to 44.5 p.s.i. and then remained constant. After removal of the catalyst and solvent, the product was distilled, yielding 5.2 g. (98%) of DL-β-benzyl-γ-butyrolactone, b.p. 161–163°/6 mm. The analytical sample, a center cut from a second distillation, had b.p. 162–163°/6 mm. Colorless liquid, n_D^{20} 1.5373.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97 H, 6.86. Found: C, 74.69; H, 6.68. Infrared spectrum: 5.64 μ (lactone-CO); a weak band appeared at 2.83 μ (indicating that the compound was contaminated by a trace of OH-containing material).

DL-β-(*3,4-Dimethoxybenzyl*)-γ-*butyrolactone* (IIIb) was similarly prepared from IIb, yield 95–97%. Slightly yellowish, rather viscous oil, b.p. 220°/6 mm., n_D^{20} 1.5519.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.08; H, 6.81. Infrared spectrum: 5.58 μ (lactone-CO); no absorption between 2 μ and 3.2 μ (no OH-containing impurity).

DL-β-(α-*Hydroxy-3,4-dimethoxybenzyl*)-γ-*butyrolactone.* A mixture of 10.1 g. of IIb, 8.2 g. of aluminum isopropoxide,[16] and 50 cc. of isopropanol (previously distilled over calcium oxide) was placed in a 500-cc. two-necked, round-bottom flask which was fitted with a Widmer column. The mixture was gently refluxed for 1 hr., then heated at such a rate that acetone distilled as it was formed. After 3 hr., 50 cc. of isopropanol were added. The reaction proceeded slowly, but after 8 hr. the distillate gave a negative test with 2,4-dinitrophenylhydrazine. The reaction mixture was then concentrated nearly to dryness, decomposed with 100 cc. of 10% hydrochloric acid, and kept overnight in the refrigerator. It was then extracted twice with chloroform, the chloroform layers dried over sodium sulfate, and the solvent evaporated. A yellowish oil remained which solidified partly after digestion with a large amount of ether and standing for several weeks. 4.8 g. (48%) of crude product, m.p. 77–81°, was obtained. One recrystallization from methanol-ether gave 2.2 g. of a product, m.p. 91–93°. Three more recrystallizations raised the m.p. to 96.5–97.5°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.95; H, 6.50. Infrared spectrum: 5.65 μ and 5.75 μ (double band) and 2.95 μ. Various attempts to isolate more crystalline material from the oily residues of the evaporated mother liquors were unsuccessful. Further investigation of this oil is in progress.

DL-β-(α-Hydroxybenzyl)-γ-butyrolactone was obtained similarly from 9.5 g. of IIa. The reaction product was a slightly yellowish oil which did not crystallize, and hence was distilled (b.p. 160–205°/5 mm., 7.3 g., 76%). After two more distillations, a fraction (4.1 g., 43%) with b.p. 195–197°/5 mm., n_D^{26} 1.5461, was analyzed.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.36; H, 6.31. Infrared spectrum: 5.65 γ and 2.90–2.95 μ (broad band).

CINCINNATI 21, OHIO

(16) The authors are indebted to Chattem Chemicals, Division of the Chattanooga Medicine Co., Chattanooga, Tenn., for a generous gift of this compound.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XLI.[1,2] *Meso*-substituted Acridiziniúm Benzologs

C. K. BRADSHER AND T. W. G. SOLOMONS

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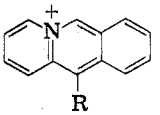
Benzacridizinium derivatives with a substituent in the central nucleus have been prepared by the acid-catalyzed cyclization of quaternary salts obtained by reaction of (1) 1-bromomethylnaphthalene with 2-pyridyl ketones or (2) benzyl (or naphthylmethyl) halides with 1-benzoylisoquinoline.

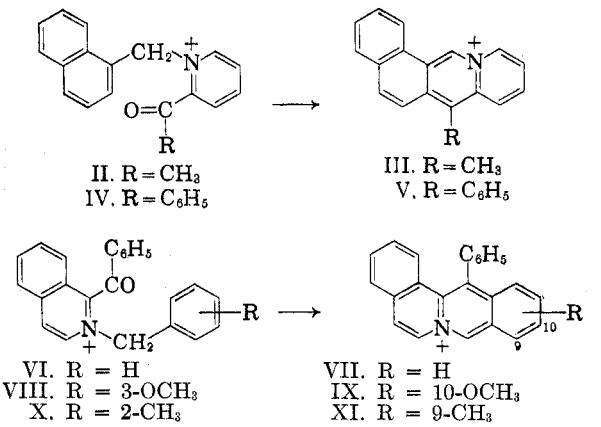
Only a single, highly activated, 1-benzoyl-2-benzylisoquinolinium salt (VIII) was found to cyclize in liquid hydrogen fluoride, but the remainder of the isoquinolinium salts could be cyclized in hot polyphosphoric acid.

In the preceding communication of this series it was shown that salts obtained by the quaternization of 2-pyridyl ketones could be cyclized to yield the first 11-substituted acridizinium salts I. It appeared interesting to examine the usefulness of



I

this approach in the synthesis of some acridizinium benzologs, since at least one of these would be isosteric with a known carcinogen and further information could be gained about the importance of steric and electronic effects on the ease of cyclization. For the synthesis of the monobenzologs two general approaches have been used, both involving the cyclization of quaternary salts. In the first, a



II. R = CH_3
IV. R = C_6H_5
III. R = CH_3
V. R = C_6H_5
VI. R = H
VIII. R = 3-OCH_3
X. R = 2-CH_3
VII. R = H
IX. R = 10-OCH_3
XI. R = 9-CH_3

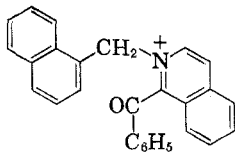
(1) For the preceding communication of this series, see *J. Am. Chem. Soc.*, in press.

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

salt (II or IV) was formed by the reaction of 1-bromomethylnaphthalene with a 2-pyridyl ketone, while in the second 1-benzoylisoquinoline formed a quaternary salt (VI) by reaction with a benzyl halide. With the exception of the quaternary salt II from 2-acetylpyridine all were obtained in good yield (83–94%). Both of the pyridinium salts cyclized readily in liquid hydrogen fluoride. The product III from the 2-acetylpyridinium salt II was of particular interest because the new cation is isosteric with the highly carcinogenic 10-methyl-1,2-benzanthracene.[3]

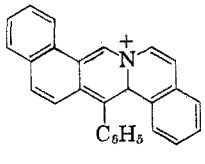
1-Benzoyl-2-benzylisoquinolinium ion (VI) is not cyclized by the action of liquid hydrogen fluoride and the 2-methylbenzyl analog X shows similar unreactivity. Since 1-benzyl-2-benzoylpyridinium bromide cyclizes in good yield under the same conditions,[1] it seems that the resistance of the benzylisoquinolinium salts (VI and X) to cyclization arises from the difficulty inherent in crowding the phenyl group into a confined position. The difficulty was overcome by carrying out the cyclization under more energetic conditions in polyphosphoric acid at 150–160° several hours. If the benzyl group is substituted by methoxyl (VIII) at a position para to the expected ring closure, cyclization is greatly facilitated, in fact a 91% yield of the 10-methoxy-13-phenylbenz[*a*]acridizinium perchlorate was obtained using hydrogen fluoride as the cyclizing agent.

Quaternization of 1-benzoylisoquinoline with 1-bromomethylnaphthalene yielded a salt XII which was cyclized to yield the first fully aromatic dibenz[*a,h*]acridizinium salt XIII.



(not isolated)

XII



XIII

EXPERIMENTAL[4]

Spectroscopy. All visible and ultraviolet spectra were determined in 95% ethanol solution, using the Warren Spectracord recording spectrophotometer and 1-cm. matched silica cells.

1-(1-Naphthylmethyl)-2-benzoylpyridinium perchlorate (IV). A mixture containing 1.83 g. of 2-benzoylpyridine, 2.21 g. of 1-bromomethylnaphthalene and 1 ml. of dimethylformamide were mixed together and allowed to stand at 10° for 50 days. The light yellow crystals which separated were washed with ether, 3.78 g. (94%), m.p. 132–136°. This material was used for the cyclization experiments, but a sample was converted to the *perchlorate* for analysis. The perchlorate gave small colorless irregular crystals from methanol, m.p. 164–165°.

Anal. Calcd. for $C_{23}H_{18}ClNO_5$: C, 65.17; H, 4.28; N, 3.31. Found: C, 65.49; H, 4.27; N, 3.29.

7-Phenylbenz[h]acridizinium perchlorate (V). Two grams of the crude bromide IV was placed in a polyethylene bottle and 25 ml. of liquid hydrogen fluoride added with magnetic stirring. After the hydrogen fluoride had evaporated the residue was taken up in ethanol, the solution treated with Norit, and filtered. The solution was concentrated, cooled, and perchloric acid added. The small yellow crystals which separated were collected and washed with cold ethanol, 1.80 g. (90%), m.p. 315.5–316.5°. The analytical sample crystallized from dimethylsulfoxide-water as small rectangular yellow prisms, m.p. 316.5–317° (sealed capillary, in block preheated to 300°) λ_{max} (log ϵ), 231 (4.54), 275 (4.46), 305.5 (4.19), 320 (4.23), 379 (4.15), 399 mμ (4.29); λ_{min} 250 (4.07), 294 (4.07), 313.5 (4.14), 339 (3.54), 388 (3.98).

Anal. Calcd. for $C_{23}H_{16}ClNO_4$: C, 68.07; H, 3.97; N, 3.45. Found: C, 68.39; H, 3.78; N, 3.29.

1-(1-Naphthylmethyl)-2-acetylpyridinium bromide (II). The quaternization of 2.28 g. of 2-acetylpyridine with 4.15 g. of 1-bromomethylnaphthalene was carried out in 2.0 ml. of dimethylformamide at 10° for two weeks, followed by 38 days at room temperature. The yield of crude bromide suitable for cyclization was 3.65 g. (57%), m.p. 122–130° dec. (capillary). The analytical sample crystallized from ethanol-ethyl acetate as very small yellow rectangular prisms, m.p. 152–165° (with decomposition into gaseous products).

Anal. Calcd. for $C_{18}lH_{16}BrNO$: C, 63.17; H, 4.71; N, 4.09. Found: C, 63.43; H, 4.67; N, 4.16.

7-Methylbenz[h]acridizinium perchlorate (III). One-half gram of the pyridinium bromide salt II was added to 50 ml. of liquid hydrogen fluoride in small portions during the course of about 20 minutes. After the hydrogen fluoride had evaporated, the residue was precipitated as the perchlorate salt as in the case of the phenyl analog V. A quantitative yield of product melting above 360° was obtained. The analytical sample, prepared by recrystallization from dimethylsulfoxide-methanol consisted of yellow microscopic needles, λ_{max} (log ϵ), 231 (4.39), 276 (4.50), 307 (4.16), 320 (4.23), 361 (3.56), 379 [4.17), 400 mμ (4.37); λ_{min} 248 (3.97), 290 (3.97), 312.5 (4.10), 337 (3.55), 366 (3.86), 388 (3.91).

Anal. Calcd. for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.10; N, 4.08. Found: C, 62.67; H, 4.07; N, 4.08.

In another experiment 3.65 g. of the pyridinium bromide salt II was cyclized, and after the hydrogen fluoride had evaporated, the residue was taken up in 75 ml. of methanol, and passed through an ion-exchange column containing Amberlite IRA-410 resin loaded with chloride ion. The methanol was removed, and the residue crystallized from ethanol as small yellow needles of the *chloride*, m.p. 359–361° dec. (sealed tube). The melting point of the analytical sample was essentially unchanged.

Anal.[5] Calcd. for $C_{18}H_{14}ClN.2H_2O$: C, 68.46; H, 5.74. Found: C, 68.48; H, 5.70.

1-Benzoyl-2-benzylisoquinolinium bromide (VI). One gram of 1-benzoylisoquinoline[6] and 1.0 g. of benzyl bromide were allowed to react for 12 days at room temperature. Crystallization of the brown oil was induced by scratching, and after trituration with ethyl acetate, 1.60 g. (92%) of a yellow powder was obtained, m.p. 166–168°. The analytical sample was crystallized from methanol-ethyl acetate, m.p. 172.5–173.5°.

Anal. Calcd. for $C_{23}H_{18}BrNO$: C, 68.32; H, 4.49; N, 3.46. Found: C, 68.40; H, 4.39; N, 3.45.

(3) *Cf.*, M. J. Shear, *Am. J. Cancer*, **33**, 499 (1938). While the positive charge makes it appear unlikely that III will exhibit carcinogenic activity, it is planned to have it tested for this as well as for possible tumor-necrotizing activity.

(4) Unless indicated otherwise all melting points were taken on the Fisher-Johns block and are not corrected. Except as noted all analyses were by Galbraith Laboratories, Knoxville, Tenn.

(5) Analyses by Drs. Weiler and Strauss, Oxford, England.

(6) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).

The *perchlorate* was prepared in water solution and recrystallized from methanol-ethyl acetate, m.p. 212–213°.

Anal. Calcd. for $C_{23}H_{18}ClNO_5$: C, 65.18; H, 4.28; N, 3.31. Found: C, 65.25; H, 4.44; N, 3.56.

13-Phenylbenz[a]acridizinium perchlorate (VII). To 32 g. of polyphosphoric acid in a beaker, 750 mg. of the benzylisoquinolinium salt was added with stirring. The top of the beaker was covered by means of a sheet of aluminum foil and the mixture heated at 150–160° for 12 hr. The mixture was diluted to a volume of about 75 ml. by the addition of ice and water, and 20 ml. of 14% perchloric acid was added slowly with stirring. Stirring was continued for 3 hr. after the addition was complete, then the mixture was cooled in ice, and the greenish yellow powder collected, yield 705 mg. (94%), m.p. 240–260°. Recrystallized from ethanol-ether (Norit) it yielded 500 mg. (67%) of yellow needles, m.p. 268–270°. The analytical sample melted at 266.5–267.5°, λ_{max} (log ϵ), 261.5 (4.56), 311.5 (4.34), 387 (4.15), 406 mμ (4.25), λ_{min} 242 (4.42), 289 (4.20), 344 (3.83), 396 mμ (4.08).

Anal. Calcd. for $C_{23}H_{16}ClNO_4$: C, 68.06; H, 3.97; N, 3.45. Found[5]: C, 67.96; H, 4.17; N, 3.92.

The *picrate* was prepared from the perchlorate in ethanol, m.p. 223–224°.

Anal. Calcd. for $C_{29}H_{18}N_4O_7$: C, 65.16; H, 3.39; N, 10.48. Found:[5] C, 64.97; H, 3.69; N, 10.05.

1-Benzoyl-2-(3-methoxybenzyl)isoquinolinium perchlorate (VIII). One gram of 1-benzoylisoquinoline was quaternized in dimethylformamide by the action of 1.2 g. of *m*-methoxybenzyl bromide and worked up in the usual way. The crude bromide suitable for cyclization consisted of yellow crystals, m.p. 148–150°, yield 1.55 g. (82%).

The *perchlorate* was prepared in water solution and crystallized from methanol-ethyl acetate, m.p. 146–147°.

Anal. Calcd. for $C_{24}H_{20}ClO_6$: C, 63.51; H, 4.44; N, 3.09. Found: C, 63.54; H, 4.41; N, 3.27.

10-Methoxy-13-phenylbenz[a]acridizinium perchlorate (IX). The cyclization of 600 mg. of the methoxybenzyl isoquinolinium salt VIII was carried out in hydrogen fluoride (75 ml.) in the usual way and the product precipitated as the perchlorate, m.p. 265.5–267.5°, yield 545 mg. (91%). Once recrystallized from methanol, it yielded 470 mg. (78%), m.p. 278.5–281°. The analytical sample was obtained from methanol as tiny yellow needles, m.p. 281.5–283°, λ_{max} (log ϵ), 223 (4.52), 269 (4.59), 311.5 (4.55), 400 (3.93), 421 mμ (4.03); λ_{min} 243 (4.07), 289 (4.37), 384 (3.72), 408 mμ (3.91).

Anal. Calcd. for $C_{24}H_{18}ClNO_5$: C, 66.13; H, 4.16; N, 3.21. Found: C, 66.00; H, 4.23; N, 3.21.

1-Benzoyl-2-(2-methylbenzyl)isoquinolinium perchlorate(X). One gram of 1-benzoylisoquinoline was quaternized in the usual way with 1.2 g. of *o*-methylbenzyl bromide. The crude bromide, 1.62 g. (86%), m.p. 134–139°, was suitable for further reactions.

The *perchlorate* was crystallized from methanol-ethyl acetate as colorless irregular plates, m.p. 175–177°.

Anal. Calcd. for $C_{24}H_{20}ClNO_5$: C, 65.79; H, 4.60; N, 3.20. Found: C, 65.56; H, 4.48; N, 3.47.

9-Methyl-13-phenylbenz[a]acridizinium perchlorate (XI). The cyclization of 500 mg. of the crude bromide salt X obtained in the preceding experiment was carried out as in the case of the lower homolog VI. The product was precipitated as the perchlorate from the diluted phosphoric acid mixture. Recrystallization of the greenish yellow powder from acetonitrile afforded 190 mg. (38%) of brown-yellow needles, m.p. 296–300°. The analytical sample melted at essentially the same temperature, λ_{max} (log ϵ), 224 (4.53), 266 (4.54), 314.5 (4.31), 396 (3.76), 416 mμ (3.84); λ_{min} 247 (4.09), 293 (4.86), 346.5 (3.75), 404 mμ (3.72).

Anal. Calcd. for $C_{24}H_{18}ClNO_4 \cdot {}^1/_2H_2O$: C, 67.21; H, 4.47; N, 3.27. Found:[5] C, 66.97; H, 4.35; N, 3.53.

15-Phenyldibenz[a,h]acridizinium bromide (XIII). A quaternary salt was formed by the reaction of 1.0 g. of 1-benzoylisoquinoline and 1.0 g. of 1-bromomethylnaphthalene at room temperature for 18 days. The crude bromide (presumably XII), m.p. 125–126°, yield 1.20 g. (61%), was not obtained in a pure condition, and was used directly in the cyclization reaction. The cyclization of 500 mg. of crude bromide was carried out in 28 g. of polyphosphoric acid at 140–150° for 8 hr. The mixture was cooled and diluted to 75 ml. and allowed to stand overnight. The greenish-yellow precipitate (presumably a phosphate) which formed was collected, yield 492 mg. Nearly all (400 mg.) of the precipitate was dissolved in 1 l. of methanol containing 30 ml. of 48% hydrobromic acid and the solution passed through an ion-exchange column containing Amberlite IRA-410 resin loaded with bromide ion. The resulting solution was concentrated *in vacuo* and the residue crystallized from methanol-ethyl acetate, yield 228 mg. (56%) of irregular yellow crystals, m.p. >360°.

The analytical sample melted at 372–374° (sealed tube), λ_{max} (log ϵ), 278.5 (4.42), 306.5 (4.56), 390 (4.31), 411 mμ (4.51); λ_{min} (log ϵ), 254 (4.29), 285.5 (4.41), 346.5 (3.78), 401 mμ (4.12).

Anal. Calcd. for $C_{27}H_{18}BrN \cdot {}^1/_2CH_4O$: C, 73.01; H, 4.46; N, 3.10. Found:[5] C, 72.93; H, 4.85; N, 3.22.

DURHAM, N. C.