7-Methylbenzo[1,m]morphanthridizinium[15] (VIII) Perchlorate.—The quaternization of 2.05 g. of 2-(1-naphthyl)pyridine[10] was carried out as usual, and the crude salt cyclized by refluxing it for 100 hr. with hydrobromic acid. The product was isolated as the perchlorate and crystallized from ethanol as a bright yellow powder, m.p. 205–210°, yield 1.01 g. (24%). The analytical sample was crystallized from ethanol–water as a yellow microcrystalline powder, m.p. 214°, λ_{max} (log ϵ), 242 (4.69), 291 (4.30), and 380 mμ (3.88); λ_{min} 265 (4.05) and 344 (3.51).

Anal. Calcd. for $C_{20}H_{16}ClNO_6$: C, 59.78; H, 4.01; N, 3.49. Found: C, 60.13; H, 4.36; N, 3.54.

5-(2-Keto-4-carbomethoxybutyl)-6-(3,4-dimethoxyphenyl)-phenanthridinium (IX) Perchlorate.—The quaternization of 1.57 g. of 6-(3,4-dimethoxyphenyl)phenanthridine[16] with 1.05 g. of methyl α-bromolevulinate (II) was carried out in 5 ml. of N-methylpyrrolidone by heating on the steam bath for about 3 hr. The solution was cooled and ether added until the solution was turbid. In the refrigerator, 1.4 g. (51%) of yellow crystals was deposited from the solution, m.p. 146–160°. Recrystallization from ethanol gave bright yellow crystals, m.p. 170–171°. A sample, converted to the perchlorate for analysis, formed a yellow microcrystalline powder, m.p. 193–195°.

Anal. Calcd. for $C_{27}H_{26}NClO_9$: C, 59.62; H, 4.82; N, 2.58. Found: C, 59.52; H, 4.66; N, 2.97.

The bromide IX was dissolved in 25 ml. of concentrated hydrochloric acid, 5 ml. of ethanol added, and the mixture refluxed for 4.5 hr. On cooling, a yellow microcrystalline powder precipitated, and was recrystallized from ethanol–ether, m.p. 123°. This substance showed no significant absorption in the carbonyl region of the infrared spectrum, and analysis indicated that the product was 6-(3,4-dimethoxyphenyl)phenanthridine hydrochloride.

Anal. Calcd. for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.15; N, 3.98. Found: C, 72.01; H, 5.03; N, 4.05.

(15) The name morphanthridizinium has been proposed [K. B. Moser and C. K. Bradsher, *J. Am. Chem. Soc.*, **81**, 2547 (1959)] for the pyro[1,2-*a*]-benzo[*d*]-3*H*-azepinium system.

(16) P. Mamalis and V. Petrow, *J. Chem. Soc.*, 703 (1950).

Aromatic Cyclodehydration. LII.[1] Carbonyl Derivatives as Intermediates in the Acridizinium Synthesis

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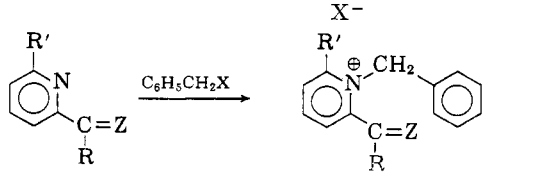
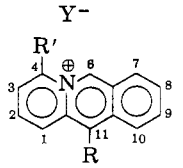
A search has been made for a picolinaldehyde derivative which might offer more advantage in the synthesis of acridizinium salts than does picolinaldoxime. The new 2-(1,3-dioxolan-2-yl)pyridine is superior to any known picolinaldehyde derivative in both the yield and quality of the acridizinium salt produced. Similarly, the dioxolan from 6-methyl-2-picolinaldehyde afforded the 4-methylacridizinium ion while that prepared from 2-acetylpyridine gave improved yields of 11-methylacridizinium salts.

The first synthesis of the acridizinium ion VII[3] involved the quaternization of 2-picolinaldehyde (I. Z = O) with benzyl bromide, followed by the acid-catalyzed cyclization of the crude salt (IV. Z = O). More recently,[4] it was shown that the unstable aldehyde (I. Z = O) could be replaced by the oxime (I. Z = NOH), with beneficial results.



I. R = R′ = H
II. R = CH_3, R′ = H
III. R = H, R′ = CH_3

IV. R = R′ = H
V. R = CH_3, R′ = H
VI. R = H, R′ = CH_3



VII. R = R′ = H
VIII. R = CH_3, R′ = H
IX. R = H, R′ = CH_3

Although the new procedure proved extremely useful,[5] there remained unsolved problems. One problem involved the rather low yield usually obtained in the cyclization of ketoximes (II. Z = NOH), and another, the complete failure of 6-methyl-2-aldoximinopyridine (III. Z = NOH) in the synthesis. A third, but minor problem, was the difficulty in the separation of the acridizinium ion from the hydroxylamine salt released in the cyclization reaction.

It seemed probable that a study of carbonyl derivatives other than the oxime might provide an intermediate which would be superior to the oxime in at least some respects. A number of derivatives related to the oxime (I. Z = NOH) were examined. The most successful of these was the semicarbazone (I. R = $NNHCONH_2$), which could be quaternized with benzyl bromide to afford a salt (IV. Z = $NNHCONH_2$) (68% yield), which when cyclized in hydrobromic acid, and then converted to the perchlorate, afforded a 47% yield of the acridizinium ion (VII). The yields, although fairly good, are inferior to those obtained with the oxime, in both the quaternization and cyclization steps, and separation of the acridizinium ion from the semicarbazide salts is tedious and accompanied by losses. The semicarbazone (III. Z = $NNHCONH_2$) of 6-methylpicolinaldehyde failed completely in the quaternization reaction with benzyl bromide. When the thiosemicarbazone (I. Z = $NNHCSNH_2$) was used, quaternization of the pyridine nitrogen[6] evidently did not occur, for the crude reaction product with benzyl bromide yielded no acridizinium ion on heating with

(1) For the preceding communication of this series see C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **28**, 81 (1963).

(2) This research was supported by a research grant (CY-5509) of the National Cancer Institute of the National Institutes of Health.

(3) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).

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

(5) *E.g.*, C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960); C. K. Bradsher and T. W. G. Solomons, *ibid.*, **82**, 1808 (1960); C. K. Bradsher and N. L. Dutta, *J. Org. Chem.*, **26**, 2231 (1961).

(6) It has been observed that reaction of thiosemicarbazones with α-chloro ketones occurs readily at the sulfur atom, J. McLean and F. J. Wilson, *J. Chem. Soc.*, 556 (1937).

hydrobromic acid. Other analogs (I) of the oxime which were tried proved to be uniformly unsatisfactory. These included the phenylhydrazone (Z = $NNHC_6H_5$), and the azine.

As a clear departure from the imino derivatives (I. Z = N—X) the new dioxolan acetal [I. Z = $(—OCH_2)_2$] was prepared. Despite the well known instability of picolinaldehyde, yields as high as 80% were obtained for the preparation of the cyclic acetal. This acetal [I. Z = $(—OCH_2)_2$] readily forms a well defined quaternary salt (92% yield) with benzyl bromide, and cyclization of the salt [IV. Z = $(—OCH_2)_2$] in hydrobromic acid affords the acridizinium ion VII in 95% yield. Less satisfactory results (65% yield) were obtained when the ring closure was carried out in liquid hydrogen fluoride or sulfuric acid (40%). Further, cyclization of the quaternary salt [IV. Z = $(—OCH_2)_2$] in polyphosphoric acid occurred in 77% yield. By comparison, the usefulness of polyphosphoric acid in the cyclization of free aldehydes (IV. Z = O) or oximes (IV. Z = NOH) in this series is very limited.

The dioxolan acetal [III. Z = $(OCH_2)_2$] of 6-methylpicolinaldehyde can be prepared in 63% yield. Quaternization of the acetal with benzyl bromide (1 month) yielded the crude salt as an oil which could not be crystallized. Cyclization of the oil in hydrobromic acid afforded 4-methylacridizinium bromide (IX. Y = Br) in 9% yield.

It has already been demonstrated that 11-methylacridizinium (VIII) salts may be synthesized by cyclization of the quaternary salt (V) obtained by the reaction of benzyl bromide with 2-acetylpyridine (II. Z = O)[7] or its oxime (II. Z = NOH).[4] The dioxolan ketal [II. Z = $(OCH_2)_2$] may be quaternized and cyclized to 11-methylacridizinium perchlorate in an overall yield of 35%. While this yield is not high, it compares favorably with those obtained *via* the ketone (3%) or oxime (18%).

It has been recognized for some time[8] that the reaction of an alkyl halide with a tertiary amine is facilitated by the presence of a polar solvent. It is important also that the solvent not react with the alkyl halide being used. It has been reported[9] that benzyl bromide reacts at a significant rate with dimethylformamide even at room temperature. In a publication dealing with the kinetics of quaternization, Coleman and Fuoss[10] pointed out that tetramethylene sulfone has a high dielectric constant (42) and "does not involve side reactions such as appear with nitrobenzene and dimethylformamide." Our observations lend further support to that statement. In tetramethylene sulfone (sulfolane) as a reaction medium, we have been able to obtain, in good yield and in crystalline form, quaternary salts which merely formed colored oils when the reaction was carried out in other solvents.

Experimental

Except as noted, all analyses were carried out by Dr. Ing. A. Schoeller, Kronach, Germany. All melting points were determined in capillaries in the Mel-Temp apparatus, and, like the boiling points, are uncorrected. Melting points determined in sealed tubes are indicated by the abbreviation (s.t.). All ultraviolet absorption spectra were measured in 95% ethanol using 1-cm. quartz cells with the Cary Model 14 spectrophotometer. The asterisk (*) is used to denote a shoulder.

1-Benzyl-2-formylpyridinium Bromide Semicarbazone (IV. Z = $NNHCONH_2$, X = Br).—A solution containing 2.45 g. of picolinaldehyde semicarbazone[11] and 2 ml. of benzyl bromide in 10 ml. of dimethylformamide was allowed to react in the dark for 4 days at room temperature. At the end of this period the mixture was triturated with ether, cooled, and collected. The yellow crystals were recrystallized from methanol, affording material, m.p. 165–168° dec. (s.t.), satisfactory for the cyclization reaction; yield 3.45 g. (68%).

An analytical sample, prepared by recrystallization from methanol, yielded white granules m.p. 196–197° (with evolution of gas and formation of a green liquid). The crystals yellowed on standing overnight and the melting point declined to about 192°.

Anal. Calcd. for $C_{14}H_{15}BrN_4O \cdot {}^3/_4H_2O$: C, 48.56; H, 4.74; N, 16.09. Found: C, 48.22; H, 4.81; N, 16.20.

The perchlorate formed fine colorless needles, m.p. 207–208.5° (with gas evolution and decomposition), which turned yellow on standing.

Anal. Calcd. for $C_{14}H_{15}ClN_4O_5$: C, 47.45; H, 4.23; N, 15.82. Found: C, 47.13; H, 4.26; N, 15.71.

Cyclization of the Semicarbazone (IV. Z = $NNHCONH_2$, X = Br) of 1-Benzyl-2-formylpyridinium Bromide.—Two grams of the salt (IV. Z = $NNHCONH_2$, X = Br) was dissolved in 10 ml. of 48% hydrobromic acid and the mixture heated on the steam bath for 8 hr. The acid was removed under vacuum (aspirator) and the residue crystallized from ethanol–ether. The resulting crude bromide (1.2 g., m.p. 181–195°) was dissolved in water and treated with perchloric acid. The resulting precipitate was crystallized from methanol–ethyl acetate as yellow prisms, m.p. 203–205°; yield 0.80 g. (47%). The product gave no melting point depression with an authentic sample[3] of acridizinium (VII) perchlorate.

2-(1,3-Dioxolan-2-yl)pyridine [I. Z = $(O—CH_2)_2$].[12]—A solution containing 21.4 g. (0.2 mole) of picolinaldehyde, 24 ml. (0.4 mole) of ethylene glycol, 10 g. of *p*-toluenesulfonic acid, and 300 ml. of benzene was refluxed for 64 hr., in an apparatus provided with a modified Dean–Stark water separator. The reaction mixture was then poured into concentrated sodium carbonate solution and the benzene layer separated. The water layer was extracted four times with benzene, then the combined benzene layers were washed once with water and dried over anhydrous magnesium sulfate. The benzene was evaporated, and the residue was vacuum distilled; yield 21.45 g. (71%), b.p. 122° (4 mm.), $n^{25}D$ 1.5225.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.05; H, 6.01; N, 9.25.

1-Benzyl-2-(1,3-dioxolan-2-yl)pyridinium [IV. Z = $(O—CH_2—)_2$] Bromide.—A solution containing 3.0 g. (0.02 mole) of 2-(1,3-dioxolan-2-yl)pyridine, and 2.5 ml. (0.021 mole) of benzyl bromide in 5 ml. of tetramethylene sulfone was allowed to stand for 4 days in a stoppered flask at room temperature. The viscous oil was triturated with several 50-ml. portions of ethyl acetate and the residue crystallized from methanol–ethyl acetate as colorless crystals, m.p. 102–104°; yield 6.0 g. (93%). The analytical sample consisted of colorless, blunt needles, m.p. 106–107°.

Anal. Calcd. for $C_{15}H_{16}BrNO_2 \cdot H_2O$: C, 52.94; H, 5.29; N, 4.11. Found: C, 53.05; H, 5.07; N, 4.46.

The perchlorate crystallized from methanol–ethyl acetate as colorless needles, m.p. 120–121°.

Anal. Calcd. for $C_{15}H_{16}ClNO_6$: C, 52.78; H, 4.69; N, 4.10. Found: C, 52.73; H, 4.53; N, 4.22.

Cyclization of 1-Benzyl-2-(1,3-dioxolan-2-yl)pyridinium Bromide to Acridizinium VII Salts. (a) In Hydrobromic Acid.—A solution containing 1.0 g. (0.0031 mole) of 1-benzyl-2-(1,3-dioxolan-2-yl)pyridinium bromide in 5 ml. of 48% hydrobromic acid was refluxed for 11 hr. The hydrobromic acid was removed under vacuum (aspirator), and the residue was dissolved in ethanol. The acridizinium bromide crystallized from the chilled flask as bright yellow needles, m.p. 244–244.5° (lit.,[3] 239–240°);

(7) C. K. Bradsher and T. W. G. Solomons, *J. Org. Chem.*, **24**, 589 (1959).

(8) *E.g.*, N. Menschutkin, *Z. physik. Chem.* (Leipzig), **6**, 41 (1890); H. v. Halban, *ibid.*, **84**, 129 (1913); R. A. Fairclough and C. N. Hinshelwood, *J. Chem. Soc.*, 1573 (1937).

(9) N. Kornblum and R. K. Blackwell, *J. Am. Chem. Soc.*, **78**, 4037 (1956).

(10) B. D. Coleman and R. M. Fuoss, *ibid.*, **77**, 5472 (1955).

(11) G. Lenart, *Ber.*, **47**, 808 (1914).

(12) *Cf.*, S. Sugasawa and M. Kirisawa, *Pharm. Bull.* (Tokyo), **3**, 190 (1955); *Chem. Abstr.*, **50**, 9415h (1956).

yield 0.76 g. (95%). The infrared spectrum was identical with that of an authentic sample.[3]

(b) **In Hydrogen Fluoride.**—In a polyethylene bottle was placed 3.2 g. (0.01 mole) of the bromide [IV. Z = $(OCH_2)_2$] and a Teflon-coated magnetic stirring bar. Approximately 50 ml. of liquid hydrogen fluoride was added, and the mixture stirred magnetically for 1 hr. The mixture was allowed to remain in the hood until the hydrogen fluoride had evaporated. The residue was dissolved in 100 ml. of water and evaporated to dryness under reduced pressure (aspirator). The residue was dissolved in 250 ml. of methanol and passed through an Amberlite 401 anion exchange column loaded with bromide. The acridizinium bromide isolated from the eluate was less pure than that obtained in the hydrobromic acid cyclization; yield 1.71 g. (65%), m.p. 230–233°.

(c) **In Sulfuric Acid.**—A solution containing 3.22 g. (0.01 mole) of the bromide [IV. Z = $(OCH_2)_2$] in 30 ml. of concentrated sulfuric acid was stirred at 80–90° for 3 hr. The cooled solution was slowly poured with stirring into 300 ml. of cold ether (−10°). The yellow precipitate was collected on a sintered-glass funnel and then dissolved in 5 ml. of water. Addition of 35% perchloric acid caused the precipitation of acridizinium perchlorate which was purified by crystallization from methanol–ethyl acetate; yield 1.12 g. (40%), m.p. 205–206° (lit.,[3] 205–206°).

(d) **In Polyphosphoric Acid.**—The bromide [1.60 g.; IV. Z = $(OCH_2)_2$] was stirred for 4 hr. at 70–80° with 30 g. of polyphosphoric acid. The mixture was cooled to room temperature and diluted by the addition of about 60 g. of ice. To the resulting solution 35% perchloric acid was added dropwise until further addition caused no further precipitation. The resulting acridizinium perchlorate was collected; yield 1.08 g. (77%), m.p. 197–200°. A sample was recrystallized from methanol–ethyl acetate as light yellow prisms, m.p. 205–206° (lit.,[3] 205–206.2°). It gave no mixed melting point depression with an authentic sample.

2-(1,3-Dioxolan-2-yl)6-methylpyridine [III. Z = $(O—CH_2—)_2$] was prepared starting with 6-methyl-2-picolinaldehyde (III. Z = O) and following the procedure used in the preparation of the lower homolog [I. Z = $(O—CH_2—)_2$] except that 3 molecular equivalents of ethylene glycol were used as well as a correspondingly greater quantity of benzene; yield 63%, b.p. 121–126° (6 mm.), $n^{25}D$ 1.5200.

Anal. Calcd. for $C_9H_{11}NO_2$: N, 8.48. Found: N, 8.54.

4-Methylacridizinium Bromide (IX. Y = Br).—A solution containing 4.95 g. (0.03 mole) of 2-(1,3-dioxolan-2-yl)-6-methylpyridine and 3.6 ml. (0.031 mole) of benzyl bromide was dissolved in 4 ml. of tetramethylene sulfone and the mixture allowed to stand for 1 month at room temperature. The addition of 100 ml. of ethyl acetate precipitated an oil which was washed with two other portions of ethyl acetate. The resulting oil, which could not be obtained in a crystalline form, was dissolved in hydrobromic acid, and refluxed for 3 hr. The acid was removed in the usual way, and the yellow residue crystallized from methanol–ethyl acetate; yield 0.73 g. (9%), m.p. 233–239°. The analytical sample formed fine yellow needles from the same solvents, m.p. 245–246°; λ_{max} (log ϵ), 200 (4.38), 243 (4.52), 250* (4.50), 364 (3.91), 381 (3.91), 400 (3.81); λ_{min} 214 (4.11), 313 (3.07), 372.5 (3.80), 391 (3.70).

Anal. Calcd. for $C_{14}H_{12}BrN \cdot {}^1/_2H_2O$: C, 59.38; H, 4.63; N, 4.95. Found: C, 59.45; H, 4.63; N, 5.12.

The perchlorate was obtained from methanol–ethyl acetate as bright yellow platelets, m.p. 180–180.5°.

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.23; H, 4.11; N, 4.76. Found[13]: C, 57.35; H, 4.03; N, 4.80.

The picrate crystallized from methanol–ethyl acetate as yellow needles, m.p. 199.5–201° (lit.,[4] 230–233°).[14]

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found[13]: C, 56.62; H, 3.87; N, 13.24.

2-(2-Methyl[1,3]dioxolan-2-yl)pyridine [II. Z = $(O—CH_2—)_2$].—The reaction of ethylene glycol (110 ml.) with 72.6 g. of 2-acetylpyridine (II. Z = O) was carried out essentially as in the case of the isomeric acetal [III. Z = $(O—CH_2)_2$]. The product was purified by vacuum distillation, b.p. 120–130° (12 mm.); yield 85.3 g. (86%). A sample was redistilled in a spinning band column at 6.2 mm. b.p. 106°, $n^{27}D$ 1.5093.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.45; H, 6.67; N, 8.48. Found: C, 65.76; H, 6.71; N, 8.54.

11-Methylacridizinium (VIII) Perchlorate.—The quaternization of 3.30 g. of 2-(2-methyl[1,3]dioxolan-2-yl)pyridine by reaction of 2.6 ml. of benzyl bromide in the presence of 4 ml. of dry tetramethylene sulfone was carried out at 64° in a sealed flask (5 days). The resulting viscous yellow oil was washed repeatedly with ethyl acetate and the solvent removed *in vacuo* on the steam bath. The residual oil was stirred for 15 hr. in polyphosphoric acid at 120–130°. The cooled reaction mixture was diluted by adding about 100 g. of ice. The diluted mixture was heated on the steam bath and filtered. To the cold filtrate, 35% perchloric acid was added. The precipitated 11-methylacridizinium perchlorate was recrystallized from methanol–ethyl acetate; yield 2.02 g. (35%), m.p. 237–238°. Recrystallized, it melted at 240–241° and was shown to be identical with a sample obtained *via* the ketone (reported, m.p. 243–244.5°).[7]

(13) Analysis by Dr. C. Daessle, Montreal, P. Q., Canada.

(14) The compound, prepared earlier (ref. 4) and reported to be 4-methylacridizinium picrate, has been shown (by actual comparison of samples) to be acridizinium picrate, m.p. 238–239°. In view of the fact that only a 2.5% yield of a very crude product was obtained in the earlier work, it seems probable that the acridizinium picrate was derived from a small amount of picolinaldehyde present as an impurity in the 6-methylpicolinaldehyde.

Reaction of Cyanuric Acid with Epoxides

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Tris(2-hydroxyethyl) isocyanurate (Ib) of 95–99% purity was prepared in 98–100% yields by the uncatalyzed reaction of cyanuric acid (Ia) with ethylene oxide in dimethylformamide or dimethylacetamide. Adjustment of the molar ratio of ethylene oxide to Ia permitted preparation of mixtures of mono- (Id), bis- (Ic), and tris(2-hydroxyethyl) isocyanurates (Ib) ranging from 99% tris at a ratio of 3.1, to 97% bis at 2.0, to 31.5% mono–68.5% bis at 1.0. The uncatalyzed reaction of Ia with propylene oxide in dimethylformamide gave quantitative yields of bis–tris mixtures containing 93–95% tris(2-hydroxypropyl) isocyanurate (Ig). Tris(2-hydroxyalkyl) isocyanurates are subject to decomposition to 2-oxazolidones (II) by bases generated during the reaction but this decomposition can be prevented by avoiding an excess of alkylene oxide. A mechanism for the decomposition is proposed. Ia reacted with styrene oxide to give a mixture of *N*-mono[2-(2-hydroxy-2-phenylethoxy)-2-phenylethyl]-*N'*,*N''*-bis(2-hydroxy-2-phenylethyl) isocyanurate (Ii), and *N*,*N'*-bis[2-(2-hydroxy-2-phenylethoxy)-2-phenylethyl]-*N''*-mono(2-hydroxy-2-phenylethyl) isocyanurate (Ij).

Epichlorohydrin is apparently the first epoxide described to react with cyanuric acid (Ia) to give an hydroxyalkyl isocyanurate believed to be substantially all tris(2-hydroxy-3-chloropropyl) isocyanurate.[1] The reaction was conducted at 100–120° in epichlorohydrin and dioxane in the presence of a variety of base catalysts. An earlier patent[2] discloses the general reaction of epoxides with Ia at 150–200° in the presence of base

(1) H. G. Cooke, Jr., U.S. Patent 2,809,942 (1957).

(2) W. P. Ericks, U.S. Patent 2,381,121 (1945).