# 124. *A New Route to the Synthesis of Dibenzfluorenones.*

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A simple method for the synthesis of 1 : 2 : 5 : 6-dibenzfluorene is described. Reaction of $N$-nitrosoaceto-2-naphthalide with amyl 2-naphthoate yields a mixture of esters, from which, after hydrolysis, 1 : *2'-dinaphthyl-2-carboxylic acid* (III; R = H) can be isolated. The acid (III; R = H) is cyclised by means of sulphuric acid to 1 : 2 : 5 : 6-dibenzfluorenone (IV), which is readily reduced to 1 : 2 : 5 : 6-dibenzfluorene with hydrazine. Separation of the pure acid (III; R = H) is unnecessary, as the crude mixture, heated with sulphuric acid, gives a product from which (IV) is easily separated.

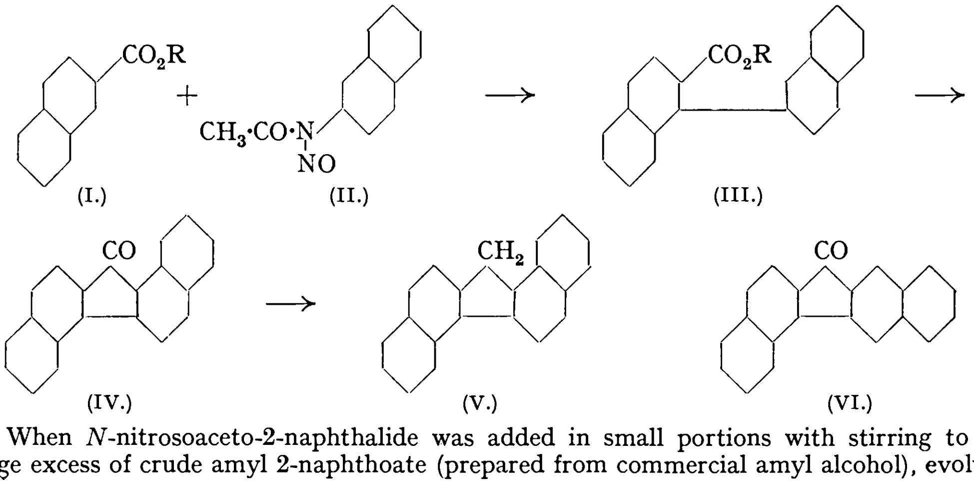
A similar sequence of reactions in the case of $N$-nitrosoaceto-2-naphthalide and amyl 1-naphthoate leads to 1 : 2 : 7 : 8-dibenzfluorenone (VII), and the reaction between $N$-nitrosoaceto-1-naphthalide and amyl 2-naphthoate to 3 : 4 : 5 : 6-dibenzfluorenone (VIII) and an unidentified isomeric compound possibly with the structure (IX). The yields of 1 : 2 : 7 : 8- and 3 : 4 : 5 : 6-dibenzfluorenone are, however, unsatisfactory.

AMONG carcinogenic hydrocarbons 1 : 2 : 5 : 6-dibenzfluorene (V) is of particular interest because of its marked tumour-inhibiting properties (Haddow and Robinson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 277). It has been synthesised by Cook, Dansi, Hewett, Iball, Mayneord, and Roe (J., 1935, 1319), but the route selected by these investigators was lengthy and the overall yield of hydrocarbon was extremely low. While a more detailed examination of the hydrocarbon and its substitution products from the standpoint of tumour-inhibition would be desirable, it was clear that it would be a matter of extreme difficulty unless some simpler synthesis could be devised. It is the purpose of this paper to describe some experiments offering a practicable route to 1 : 2 : 5 : 6-dibenzfluorene; the overall yield is not very high, but the process has the merit of simplicity and the starting materials are readily accessible.

Consideration of the formula (V) of the desired hydrocarbon suggested that the most direct procedure would be cyclisation of 1 : *2′-dinaphthyl-2-carboxylic acid* (III; R = H) to 1 : 2 : 5 : 6-dibenzfluorenone (IV), followed by reduction of this ketone. Theoretically the cyclisation of (III; R = H) might also give rise to 2 : 3 : 5 : 6-dibenzfluorenone (VI); in practice, however, we were unable to isolate any of this substance, ring closure, under the conditions employed, occurring almost exclusively in the desired direction, giving (IV). The preparation of 1 : 2′-dinaphthyl-2-carboxylic acid (III; R = H) by simple means appeared to rest on the possibility of direct introduction of a naphthyl residue into the nucleus of 2-naphthoic acid. The union of aryl nuclei can be effected amongst other methods by the reaction of *N*-nitrosoacylarylamines with aromatic compounds according to the scheme :

$$\text{Ar·N(NO)Ac} + \text{Ar'H} \longrightarrow \text{Ar·Ar'} + N_2 + \text{AcOH}.$$

This reaction, originally discovered by Bamberger (*Ber.*, 1897, **30**, 366), has in recent years been the subject of investigation in these laboratories (cf. Grieve and Hey, J., 1934, 1797), where it has been extended to the synthesis not only of terphenyl derivatives (France, Heilbron, and Hey, J., 1938, 1364; 1939, 1283, 1288) but also of phenylnaphthalenes (Hey and Lawton, J., 1940, 374). In general it has been found that the highly reactive nature of the nitroso-compound necessitates the second component of the reaction being in the liquid state at normal temperatures and it must be present in considerable excess (cf. Haworth and Hey, J., 1940, 361). Although no case of dinaphthyl synthesis by this method had hitherto been recorded, there seemed no reason to suppose that the method would not apply equally well in such a case provided that a liquid or low-melting naphthalene derivative could be employed as second component. For the preparation of the acid (III; R = H) by the Bamberger synthesis the most obvious procedure was the condensation of *N*-nitrosoaceto-2-naphthalide (II) with 2-naphthoic acid; to get over the difficulty presented by the high m. p. of 2-naphthoic acid, its amyl ester (I; R = $C_5H_{11}$), which is liquid at room temperature, was chosen.



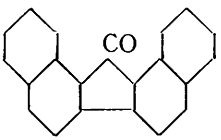
(I.) (II.) (III.)

(IV.) (V.) (VI.)

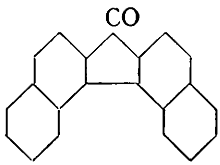
When *N*-nitrosoaceto-2-naphthalide was added in small portions with stirring to a large excess of crude amyl 2-naphthoate (prepared from commercial amyl alcohol), evolution of nitrogen took place and a deep red solution was obtained. The product, apparently a mixture of esters, was isolated by distillation as a viscous orange-coloured syrup. In the condensation of *N*-nitrosoacylarylamines with monosubstituted benzenes it is known that the entering group always takes up a position ortho or para to the substituent already present and as a rule both types of substitution occur simultaneously (Grieve and Hey, *loc. cit.*). Hence, although in the present case substitution in the 1-position of the 2-naphthoic ester was probable, substitution elsewhere was also to be expected. This proved to be the case, since the above reaction product gave, on hydrolysis, a mixture from which two crystalline acids were isolated. One of these (m. p. 204—205°) was the expected 1 : 2′-dinaphthyl-2-carboxylic acid (III ; R = H), which readily yielded 1 : 2 : 5 : 6-dibenzfluorenone (IV) on heating with sulphuric acid. The other (m. p. 231—232°) was an isomeric acid, which could not be cyclised with sulphuric acid and on decarboxylation afforded 1 : 2′-dinaphthyl. This acid is therefore 1 : 2′-dinaphthyl-*x*-carboxylic acid, where $x = 3$, 6, or 7 ; a definite structure cannot be assigned on the available evidence, but from the mode of preparation the carboxyl group is probably in position 6.

For the preparation of (IV) the separation of the isomeric dinaphthylcarboxylic acids is both wasteful and unnecessary, since only (III ; R = H) can undergo cyclisation. Treatment of the crude product with sulphuric acid gives a mixture from which (IV) is readily separated as a neutral fraction. Reduction of (IV) to 1 : 2 : 5 : 6-dibenzfluorene (V) by the Clemmensen method is unsatisfactory, but it is smoothly accomplished by heating with hydrazine, a method suggested to us by Professor J. W. Cook, who has used it successfully in similar cases.

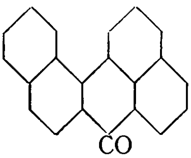
The synthetic method described should be applicable to the preparation of other dibenzfluorenones. For instance, from the reaction product of *N*-nitrosoaceto-2-naphthalide and amyl 1-naphthoate, 1 : 2 : 7 : 8-dibenzfluorenone (VII) should be obtained, and from that of *N*-nitrosoaceto-1-naphthalide and amyl 2-naphthoate, 3 : 4 : 5 : 6-dibenzfluorenone (VIII) ; this has been experimentally verified. The crude reaction product from *N*-nitrosoaceto-2-naphthalide and amyl 1-naphthoate, hydrolysed and treated with sulphuric acid, gave three products. One of these was 1 : 2 : 7 : 8-dibenzfluorenone, m. p. 265—266°, its identity being established by a mixed m. p. determination with a specimen prepared by a different route and kindly supplied by Dr. R. Martin and by reduction to 1 : 2 : 7 : 8-dibenzfluorene. This ketone corresponds in properties to the dibenzfluorenone, m. p. 255°, described by Schmidlin and Huber (*Ber.*, 1910, **43**, 2833) and to that, m. p. 269—270°, of Tschitschibabin and Magidson (*J. pr. Chem.*, 1914, **90**, 174). The second product, obtained only in small amount, crystallised in yellow needles, m. p. 182—183° ; it gave unsatisfactory analytical values and was possibly a mixture. On account of the small amount available it was not further examined. The third substance isolated had m. p. 206—207° and showed the properties of a dinaphthylcarboxylic acid. Since it yielded 1 : 2′-dinaphthyl on decarboxylation and did not undergo cyclisation with sulphuric acid, it is evidently a 1 : 2′-dinaphthylcarboxylic acid in which the carboxyl group is located in position 4, 5, or 8. The isolation of 2 : 2′-dinaphthyl-1-carboxylic acid, which must have been the precursor of 1 : 2 : 7 : 8-dibenzfluorenone, was not attempted.



(VII.)



(VIII.)



(IX.)

Reaction of *N*-nitrosoaceto-1-naphthalide with amyl 2-naphthoate led to the production of large amounts of azo-compounds and the crude product on hydrolysis and ring-closure gave only a small amount of solid material. From this a very small amount of 3 : 4 : 5 : 6-dibenzfluorenone (VIII) was isolated. It had m. p. 222—223°, undepressed on admixture with a specimen synthesised by a different route (Martin, following paper) and kindly supplied by Dr. R. Martin. The dibenzfluorenone was accompanied by a somewhat larger amount of a yellow, apparently isomeric substance, m. p. 186—187°. From its occurrence as a product in the above series of reactions it would appear likely that it is 1 : 2 : 8 : 9-dibenz-10-anthrone (IX), but synthesis of the latter substance for purposes of comparison has not yet been completed.*

It is evident from the results obtained that, while the synthetic method does in each case yield the expected dibenzfluorenone, its value as a preparative method is confined to 1 : 2 : 5 : 6-dibenzfluorenone.

## EXPERIMENTAL.

*Amyl 2-Naphthoate.*—2-Naphthoic acid was prepared from β-naphthylamine in 46% yield by means of a Sandmeyer reaction, followed by hydrolysis of the crude tarry nitrile with sulphuric acid. The acid was esterified by a refluxing for 10 hours with commercial amyl alcohol containing a little sulphuric acid. The product, a yellowish syrupy liquid, b. p. 195—200°/13 mm., was doubtless a mixture of isomeric amyl esters with *iso*amyl 2-naphthoate preponderating. Since the sole reason for esterification was to obtain a liquid derivative of the acid, no attempt was made to purify the product further.

*Reaction of* N-*Nitrosoaceto-2-naphthalide with Amyl 2-Naphthoate.*—(a) *Small scale. N*-Nitrosoaceto-2-naphthalide (28 g.) (Hey and Lawton, *loc. cit.*) in powder form was added in small portions during 6 hours to amyl 2-naphthoate (230 g.) stirred and maintained at 27—29°; nitrogen was evolved and a deep red colour developed. After being stirred for a further 2 hours, the mixture was left at room temperature during 18 hours, and the small amount of acetic acid formed removed by heating on a steam-bath under 13 mm. pressure. Unchanged amyl 2-naphthoate (212 g.) was recovered by distillation at 140—145°/0·015—0·02 mm. (bath temp. *ca.* 170°). [At the commencement of the distillation a small sublimate of naphthalene (0·6 g.) was obtained.] The dark reddish-brown residue was subjected to distillation under a pressure of $10^{-4}$ mm. An orange-red viscous syrup (17 g.) distilled slowly at 170—180° (bath temp.). This product, which was sparingly soluble in light petroleum, moderately so in alcohol, and very soluble in acetone and ether, could not be crystallised and analysis indicated that it was a mixture (Found : C, 82·9; H, 6·6%).

(b) *Large scale.* For the preparation of larger amounts it was found convenient to reduce the excess of amyl 2-naphthoate. *N*-Nitrosoaceto-2-naphthalide (72 g.) was added during 12 hours to stirred amyl 2-naphthoate (497 g.) maintained at 27—29°. The solution was stirred for 12 hours, and a further amount of nitroso-compound (40 g.) added during 8 hours at the same temperature. After standing for 24 hours, unchanged ester (424 g.) was recovered as before. The residue (136 g.) was distilled in portions of 30 g. over a free flame under 0·02 mm. pressure, yielding an orange-red distillate (63 g.) suitable for proceeding to the next step in the synthesis. Failure to distil the product at this stage led to lower and inconsistent yields of 1 : 2 : 5 : 6-dibenzfluorenone.

1 : 2'-*Dinaphthyl-2-carboxylic Acid* (III; R = H) *and* 1 : 2'-*Dinaphthyl*-x-*carboxylic Acid.*—The above orange-red syrup (63 g.) was refluxed for 2 hours with alcoholic potassium hydroxide (550 c.c. of 10%). A small amount of unidentified solid separated; this was removed, and the dark brown filtrate concentrated, poured on ice, and acidified with hydrochloric acid. The resinous solid was collected, washed with water, and dissolved in glacial acetic acid (100 c.c.). On standing for 3 days brownish crystalline acid *A* (10 g.), m. p. 198—205°, separated; it was collected and washed with acetic acid (30 c.c.). The combined filtrate and washings, after concentration to smaller bulk (65 c.c.) and keeping for some days, yielded crystalline acid *B* (6·5 g.), m. p. 175—180°.

*Acid* A. After several recrystallisations from acetic acid (charcoal) the acid (1 : 2'-*dinaphthyl*-x-*carboxylic acid*) formed colourless plates, m. p. 231—232° after slight sintering at 225° (Found : C, 84·0; H, 4·2. $C_{21}H_{14}O_2$ requires C, 84·6; H, 4·7%). When heated under reflux for 3 hours in quinoline (6 c.c.) with copper chromite (0·15 g.), the acid (1·0 g.) underwent decarboxylation and gave 1 : 2'-dinaphthyl, m. p. 76°.

*Acid* B. After five recrystallisations from acetic acid (charcoal) the acid formed pale yellowish prisms, m. p. 204—205°, which on drying in a desiccator became white and opaque

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* (Note added, October 7th.) The suggested structure for the compound, m. p. 186—187°, has since been confirmed; no depression in m. p. was observed in admixture with a specimen of (IX), m. p. 186°, kindly supplied by Dr. R. Martin, who prepared it by fusion of 3 : 4 : 5 : 6-dibenzfluorenone with sodium and aluminium chlorides.

(Found: C, 84·2; H, 4·6%). Its constitution as 1 : 2′-*dinaphthyl*-2-*carboxylic acid* (III; R = H) follows from its ready conversion into 1 : 2 : 5 : 6-dibenzfluorenone (IV) (see below).

1 : 2 : 5 : 6-*Dibenzfluorenone* (IV).—(a) *From isolated* 1 : 2′-*dinaphthyl*-2-*carboxylic acid.* The acid (0·3 g.) isolated as above was heated on a steam-bath for 1¾ hours with a mixture of glacial acetic acid (2 c.c.) and sulphuric acid (2 c.c. of 80%). The mixture was diluted with water, and the red-brown precipitate collected, washed with water, dried, and recrystallised from ethyl acetate. 1 : 2 : 5 : 6-Dibenzfluorenone (0·22 g.) formed deep red, diamond-shaped plates, m. p. 164—165°, undepressed by admixture with a specimen (m. p. 164—165°) prepared by oxidation of 1 : 2 : 5 : 6-dibenzfluorene and kindly supplied by Prof. J. W. Cook.

(b) *Without isolation of the dinaphthylcarboxylic acids.* The distilled product (17 g.) from the reaction between *N*-nitrosoaceto-2-naphthalide and amyl 2-naphthoate was hydrolysed in the manner above described, and the resinous solid dissolved in glacial acetic acid (60 c.c.). Sulphuric acid (100 c.c. of 80%) was added, and the mixture heated on the steam-bath with occasional shaking for 1½ hours, then poured into ice-water (1 l.) with stirring. The solid was collected and stirred with sodium hydroxide solution (250 c.c. of 2%) at room temperature. The filter residue was dissolved in chloroform (350 c.c.), and the extract freed from traces of acidic material by two washings with sodium hydroxide solution (2%), dried, and evaporated. The dark brown solid obtained (5·5 g.), recrystallised from ethyl acetate, gave diamond-shaped red plates (3 g.), m. p. 158—160°, raised by further recrystallisation to 165°, undepressed by authentic 1 : 2 : 5 : 6-dibenzfluorenone (Found: C, 90·4; H, 4·5. Calc. for $C_{21}H_{12}O$: C, 90·0; H, 4·3%).

1 : 2 : 5 : 6-*Dibenzfluorene* (V).—The ketone (IV) (2 g.) and aqueous hydrazine hydrate (8 c.c. of 50%) were heated together in a sealed tube at 200° for 6 hours. The dark-coloured solid product on crystallisation from ethyl acetate gave brownish-yellow plates, m. p. 172—173°. The colour was not removed by recrystallisation alone, but sublimation at $120°/10^{-4}$ mm., followed by crystallisation from ethyl acetate, gave 1 : 2 : 5 : 6-dibenzfluorene in colourless plates, m. p. 174—175°, undepressed on admixture with a specimen (m. p. 171—172°) kindly supplied by Prof. J. W. Cook.

*Reaction of* N-*Nitrosoaceto*-2-*naphthalide with Amyl* 1-*Naphthoate.*—*N*-Nitrosoaceto-2-naphthalide (28 g.) (Hey and Lawton, *loc. cit.*) in powder form was added in small amounts during 10 hours to amyl 1-naphthoate (125 g.) stirred and maintained at 27—29°. Nitrogen was evolved and after stirring overnight at room temperature the acetic acid formed during the reaction was removed by heating on a steam-bath under 13 mm. pressure. Unchanged amyl 1-naphthoate (103 g.) was recovered by distillation at 135—145°/0·02 mm. (bath temp. *ca.* 150—160°). The remaining deep red tarry resin (34 g.) was distilled under $10^{-4}$ mm. (bath temp. *ca.* 180°). The distillate (16 g.), a viscous red-brown syrup, was sparingly soluble in light petroleum, moderately so in alcohol, and very soluble in acetone and ether, but could not be crystallised.

1 : 2 : 7 : 8-*Dibenzfluorenone.*—The above red viscous distillate (16 g.) was hydrolysed with alcoholic potassium hydroxide (160 c.c. of 10%) in the manner already described for the product of reaction between *N*-nitrosoaceto-2-naphthalide and amyl 2-naphthoate. The mixture of crude acids (14·5 g.) so obtained was dissolved in acetic acid (50 c.c.), sulphuric acid (66 c.c., *d* 1·84, diluted with 16 c.c. of water) added, and the mixture heated on the steam-bath for 2 hours. The product was poured into ice-water (500 c.c.), and the ochre-brown precipitate together with some solid resin collected, washed, and stirred with 2% sodium hydroxide solution (300 c.c.). With a view to extracting undissolved solid, chloroform was added, but it caused separation of insoluble solid at the interface. The extraction was therefore not proceeded with, the solid in suspension being removed by filtration and the chloroform then separated from the aqueous layer.

The filtered solid (*ca.* 3·0 g.) was heated with acetic acid (*ca.* 60 c.c.) and, after cooling, insoluble solid (0·8 g.) (A) removed by filtration and crystallised from pyridine. 1 : 2 : 7 : 8-Dibenzfluorenone (0·6 g.) separated in orange-brown plates, m. p. 261—263°. A further crystallisation from the same solvent (charcoal) raised the m. p. to 265—266°, undepressed in admixture with a specimen, m. p. 263·5—265°, kindly supplied by Dr. R. Martin (Found: C, 90·3; H, 4·4. Calc. for $C_{21}H_{12}O$: C, 90·0; H, 4·3%). With concentrated sulphuric acid the ketone gave a crimson colour.

The chloroform extract, after drying and removal of the solvent, gave an oily brown solid (4·0 g.), which was crystallised from ethyl acetate. 1 : 2 : 7 : 8-Dibenzfluorenone (*ca.* 0·15 g.) was separated and the mother-liquor deposited a yellow-brown crystalline solid (0·5 g.), which after repeated crystallisation yielded pale yellow needles (0·15 g.), m. p. 182—183° (Found: C, 79·9, 81·5; H, 4·4, 4·6%).

1 : 2 : 7 : 8-*Dibenzfluorene.*—1 : 2 : 7 : 8-Dibenzfluorenone (0·2 g.) and hydrazine (2 c.c. of 50%) were heated together in a sealed tube at 200° for 6 hours. The red-brown crystalline solid was collected and crystallised several times from ethyl acetate (charcoal). 1 : 2 : 7 : 8-Dibenzfluorene separated in colourless plates, m. p. 230—231° (literature, m. p. 234°).

1 : 2′-*Dinaphthylcarboxylic Acid*, m. p. 206—207°.—The acetic acid mother-liquor from (A) after concentration deposited 1 : 2′-*dinaphthylcarboxylic acid* (*ca.* 1·5 g.). Recrystallisation from acetic acid (charcoal) yielded the acid in small colourless plates, m. p. 206—207° (Found : C, 84·9; H, 4·9. $C_{21}H_{14}O_2$ requires C, 84·6; H, 4·7%).

By heating under reflux for 10 hours with quinoline (6 c.c.) and copper bronze (0·1 g.) the acid (0·9 g.) was decarboxylated to 1 : 2′-dinaphthyl, m. p. 77—78·5°, undepressed by the specimen obtained by decarboxylation of the acid, m. p. 231—232°, isolated during the preparation of 1 : 2 : 5 : 6-dibenzfluorenone.

*Reaction of* N-*Nitrosoaceto*-1-*naphthalide with Amyl* 2-*Naphthoate.*—*N*-Nitrosoaceto-1-naphthalide (cf. Haworth and Hey, J., 1940, 361) was prepared from aceto-1-naphthalide, nitrosyl chloride being used, in an exactly similar manner to the corresponding 2-compound (Hey and Lawton, *loc. cit.*). The freshly prepared dry nitroso-compound (29 g.) was added in powder form during 6 hours to amyl 2-naphthoate (200 g.), stirred and maintained at 27—30°. After a further 12 hours' stirring, acetic acid was removed by heating on a steam-bath under 13 mm. pressure. The excess of amyl 2-naphthoate (188 g.) was recovered by distillation under reduced pressure (b. p. 140—145°/0·015—0·02 mm.). The deep red, resinous residue (28 g.) was subjected to distillation under $10^{-4}$ mm. pressure (bath temp. *ca.* 180°). A red viscous syrup (11 g.) was obtained together with a sublimate of crystalline azo-compound which was not examined.

3 : 4 : 5 : 6-*Dibenzfluorenone.*—The distillate (11 g.) was hydrolysed with alcoholic potassium hydroxide (100 c.c. of 10%) in the usual manner, and the crude resinous acid (9·5 g.) dissolved in acetic acid (40 c.c.) and heated on the steam-bath for 1½ hours with sulphuric acid (48 c.c., *d*, 1·84, diluted with 12 c.c. of water). The product was poured into ice-water (1 l.), and the precipitated solid collected, washed, and digested with cold 2% sodium hydroxide solution (*ca.* 300 c.c.). The small amount of residual solid was extracted with chloroform, and the chloroform solution washed with sodium hydroxide (2% soln.) and water and dried (sodium sulphate). Removal of the chloroform left a deep yellow-brown resin (1·4 g.), which was dissolved in benzene (50 c.c.) and passed through a column of aluminium oxide (20 cm. in length, 2 cm. in diam.). The column was washed with benzene (100 c.c.), and the filtrates collected, concentrated (to 20 c.c.), and again passed through a column of aluminium oxide (27 cm. × 2 cm.). The column was washed with benzene, and two fractions collected : I, washed with 120 c.c. of benzene; the residue after removal of solvent was a red resin (0·4 g.). II, washed with 100 c.c. of benzene; the residue after removal of solvent was an orange-brown resin (0·7 g.).

Fraction I, crystallised from ethyl acetate, yielded 3 : 4 : 5 : 6-dibenzfluorenone (50 mg.) in red prisms, m. p. 222—223°, undepressed in admixture with a specimen kindly supplied by Dr. R. Martin (Found : C, 90·2; H, 4·3. Calc. for $C_{21}H_{12}O$ : C, 90·0; H, 4·3%). With concentrated sulphuric acid it gave a deep orange colour.

Fraction II, crystallised several times from ethyl acetate, gave yellow needles (0·2 g.), m. p. 186—187° (Found : C, 89·4; H, 4·3. $C_{21}H_{12}O$ requires C, 90·0; H, 4·3%). With sulphuric acid an orange-red colour was obtained.

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