[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XLII.[1,2] Synthesis of Benzo[a]- and Dibenzo[a,c]phenanthridizinium Salts. The Effect of Activating Groups

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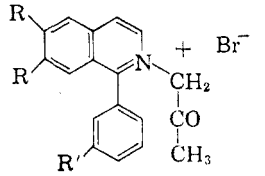
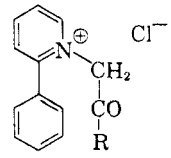
By introduction of alkoxyl groups at suitable positions, it has been possible to bring about the cyclization of the 1-phenyl-2-acetonylisoquinolinium (I) as well as the 5-acetonyl-6-phenylphenanthridinium system (IV). The cyclization products are the first benzo[a]- (IX) and dibenzo[a,c]phenanthridizinium (X) salts. Three new 9-arylphenanthridines have been prepared.

In an earlier paper[4] it was shown that 1-phenyl-2-acetonylisoquinolinium bromide (I) does not cyclize under conditions considerably more drastic than those employed in the acid-catalyzed cyclization of 2-phenyl-1-acetonylpyridinium chloride

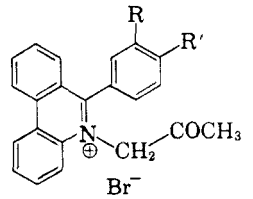


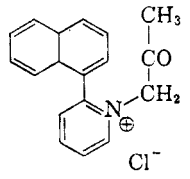


I. R = R′ = H
II. R—R = —O—CH_2O—, R′ = OCH_3

III

(III).[5] It seemed reasonable to assume that the failure of I to cyclize, arose from the overlapping of the hydrogen atom at position 8 of the isoquinoline ring with those of the *ortho* positions of the phenyl ring, since this would interfere with the achievement of the coplanarity necessary for ring closure. A similar explanation could be advanced for the failure of 5-acetonyl-6-phenylphenanthridinium bromide (IV) to undergo cyclization. Since 1-acetonyl-2-(1-naphthyl)pyridinium chloride (VIII) has a geometry closely related to that of I, yet undergoes cyclization[4] readily, it appeared likely that cyclization of systems such as I and IV could likewise be brought about if a highly active position were available for the attack of the carbonyl function. The present paper described the use of alkoxyl groups to promote such cyclizations.

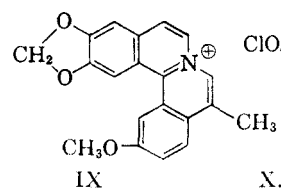


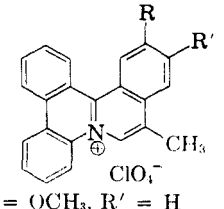


IV. R = R′ = H
V. R = OCH_3, R = H
VI. R = R′ = OCH_3
VII. R—R′ = —O—CH_2—O—

VIII

Activation in the 1-phenylisoquinoline was to be brought about by a methoxyl group in the *meta* position of the phenyl ring, but since 1-substituted isoquinolines are more readily prepared by the Bischler-Napieralski reaction[6] if cyclization can take place in an activated position, it seemed better to synthesize 1-(3-methoxyphenyl)-6,7-methylenedioxyisoquinoline. It was felt that the presence of the methylenedioxy group in the isoquinolinium salt II would not alter the outcome of the final cyclization experiment. The new 1-(3-methoxyphenyl)-6,7-methylenedioxyisoquinoline was synthesized and found to react readily with bromoacetone, affording a 95% yield of the quaternary salt II. Cyclization of II in boiling hydrochloric acid, followed by conversion to the perchlorate yielded a mixture of products[7] from which was isolated a pure compound, believed to be 2,3-methylenedioxy-12-methoxy-9-methylbenzo[a]phenanthridizinium perchlorate (IX)[8] rather than the 10-methoxy isomer. The ultraviolet absorption spec-





IX

X. R = OCH_3, R′ = H
XI. R = R′ = OCH_3
XII. R—R′ = —O—CH_2—O—

(1) For the preceding communication of this series see *J. Org. Chem.*, **24**, 589 (1959).

(2) Taken in part from a thesis to be submitted in partial fulfillment of the Ph.D. degree, Duke University. This research was supported by a research grant (NSF-G2364) of the National Science Foundation.

(3) Monsanto Chemical Company Fellow (1957–58).

(4) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

(5) While it was shown [C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 453 (1955)] that 2-phenyl-1-acetenylpyridinium chloride (III) can be cyclized in 51 hours (75% yield) the comparable isoquinolinium bromide (I) was recovered unchanged (84%) after 10 days refluxing with hydrobromic acid.

(6) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 90 (1951).

(7) The absence of infrared absorption in the 5.75 μ region testifies to the absence of the starting material in the product mixture.

trum compared with that of the starting material II shows the expected shift toward longer wave lengths.

The demonstration that activation could overcome the inhibition due to steric interference led us to investigate activated 5-acetonyl-6-phenylphenanthridinium salts (V–VII). The requisite 6-arylphenanthridines are readily prepared from 2-aminobiphenyl by the cyclization[9] of suitable 2-phenylanilides. The formation of the quaternary salts (V–VII) proved slow even at the boiling point of acetone, and a considerable portion of the phenanthridine was converted to the hydrobromide. Separation of the desired quaternary salt from the hydrobromide proved difficult.

Once pure samples of the 5-acetonylphanthridinium salts were prepared, cyclization in hydrochloric acid afforded 55–70% of the expected 11-methyldibenzo[a,c]phenanthridizinium salts (X–XII). In every case the cyclized products gave evidence of increased conjugation by an ultraviolet absorption shift toward the visible region.

Three new phenanthridines were prepared. All three, the 6-(2-naphthyl)-, the 6-(2,3-dimethoxyphenyl)-, and the 6-(3,4,5-trimethoxyphenyl) gave unsatisfactory results in the quaternization attempts.

EXPERIMENTAL[10]

N-(3-Methoxybenzoyl)homopiperonylamine.[11] To 13.85 g. of hompiperonylamine hydrochloride[12] in 250 ml. of ice-cold 3% sodium hydroxide solution, 12.8 g. of 3-methoxybenzoyl chloride was added dropwise with stirring. After addition was complete (1 hr.), stirring was continued for three more hours at ice-bath temperature. The solids were collected and added to a mixture of 2% sodium hydroxide and ether. The layers were separated and the basic layer extracted with ether. The combined ether layers were extracted once with *N* hydrochloric acid and then concentrated and cooled, yielding 17.4 g. (85%) of colorless needles, m.p. 73–76°. The analytical sample was obtained by crystallization from ethanol, m.p. 74.5–76°.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.40; H, 5.79; N, 4.94.

1-(3-Methoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline.[11] A mixture containing 11.8 g. of *N*-(3-methoxybenzoyl)homopiperonylamine, 80 ml. of anhydrous toluene and 30 ml. of phosphorus oxychloride was refluxed for 2.5 hr. When the reaction mixture was cooled in ice, two layers formed, and addition of petroleum ether initiated crystallization of the entire lower layer. The mixture was cooled in ice for 4 hr., the mother liquor was decanted, and the residue was dissolved in warm ethanol. The ethanol solution was made alkaline by addition of ethanolic potassium hydroxide, and the mixture was poured on 300 g. of crushed ice. The solid was collected and dried, yielding 10.6 g. (95%) of crude product, m.p. 157–161.5°. Recrystallization from benzene-petroleum ether yielded 9.85 g. (89%) of colorless crystals, m.p. 158.5–161.5°. The analytical sample melted at 160.5–161.5°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found: C, 72.92; H, 5.55; N, 5.18.

1-(3-Methoxyphenyl)-6,7-methylenedioxyisoquinoline. Three g. of 1-(3-methoxyphenyl)-3,4-dihydroisoquinoline was mixed with 0.3 g. of 10% palladium charcoal in a large test tube. A stream of dry nitrogen gas was directed on the surface of the mixture while the test tube was slowly lowered into a metal bath at 175–185°. When evolution of gas had almost ceased (30 min.) the dark residue was alternately extracted with 10% hydrochloric acid and with benzene until all the organic matter had dissolved. The combined benzene layers were extracted with 10% hydrochloric acid and filtered acid extracts made basic. The mixture was cooled for 3 hr. and the aqueous solution decanted. The light tan residue was crystallized from benzene-hexane as colorless prisms, yield 1.4 g. (47%), m.p. 98–101°. The analytical sample melted at 100–101°.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.44; H, 4.86; N, 5.29.

1-(3-Methoxyphenyl)-2-acetonyl-6,7-methylenedioxyisoquinolinium bromide (II). A solution containing 0.95 g. of 1-(3-methoxyphenyl)-6,7-methylenedioxyisoquinoline, 2.0 g. of bromoacetone, and 10 ml. of anhydrous reagent grade acetone was refluxed until formation of quaternary salt caused severe bumping. The mixture was allowed to stand for 2 days and the precipitated salt was collected and washed with dry acetone. A second crop was obtained by addition of ethyl acetate to the combined and concentrated filtrate and washings. The total yield of light yellow powder, m.p. 223–226° was 1.35 g. (95%). The analytical sample was crystallized from methanol-ethyl acetate, m.p. 224–226.5°.

Anal. Calcd. for $C_{20}H_{18}BrNO_4$: C, 57.70; H, 4.36; N, 3.36. Found: C, 57.62; H, 4.47; N, 3.52.

The *picrate* crystallized from ethanol as yellow crystals, m.p. 197–198.5°.

Anal. Calcd. for $C_{26}H_{20}N_4O_{11}$: C, 55.32; H, 3.57; N, 9.93. Found: C, 55.43; H, 3.80; N, 10.05.

2,3-Methylenedioxy-12-methoxy-9-methylbenzo[a]phenanthridizinium perchlorate (IX). A solution of 1.31 g. of the acetonyl derivative II in 15 ml. of concentrated hydrochloric acid was refluxed for 5.5 hr. The acid was removed *in vacuo* and the residue dissolved in hot water. Addition of 72% perchloric acid brought about the precipitation of an orange solid which, when crystallized from methanol, afforded 0.90 g. (69%) of crude product, m.p. 243–267°. This product showed no infrared absorption in the 5.75 μ region. Recrystallized three times from methanol and twice from acetone, the product was obtained as soft yellow-orange needles, m.p. 269–272°, λ_{max} (log ϵ), 226 (4.47), 245 (4.57), 284 (4.41), 403 (4.22) and 424 mμ (4.44); λ_{min}, 232 (4.39), 260 (4.35), 343 (3.43), and 409 mμ (4.20).

Anal. Calcd. for $C_{20}H_{16}ClNO_7$: C, 57.49; H, 3.86; N, 3.35. Found[13]: C, 57.51; H, 4.27; N, 3.47.

5-Acetonyl-6-(3-methoxyphenyl)phenanthridinium bromide (V). A solution containing 5.0 g. of 6-(3-methoxyphenyl)-phenanthridine,[14] 10 g. of bromoacetone, and 25 ml. of dry reagent grade acetone was refluxed on the steam bath for 60 hr., and the precipitated salt collected and washed with dry acetone. The combined filtrate and washings were concen-

(8) The possibility that our pure product is the 10-methoxy, formed by cyclization *ortho* to the methoxyl group has been excluded solely on the basis of analogy, *cf.*, C. K. Bradsher, F. C. Brown and P. H. Leake, *J. Am. Chem. Soc.*, **79**, 1471 (1957).

(9) *Cf.* R. S. Rheobald and K. Schofield, *Chem. Revs.*, **46**, 171 (1950).

(10) Except as noted all analyses are by Micro-Tech Laboratories, Skokie, Ill. The abbreviation s.t. is used to indicate melting points taken in a sealed capillary, and unless otherwise indicated all melting points are uncorrected.

(11) *Cf.*, W. J. Gensler and C. M. Samour, *J. Am. Chem. Soc.*, **73**, 5555 (1951).

(12) M. Erne and E. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950).

(13) Analysis by Galbraith Laboratories, Knoxville, Tenn.

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

trated and refluxed for 6.5 days, with occasional interruptions for isolation of the insoluble quaternary salt. The total yield was 4.0 g. (54%), m.p. 195–205°. After recrystallization from ethanol, and from methanol–ethyl acetate, an analytical sample was obtained as a light yellow hygroscopic powder, m.p. 208–209°. The sample was dried to constant weight at 100° before analysis.

Anal. Calcd. for $C_{23}H_{20}BrNO_2$: C, 65.41; H, 4.77; N, 3.32. Found: C, 65.22; H, 4.83; N, 3.45.

The *picrate* crystallized from ethanol as yellow crystals, m.p. 215–217°.

Anal. Calcd. for $C_{29}H_{22}N_4O_9$: C, 61.05; H, 3.89; N, 9.82. Found: C, 61.17; H, 3.91; N, 10.00.

14-Methoxy-11-methyldibenzo[a,c]phenanthridizinium perchlorate (X). A solution containing 1.5 g. of 5-acetonyl-6-(3-methoxyphenyl)phenanthridinium bromide (V), m.p. 202–205°, in 15 ml. of concentrated hydrochloric acid was refluxed for 2 hr. The acid was evaporated *in vacuo* and the residue dissolved in hot distilled water. Addition of perchloric acid to the hot aqueous solution afforded a yellow-orange precipitate that was crystallized first from acetone-ethanol and then from methanol as yellow needles, m.p. 263–266°, yield 0.82 g. (55%).

The analytical sample, recrystallized from methanol, exhibited a very bright green fluorescence, m.p. 264.5–266°, λ_{max} (log ϵ), 228 (4.36), 257 (4.57), 292 (4.52) and 430 mμ (4.07); λ_{min}, 225 (4.35), 231 (4.35), 282 (4.46) and 355 mμ (3.58).

Anal. Calcd. for $C_{23}H_{18}ClNO_5$: C, 65.17; H, 4.28; N, 3.31. Found[13]: C, 64.63; H, 4.22; N, 3.31.

5-Acetonyl-6-(3,4-dimethoxyphenyl)phenanthridinium bromide (VI). The quaternization of 2.5 g. of 6-(3,4-dimethoxyphenyl)phenanthridine[14] was carried out as in the case of the 3-methoxy analog. The total yield was 1.30 g. (35%) of soft yellow crystals, m.p. 229.5–231.5°. After several recrystallizations from ethanol the analytical sample, m.p. 232–235° was apparently obtained as a hydrate.

Anal. Calcd. for $C_{24}H_{22}BrNO_3 \cdot H_2O$: C, 61.28; H, 5.14; N, 2.98. Found[13]: C, 61.69; H, 5.37; N, 2.93.

13,14-Dimethoxy-11-methyldibenzo[a,c]phenanthridizinium perchlorate (XI). The cyclization of 1.25 g. of the acetonylphenanthridinium derivative VI was carried out as in the case of the analog V. The product, isolated as the perchlorate, crystallized from acetonitrile–ethyl acetate as yellow needles, m.p. 314–316°, dec. (s.t., corr.). The analytical sample was recrystallized from methanol, m.p. 319–321°, dec. (s.t., corr.), λ_{max} (log ϵ), 229 (4.45), 256 (4.57), 292 (4.59) and 414 mμ (4.19); λ_{min}, 223 (4.39), 239 (4.41), 266 (4.46) and 323 mμ (3.72).

Anal. Calcd. for $C_{24}H_{20}ClNO_6$: C, 63.51; H, 4.44; N, 3.09. Found[13]: C, 63.11; H, 4.42; N, 3.21.

5-Acetonyl-6-(3,4-methylenedioxyphenyl)phenanthridinium salts (VII). The quaternization of 2.0 g. of 6-(3,4-methylenedioxyphenyl)phenanthridine[14] with bromoacetone was carried out in the usual way. A total of 1.55 g. (50%) of crude bromide decomposing at about 240° (s.t.) was obtained. For analysis the bromide was converted to the *perchlorate* which formed yellow needles from methanol, m.p. 293–295.5° with previous shrinking and decomposition at 288° (s.t., corr.).

Anal. Calcd. for $C_{23}H_{18}ClNO_7$: C, 60.60; H, 3.98; N, 3.07. Found: C, 60.41; H, 4.13; N, 3.15.

13,14-Methylenedioxy-11-methyldibenzo[a,c]phenanthridizinium perchlorate (XII). The cyclization of 1.45 g. of the crude bromide VII was carried out in the usual way and the perchlorate crystallized from methanol as a brilliant orange solid, m.p. 297°, dec. (s.t., corr.) yield 0.7 g. (56%).

The analytical sample was crystallized from dimethylformamide-ether as a yellow-brown powder, m.p. 304°, dec. (s.t., corr.). Best results were obtained when the sample was not heated in the presence of dimethylformamide, λ_{max} 228, 258, 284, and 415 mμ; λ_{min} 239, 266, and 321 mμ.

Anal. Calcd. for $C_{23}H_{16}ClNO_6$: C, 63.09; H, 3.68; N, 3.20. Found[13]: C, 63.02; H, 3.64; N, 3.42.

2'-Phenyl-2-naphthanilide.[15] A stirred suspension of 19.8 g. of 2-naphthoic acid in 100 ml. of anhydrous benzene was refluxed while 25 ml. of thionyl chloride was added dropwise over a period of 15 min. The reaction mixture was refluxed for 6 hr., and the benzene and excess thionyl chloride were removed *in vacuo*. The crude 2-naphthoyl chloride was added cautiously to a cooled solution of 19.5 g. of 2-aminobiphenyl in 40 ml. of anhydrous pyridine. The mixture was heated on the steam bath for 1 hr. and while still hot poured into a mixture containing ice and 6*N* hydrochloric acid. The oil which formed crystallized readily and was collected and recrystallized from ethanol (Norit) to give 32.4 g. (87%) of product, m.p. 126.5–130°. The analytical sample crystallized from ethanol as colorless needles, m.p. 129.5–130.5°.

Anal. Calcd. for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found[13]: C, 85.16; H, 5.39; N, 4.49.

6-(2-Naphthyl)phenanthridine.[15] A solution of 20 g. of 2'-phenyl-2-naphthanilide in 40 ml. of phosphorus oxychloride was refluxed for 70 min. and the excess phosphorus oxychloride was removed *in vacuo*. The residue was heated on the steam bath with 50 ml. of water until a yellow solid was produced. The water was removed and the solid dissolved in 150 ml. of methanol, and methanolic potassium hydroxide solution added until the solution was alkaline. This solution was poured into 500 ml. of water and allowed to stand overnight. The precipitate was collected and washed, and then recrystallized from methanol, m.p. 156.5–159.5°, yield 11.0 g. (58%). The analytical sample consisted of colorless needles, m.p. 158–159.5°.

Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95. Found[13]: C, 90.35; H, 4.63.

2,3-Dimethoxy-2'-phenylbenzanilide was prepared from 18.2 g. of 2,3-dimethoxybenzoic acid[16] as in the preparation of the 2'-phenyl-2-naphthanilide. The product was crystallized from ethanol, m.p. 131.5–134°, yield 29.6 g. (89%). The analytical sample formed colorless needles from ethanol, m.p. 133–134°.

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found[13]: C, 75.87; H, 5.74; N, 4.40.

6-(2,3-Dimethoxyphenyl)phenanthridine. A solution of 20 g. of 2,3-dimethoxy-2-phenylbenzanilide and 25 ml. of phosphorus oxychloride in 50 ml. of nitrobenzene was refluxed for 2.5 hr. Then the mixture was poured into a flask containing ice and an excess of 20% sodium hydroxide solution. The resulting mixture was steam distilled to remove the nitrobenzene. Recrystallization of the residue from ethanol gave 17.4 g. (92%) of almost colorless crystals, m.p. 130–133°. The analytical sample was prepared by recrystallization from ethanol, m.p. 132.5–134°.

Anal. Calcd. for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found[13]: C, 79.84; H, 5.31; N, 4.40.

3,4,5-Trimethoxy-2'-phenylbenzanilide was prepared from 21.2 g. of 3,4,5-trimethoxybenzoic acid essentially as the other phenylbenzanilides were prepared. The product was crystallized from ethanol, m.p. 119–120°, yield 27.3 g. (75%). The analytical sample melted at 120–120.5°.

Anal. Calcd. for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82. Found[13]: C, 72.83; H, 5.42.

6-(3,4,5-Trimethoxyphenyl)phenanthridine was prepared from 22.2 g. of 3,4,5-trimethoxy-2'-phenylbenzanilide essentially as in the case of 6-(2,3-dimethoxyphenyl)phenanthridine. The product was crystallized from ethanol-water as colorless needles, m.p. 124–125°, yield 16.6 g. (79%). The analytical sample was recrystallized from ethanol, m.p. 124.5–125°.

Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.55. Found[13]: C, 76.74; H, 5.61.

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(15) *Cf.*, E. Ritchie, *J. Proc. Roy. Soc., N. S. Wales*, **78**, 147 (1944).

(16) *Cf.*, R. L. Shriner and E. C. Kleiderer, *Org. Syntheses*, **Coll. Vol. II**, 538 (1943).