Department of Chemistry, Duke University

6-Substituted Acridizinium Derivatives

C. K. Bradsher and J. C. Parham(1)

Through quaternization of an acetal of picolinaldehyde with suitable α-haloalkylarenes, a number of acridizinium salts, having a substituent at the *meso* position adjacent to nitrogen, have been prepared. Similarly, the ketal derived from α-acetopyridine has been used to prepare the first acridizinium derivatives having methyl groups at both of the *meso* positions.

Information concerning acridizinium salts with an alkyl or aryl group at position 6 is limited. It was found earlier that treatment of acridizinium bromide with phenylmagnesium bromide yielded a compound which could be aromatized with picric acid to yield 6-phenylacridizinium (IV. $R_1 = C_6H_5$, $R_2 = H$) picrate (2). Further, 6-methyl- and ethylacridizinium salts have been prepared by acylative cyclization (3, 4) of 2-(3,4-dialkoxybenzyl)pyridines, but the method is limited to the synthesis of 6-alkyl-8,9-dialkoxyacridizinium salts.

A logical approach to the synthesis of 6-alkylacridizinium salts would appear to be the quaternization of picolinaldehyde with an α-haloalkylarene, followed by cyclization of the quaternary salt (I). Unfortunately, attempts to use this approach (5) proved unsuccessful, perhaps due to beta-elimination of hydrogen bromide from the secondary halide.

The successful application of 2-(1,3-dioxolan-2-yl)pyridine (6) to the synthesis of other previously unobtainable acridizinium systems (7, 8) suggested that this reagent might succeed where picolinaldehyde had failed.

The reaction of 2-dioxolanylpyridine with α-bromoethylbenzene gave a 66% yield of the quaternary salt (III. $R_1 = CH_3$, $R_2 = H$, X = Br) which cyclized in 57% yield to the new 6-methylacridizinium (IV. $R_1 = CH_3$, $R_2 = H$) bromide. In the same way α-bromobutylbenzene, was converted to the crude quaternary salt (III. $R_1 = C_3H_7$, $R_2 = H$, X = Br) which was cyclized in polyphosphoric acid, affording an 11% yield of 6-propylacridizinium (IV. $R_1 = C_3H_7$, $R_2 = H$) perchlorate. It was found that 1-bromoindane and 1-bromoacenaphthene underwent elimination rather than quaternary salt formation, but 9-bromofluorene afforded a quaternary salt (V) which on cyclization gave a small yield of the perchlorate of 12a-azoniabenzo[a]fluoranthene (VI). The salts of this unusual cationoid system are bright orange and exhibit a faint yellow fluorescence in solution. The ultraviolet absorption spectrum bears a strong resemblance to that of benzo[a]fluoranthene which is yellow in color (9).

The reaction of 2-(1-bromoethyl)naphthalene with 2-dioxolanylpyridine afforded a crystalline salt (VII) which cyclized in 86% yield to produce 7-methylbenz[j]acridizinium bromide (VIII). The lower yield (24%) obtained in the cyclization of the isomeric quaternary salt to afford IX is probably due in part to the lower activity of the beta position of the naphthalene nucleus, but there is little doubt that an important factor is the steric strain involved in achieving the coplanarity requisite for aromatization (10). The cations VIII and IX are of particular interest since they are isosteric with the known carcinogens, 10-methyl- (11) and 9-methyl- (11) 1,2-benzanthracene.

The only known example of an acridizinium salt (IV) with substituents in both of the *meso* positions, was obtained earlier (12) by cyclization of the salt (II. X = Br) obtained by reaction for 222 days of 2-benzoylpyridine with α-bromoethylbenzene. Through quaternization of the ketal of 2-acetopyridine with α-bromoethylbenzene and cyclization of the crude salt, a small amount of the new 6,11-dimethylacridizinium (IV. $R_1 = R_2 = CH_3$) salt was obtained. In analogous fashion, the ketal with 2-(1-bromoethyl)naphthalene provided a route to 7,13-dimethylbenz[j]acridizinium (X) perchlorate, isosteric with the very potent carcinogen 9,10-dimethyl-1,2-benzanthracene (13).

EXPERIMENTAL

All analyses were carried out by Dr. Ing. A. Schoeller, Kronach, Germany or by Galbraith Laboratories, Knoxville, Tenn. The melting points were determined in capillary tubes, using the Laboratory Devices Mel-Temp apparatus and are uncorrected. The ultraviolet absorption spectra were measured in 95% ethanol using the Cary Model 14 spectrophotometer and 1 cm. quartz cells. The asterisk (*) has been used to denote a shoulder. The quaternization reactions were carried out in stoppered flasks in the absence of light.

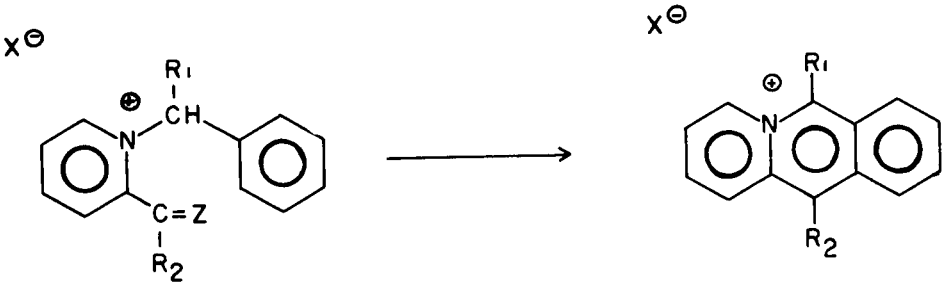
1-(1-Phenylethyl-2-(1,3-dioxolan-2-yl)pyridinium (III. $R_1 = CH_3$, $R_2 = H$) bromide.

A solution containing 6.04 g. of 2-(1,3-dioxolan-2-yl)pyridine (6), 8.0 g. of α-bromoethylbenzene and 4 ml. of tetramethylene sulfone was allowed to react for 14 days at room temperature. The crystals which precipitated were collected and washed with ethyl acetate, then recrystallized from methanol-ethyl acetate, yield 8.89 g. (66%) m.p. 133-136°. The analytical sample consisted of fine colorless needles, m.p. 140-141°.

Anal. Calcd. for $C_{16}H_{18}BrNO_2$: C, 57.14; H, 5.36; N, 4.17. Found: C, 57.29; H, 5.57; N, 4.41.

The *perchlorate* formed colorless prismatic needles from methanol-ethyl acetate, m.p. 144.5-145.5°.

Anal. Calcd. for $C_{16}H_{18}ClNO_6$: C, 54.08; H, 5.07; N, 3.94. Found: C, 54.26; H, 5.05; N, 4.10.

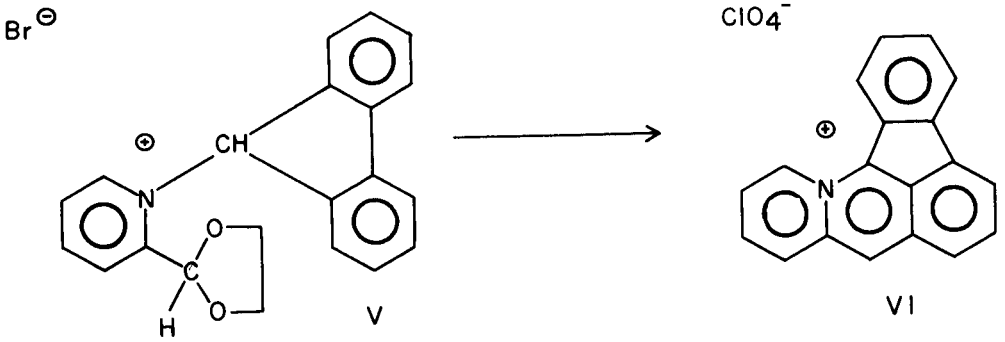


I. $R_1 = CH_3$, $R_2 = H$, $Z = O$

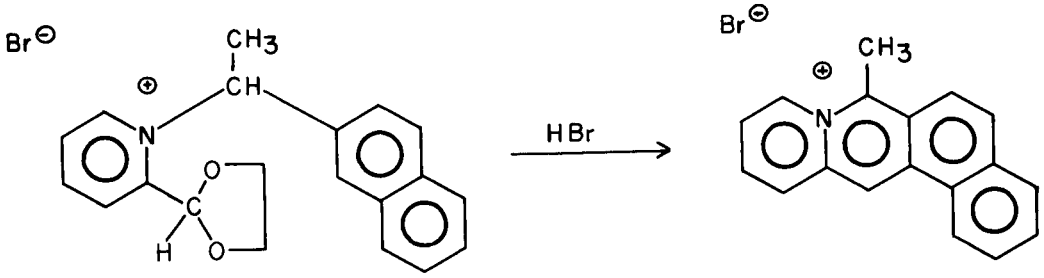
II. $R_1 = CH_3$, $R_2 = C_6H_5$, $Z = O$

III. $Z = O(CH_2)_2O$

IV.



V VI



VII VIII

IX X

6-Methylacridizinium (IV. $R_1 = CH_3$, $R_2 = H$) Bromide.

Cyclization of 1.0 g. of the quaternary bromide (III. $R_1 = CH_3$, $R_2 = H$) in 10 ml. of 48% hydrobromic acid was accomplished by refluxing for 19 hrs. The acid was removed *in vacuo* (aspirator) and the residue recrystallized from methanol-ethyl acetate (charcoal), yield 0.47 g. (57%), m.p. 223-228°. The analytical sample formed large yellow prisms, m.p. 230-231.5°, λ max (log ε), 246* (4.54), 251 (4.61), 364 (3.88), 383 (3.89), and 404 mμ (3.83).

Anal. Calcd. for $C_{14}H_{12}BrN$: C, 61.31; H, 4.38; N, 5.11. Found: C, 61.17; H, 4.31; N, 5.19.

The *perchlorate* crystallized from methanol-ethyl acetate as small yellow needles, m.p. 213-214°.

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.34; H, 4.09; N, 4.77. Found: C, 57.19; H, 4.33; N, 4.83.

The *picrate* was obtained as a fine yellow microcrystalline powder from methanol-ethyl acetate, m.p. 174-175°.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.32; N, 13.27. Found: C, 56.52; H, 3.51; N, 13.23.

6-Propylacridizinium (IV. $R = CH_3CH_2CH_2$, $R' = H$) Perchlorate.

The quaternization of 3.02 g. of 2-(1,3-dioxolan-2-yl)pyridine with 4.36 g. of α-bromobutylbenzene (14) in 2 ml. of tetramethylene sulfone was allowed to proceed for 20 days at room temperature. The addition of ethyl acetate precipitated a red oil which could not be crystallized. The oil was dissolved in 40 g. of polyphosphoric acid and heated on the steam bath with stirring for 6 hrs. The solution was diluted with 60 ml. of ice water and heated on the steam bath for an additional 2 hrs. The perchlorate salt was precipitated by addition of 35% perchloric acid, and recrystallized from methanol-ethyl acetate, yield 0.70 g., 11%, m.p. 222-226°. The analytical sample consisted of bright yellow needles, m.p. 226-226.5°.

Anal. Calcd. for $C_{16}H_{16}ClNO_4$: C, 59.72; H, 5.01; N, 4.35. Found: C, 60.05; H, 5.10; N, 4.65.

An attempted cyclization of the crude quaternary salt in hydrobromic acid gave evidence of much decomposition and afforded no 6-propylacridizinium bromide.

1-(9-Fluorenyl)-2-(1,3-dioxolan-2-yl)pyridinium bromide (V).

Quaternization of 6.0 g. of 2-(1,3-dioxolan-2-yl)pyridine with 10.3 g. of 9-bromofluorene (15) in 15 ml. of tetramethylene sulfone was carried out at room temperature in 31 days. The salt was precipitated by addition of ether, and recrystallized from methanol-ethyl acetate, yield 6.60 g. (41%), m.p. 139-144°. The analytical sample consisted of ivory colored prisms, m.p. 159-160°.

Anal. Calcd. for $C_{21}H_{18}BrNO_2$: C, 63.63; H, 4.57; N, 3.53. Found: C, 63.60; H, 4.51; N, 3.56.

12a-Azoniabenzo[a]fluoranthene Perchlorate (VI).

Two grams of the quaternary salt (VI) was heated at 110-120° for 2 hr. with 35 g. of polyphosphoric acid. When the cooled mixture was diluted with 50 g. of ice a gummy orange precipitate (polyphosphate salts?) was formed. The precipitate was collected and dissolved in a large quantity of methanol and the solution percolated through a column containing Amberlite IRA-401 anion exchange resin in the bromide form. The bromide salt could not be crystallized and was converted to the perchlorate. The perchlorate was recrystallized from methanol-ethyl acetate as fine orange needles, m.p. > 400° (charring above 350°), λ max (log ε) 225 (4.39), 252 (4.58), 272* (4.30), 295* (3.94), 313 (3.80), 335 (3.87), 352 (3.85), 370 (3.77), 437 (3.97), 461 (4.00).

Anal. Calcd. for $C_{19}H_{12}ClNO_4$: C, 64.50; H, 3.42; N, 3.69. Found: C, 64.36; H, 3.57; N, 3.93.

1-(1-[2-Naphthyl]ethyl)-2-(1,3-dioxolan-2-yl)pyridinium Bromide (VII).

2-(1-Bromoethyl)naphthalene (m.p. 59-60°) was prepared by the action of phosphorus tribromide on methyl-2-naphthylcarbinol (16). Quaternization of 6.0 g. of 2-(1,3-dioxolan-2-yl)pyridine with 7.87 g. of 2-(1-bromoethyl)naphthalene in 5 ml. of dimethylformamide was carried out for five days in the refrigerator (10°). The crystals which precipitated were collected and washed with ether, yield 4.35 g. (28%), m.p. 143-145°. The pure product crystallized from methanol-ethyl acetate as colorless, small irregular prisms, m.p. 141.5-142°.

Anal. Calcd. for $C_{20}H_{20}BrNO_2$: C, 62.18; H, 5.22; N, 3.63. Found: C, 62.40; H, 5.17; N, 3.84.

The *perchlorate* formed colorless irregular prisms from methanol-ethyl acetate, m.p. 139-140°.

Anal. Calcd. for $C_{20}H_{20}ClNO_6$: C, 59.19; H, 4.93; N, 3.45. Found: C, 59.03; H, 4.89; N, 3.60.

7-Methylbenz[j]acridizinium Bromide (VIII).

The cyclization of 3.86 g. of the quaternary salt (VIII) was carried out at 100° in 15 ml. of 48% hydrobromic acid in six hrs. Worked up in the usual way, and crystallized from methanol, 2.80 g. (86%) of product was obtained dec. > 350°. The analytical sample consisted of well-defined orange-yellow needles, m.p. > 400° dec., λ max (log ε) 217* (4.32), 230 (4.40), 268 (4.48), 277.5 (4.60), 310* (4.36), 321 (4.57), 368 (3.95), 386 (3.92), 407.5 (3.91).

Anal. Calcd. for $C_{18}H_{14}BrN$: C, 66.67; H, 4.32; N, 4.32. Found: C, 66.91; H, 4.38; N, 4.29.

The *perchlorate* crystallized from acetone as long yellow needles, m.p. 320° (dec., with mild explosion).

Anal. Calcd. for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.10; N, 4.08. Found: C, 62.70; H, 4.05; N, 4.22.

The *picrate* was obtained from methanol as tiny yellow needles, m.p. 241-241.5°.

Anal. Calcd. for $C_{24}H_{16}N_4O_7$: C, 61.01; H, 3.40; N, 11.86. Found: C, 60.99; H, 3.74; N, 11.63.

1-(1-[1-Naphthyl]ethyl)-2-(1,3-dioxolan-2-yl)pyridinium Bromide.

Crude 1-(1-bromoethyl)naphthalene (17) was prepared from 8.60 g. of methyl-1-naphthylcarbinol and allowed to react with 6.0 g. of 2-(1,3-dioxolan-2-yl)pyridine for two days at 10°. The crystalline product was collected and washed with ether, yield 6.04 g. (37%), m.p. 110-112°. The pure product crystallized from methanol-ethyl acetate as small colorless platelets, m.p. 117-118.5°.

Anal. Calcd. for $C_{20}H_{20}BrNO_2$: C, 62.18; H, 5.22; N, 3.63. Found: C, 62.35; H, 5.08; N, 3.94.

The *perchlorate* formed very fine colorless needles from methanol-ethyl acetate, m.p. 135-136°.

Anal. Calcd. for $C_{20}H_{20}ClNO_6$: C, 59.19; H, 4.97; N, 3.45. Found: C, 59.05; H, 4.94; N, 3.54.

13-Methylbenz[h]acridizinium Bromide (IX).

The quaternary salt was cyclized as in the case of the isomer (VII), except that the heating period was seven hrs. The product crystallized from methanol-ethyl acetate (charcoal), yield 0.77 g. (24%), m.p. 244-249°. The analytical sample consisted of fine bright yellow needles, m.p. 249-250°, λ max (log ε) 229 (4.39), 233* (4.38), 273 (4.45), 308 (4.22), 321 (4.28), 364* (3.84), 380 (4.10), 400 (4.22), 437 (2.87).

Anal. Calcd. for $C_{18}H_{14}BrN \cdot 1/8H_2O$: C, 66.20; H, 4.36; N, 4.29. Found: C, 66.15; H, 4.58; N, 4.32.

The *picrate* crystallized from methanol-ethyl acetate, as small yellow needles, m.p. 199-200°.

Anal. Calcd. for $C_{24}H_{16}N_4O_7$: C, 61.01; H, 3.41; N, 11.86. Found: C, 60.86; H, 3.29; N, 11.79.

6,11-Dimethylacridizinium (IV. $R_1 = R_2 = CH_3$) Bromide.

A solution containing 4.95 g. of 2-(2-methyl[1,3]dioxolan-2-yl)pyridine (6) and 6.0 g. of α-bromoethylbenzene in 5 ml. of tetramethylene sulfone (dimethylformamide was unsatisfactory) was allowed to stand for 20 days at room temperature. The crude oil which precipitated upon addition of ethyl acetate was dissolved in 63 g. of polyphosphoric acid and stirred for 5 hr. at 110-120°. The cooled solution was diluted by addition of 85 g. of ice, and then 200 ml. of saturated potassium iodide solution was added. The resulting dark yellow precipitate was collected and converted to the chloride by stirring it in distilled water with an excess of silver chloride. Since the resulting chloride salt would not crystallize, 35% perchloric acid was added to precipitate the perchlorate. The perchlorate (0.6 g., m.p. 264-265°) could not be obtained pure so it was dissolved in water and precipitated as the tribromide salt by addition of the "tribromide reagent" (three volumes of 48% hydrobromic acid to one of bromine). When the tribromide precipitate was allowed to react with acetone the resulting product was the bromide, which was crystallized from methanol-ethyl acetate as bright yellow needles, m.p. 310-311° dec., λ max (log ε) 210* (3.86), 247* (4.52), 254 (4.62), 371 (4.00), 389 (4.00) and 411 mμ (3.90).

Anal. Calcd. for $C_{15}H_{14}BrN \cdot 1/3H_2O$: C, 61.24; H, 5.03; N, 4.76. Found: C, 61.06; H, 4.94; N, 4.86.

The *perchlorate* crystallized as small bright yellow prisms, m.p. 296-297° dec.

Anal. Calcd. for $C_{15}H_{14}ClNO_4$: C, 58.54; H, 4.58; N, 4.55. Found: C, 58.65; H, 4.55; N, 4.87.

7,13-Dimethylbenz[j]acridizinium Perchlorate (X).

A solution containing 8.25 g. of 2-(2-methyl[1,3]dioxolan-2-yl)pyridine (6) and 13.6 g. of 2-(1-bromoethyl)naphthalene in 10 ml. of dimethylformamide was allowed to react for 7 days at 10° (refrigerator). The yellow oil produced by addition of ether to the mixture was cyclized by heating it for 2 hr. with 60 g. of polyphosphoric acid. After the usual dilution and digestion, the product was precipitated as the perchlorate, which was recrystallized from methanol, yield 0.87 g. (5%), m.p. 245-247° dec. The pure product crystallized from methanol-ethyl acetate as bright yellow irregular prisms, m.p. 251-252° dec., λ max (log ε) 215 (4.19), 233 (4.27), 274 (4.55), 315* (4.35), 325 (4.51), 378 (4.01), 393 (4.01), and 416 mμ (3.93).

Anal. Calcd. for $C_{19}H_{16}ClNO_4$: C, 63.78; H, 4.51; N, 3.92. Found: C, 63.93; H, 4.42; N, 4.04.

REFERENCES

(1) This research was supported by a research grant (CA-05509) of the National Cancer Institute of the National Institutes of Health.
(2) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **81**, 1938 (1959).
(3) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **25**, 293 (1960).
(4) W. Schneider and O. Böger, *Ber.*, **54B**, 2021 (1921).
(5) L. E. Beavers, Ph.D. Thesis, Duke University 1955, p. 88.
(6) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).
(7) C. K. Bradsher and J. C. Parham, *J. Heterocyclic Chem.*, **1**, 30 (1964).
(8) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **29**, 856 (1964).
(9) N. Campbell and A. Marks, *J. Chem. Soc.*, 2942 (1951).
(10) C.f., C. K. Bradsher and T. W. G. Solomons, *J. Org. Chem.*, **24**, 589 (1959).
(11) E.g., M. J. Shear, *Am. J. Cancer*, **33**, 499 (1938).
(12) C. K. Bradsher and T. W. G. Solomons, *J. Am. Chem. Soc.*, **81**, 2550 (1959).
(13) E.g., W. E. Bachmann, E. L. Kennaway and N. M. Kennaway, Yale, *J. Biol. Med.*, **11**, 97 (1938).
(14) E. B. Evans, E. E. Mabbott, and E. E. Turner, *J. Chem. Soc.*, 1166 (1927).
(15) H. Staudinger, *Ber.*, **39**, 3061 (1906).
(16) T. A. Collier and J. Kenyon, *J. Chem. Soc.*, 677 (1940).
(17) W. E. Bachmann and R. O. Edgerton, *J. Am. Chem. Soc.*, **62**, 2221 (1940).

Received March 18, 1964

Durham, N. C.