17. *Condensation Products of Phenols and Ketones Part VI. Proof of the Flavan Structure of the Dimeride of* 4-iso*Propenyl*-m-*cresol.*

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The dimeride of 4-*iso*propenyl-*m*-cresol, readily prepared from *m*-cresol and acetone, is proved to be 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan (II). Structure (II) has been established by a synthesis of the acid (III) obtained by oxidative degradation of the dimeride. The synthesis started from *m*-cresol or its methyl ether and ββ-dimethylacrylic acid, and proceeded *via* β-(2-methoxy-4-methylphenyl)*iso*valeric acid (V), the methyl ketone (XII), and the derived cyanohydrin.

4-*iso*Propenyl-*m*-cresol (I) readily undergoes dimerisation to yield a product, the descriptions of which are somewhat conflicting. The monomer (I) was first prepared by Fries and Fickewirth by heating 2-hydroxy-4 : β-dimethylcinnamic acid (*Ber.*, 1908, **41**, 371), and was found to yield the dimeride on long standing, or more quickly when heated with aqueous hydrochloric acid. It was stated that the dimeride could be distilled under diminished pressure and, although itself a non-crystalline resin at ordinary temperatures, it yielded a well-crystalline adduct with one molecule of diethyl ether; the adduct lost ether on exposure to the air or more quickly in a vacuum, leaving a white powder, m. p. 72—74°, but the melt would not crystallise even when seeded, presumably with the powder. These authors also obtained the same product from 4 : 7-dimethylcoumarin by treatment with zinc dust and alkali to give a hydroxythymol, followed by condensation in presence of acid (*Annalen*, 1908, **362**, 42), and it was shown later (Fries, Gross-Selbeck, and Wicke, *ibid.*, 1914, **402**, 309) that, contrary to earlier statements, the dimeride showed very weak phenolic properties.

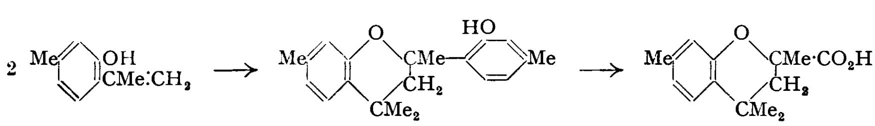
The preparation of the same compound in a more direct manner from *m*-cresol, acetone, and hydrogen chloride is described in a number of patents taken out by Schering-Kahlbaum A.-G. (B.P. 273,684, 279856/1927; F.P. 636,119/1927; Swiss P. 127,522/1927; U.S.P. 1,696,769/1927), and the similar preparation recorded by Baker and Besly (*J.*, 1940, 1105), which gives a 40% yield, is based on B.P. 273,684. The modification given in U.S.P. 2,418,458–9/1947 (E.I. du Pont de Nemours and Co.; *Chem. Abs.*, 1947, **41**, 3918) is the most convenient and readily gives the dimeride in a yield of over 50%. The descriptions of the compound recorded in these references are essentially in agreement with the earlier work, but in B.P. 273,684, F.P. 636,119, and in Swiss P. 127,522, the acetyl derivative is stated to melt at 122—123°, whereas Baker and Besly (*loc. cit.*) showed that the m. p. is 108°, and in U.S.P. 2,418,458–9 it is stated to be 100—102°. It is thus possible that the acetyl derivative may be dimorphic, but we have been unable to obtain the higher-melting form. In Swiss P. 127,522 is the only previously recorded claim to have obtained the free dimeride in the crystalline form; it was stated to crystallise from light petroleum and had m. p. 82—83°.

Niederl, Smith, and McGreal (*J. Amer. Chem. Soc.*, 1931, **53**, 3393) reported the preparation of the same dimeride of (I) by condensation of *m*-cresol with allyl alcohol in presence of concentrated sulphuric acid, but although the product formed with diethyl ether an adduct, m. p. 72—74°, it dissolved in aqueous potassium hydroxide and gave a dark green colour with aqueous ferric chloride, and is clearly not identical with the true dimeride, which exhibits neither of these properties. There is also doubt about the nature of the product, claimed to be the dimeride of (I), obtained by Smith and Niederl (*ibid.*, 1933, **55**, 4151) from *m*-cresol, allyl chloride, and sulphuric acid, which was stated to have m. p. 74° after crystallisation (solvent not recorded).

The dimeride of 4-*iso*propenyl-*m*-cresol has now been obtained in a beautifully crystalline state, and the isolated claim in Swiss P. 127,522 is thus substantiated. Earlier workers must, unknowingly, have handled this compound in a microcrystalline form, since it had been observed that the ether adduct, when exposed to the air, slowly lost the solvent and became a powder. This stable, free-flowing powder is, in fact, microcrystalline, and readily induces crystallisation of a solution of the dimeride in light petroleum. In comparison, the powdered non-crystalline dimeride very soon sets to a resinous mass which, although brittle, flows extremely slowly at room temperature. These physical properties of the non-crystalline dimeride are of interest and importance in connection with the study of the properties of matter which is intermediate in state between a glass and a liquid. Its advantages over other products of comparable physical properties are that it is a chemically homogeneous substance readily prepared in quantity in a state of complete purity, and that it has a very convenient temperature range for the transition from a brittle resin to a liquid. It also exhibits strain birefringence, which at room temperature disappears in a few seconds but becomes more lasting with diminished temperature. The physical properties of this compound are under investigation at the Butterwick Research Laboratories of Imperial Chemical Industries Limited, Welwyn, Herts.

The structure of this dimeride of 4-*iso*propenyl-*m*-cresol and of related compounds has been the subject of speculation, and the position was reviewed by Baker and Besly (*Nature*, 1939, **144**, 865; this series, Part V, *J.*, 1940, 1103). After the known properties of the dimeride and the most probable course of the dimerisation which leads to a saturated product with one very weakly phenolic group had been taken into account, the conclusion was reached that the substance was most probably 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan (II). Support for this view was found in the fact that the dimeride could be degraded by oxidation with potassium permanganate in acetone with loss of six carbon atoms, to give a carboxylic acid which resisted decarboxylation, and was therefore unlikely to possess an α-hydrogen atom. This degradation corresponded to the conversion of a 2-hydroxy-4-methylphenyl group into a carboxyl group, and the acid was formulated as 2 : 4 : 4 : 7-tetramethylchroman-2-carboxylic acid (III).

An unambiguous synthesis of the acid (III) has now been achieved, and this synthetic acid is identical in all respects with that prepared by degradation of the dimeride. Moreover, it acts as a tertiary carboxylic acid by yielding carbon monoxide when treated with concentrated sulphuric acid, even at room temperature (see Bistrzychi and Mauron, *Ber.*, 1907, **40**, 4370).



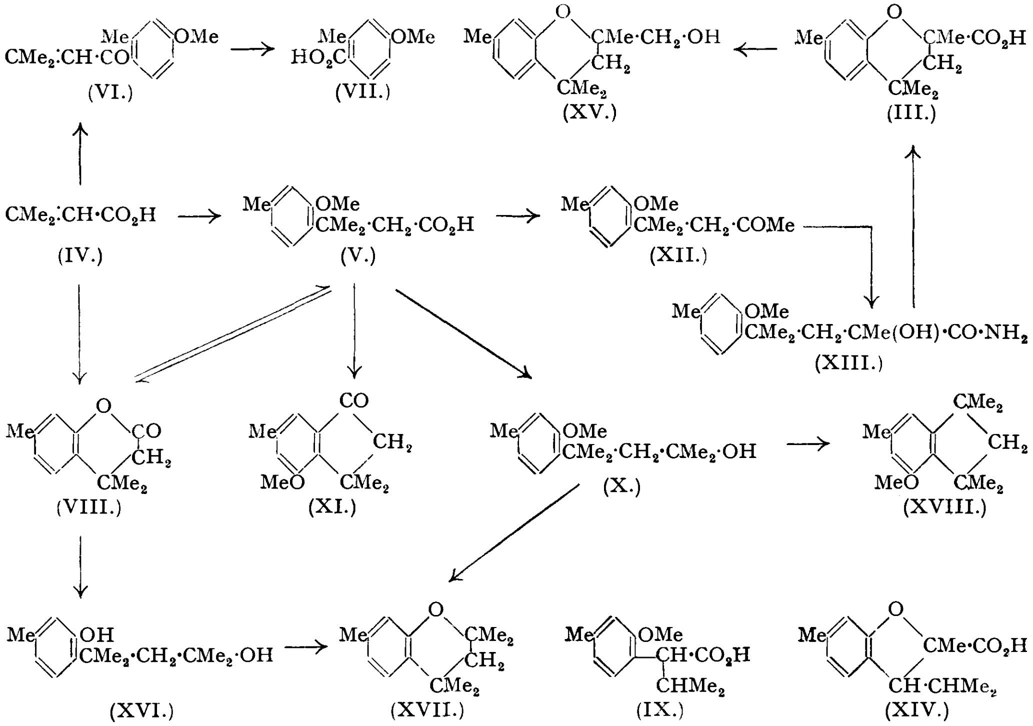
(I.) (II.) (III.)

The structure of the dimeride is thus definitely proved to be 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan (II). The very simple production of a flavan in the laboratory from the *o*-*iso*propenylphenol (I) recalls the wide occurrence of flavan derivatives in Nature, but methyl groups in positions 2 and 4 are not commonly found in natural products, and the observation is possibly without phytochemical significance. A model of the flavan (II) shows that, by rotation of the 2-hydroxy-4-methylphenyl group, the two oxygen atoms can approach to within about 2·5 A., so the formation of a hydrogen bond is possible. This may, in part, account for the very weakly phenolic properties of the dimeride (cf. the very weakly phenolic properties of the hydroxyl group in position 5 of flavones, flavonols, etc.), but the large group in the *o*-position to the hydroxyl may also be a contributing factor.

The synthesis of the acid (III) started from ββ-dimethylacrylic acid (IV) and *m*-tolyl methyl ether, which condensed in presence of aluminium chloride to give the desired β-(2-methoxy-4-methylphenyl)*iso*valeric acid (V) in 43% yield. In addition, there was produced in smaller quantity a neutral ketone, 4-methoxy-2-methylphenyl ββ-dimethylvinyl ketone (VI), which was characterised as a 2 : 4-dinitrophenylhydrazone, and orientated by oxidation to the known 4-methoxy-2-methylbenzoic acid (VII). It was necessary to establish the structure (V) assigned to the acid, since this is a key intermediate in the synthesis. Condensation might have occurred in either of the two *ortho*-positions or in the *para*-position to the methoxyl group, and at either the α- or the β-carbon atom of the ββ-dimethylacrylic acid. That condensation had occurred *ortho* to the methoxyl group was shown by treating the acid with hydrobromic acid in acetic acid, whereupon simultaneous demethylation and lactone formation took place; methylation of the lactone (now known to be 3 : 4-dihydro-4 : 4 : 7-trimethylcoumarin, VIII) in alkaline solution with methyl sulphate regenerated the methoxy-acid (V). This lactone formation proves that the acid must be either β- (V) or α-(2-methoxy-4-methylphenyl)*iso*valeric acid (IX), or the corresponding 2-methoxy-6-methylphenyl derivatives. Attempts to prove the presence of a methylene group adjacent to the carboxyl group in either the acid or the lactone proved unexpectedly difficult, probably owing to the steric effect of the quaternary β-carbon atom; *e.g.*, no derivative of the acid could be obtained by reaction with aromatic aldehydes under the conditions of the Perkin reaction. This recalls the failure of Eijkmann to prove the presence of a methylene group in β-phenyl*iso*valeric acid (*Chem. Weekblad*, 1908, **5**, 655; for proof of structure of this acid see Hoffmann, *J. Amer. Chem. Soc.*, 1929, **51**, 2542). Again, in an attempt to apply the Barbier–Wieland degradation, the methyl ester of the acid

(V) was converted into the related tertiary alcohol [now known to be 4-(2-methoxy-4-methylphenyl)-2 : 4-dimethylpentan-2-ol (X)] by treatment with methylmagnesium iodide, but the usual degradation of *tert.*-carbinols did not occur on oxidation with chromic acid. This abnormal behaviour in an important degradative process is noteworthy, and will be described in a later communication; it is probably attributable to the quaternary β-carbon atom.

Two pieces of evidence prove that the condensation of *m*-tolyl methyl ether with ββ-dimethylacrylic acid gives the β-phenyl*iso*valeric acid (V). (*a*) Cyclodehydration of the acid with phosphoric anhydride in syrupy phosphoric acid gave a mixture containing 3 : 4-dihydro-4 : 4 : 7-trimethylcoumarin (VIII) and a ketone containing a methoxyl group, which can only be 4-methoxy-3 : 3 : 6-trimethylindan-1-one (XI); cyclodehydration could not occur either if the acid was a derivative of α-phenyl*iso*valeric acid or if the original condensation had occurred in the alternative *o*-position to the methoxyl group. (*b*) The acid has been successfully converted *via* intermediates, now known to be (XII) and (XIII), into an acid identical with that obtained by oxidative degradation of the dimeride of 4-*iso*propenyl-*m*-cresol. If the acid possessed the structure (V) it would give ultimately the " degradation acid " (III), but if it possessed the alternative structure (IX) the acid finally synthesised would have the structure (XIV). Inspection of the carbon skeleton of the acid (XIV) shows that it could not possibly result from the degradation of any dimeride of an *iso*propenyl compound, and, therefore, structure (V) correctly represents the acid derived from *m*-tolyl methyl ether and ββ-dimethylacrylic acid. The β-addition of the aromatic nucleus to the molecule of ββ-dimethylacrylic acid is thus in line with the addition to the same acid of benzene (Eijkmann, *Chem. Weekblad*, 1908, **5**, 655; Bergmann, Taubadel, and Weiss, *Ber.*, 1931, **64**, 1493), hemimellitene, ψ-cumene, mesitylene, and *p*-xylene (Smith and Prichard, *J. Amer. Chem. Soc.*, 1940, **62**, 771), *m*-xylene (Smith and Spillane, *ibid.*, 1943, **65**, 202), 2 : 4-dimethylphenol (*idem, ibid.*, p. 283), and tetralin (Smith and Lo, *ibid.*, 1948, **70**, 2215), the β-addition having been established in most cases by cyclodehydration to an indanone.



The final steps in the synthesis of the acid (III) were as follows. The chloride of the acid (V) reacted with dimethylcadmium to give 4-(2-methoxy-4-methylphenyl)-4-methylpentan-2-one (XII) in 88% yield, and although this ketone readily gave a semicarbazone and a 2 : 4-dinitrophenylhydrazone it failed to give recognisable mono- or di-arylidene derivatives with aromatic aldehydes. It likewise failed to give a derivative of *p*-nitrophenol when treated with nitromalondialdehyde and alkali (for references, see Prelog, *J.*, 1950, 426). Reaction of the ketone (XII) with anhydrous hydrogen cyanide and a trace of potassium cyanide gave a cyanohydrin which was not isolated but subjected to direct hydrolysis with concentrated hydrochloric acid in the cold, giving the hydroxy-amide, 2-hydroxy-4-(2-methoxy-4-methylphenyl)-4-methylpentane-2-carboxyamide (XIII). Finally, the amide (XIII) was boiled with aqueous hydrobromic acid in acetic acid, simultaneous hydrolysis of the amido-group, demethylation, and ring closure occurring to give the acid (III) in 41% yield.

The hydroxy-amide (XIII) is remarkable for crystallising from light petroleum (b. p. 40—60°) or pure *n*-hexane with just over one quarter of a molecule of *n*-hexane of crystallisation. In view of the chemical inertness of the aliphatic hydrocarbons, this molecular compound must be of the nature of a " clathrate," where the hydrocarbon merely occupies spaces in the crystal lattice (see Palin and Powell, *J.*, 1948, 815) and may not be present in precise stoicheiometrical proportions. The observation particularly recalls the recently investigated crystal complexes of urea with straight-chain aliphatic hydrocarbons (Schlenck, *Annalen*, 1949, **565**, 204; Zimmerscheid, Dinerstein, Weitkamp, and Marschner, *J. Amer. Chem. Soc.*, 1949, **71**, 2947), and similar complexes with thiourea (Angla, *Bull. Soc. chim.*, 1949, **16**, 12) (see also Smith, *J. Chem. Physics*, 1950, **18**, 150), and prompted us to attempt such complex formation with α-hydroxy*iso*butyramide, $Me_2C(OH)\cdot CO\cdot NH_2$, but no evidence of the formation of crystalline adducts was obtained.

A number of other noteworthy observations have been made during the course of this work. An alternative synthesis of β-(2-methoxy-4-methylphenyl)*iso*valeric acid (V), which has practical advantages over the method already described, is first to prepare 3 : 4-dihydro-4 : 4 : 7-trimethylcoumarin (VIII) by condensation of ββ-dimethylacrylic acid with *m*-cresol, and then to methylate this as described to give the acid (V). The overall yield is 55% from ββ-dimethylacrylic acid, compared with 43% by the alternative route, and the process is simpler to carry out. The acid (V) did not undergo normal decarboxylation when heated with soda–lime. It was hoped that a much shorter synthesis of the acid (III) might be achieved by a direct preparation of the ketone (XII) from *m*-tolyl methyl ether and mesityl oxide, in view of Niederl's claim (*J. Amer. Chem. Soc.*, 1929, **51**, 2426) to have prepared 2-hydroxy-2 : 4 : 4 : 7-tetramethylchroman by condensation of *m*-cresol with mesityl oxide in presence of concentrated sulphuric acid. We found, however, that *m*-tolyl methyl ether and mesityl oxide did not condense under these conditions, and we were moreover unable to confirm Niederl's observations (cf. Smith and Prichard, *ibid.*, 1940, **62**, 771).

Unsuccessful attempts to decarboxylate the tertiary acid 2 : 4 : 4 : 7-tetramethylchroman-2-carboxylic acid (III) by heating it either with soda–lime or with copper bronze in boiling quinoline were described in Part V of this series, but the carboxyl group was readily reduced by lithium aluminium hydride in ether, giving 2-hydroxymethyl-2 : 4 : 4 : 7-tetramethylchroman (XV). The hydroxymethyl group in (XV) could not be reduced by hydriodic acid and red phosphorus. 3 : 4-Dihydro-4 : 4 : 7-trimethylcoumarin (VIII) reacts with methylmagnesium iodide to give 2-hydroxy-4-(2-hydroxy-4-methylphenyl)-2 : 4-dimethylpentane (XVI). When treated with hydrogen chloride in methanol, (XVI) undergoes cyclodehydration to a liquid, probably 2 : 2 : 4 : 4 : 7-pentamethylchroman (XVII), characterised as a solid dibromo-derivative which is probably 6 : 8-dibromo-2 : 2 : 4 : 4 : 7-pentamethylchroman. The very slight doubt about the structure of (XVII) lies in the possibility that the tertiary carbinol group might first dehydrate to give either of two isomeric olefins, and subsequent cyclisation involving the phenolic hydroxyl group might then give rise to (XVII), or to a substituted coumaran with a five-membered ring, or to a seven-membered cyclic oxide. The last is most unlikely, and with regard to the coumaran structure the tertiary carbinol (X) is not dehydrated to an olefin by phosphoric anhydride in benzene, but gives a saturated product possessing a methoxyl group, which must therefore be either 4-methoxy-1 : 1 : 3 : 3 : 6-pentamethylindane (XVIII), or much less probably 1 : 2 : 3 : 4-tetrahydro-5-methoxy-2 : 4 : 4 : 7-tetramethylnaphthalene. Reaction of 2-hydroxy-4-(2-methoxy-4-methylphenyl)-2 : 4-dimethylpentane (X) with hydrobromic acid in acetic acid gives an alternative route to 2 : 2 : 4 : 4 : 7-pentamethylchroman (XVII), which was again characterised as the dibromo-derivative.

The properties of the acid (V) and of the related carbinol (X) are very similar to those of β-3 : 5-dimethylphenyl*iso*valeric acid and the derived dimethylcarbinol (Smith and Spillane, *loc. cit.*).

EXPERIMENTAL.

(M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.)

2′-Hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan (*Dimeric Form of* 4-iso*Propenyl*-m-*cresol*) (II).—The preparation of this compound from *m*-cresol, acetone, and hydrogen chloride was carried out either according to Baker and Besly (*loc. cit.*), or by the process recorded in U.S.P. 2,418,458–9. In either case the product was distilled under diminished pressure and further purified by crystallisation from ether–light petroleum (b. p. 40—60°) as the adduct with one molecule of diethyl ether.

The ether-free compound is readily obtained by heating the adduct on the water-bath, finally under reduced pressure, and was obtained as very large, well-developed, thick prisms from light petroleum (b. p. 40—60°) as described on p. 76. In spite of their purity, these crystals have a somewhat ill-defined m. p. of 82—84° (Found : C, 81·4; H, 7·9. Calc. for $C_{20}H_{24}O_2$: C, 81·1; H, 8·1%). At room temperature the non-crystalline dimeride crystallises extremely slowly (many months) after seeding, but the process is shortened to weeks at 35°, and is much more rapid at temperatures close to the m. p.

2 : 4 : 4 : 7-*Tetramethylchroman*-2-*carboxylic Acid* (III).—The oxidation of 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan (II) by potassium permanganate in acetone to give 2 : 4 : 4 : 7-tetramethylchroman-2-carboxylic acid (III) was described by Baker and Besly (*loc. cit.*), the yield being *ca.* 8% before final purification. The oxidation has been investigated in detail, and the process now described gives this important acid in the pure state in 33% yield. Owing to the large volumes of acetone required, the oxidation can only be carried out in a single experiment on a few grams of the flavan (II). The considerable improvement in yield is due to the realisation that the degradation of the 2-hydroxy-4-methylphenyl group to a carboxyl group occurs *via* a number of intermediate carboxylic acids, and if the oxidation is carried out slowly these acids are prevented from further oxidation by being precipitated from the acetone as insoluble potassium salts. The aim has, therefore, been to oxidise (II) as rapidly as possible to the very stable acid (III), and this procedure is likely to find other useful applications. Addition of water to the acetone is not of advantage.

The flavan (II) (3 g.) was dissolved in warm acetone (30 c.c.) in a 2-l. flask, and a saturated solution of potassium permanganate in boiling acetone (900 c.c.) added rapidly. The mixture boiled spontaneously and all the permanganate was reduced in 2 minutes; the acetone was next recovered by distillation, and the residue shaken with water (100 c.c.), sodium pyrosulphite (15 g.), and 2N-hydrochloric acid (20 c.c.). The mixture was then extracted with ether (50 c.c.; 20 c.c.; 20 c.c.), the combined extracts were shaken three times with aqueous sodium carbonate, and the alkaline extracts were shaken with ethyl acetate until a colourless organic layer was obtained, then with ether, and acidified. The liberated acid rapidly solidified and was collected and dried (yield, 1·6 g.); after crystallisation from ethylene dichloride (7 c.c.) at 0° it yielded the flavan-carboxylic acid (III) (0·75 g.), m. p. 146—147°. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave a product, m. p. 148—149°, undepressed when mixed with the acid (m. p. 148—149°) prepared by Baker and Besly's method. This purified, but not the crude, acid may be recrystallised from warm, dilute methyl alcohol; it then forms small, almost rectangular tablets. The loss during crystallisation from ethylene dichloride is due to unfavourable solubility relationships, and to the presence of other acids which have not been investigated.

This acid (III) (0·1 g.), when treated with concentrated sulphuric acid (0·6 c.c.), begins to evolve carbon monoxide at 16°, and at 33° the evolution is rapid. The product, which is soluble in water and insoluble in ether, is probably a sulphonic acid.

Amide of 2 : 4 : 4 : 7-*Tetramethylchroman*-2-*carboxylic Acid*.—The acid (III) (1 g.), chloroform (10 c.c.), and thionyl chloride (1 c.c.) were refluxed for 3 hours, excess of solvent and reagent was distilled from the water-bath, and the residue shaken vigorously with concentrated aqueous ammonia and a little ether. Removal of the ether in a current of air gave the *amide* (0·93 g.), which was crystallised first from 50% methyl alcohol (35 c.c.) (charcoal) and then from light petroleum (b. p. 100—120°), and obtained as flat, square-ended prisms, m. p. 148° (Found : C, 71·8; H, 8·1; N, 5·7. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2; N, 6·0%).

β-(2-*Methoxy*-4-*methylphenyl*)iso*valeric Acid* (V).—ββ-Dimethylacrylic acid (IV) (10 g.) and *m*-tolyl methyl ether (12·2 g.) were dissolved in anhydrous benzene (25 c.c.), and to the solution powdered anhydrous aluminium chloride (16 g.) was added with vigorous stirring during ½ hour, the temperature being kept below 40°. The deep-red solution was stirred for a further 2½ hours at room temperature, and next day was poured on ice and hydrochloric acid and extracted with ether. The ethereal layer was shaken with concentrated sodium carbonate solution, separated, and worked up as described below (*A*); the alkaline layer on acidification yielded a solid acid which was collected and distilled. The fraction, b. p. 180—185°/13 mm., was crystallised from light petroleum (b. p. 40—60°), giving β-(2-*methoxy*-4-*methylphenyl*)iso*valeric acid* (V) as rhombic prisms (9·5 g., 43% yield), m. p. 93°, b. p. 183°/13 mm. (Found : C, 70·6; H, 7·9; OMe, 13·9%; equiv., 224. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1; MeO, 14·0%; equiv., 222). The yield was not improved by carrying out the reaction at −10°, as recommended by Smith and Spillane for the condensation of *m*-xylene with ββ-dimethylacrylic acid (*loc. cit.*).

Amide and p-*toluidide*. β-(2-Methoxy-4-methylphenyl)*iso*valeric acid (V) (11·5 g.) was refluxed with thionyl chloride (15 c.c.) for 20 minutes, and then distilled, giving the acid chloride as an oil, b. p. 117—118°/2 mm. (9·9 g.). The chloride (1 g.) in anhydrous ether (10 c.c.) was treated with excess of gaseous ammonia, and after ½ hour the ethereal solution was shaken with water, dried, and distilled, leaving the solid *amide* (0·65 g.), which separated from benzene–light petroleum (b. p. 60—80°) as thin plates, m. p. 111° (Found : C, 70·3; H, 8·7; N, 6·1. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6; N, 6·3%). The p-*toluidide* was prepared by reaction between the acid chloride (1·2 g.) and *p*-toluidine (1·1 g.) in benzene (10 c.c.) for ¼ hour at room temperature. The benzene solution, after being washed with dilute hydrochloric acid, yielded a solid which separated from benzene–light petroleum as thin needles (1·37 g.), m. p. 103° (Found : C, 76·9; H, 7·8; N, 4·7. $C_{20}H_{25}O_2N$ requires C, 77·2; H, 8·0; N, 4·5%).

4-Methoxy-2-methylphenyl β-Methylprop-1-enyl Ketone (VI).—The ethereal solution mentioned above (*A*) was washed with water, dried ($MgSO_4$), and distilled, giving *m*-tolyl methyl ether (3·2 g.; b. p. 65°/13 mm.) and the *ketone* (VI) (3·9 g., 19%), b. p. 165°/13 mm., 126—127°/0·5 mm., as a pale yellow, viscous oil (Found : C, 76·2; H, 7·5. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). The preparation of the 2 : *4-dinitrophenylhydrazone* of the ketone (VI) requires closely defined conditions. The ketone (3 drops) in dry ethanol (2 c.c.) was added to 2 : 4-dinitrophenylhydrazine (0·3 g.) in concentrated sulphuric acid (1 c.c.) and ethanol (10 c.c.), and the mixture gently warmed. The bright-red 2 : 4-dinitrophenylhydrazone slowly separated and after eight crystallisations from ethanol was obtained as dark-red, glistening needles, m. p. 156° (Found : C, 59·3; H, 5·3; N, 14·8. $C_{19}H_{20}O_5N_4$ requires C, 59·4; H, 5·2; N, 14·6%).

4-Methoxy-2-methylbenzoic Acid (VII).—To the ketone (1 g.) in acetone (20 c.c.) was added in portions at room temperature a saturated solution of potassium permanganate in acetone (*ca.* 100 c.c.). When an excess of potassium permanganate persisted for 10 minutes, the acetone was removed *in vacuo*, and the residue treated with excess of sulphur dioxide and water (20 c.c.), and then extracted with ether. The extract was shaken with aqueous sodium carbonate, and acidification of the alkaline layer yielded 4-methoxy-2-methylbenzoic acid, which, after recrystallisation from aqueous ethanol and then benzene–light petroleum (b. p. 60—80°), was obtained as fine needles (0·31 g., 38%), m. p. 175—176°, mixed m. p. with an authentic specimen, 175—176° (Found : C, 65·3; H, 6·1. Calc. for $C_9H_{10}O_3$: C, 65·1; H, 6·0%).

3 : *4-Dihydro-4* : 4 : *7-trimethylcoumarin* (VIII).—β-(2-Methoxy-4-methylphenyl)*iso*valeric acid (V) (8·2 g.) was boiled under reflux for 6 hours with glacial acetic acid (50 c.c.) and aqueous hydrobromic acid (10 c.c.; *d* 1·48), and then poured into water (600 c.c.). The solution was neutralised by addition of sodium carbonate solution and cooled, and the solid 3 : *4-dihydro-4* : 4 : *7-trimethylcoumarin* (6·8 g.) collected, washed, dried, and recrystallised from light petroleum (b. p. 60—80°), giving thick, almost rectangular tablets, m. p. 59·5° (5·9 g., 86%) (Found : C, 75·7; H, 7·4. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%).

*β-(2-Methoxy-4-methylphenyl)*iso*valeric Acid* (V) *from* 3 : *4-Dihydro-4* : 4 : *7-trimethylcoumarin* (VIII).—The dihydrocoumarin (VIII) (3·8 g.) was dissolved by heating it in a solution of sodium hydroxide (20 g.) in water (50 c.c.), and then cooled; ethanol (10 c.c.) was added, and the whole treated with methyl sulphate (25·2 g.) in small portions during 10 minutes, the temperature being kept at about 50°. The solution was then heated on the water-bath for 1 hour, diluted with water (70 c.c.), and acidified with hydrochloric acid. The precipitated solid was collected after cooling to 0°, washed, dried, and recrystallised from light petroleum (b. p. 40—60°), giving rhombs (3·9 g., 88%), m. p. and mixed m. p. 93°.

4-(2-Methoxy-4-methylphenyl)-2 : *4-dimethylpentan-2-ol* (X).—The acid (V) (5 g.) was converted into the methyl ester by boiling it with a saturated methanolic solution of hydrogen chloride (20 c.c.) for 4 hours. The ester, isolated in the usual way, was obtained as a colourless oil, b. p. 110—112°/0·7 mm. (5·05 g.). This ester (4·9 g.) in dry ether was added to the Grignard reagent prepared from magnesium (1·17 g.) and methyl iodide (7·1 g.) in ether (50 c.c.) in an atmosphere of nitrogen, and the mixture was refluxed for 12 hours and treated with ice and dilute hydrochloric acid. Ether-extraction yielded an oil which was boiled under reflux for 4 hours with ethanol (20 c.c.), sodium hydroxide (1 g.), and water (5 c.c.) to hydrolyse unchanged ester. Neutral material was extracted into ether, and the *pentanol* obtained as a colourless, viscous liquid, b. p. 107—109°/0·6 mm. (3·8 g.) (Found : C, 76·2; H, 10·4. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%).

4-Methoxy-3 : 3 : *6-trimethylindan-1-one* (XI).—β-(2-Methoxy-4-methylphenyl)*iso*valeric acid (V) (6·0 g.) was finely powdered and added to a cooled mixture of phosphoric anhydride (30 g.) and syrupy phosphoric acid (30 c.c.; *d* 1·75). The mixture was heated and shaken on a steam-bath for 10 minutes, and the deep-red viscous product was poured on ice (200 g.), and the semi-solid extracted into ether (2 × 100 c.c.). The extracts were washed with 2N-sodium hydroxide (100 c.c.) (acidification gave no unchanged acid V), then with water, and dried ($MgSO_4$). Distillation of the ether left an oil, which on the addition of light petroleum (b. p. 40—60°; 5 c.c.) deposited a solid which was collected and crystallised from light petroleum (b. p. 60—80°), giving clusters of colourless, flat prisms, m. p. 230° (0·34 g.), which were not further investigated. The filtrate, after removal of the high-melting solid, gave a colourless oil, b. p. 71—100°/0·1 mm. (1·89 g.), which was boiled for 2 hours with a solution of sodium hydroxide (1·0 g.) in water (5 c.c.) and ethanol (5 c.c.), the ethanol removed under reduced pressure, and the mixture diluted and extracted with ether (2 × 50 c.c.) to remove neutral material (below). Acidification of the alkaline layer gave crude 3 : 4-dihydro-4 : 4 : 7-trimethylcoumarin (VIII), m. p. 56° (0·80 g., 15%), which after crystallisation from aqueous methanol and then from light petroleum (b. p. 40—60°) gave the characteristic, almost rectangular tablets of the pure compound, m. p. and mixed m. p. 59·5°.

The neutral ethereal extract (above) yielded an oil, and addition of light petroleum (1 c.c.) caused separation of pale yellow needles, m. p. 110° (0·156 g., 2·8%). Sublimation (100°/2 mm.) gave the *ketone* (XI) as colourless needles, m. p. 115°, both before and after crystallisation from light petroleum (Found : C, 75·8, 75·5; H, 7·6, 7·4; OMe, 15·0. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8; OMe, 15·2%). The 2 : *4-dinitrophenylhydrazone* separated from ethanol as fine, orange needles, m. p. 229° (Found : C, 59·4; H, 5·1; N, 14·5; OMe, 8·5. $C_{19}H_{20}O_5N_4$ requires C, 59·4; H, 5·2; N, 14·6; OMe, 8·1%).

Attempts to prepare this ketone by treatment of the acid (V) with phosphoric anhydride in boiling benzene, or by the action of stannic or aluminium chloride on the acid chloride, gave almost quantitative yields of 3 : 4-dihydro-4 : 4 : 7-trimethylcoumarin (VIII) but no ketonic material.

4-(2-Methoxy-4-methylphenyl)-4-methylpentan-2-one (XII).—This preparation was carried out in an atmosphere of nitrogen. The Grignard reagent, prepared from methyl bromide (19 g.), magnesium

(4·9 g.), and anhydrous ether (100 c.c.), was cooled to 0°, and anhydrous cadmium chloride (19·6 g.) added during 5 minutes with vigorous mechanical stirring. The mixture began to boil, and was refluxed for ½ hour on the water-bath. The ether was now rapidly removed by distillation, and dry benzene (65 c.c.) added and distilled off until 25 c.c. of distillate had collected, more benzene (120 c.c.) added, and the solution then refluxed during, and ½ hour after, the rapid addition of a solution of the chloride of β-(2-methoxy-4-methylphenyl)*iso*valeric acid (11·8 g.) in benzene (30 c.c.). After addition of ice and dilute sulphuric acid, the benzene layer was separated, the liquid extracted with ether, and the united benzene and ether extracts were dried and distilled, yielding 4-(2-*methoxy*-4-*methylphenyl*)-4-*methylpentan*-2-*one* (XII) (9·5 g., 88%) as a colourless, rather viscous liquid, b. p. 133—134°/4 mm. (Found : C, 76·3; H, 8·8. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%). This preparation must be carried out rapidly, or lower yields result. The semicarbazone separated from the usual reaction mixture at room temperature (40 hours), and was obtained from benzene–light petroleum (b. p. 40—60°) as thin plates, m. p. 138° (Found : C, 65·2; H, 8·3; N, 15·1. $C_{15}H_{23}O_2N_3$ requires C, 65·0; H, 8·3; N, 15·1%). The 2 : 4-*dinitrophenylhydrazone*, prepared by means of Brady's reagent, was precipitated after 24 hours by the addition of water and washed with dilute hydrochloric acid. It separated from alcohol as orange, microcrystalline plates, m. p. 138° (Found : C, 59·6; H, 6·0; N, 14·0. $C_{20}H_{24}O_5N_4$ requires C, 60·0; H, 6·0; N, 14·0%).

2-*Hydroxy*-4-(2-*methoxy*-4-*methylphenyl*)-4-*methylpentane*-2-*carboxyamide* (XIII).—The preceding ketone (XII) (2·2 g.) was kept for 40 hours with excess of anhydrous hydrogen cyanide (1·5 c.c.) and potassium cyanide (2 mg.). The dark mixture was then cautiously treated with concentrated hydrochloric acid (10 c.c.; saturated with hydrogen chloride at 0°) at 0°, and allowed to reach room temperature during 24 hours. After dilution with water, the mixture was extracted twice with ether, and the ethereal layer washed with dilute sodium carbonate and water, dried ($MgSO_4$), and distilled, leaving a viscous, pale brown oil. Addition of light petroleum (b. p. 60—80°) gave a solid which recrystallised from the same solvent as fine needles (0·57 g.), m. p. (rapid heating) 66—67° [the mother-liquors from the precipitation and the recrystallisation yielded unchanged ketone (XII); 1·35 g.]. The product so obtained contains *n*-hexane of crystallisation which is lost at the m. p., giving a resinous solid which may very slowly crystallise on storage and can be recrystallised from very dilute aqueous methanol as fine needles. This 2-*hydroxy*-4-(2-*methoxy*-4-*methylphenyl*)-4-*methylpentane*-2-*carboxyamide* (XIII) has m. p. 85° (Found : C, 67·9; H, 8·5; N, 5·0. $C_{15}H_{23}O_3N$ requires C, 67·9; H, 8·7; N, 5·3%). Loss of weight determinations were carried out upon the *n*-hexane *complex* by heating *in vacuo* at 80°; the complex was recovered from the resulting solid by crystallisation from pure *n*-hexane. This process was carried out repeatedly with constant loss in weight, and subsequent regeneration of the complex [Found : (*a*) C, 69·6; H, 8·9; N, 5·1; loss of weight, 7·9. (*b*) C, 69·4; H, 9·1; N, 4·9; loss of weight, 8·1. (*c*) C, 68·8; H, 9·1; loss of weight, 7·9. $C_{15}H_{23}O_3N,0·25C_6H_{14}$ requires C, 69·1; H, 9·25; N, 4·9; loss of weight, 7·5%].

2 : 4 : 4 : 7-*Tetramethylchroman*-2-*carboxylic Acid* (III).—The amide (XIII) as the *n*-hexane complex (0·200 g.) was heated in an oil-bath at 90° for 17 hours with glacial acetic acid (2·5 c.c.) and aqueous hydrobromic acid (2·5 c.c.; *d* 1·5), then poured into water and extracted with ether. The ethereal solution yielded to aqueous sodium carbonate a solid acid (0·066 g., 41%; m. p. 142—144°), which sublimed (at 150°/360 mm.) as needles and then crystallised from aqueous methanol as the characteristic rectangular tablets of 2 : 4 : 4 : 7-tetramethylchroman-2-carboxylic acid (III), m. p. 148—149° (Found : C, 71·6; H, 7·5. Calc. for $C_{14}H_{18}O_3$: C, 71·8; H, 7·7%). The acid prepared by oxidation of the dimeride (II) after purification by the above method had m. p. 148°, and a mixed m. p. determination of the two specimens showed no depression. The identity of the two specimens was further established by *X*-ray powder photographs kindly taken by Dr. T. Malkin. The acid is dimorphic, and at certain concentrations separates from aqueous methanol in the form of fine needles. These are unstable and change into the rectangular form when kept in the solution from which they have crystallised. The needle form appears to have the same m. p., 148—149°, as the rectangular form.

Preparation of 3 : 4-*Dihydro*-4 : 4 : 7-*trimethylcoumarin* (VIII) *from* m-*Cresol and ββ-Dimethylacrylic Acid*.—ββ-Dimethylacrylic acid (10·0 g., 1 mol.) was dissolved in *m*-cresol (21·6 g., 2 mols.) and treated with a rapid stream of dry hydrogen chloride for 5 minutes. Powdered aluminium chloride (28·0 g., 2·1 mols.) was then added with vigorous stirring during 15 minutes; the mixture became warm and finally very viscous, so that further stirring was impossible, after which it was kept overnight, and then heated on the steam-bath for 1 hour. The product was decomposed with ice and concentrated hydrochloric acid (50 c.c.) and extracted with ether (3 × 75 c.c.), and the extracts were shaken with 2N-sodium hydroxide (5 × 50 c.c.), dried ($MgSO_4$), and distilled, leaving an oil which rapidly crystallised on addition of light petroleum (20 c.c.; b. p. 40—60°). The colourless solid was collected (11·7 g.; m. p. 59°) and recrystallised from light petroleum (b. p. 40—60°), giving the pure 3 : 4-dihydro-4 : 4 : 7-trimethylcoumarin, m. p. and mixed m. p. with that previously described, 59·5°.

2-*Hydroxymethyl*-2 : 4 : 4 : 7-*tetramethylchroman* (XV).—Powdered lithium aluminium hydride (0·5 g.) was dissolved in sodium-dried ether (25 c.c.) with gentle warming in an atmosphere of nitrogen. A solution of 2 : 4 : 4 : 7-tetramethylchroman-2-carboxylic acid (III) (2·34 g.) in dry ether (20 c.c.) was then added dropwise during ½ hour, a vigorous reaction occurring as each drop was added. After 12 hours damp ether was added to decompose excess of reagent, then dilute hydrochloric acid, and the whole was shaken, and the ethereal layer separated, washed with dilute sodium hydroxide, then with water, dried, and distilled, leaving a colourless oil which crystallised slowly. Crystallisation from light petroleum (b. p. 40—60°) (3·5 c.c.) at 0° gave 2-*hydroxymethyl*-2 : 4 : 4 : 7-*tetramethylchroman* (XV) (1·04 g.) as large, thick, hexagonal plates which were washed with a little light petroleum at 0° and then had m. p. 47° (Found : C, 76·7; H, 8·8. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%).

4-(2-*Hydroxy*-4-*methylphenyl*)-2 : 4-*dimethylpentan*-2-*ol* (XVI).—A solution of 3 : 4-dihydro-4 : 4 : 7-trimethylcoumarin (VIII) (1·9 g.) in dry benzene (30 c.c.) was added to the Grignard reagent prepared from methyl iodide (8·66 g.), magnesium (1·36 g.), and ether (20 c.c.) in an atmosphere of nitrogen. The ether was then removed by distillation, and the remaining mixture refluxed for 12 hours, cooled, and poured on ice and sulphuric acid (30 c.c.; 10%), and the organic layer separated; the aqueous layer was extracted with ether (100 c.c.), and the combined extracts were washed with aqueous sodium sulphite, dilute sodium carbonate, and water, dried ($MgSO_4$), and distilled. The residual oil crystallised on addition of light petroleum (20 c.c.; b. p. 40—60°), and the solid was then recrystallised from light petroleum (b. p. 60—80°), giving the *pentanol* (XVI) as fine needles (1·95 g.), m. p. 100° (Found: C, 75·7; H, 10·1. $C_{14}H_{22}O_2$ requires C, 75·7; H, 9·9%).

2 : 2 : 4 : 4 : 7-*Pentamethylchroman* (XVII).—The preceding compound (XVI) (0·75 g.) was dissolved in dry methanol (10 c.c.) and saturated with hydrogen chloride during 20 minutes, and the mixture heated for 15 minutes, and then distilled, giving a colourless oil (0·51 g.), b. p. 65—67°/0·3 mm. (Found: C, 82·2; H, 10·1. $C_{14}H_{20}O_2$ requires C, 82·3; H, 9·8%). Bromination of this 2 : 2 : 4 : 4 : 7-*pentamethylchroman* with bromine in chloroform at 50°, the solvent being allowed to evaporate, gave a solid residue which separated from aqueous methanol in needles, m. p. 68° (Found: C, 46·3; H, 5·2; Br, 44·0. $C_{14}H_{18}OBr_2$ requires C, 46·4; H, 5·0; Br, 44·2%). This compound is undoubtedly 6 : 8-*dibromo*-2 : 2 : 4 : 4 : 7-*pentamethylchroman.*

4-*Methoxy*-1 : 1 : 3 : 3 : 6-*pentamethylindane* (XVIII).—4-(2-Methoxy-4-methylphenyl)-2 : 4-dimethylpentan-2-ol (X) (1·0 g.) in anhydrous benzene (5 c.c.) was boiled under reflux for 1 hour with phosphoric anhydride (0·2 g.). The benzene was decanted, the residue washed with benzene, and the combined solutions were washed with dilute aqueous sodium carbonate, dried, and distilled, giving 4-*methoxy*-1 : 1 : 3 : 3 : 6-*pentamethylindane* (XVIII) as a colourless viscous oil (0·46 g.), b. p. 69—71°/0·3 mm. (Found: C, 82·7; H, 9·7; OMe, 13·9. $C_{15}H_{22}O$ requires C, 82·6; H, 10·1; OMe, 14·2%).

Formation of 2 : 2 : 4 : 4 : 7-*Pentamethylchroman* (XVII) *from* 4-(2-*Methoxy*-4-*methylphenyl*)-2 : 4-*dimethylpentan*-2-*ol* (X).—The carbinol (X) (0·205 g.), hydrobromic acid (0·5 c.c.; *d* 1·48), and acetic acid (5 c.c.) were boiled for 6 hours, poured into water, and extracted with ether (2 × 5 c.c.). The extracts yielded an oil which was treated with excess of bromine in hot chloroform (5 c.c.) and evaporation in a current of air, leaving a crystalline solid. One crystallisation from methanol gave fine needles, m. p. 65° (0·205 g., 65%), raised by further crystallisation to 68°, undepressed when mixed with a specimen of the dibromo-derivative of 2 : 2 : 4 : 4 : 7-pentamethylchroman (XVII) previously described.

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