82. *Polycyclic Aromatic Hydrocarbons. Part XV. New Homologues of* 1 : 2-*Benzanthracene.*

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The unsymmetrical 1 : 2-benzanthracene molecule contains no less than 12 positions of monosubstitution (see formula VI), and as this molecule is endowed with latent carcinogenic activity, a systematic study of benzanthracene derivatives has been in progress here for some years in order to define the nature and positions of substituents necessary for the development of cancer-producing properties. Seven of the 12 possible monomethylbenzanthracenes have been described (Cook, J., 1930, 1087; 1932, 456; 1933, 1592). Three more have since been prepared, and their synthesis is now recorded on account of the preparation by Fieser and Newman (*J. Amer. Chem. Soc.*, 1936, **58**, 2376) of one of our new homologues (10-methyl-1 : 2-benzanthracene) by a different method. The two methylbenzanthracenes which now remain unknown are the 8- and the 1′-compound, and we are engaged in their synthesis.

Of the 7 methylbenzanthracenes which have had adequate biological test, the 5-methyl compound gave malignant tumours in a large proportion of the mice, although the appearance was considerably delayed; the 6-methyl compound had very feeble activity; the 4-methyl compound gave one non-malignant tumour, and the other compounds were inactive (Barry, Cook, Haslewood, Hewett, Hieger, and Kennaway, *Proc. Roy. Soc.*, 1935, *B*, **117**, 318). These results, coupled with the fact that nearly all of the highly active carcinogenic compounds have additional rings attached at position 5 of the benzanthracene ring system, suggested that substitution at this position is especially favourable for carcinogenic activity. This is further borne out by the fact that both 5-*ethyl*-1 : 2-*benzanthracene* (now described) and 5-*n*-propyl-1 : 2-benzanthracene (Cook and Haslewood, J., 1935, 767) are moderately potent carcinogenic compounds. For these biological tests we are indebted to Professor E. L. Kennaway.

Commenting on the carcinogenic potency of cholanthrene and methylcholanthrene, Fieser and Newman (*loc. cit.*) remark "that it is a matter of considerable interest to attempt to define the features of structure responsible for their striking activity," a sentiment with which we are in complete agreement. Then, on the basis of the carcinogenic activity of their newly-synthesised 5 : 10-dimethyl-1 : 2-benzanthracene and of ulcerations obtained in mice after injection of 10-methyl-1 : 2-benzanthracene during a period in which 5-methyl-1 : 2-benzanthracene was without effect, these authors infer that "the five-membered ring characteristic of the cholanthrene system is of importance in contributing to the carcinogenic potency of hydrocarbons of this type only in that it includes carbon substituents at the 5- and 10-positions. The presence of the intact ring is by no means essential, for simple alkyl groups at these positions produce nearly the same effect. Substitution at the meso-position 10 seems to be particularly important." * We regard this last conclusion as premature. The only 10-alkylbenzanthracene which has received adequate biological test is the 10-*iso*propyl compound, which gave completely negative results in an experiment lasting 611 days (Barry *et al.*, *loc. cit.*). Tests with our sample of 10-methyl-1 : 2-benzanthracene have been in progress for only 130 days, so that we are not in a position to comment on its activity or otherwise, except to say that no tumours have yet arisen.

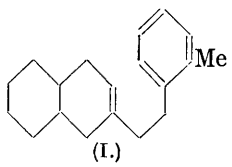
From the facts at present available, the conclusion seems warranted that position 5 is the most favourable position of substitution for carcinogenic activity in derivatives of 1 : 2-benzanthracene, and that the influence of the group in this position may be re-

* This theme has been further elaborated by Fieser in two papers which have appeared since the present communication was submitted for publication (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1937, **59**, 394; L. F. Fieser, M. Fieser, Hershberg, Newman, Seligman, and Shear, *Amer. J. Cancer*, 1937, **29**, 260). It is stated in these papers that 10-methyl-1 : 2-benzanthracene has high cancer-producing activity comparable with that of the cholanthrene group. We prefer to defer discussion of this question until the biological testing of our own specimen of 10-methyl-1 : 2-benzanthracene is complete.

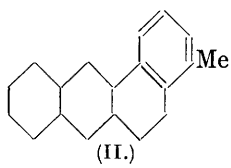
inforced by a second substituent at position 6 or 10 (compare Cook, *Bull. Soc. chim.*, in the press).

For the synthesis of 5-ethyl-1 : 2-benzanthracene, 5-ketododecahydro-1 : 2-benzanthracene was treated with ethylmagnesium bromide, and the crude tertiary carbinol dehydrated and dehydrogenated. This highly hydrogenated ketone seemed more suitable than the sparingly soluble 5-ketotetrahydro-1 : 2-benzanthracene used for the preparation of 5-methyl-1 : 2-benzanthracene (J., 1933, 1592). Extension to the synthesis of higher 5-alkylbenzanthracenes has been impeded by the variable compositions of different batches of *as*-octahydrophenanthrene used in the preparation of ketododecahydrobenzanthracene (Cook and Haslewood, *loc. cit.*), which led to the isolation, from some batches, not of the desired tetracyclic ketone, but of an isomeric ketone derived from 1-hydrindene*spirocyclo*hexane present in the " octahydrophenanthrene." These experiments form part of a separate study of the stereochemistry of hydrophenanthrene derivatives, and will be reported later.

4'-*Methyl*-1 : 2-*benzanthracene* was synthesised by extension of the benzanthracene synthesis of Cook and Hewett (J., 1934, 365), for which purpose 2-(β-o-*tolylethyl*)-trans-2-*decalol* was dehydrated to the corresponding *octalin* (I), which was cyclised to 4'-*methyldodecahydro*-1 : 2-*benzanthracene* (II), the latter being finally dehydrogenated with selenium.



(I.)



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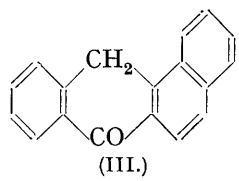
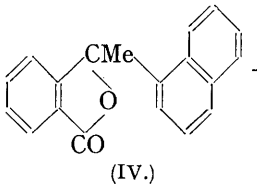


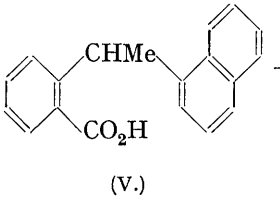
(III.)

10-Methyl-1 : 2-benzanthracene was obtained by the action of methylmagnesium iodide on 1 : 2-benz-10-anthrone (III). The m. p.'s of the hydrocarbon and its picrate agreed with those recorded by Fieser and Newman (*loc. cit.*), who used a completely different method of synthesis.

An attempt to obtain 9-methyl-1 : 2-benzanthracene by a similar Grignard condensation with 1 : 2-benz-9-anthrone was unsuccessful, and this hydrocarbon was thereupon prepared by a method which is essentially that employed by Fieser and Newman for the 10-methyl compound, although our own experiments were completed before the appearance of their paper. 1-Naphthoylbenzoic acid reacted smoothly with an excess of methylmagnesium iodide to give (1-*naphthyl*)*methylphthalide* (IV) which, after hydrolysis with alcoholic alkali, was reduced by zinc dust and sodium hydroxide to o-α-(1-*naphthyl*)-*ethylbenzoic acid* (V). This was dehydrated by zinc chloride to the corresponding anthrone, which was immediately reduced with zinc dust and alkali, giving 9-*methyl*-1 : 2-*benzanthracene* (VI) in good yield.



(IV.)



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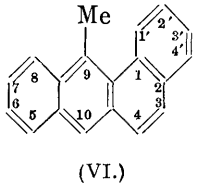

(VI.)

Experimental.

5-*Ethyl*-1 : 2-*benzanthracene*.—5-Ketododecahydro-1 : 2-benzanthracene (Cook and Haslewood, *loc. cit.*) (3 g.) was added to an ice-cold Grignard reagent from ethyl bromide (1·33 g.) and magnesium turnings (0·3 g.) in anhydrous ether (20 c.c.). The whole was then heated on the water-bath for 2 hours, decomposed with ice and ammonium chloride, and the ether removed from the dried extract. The crude carbinol was dehydrated with potassium hydrogen sulphate at 160°, and the distilled hydrocarbon (b. p. 161—165°/0·2 mm.; 3 g.) was dehydrogenated with platinum-black at 300°. The product was treated with picric acid in benzene, and the

dark red picrate was recrystallised from benzene until it had constant m. p. 150—151° (yield 1·1 g.). The regenerated *5-ethyl-1 : 2-benzanthracene* crystallised from alcohol in colourless leaflets, m. p. 120° (Found : C, 93·2; H, 6·3. $C_{20}H_{16}$ requires C, 93·7; H, 6·3%).

5-Ethyl-1 : 2-benzanthraquinone, obtained by boiling a solution of the hydrocarbon (0·1 g.) and sodium dichromate (0·2 g.) in acetic acid (3 c.c.) for 10 minutes, crystallised from methyl alcohol in orange needles, m. p. 97—98° (Found : C, 83·65; H, 5·0. $C_{20}H_{14}O_2$ requires C, 83·9; H, 4·9%).

9-Methyl-1 : 2-benzanthracene.—Finely powdered *o*-1-naphthoylbenzoic acid (18·7 g.) was added gradually to an ice-cold Grignard solution prepared from methyl iodide (20 g.), magnesium turnings (3·3 g.), and anhydrous ether (150 c.c.). The flask was shaken vigorously in order to powder the precipitated magnesium complex. The suspension was boiled for 2 hours, and then decomposed with dilute sulphuric acid. The ethereal layer deposited crystals of (*1-naphthyl*)*methylphthalide* (IV) (7·5 g.), which, after washing with dilute sodium carbonate, were recrystallised from alcohol and then light petroleum, forming thick colourless plates, m. p. 152—153° (Found : C, 83·3; H, 5·4. $C_{19}H_{14}O_2$ requires C, 83·2; H, 5·1%).

This phthalide (18 g.) was hydrolysed with sodium hydroxide (18 g.) in boiling alcohol (300 c.c.), and the alcohol distilled off. Then water (300 c.c.) and concentrated ammonium hydroxide (75 c.c.) were added, and the solution boiled with zinc dust (35 g.) for 24 hours. The filtered solution was acidified, and the precipitated o-α-(*1-naphthyl*)*ethylbenzoic acid* (V) was recrystallised from aqueous alcohol, forming colourless needles (15·5 g.), m. p. 167—168° (Found : C, 82·7; H, 6·05. $C_{19}H_{16}O_2$ requires C, 82·6; H, 5·8%).

Cyclisation of this acid (10 g.) was effected by heating with anhydrous zinc chloride (30 g.) at 180° for 20 minutes. After cooling, the mass was powdered, and extracted with dilute hydrochloric acid, and then dilute sodium carbonate solution. The crude residual anthrone was then suspended in 2*N*-sodium hydroxide solution (300 c.c.) and boiled with zinc dust (20 g.) for 3 hours. The solid was collected, excess zinc extracted with hydrochloric acid, and the hydrocarbon recrystallised from acetic acid. The *9-methyl-1 : 2-benzanthracene* (VI) (5·2 g.), m. p. 136—139°, was purified through its *picrate*, which crystallised from benzene in dark red needles, m. p. 115—116° (Found : C, 63·7; H, 4·5.* $C_{25}H_{17}O_7N_3$ requires C, 63·7; H, 3·6%). The hydrocarbon regenerated from the picrate was sublimed in a vacuum and recrystallised from alcohol, forming yellowish plates, m. p. 138—139° (Found : C, 94·2; H, 6·1. $C_{19}H_{14}$ requires C, 94·2; H, 5·8%). In conformity with its structure (VI), oxidation of this hydrocarbon with sodium dichromate in boiling acetic acid gave 1 : 2-benzanthraquinone, m. p. 168—169°, alone or mixed with an authentic specimen.

10-Methyl-1 : 2-benzanthracene.—Crude 1 : 2-benz-10-anthrone, prepared by zinc chloride dehydration of 1-naphthylphenylmethane-2′-carboxylic acid (Cook, J., 1930, 1093) (20 g.), was added to an ice-cold Grignard solution prepared from methyl iodide (73 g.), magnesium turnings (12 g.), and anhydrous ether (200 c.c.). After an hour at 0°, the whole was heated on the water-bath for 1½ hours. The product was decomposed with ice and ammonium chloride, the ethereal solution dried (sodium sulphate), and the ether removed. The residue (12 g.) was treated, in acetic acid solution, with an equal weight of picric acid. This treatment suffices to complete the dehydration to the hydrocarbon of the primarily formed tertiary carbinol. The dark red crystals were freed from picric acid by extraction with dilute sodium carbonate, and the product extracted with about 20 c.c. of boiling benzene, and filtered. Some dianthrone-like material, m. p. above 300°, evidently the product of atmospheric oxidation of the anthrone, remained undissolved. The hydrocarbon recovered from the filtrate was sublimed at 150°/0·15 mm., and recrystallised from alcohol, forming slender yellowish needles (1·4 g.), m. p. 138°. Final purification was accomplished through the picrate, which crystallised from benzene in dark red needles, m. p. 172—173·5° (corr.) (Found : C, 63·7; H, 3·5. Calc. for $C_{25}H_{17}O_7N_3$: C, 63·7; H, 3·6%). Fieser and Newman (*loc. cit.*) give m. p. 173·5—174° (corr.). 10-Methyl-1 : 2-benzanthracene, regenerated from this picrate, had m. p. 140·5—141·5° (corr.) (Found : C, 94·0; H, 5·85. Calc. for $C_{19}H_{14}$: C, 94·2; H, 5·8%). Fieser and Newman give m. p. 140·2—140·8° (corr.). Oxidation with sodium dichromate in boiling acetic acid gave 1 : 2-benzanthraquinone.

4′-Methyl-1 : 2-benzanthracene.—Thionyl chloride (23 c.c.) was added dropwise with agitation to an ice-cold mixture of β-*o*-tolylethyl alcohol (40 g.) and dimethylaniline (36 g.). The mixture was then heated on the water-bath for ½ hour, and the resulting β-o-*tolylethyl chloride* (40 g.) isolated in the normal way. It formed a colourless liquid, b. p. 100°/15—20 mm. (Found : C, 69·5; H, 7·1. $C_9H_{11}Cl$ requires C, 69·9; H, 7·2%). *trans*-β-Decalone (39 g.) was added to

* The high value for hydrogen is due to unreduced oxides of nitrogen.

an ice-cold Grignard solution prepared from this chloride (40 g.) and magnesium turnings (6·2 g.) in anhydrous ether (200 c.c.). After being kept at room temperature for an hour, the whole was heated on the water-bath for 1½ hours, decomposed with ice and ammonium chloride, and the tertiary carbinol isolated by distillation. 2-(β-o-*Tolylethyl*)-trans-2-*decalol* (40 g.) formed a colourless viscous liquid, b. p. 170—180°/0·6 mm., which slowly crystallised when kept in the ice chest, but could not be satisfactorily recrystallised (Found: C, 83·5; H, 10·5. $C_{19}H_{28}O$ requires C, 83·7; H, 10·4%).

2-(β-o-*Tolylethyl*)-$\Delta^{2:3}$-*octalin* (I) was obtained when this carbinol (37 g.) was heated with potassium hydrogen sulphate (78 g.) at 170—180° for 2 hours. After redistillation over sodium, the octalin formed a colourless liquid (30 g.), b. p. 160—162°/0·7 mm. (Found: C, 89·2; H, 10·2. $C_{19}H_{26}$ requires C, 89·7; H, 10·3%).

For cyclisation, an ice-cold solution of this unsaturated hydrocarbon (I; 28 g.) in carbon disulphide (280 c.c.) was treated gradually with anhydrous aluminium chloride (40 g.), and then kept overnight at room temperature. The clear solution was decanted from the aluminium chloride sludge, washed with dilute acid and dilute alkali, dried, and distilled. Two fractions were collected at 0·2 mm.: (i) b. p. 156—170° (14 g.); (ii) b. p. 170—180° (5 g.). Fraction (ii) crystallised on standing, and was twice recrystallised from methyl alcohol. This crystalline 4′-*methyldodecahydro*-1 : 2-*benzanthracene* (II) formed colourless rectangular plates, m. p. 92·5—93·5° (Found: C, 89·7; H, 10·3. $C_{19}H_{26}$ requires C, 89·7; H, 10·3%). A further quantity of this crystalline isomeride was isolated from fraction (i) by seeding. In all, about 2 g. of the pure material were isolated. Dehydrogenation with selenium at 300° for 24 hours gave in good yield 4′-*methyl*-1 : 2-*benzanthracene*, which was freed from the last traces of selenium by adsorption on alumina, then sublimed at 160—170°/0·2 mm., and the sublimate treated in benzene solution with an equal weight of picric acid. The picrate separated in light red needles, m. p. 139—140°, but was too readily dissociated to be recrystallised. The regenerated hydrocarbon crystallised from benzene in colourless irregular plates, m. p. 194—195° (Found: C, 94·0; H, 5·9. $C_{19}H_{14}$ requires C, 94·2; H, 5·8%). The non-crystalline isomerides of (II) also gave this 4′-methyl-1 : 2-benzanthracene on selenium dehydrogenation.

4′-*Methyl*-1 : 2-*benzanthraquinone*, obtained by oxidation of the foregoing hydrocarbon with sodium dichromate in boiling acetic acid, crystallised from benzene in golden-orange needles, m. p. 219—220° (Found: C, 83·45; H, 4·4. $C_{19}H_{12}O_2$ requires C, 83·8; H, 4·4%).

We are indebted to the International Cancer Research Foundation for a maintenance grant (to A. M. R.), and to the British Empire Cancer Campaign, who have assisted this work.

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[*Received, January 8th,* 1937.]