitric acid and heated on the steam bath for 4 hr. Worked up in the usual way, the product (0.22 g, 24%) crystallized from ethanol–water as colorless plates, mp 154–155°.

Anal. Calcd for $C_{13}H_7Cl_2NO_3$: C, 52.73; H, 2.38; N, 4.73. Found: C, 52.80; H, 2.40; N, 4.75.

3,5-Dichlorobenzyl Bromide.—A method for the preparation of this compound has been described earlier,[18] but, since the 3,5-dichlorotoluene required is not commercially available, the following method, starting with 3,5-dichlorobenzoic acid, was found convenient. Five grams of 3,5-dichlorobenzoic acid dissolved in 200 ml of dry ethyl ether was added over a period of 1 hr to a stirred suspension of 7 g of lithium aluminum hydride in 200 ml of dry ether, the reaction flask being cooled in an ice bath. Stirring was continued for an additional 2 hr at the same temperature. The reaction mixture was decomposed by the addition of 10% sodium hydroxide solution. The combined ether extracts were dried with sodium sulfate and concentrated to 150 ml. The solution was cooled in an ice bath while 6 ml of phosphorus tribromide was added slowly and then allowed to stand for 15 hr. After cautious addition of saturated sodium bicarbonate solution, the ether solution was dried (magnesium sulfate) and concentrated. The residue crystallized from isopropyl alcohol as colorless needles, mp 57–58°, yield 5.8 g (92%).

Anal. Calcd for $C_7H_5BrCl_2$: C, 35.04; H, 2.10. Found: C, 35.23; H, 2.10.

1-(3′,5′-Dichlorobenzyl)-2-(1,3-dioxolan-2-yl)pyridinium Bromide (XIIB).—Three grams of 3,5-dichlorobenzyl bromide and 2.5 g of 2-(1,3-dioxolan-2-yl)pyridine[15] were dissolved in 3 ml of tetramethylenesulfone and heated for 48 hr at 45°. Ethyl acetate was added and the mixture was allowed to stand for 1 hr at −15°. The ethyl acetate was decanted and the residue was crystallized from methanol–ethyl acetate to give 3.8 g (71%) of a colorless, microcrystalline powder, mp 100–102°.

Anal. Calcd for $C_{15}H_{14}BrCl_2NO_2$: C, 46.06; H, 3.61; N, 3.58. Found: C, 45.94; H, 3.65; N, 3.66.

8,10-Dichloroacridizinium (XVIII) Perchlorate.—To the quaternary salt (XIIb), 12 ml of concentrated sulfuric acid was added slowly, and the solution was heated on a steam bath for

(17) Reference 16, p 203.

(18) M. B. Pybus, R. L. Wain, and F. Wightman, *Ann. Appl. Biol.*, **47**, 593 (1959).

0.5 hr. The cooled sulfuric acid solution was poured into ether, and the ether was decanted. The residue was dissolved in water and 35% perchloric acid added. The perchlorate salt was collected and recrystallized from methanol–ethyl acetate affording 2.8 g (89%) of yellow needles, mp 209–211°.

Anal. Calcd for $C_{13}H_8Cl_3NO_4$: C, 44.79; H, 2.31; N, 4.02. Found: C, 44.82; H, 2.28; N, 4.31.

1-(2′,5′-Dichlorobenzyl)-2-(1,3-dioxolan-2-yl)pyridinium Bromide (XIIc).—The crude 2,5-dichlorobenzyl bromide (obtained by bromination of 5 g of 2,5-dichlorotoluene in carbon tetrachloride solution, under irradiation from a sunlamp and isolated simply by evaporation of the solvent) was allowed to react with 3 g of 2-(1,3-dioxolan-2-yl)pyridine in 3 ml of tetramethylenesulfone as described in the preparation of XIIb. The product crystallized from methanol–ethyl acetate as colorless plates, mp 144–146°.

Anal. Calcd for $C_{15}H_{14}BrCl_2NO_2$: C, 46.06; H, 3.61; N, 3.58. Found: C, 46.13; H, 3.68; N, 3.54.

7,10-Dichloroacridizinium (XIX) Perchlorate *via* Cyclization.—The quaternary salt XIIc was cyclized in sulfuric acid as described for the preparation of 8,10-dichloroacridizinium (XVIII) perchlorate. The product, obtained in 76% yield, consisted of yellow plates, mp 226–228°. The infrared spectrum and melting point were identical with those observed for the dichlorination product of the acridizinium cation and no depression of mixture melting point was observed.

Registry No.—I, 7547-88-8; III, 7777-88-0; III perchlorate, 7777-89-1; II, 7777-90-4; IV bromide, 7777-91-5; 11-methylacridizinium perchlorate, 7777-92-6; VIII, 7777-93-7; VIII picrate, 7777-94-8; X, 10026-46-7; VI bromide, 7777-95-9; IX methoperchlorate, 10026-47-8; XIII bromide, 7777-96-0; XIII perchlorate, 10043-44-4; XV, 7777-97-1; XVII, 10026-49-0; acridizinium chloride, 7777-98-2; XIX perchlorate, 10026-50-3; XIX bromide, 7777-99-3; XX, 7778-00-9; 3,5-dichlorobenzyl bromide, 7778-01-0; XIIb, 7778-02-1; XVIII perchlorate, 10026-51-4; XIIc, 10026-52-5.

Optical Rotatory Dispersion and Absolute Configuration of Some Long-Chain Hydroxy Acids[1]

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Several long-chain, unsaturated, hydroxy acids from plant sources and selected derivatives have been examined spectropolarimetrically. These measurements coupled with earlier unequivocal syntheses allow configurational assignments to be made for the saturated and, hence, the parent unsaturated hydroxy acids. Evidence is presented that the low-intensity ester transition has no effect on the observed optical rotatory dispersion (ORD) of the hydroxy acid esters. Studies with derivatives allow some suggestions to be made concerning interaction of other functional groups with the asymmetric chromophore. Where they could be rationally applied, values calculated from Brewster's rules were in good agreement with observed results in all but one case.

Several long-chain hydroxy acids which contain asymmetric centers have been isolated from natural sources.[2] The structures and, in some cases, the absolute configurations of these compounds have been determined. Serck-Hanssen[3] synthesized (+)-12-L-hydroxyoctadecanoic (hydroxystearic) acid and showed that this isomer was enantiomeric with the hydroxystearic acid derivable from castor oil thus assigning the D configuration to (−)-12-hydroxyoctadecanoic acid and to (+)-12-hydroxy-*cis*-9-octadecenoic acid (ricinoleic acid). Baker and Gunstone[4] synthesized 9-D-hydroxyoctadecanoic acid using Serck-Hanssen's method,[3] but were unable to detect measurable optical activity in their synthetic sample or in 9-hydroxyoctadecanoic acid prepared by the hydrogenation of (+)-9-hydroxy-*cis*-12-octadecenoic acid from *Strophanthus* seed oil. They suggested, however, that these acids have the same configuration by consideration of mixture melting point data. Recently Schroepfer and Bloch[5] reexamined the synthetic sample of 9-D-hydroxyoctadecanoic acid of Baker and Gunstone and found, by means of ORD measurements, that it is identical in configuration with the naturally occurring acid, thus confirming the earlier[4] suggestion.

Availability of improved instrumentation coupled with our interest in the optically active hydroxy acids of the *Dimorphothecae*[6a] and *Lesquerellae*[6b,c] led us to an ORD study of these acids and some of their derivatives. From the results with the saturated derivatives we established the absolute configurations of the dimorphecolic[6a] [(+)-9-hydroxy-*trans,trans*-10,12-octadecadienoic] and densipolic[6c] [(−)-12-hydroxy-*cis,cis*-9,15-octadecadienoic] acids and suggested the absolute configuration of lesquerolic[6b] [(+)-14-hydroxy-*cis*-11-eicosenoic] acid.[7] Our suggestion concerning lesquerolic acid was confirmed by its synthesis from ricinoleic [(+)-12-D-hydroxy-*cis*-9-octadecenoic] acid which unequivocally established the structure as (+)-14-D-hydroxy-*cis*-11-eicosenoic acid.[8]

(1) Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 13–17, 1965, Abstracts, p 26S.

(2) (a) T. P. Hilditch and P. N. Williams, "The Chemical Constitution of Natural Fats," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1964; (b) F. B. Shorland in "Chemical Plant Taxonomy," T. Swain, Ed., Academic Press Inc., New York, N. Y., 1963, p 253; (c) R. G. Powell and C. R. Smith, Jr., *Chem. Ind.* (London), 470 (1965); (d) R. G. Powell, C. R. Smith, Jr., C. A. Glass, and I. A. Wolff, *J. Org. Chem.*, **30**, 610 (1965).

(3) K. Serck-Hanssen, *Chem. Ind.* (London), 1554 (1958).

(4) C. D. Baker and F. D. Gunstone, *J. Chem. Soc.*, 759 (1963).

(5) G. J. Schroepfer, Jr., and K. Bloch, *J. Am. Chem. Soc.*, **85**, 3310 (1963); *J. Biol. Chem.*, **240**, 54 (1965).

(6) (a) C. R. Smith, Jr., T. L. Wilson, E. H. Melvin, and I. A. Wolff, *J. Am. Chem. Soc.*, **82**, 1417 (1960); (b) C. R. Smith, Jr., T. L. Wilson, T. K. Miwa, H. Zobel, R. L. Lohmar, and I. A. Wolff, *J. Org. Chem.*, **26**, 2903 (1961); (c) C. R. Smith, Jr., T. L. Wilson, R. B. Bates, and C. R. Scholfield, *ibid.*, **27**, 3112 (1962).

(7) T. H. Applewhite, R. G. Binder, and W. Gaffield, *Chem. Commun.*, 255 (1965). Others have since used similar methods and results[3-5] to establish absolute configurations of helenynolic[2d] [(−)-9-hydroxy-*trans*-10-octadecen-12-ynoic] acid as D [J. C. Craig, S. K. Roy, R. G. Powell, and C. R. Smith, Jr., *J. Org. Chem.*, **30**, 4342 (1965)]; (+)-9-hydroxy-10,12-octadecadienoic acid from *Calendula officinalis* L. and dimorphecolic acid[6a] as D [R. C. Bandami and L. J. Morris, *J. Am. Oil Chemists' Soc.*, **42**, 1119 (1965)]; and dimorphecolic acid[6a] as D, by mixture melting point only [C. Y. Hopkins and M. J. Chisholm, *Can. J. Chem.*, **43**, 3160 (1965)].

(8) (a) T. H. Applewhite, *Tetrahedron Letters*, 3391 (1965); (b) *ibid.*, 4160 (1965).