93. *The Synthesis of Growth-inhibitory Polycyclic Compounds. Part III.*

By G. M. BADGER.

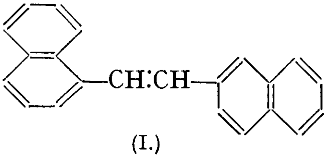
The preparation of 9-*methyl*-1 : 2-*benzfluorene* (V), α-1-*naphthyl*-β-2-*naphthylethylene* (I), and compounds of the general formulæ (III) and (IV) (in which R and R′ = Me or Et) is described. All three classes of compound are related to known potent tumour-inhibiting agents and have been prepared for biological test.

THE experiments of Haddow and his co-workers on the growth-inhibitory properties of carcinogenic and chemically related non-carcinogenic compounds have shown that many feeble cancer-producing agents have potent growth-inhibitory properties. Striking results have been obtained with the non-carcinogenic 1 : 2′-azonaphthalene (Haddow and others, unpublished) and the feebly carcinogenic 1 : 2 : 5 : 6-dibenzfluorene (Haddow and Robinson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 277). Further, many of the synthetic oestrogenic agents have been shown to be growth-inhibitory (see, for example, Noble, *J. Endocrinol.*, 1939, **1**, 128). The present paper describes several compounds related to these three types of active tumour-inhibiting agent, and forms part of an extensive search for a substance for use as a chemotherapeutic agent against cancer.

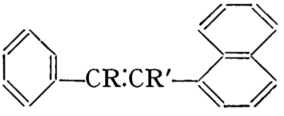
The preparation of 1- and 2-naphthaldehydes from the corresponding bromomethyl compounds with hexamethylenetetramine has been improved by the substitution of acetic acid for alcohol as the solvent. In acetic acid solution the reaction is complete in about 30 seconds (compare Hewett, J., 1940, 297), whereas the reaction time in alcohol is 8 hours (Mayer and Sieglitz, *Ber.*, 1922, **55**, 1859). The condensation of 1-naphthaldehyde and sodium 2-naphthylacetate, 2-naphthaldehyde and sodium 1-naphthylacetate, 1-naphthaldehyde and sodium 1-naphthylacetate has given a series of dinaphthylacrylic acids. One of these, α-2-*naphthyl*-β-1-*naphthylacrylic acid*, has been decarboxylated with copper bronze in quinoline to give α-1-*naphthyl*-β-2-*naphthylethylene* (I).

1-Phenylacetylnaphthalene and 2-phenylacetylnaphthalene (II) (Cook and Hewett, J., 1934, 376) have been converted into compounds of the types (III) and (IV) by the method of Dodds, Golberg, Lawson, and Robinson (*Proc. Roy. Soc.*, 1939, *B*, **127**, 140). The group R was first introduced by treatment of the sodio-derivative of the phenylacetylnaphthalene with an alkyl iodide. The resulting ketone on treatment with an alkylmagnesium halide gave the carbinol, which was smoothly dehydrated to the hydrocarbons (III) and (IV) with phosphorus tribromide in chloroform.

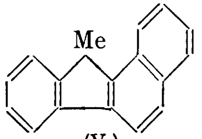
The oxidation of fluorene, 1 : 2-benzfluorene and 1 : 2 : 5 : 6-dibenzfluorene with selenium dioxide (Cook, J., 1932, 1476) proceeded normally to give fluorenone, 1 : 2-benzfluorenone, and 1 : 2 : 5 : 6-*dibenzfluorenone* respectively, in satisfactory yield (compare Postowsky and Lugowkin, *Ber.*, 1935, **68**, 852). Previous attempts to oxidise the dibenzfluorene with sodium dichromate in acetic acid led to resinous and acidic products.



(I.)

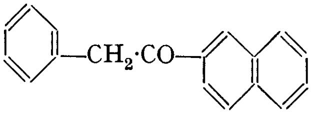


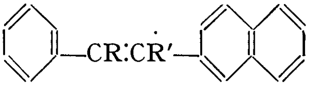
(IV.)



(V.)

(II.)





(III.)

9-*Methyl*-1 : 2-*benzfluoren*-9-*ol* has been prepared by the action of methylmagnesium iodide on 1 : 2-benzfluorenone in the usual way. Dehydration of this carbinol with boiling acetic acid and hydrogenation with hydrogen in the presence of platinum catalyst by the method of Fieser and Joshel (*J. Amer. Chem. Soc.*, 1940, **62**, 957) gave the desired 9-*methyl*-1 : 2-*benzfluorene* (V). In the same way, 9-methylfluorene has been prepared from fluorenone, for comparison.

EXPERIMENTAL.

1-*Naphthaldehyde*.—A solution of 1-bromomethylnaphthalene (44 g.) in boiling acetic acid (100 c.c.) was treated with hexamethylenetetramine (28 g.), and the solution boiled until clear (1 min.). The mixture was poured into water and the oil which separated was purified through the bisulphite compound. The product distilled at 150°/13 mm.; yield 21 g.

2-*Naphthaldehyde*.—In the same way, 2-bromomethylnaphthalene (90 g.) was treated with hexamethylenetetramine (70 g.) in boiling acetic acid (200 c.c.). After purification through the bisulphite compound, 2-naphthaldehyde distilled at 150°/15 mm., yield, 32·8 g.

α-1-*Naphthyl*-β-2-*naphthylacrylic Acid*.—A mixture of sodium 1-naphthylacetate (6·9 g.), 2-naphthaldehyde (5·2 g.), and acetic anhydride (45 c.c.) was heated at 130° for 7 hours. The product was poured into water and allowed to decompose overnight. The brown gum obtained was extracted with boiling dilute sodium carbonate solution, and the acid precipitated and washed with a little acetic acid. After purification through its sparingly soluble sodium salt, α-1-*naphthyl*-β-2-*naphthylacrylic acid* (3·5 g.) formed colourless needles from acetic acid or a microcrystalline powder from xylene, m. p. 215—216° (after sintering) (Found : C, 85·5; H, 5·0. $C_{23}H_{16}O_2$ requires C, 85·2; H, 5·0%).

α-2-*Naphthyl*-β-1-*naphthylacrylic acid*, prepared by heating sodium 2-naphthylacetate (14 g.), 1-naphthaldehyde (10·4 g.), and acetic anhydride (90 c.c.) at 130—140° for 8 hours and purified as described above, formed pale yellow needles (5·9 g.), m. p. 213—214° (after sintering), from acetic acid (Found : C, 85·6; H, 5·0%).

α-1-*Naphthyl*-β-2-*naphthylethylene* (I).—A mixture of the preceding acid (1·6 g.), copper bronze (1 g.), and freshly distilled quinoline (15 c.c.) was heated at 240—250° for 1 hour. The cooled mixture was diluted with ether and filtered, and the ethereal solution washed with dilute hydrochloric acid, sodium carbonate solution, and water. The dark brown crystals obtained on evaporation were recrystallised from benzene–alcohol, sublimed at 120°/0·1 mm., and further recrystallised from benzene–alcohol. α-1-*Naphthyl*-β-2-*naphthylethylene* (1·15 g.) formed colourless crystals, m. p. 103—105° (Found : C, 94·3; H, 5·55. $C_{22}H_{16}$ requires C, 94·25; H, 5·75%).

αβ-*Di*-1-*naphthylacrylic acid*, obtained from sodium 1-naphthylacetate (7 g.), 1-naphthaldehyde (5·2 g.), and acetic anhydride (45 c.c.), formed yellow plates, m. p. 227—228°, from acetic acid (Found : C, 85·1; H, 5·0%).

1-*Phenylmethylacetylnaphthalene*.—1-Phenylacetylnaphthalene (17·3 g.) (Cook and Hewett, *loc. cit.*) and methyl iodide (10 g.) were added to a hot solution of sodium (1·5 g.) in absolute alcohol (45 c.c.). The mixture was boiled for 10 minutes and then treated with a further quantity of sodium (0·6 g.) in absolute alcohol (15 c.c.), followed by methyl iodide (6·4 g.). After boiling for 4 hours, the solution was poured into water, and the alcohol removed under reduced pressure. The cooled mixture was extracted with ether, and the combined extracts washed with a solution of sodium thiosulphate and finally with water. The oil obtained on evaporation was distilled at 172—175°/0·5 mm. and redistilled at 172—173°/0·5 mm., 1-*phenylmethylacetylnaphthalene* (17·5 g.) being obtained as a colourless viscous oil (Found : C, 87·35; H, 6·3. $C_{19}H_{16}O$ requires C, 87·65; H, 6·2%).

γ-*Phenyl*-β-1-*naphthylbutan*-β-*ol*.—A solution of the above phenylmethylacetylnaphthalene (16·0 g.) in dry ether (100 c.c.) was added dropwise to a Grignard solution prepared from methyl iodide (26·0 g.), magnesium (4·25 g.), and ether (100 c.c.), and the mixture boiled for 2 hours. After decomposition with ice and dilute sulphuric acid, the ethereal solution was washed, dried, and evaporated. On standing with a few drops of methyl alcohol, the product crystallised. Its solution in boiling methyl alcohol deposited only 5·0 g. of crystalline material on cooling. After further recrystallisations, γ-*phenyl*-β-1-*naphthylbutan*-β-*ol* formed colourless crystals, m. p. 97—99° (Found : C, 87·0; H, 5·9. $C_{20}H_{20}O$ requires C, 86·9; H, 7·2%).

The oil obtained by evaporation of the methyl-alcoholic solution was distilled, b. p. 160—170°/0·8 mm. (10 g.). Analysis of this product showed almost complete dehydration (Found : C, 91·7; H, 7·15%).

α-*Phenyl*-β-1-*naphthyl*-αβ-*dimethylethylene* (IV, R = R′ = Me).—Solutions of the above oil (13·2 g.) in chloroform (35 c.c.) and of phosphorus tribromide (13 g.) in chloroform (25 c.c.) were cooled below 0°, mixed, and kept overnight at room temperature. The mixture was poured slowly into ice-cold alcohol (70 c.c.) and diluted with water. The chloroform layer and chloroform extracts of the aqueous layer were combined, washed with water, and dried over calcium chloride. The oil obtained on evaporation was distilled, b. p. 170—178°/3 mm. (yield, 11·7 g.). After 4 days the product partly crystallised. It was dissolved in light petroleum (b. p. 40—60°) and kept at − 10° for 24 hours. The crystals (5·2 g.) were collected and recrystallised from light petroleum, α-*phenyl*-β-1-*naphthyl*-αβ-*dimethylethylene* forming colourless prisms, m. p. 68·5—70° (Found : C, 93·1; H, 7·2. $C_{20}H_{18}$ requires C, 93·0; H, 7·0%).

α-*Phenyl*-β-1-*naphthyl*-α-*methyl*-β-*ethylethylene* (IV; R = Me, R′ = Et).—In the same way, 1-phenylmethylacetylnaphthalene (16·2 g.) was allowed to react with ethylmagnesium bromide (from 22 g. of ethyl bromide). The product was a colourless oil, b. p. 185—187°/0·9 mm. (14·5 g.). Analysis showed it to be partly dehydrated. A solution of this oil (13·6 g.) in chloroform was dehydrated with phosphorus tribromide (14 g.). α-*Phenyl*-β-1-*naphthyl*-α-*methyl*-β-*ethylethylene* was obtained as a colourless viscous oil, b. p. 161—164°/0·6 mm. (yield, 12·3 g.) (Found : C, 92·9; H, 7·15. $C_{21}H_{20}$ requires C, 92·6; H, 7·4%).

2-*Phenylethylacetylnaphthalene*.—2-Phenylacetylnaphthalene (II) (26·0 g.) (Cook and Hewett, *loc. cit.*) and ethyl iodide (16·5 g.) were added to a hot solution of sodium (2·4 g.) in alcohol (50 c.c.). After 10 minutes a further quantity of sodium (0·9 g.) in alcohol (30 c.c.) was added, followed by ethyl iodide (10 g.). The 2-*phenylethylacetylnaphthalene* (24·3 g.) formed colourless prisms, m. p. 116—118°, from alcohol (Found : C, 87·25; H, 6·8. $C_{20}H_{18}O$ requires C, 87·55; H, 6·6%).

α-*Phenyl*-β-2-*naphthyl*-αβ-*diethylethylene* (III, R = R′ = Et).—The above 2-phenylethylacetylnaphthalene (10 g.) in benzene solution was added to excess of ethylmagnesium bromide as above. The pale yellow, viscous oil obtained (10·5 g.), b. p. 199—201°/2 mm., was found on analysis to be almost completely dehydrated. This oil (9·75 g.) was completely dehydrated with Phosphorus tribromide, and α-*phenyl*-β-2-*naphthyl*-αβ-*diethylethylene* (8·75 g.) obtained as a colourless viscous oil, b. p. 165—168°/0·5 mm. (Found : C, 92·3; H, 7·8. $C_{22}H_{22}$ requires C, 92·2; H, 7·8%).

α-*Phenyl*-β-2-*naphthyl*-β-*methyl*-α-*ethylethylene* (III; R = Et, R′ = Me).—In the same way, 2-phenylethylacetylnaphthalene (10 g.) was treated with methylmagnesium iodide. The almost colourless oil (9·4 g.), b. p. 193—197°/2 mm., was found on analysis to be almost completely dehydrated. Complete dehydration of the oil (8·75 g.) was effected with phosphorus tribromide (10 g.), α-*phenyl*-β-2-*naphthyl*-β-*methyl*-α-*ethylethylene* being obtained as a colourless viscous oil (8·0 g.), b. p. 178—180°/1 mm. (Found : C, 92·35; H, 7·4. $C_{21}H_{20}$ requires C, 92·6; H, 7·4%).

Oxidation of Fluorenes with Selenium Dioxide.—A mixture of fluorene (2 g.), selenium dioxide (4 g.), and water (4 c.c.) was heated in a sealed tube at 230—240° for 4 hours. After cooling, the solid was filtered off, washed with water, extracted from the selenium with alcohol, sublimed at 100°/0·5 mm., and recrystallised from alcohol, forming bright yellow crystals (1·5 g.), m. p. 80—83° alone or mixed with authentic fluorenone.

In the same way, 1 : 2-benzfluorene (1 g.) was oxidised to 1 : 2-benzfluorenone (0·85 g.), m. p. 131—132°. The same yield of 1 : 2-benzfluorenone was obtained in a parallel experiment with sodium dichromate in boiling acetic acid as an oxidising agent.

Oxidation of 1 : 2 : 5 : 6-dibenzfluorene (0·25 g.) in the same manner gave 1 : 2 : 5 : 6-*dibenzfluorenone* (0·1 g.), which formed red plates or needles, m. p. 164—165°, from benzene (Found : C, 90·1; H, 4·35. $C_{21}H_{12}O$ requires C, 90·0; H, 4·3%).

9-*Methyl*-1 : 2-*benzfluoren*-9-*ol*.—A solution of 1 : 2-benzfluorenone (2·6 g.) in dry benzene (50 c.c.) was added to a Grignard solution prepared from methyl iodide (4·26 g.), magnesium (0·7 g.), and ether. The mixture was boiled for 2 hours, cooled, and decomposed with ice and ammonium chloride. The 9-*methyl*-1 : 2-*benzfluoren*-9-*ol* (2·30 g.) formed colourless transparent plates, m. p. 170·5—171·5°, from benzene (Found : C, 88·1; H, 5·5. $C_{18}H_{14}O$ requires C, 87·8; H, 5·7%).

9-*Methyl*-1 : 2-*benzfluorene* (V).—A solution of the above fluorenol (1·6 g.) in pure acetic acid (50 c.c.) was refluxed for 1 hour. After cooling, the solution was shaken with hydrogen in the presence of Adams's catalyst (0·1 g.). The filtered solution was poured into water and extracted with benzene, the extracts freed from acetic acid and evaporated, and the residue distilled from an air-bath under high vacuum. 9-*Methyl*-1 : 2-*benzfluorene* (0·75 g.) was obtained in pale yellow plates, m. p. 120·5—122·5°, from acetic acid (Found : C, 94·0; H, 5·9. $C_{18}H_{14}$ requires C, 93·9; H, 6·1%).

The *bis*-s-*trinitrobenzene complex* formed orange blades, m. p. 109—111°, from alcohol (Found : C, 55·2; H, 3·1. $C_{18}H_{14},C_{12}H_6O_{12}N_6$ requires C, 54·9; H, 3·1%).

9-*Methylfluoren*-9-*ol*.—This was prepared in an identical manner from fluorenone (3·6 g.) and methylmagnesium iodide. It formed large colourless prisms (3·35 g.), m. p. 173—174° (Ullmann and Wurstenberger, *Ber.*, 1905, **38**, 4107, give m. p. 174·5°).

9-*Methylfluorene*.—The above fluorenol (1 g.) was boiled with acetic acid (40 c.c.) for 1 hour, and the cooled solution hydrogenated as above. This was complete in 20 minutes. The 9-methylfluorene (0·7 g.) formed colourless crystals, m. p. 45—46°, from methyl alcohol (Mayer, *Ber.*, 1913, **46**, 2586, gives m. p. 46°).

My thanks are due to Professor J. W. Cook, F.R.S., for his interest in this work, to the Finney-Howell Research Foundation for a fellowship, and to the British Empire Cancer Campaign for a grant to the Institute.

THE CHESTER BEATTY RESEARCH INSTITUTE, THE ROYAL CANCER HOSPITAL (FREE),
LONDON, S.W. 3.
[*Received, June* 10*th*, 1941.]