[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XXXV.[1] Alkoxyl Derivatives of the Acridizinium Ion[2]

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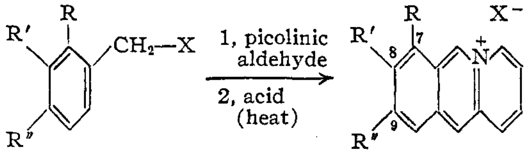
The acridizinium ion synthesis has been extended to the preparation of the 8-methoxy and some 7,8- and 8,9-dialkoxy derivatives. Cyclization is facilitated by the presence of an alkoxyl group *ortho* or *para* to the position where cyclization is to occur.

In earlier communications of this series it was shown that homologs[4] as well as benzologs[5] of the acridizinium[6] ion II[7] could be prepared by cyclizing the crude quaternary salt formed by reaction of an appropriate arylmethyl halide I with picolinic aldehyde. It seemed of interest to attempt the extension of the same general method to the synthesis of alkoxyl derivatives of the acridizinium ion II. This study was expected to provide information concerning the effect of alkoxyl groups on the ease of cyclization and to serve as a model for the synthesis of more complex compounds related to the protoberberine alkaloids.[8]



I II

unless otherwise stated R groups = H

The requisite benzyl halides I were obtained from alcohols, prepared by hydride reduction of the appropriate acid, ester or aldehyde. While it had been suggested earlier that the reaction between 2-pyridine aldehyde and benzyl halides occurred best at room temperature during a reaction period of one to three weeks, it now has been found that satisfactory quaternization can be effected in one to three hours at steam-bath temperature in the presence of methanol.[9]

Cyclization in boiling hydrobromic acid of the salt obtained from 2,3-dimethoxybenzyl bromide (I, R = R' = OCH_3) afforded the expected 7,8-dimethoxyacridizinium salt (II, R = R' = OCH_3) in 75% yield. However the salt from 3-methoxybenzyl bromide I, R' = OCH_3, in the same medium for the same period (15 minutes) yielded 8-hydroxyacridinium bromide as the only isolable product. Hydrochloric acid was found to bring about cyclization in good yields and without noticeable ether cleavage, and was used in subsequent experiments. In addition to proving effective in the preparation of the 8-methoxy and 7,8-dimethoxy derivatives, hydrochloric acid served as the catalyst in the cyclization to yield the 7,8- and 8,9-methylenedioxy acridizinium salts. The synthesis of the 7,8-dialkoxyacridizinium salts affords a model for the introduction of alkoxyl groups into the 9- and 10-positions[10] of the protoberberine nucleus.

As might have been predicted, the presence of alkoxyl groups *ortho* or *para* to the position at which cyclization is to occur facilitates the cyclization. In the one case studied in which cyclization in hydrobromic acid was used successfully, the 7,8-dimethoxyacridizinium salt was formed in 75% yield after only 15 minutes refluxing, while under comparable conditions, only a 60% yield of acridizinium bromide is formed in an eight hour reflux period.

Experimental[11]

8-Methoxyacridizinium Chloride (II, R' = OCH_3; X = Cl).—A mixture containing 1.8 g. of *m*-methoxybenzyl bromide,[12] 0.9 g. of picolinic aldehyde and 20 ml. of absolute methanol was refluxed for 3 hours. To this mixture 15 ml. of concentrated hydrochloric acid was added and refluxing continued for 2 additional hours. Vacuum evaporation of the solution afforded a yellow solid, which was washed with ether and then crystallized from ethanol as very small irregular yellow crystals, m.p. 180–182°.

Anal. Calcd. for $C_{14}H_{12}ClNO \cdot H_2O$: C, 63.70; H, 5.32; N, 5.32. Found: C, 63.45; H, 4.89; N, 5.38.

The perchlorate was prepared by adding perchloric acid to a water solution of the chloride. Fine yellow needles separated and were recrystallized from ethanol, m.p. 218–219°; λ_{max} 356, 394 and 410 mμ.

Anal. Calcd. for $C_{14}H_{12}ClNO_5$: C, 54.29; H, 3.91; N, 4.52. Found: C, 54.11; H, 3.95; N, 4.63.

The picrate was prepared from the chloride in ethanol. On recrystallization bright yellow crystals were obtained, m.p. 233°.

Anal. Calcd. for $C_{20}H_{14}N_4O_8$: C, 53.00; H, 3.12; N, 12.39. Found: C, 52.69; H, 3.26; N, 12.04.

8-Hydroxyacridizinium Bromide (II, R' = OH, X = Br). (a) **By Cyclization in 48% Hydrobromic Acid.**—After the mixture containing picolinic aldehyde (1.0 g.) and *m*-methoxybenzyl bromide (1.9 g.) in 15 ml. of methanol had been refluxed for 1.5 hours the solvent was removed under vacuum and the residual oil refluxed for 15 minutes with 15 ml. of 48% hydrobromic acid. Vacuum evaporation of the acid left a yellow solid which was washed with ether and then

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[1] For the preceding communication of this series see THIS JOURNAL, **79**, 1471 (1957).

[2] This investigation was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health, Public Health Service.

[3] Abstracted from part of a dissertation to be submitted by James H. Jones in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Duke University.

[4] C. K. Bradsher and L. E. Beavers, THIS JOURNAL, **77**, 4812 (1955).

[5] C. K. Bradsher and L. E. Beavers, *ibid.*, **78**, 2459 (1956).

[6] The name acridizinium has been proposed for the benzo-b-quinolizinium ion (ref. 4). The *Chemical Abstracts* numbering has been retained.

[7] In this paper R groups not otherwise designated represent hydrogen.

[8] R. H. F. Manske and H. L. Holmes, "The Alkaloids," Academic Press, Inc., New York, N. Y., 1954, p. 78.

[9] The presence of methanol, even in small quantity, tends to promote a cleaner reaction. The alcohol may function by helping to prevent the usually rapid air oxidation of the aldehyde, *cf.* J. Klosa. *Arch. Pharm.*, **288**, 426 (1955).

[10] Numbering used in reference 8.

[11] All analyses were by Micro Tech Laboratories, Skokie, Ill. All melting points were taken on the Fisher–Johns block and are uncorrected. The ultraviolet absorption spectra were measured in 95% ethanol solution using a Warren Spectracord spectrophotometer and 1-cm. quartz cells.

[12] E. Späth, *Monatsh.*, **34**, 1965 (1913).

crystallized from 95% ethanol as small yellow crystals, m.p. 250–252°, yield 0.8 g. (37%); λ_{max} 364, 417 and 472 mμ.

(b) From 8-Methoxyacridizinium Bromide by Ether Cleavage.—One hundred milligrams of 8-methoxyacridinium bromide was dissolved in a few milliliters of 48% hydrobromic acid and the mixture refluxed for three minutes. The acid was removed under vacuum and the residue was crystallized from ethanol, m.p. 245–250° (mixed m.p. with product from (a) 249°), yield 60 mg. (60%).

The compound gives an intense dark blue color in the presence of ferric chloride.

Anal. Calcd. for $C_{13}H_{10}BrNO \cdot H_2O$: C, 53.08; H, 4.11; N, 4.76. Found: C, 53.40; H, 4.14; N, 4.92.

The perchlorate, m.p. 263–264°, was prepared from the bromide in water. It formed irregular clusters of microscopic yellow needles.

Anal. Calcd. for $C_{13}H_{10}ClNO_5$: C, 52.80; H, 3.41; N, 4.74. Found: C, 52.45; H, 3.60; N, 4.60.

The picrate, m.p. 193–195°, was obtained from ethanol as yellow powder.

Calcd.[13] for $(C_{19}H_{12}N_4O_8)_2 \cdot C_6H_3N_3O_7$: C, 49.03; H, 2.53; N, 14.30. Found: C, 48.98; H, 2.73; N, 14.46.

7,8-Dimethoxyacridizinium Perchlorate (II, R = R′ = OCH_3, X = ClO_4).—A mixture containing 1 g. of picolinic aldehyde and 2.15 g. of 2,3-dimethoxybenzyl bromide[14] in 15 ml. of methanol was refluxed for one hour. The methanol was removed by vacuum evaporation, 15 ml. of 48% hydrobromic acid was added, and the mixture refluxed for 15 minutes. Vacuum evaporation of the acid left an oil which was taken up in ethanol. Addition of perchloric acid to the ethanolic solution caused the precipitation of an orange solid. Recrystallization from ethanol afforded orange needles, m.p. 198–202° dec., yield 2.24 g. (75%). There was no improvement in the melting point on recrystallization. Essentially the same result was obtained when the cyclization was carried out in concentrated hydrochloric acid for 1.5 hours. The ferric chloride test for phenolic hydroxyl was negative. The ultraviolet absorption spectrum was as follows: λ_{max} 260, 302, 372 and 438 mμ; λ_{min} 290, 342 and 407 mμ.

Anal. Calcd. for $C_{15}H_{14}ClNO_6$: C, 53.33; H, 4.33; N, 4.30. Found: C, 53.30; H, 4.24; N, 4.27.

The tribromide salt was formed by addition of bromine water to an alcoholic solution containing crude 7,8-dimethoxyacridizinium bromide. The product consisted of red crystals, m.p. 130–133°.

Anal. Calcd. for $C_{15}H_{14}O_2NBr_3$: C, 37.54; H, 2.94; N, 2.92. Found: C, 37.53; H, 3.35; N, 2.92.

The picrate was formed in ethanol as yellow crystals, m.p. 152°.

Anal. Calcd. for $C_{21}H_{16}N_4O_9 \cdot {}^1/_2H_2O$: C, 52.98; H, 3.59; N, 11.75. Found: C, 53.26; H, 3.76; N, 11.86.

8,9-Methylenedioxyacridizinium Bromide (II, R′ = R–OCH_2O, X = Br).—Two grams of 3,4-methylenedioxybenzyl bromide (prepared from the alcohol by the method of Robinson and Robinson[15]) was mixed with 1 g. of picolinic aldehyde in 5 ml. of dry benzene[16] and the mixture heated at 80° for three hours. The benzene was decanted from the red glass formed, and 50 ml. of concentrated hydrochloric acid was added to the viscous salt. This solution was heated on the steam-bath for one hour during which yellow crystals separated. This product was collected and recrystallized from absolute methanol as yellow needles, m.p. 260–270°, yield 0.9 g. (31%). The analytical sample melted at 270–275° with decomposition and appeared to be solvated; λ_{max} 258, 377 and 396 mμ.

Anal. Calcd. for $C_{14}H_{10}BrNO_2 \cdot CH_4O$: C, 53.59; H, 4.19; N, 4.16. Found: C, 53.63; H, 4.08; N, 3.83.

The picrate, m.p. 299–300° dec., was prepared in ethanol.

Anal. Calcd. for $C_{20}H_{12}N_4O_9 \cdot {}^1/_3\ C_2H_6O$: C, 53.20; H, 3.02; N, 11.98. Found: C, 53.46; H, 3.39; N, 12.24.

2,3-Methylenedioxybenzyl Bromide (I, R–R′ = OCH_2O, X = Br).—The benzyl alcohol[17] (6.61 g.) was converted in the usual way to the bromide by the action of phosphorus tribromide. The product, m.p. 62.0–62.5°, crystallized from ether as white needles, yield 9.24 g. (98%). The product was not isolated in a state of analytical purity, but had a composition approximately that expected.

Anal. Calcd. for $C_8H_7BrO_2$: C, 44.68; H, 3.28; Found: C, 44.07; H, 3.46.

7,8-Methylenedioxyacridizinium Bromide (II, R–R′ = OCH_2O, X = Br).—A mixture containing picolinic aldehyde (1.5 g.), 2,3-methylenedioxybenzyl bromide (3.0 g.) and methanol (2 ml.) was heated on the steam-bath for two hours. At the end of this period, 65 ml. of concentrated hydrochloric acid was added and heating continued for two hours longer. The acid was removed by vacuum evaporation leaving a red oil which was washed with ether and separated from the ether by decantation. The oil was dissolved in propyl alcohol, the solution concentrated and cooled, and the red crystals (m.p. 250–254°) collected, yield 1.8 g. (42%). The analytical sample was crystallized from a mixture of methanol and propyl alcohol as clusters of small red prisms, m.p. 250–254°; λ_{max} 318, 387, and 482 mμ; λ_{min} 294 and 354 mμ.

Anal. Calcd. for $C_{14}H_{10}BrNO_2 \cdot H_2O \cdot {}^1/_2CH_4O$: C, 51.49; H, 4.17; N, 4.14. Found: C, 51.59; H, 4.06; N, 4.16.

The perchlorate was formed by addition of perchloric acid to a water solution of the bromide and recrystallized from ethanol, m.p. 260–262°.

Anal. Calcd. for $C_{14}H_{10}ClNO_6$: C, 51.95; H, 3.11; N, 4.32. Found: C, 52.36; H, 3.53; N, 4.28.

The picrate consists of orange crystals, m.p. 248–249°.

Anal. Calcd. for $C_{20}H_{12}N_4O_9$: C, 53.10; H, 2.67. Found: C, 53.26; H, 2.98.

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(13) Analysis of the picrate showed definitely that it was not a simple 1:1 combination of the acridizinium ion with a picrate anion. If one assumes that for every two moles of acridizinium picrate there is one additional molecule of picric acid the calculated values are in excellent agreement with those observed.

(14) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **127**, 1434 (1925). Our sample was prepared from the corresponding aldehyde by reduction with lithium aluminum hydride to the carbinol followed by treatment with phosphorus tribromide.

(15) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **105**, 1456 (1914).

(16) When alcohols were used there seemed to be a greater tendency toward self-condensation of the halide.

(17) T. J. Stevens, *J. Chem. Soc.*, 725 (1935). Our sample was prepared from the corresponding ester by reduction with lithium aluminum hydride.