

202. *Condensation Products of Phenols and Ketones. Part V.* *Structure of the Dimeric Forms of o-isoPropenylphenols.*

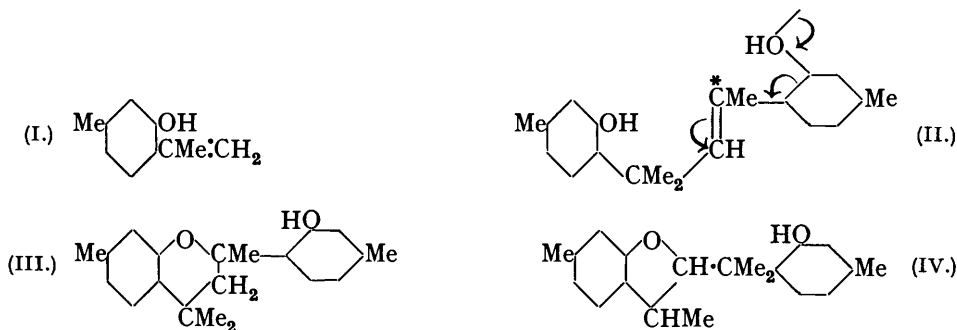
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4-isoPropenyl-*m*-cresol (I) is isolated as a dimeric form by the condensation of *m*-cresol with acetone in presence of hydrogen chloride. The dimeride is a weak monohydric phenol in which degradation of a *m*-tolyl to a carboxyl group occurs on oxidation. These facts, and a consideration of the mechanism of its formation, lead to the flavan structure (III) for the dimeride. Other *o*-isopropenylphenols and related compounds are, without doubt, of similar structure.

o-HYDROXY*iso*PROPENYL compounds such as (I) are formed, amongst other methods, by the condensation of phenols with ketones in acetic acid solution in presence of hydrogen chloride. Under these conditions, however, they are usually isolated as dimeric modifications, which, owing to their properties, must be regarded as genuine chemical compounds whose formation involves primary valencies. The dimeric forms are, moreover, formed from the simple molecules either on standing for a long time, or, more usually, on treatment with hydrogen chloride. Compounds of this type are the dimerides of *o*-isopropenylphenol (Fries, Gross-Selbeck, and Wicke, *Annalen*, 1913, **402**, 306), 4-methyl-2-isopropenylphenol (Fries and Fickewirth, *Ber.*, 1908, **41**, 368; Fries, Gross-Selbeck, and Wicke, *loc. cit.*; Eng. Pat. 279,856, 1929; Amer. Pat. 1,696,769, 1928), 5-methyl-2-isopropenylphenol (I) (4-isopropenyl-*m*-cresol; previous references; Eng. Pat. 273,684, 1927; Baker and Besly, *J.*, 1939, 199), 5-ethyl-2-isopropenylphenol (Niederl and Nagel, *J. Amer. Chem. Soc.*, 1940, **62**, 324), the similarly constituted 2-cyclohexenyl-4- and -5-methylphenol (Boettcher, *Dissert.*, Berlin, 1930), and 2-cyclohexenyl-5-ethylphenol (Niederl and Ziering, *J. Amer. Chem. Soc.*, 1940, **62**, 1157).

A general study of these dimeric *o*-isopropenylphenols was begun some years ago, and our view that these substances are derivatives of flavan (as III) was outlined in a letter to *Nature* (1939, **144**, 865). Further work on this subject is precluded for the time being, and, in view of the recent publication by Niederl and Ziering (*loc. cit.*) we now wish to record our observations and conclusions in greater detail. Niederl and Ziering prepared the dimeric form of 2-cyclohexenyl-5-ethylphenol by condensing *m*-ethylphenol with cyclohexanone in presence of hydrogen chloride, and suggested for it a flavan structure which was supported by an independent, but not entirely unambiguous, synthesis. They make no reference to our work, although in suggesting that the dimeric form of 4-isopropenyl-*m*-cresol was 2'-hydroxy-2 : 4 : 4 : 7 : 4'-pentamethylflavan (III) we stated that other such

dimerides, including those of *cyclohexenyl-m*- and *-p*-cresols, are, without doubt, similarly constituted.



The dimerides are liquids, except those derived from *o*-isopropenylphenol and the *cyclohexenylphenols*, or, in the cases of the dimerides of (I) and 3-isopropenyl-*p*-cresol, amorphous solids, and may be distilled unchanged under diminished pressure, but are depolymerised when distilled at atmospheric pressure. The dimerides of 4-isopropenyl-*m*-cresol and 4-*cyclohexenyl-m*-cresol form crystalline adducts with one molecule of diethyl ether. All the dimerides are monohydric phenols, so that one of the oxygen atoms must be in the form of an ether group. Moreover, the phenolic function of the free hydroxyl group is extremely feeble, and was, in fact, originally overlooked (Fries and Fickewirth, *loc. cit.*) but later recorded (Fries, Gross-Selbeck, and Wicke, *loc. cit.*). The dimerides do not dissolve in dilute sodium hydroxide solution, but a suspension in dilute alcohol or acetone dissolves on the addition of alkali; on dilution the dimeride is thrown out of solution or may be extracted with an organic solvent. They give no ferric chloride reaction in alcoholic or dilute alcoholic solution, but give crystalline monoacetyl or monoacyl derivatives.

It has now been found that the dimeride of 4-isopropenyl-*m*-cresol, $C_{20}H_{24}O_2$, is oxidised by potassium permanganate in acetone solution to give a stable carboxylic acid, $C_{13}H_{17}O \cdot CO_2H$, which resists further oxidation or decarboxylation, and is, therefore, unlikely to possess an α -hydrogen atom. This corresponds to the degradation of a *m*-tolyl group to a carboxyl group. The dimeride of isopropenyl-*m*-cresol reacts with methyl sulphate and alkali to give an amorphous methyl ether, which has not been obtained pure; it separates from organic solvents in the form of a jelly.

Apart from a tentative suggestion for the structure of the dimeride of (I) put forward by Fries and Fickewirth and subsequently withdrawn by Fries, Gross-Selbeck, and Wicke, only one very improbable structure has been proposed for these compounds (Jordan, Eng. Pat. 279,856, 1929; this structure has been accepted by Boettcher, *loc. cit.*). This contained an olefinic link, although the substance was known to be saturated, and was based on a formula for a condensation product of *m*-cresol and acetone now known to be incorrect (Baker and Besly, *loc. cit.*). It is clear from the properties of the dimeride of (I) that it is produced by the mutual addition of the two isopropenyl groups and ring closure to a saturated cyclic ether. Solely on valency considerations there are fourteen possible structures for the compound, one containing an eight-membered ring, three containing seven-membered rings, three chromans, and seven coumarans. Of these structures, only three, namely, one chroman (III) and two coumarans, (IV) and 2- α -(2'-hydroxy-4'-methylphenyl)-ethyl-3 : 3 : 6-trimethylcoumaran, involve the $\alpha\beta'$ -linking of the two isopropenyl groups, as occurs all but universally in the polymerisation of styrenes and related compounds (see Baker and Enderby, this vol., p. 1094), and only (III) and (IV) could be expected to yield the carboxylic acid $C_{13}H_{17}O \cdot CO_2H$ on oxidation. The final choice between the flavan (2-phenylchroman) structure (III) and the two coumarans can be made with certainty by a consideration of the probable mechanism of the reaction. This undoubtedly takes place by the formation of a $\cdot CMe_2 \cdot CH \cdot CMe \cdot$, formula (II), or less probably $\cdot CMe_2 \cdot CH_2 \cdot \overset{*}{C}(:CH_2) \cdot$ bridge between the two aromatic nuclei (cf. structure of isoanethole; Goodall and Haworth, J., 1930, 2482), and in the subsequent ring closure a phenolic oxygen atom must unite with

the more cationoid of the two unsaturated carbon atoms (marked with *), the double bonds being polarised by the adjacent phenolic group. In either case ring closure will thus lead to the formation of 2'-hydroxy-2 : 4 : 4 : 7 : 4'-pentamethylflavan (III).

This flavan structure adequately accounts for the cryptophenolic properties by the presence of the large group $\cdot\text{C}(\text{O})\text{Me}\cdot\text{CH}_2\cdot\text{CMe}_2\cdot$ in the *o*-position to the hydroxyl. This group closely resembles the octyl group $\cdot\text{CMe}_2\text{CH}_2\cdot\text{CMe}_3$, which is sufficient, even in the simple *p*-octylphenol, to cause the compound to exhibit strongly cryptophenolic properties. The acid obtained by the degradation of the dimeride (III) must be 2 : 4 : 4 : 7-tetramethylchroman-2-carboxylic acid. There can be little doubt that the dimeric forms of other *o*-isopropenylphenols are flavans analogous to (III). The dimeric *o*-cyclohexenylphenols are also without doubt flavans of the structure advanced by Niederl and Ziering, a structure previously implied in our letter to *Nature*.

Attempts were made to synthesise simple 2'-hydroxyflavans for comparison purposes by the catalytic reduction of 2'-hydroxy-6-methylflavone and 2'-hydroxyflavone, but the products were complex mixtures from which the flavans could not be isolated. It is worthy of note that these 2'-hydroxyflavones give no ferric chloride reaction.

EXPERIMENTAL.

Dimeric Form (III) of 4-isoPropenyl-m-cresol (I).—The following method, based on Eng. Pat. 273,684 (cf. Baker and Besly, *loc. cit.*), is convenient for preparing the compound in quantity. A mixture of *m*-cresol (110 g.) and acetone (65 g.) was saturated with hydrogen chloride without cooling, and kept at 40° for 2 days with the exclusion of water. The dark product was added to an excess of 20% sodium hydroxide solution, a layer of ether poured on the surface, and the mixture vigorously stirred, causing the ether addition product of the dimeride to crystallise; after standing overnight in an open vessel, the solid was collected, washed thoroughly with water, dissolved and dried with calcium chloride in hot light petroleum (b. p. 40—60°), and to the filtered solution was added a little ether. The ether addition product of the dimeride, $\text{C}_{20}\text{H}_{24}\text{O}_2\cdot\text{Et}_2\text{O}$, separated in large, colourless, highly refracting, thick, rhombic plates, m. p. 76—77° when rapidly heated (yield, 75 g.). On standing in air, the crystals lose some of the ether and become opaque and sticky; at 100° the ether is completely lost and the melt sets to a glass, which crystallises in contact with ether, a fact which can be used as the basis of a delicate and specific test for diethyl ether.

2'-Acetoxy-2 : 4 : 4 : 7 : 4'-pentamethylflavan.—The dimeride (III) (3 g.) was refluxed with acetic anhydride (15 c.c.) and anhydrous sodium acetate (1 g.) for 4 hours, and poured into water. The solid product was washed with alcohol and crystallised twice from the same solvent, being obtained in small rhombic crystals, m. p. 108° (Found: C, 78.0; H, 7.6; Ac, 12.6; *M*, 325. $\text{C}_{20}\text{H}_{23}\text{O}_2\text{Ac}$ requires C, 78.1; H, 7.7; Ac, 12.7%; *M*, 338). Hydrolysis with alcoholic potassium hydroxide regenerated the dimeride (III).

Oxidation of the Dimeride (III), and Isolation of 2 : 4 : 4 : 7-Tetramethylchroman-2-carboxylic Acid.—The pure ether addition product of the dimeride (III) (20 g.), dissolved in acetone (100 c.c.), was treated at the b. p. in portions with a saturated solution of potassium permanganate in boiling acetone, until an excess of permanganate was present. After standing for 2 hours, the mixture was diluted with water to twice its volume, excess of sulphur dioxide passed, and, after filtration, the acetone removed by distillation under diminished pressure. The mainly solid material which separated was treated with aqueous sodium bicarbonate, and the resulting solution acidified, yielding a crystalline carboxylic acid (1.1 g.). It separated from benzene in small, stout, rhombic crystals, m. p. 148—149° (Found: C, 71.7; H, 7.7; equiv., 232. $\text{C}_{15}\text{H}_{17}\text{O}\cdot\text{CO}_2\text{H}$ requires C, 71.8; H, 7.7%; equiv., 234). The acid was not decarboxylated in boiling quinoline, even in presence of copper chromite (Adkins and Connor, *J. Amer. Chem. Soc.*, 1931, 53, 1091), nor did it appear to be decarboxylated when heated with or without copper chromite to temperatures at which charring occurred.

2-(2'-Methoxybenzoyloxy)-5-methylacetophenone.—A mixture of 2-hydroxy-5-methylacetophenone (15 g.), pyridine (30 c.c.), and 2-methoxybenzoyl chloride (17 g.; 1 mol.) was heated on the water-bath for 20 minutes and then poured into excess of dilute hydrochloric acid. The oily product, which solidified, was collected, washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water, and crystallised twice from methyl alcohol (yield, 23 g.). It was obtained in very faintly yellow, stout rhombic prisms, m. p. 85° (Found: C, 71.8; H, 5.8. $\text{C}_{17}\text{H}_{16}\text{O}_4$ requires C, 71.8; H, 5.6%).

ω-2'-Methoxybenzoyl-2-hydroxy-5-methylacetophenone.—The preceding compound (20 g.) in toluene (200 c.c.) was stirred on the steam-bath for 8 hours with anhydrous potassium carbonate (60 g.), and the yellow solids, consisting of the potassium salt of the dibenzoylmethane derivative and excess of potassium carbonate, collected while hot, washed with hot benzene, and dried. On stirring into water the free compound separated; it was collected, washed with much water, dried (yield, 15 g.), and crystallised first from acetic acid and then from ethyl alcohol. It formed yellow, stout, rhombic crystals, m. p. 106° (Found: C, 72.0; H, 5.6. C₁₇H₁₆O₄ requires C, 71.8; H, 5.6%). It dissolved slightly in aqueous sodium hydroxide to a yellow solution. Its alcoholic solution gave a reddish-brown colour with ferric chloride.

2'-Methoxy-6-methylflavone.—The preceding compound (13 g.) was refluxed with acetic acid (50 c.c.) and anhydrous sodium acetate (10 g.) for 3 hours. The solid obtained on the addition of water was collected, washed, and dried (yield, 11 g.); it crystallised from alcohol in long, prismatic needles, m. p. 110° (Found: C, 76.6; H, 5.2. C₁₇H₁₄O₃ requires C, 76.7; H, 5.2%). In concentrated sulphuric acid it gave a pale yellow solution which, when warmed, became almost colourless and developed a blue fluorescence.

2'-Hydroxy-6-methylflavone.—2'-Methoxy-6-methylflavone (10 g.) was refluxed for 24 hours with acetic acid (40 c.c.) and hydrobromic acid (*d* 1.5; 40 c.c.), the mixture poured into water, and the solid collected, washed, dried (9.4 g.), and crystallised from acetic acid (yield, 6.6 g.). After recrystallisation from a large volume of alcohol it was obtained in very faintly yellow prisms, m. p. 255–256° (Found: C, 76.2; H, 4.7. C₁₆H₁₄O₃ requires C, 76.2; H, 4.7%). 2'-Hydroxy-6-methylflavone dissolves in hot dilute sodium hydroxide to a bright yellow solution, from which the very sparingly soluble sodium salt separates in fine, golden-yellow prisms. Its alcoholic or dilute alcoholic solutions show no ferric chloride reaction. In concentrated sulphuric acid it gives a yellow solution whose colour gradually fades and a weak blue fluorescence develops. The acetyl derivative, obtained by boiling with excess of acetic anhydride for 3 hours and then shaking with water, separated from light petroleum (b. p. 40–60°) in colourless, rhombic prisms, m. p. 101° (Found: C, 73.6; H, 4.8. C₁₈H₁₄O₄ requires C, 73.5; H, 4.7%).

2-(2'-Methoxybenzoyloxy)acetophenone.—*o*-Hydroxyacetophenone (13.6 g.), pyridine (30 c.c.), and 2-methoxybenzoyl chloride (17 g.; 1 mol.) were heated for 20 minutes on the water-bath, and stirred into excess of dilute hydrochloric acid. The oily product solidified overnight and was collected, crushed, washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water, and crystallised from methyl alcohol (yield, 20 g.). It formed colourless, blunt-ended, rhombic prisms, m. p. 79° (Found: C, 70.7; H, 5.2. C₁₆H₁₄O₄ requires C, 71.1; H, 5.2%).

ω-2'-Methoxybenzoyl-2-hydroxyacetophenone.—A mixture of the preceding compound (18 g.), toluene (200 c.c.), and anhydrous potassium carbonate (60 g.) was stirred on the steam-bath for 10 hours. The product (7 g.), isolated as in the case of the corresponding methyl derivative, and twice crystallised from alcohol, formed yellow prisms, m. p. 80° (Found: C, 71.2; H, 5.2. C₁₆H₁₄O₄ requires C, 71.1; H, 5.2%).

2'-Methoxyflavone.—Ring closure of the preceding compound with acetic acid and sodium acetate as in the case of the methyl homologue gave 2'-methoxyflavone in stout, colourless, four-sided prisms from alcohol, m. p. 105° (cf. Pistermann and Tambor, *Ber.*, 1912, 45, 1239; Hattori, *Acta Phytochim.*, 1928, 4, 41).

2'-Hydroxyflavone.—Demethylation of the preceding compound as in the case of the methyl homologue gave 2'-hydroxyflavone in long, very pale yellow needles from alcohol, m. p. 244° (rapid heating) (Pistermann and Tambor, and Hattori, *loc. cit.*, record m. p. 238.5°). The compound gives no colour reaction with alcoholic ferric chloride.