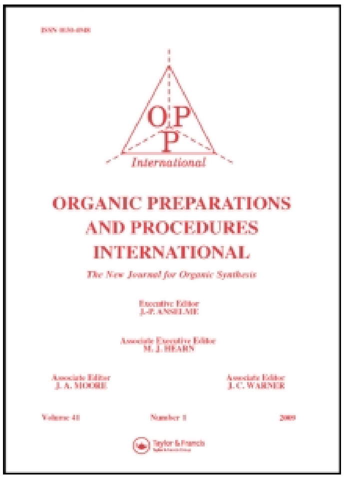

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SYNTHESIS OF BENZO[a]PYRENE-12-OL

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SYNTHESIS OF BENZO[a]PYRENE-12-OL

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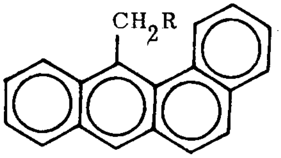
An efficient synthesis of benzo[a]pyrene-12-ol, needed in connection with studies of the metabolism of carcinogenic polycyclic aromatic hydrocarbons, has been achieved from 12-methylbenz[a]anthracene (Ia) *via* the sequence: (1) bromination with N-bromosuccinimide to Ib; (2) reaction with KCN to afford Ic; (3) hydrolysis with KOH in aqueous ethylene glycol to the acid Ie; and (4) cyclization in liquid HF to II. This synthetic approach provides higher overall yield than the reported synthesis of II from benzo[a]pyrene.[1] The NMR spectra[2] of Ib-e and II were entirely consistent with the assigned structures. In particular, the 270 MHz NMR spectrum of II gave no indication of the presence of the *keto* tautomer in agreement with molecular orbital theoretical prediction by Pullman.[3]



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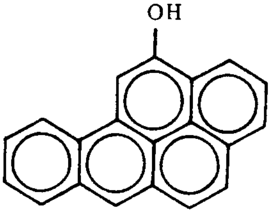

II

a) R = H b) R = Br c) R = CN d) R = $CONH_2$ e) R = CO_2H

Compound II has been furnished to the Chemical Repository, Illinois Institute of Technology Research Institute (IITRI) for distribution to qualified investigators for research in carcinogenesis.

EXPERIMENTAL

12-(Bromomethyl)benz[a]anthracene (Ib).- To a solution of Ia[4] (3.0 g, 12.4

mmol) in 50 ml of CCl_4 was added N-bromosuccinimide (4.41 g, 24.8 mmol). The resulting heterogeneous solution was refluxed under N_2 for 2 hrs, then partitioned between $CHCl_3$ and water and worked up by conventional procedure. The crude Ib (4.0 g) on crystallization from CCl_4 afforded pure Ib (3.60 g, 91%) as yellow needles, mp. 137-138°; NMR:[2] δ 5.58 (s, 2, benzyl) ic), and 7.5-9.25 ppm (m, 11, aromatic). An analogous reaction in the presence of benzoyl peroxide catalyst furnished more complex product mixtures.

Anal. Calcd for $C_{19}H_{13}Br$: C, 71.04; H, 4.08; Br, 24.88.

Found: C, 70.88; H, 4.20; Br, 25.12.

12-(Cyanomethyl)benz[a]anthracene (Ic).- Solid Ib (2.41 g, 7.5 mmol) was added over a 20 min period to a rapidly stirred suspension of KCN (490 mg, 7.5 mmol) in freshly distilled DMSO (50 ml) at 75°. The resulting solution was maintained at 75° for 45 min, then cooled to room temp, diluted with water, extracted with $CHCl_3$ and worked up to afford 2.36 g of a solid residue. Chromatography on silica gel gave on elution with benzene-hexane (2:3) recovered Ib (274 mg). Further elution with benzene-hexane provided Ic as pale yellow needles from CH_2Cl_2-hexane (1.70 g, 84%), mp. 176-177°; NMR: δ 4.60 (s, 2, benzylic), and 7.42-8.60 ppm (m, 11, aromatic); IR ($CHCl_3$): 2230 cm^{-1} (CN).

Anal. Calcd for $C_{20}H_{13}N$: C, 89.86; H, 4.90; N, 5.24.

Found: C, 90.12; H, 5.08; N, 4.99.

Hydrolysis of Ic.- A solution of Ic (740 mg, 2.8 mmol) in warm ethylene glycol (100 ml) to which was added KOH (1.25 g) in 15 ml of water was heated at reflux for 3 days, with occasional swirling to remove the precipitate which tended to creep up the walls of the flask. The product was cooled, ice-water (1L) was added, and the suspension was stirred for 30 min. The solid was removed by filtration, washed with water, and dried over P_2O_5 to afford pure Id (424 mg, 54%) as white silky needles ($CHCl_3$);

mp. > 280°; NMR: δ 4.78 (s, 2, benzylic), 5.50-6.0 (broad, 2, NH_2), and 7.50-8.45 ppm (m, 11, aromatic).

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91.

Found: C, 84.33; H, 5.04; N, 4.96.

Acidification of the filtrate with dilute HCl precipitated Ie (320 mg, 40%). Crystallization from benzene-hexane afforded pure Ie as white silky needles, mp. 216-218°; NMR (acetone-d_6) δ 4.77 (s, 2, benzylic), and 7.50-8.75 ppm (m, 11, aromatic).

A suspension of Id (425 mg, 1.48 mmol) in a solution of KOH (1.2 g) in ethylene glycol (80 ml) and water (15 ml) was heated at reflux for 56 hrs. Unreacted Id (162 mg) was recovered by filtration, and the filtrate was acidified and worked up as before to yield Ie (260 mg, 61% yield or 98% conversion of Id).

Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93.

Found: C, 84.13; H, 4.78.

Benzo[a]pyren-12-ol (II).- A solution of Ie (118 mg., 0.41 mmol) in 15 ml of liquid HF in a Teflon bottle was allowed to evaporate overnight in a hood. The residue was extracted with aqueous $NaHCO_3$ and ether and worked up to afford a brown resin. Chromatography on Florisil gave on elution with benzene-hexane (1:1), II as yellow silky needles from the same solvent (80 mg, 72%), mp. 228-230° (dec.), lit.[1] mp. 230-231°; NMR (acetone-d_6): δ 7.78 (m, 2, $H_{8,9}$), 7.95-8.08 (m, 3, $H_{2,4,5}$), 8.21 (d, 1, J = 8Hz, H_3), 8.32 (m, 1, H_7), 8.45 (s, 1, H_6), 8.55 (s, 1, H_{11}), 8.67 (d, 1, J = 8 Hz, H_1) and 8.96 ppm (m, 1, H_{10}).

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SYNTHESIS OF NEW NAPHTHALENE DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL EFFECT. PART X[†]

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It has been reported[1] that glycolysis and not oxidation metabolism is responsible for the survival of adult schistosomes and that naphthoquinones