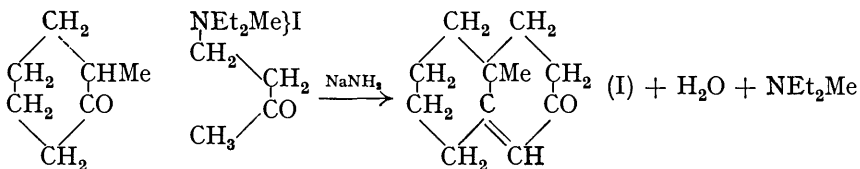


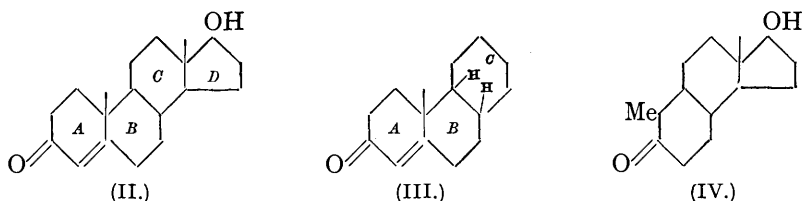
73. Experiments on the Synthesis of Substances related to the Sterols.
Part XXX.

By SIR ROBERT ROBINSON and F. WEYGAND.

The method of Du Feu, McQuillin, and Robinson (Part XIV, J., 1937, 53; cf. Rapson and Robinson, J., 1935, 1285) is essentially the condensation of the metho-salt of a β -dialkylamino-ketone with a cyclic ketone and it was shown that 2-methyl-cyclohexanone affords (I) as the main product in the case illustrated below.



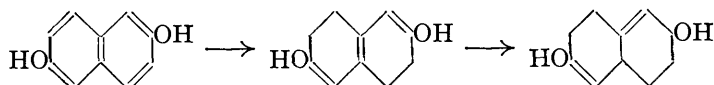
The new ring is constituted like one of the terminal nuclei of testosterone (II) and we have carried the development a stage further by applying the synthesis to 1-methyl-2-decalone. The product was proved to be (III) by degradation to phenanthrene



and 2-hydroxyphenanthrene. There is accordingly little doubt that the synthesis of testosterone could be effected if the intermediate (IV) were available in the correct stereoisomeric modification. Other experiments described in this communication were made with the object of introducing a reactive group in ring C and are of a preliminary nature.

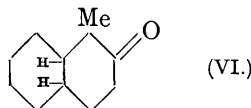
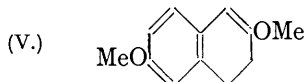
The condensation of ethyl acetoacetate with 1 : 5-dihydroxynaphthalene has been studied because the dicoumarin has a molecular shape and disposition of oxygen atoms that have some resemblance to the corresponding features of the sex hormones.

THE preparation of 1-methyl-2-naphthol by reduction of methylenedinaphthol (Fries and Hübner, *Ber.*, 1906, 39, 439) was found to be unsatisfactory in its original form, but consistent results are obtainable by use of the modification described in the experimental section. An alternative procedure which may be of value in the case of less accessible intermediates is the catalytic reduction of 2-hydroxy-1-naphthaldehyde. The full reduction of 1-methyl-2-naphthol was effected by hydrogen at 3 atms. in acetic acid solution in the presence of Adams's catalyst. The resulting 1-methyl-2-decalol is doubtless a mixture of stereoisomerides, but these are probably all derivatives of *cis*-decalin because reduction in acetic acid solution is known to promote the formation of *cis*-2-decalols from β -naphthol (cf. Hüchel, Mentzel, Brinkmann, and Kamenz, *Annalen*, 1926, 451, 109). In confirmation it may be mentioned that the hydrogenation of 2 : 6-dihydroxynaphthalene under similar conditions afforded *cis*-2-decalol, m. p. 104°. This elimination of one hydroxyl group is an indication that the group C=C-C(OH) is produced in an intermediate stage and perhaps by way of the steps :



2 : 6-Dimethoxynaphthalene and 2 : 6-diacetoxynaphthalene also gave deoxygenated

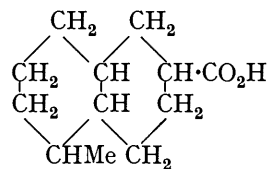
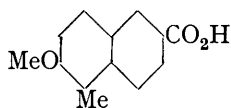
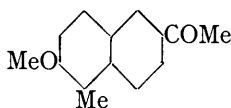
products on catalytic reduction; sodium and *isoamyl* alcohol reduced the dimethyl ether to a *dihydro*-derivative, probably (V).



Oxidation of 1-methyl-2-decalol by means of chromic acid afforded 1-methyl-(*cis*)-2-decalone (VI), which, assuming the *cis*-decalin configuration, might exist in two stereoisomeric forms. The ketone was purified by way of a crystalline *semicarbazone* and therefore in all probability is a pure substance. Under the conditions of the condensation to a tricyclic ketone the labile $-\text{CHMe}\cdot\text{CO}-$ group will certainly assume its more stable arrangement, which by analogy will be that in which the methyl group is *trans* with respect to the non-oxygenated cyclohexane ring. It would not be safe, however, to premise that this arrangement persists when a second carbon atom is attached to the 1-position, because the methyl group will "sit on the fence" in a neutral position in the ion of the enolic form of the ketone and may fall either way.

Hence the *ketone* (III) obtained from (VI) by the method indicated in the summary (above) may be a mixture of two stereoisomerides and if it is a pure substance there is no sound indication of the disposition of the methyl group relative to ring C. Dehydrogenation of (III) to phenanthrene and 2-phenanthrol was effected by heating with selenium.

Acetylation of 2-methoxy-1-methylnaphthalene by means of the Friedel-Crafts reaction furnishes an excellent yield of 6-methoxy-5-methyl-2-acetonaphthone (VII), from which the corresponding β -naphthoic acid (VIII) is readily obtained by oxidation with sodium hypochlorite. On catalytic hydrogenation of the related phenolic acid the hydroxyl group was eliminated and the *methyldecahydro-2-naphthoic acid* (IX) was produced.



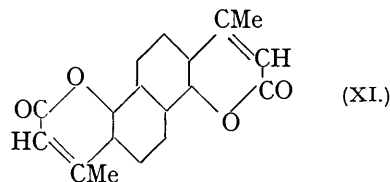
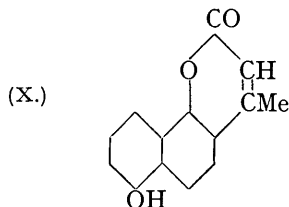
(VII.)

(VIII.)

(IX.)

These observations on the reduction of β -naphthols substituted in position 6 suggested that the desired intermediates must be acquired by nuclear synthesis, and some progress in this direction is recorded in the next paper.

The condensation of 1:5-dihydroxynaphthalene with ethyl acetoacetate was effected by means of alcoholic hydrogen chloride and irrespective of the amount of the ester employed the sole product was (X). The introduction of the second α -pyrone ring is possible but difficult. The *dicoumarin* (XI) is obtained when (X) is heated at 120° with ethyl acetoacetate and sulphuric acid.



EXPERIMENTAL.

1-Methyl-2-naphthol.—A mixture of β -naphthol (100 g.), water (500 c.c.), potassium hydroxide (120 g.), and aqueous formaldehyde (50 c.c. of 40%) was heated for an hour on the steam-bath; the formation of methylenedinaphthol was then complete, as was shown by the negative chloroform reaction (β -naphthol gives a blue coloration when heated with chloroform and aqueous alcoholic sodium hydroxide). Zinc (250 g.) was introduced with stirring and followed by the gradual addition of a solution of cuprammonium nitrate (copper nitrate, 20 g.; water, 30 c.c.;

and enough ammonia to give a clear solution). Heptanol was added to prevent frothing and if the reaction became too violent it was controlled by cooling. After 1—2 hours the mixture was transferred to a copper flask, and refluxed for 14—16 hours. The warm liquid was filtered (pump), and the zinc residue washed with aqueous sodium hydroxide (150 c.c. of 10%). After addition of formaldehyde solution (40 c.c. of 40%) the solution was heated for an hour on the steam-bath. Zinc (200 g.) and cuprammonium solution (20 g. of copper nitrate) were again added with stirring and heating on the steam-bath and after 2 hours the mixture was refluxed for 14—16 hours in the copper flask. After filtration the zinc residue was washed with aqueous sodium hydroxide (150 c.c. of 10%), formaldehyde (40 c.c. of 40%) added, and the mixture heated for an hour on the steam-bath. It was not found worth while to carry out a third reduction and condensation. The cooled solution was acidified with hydrochloric acid, and the precipitate collected, dried, and distilled, b. p. 180°/12 mm.; m. p. 109—110° after recrystallisation from benzene-light petroleum (b. p. 40—60°) (yield, 45—55 g.).

If 2-methoxy-1-methylnaphthalene was required, the solution was not acidified but methylation was effected by the gradual addition of methyl sulphate (150 c.c.) and enough aqueous sodium hydroxide (30%) to keep the solution always alkaline. The product, isolated in the known manner, had b. p. 145—150°/12 mm., m. p. 38—40° (yield, 40—50 g.).

1-Methyl-2-decalol.—1-Methyl-2-naphthol (10 g.) in acetic acid (40 c.c.) together with platinum oxide (1.5 g.) was shaken under hydrogen (3—4 atms.). After 20 hours absorption of hydrogen ceased (about 7 mols. taken up). The solvent was evaporated under diminished pressure, and the oily residue shaken with *n*-sodium hydroxide (30 c.c.) and light petroleum (30 c.c., b. p. 40—60°). The dried solution was evaporated, and the residue distilled; the main fraction had b. p. 121—123°/16 mm., $n_D^{19.5}$ 1.5000 (yield, 7.0 g.) (Found: C, 78.6; H, 11.9. $C_{11}H_{20}O$ requires C, 78.5; H, 12.0%).

1-Methyl-2-decalone (VI).—1-Methyl-2-decalol (2.9 g.) was added to a solution of potassium dichromate (3.5 g.) in water (18 c.c.) and concentrated sulphuric acid (3 c.c.) and vigorously stirred; the temperature rose to 65°. After cooling to 55°, the mixture was kept for 10 minutes at that temperature and then allowed to cool. The ketone was isolated by means of ether and directly converted into its semicarbazone (yield, 1.75 g. of ketone, calc. from semicarbazone). The *semicarbazone* crystallised from aqueous alcohol in bunches of needles, m. p. 185—191° (Found: C, 64.6; H, 9.4; N, 18.8. $C_{12}H_{21}ON_3$ requires C, 64.5; H, 9.5; N, 18.9%).

Hydrolysis of the semicarbazone (10 g.) was effected by boiling for 30 minutes with a solution of oxalic acid (50 g., cryst.) in water (175 c.c.). The ketone, isolated in the usual way, had b. p. 117—120°/15 mm., n_D^{19} 1.4898.

The 2:4-dinitrophenylhydrazone, purified by filtration of a benzene solution through alumina, crystallised from each alcohol in long, slender needles, m. p. 144—146° (Found: C, 59.0; H, 6.4; N, 16.2. $C_{17}H_{22}O_4N_4$ requires C, 58.9; H, 6.4; N, 16.2%).

Semicarbazone of 2-Keto-12-methyl- $\Delta^{1:11}$ -dodecahydrophenanthrene (III).—A mixture of 1-methyl-2-decalone (6.5 g.), dry ether (20 c.c.), and powdered sodamide (3.0 g.) was stirred at 20° for 6 hours under nitrogen. A solution of 4-diethylaminobutan-2-one methiodide (23 g.) in absolute alcohol (20 c.c.) was then added, and stirring continued at room temperature for 3 hours; the mixture was then refluxed for 3 hours. Water was added to the cooled solution with agitation, and the ethereal layer separated, dried with sodium sulphate, and distilled. The fraction (2.8 g.), b. p. up to 126°/16 mm., consisted of the unchanged methyldecalone; that having b. p. 126—190°/16 mm. (1.6 g.) afforded a *semicarbazone* (0.7 g.), which, recrystallised from dioxan-alcohol, formed small needles (0.5 g.), m. p. 225—230° (decomp.) (Found: C, 69.9; H, 8.9; N, 15.6. $C_{16}H_{25}ON_3$ requires C, 69.7; H, 9.2; N, 15.3%).

Dehydrogenation.—The above semicarbazone (0.4 g.) was refluxed for 2 hours with a solution of oxalic acid (2.5 g., cryst.) in water (10 c.c.). The ketone formed was isolated and heated with selenium (1.0 g.) for 16 hours at or about 340°. The melt was extracted with hot benzene, the solvent removed, and the residue sublimed at 0.02 mm. A substance (A) sublimed at a bath-temperature of 90—100° and a second substance (B) sublimed at 160° (bath). The two substances occurred in different zones of the tubular receiver and could easily be separated. (A) (30 mg.) was insoluble in aqueous alkali and proved to be phenanthrene; it crystallised from light petroleum (b. p. 40—60°) in colourless leaflets, m. p. 86—89°, 90—92° after recrystallisation, 92—94° when mixed with phenanthrene (m. p. 95—96°). If the original ketone had been an anthracene derivative, the hydrocarbon produced might have been anthracene, m. p. 216°, or 9-methylanthracene, yellowish-green crystals, m. p. 81°.

The product (B) (21 mg.) was soluble in aqueous sodium hydroxide and was precipitated when the solution was acidified. Crystallised from benzene-light petroleum, it had m. p.

164—164.5°. A sample of 2-hydroxyphenanthrene was prepared by fusion of phenanthrene-2-sulphonic acid with potassium hydroxide. It had m. p. 163—164° and a mixture of the two specimens had m. p. 163—163.5°. The colourless leaflets had the same superficial characters. 2-Hydroxyphenanthrene (Werner and Kunz, *Ber.*, 1901, **34**, 2524) is stated to melt at 168° (corr.); the above m. p.'s are uncorrected.

1: 1'-*Methylenebis-2-hydroxy-6-methoxynaphthalene*.—This substance was prepared because it is a possible intermediate for 2-hydroxy-6-methoxy-1-methylnaphthalene.

A mixture of 2-hydroxy-6-methoxynaphthalene (3.3 g.), aqueous formaldehyde (1 c.c. of 40%) (a further 1 c.c. was added after 30 minutes), and *N*-sodium hydroxide (40 c.c.) was heated on the steam-bath for an hour. The product gave no coloration with chloroform and aqueous alcoholic sodium hydroxide. It was isolated by acidification and crystallisation from alcohol; m. p. 202° (Found: C, 76.8; H, 5.4. $C_{23}H_{20}O_4$ requires C, 76.6; H, 5.6%). When the condensation was carried out in acetic acid solution, the product was always coloured, probably by a dinaphthapyrylium salt.

2: 6-*Dihydroxy-1-naphthaldehyde*.—This substance has been described by Gattermann (*Annalen*, 1907, **357**, 343) as yellow needles, m. p. 185—190° (decomp.). The convenient method of Adams (*J. Amer. Chem. Soc.*, 1923, **45**, 2375) is satisfactory in this case.

Hydrogen chloride was passed during 30 minutes into a mixture of technical 2: 6-dihydroxynaphthalene (15 g.), zinc cyanide (25 g.), and benzene (80 c.c.) cooled in ice and salt; the temperature was then raised to, and kept for 2½ hours at, 40—45° with occasional introduction of hydrogen chloride. The cooled mixture was stirred for 1 hour with water (70 c.c.) and concentrated hydrochloric acid (30 c.c.) and then boiled for 1 hour. On cooling, the aldehyde crystallised from both layers; recrystallised from aqueous alcohol, it had m. p. 186—189° (decomp.) (yield, 10.7 g.).

The intention to reduce this aldehyde to 2: 6-dihydroxy-1-methylnaphthalene was abandoned when it was found that deoxygenation of 2: 6-dihydroxynaphthalene occurs in the course of its hydrogenation. However, 2-hydroxy-1-naphthaldehyde was reduced as a model and the following method gave an excellent yield. A solution of the hydroxy-aldehyde (5 g.) in acetic acid (20 c.c.) was dropped into boiling acetic acid (100 c.c.) and copper-coated zinc dust (50 g.) during 1½ hours. The mixture was then refluxed for 1 hour, and the product worked up in the usual way; m. p. 108—109°. There was a small by-product of higher m. p.

Reduction of 2: 6-Dihydroxynaphthalene.—The conditions were those used for the reduction of 2-hydroxy-1-methylnaphthalene [3.0 g. of the dihydroxynaphthalene in 40 c.c. of acetic acid; two portions (0.5 g. each) of platinum oxide]. The product was isolated in the known manner and crystallised from light petroleum (b. p. 60—80°); m. p. 103.5—104.5° (Found: C, 77.6; H, 12.0. Calc. for $C_{10}H_{18}O$: C, 77.9; H, 11.8%). The substance is therefore *cis*- β -decalol, m. p. 104°. In the above experiment 2.3 l. of hydrogen were absorbed, corresponding to saturation of five double bonds (calc., 2.2 l.). *cis*- β -Decalol was, however, the only isolable product when the reduction was interrupted after 1.7 l. of hydrogen had been absorbed. Analysis of the products showed that 2: 6-dimethoxynaphthalene suffered loss of a methoxy-group on hydrogenation in the presence of Adams's catalyst, and deoxygenation also occurred in the reduction of 2: 6-diacetoxynaphthalene.

2: 6-*Dimethoxydihydronaphthalene* (V, or $\Delta^{2:3}$).—A mixture of 2: 6-dimethoxynaphthalene (4 g.) (m. p. 150°), *iso*amyl alcohol (100 c.c.), and cut sodium (10 g.) was refluxed for 2 hours. *iso*Amyl alcohol (50 c.c.) was then added, and refluxing continued for 5 hours more. Water was added, and the undried organic layer distilled; the residue solidified on cooling. The product, crystallised from alcohol, had m. p. 83—84°, unchanged by recrystallisation (Found: C, 76.2; H, 7.3; OMe, 32.2. $C_{12}H_{14}O_2$ requires C, 75.7; H, 7.4; 2OMe, 32.6%). This substance appears to be homogeneous and it is hoped that an opportunity will be found to return to its investigation in greater detail.

6-*Methoxy-5-methyl-2-acetonaphthone* (VII).—A direct proof of the constitution of this substance cannot be given, but the conditions employed are those under which 2-methoxynaphthalene is acetylated in position 6 (Haworth and Sheldrick, *J.*, 1934, 864; cf. Robinson and Rydon, *J.*, 1939, 1395) and in other work in this laboratory it has been found that 1-chloro-2-methoxynaphthalene behaves similarly.

Finely powdered aluminium chloride (130 g.) was added to nitrobenzene (600 c.c.) with stirring and cooling in ice; 2-methoxy-1-methylnaphthalene (118 g.) and acetyl chloride (70 g.) were then successively introduced with continued agitation and cooling. After a short time the mixture was allowed to reach room temperature and kept for 48 hours. It was decomposed by ice and concentrated hydrochloric acid, diluted with chloroform (300 c.c.), and the organic

layer washed several times with water, separated, and steam-distilled. The residue in the flask crystallised and was purified by recrystallisation (charcoal) from aqueous alcohol (yield, 70—80%). The *substance* crystallised from alcohol in colourless leaflets, m. p. 97—98° (Found : C, 78.5; H, 6.5. $C_{14}H_{14}O_2$ requires C, 78.5; H, 6.6%).

The 2 : 4-dinitrophenylhydrazone was sparingly soluble in the usual organic solvents, and formed red prisms, m. p. 282—283°, from nitrobenzene.

The *oxime*, obtained by the pyridine method, crystallised from alcohol in colourless needles, m. p. 171° (Found : C, 72.9; H, 6.7; N, 5.9. $C_{14}H_{15}O_2N$ requires C, 73.3; H, 6.6; N, 6.1%).

Demethylation of the ketone (5.0 g.) was effected by boiling for 2 hours with acetic acid (50 c.c.) and hydriodic acid (10 c.c., *d* 1.7). After addition of sulphurous acid the precipitate was dissolved in aqueous sodium hydroxide, reprecipitated, dried, and sublimed in a high vacuum. The sublimate, crystallised from alcohol, had m. p. 164° (Found : C, 78.1; H, 6.2. $C_{13}H_{12}O_2$ requires C, 78.0; H, 6.0%). The oxime of this *6-hydroxy-5-methyl-2-acetonaphthone* gave a non-phenolic base on catalytic reduction, another example of the elimination of hydroxyl in a 6-substituted β -naphthol.

6-Methoxy-5-methyl-2-naphthoic Acid (VIII).—A suspension of finely powdered methoxy-methylacetonaphthone (5 g.) in aqueous sodium hypochlorite (50 c.c. of 18%) and *n*-sodium hydroxide (400 c.c.) was stirred on the steam-bath. When the temperature reached 95°, further hypochlorite solution (20 c.c.) was added and after a short time the solution was boiled for 10 minutes. The sodium salt of the new acid soon began to crystallise from the hot liquid. Boiling water was added to redissolve the salt and sulphur dioxide was passed through the cooled solution. The precipitate was collected and crystallised from acetic acid, forming white prisms (4.1 g.). A portion sublimed in a high vacuum had m. p. 266—267° (Found : C, 72.3; H, 5.5. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.6%). This *acid* is sparingly soluble in the usual organic solvents, moderately readily soluble in hot acetic acid, and more readily soluble in hot dioxan.

Demethylation (of 4.0 g.) by a boiling mixture of acetic acid (50 c.c.) and hydriodic acid (16 c.c., *d* 1.7) was complete in 2 hours. The colourless prisms obtained from aqueous acetic acid were sublimed in a high vacuum; m. p. 247—249° (Found : C, 71.4; H, 5.0. $C_{12}H_{10}O_3$ requires C, 71.3; H, 5.0%).

1-Methyldecalin-6-carboxylic Acid (IX).—The last-described *6-hydroxy-5-methyl-2-naphthoic acid* (5.0 g.), dissolved in acetic acid (40 c.c.), was shaken under hydrogen with Adams's catalyst (2.0 g.) at 40°. Absorption of the gas ceased after 30 hours (2.1 l.; calc. for five double bonds, 2.8 l.). The product was distilled, b. p. 170°/12 mm.; the distillate at once crystallised completely. The *acid*, recrystallised from light petroleum (b. p. 40—60°), had m. p. 127—128° (Found : C, 73.4; H, 9.9. $C_{12}H_{20}O_2$ requires C, 73.4; H, 10.3%). All these troublesome eliminations of the β -naphtholic hydroxyl occurred with the use of a platinum oxide catalyst and it will certainly be worth while to explore the possibilities of the use of Raney nickel and copper chromite as well as to attempt full reduction in definite steps.

6'-Hydroxy-4-methyl-7 : 8-benzocoumarin (X).—Hydrogen chloride was led into a cooled mixture of 1 : 5-dihydroxynaphthalene (4.0 g.), ethyl acetoacetate (10 g.), and alcohol (40 c.c.), whereby the temperature rose to 30°. After 1½ hours the crystals had filled the solution. After a few hours' passage of the gas without cooling, the product was collected, washed with cold alcohol, and dried (4.9 g., and 0.3 g. on addition of water to the mother-liquor). The *substance* crystallised from pyridine in flat prisms, m. p. 299—302° (decomp.) (Found in material dried at 100°/0.5 mm. : C, 74.1; H, 4.4. $C_{14}H_{10}O_3$ requires C, 74.4; H, 4.5%). It is sparingly soluble in the usual organic solvents, soluble in cold aqueous sodium hydroxide to a yellow solution. It couples with diazo-salts to azo-compounds and gives a green coloration with chloroform and hot aqueous alcoholic sodium hydroxide. It sublimes on heating in a high vacuum. The condensation can also be effected (yield, 2.2 g. from 2 g. of the dihydroxynaphthalene) by means of an ethereal solution of aluminium chloride (Shah's reagent).

The *p*-nitrobenzoate, obtained by the action of *p*-nitrobenzoyl chloride in cold pyridine solution, crystallised from pyridine in elongated, lemon-yellow prisms; recrystallised from acetic acid, it had m. p. 262° (Found : C, 67.0; H, 3.6; N, 3.9. $C_{21}H_{13}O_6N$ requires C, 67.2; H, 3.5; N, 3.7%). This intensely yellow substance gives a colourless solution in hot acetic acid.

4 : 4'-Dimethyl-7 : 8 : 8' : 7'-coumarinocoumarin (XI).—Concentrated sulphuric acid (10 c.c.) was added to a mixture of hydroxymethylbenzocoumarin (5.0 g.), ethyl acetoacetate (10 c.c.), and sulphuric acid (10 c.c. of 70%). The mixture was heated (oil-bath at 120°) and during ½ hour two further portions of ethyl acetoacetate (10 c.c.) were added. The bath temperature was kept at 110° for 10 minutes, the product cooled, water added, and the solid washed with

dilute aqueous sodium hydroxide and crystallised from pyridine (500 c.c.). It sublimed at 290—300°/0.05 mm. and did not melt at 360° (Found : C, 74.5; H, 4.0. $C_{18}H_{12}O_4$ requires C, 74.0; H, 4.0%). The *dicoumarin* does not couple with diazo-salts; it is practically insoluble in the common organic solvents.

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