A Heterocyclic Arene Oxide. 5,6-Diphenylbenz[c]acridine 5,6-Oxide

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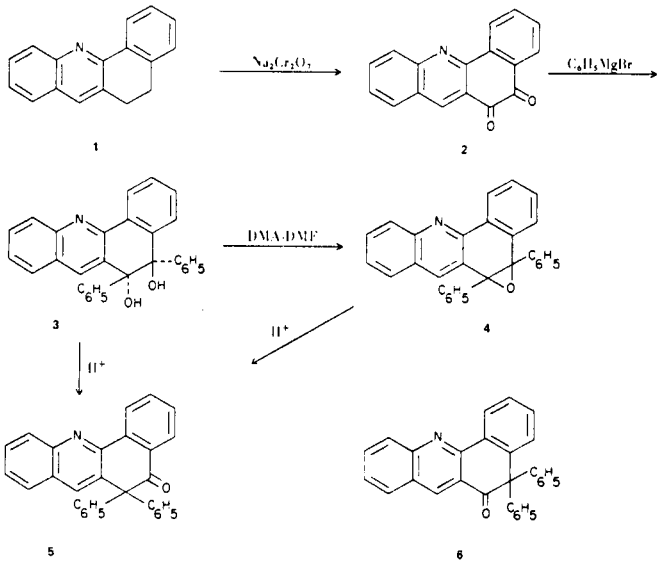
The first synthesis of a benz[c]acridine 5,6-oxide is described. Treatment of 5,6-benz[c]-acridinequinone with phenylmagnesium bromide results in the formation of a *trans*-diol, which gives the title compound upon dehydration with dimethylformamide dimethylacetal. In sulfuric acid, the epoxide rearranges mainly into 6,6-diphenyl-5-benz[c]acridone.

J. Heterocyclic Chem., 13, 619 (1976).

Arene oxide derivatives of *carbocyclic* hydrocarbons have been the focus of considerable research in recent years owing to their biological relevance (1,2). They have been identified as intermediates in metabolic oxidation of aromatic compounds (3) and are thought to be the causative agents for carcinogenicity of the parent polycyclic hydrocarbons (4). Epoxide derivatives of *heterocyclic* aromatic compounds (5) should be of similar interest, but, curiously, none has been mentioned in any of the recent comprehensive reviews on arene oxides (1).

We now wish to report the first synthesis of an epoxybenz[c]acridine, which for reasons stated previously (6) is disubstituted in the K region. 5,6-Benz[c]acridinequinone (**2**) [prepared by oxidation of 5,6-dihydrobenz[c]-acridine (**1**) (7,8)] was treated with 2.2 equivalents of phenylmagnesium bromide to yield *trans*-5,6-dihydroxy-5,6-diphenylbenz[c]acridine (3). Dehydration of the latter compound by dimethylformamide dimethyl acetal (DMA-DMF) afforded the expected epoxide **4** in 77% yield.



Both the diol **3** and the oxide **4** readily undergo pinacol-pinacolone rearrangement under acidic conditions to give 6,6-diphenyl-5-benz[c]acridone (**5**) as the major product. Ring contraction is not likely to occur under these conditions [*cf. e.g.*, the behavior of 9,10-disubstituted-9,10-dihydroxyphenanthrene (6,9)].

The structure of **5** was established by virtue of the intense peak m/e = 292 $[C_{22}H_{14}N]^+$ in the mass spectrum. The second possible ketone, *viz.* 5,5-diphenyl-6-benz[c]acridone (**6**) would, by similar fragmentation give rise to some of the fragments $[C_{18}H_{15}O]^+$ (m/e = 247), $[C_{10}H_5NO]^{\cdot+}$ (m/e = 155) and $[C_9H_5N]^+$ (m/e = 127). None of these is present in the mass spectrum of **5**. However, upon concentration of the mother liquor of **5**, minute quantities of a ketone could be detected (tlc) which cleaves into fragments of masses 155 and 127. This suggests that traces of **6** may be formed from **3** and **4**.

It is notable that epoxide **4** undergoes pinacol-pinacolone rearrangement also under electron impact (10). Peaks at 369 and 292 of significant intensities indicate that ketone **5** is formed predominantly.

Attempts to apply the method of Newman and Blum (11) for the synthesis of benz[c]acridine oxides were unsuccessful since osmium tetroxide oxidation of 7,9- and 7,10-dimethylbenz[c]acridine led to *vic*-diols which give unstable dialdehydes upon further oxidation with sodium periodate.

EXPERIMENTAL

All experiments were carried out under dry nitrogen atmosphere.

5,6-Benz[c]acridinquinone (**2**).

A solution of 3.87 g. of sodium dichromate dihydrate in 25 ml.

of acetic acid and 25 ml. of acetic anhydride was added dropwise at 2-4° (1 hour) to a solution of 2.0 g. of 5,6-dihydrobenz[c]-acridine (**1**) [prepared according to v. Braun from isatin and α-tetralone (8)] in 50 ml. of the same mixture of solvents. The reaction mixture was then stirred at room temperature for 8 days, during which the quinone precipitated. The stirring was discontinued when tlc analysis indicated the entire disappearance of **1**. This prolonged stirring proved to give better results than the general procedure described by Cho and Harvey (7). The yellow precipitate was filtered, washed with water and dried over phosphorus pentoxide *in vacuo* at 80°. A second crop of 0.30 g. of the quinone was obtained by addition of water to the filtrate. The total yield of pure **2** was 1.89 g. (83%); m.p. 240-242° [lit. (8) 242°]; ir (Nujol): 1680 cm^{-1}; uv (chloroform): λ max (log ε) 258 (4.32), 3.22 (4.52), 430 mμ (3.02 sh); mass spectrum (70 eV) m/e (relative intensity): 259 (9), 231 (100), 103 (28), 176 (8).

trans-5,6-Dihydroxy-5,6-diphenylbenz[c]acridine (**3**).

To a solution of phenylmagnesium bromide (prepared from 6.4 g. of bromobenzene and 1.0 g. of magnesium in 100 ml. of ether and 100 ml. of benzene) there was added 4.87 g. of the powdered quinone **2**. The reaction mixture turned green immediately. After refluxing for 22 hours, the ether was *slowly* distilled off (during 3 hours). Decomposition was effected by a solution of 18 g. of ammonium chloride in 150 ml. of water. The organic material was extracted with methylene chloride to yield a mixture of compounds which were separated by column chromatography on silica gel (Merck's Kisilgel 60, 70-230 mesh, 1 l. of benzene serving as eluent). There were obtained 2.27 g. (30%) of light yellow crystals of **4**, m.p. 184° (from hexane-benzene 1:1). The analytical sample was recrystallized once again from cyclohexane; ir (Nujol): 3500 cm^{-1}(br); uv (ethanol): λ max (log ε) 260 (4.41), 314 (3.68), 330 (3.73), 345 mμ (3.81); mass spectrum (70 eV) m/e (relative intensity): 415 (16), 398 (2), 380 (2), 337 (11), 310 (100), 293 (8), 230 (24), 173 (11), 105 (27), 77 (23).

Anal. Calcd. for $C_{29}H_{21}NO_2$: C, 83.83; H, 5.10; N, 3.37. Found: C, 83.95; H, 5.21; N, 3.34.

5,6-Diphenylbenz[c]acridine 5,6-Oxide (**4**).

Freshly distilled DMA-DMF (740 mg.) was added to a solution of 1.03 g. of diol **4** in 30 ml. of dry dimethylformamide. The reaction mixture which turns red immediately was heated for 23 hours at 90°. Another portion of 320 mg. of DMA-DMF reagent was added and the heating was continued at 108° for 22 hours. After further addition of 100 mg. of reagent, the temperature was raised to 120°, and then after 24 hours, the reaction mixture was heated briefly (30 minutes) at 130°, cooled and poured into water. The crude product was dried over phosphorus pentoxide, chromatographed on silica gel (Merck's Kiselgel 60, 70-230 mesh, 200 ml. of benzene as eluent) to yield 530 mg. of **4**. Further elution with 200 ml. of ethyl acetate-chloroform (1:1) afforded 310 mg. of the starting material. The yield (from **3** that had reacted) was 77%. The analytical sample was recrystallized from methylcyclohexane, m.p. 230°; it shows no hydroxyl or carbonyl bands in the ir spectrum; uv (ethanol): λ max (log ε) 262 (4.57), 272 (4.62), 326 (3.98), 346 mμ (3.96); mass spectrum (70 eV) m/e (relative intensity): 397 (58), 381 (12), 369 (9), 292 (56), 105 (100).

Anal. Calcd. for $C_{29}H_{19}NO$: C, 87.66; H, 4.78; N, 3.52. Found: C, 87.85; H, 4.76; N, 3.86.

6,6-Diphenyl-5-benz[c]acridone (**5**).

Concentrated sulfuric acid, 0.5 ml., was added to a solution of 100 mg. of **4** in 50 ml. of methylene chloride (12). The yellow solution was stirred at room temperature for 30 minutes, then neutralized and decolorized by addition of solid sodium bicarbonate and the solvent evaporated. The residue was recrystallized from 100 ml. of petroleum to yield 45 mg. of analytically pure **5**, m.p. 324-325°; ir (Nujol): 1685 cm^{-1}; nmr (upfield from trifluoroacetic acid, p.p.m.) 1.96 (s, 1H), 4.38-6.46 (m, 18H); mass spectrum (70 eV) m/e (relative intensity): 397 (3.4), 369 (100), 292 (55).

Anal. Calcd. for $C_{29}H_{19}NO$: C, 87.66; H, 4.78; N, 3.52. Found: C, 87.42; H, 4.96; N, 3.84.

The mother liquor contained a further amount of **5** which is, however, admixed with traces (tlc) of a second isomer (presumably **6**).

The same mixture of ketones was obtained also from diol **3** by treatment, as above, with concentrated sulfuric acid and methylene chloride.

cis-5,6-Dihydroxy-7,10-dimethylbenz[c]acridine.

By a procedure similar to that described by Hadler and Kryger (13), 1.4 g. of 7,10-dimethylbenz[c]acridine (15) was oxidized with 1.4 g. of osmium tetroxide to give 1.11 g. (70%) of the expected diol, m.p. 251-253° (from benzene); ir (Nujol): 3500 cm^{-1} (br); uv (ethanol): λ max (log ε) 263.5 (4.55), 271 (4.58), 333 (3.99), 348 mμ (4.03); mass spectrum (70 eV) m/e (relative intensity): 291 (71), 290 (33), 276 (17), 273 (25), 263 (23), 262 (100), 244 (11).

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.30; H, 5.89. Found: C, 78.53; H, 5.80.

cis-5,6-Dihydroxy-7,9-dimethylbenz[c]acridine.

Oxidation of 0.60 g. of 7,9-dimethylbenz[c]acridine (14) with 0.60 g. of osmium tetroxide afforded the colorless diol, m.p. 240-244° [lit. (15) 144°]; ir (Nujol): 3490 cm^{-1}; uv (ethanol): λ max (log ε) 265.5 (4.51), 273 (4.57), 334 (3.96), 349 mμ (3.99)(16); nmr (80% DMSO-d_6 and 20% carbon tetrachloride): δ 2.54 (s, 3H, C_9-C*H*$_3$), 2.73 (s, 3H, C_7-C*H*$_3$), 4.99 (distorted AB, J = 4 cps, 2H, C_5-*H* and C_6-*H*), 7.30-8.45 (m, 7H); mass spectrum (70 eV) m/e (relative intensity): 291 (65), 290 (31), 276 (23), 273 (19), 263 (21), 262 (100), 244 (27).

Acknowledgment.

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(3) *Cf.*, however, recent studies on oxidative metabolism of electron-deficient aromatic systems by J. E. Tomaszewski, D. M. Jerina and J. W. Daly, *Biochemistry*, **14**, 2024 (1975).

(4) The arguments in favor and disfavor of the idea are summarized by B. Pullman in "Chemical Carcinogenesis," P. O. P. Ts'o and J. A. Diapallo, Eds., Marcel Dekker Inc., New York, N.Y., 1974, pp. 713-727.

(5) Epoxides of indoles [*cf.* F. J. Mayers and H. G. Lindwall, *J. Am. Chem. Soc.*, **60**, 2153 (1938); W. C. Sumpter, *ibid.*, **64**, 1736 (1942); K. Ishizumi, K. Mori, S. Inaba and H. Yamamoto, Japanese patent, 73, 19,555 [Chem. Abstr., **78**, 159276b (1973)] and of benzofuran [E. Bisagni and R. Royer, *Bull. Chem. Soc. France*, 925 (1962)] may not be true arene oxides by definition, and the early reports on benzophenazine oxide [Th. Zincke, *Ber.*, **26**, 613 (1893)] and dibenzophenanthrocinnoline oxide [A. Schönberg and B. Rosenthal, *ibid.*, **54**, 1791 (1921)] may be in error [*cf.* reference (6)]. However, the synthesis of 7,8-dihydrobenzo[1,2-*c*:3,4-*c*′]dithiophene 7,8-oxide is unambiguous [D. W. H. MacDowell and M. H. Maxwell, *J. Org. Chem.*, **35**, 799 (1970)], the electronic structure resembles that of phenanthrene 9,10-oxide.

Heterocyclic arene oxides have frequently been postulated to be reaction intermediates in photochemical transformations of azoxy compounds [*cf.* G. G. Spence, E. C. Taylor and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970)]; to play a part in the NIH shift [*cf. e.g.*, J. W. Daly, D. M. Jerina and B. Witkop, *Experienta*, **28**, 1129 (1972)] and are assumed to be involved in enzymatic oxidation of aromatic heterocyclic systems [R. R. Schmidt, *Angew. Chem. Int. Ed. Engl.*, **14**, 581 (1975)].

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(16) These data are identical with those calculated from Fig. 2 in reference (15), but differ from those reported in the text.