

596. Condensation Products of Phenols and Ketones. Part XII.*
 Studies with *m*-Cresol, *m*-Ethylphenol, and 3:4-Dimethylphenol.

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m-Ethylphenol condenses with acetone to give 7:4'-diethyl-2'-hydroxy-2:4:4-trimethylflavan (II; R = Et, R' = H) and a small amount of 4:4:4':4'-tetramethyl-7:7'-diethyl-2:2'-spirobischroman (V; R = Et, R' = H).

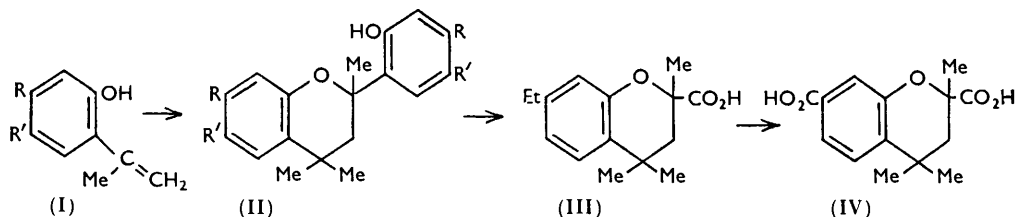
3:4-Dimethylphenol similarly gives the related flavan (II; R = R' = Me) convertible by acid into the *spirochroman* (V; R = R' = Me).

m-Cresol and *cyclohexanone* give *cyclohexanespiro-4-(2'-hydroxy-7:4'-dimethyl-2:3-tetramethylene)flavan* (VI).

Some crystalline complexes of these flavans are described.

m-ETHYLPHENOL condenses with acetone and hydrogen chloride to give as the major reaction product the crystalline 7:4'-diethyl-2'-hydroxy-2:4:4-trimethylflavan (II; R = Et, R' = H). The structure of this product was established by a two-stage oxidation with potassium permanganate which gave first 7-ethyl-2:4:4-trimethylchroman-2-carboxylic acid (III) by oxidation in boiling acetone, and then the known 2:4:4-trimethylchroman-2:7-dicarboxylic acid¹ (IV) by oxidation in aqueous sodium carbonate. Compound (II; R = Et, R' = H) is cryptophenolic as are other related 2'-hydroxyflavans, but the hydroxyl group may be acetylated and methylated. The minor product of the reaction between *m*-ethylphenol and acetone is the non-phenolic 4:4:4':4'-tetramethyl-7:7'-diethyl-2:2'-spirobischroman (V; R = Et, R' = H).

A similar condensation of 3:4-dimethylphenol and acetone yielded 2'-hydroxy-2:4:4:6:7:4':5'-heptamethylflavan (II; R = R' = Me).



Flavans of type (II) have been shown in the present series of papers to result from the dimerisation of *o*-isopropenylphenols (I) in presence of hydrogen chloride;^{1,2,3,4,5} the *o*-isopropenylphenols may result from the direct condensation of the phenol with acetone as in the cases of *m*-^{2,3,4} and *p*-cresol,¹ and of *m*-ethylphenol and 3:4-dimethylphenol (this paper), but in the more general case they must be prepared in other ways, *e.g.*, by thermal dehydration of the alcohols derived from methylmagnesium iodide and the sodium salt of a methyl *o*-hydroxybenzoate.^{1,5} The reaction between *m*-ethylphenol, acetone, and hydrogen chloride was first investigated by Niederl and Nagel,⁶ who described the dimeride of the derived *isopropenyl* compound as a viscous, yellow liquid with a thymol-like odour; this product was obviously very crude and no structural formula was proposed.

The *spirobischroman* (V; R = Et, R' = H) obtained in small quantity by condensation of *m*-ethylphenol with acetone was identical with the product obtained by Niederl

* Part XI, *J.*, 1956, 2018.

¹ Baker, Curtis, and McOmie, *J.*, 1952, 1774.

² Baker and Besly, *Nature*, 1939, **144**, 865.

³ Baker and Besly, *J.*, 1940, 1103.

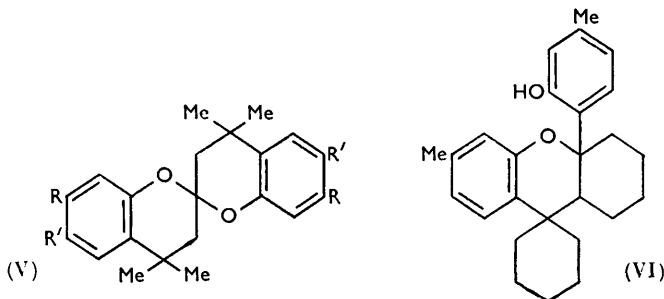
⁴ Baker, Curtis, and McOmie, *J.*, 1951, 76.

⁵ Baker, Downing, Hewitt-Symonds, and McOmie, *J.*, 1952, 3796.

⁶ Niederl and Nagel, *J. Amer. Chem. Soc.*, 1940, **62**, 324.

and Nagel⁶ from their crude dimeride, now proved to be (II; R = Et, R' = H), by treatment with hot concentrated sulphuric acid according to the directions of Boettcher.⁷ This deep-seated reaction, brought about by the influence of acid, has been shown by Baker and Besly⁸ in the case of 2'-hydroxy-2 : 4 : 4 : 7 : 4'-pentamethylflavan (II; R = Me, R' = H) to involve three molecules of the flavan which yield two molecules of the *spiro*-bischroman (V; R = Me, R' = H) and two of *m*-cresol. In a similar way the flavan (II; R = R' = Me) has now been converted into 4 : 4 : 6 : 7 : 4' : 4' : 6' : 7'-octamethyl-2 : 2'-*spiro*bischroman (V; R = R' = Me) and 3 : 4-dimethylphenol. The *spiro*bischroman (V; R = Et, R' = H) obtained by the condensation of *m*-ethylphenol and acetone may have been formed in this way from the flavan (II; R = Et, R' = H) or may have been formed by the condensation of *m*-ethylphenol with phorone, the latter being derived from acetone by self-condensation.⁹

Re-investigation of the condensation of *m*-cresol with *cyclohexanone* in presence of hydrogen chloride, originally carried out by Boettcher,⁷ has shown that it yields a cryptophenolic, monohydric phenol, which by analogy must be regarded as *cyclohexanespiro-4*-(2'-hydroxy-7 : 4'-dimethyl-2 : 3-tetramethyleneflavan) (VI). This compound is exactly analogous to the flavans (II), a suggestion originally advanced by Baker and Besly,² and it appears to be identical with the substance isolated by Boettcher, but he ascribed to it an erroneous structure and mistakenly regarded it as unsaturated.



Like many other 2'-hydroxy-2 : 4 : 4-trimethylflavans described in this series, the flavans (II; R = Et, R' = H) and (VI) form crystalline complexes with a large number of substances, particularly cyclic nitrogenous bases. These complexes are listed in the Experimental section, as are those formed from dimethyl-*p*-nitrosoaniline and 2'-hydroxy-2 : 4 : 4 : 6 : 5'- and 2'-hydroxy-2 : 4 : 4 : 7 : 4'-pentamethylflavan (II; R = H, R' = Me) and (II; R = Me, R' = H).^{1, 10} That these complexes are not purely inclusion compounds (clathrates) is indicated by the 1 : 1 molecular ratio of flavan to component, and by the fact that only molecules which are proton acceptors form such complexes; molecular size and shape is not the sole factor in controlling complex formation as has already been discussed in greater detail in similar instances.^{10, 1}

2'-Hydroxy-2 : 4 : 4 : 6 : 7 : 4' : 5'-heptamethylflavan (II; R = R' = Me) appears to form no crystalline complexes. The only other flavan of this type which also fails to form complexes is 2'-hydroxy-2 : 4 : 4 : 8 : 3'-pentamethylflavan.¹

EXPERIMENTAL

7 : 4'-Diethyl-2'-hydroxy-2 : 4 : 4-trimethylflavan (II; R = Et, R' = H).—*m*-Ethylphenol (freshly distilled, 111 g.) in anhydrous acetone (45 g.) was saturated with anhydrous hydrogen chloride at 0°, kept at room temperature for 2 days, then warmed to 40° for 6 hr. and stirred

⁷ Boettcher, Diss., Berlin, 1930.

⁸ Baker and Besly, *J.*, 1939, 198.

⁹ Fisher, Furlong, and Grant, *J. Amer. Chem. Soc.*, 1936, **58**, 820; Niederl, *Sitzungsber. Akad. Wiss. Wien*, 1932, **141**, Iib, 150.

¹⁰ Baker, Curtis, and Edwards, *J.*, 1951, 83.

into 2*N*-sodium hydroxide (500 c.c.) to which diethyl ether (60 c.c.) had been added. After 2 days at 0° the semi-solid product was collected, washed with water, dried *in vacuo*, and crystallised from light petroleum (150 c.c.; b. p. 40–60°)—diethyl ether (5 c.c.), giving the ether adduct of the flavan as large rhombs (40 g.), m. p. 72–73° (with loss of solvent). This adduct effloresces too rapidly for accurate analysis, and the crystals fall to a microcrystalline powder. The free 7 : 4'-diethyl-2'-hydroxy-2 : 4 : 4-trimethylflavan (II; R = Et, R' = H) was prepared by heating the ether adduct to 100° *in vacuo* and recrystallisation from light petroleum (b. p. 40–60°); it formed large rhombs, m. p. 70–71° (Found : C, 81.4; H, 8.9. C₂₂H₂₈O₂ requires C, 81.5; H, 8.6%). The flavan is insoluble in aqueous sodium hydroxide, and dissolves in concentrated sulphuric acid with a bright yellow colour. The *acetyl derivative*, prepared by adding acetyl chloride (0.25 g.) to the flavan (0.8 g.) in pyridine (10 c.c.), heating on the water-bath for ½ hr., and pouring the whole into water, separated from methanol in rhombs, m. p. 126–127° (Found : C, 78.2; H, 7.9. C₂₄H₃₀O₃ requires C, 78.6; H, 8.2%).

7 : 4'-Diethyl-2'-methoxy-2 : 4 : 4-trimethylflavan.—The preceding flavan (2.0 g.) was heated on the steam-bath for 48 hr. in acetone (50 c.c.) and benzene (40 c.c.) with methyl sulphate (8 c.c.) and anhydrous potassium carbonate (15 g.); water (5 c.c.) was then added and the heating continued for ½ hr. The mixture was filtered whilst hot, the solvents were removed, the residue was shaken with water (30 c.c.), and the solid (1.92 g.; m. p. 75–76°) collected. Two crystallisations from methanol gave the ether as rods, m. p. 77–78° (Found : C, 81.4; H, 8.7. C₂₃H₃₀O₂ requires C, 81.6; H, 8.9%).

7-Ethyl-2 : 4 : 4-trimethylchroman-2-carboxylic Acid (III).—The flavan (3 g.) in warm acetone (30 c.c.) was oxidised by the rapid addition of a boiling, saturated solution of potassium permanganate in acetone (1 l.); a gentle reaction set in which was complete in 2 min. The bulk of the acetone was removed by distillation and to the residue was added water (100 c.c.), sodium dithionite (40 g.), and concentrated hydrochloric acid (5 c.c.); then sulphur dioxide was passed in with shaking till the manganese dioxide had disappeared. The ethereal extract (4 × 50 c.c.) of the mixture was shaken thrice with excess of aqueous sodium hydrogen carbonate, and the alkaline layers were acidified, and the solid was collected after being kept at 0°, washed, and dried (yield 0.9 g.). After twice crystallising from light petroleum (b. p. 60–80°) the acid (III) was obtained as needles, m. p. 123° (Found : C, 72.4; H, 8.2. C₁₅H₂₀O₃ requires C, 72.6; H, 8.1%).

2 : 4 : 4-Trimethylchroman-2 : 7-dicarboxylic Acid (IV).—The preceding acid (III) (0.2 g.) in 5% aqueous sodium carbonate (20 c.c.) was boiled and powdered potassium permanganate added in portions till an excess was present, and after addition of more water (5 c.c.) boiling was continued for 20 min. The cooled solution was treated with sulphur dioxide. Extraction with ethyl acetate (2 × 10 c.c.) yielded a solid which was crystallised twice from ethyl acetate–light petroleum (b. p. 60–80°), giving the dicarboxylic acid (IV), m. p. and mixed m. p. with an authentic specimen¹ 260–261°.

4 : 4 : 4' : 4'-Tetramethyl-7 : 7'-diethyl-2 : 2'-spirobischroman (V; R = Et, R' = H).—(a) The light petroleum–ethyl ether mother-liquor from the first crystallisation of the flavan (II; R = Et, R' = H) (see above) were evaporated to dryness, and the residue crystallised twice from ethanol (charcoal), giving the *spirochroman* (V; R = Et, R' = H) as needles (2.2 g.), m. p. 114°. (b) The flavan (II; R = Et, R' = H) was heated with concentrated sulphuric acid at 190° for ½ min. and the product isolated as described by Niederl and Nagel,⁶ giving the *spirochroman*, m. p. and mixed m. p. 114°.

2'-Hydroxy-2 : 4 : 4 : 6 : 7 : 4' : 5'-heptamethylflavan (II; R = R' = Me).—A solution of 3 : 4-dimethylphenol (37 g.) in acetone (15 g.) at 25° was saturated with anhydrous hydrogen chloride, after which it rapidly set to a red, crystalline mass. After 3 days it was crushed with excess of dilute aqueous sodium hydroxide, washed, dried (yield 29 g.), and crystallised twice from ethanol, giving the flavan (II; R = R' = Me) as colourless, rhombic prisms, m. p. 160–161° (Found : C, 81.2; H, 8.6. C₂₂H₂₈O₂ requires C, 81.5; H, 8.6%). Its solution in concentrated sulphuric acid is intensely red. The *acetyl derivative*, prepared in hot pyridine with a large excess of acetyl chloride for 20 min., formed prisms, m. p. 136–137° (Found : C, 78.2; H, 8.4. C₂₄H₃₀O₃ requires C, 78.6; H, 8.3%).

4 : 4 : 6 : 7 : 4' : 4' : 6' : 7'-Octamethyl-2 : 2'-spirobischroman (V; R = R' = Me).—The preceding flavan (1.0 g.) was melted, concentrated sulphuric acid (1 drop) was added, and the mixture heated to 190° for ½ min.; crystals of 3 : 4-dimethylphenol separated on the upper parts of the tube. The product was treated with 50% aqueous methanol (10 c.c.), and the

insoluble residue crystallised from 95% ethanol (yield 0.72 g.; m. p. 195—197°), and then twice from benzene-ethanol, giving the *spirochroman* as needles, m. p. 199—200° (Found: C, 81.9; H, 8.4. $C_{25}H_{32}O_2$ requires C, 82.3; H, 8.9%).

cycloHexanespiro-4-(2'-hydroxy-7 : 4'-dimethyl-2 : 3-tetramethylene)flavan (VI).—A mixture of *m*-cresol (100 g.) and *cyclohexanone* (60 g.) was saturated with hydrogen chloride at 0°, kept for 3 days at room temperature and 1 day at 40—50°, and stirred into 2*N*-sodium hydroxide (1 l.). The product was extracted into ether (250 c.c.)—light petroleum (100 c.c.; b. p. 60—80°), and the solution washed with water, dried, and evaporated to dryness after treatment with charcoal. The yellow resin (80 g.) was crystallised twice from light petroleum (b. p. 60—80°) (charcoal), giving the flavan (VI) as needles (25 g.), m. p. 140—142° (Found: C, 83.4; H, 8.5. $C_{26}H_{32}O_2$ requires C, 83.0; H, 8.5%). Crystallisation from ethanol which is slow gave a second crystalline modification as prisms, m. p. 149—150° (Found: C, 83.1; H, 8.6%). The flavan dissolves in concentrated sulphuric acid with a deep yellow colour. The *acetyl derivative*, prepared by refluxing the flavan (1 g.), for 4 hr. with acetic anhydride (10 c.c.) and anhydrous sodium acetate (1 g.), crystallised from ethanol as needles, m. p. 170—172° (Found: C, 80.8; H, 8.1. $C_{28}H_{34}O_3$ requires C, 80.4; H, 8.1%).

cycloHexanespiro-4-(2'-methoxy-7 : 4'-dimethyl-2 : 3-tetramethylene)flavan.—The flavan (VI) (1 g.), acetone (50 c.c.), methyl sulphate (6.0 c.c.), and anhydrous potassium carbonate (10 g.) were refluxed for 25 hr., cooled, filtered, and evaporated under reduced pressure. The solid product was washed with cold 2*N*-sodium hydroxide (50 c.c.), dried (0.62 g.), and crystallised from ethanol and then from ethanol-acetone, giving *cyclohexanespiro-4-(2'-methoxy-7 : 4'-dimethyl-2 : 3-tetramethyl)flavan* as prisms, m. p. 181—182° (Found: C, 83.3; H, 8.9. $C_{27}H_{34}O_2$ requires C, 83.0; H, 8.8%).

Preparation of Crystalline Complexes.—The flavans (0.5 g.) were dissolved in light petroleum [5 c.c., b. p. 40—60°, in the case of the flavan (II; R = Et, R' = H)]; 10 c.c., b. p. 60—80°,

Crystalline complexes formed by 2'-hydroxy-2 : 4 : 4-trimethylflavans (II) and (VI).

Component	M. p. (dissocn.)	Ratio, flavan : component	Analyses: Found, % (required % in parentheses)		
			Carbon	Hydrogen	Nitrogen
7 : 4'-Diethyl-2'-hydroxy-2 : 4 : 4-trimethylflavan (II; R = Et, R' = H) ^a					
<i>cyclo</i> Hexylamine	84—85°	1 : 1	79.8 (79.5)	9.7 (9.7)	3.4 (3.3)
Quinoline	69—70	1 : 1	81.8 (82.0)	7.5 (7.7)	3.1 (3.0)
<i>NN</i> -Dimethyl- <i>p</i> -nitrosoaniline	93—94 ^b	1 : 1	76.3 (76.0)	7.8 (8.0)	5.8 (5.9)
Dioxan and water	70—72 ^c	1 : 1 : 2	69.1 (69.6)	8.2 (8.9)	—
<i>cyclo</i> Hexanespiro-4-(2'-hydroxy-7 : 4'-dimethyl-2 : 3-tetramethylene)flavan (VI) ^d					
<i>cyclo</i> Hexylamine	127—128	1 : 1	—	—	2.6 (2.9)
Morpholine	133—134	1 : 1	77.8 (78.1)	8.9 (8.8)	—
Benzylamine	117—118	1 : 1	81.8 (82.0)	8.4 (8.5)	3.0 (2.9)
<i>o</i> -Chloroaniline	87—89	1 : 1	—	—	3.3 (2.8) ¹
<i>p</i> -Chloroaniline	122—123	1 : 1	75.9 (76.3)	7.4 (7.5)	2.8 (2.8) ²
Pyridine	118—119	1 : 1	81.7 (81.8)	8.1 (8.1)	3.5 (3.1)
3-Methylpyridine	105—107	1 : 1	82.0 (81.9)	8.3 (8.3)	3.1 (3.0)
2 : 6-Dimethylpyridine	138—140	1 : 1	—	—	2.6 (2.9)
2 : 4 : 6-Trimethylpyridine ...	109—110	1 : 1	82.3 (82.8)	8.6 (8.7)	2.6 (2.8)
Quinoline	130—132	1 : 1	83.2 (83.2)	7.7 (7.7)	2.9 (2.8)
2-Chloroquinoline	107—109	1 : 1	78.0 (77.8)	6.9 (7.0)	2.8 (2.6) ³
2'-Hydroxy-2 : 4 : 4 : 6 : 5'-pentamethylflavan (II; R = H, R' = Me) ^e					
<i>NN</i> -Dimethyl- <i>p</i> -nitrosoaniline	100—101 ^f	1 : 1	75.1 (75.4)	7.5 (7.6)	6.3 (6.3)
2'-Hydroxy-2 : 4 : 4 : 7 : 4'-pentamethylflavan (II; R = Me, R' = H) ^e					
<i>NN</i> -Dimethyl- <i>p</i> -nitrosoaniline	116—117 ^g	1 : 1	74.9 (75.4)	7.4 (7.6)	6.2 (6.3)

^a Crystalline complexes which were too unstable for accurate analysis were formed with diethyl ether, diisopropyl ether, and tetrahydrofuran. Complexes were not obtained with aniline, morpholine, aliphatic bases, or aliphatic ketones. ^b Crystals are yellow-green. ^c Dioxan does not form a complex in the absence of water. This flavan-dioxan-water complex was prepared by cooling to 0° a solution of the flavan (1 g.) in light petroleum (10 c.c.; b. p. 40—60°), dioxan (0.5 c.c.), water (2 drops), and ethanol (to give a clear solution). ^d A complex with diethyl ether was too unstable for accurate analysis. Complexes were not formed with aliphatic ketones, di-*n*-propylamine, diethylamine, *n*-octylamine, *n*-hexylamine, aniline, dioxan. ^e Complexes formed in methanol solution. ^f Olive-green needles from aqueous methanol or brown needles from petroleum (b. p. 60—80°) which change to the olive-green form after 2 weeks in contact with the solvent. ^g Dark olive-green or almost black needles, according to size. ^{1,2,3} Found: Cl, (1) 7.4, (2) 7.3, (3) 6.5. Required: Cl, (1, 2) 7.2, (3) 6.6%.

in the case of the flavan (VI)], and the other component (1.2 mol.) added. If crystallisation did not occur rapidly, the mixture was kept at 0°; the complexes were collected, washed with a little light petroleum, and dried by exposure to the air (see Table).

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[Received, February 21st, 1957.]
