

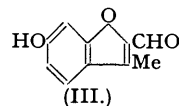
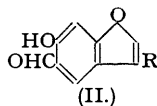
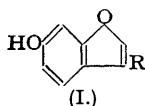
**457. *Furano-compounds. Part VII. A Synthesis of
2 : 3-Dihydropsovalene.***

By R. T. FOSTER, ALEXANDER ROBERTSON, and (in part) ANIS BUSHRA.

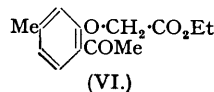
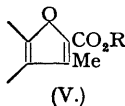
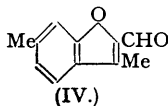
The product obtained by the application of Gattermann's aldehyde synthesis to 6-hydroxy-3-methylcoumarone has been shown to be the 2-formyl derivative. Attempts to prepare 6-hydroxy-2-carbethoxy-5-formylcoumarone required for the synthesis of psoralene were unsuccessful, but dihydropsovalene and its 3-methyl derivative have been synthesised from the requisite coumarans.

IN the course of synthetical experiments in this group of compounds, it has been established that the application of the Gattermann reaction for the synthesis of aldehydes to 3-methylcoumarones, having a free 2-position, invariably gives rise to the 2-formyl derivatives (*J.*, 1938, 306; 1939, 92, 1594; and unpublished work) and consequently it became clear that *o*-hydroxyaldehydes of the type (II) required as intermediates for the rational synthesis of furanocoumarins by the route employed in the case of *allobergapten* (Part IV, *J.*, 1939, 930) cannot be obtained by this procedure unless the 2-position of the coumarone ring is first protected by a group which can be conveniently eliminated at a later stage in the synthesis.

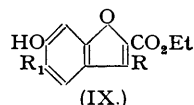
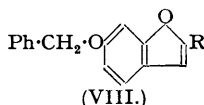
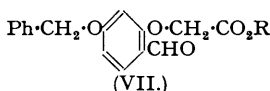
This conclusion was clearly at variance with the claims of Karrer and his co-workers (*Helv. Chim. Acta*, 1920, 3, 541) who, in the course of attempts to synthesise furanocoumarins of the bergapten type, applied the Gattermann reaction to 6-hydroxy- and to 6-hydroxy-3-methylcoumarone, obtaining products which they considered to have structures (II; R = H) and (II; R = Me). When it was found that the aldehydes gave the corresponding acrylic acids by the Perkin reaction but not the expected coumarins, these authors suggested that the failure of the latter acids to undergo cyclisation was due to their existence as *trans*-isomerides (compare Karrer and co-workers, *Helv. Chim. Acta*, 1921, 4, 718). Before proceeding with synthetical work on psoralene and related furanocoumarins it seemed desirable to re-examine the aldehydes obtained from (I; R = H) and (I; R = Me), more especially in view of the claim of Rây and his co-workers (*J.*, 1935, 813) that the acrylic acid obtained by the hydration of 3'-methylfuran(5' : 4' : 7 : 6)coumarin in ultraviolet light was identical with that synthesised by the Swiss workers from the aldehyde which they considered to have formula (II; R = Me).



In agreement with the earlier results obtained in these laboratories (*loc. cit.*), the aldehyde from 6-hydroxy-3-methylcoumarone (I; R = Me), which appears to be identical with that described by Karrer and his co-workers (*loc. cit.*), has been shown to have the structure (III), since on oxidation its *acetate* gave rise to 6-*acetoxy*-3-*methylcoumarone*-2-*carboxylic acid*, identical with the acetate of an authentic specimen of 6-hydroxy-3-methylcoumarone-2-carboxylic acid. Consequently, the acrylic acid and its methyl ether (Karrer and co-workers, *loc. cit.*) formed from the aldehyde (III) by Perkin's method is β -6-hydroxy-3-methylcoumarone-2-acrylic acid and its methyl ether. Unlike Karrer and his co-workers, we failed to obtain a crystalline product by application of the Gattermann reaction to 6-hydroxycoumarone (I; R = H) with or without zinc chloride or aluminium chloride as an auxiliary condensing agent (compare Part II, *J.*, 1939, 921). It seems probable that in our experiments the initial condensation product was the required aldimine but that the hydrolysis of the latter was accompanied by polymerisation of the resulting aldehyde (compare thiophen, Barger and Sasson, *J.*, 1938, 2600; and 4-hydroxycoumarone, Manjunath *et al.*, *Ber.*, 1939, 72, 93).

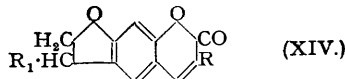
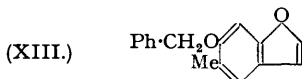
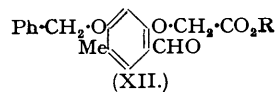
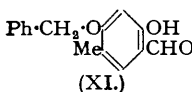
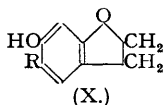


A further example of the behaviour of coumarones of the type (I) when subjected to Gattermann's aldehyde synthesis is seen in the case of 3 : 6-dimethylcoumarone which gives rise to 2-formyl-3 : 6-dimethylcoumarone (IV), the orientation of which is established by its oxidation to 3 : 6-dimethylcoumarone-2-carboxylic acid (V; R = H), identical with a specimen prepared by cyclisation of *ethyl 2-acetyl-5-methylphenoxyacetate* (VI) and hydrolysis of the resulting *ester* (V; R = Et). 3 : 6-Dimethylcoumarone-2-acetic acid, an analogue of pyrousnic acid, was synthesised from 2-formyl-3 : 6-dimethylcoumarone (IV) according to the general method (*J.*, 1938, 306).

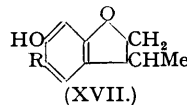
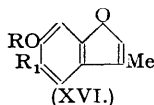
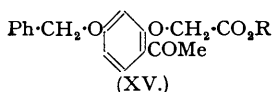


In deciding to attempt a synthesis of psoralene by the route employed for *allobergapten* (Part IV, *loc. cit.*), *i.e.* by way of the aldehyde (IX; R = H, R₁ = CHO), we expected to be able to prepare the latter compound by application of the Gattermann reaction to 6-hydroxy-2-carbethoxycoumarone (IX; R = R₁ = H), which was obtained by the cyclisation of the *phenoxyacetate* (VII; R = Et) with alcoholic sodium ethoxide and subsequent debenzoylation of the resulting *carbethoxycoumarone* (VIII; R = CO₂Et) by hydrogenolysis. It was found, however, that (IX; R = R₁ = H) as well as its homologue (IX; R = Me, R₁ = H), prepared in a similar way from the *ester* (XV; R = Et), failed to yield formyl derivatives when subjected to Gattermann's reaction or the usual variations of it. In connection with the hydrogenolysis

of (VIII; R = CO₂Et) with a palladium-charcoal catalyst it is noteworthy that, as in the case of 2-carbethoxy-6-benzyloxy-4-methoxycoumarone (Part IV, *loc. cit.*), the α -carbethoxy-group in (VIII; R = CO₂Et) inhibits the hydrogenation of the double bond of the furan residue. Moreover, in the present instance this inhibitory effect is sufficient to allow the hydrogenation of (VIII; R = CO₂Et) by means of Adams's platinum catalyst with the formation of 2-carbethoxy-6-hexahydrobenzyloxy coumarone, in which the retention of the furan ring is confirmed by the fact that this product gives the same intense sulphuric acid reaction as the parent substance (VIII; R = CO₂Et). Under the conditions employed, this platinum catalyst does not effect hydrogenolysis of benzyl ethers.

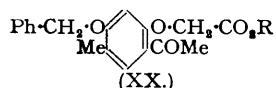
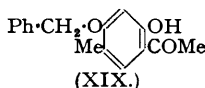
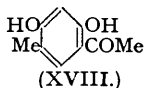


Having failed to obtain the required intermediate aldehyde, we abandoned for the present the project of synthesising psoralene by the route employed for *allobergapten* (*loc. cit.*) and turned our attention to a rational synthesis of its 2 : 3-dihydro-derivative (XIV; R = R₁ = H) which Späth and his co-workers (*Ber.*, 1936, 69, 1087) have shown can be dehydrogenated to yield psoralene. This objective was achieved as follows. 6-Benzyloxy coumarone (VIII; R = H) was prepared by cyclisation of 5-benzyloxy-2-formylphenoxyacetic acid (VII; R = H) with simultaneous decarboxylation of the resulting acid (VIII; R = CO₂H) and on hydrogenation gave rise to 6-hydroxycoumaran in good yield. The aldehyde obtained from the latter compound is shown to have the structure (X; R = CHO) because on reduction by Clemmensen's method it yielded 6-hydroxy-5-methylcoumaran (X; R = Me), identical with a specimen prepared from (XI) by way of the stages (XII; R = Et), (XII; R = H), and (XIII). The condensation of (X; R = CHO) with cyanoacetic acid followed by hydrolysis of the initial product gave rise to the acid (XIV; R = CO₂H, R₁ = H), and on decarboxylation the latter furnished dihydropsoalene (XIV; R = R₁ = H) which was dehydrogenated by being heated with palladium-black, yielding psoralene.



Similarly 3'-methyl dihydropsoalene (XIV; R = H, R₁ = Me) was synthesised from *ethyl 5-benzyloxy-2-acetylphenoxyacetate* (XV; R = Et) by way of the stages (XV; R = H), (XVI; R = CH₂Ph, R₁ = H), (XVII; R = H), (XVII; R = CHO), and (XIV; R = CO₂H, R₁ = Me).

In connection with the latter synthesis it may be noted that Karrer and Widmer (*Helv. Chim. Acta*, 1919, 2, 454) claim to have obtained 6-hydroxy-3-methylcoumaran (XVII; R = H), m. p. 96°, by reduction of 6-hydroxy-3-methylcoumarone (I; R = Me), m. p. 103°, with sodium and alcohol and from this reduction product to have prepared the aldehyde (XVII; R = CHO), m. p. 185°. Repeated attempts in this laboratory to reduce 6-hydroxy-3-methylcoumarone according to the directions of the Swiss workers gave only slightly impure starting material, m. p. 98—100°. On the other hand, hydrogenation of 6-benzyloxy-3-methylcoumarone (XVI; R = CH₂Ph, R₁ = H) gave rise to 6-hydroxy-3-methylcoumaran (XVII; R = H), m. p. 62°, which furnished the aldehyde (XVII; R = CHO), m. p. 74°. The orientation of the latter compound is established by the fact that on reduction it yields 6-hydroxy-3 : 5-dimethylcoumaran (XVII; R = Me), identical with a specimen obtained by simultaneous hydrogenation and debenylation of 6-benzyloxy-3 : 5-dimethylcoumarone (XVI; R = CH₂Ph, R₁ = Me). In our opinion the aldehyde, m. p. 185°, obtained in small yield by Karrer and his co-workers is clearly the 2-formylcoumarone (III), formed from unchanged (I; R = Me).



In the synthesis of (XVI; $R = \text{CH}_2\text{Ph}$, $R_1 = \text{Me}$) the ketone (XVIII) was converted into the *monobenzyloxy ether* (XIX), and on condensation with ethyl bromoacetate by the potassium carbonate-acetone method this ether (XIX) gave rise to the *phenoxy-ester* (XX; $R = \text{Et}$), which on hydrolysis furnished the *acid* (XX; $R = \text{H}$). Cyclisation of the latter compound by the standard procedure yielded the coumarone (XVI; $R = \text{CH}_2\text{Ph}$, $R_1 = \text{Me}$). The orientation of (XX; $R = \text{Et}$) and consequently of (XIX) follows from the successful conversion of the acid (XX; $R = \text{H}$) into a coumarone.

EXPERIMENTAL.

2-Carboethoxy-6-benzyloxy coumarone (VIII; $R = \text{CO}_2\text{Et}$).—Interaction of 2-hydroxy-4-benzyloxy-benzaldehyde (10 g.), ethyl bromoacetate (8.5 g.), and potassium carbonate (15 g.) in boiling acetone (100 ml.) during 3 hours gave *ethyl 5-benzyloxy-2-formylphenoxyacetate* (VII; $R = \text{Et}$) which formed needles (12 g.), m. p. 88°, from light petroleum (b. p. 60–80°) (Found: C, 68.7; H, 5.8. $\text{C}_{18}\text{H}_{18}\text{O}_5$ requires C, 68.8; H, 5.7%). On addition of alcoholic sodium ethoxide (from 0.75 g. of sodium and 50 ml. of alcohol) a solution of the foregoing ester (10 g.) in alcohol (175 ml.) became yellow and in the course of 5 minutes deposited a yellow amorphous solid which dissolved on dilution with water and was replaced by a crystalline precipitate of *ethyl 6-benzyloxy coumarone-2-carboxylate* (VIII; $R = \text{CO}_2\text{Et}$). Recrystallised from aqueous alcohol, this compound formed colourless plates (6.5 g.), m. p. 94°, having a violet, becoming blue-violet, sulphuric acid reaction (Found: C, 73.0; H, 5.5. $\text{C}_{18}\text{H}_{16}\text{O}_4$ requires C, 73.0; H, 5.4%). The yield of this product was not improved by the use of potassium ethoxide. Acidification of the aqueous alcoholic liquors with hydrochloric acid furnished *5-benzyloxy-2-formylphenoxyacetic acid* (VII; $R = \text{H}$) which separated from water in needles, m. p. 145° (Found: C, 67.2; H, 4.8. $\text{C}_{18}\text{H}_{14}\text{O}_5$ requires C, 67.1; H, 4.9%).

Debenzyloxylation of the ester (VIII; $R = \text{CO}_2\text{Et}$) (2 g.), dissolved in acetic acid (50 ml.), was effected with hydrogen and a palladium-charcoal catalyst (from 0.2 g. of palladium chloride and 2 g. of charcoal) in 15 minutes, and on isolation *6-hydroxy-2-carboethoxy coumarone* (IX; $R = \text{R}_1 = \text{H}$) formed colourless plates (1.2 g.), m. p. 156°, from aqueous alcohol (Found: C, 64.5; H, 5.0. $\text{C}_{11}\text{H}_{10}\text{O}_4$ requires C, 64.1; H, 4.9%). A solution of the compound in warm sulphuric acid became blue-violet and then purple. Formed by the pyridine method, the *acetate* was obtained in rectangular plates, m. p. 104°, from alcohol (Found: C, 62.7; H, 4.9. $\text{C}_{13}\text{H}_{12}\text{O}_5$ requires C, 62.9; H, 4.8%).

When 6-benzyloxy-2-carboethoxy coumarone (1 g.) was hydrogenated with a platinum oxide catalyst (0.1 g.) in acetic acid (30 ml.) during 2½ hours, a compound was obtained which appeared to be *2-carboethoxy-6-hexahydrobenzyloxy coumarone*, forming plates (0.5 g.), m. p. 91°, from alcohol (Found: C, 71.4; H, 7.3. $\text{C}_{18}\text{H}_{22}\text{O}_4$ requires C, 71.5; H, 7.3%). That the furano-system had not been hydrogenated was shown by the fact that the compound gave the same intense blue-violet sulphuric acid reaction as the parent substance.

Hydrolysis of 6-hydroxy-2-carboethoxy coumarone (5 g.) with 2N-aqueous sodium hydroxide (100 ml.) on the steam-bath for ½ hour gave 6-hydroxy-2-carboxy coumarone, m. p. 257–259°, after purification from water (compare Karrer *et al.*, *loc. cit.*), which yielded the *acetate*, forming rectangular prisms, m. p. 213°, from aqueous acetone (Found: C, 60.0; H, 3.8. $\text{C}_{11}\text{H}_8\text{O}_5$ requires C, 60.0; H, 3.6%). Decarboxylation of this acid (2 g.) in boiling quinoline (10 ml.) containing copper-bronze (2 g.) was complete in 10 minutes, and on isolation the resulting 6-hydroxy coumarone was purified by distillation in a high vacuum and then by crystallisation from light petroleum (b. p. 40–60°), forming long needles m. p. 56° (compare Karrer *et al.*, *loc. cit.*).

6-Hydroxy-5-formyl coumaran (X; $R = \text{CHO}$).—On being refluxed with acetic anhydride (100 ml.) and sodium acetate (25 g.) 5-benzyloxy-2-formylphenoxyacetic acid (VII; $R = \text{H}$) (10 g.) gave an oil which on distillation in a high vacuum furnished 6-benzyloxy coumarone (VIII; $R = \text{H}$) (6 g.), b. p. 140–142°/0.3 mm., m. p. 39°, having a cherry-red sulphuric acid reaction (Found: C, 80.3; H, 5.4. $\text{C}_{18}\text{H}_{12}\text{O}_2$ requires C, 80.4; H, 5.4%). Hydrogenation and simultaneous debenzyloxylation of this ether (3 g.), dissolved in acetic acid (50 ml.), with hydrogen and a palladium-charcoal catalyst gave 6-hydroxy coumaran (X; $R = \text{H}$) (1.5 g.), m. p. 60°, which furnished a *p-nitrobenzoate*, forming rectangular plates, m. p. 179°, from alcohol (Found: C, 62.8; H, 3.9; N, 5.1. $\text{C}_{15}\text{H}_{11}\text{O}_5\text{N}$ requires C, 63.2; H, 3.9; N, 4.9%) (compare Späth and co-workers, *Ber.*, 1936, **69**, 1087, who give the m. p. of 6-hydroxy coumaran as 61°).

Condensation of 6-hydroxy coumaran (2 g.) and hydrogen cyanide (2 ml.) was effected in ether (75 ml.) with zinc chloride (2 g.) and excess of hydrogen chloride. Next day the purple aldimine was isolated and hydrolysed with water (100 ml.) on the steam-bath for 20 minutes, giving the *5-aldehyde*, which formed colourless rectangular plates (2 g.), m. p. 113°, from aqueous alcohol and had a red-brown ferric reaction in alcohol (Found: C, 65.8; H, 5.1. $\text{C}_9\text{H}_8\text{O}_3$ requires C, 65.7; H, 4.9%). The 2:4-dinitrophenylhydrazones separated from ethyl acetate in red needles, m. p. 274° (Found: N, 16.2. $\text{C}_{15}\text{H}_{12}\text{O}_6\text{N}_4$ requires N, 16.3%).

2' : 3'-Dihydrofurano(4' : 5' : 6 : 7) coumarin (Dihydropsoralene) (XIV; $R = \text{R}_1 = \text{H}$). (With J. B. D. MACKENZIE).—A solution of the foregoing aldehyde (X; $R = \text{CHO}$) (1 g.) in 20% aqueous sodium hydroxide (10 ml.) was treated with aqueous cyanoacetic acid (7 ml. of Phelps and Tillotson's solution, *Amer. J. Sci.*, 1908, **26**, 267). Next day the sodium salt of the salicylidencyanoacetic acid was dissolved by addition of water (10 ml.) to the mixture, and the yellow product was precipitated with concentrated hydrochloric acid and boiled with *n*-hydrochloric acid (100 ml.) for ½ hour. On isolation the resulting *coumarin-3-carboxylic acid* (XIV; $R = \text{CO}_2\text{H}$, $R_1 = \text{H}$) formed almost colourless rectangular prisms (1.2 g.), m. p. 244° (decomp.), from ethyl acetate (Found: C, 62.2; H, 3.6. $\text{C}_{12}\text{H}_8\text{O}_5$ requires C, 62.1; H, 3.5%). A mixture of this acid (0.8 g.), copper-bronze (1 g.), and quinoline (4 ml.) was gently boiled (oil-bath) for 10 minutes, cooled, and diluted with ether, and the product was filtered off and washed with dilute hydrochloric acid, followed by aqueous sodium hydroxide and then water.

Evaporation of the dried ethereal solution left dihydropsovalene which, after sublimation in a high vacuum at 140—150°/0.1 mm., formed rectangular prisms, m. p. 200°, from alcohol (Found : C, 70.4; H, 4.4. Calc. for $C_{11}H_8O_3$: C, 70.2; H, 4.3%) (Späth *et al.*, *loc. cit.*, give m. p. 204°). An intimate mixture of dihydropsovalene (0.3 g.) and Willstätter palladium-black (0.3 g.) was kept at 170—180° for 11 hours. On isolation, the resulting psoralene was purified by sublimation in a vacuum and then by crystallisation from water, forming needles, m. p. 167° (compare Späth *et al.*, *loc. cit.*).

Application of the Perkin reaction to 6-hydroxy-5-formylcoumaran gave rise to a mixture containing β -6-acetoxycoumarone-5-acrylic acid, forming prismatic needles, m. p. 197°, from aqueous acetone (Found : C, 63.0; H, 4.8. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.8%), along with unchanged aldehyde and its acetate. The latter derivative was characterised by formation of the 2 : 4-dinitrophenylhydrazone, which separated from acetic acid in orange-red prisms, m. p. 266° (Found : C, 53.0; H, 3.8; N, 14.7. $C_{17}H_{14}O_7N_4$ requires C, 53.1; H, 3.9; N, 14.5%).

5-Benzylxy-2-formyl-4-methylphenoxyacetic Acid (XII; R = H).—The condensation of 4-methylresorcinol (9 g.) and hydrogen cyanide (8 ml.) in ether (200 ml.) was effected with hydrogen chloride, and the resulting aldime hydrolysed with water (200 ml.) on the steam-bath for $\frac{1}{2}$ hour, giving 5-methylresorcyraldehyde, which formed plates (7 g.), m. p. 146°, from benzene (compare Gattermann, *Annalen*, 1907, 357, 340). A mixture of this aldehyde (3 g.), benzyl bromide (3.7 g.), potassium carbonate (5 g.), and acetone (50 ml.) was refluxed for 4 hours. On isolation, the solid product was dissolved in ether (250 ml.), the solution was extracted with dilute aqueous sodium hydroxide (200 ml. \times 2), the combined extracts were acidified with dilute hydrochloric acid, and the precipitate collected, washed, and crystallised from dilute alcohol, giving 4-O-benzyl-5-methylresorcyraldehyde (XI) in colourless needles (1.5 g.), m. p. 65° (Found : C, 74.0; H, 6.0. $C_{18}H_{14}O_3$ requires C, 74.4; H, 5.8%). This compound gives a dark reddish-purple ferric reaction in alcohol.

Interaction of this aldehyde (2 g.), ethyl bromoacetate (1.5 g.), and potassium carbonate (3 g.) in boiling acetone (50 ml.) during 7 hours gave rise to ethyl 5-benzylxy-2-formyl-4-methylphenoxyacetate (XII; R = Et) which formed colourless prisms (2 g.), m. p. 93°, from dilute alcohol, having a negative ferric reaction (Found : C, 69.6; H, 6.0. $C_{18}H_{20}O_5$ requires C, 69.5; H, 6.1%). A solution of this ester (2 g.) in alcohol (30 ml.) and water (20 ml.) containing potassium hydroxide (2.5 g.) was refluxed for $\frac{1}{2}$ hour, the greater part of the alcohol was removed in a vacuum, and the residual liquor was cooled and acidified with dilute hydrochloric acid. Crystallisation of the resulting precipitate from ethyl acetate-light petroleum (b. p. 60—80°) gave the acid (XII; R = H) in colourless needles (1.5 g.), m. p. 185° (Found : C, 67.9; H, 5.2. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

6-Hydroxy-5-methylcoumaran (X; R = Me).—(A) A mixture of the foregoing acid (2 g.), sodium acetate (5 g.), and acetic anhydride (20 ml.) was refluxed (oil-bath) for $\frac{1}{2}$ hour, and the mixture diluted with water (200 ml.). Three days later the product was collected, washed with aqueous sodium hydrogen carbonate, dried, and distilled in a high vacuum, giving 6-benzylxy-5-methylcoumarone (XIII), b. p. 110°/0.03 mm., which formed colourless needles (1.0 g.), m. p. 38°, from 50% acetic acid, having a port-wine sulphuric acid reaction (purple in warm acid) (Found : C, 80.4; H, 6.0. $C_{18}H_{14}O_2$ requires C, 80.7; H, 5.8%). Hydrogenation of this compound (1 g.), dissolved in acetic acid (150 ml.), with hydrogen and a palladium-charcoal catalyst (from 1 g. of charcoal and 0.1 g. of palladium chloride) gave rise to 6-hydroxy-5-methylcoumaran, which was isolated by evaporation of the filtered reaction mixture, washed with aqueous sodium hydrogen carbonate, and crystallised from carbon tetrachloride, forming colourless, irregular plates (0.5 g.), m. p. 154° (Found : C, 71.9; H, 6.8. $C_9H_{10}O_2$ requires C, 72.0; H, 6.7%). This substance is soluble in alcohol, ethyl acetate, or benzene and has a negative ferric reaction and a negative sulphuric acid reaction. The p-nitrobenzoate of this coumaran formed pale yellow, hexagonal plates, m. p. 176°, from alcohol (Found : N, 4.7. $C_{16}H_{13}O_5N$ requires N, 4.7%).

(B) A mixture of 6-hydroxy-5-formylcoumaran (2 g.), zinc amalgam (from 16 g. of zinc), concentrated hydrochloric acid (16 ml.), and water (15 ml.) was refluxed for 8 hours, and the product isolated by means of ether. Crystallised from carbon tetrachloride, the resulting 6-hydroxy-5-methylcoumaran formed colourless plates (1.3 g.), m. p. 154°, identical in every way with a specimen prepared by method (A) (Found : C, 71.7; H, 6.6%).

6-Hydroxy-2-formyl-3-methylcoumarone (III).—This aldehyde, m. p. 182—183° (slight decomp.), which was prepared according to the directions of Karrer and Widmer (*loc. cit.*) who give m. p. 181°, did not give a ferric reaction and on acetylation by the pyridine method furnished the acetate, forming needles, m. p. 117°, from alcohol, which on being kept in contact with the solvent changed into diamond-shaped plates, m. p. 117° (Found : C, 66.1; H, 4.5. $C_{12}H_{10}O_4$ requires C, 66.1; H, 4.5%). The 2 : 4-dinitrophenylhydrazone of the latter derivative separated from ethyl acetate in red needles, m. p. 275° (Found : N, 14.2. $C_{18}H_{14}O_7N_4$ requires N, 14.1%). The oxime of (III), which separated from water in long needles, had m. p. 186°, as given by Karrer and Widmer (*loc. cit.*).

Potassium permanganate (0.3 g.), dissolved in water (12 ml.), was gradually added to a solution of the acetate of the aldehyde (0.5 g.) in acetone (15 ml.), and $\frac{1}{2}$ hour later the mixture was cleared with sulphur dioxide and 6-acetoxo-3-methylcoumarone-2-carboxylic acid mixed with unchanged aldehyde was precipitated with water. Purified with the aid of aqueous sodium hydrogen carbonate, the acid formed rectangular prisms, m. p. 226°, from ethyl acetate, identical in every way with a specimen obtained by acetylation of authentic 6-hydroxy-3-methylcoumarone-2-carboxylic acid (Found : C, 61.4; H, 4.6. $C_{12}H_{10}O_4$ requires C, 61.5; H, 4.3%).

6-Hydroxy-3-methylcoumaran (XVII; R = H).—A mixture of 2-hydroxy-4-benzylxyacetophenone (*J.*, 1937, 1530) (10 g.), ethyl bromoacetate (5.5 ml.), potassium carbonate (15 g.), and acetone (100 ml.) was refluxed until a sample of the product did not give a ferric reaction (about 5 hours). The resulting ethyl 5-benzylxy-2-acetylphenoxyacetate (XV; R = Et) was obtained on evaporation of the filtered solution and trituration of the residue with water, and crystallised from alcohol, forming rectangular prisms (12 g.), m. p. 124° (Found : C, 69.5; H, 6.1. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%). On hydrolysis with warm 4% aqueous-alcoholic sodium hydroxide (250 ml.) for 10 minutes this ester (10 g.) gave the phenoxyacetic acid (XV; R = H), forming rectangular plates (8.5 g.), m. p. 143°, from dilute acetic acid (Found : C, 68.1; H, 5.5. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%). Simultaneous cyclisation

and decarboxylation of this acid (10 g.) was effected with boiling acetic anhydride (100 ml.) and sodium acetate (25 g.) during $\frac{1}{2}$ hour, and on isolation the resulting 6-benzoyloxy-3-methylcoumarone (XVI; R = CH₂Ph, R₁ = H) separated from 80% acetic acid in rectangular prisms (7 g.), m. p. 80°, having a red sulphuric acid reaction (Found: C, 80.6; H, 5.9. C₁₆H₁₄O₂ requires C, 80.7; H, 5.9%).

Hydrogenation of the foregoing benzyl ether (3 g.) in acetic acid (50 ml.) with a palladium-charcoal catalyst was complete in 20 minutes, and after filtration the greater part of the solvent was removed in a vacuum. After the addition of water to the residue, followed by excess of sodium carbonate, 6-hydroxy-3-methylcoumaran was isolated with ether and purified by distillation in a vacuum and then by crystallisation from light petroleum (b. p. 40–60°); it formed needles (1.7 g.), m. p. 62°, having a negative sulphuric acid reaction (Found: C, 72.3; H, 6.9. C₉H₁₀O₂ requires C, 72.0; H, 6.7%).

3'-Methyl-2' : 3'-dihydrofurano(4' : 5' : 6 : 7)coumarin (XIV; R = H, R₁ = Me).—Condensation of 6-hydroxy-3-methylcoumaran (XVII; R = H) (3 g.) with hydrogen cyanide (4 ml.) in ether (100 ml.) by means of zinc chloride (4 g.) and excess of hydrogen chloride gave rise to an oily product which, on being washed several times with ether and then hydrolysed with water (100 ml.) on the steam-bath for 20 minutes, yielded the 5-formyl derivative (XVII; R = CHO), forming colourless rectangular prisms (3 g.), m. p. 72°, from alcohol, which gave a deep red ferric reaction in alcohol (Found: C, 67.3; H, 5.7. C₁₀H₁₀O₃ requires C, 67.4; H, 5.7%). The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate in scarlet needles, m. p. 282° (Found: C, 53.7; H, 4.0; N, 15.8. C₁₄H₁₄O₆N₄ requires C, 53.6; H, 3.9; N, 15.6%).

A solution of this aldehyde (1 g.) in 20% aqueous sodium hydroxide (10 ml.) was brought into reaction with aqueous cyanoacetic acid (7 ml.), and the yellow product precipitated by hydrochloric acid and boiled with n-hydrochloric acid (100 ml.) for $\frac{1}{2}$ hour as in the case of the lower homologue (X; R = CHO). On isolation the resulting furanocoumarin-3-carboxylic acid (XIV; R = CO₂H, R₁ = Me) (1.1 g.) separated from aqueous acetone in almost colourless rectangular plates, m. p. 216° (Found: C, 63.5; H, 4.1. C₁₃H₁₀O₅ requires C, 63.4; H, 4.1%). Like the homologue (XIV; R = CO₂H, R₁ = H), this acid was decarboxylated by the quinoline method and gave the dihydrofuranocoumarin (XIV; R = H, R₁ = Me), which was purified by sublimation in a vacuum at 140–150°/0.1 mm., and then by crystallisation from methyl alcohol, forming pale yellow needles (0.4 g.), m. p. 137° (Found: C, 71.3; H, 5.1. C₁₂H₁₀O₃ requires C, 71.3; H, 5.0%).

6-Hydroxy-5-formyl-3-methylcoumaran (1 g.) was heated (oil-bath at 180°) with acetic anhydride and sodium acetate (1 g.) for 8 hours, and after decomposition of the excess anhydride with water an oily product was isolated by means of ether. Extraction of the ethereal solution with aqueous sodium hydrogen carbonate gave β-6-acetoxy-3-methylcoumaran-5-acrylic acid, which separated from aqueous acetone in needles (0.07 g.), m. p. 207° (Found: C, 64.4; H, 4.8. C₁₄H₁₄O₅ requires C, 64.1; H, 5.3%). From the ethereal solution left on separation of the acrylic acid, unchanged aldehyde (XVI; R = CHO) was then extracted with 4% aqueous sodium hydroxide, and finally evaporation of the residual ethereal liquors left the acetate of the aldehyde as an oil which was converted into the 2 : 4-dinitrophenylhydrazone, forming orange needles, m. p. 245°, from acetic acid (Found: C, 53.6; H, 4.0; N, 14.0. C₁₈H₁₆O₇N₄ requires C, 54.0; H, 4.0; N, 14.0%).

5-Benzoyloxy-2-acetyl-4-methylphenoxyacetic Acid (XX; R = H).—A mixture of 5-C-methylresacetophenone (Yanagita, *Ber.*, 1938, 71, 2270) (5 g.), benzyl chloride (15 g.), potassium carbonate (10 g.), and acetone (50 ml.) was refluxed for 8 hours and, after removal of the potassium salts (washed with acetone) by filtration, the solvent was evaporated and the excess of benzyl chloride removed by means of a current of steam, leaving the benzyl ether (XIX) as a solid which separated from alcohol in colourless needles (5 g.), m. p. 94° (Found: C, 74.9; H, 6.3. C₁₆H₁₆O₃ requires C, 75.0; H, 6.3%). This compound gave a dark red ferric reaction in alcohol.

Interaction of the foregoing benzyl ether (1 g.) and ethyl bromoacetate (0.75 g.) in boiling acetone (25 ml.), containing potassium carbonate (2 g.), for 20 hours gave rise to ethyl 5-benzoyloxy-2-acetyl-4-methylphenoxyacetate (XX; R = Et), which formed colourless prisms (1 g.), m. p. 109°, from alcohol, having a negative ferric reaction (Found: C, 70.4; H, 6.6. C₂₀H₂₂O₅ requires C, 70.2; H, 6.4%). This ester (2 g.) was hydrolysed by being boiled with a solution of potassium hydroxide (2.5 g.) in water (20 ml.) and alcohol (30 ml.) for $\frac{1}{2}$ hour. After the removal of the greater part of the alcohol in a vacuum, the residual cooled liquor was acidified with dilute hydrochloric acid and the resulting acid collected, washed with water, and crystallised from ethyl acetate-light petroleum (b. p. 60–80°), forming colourless prisms (1.5 g.), m. p. 156°, soluble in alcohol or hot benzene (Found: C, 68.6; H, 5.6. C₁₈H₁₈O₅ requires C, 68.8; H, 5.7%).

6-Hydroxy-3 : 5-dimethylcoumaran (XVII; R = Me).—(A) A mixture of the foregoing acid (1 g.), sodium acetate (2.5 g.), and acetic anhydride (10 ml.) was refluxed (oil-bath) for $\frac{1}{2}$ hour, cooled, and diluted with water (100 ml.). Three days later the resulting 6-benzoyloxy-3 : 5-dimethylcoumarone (XVI; R = CH₂Ph, R₁ = Me) was collected, washed with aqueous sodium hydrogen carbonate, and purified by distillation in a vacuum and then by recrystallisation from 50% acetic acid, being obtained in colourless needles (0.5 g.), b. p. 170°/0.02 mm., m. p. 50°, which gave a dark red sulphuric acid reaction (warm) (Found: C, 80.7; H, 6.5. C₁₇H₁₆O₂ requires C, 81.0; H, 6.3%). Hydrogenation of this substance (2 g.), dissolved in acetic acid (150 ml.), with hydrogen and a palladium-charcoal catalyst gave rise to 6-hydroxy-3 : 5-dimethylcoumaran, which, on isolation by the method used for the homologue (X; R = Me), formed colourless prisms (1 g.), m. p. 100°, from light petroleum (b. p. 60–80°), having a negative sulphuric acid reaction (Found: C, 73.1; H, 7.4. C₁₀H₁₂O₂ requires C, 73.2; H, 7.3%).

(B) A mixture of 6-hydroxy-5-formyl-3-methylcoumaran (2 g.), zinc amalgam (from 16 g. of zinc dust), water (30 ml.), and concentrated hydrochloric acid (12 ml.) was refluxed for 12 hours. On isolation with ether the resulting 6-hydroxy-3 : 5-dimethylcoumaran separated from light petroleum (b. p. 60–80°) in colourless prisms (1.2 g.), m. p. 100°, identical in every way with a specimen prepared by method (A) (Found: C, 73.5; H, 7.5%). Prepared by the pyridine method at room temperature, the p-nitrobenzoate of 6-hydroxy-3 : 5-dimethylcoumaran formed pale yellow, slender prisms, m. p. 145°, from alcohol (Found: N, 4.4. C₁₇H₁₇O₆N requires N, 4.4%).

(With T. V. HEALEY.)

3 : 6-Dimethylcoumarone.—Prepared by the interaction of 2-hydroxy-4-methylacetophenone (Rosenmund and Schnurr, *Annalen*, 1927, **460**, 88) (7 g.), ethyl bromoacetate (6.2 ml.), and potassium carbonate (14 g.) in boiling acetone (40 ml.) during 12 hours, *ethyl 2-acetyl-5-methylphenoxyacetate* (VI) formed rectangular prisms (10.5 g.), m. p. 76°, from light petroleum (b. p. 60—80°) (Found : C, 66.3; H, 6.8. $C_{13}H_{14}O_4$ requires C, 66.1; H, 6.8%). Hydrolysis of this ester (6 g.) with 5% aqueous-alcoholic potassium hydroxide (120 ml.) on the steam-bath for one hour gave *2-acetyl-5-methylphenoxy-acetic acid* (4 g.), which separated from water in plates, m. p. 142° (Found : C, 63.5; H, 5.7. $C_{11}H_{12}O_4$ requires C, 63.5; H, 5.8%). On being boiled with acetic anhydride (60 ml.) and sodium acetate (25 g.) for 40 minutes, this acid (10 g.) yielded the coumarone which, on isolation with ether and distillation in a vacuum, was obtained as a colourless oil, b. p. 109—112°/22 mm., formed a picrate, m. p. 76°, and gave a violet-red colour with sulphuric acid changing to blue on addition of a little water (compare Stoermer, *Annalen*, 1900, **312**, 290).

Cyclisation of ethyl 2-acetyl-5-methylphenoxyacetate (5 g.), dissolved in the minimum amount of alcohol, with sodium ethoxide (from 0.25 g. of sodium) on the steam-bath during one hour and subsequent addition of water (150 ml.) to the cooled reaction mixture gave ethyl 3 : 6-dimethylcoumarone-2-carboxylate, which formed slender needles (1.6 g.), m. p. 42°, from dilute methyl alcohol. Acidification of the alkaline liquor left on separation of the ester gave 3 : 6-dimethylcoumarone-2-carboxylic acid (V; R = H) (1.8 g.), which separated from benzene in tiny rectangular prisms, m. p. 220° (decomp.) (Found : C, 69.5; H, 5.2. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%). The acid, which was also obtained by hydrolysis of the ester with 7% aqueous-alcoholic potassium hydroxide on the steam-bath for $\frac{1}{2}$ hour, gave an intense scarlet-red coloration with alcoholic ferric chloride and a red sulphuric acid reaction (warm).

2-Formyl-3 : 6-dimethylcoumarone (IV).—3 : 6-Dimethylcoumarone (2 g.) was added to a solution of aluminium chloride (4 g., 2 mols.) in ether (70 ml.) followed by hydrogen cyanide (0.5 ml.), and the mixture saturated with hydrogen chloride. Next day the almost colourless crystalline product was separated from the dark green liquor, thoroughly washed with ether, and treated with ice and dilute hydrochloric acid, and the mixture was warmed on the water-bath for $\frac{1}{2}$ hour, giving rise to the aldehyde, which formed prismatic needles, m. p. 81°, from alcohol (Found : C, 75.9; H, 5.9. $C_{11}H_{10}O_2$ requires C, 75.9; H, 5.7%). A further quantity of the compound (0.6 g.) was obtained by extracting the combined ethereal liquors with water and warming the extract on the water-bath. The 2 : 4-dinitrophenylhydrazone separated from much ethyl acetate in tiny, dark red, rectangular prisms, m. p. 278° (Found : N, 16.0. $C_{17}H_{14}O_5N_4$ requires N, 15.8%).

When the foregoing reaction was carried out with 1 mol. of aluminium chloride, with excess of zinc chloride, and without an auxiliary condensing agent the respective yields of aldehyde from 2 g. of coumarone were 1.2 g., 0.9 g., and 0.2 g. The orientation of this aldehyde was established by the fact that on oxidation in acetone with aqueous potassium permanganate it gave rise to 3 : 6-dimethylcoumarone-2-carboxylic acid, m. p. 220° (decomp.), after purification from benzene, identical with an authentic specimen.

3 : 6-Dimethylcoumarone-2-acetic Acid.—Condensation of the aforementioned aldehyde (6 g.) with hippuric acid (10 g.) by means of acetic anhydride (40 ml.) and sodium acetate (6 g.) on the steam-bath for $1\frac{1}{2}$ hours yielded the *azlactone*, which separated from alcohol in long orange needles (9 g.), m. p. 168° (Found : C, 75.8; H, 4.7; N, 4.4. $C_{20}H_{15}O_3N$ requires C, 75.7; H, 4.7; N, 4.4%). Hydrolysis of this compound (10 g.) with boiling 10% aqueous sodium hydroxide (160 ml.) for 6 hours gave 3 : 6-dimethylcoumarone-2-pyruvic acid which, on being separated from the accompanying benzoic acid by the sulphur dioxide method, formed pale yellow plates (2.5 g.), m. p. 208° (decomp.), from alcohol. Oxidation of the pyruvic acid (1 g.), dissolved in 5% aqueous sodium hydroxide (20 ml.), with 30% hydrogen peroxide (1.6 ml.) in the course of one hour furnished an almost theoretical yield of 3 : 6-dimethylcoumarone-2-acetic acid, which separated from dilute alcohol in colourless rectangular plates, m. p. 153°, having a cherry-red sulphuric acid reaction (Found : C, 70.4; H, 6.0. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%).

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