3. 5-*Hydroxy*-1 : 2-*benzanthracene and* 1′-*Hydroxy*-1 : 2-5 : 6-*dibenzanthracene.*

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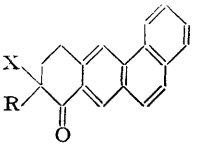
1′ Hydroxy-1 : 2-5 : 6-dibenzanthracene has been synthesised from 5 : 6 : 7 : 8-tetrahydro-5-keto-1 : 2-benzanthracene, which has also been dehydrogenated to 5-hydroxy-1 : 2-benzanthracene. The dibenzanthracene derivative was different from a metabolite of the related hydrocarbon; the 5-hydroxybenzanthracene was required for comparison of the carcinogenic properties of its methyl ether with those other 5-substituted 1 : 2-benzanthracenes.

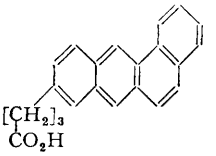
The carcinogenic hydrocarbon 1 : 2-5 : 6-dibenzanthracene is metabolised by rats and mice to the 4′ : 4″-dihydroxy-derivative, and by rabbits to an isomeric dihydroxy-compound of unknown orientation (for references, see Williams, "Detoxication Mechanisms," London, 1947, p. 51). We have re-examined the metabolism of 1 : 2-5 : 6-dibenzanthracene in rabbits, using the procedure described by Berenblum and Schoental (*Cancer Research*, 1943, **3**, 145) for analogous cases. The benzene and chloroform extracts of the dried fæces, excreted after intraperitoneal injection of a suspension of dibenzanthracene in tricaprylin, were adsorbed on a column of alumina, and the material from the fluorescent zone was treated with methyl sulphate and sodium hydroxide solution at 100°. Further chromatographic purification then led to two crystalline products. One of these crystallised from benzene in almost colourless needles, m. p. 244—245°, and was probably the dimethoxy-1 : 2-5 : 6-dibenzanthracene isolated from the methylated phenols from the urine of rabbits dosed with 1 : 2-5 : 6-dibenzanthracene by Boyland, Levy, Mawson, and Roe (*Biochem. J.*, 1941, **35**, 184), whose product had this m. p. A less strongly adsorbed fluorescent substance crystallised from methanol in fine colourless needles, m. p. 214°. The band of shortest wave-length in its fluorescent spectrum had its maximum intensity at 4005 Å, compared with a value of 4070 Å for the dimethoxydibenzanthracene. These relations are consistent with the view that the new methoxy-compound is a monomethoxydibenzanthracene. 9-Methoxy-1 : 2-5 : 6-dibenzanthracene gave a value of 3995 Å for the maximum of its corresponding fluorescence band, and 3-methoxy-1 : 2-5 : 6-dibenzanthracene a value of 4027 Å. The non-identity of the new methylated metabolite with either of these methoxydibenzanthracenes was confirmed by mixed m. p. determinations.

Although 55 isomeric dimethoxy-1 : 2-5 : 6-dibenzanthracenes are possible, the number of possible monomethoxy-compounds is only 7. Two of these have been excluded by the comparisons just mentioned. Moreover, all the identified phenolic metabolic products of fused-ring aromatic hydrocarbons have hydroxyl groups in α-positions to points of ring-fusion. Consequently, if the new compound is, as suggested, a monomethoxy-dibenzanthracene, the substituent is unlikely to be in the β-positions 2′ or 3′, and we are left with three positions for consideration (1′, 4′, and 4). The synthesis of all three seemed feasible, and the present communication deals with the synthesis of 1′-hydroxy-1 : 2-5 : 6-dibenzanthracene and its methyl ether, which proved to be different from the methylated metabolite, m. p. 214°.

The starting point in our synthesis was 5 : 6 : 7 : 8-tetrahydro-5-keto-1 : 2-benzanthracene (I; R = X = H), the 6-carbomethoxy-derivative of which was condensed with γ-iodobutyronitrile to give, after hydrolysis and dehydrogenation, γ-(1 : 2-benzanthr-6-yl)butyric acid (II). This was cyclised to 1′ : 2′ : 3′ : 4′-tetrahydro-1′-keto-1 : 2-5 : 6-dibenzanthracene (III), from which 1′-hydroxy-1 : 2-5 : 6-dibenzanthracene was obtained by treatment with palladium black in boiling 1-methylnaphthalene.



(I)



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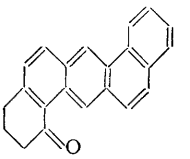

(III)

The very high carcinogenic potency of 8-methoxy-3 : 4-benzpyrene (Cook, Ludwiczak, and Schoental, *J.*, 1950, 1112) made it of interest to compare the biological properties of 5-methoxy-1 : 2-benzanthracene with those of other 5-substituted 1 : 2-benzanthracenes, several of which are carcinogenic. To this end, 5 : 6 : 7 : 8-tetrahydro-5-keto-1 : 2-benzanthracene was dehydrogenated to 5-hydroxy-1 : 2-benzanthracene, which was then methylated.

Experimental

Methyl 6-3′-*Cyanopropyl*-5 : 6 : 7 : 8-*tetrahydro*-5-*keto*-1 : 2-*benzanthracene*-6-*carboxylate* (I; R = $[CH_2]_3$·CN, X = CO_2Me).—Methyl 5 : 6 : 7 : 8-tetrahydro-5-keto-1 : 2-benzanthracene-6-carboxylate (Bachmann and Chemerda, *J. Org. Chem.*, 1941, **6**, 47) (5 g.) was added to sodium methoxide solution prepared from sodium (0·8 g.) and methanol (10 c.c.) in benzene (50 c.c.), and the suspension heated on the water-bath for ½ hour. γ-Iodobutyronitrile (Cook and Lawrence, *J.*, 1937, 821) (10 c.c.) was then added and heating continued for 18 hours. A further quantity (5 c.c.) of the iodo-nitrile was added, and heating continued for a further 24 hours. Water was then added to the cooled suspension, and the oil which separated was extracted with chloroform. The concentrated extract gave a solid which was further purified by passage of its benzene solution through a column of alumina. The resulting *keto*-ester (I; R = $[CH_2]_3$·CN; X = CO_2Me) formed colourless silky needles (from ethyl acetate), m. p. 178—179° (Found: C, 77·3; H, 6·0; N, 3·55. $C_{24}H_{21}O_3N$ requires C, 77·6; H, 5·7; N, 3·8%).

γ-(5 : 6 : 7 : 8-*Tetrahydro*-5-*keto*-1 : 2-*benzanthr*-6-*yl*)*butyric Acid* (I; R = $[CH_2]_3$·CO_2H, X = H).—A solution of the aforesaid keto-ester (3 g.) in acetic acid (30 c.c.) and concentrated hydrochloric acid (30 c.c.) was boiled under reflux for 3 hours. More hydrochloric acid (10 c.c.) was added and boiling continued for 2 hours. The solid which separated on cooling (1 g.) was collected and recrystallised from acetic acid (charcoal). The substituted *butyric acid* (I; R = $[CH_2]_3$·CO_2H; X = H) formed colourless leaflets, m. p. 191—192° (Found: C, 79·6; H, 5·9. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·1%). Its *methyl* ester formed thin elongated crystals (from methanol), m. p. 124—125° (Found: C, 79·8; H, 6·3; OMe, 9·3. $C_{23}H_{22}O_3$ requires C, 79·7; H, 6·4; OMe, 9·0%).

γ-(5 : 6 : 7 : 8-*Tetrahydro*-1 : 2-*benzanthr*-6-*yl*)*butyric Acid*.—A solution of the keto-acid (1 g.) in diethylene glycol (10 c.c.) containing potassum hydroxide (0·8 g.) was reduced with hydrazine hydrate (1 c.c.), following the procedure of Huang-Minlon (*J. Amer. Chem. Soc.*, 1946, **68**, 2487). The reduced *acid* formed colourless leaflets (from ethyl acetate), m. p. 175·5—176·5° (Found: C, 82·9; H, 7·1. $C_{22}H_{22}O_2$ requires C, 82·95; H, 7·0%), and gave a *methyl* ester, m. p. 90—91·5° (Found: C, 83·3; H, 7·35. $C_{23}H_{24}O_2$ requires C, 83·1; H, 7·3%).

γ-(1 : 2-*Benzanthr*-6-*yl*)*butyric Acid* (II).—The aforesaid ester (1 g.) was heated with palladium black (100 mg.) in a nitrogen atmosphere at 280° for 3 hours. The product was hydrolysed with methanolic potassium hydroxide and separated into neutral and acidic components. The neutral material, purified by passage of its solution in benzene–light petroleum through alumina, was evidently 6-n-*propyl*-1 : 2-*benzanthracene*, which formed colourless leaflets (from methanol), m. p. 129° after softening (Found: C, 92·8; H, 7·3. $C_{21}H_{18}$ requires C, 93·3; H, 6·7%). Its deep orange s-*trinitrobenzene* complex had m. p. 127—128° (Found: C, 66·9; H, 4·6; N, 9·0. $C_{27}H_{21}O_6N_3$ requires C, 67·1; H, 4·4; N, 8·7%).

The acidic fraction from the dehydrogenation yielded γ-(1 : 2-*benzanthr*-6-*yl*)*butyric acid*

(II) as colourless leaflets (from benzene), m. p. 192—193° (Found : C, 83·9; H, 5·8. $C_{22}H_{18}O_2$ requires C, 84·0; H, 5·8%).

1′ : 2′ : 3′ : 4′-*Tetrahydro*-1′-*keto*-1 : 2-5 : 6-*dibenzanthracene* (III).—A solution of the acid (II) (150 mg.) in benzene (5 c.c.) was treated with phosphorus pentachloride (0·2 g.) and kept at room temperature for 2 hours. Anhydrous stannic chloride (0·2 c.c.) was then added to the ice-cold solution, which was kept at 0° for ½ hour and then treated with ice and hydrochloric acid. The resulting 1′ : 2′ : 3′ : 4′-*tetrahydro*-1′-*keto*-1 : 2-5 : 6-*dibenzanthracene* (III), recovered from an ethereal extract which had been washed with sodium carbonate solution, formed rhombic yellowish crystals (from benzene), m. p. 168—169° (Found : C, 89·2; H, 5·1. $C_{22}H_{16}O$ requires C, 89·1; H, 5·4%).

1′-*Hydroxy*-1 : 2 - 5 : 6-*dibenzanthracene*.—A solution of the pentacyclic ketone (60 mg.) in 1-methylnaphthalene (3 c.c.) was boiled in a nitrogen atmosphere with palladium black (10 mg.) for 12 hours. Benzene was added to the cooled solution. 1′-*Hydroxy*-1 : 2-5 : 6-*dibenzanthracene* crystallised and after recrystallisation from benzene formed pale yellow threads, m. p., in an evacuated sealed capillary, 269—270° (decomp.) (Found : C, 89·8; H, 5·0. $C_{22}H_{14}O$ requires C, 89·8; H, 4·8%). Its *methyl ether*, prepared by treatment with methyl sulphate and sodium hydroxide solution and purified by chromatography on alumina, formed colourless needles (from benzene–methanol), micro-m. p. 157—160° (Found : C, 89·2; H, 5·6. $C_{23}H_{16}O$ requires C, 89·5; H, 5·2%).

The ultra-violet absorption spectrum of this methoxy-compound closely resembled that of 1 : 2-5 : 6-dibenzanthracene. The wave-lengths and extinction coefficients of the maxima were as follows : λ 400, 380, 350, 335, 325, 294, 280 mμ.; log ε 3·25, 3·30, 4·12, 4·32, 4·49, 5·06, 4·78.

5-*Hydroxy*-1 : 2-*benzanthracene*.—A solution of 5 : 6 : 7 : 8-tetrahydro-5-keto-1 : 2-benzanthracene (I; R = X = H) (Haworth and Mavin, *J.*, 1933, 1012) (1 g.) in 1-methylnaphthalene (10 c.c.) was boiled in a nitrogen atmosphere with palladium black (100 mg.) for 12 hours. The crystals which separated on cooling were recrystallised from benzene and gave 5-*hydroxy*-1 : 2-*benzanthracene* as yellowish silky threads, m. p. 217—218°, in an evacuated sealed capillary (Found : C, 88·3; H, 5·2. $C_{18}H_{12}O$ requires C, 88·5; H, 5·0%). Its *methyl ether* formed colourless needles (from benzene–light petroleum), m. p. 186—187° (Found : C, 88·4; H, 5·6. $C_{19}H_{14}O$ requires C, 88·3; H, 5·5%), and gave a crimson s-*trinitrobenzene* complex, m. p. 197—198° (decomp.) (Found : C, 63·6; H, 4·0; N, 9·3. $C_{25}H_{17}O_7N_3$ requires C, 63·7; H, 3·6; N, 8·9%).

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