

*Synthesis of 2 : 4 : 6-Trishydroxymethylphenol and of
2 : 4 : 6-Trishydroxybenzylphenol Derivatives.*

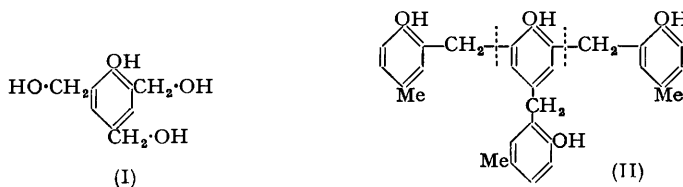
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2 : 4 : 6-Trishydroxymethylphenol has been synthesised from 2 : 4-diformylphenol by way of 2-chloromethyl-4 : 6-diformylphenol, hydrolysis to the corresponding hydroxymethyl derivative, and subsequent reduction with platinum and hydrogen, and by a modification of this route involving dichloromethylation of salicylaldehyde with subsequent hydrolysis and reduction of 2-formyl-4 : 6-bishydroxymethylphenol. The trialcohol has also been prepared by reduction of 2 : 4 : 6-trisacetoxymethylphenyl acetate with lithium aluminium hydride.

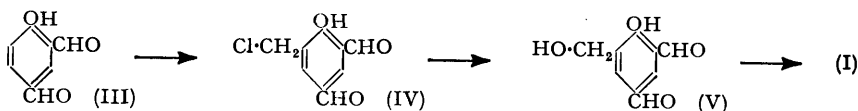
Confirmation of the constitution of tetranuclear Novolaks formed by condensation of 2 : 4 : 6-trishydroxymethylphenol and 2 : 4 : 6-trisacetoxymethylphenyl acetate with *p*-substituted phenols has been provided by synthesis of 2 : 4 : 6-tri-(2-hydroxy-3 : 5-dimethylbenzyl)phenol from 4-bromo-2 : 6-di-(2-hydroxy-3 : 5-dimethylbenzyl)phenol by a lithium exchange reaction, reduction of the 4-carboxy-phenol with lithium aluminium hydride, and condensation of the resulting hydroxymethyl derivative with 2 : 4 : 1-xylene.

THE isolation of 2 : 4 : 6-trishydroxymethylphenol (I) which had figured for several years in reviews and standard works on plastics as a crystalline individual was announced at the Symposium on Polymer Chemistry as Applied to Plastics in 1950. The trialcohol was obtained in small yield by reduction of ethyl trimesate with lithium aluminium hydride in dioxan and characterised by the tetranuclear Novolak (II) obtained by condensation with

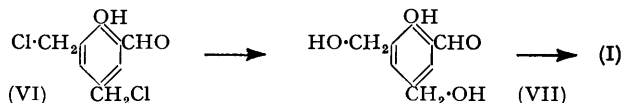


p-cresol (Carpenter and Hunter, *J. Appl. Chem.*, 1951, 1, 217). Attempts to prepare 2 : 4 : 6-trishydroxymethylphenol by reduction of 2 : 4 : 6-trisacetoxymethylphenyl acetate obtained by Bruson and MacMullen's method (*J. Amer. Chem. Soc.*, 1941, 63, 270) with

lithium aluminium hydride in ether proved unsuccessful (*loc. cit.*). From material purified by high-vacuum distillation, however, we obtained quite substantial yields of the trialcohol from the trisacetoxymethyl derivative.

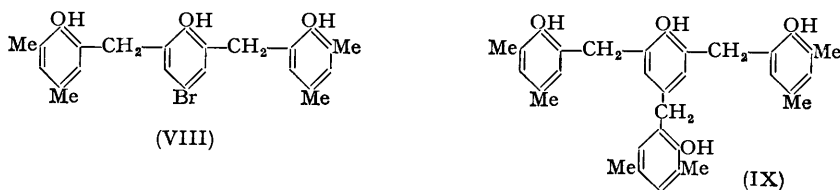


The rational synthesis of the trialcohol from 2:4-diformylphenol (III) by way of 2-chloromethyl-4:6-diformylphenol (IV) and subsequent hydrolysis to the hydroxymethyl derivative (V) and catalytic reduction of the latter with platinum is now described. This route, from salicylaldehyde as starting material, was modified by direct introduction of two chloromethyl groups into the latter to give the dichloromethyl derivative (VI), which was



hydrolysed to 2-formyl-4:6-bishydroxymethylphenol (VII) and then reduced to the trialcohol.

The constitution of tetranuclear Novolak obtained by condensation of the trialcohol and 2:4:6-trisacetoxymethylphenyl acetate with *p*-substituted phenols has been confirmed by synthesis of 2:4:6-tri-(2-hydroxy-3:5-dimethylbenzyl)phenol (IX) from 4-bromo-2:6-di-(2-hydroxy-3:5-dimethylbenzyl)phenol (VIII) by a lithium exchange reaction to give the acid (VIII with CO₂H in place of Br), reduction with lithium aluminium hydride to the corresponding hydroxymethyl derivative, and condensation of the last with 2:4:1-xyleneol to give the tetranuclear compound (IX) identical with that obtained from 2:4:6-trisacetoxymethylphenyl acetate and 2:4:1-xyleneol.



In an unsuccessful attempt to prepare 2:4:6-tri-(2-hydroxy-5-methylbenzyl)phenol (II) from 2:4:6-trisacetoxymethylphenyl acetate and *p*-cresol in which heating was conducted for a longer period, a small amount of 2:7-dimethylxanthen was formed, and in later experiments was accompanied by larger amounts of 2:2'-dihydroxy-5:5'-dimethyldiphenylmethane which is presumably the precursor of the former (cf. Megson, *J. Soc. Chem. Ind.*, 1939, 58, 131). The effect of prolonged heating of 2:4:6-tri-(2-hydroxy-5-methylbenzyl)phenol with *p*-cresol in the presence of hydrochloric acid was therefore examined. By high-vacuum distillation fractions were separated containing both 2:2'-dihydroxy-5:5'-dimethyldiphenylmethane and 2:4'-dihydroxy-5-methyldiphenylmethane which was identified by comparison with a specimen synthesised from *p*-hydroxybenzyl alcohol and *p*-cresol. The formation of these two-ring molecules may be attributed to bond fission at the positions indicated in formula (II) with subsequent reaction with *p*-cresol. It may be noted that these are the bonds which would be expected from ultra-violet absorption spectroscopical results to be sterically hindered (Hunter, Morton, and Carpenter, *J.*, 1950, 441).

EXPERIMENTAL

Reduction of 2:4:6-Trisacetoxymethylphenyl Acetate to 2:4:6-Trishydroxymethylphenol by Lithium Aluminium Hydride.—The oil (50 g.) obtained by treatment of 2:4:6-tri(dimethylaminomethyl)phenol with acetic anhydride following Bruson and MacMullen's directions

(*loc. cit.*) was distilled at 10^{-3} mm. from a retort and three fractions were collected : b. p. 180—185° (furnace-temp.), n_D^{25} 1.5023 (8 g.); b. p. 185—190°, n_D^{25} 1.5026 (28 g.); b. p. 190—195°, n_D^{25} 1.5025 (10 g.). The two later fractions were used for reduction experiments. The tetraacetate (2.5 g.) in ether (25 c.c.) was treated with lithium aluminium hydride (5 g.) in ether (25 c.c.). After subsidence of a vigorous reaction, the mixture was heated under reflux for 3 hr. and kept overnight at room temperature. After decomposition of excess of reagent with water in ether and acidification with dilute sulphuric acid, sufficient sodium carbonate was added to start precipitation and the mixture was extracted with ethyl acetate. Evaporation of the united extracts under reduced pressure furnished an oil which when washed with benzene crystallised in needles (0.5 g.) which on recrystallisation from ethyl acetate gave 2 : 4 : 6-trishydroxymethylphenol, m. p. 75—78° (0.28 g.) undepressed by admixture with a specimen prepared by reduction of ethyl trimesate. On further recrystallisation from ethyl acetate the trialcohol was obtained in fine flakes, m. p. 79—82°.

2-Chloromethyl-4 : 6-diformylphenol.—A mixture of 2 : 4-diformylphenol (Angyal, Morris, Tetaz, and Wilson, *J.*, 1950, 2141) (1 g.), trioxan (1 g.), concentrated hydrochloric acid (5 c.c.), acetic acid (5 c.c.), and powdered zinc chloride (3 g.) was saturated with dry hydrogen chloride at 10° and thereafter heated (closed vessel) at 35° for 72 hr. and then at 55° for a further 24 hr., and finally cooled and poured into water. *2-Chloromethyl-4 : 6-diformylphenol* was obtained in small pink crystals (0.7 g.), m. p. 97—100°, which on recrystallisation from cyclohexane furnished colourless plates, m. p. 112—113° (Found : C, 54.7; H, 3.7; Cl, 18.3. $C_9H_7O_3Cl$ requires C, 54.4; H, 3.5; Cl, 17.9%). *2 : 4-Diformyl-6-hydroxymethylphenol* was obtained by keeping a solution of the 6-chloromethyl derivative in 50% aqueous acetone at room temperature for 24 hr. and removing acetone under reduced pressure. On recrystallisation from benzene it formed prisms, m. p. 129—130° (Found : C, 59.7; H, 4.7. $C_9H_8O_4$ requires C, 60.0; H, 4.45%). The diformylhydroxymethylphenol (0.18 g.) was hydrogenated in the usual way with platinum oxide (0.05 g.) in alcohol (10 c.c.). The uptake after $2\frac{1}{2}$ hr. was that required for reduction of two aldehyde groups, and the product on recrystallisation from ethyl acetate furnished 2 : 4 : 6-trishydroxymethylphenol in cream-coloured flakes, m. p. 80—82°, undepressed by admixture with the specimen obtained by reduction of 2 : 4 : 6-trisacetoxymethylphenyl acetate.

Synthesis of 2 : 4 : 6-Trishydroxymethylphenol from 3 : 5-Bischloromethylsalicylaldehyde.—*3 : 5-Bischloromethylsalicylaldehyde.* A mixture of salicylaldehyde (2 g.), trioxan (1 g.), acetic acid (4 c.c.), zinc chloride (2 g.) and concentrated hydrochloric acid (4 c.c.) was saturated at 10° with hydrogen chloride. After an hour, when precipitation of the monochloromethyl derivative had occurred, the mixture was sealed and heated at 35° for 72 hr. On dilution with water the *bischloromethyl* derivative was obtained in quantitative yield and having m. p. 90—94°; on recrystallisation from light petroleum it formed needles, m. p. 98—99° (Found : C, 49.0; H, 4.0; Cl, 31.9. $C_9H_8O_3Cl_2$ requires C, 49.3; H, 3.7; Cl, 32.4%). The preparation was repeated on a larger scale with slightly varying conditions, the most satisfactory yield (53%) being obtained from salicylaldehyde (72 g.), trioxan (60 g.), zinc chloride (60 g.), hydrochloric acid (240 c.c.), and acetic acid (240 c.c.). *2-Formyl-4 : 6-bishydroxymethylphenol* was prepared by vigorously stirring the bischloromethylsalicylaldehyde in small batches (6 g.) with boiling water (300 c.c.) for 5 min. and extracting the combined solutions with ethyl acetate in a liquid-extraction apparatus at room temperature at 80 mm. for 11 hr. On recrystallisation from ethylene dichloride, the bishydroxymethyl derivative separated in small prisms, m. p. 119—121° (Found : C, 59.0; H, 5.8. $C_9H_{10}O_4$ requires C, 59.3; H, 5.5%). The yields in larger-scale preparations (58 g. and 48 g. of bischloromethylsalicylaldehyde) were 37 and 56% respectively. On being heated with water for 10 min., the crude bischloromethyl derivative yielded a small quantity of a substance readily separated on account of its sparing solubility in ethyl acetate, which, crystallised from glacial acetic acid, had m. p. 220—222° (Found : C, 57.3; H, 4.3; Cl, 19.1. $C_{17}H_{14}O_4Cl_2$ requires C, 57.8; H, 4.0; Cl, 20.1%). This is probably *3 : 3'-bischloromethyl-5 : 5'-diformyl-4 : 4'-dihydroxydiphenylmethane*. The bishydroxymethylformylphenol (21.05 g.) in alcohol (275 c.c.) with platinum oxide (0.8 g.) absorbed hydrogen corresponding to reduction of a single aldehyde group after 13 hr. Evaporation of alcohol under reduced pressure after removal of catalyst, followed by recrystallisation from ethyl acetate, furnished 2 : 4 : 6-trishydroxymethylphenol in prisms, m. p. 87—89° (16 g., 76%). By further recrystallisation from ethyl acetate this was raised to 89—91° (Found : C, 58.5; H, 6.8. Calc. for $C_9H_{12}O_4$: C, 58.6; H, 6.5%).

Synthesis of 2 : 4 : 6-Tri-(2-hydroxy-3 : 5-dimethylbenzyl)phenol from 2 : 4 : 6-Trisacetoxymethylphenyl acetate and 2 : 4 : 1-Xylenol and from 4-Bromo-2 : 6-di-(2-hydroxy-3 : 5-dimethylbenzyl)phenol by Way of 4-Hydroxy-3 : 5-di-(2-hydroxy-3 : 5-dimethylbenzyl)benzoic Acid.—(i) A

mixture of 2 : 4 : 6-trisacetoxymethylphenyl acetate (3.25 g.), 2 : 4 : 1-xylenol (80 g.), and hydrochloric acid (3 c.c.) was heated on a water-bath, under reflux, for 16 hr., the excess of xylenol was removed by distillation in steam, and the residue (4.8 g.) was twice crystallised from toluene. The tetranuclear Novolak was obtained in needles, m. p. 182—183°, which gave unsatisfactory analyses (Found : C, 77.1, 77.1; H, 7.3, 7.3%) and was therefore distilled at 10^{-4} mm. from a retort (2 hr.; 220—260°). Pure 2 : 4 : 6-tri-(2-hydroxy-3 : 5-dimethylbenzyl)-phenol was thereby separated from an impurity of higher vapour-pressure, and had m. p. 185—186° [Found : C, 79.6; H, 7.4%; *M* (micro-Rast), 460. $C_{33}H_{36}O_4$ requires C, 79.8; H, 7.3%; *M*, 496]. The small and more volatile fraction, m. p. 140—141°, was identified as 2 : 2'-dihydroxy-3 : 5 : 3' : 5'-tetramethyldiphenylmethane which after recrystallisation from benzene-light petroleum had m. p. 145—146.5° alone and when mixed with an authentic specimen.

(ii) 4-Bromo-2 : 6-di-(2-hydroxy-3 : 5-dimethylbenzyl)phenol was prepared by heating 4-bromo-2 : 6-bishydroxymethylphenol (25 g.) and 2 : 4 : 1-xylenol (250 g.) with a small amount of toluene-*p*-sulphonic acid on a water-bath for 5 hr. Sodium carbonate (0.6 g.) was added and the excess of xylenol removed in steam. The residue on recrystallisation from ethylene dichloride furnished the bishydroxydimethylbenzyl derivative in prisms, m. p. 179—181° (11.2 g.) (Found : C, 65.3; H, 5.7; Br, 18.05. $C_{24}H_{25}O_3Br$ requires C, 65.3; H, 5.7; Br, 18.1%). *n*-Butyl-lithium (Gilman and Haubein, *J. Amer. Chem. Soc.*, 1944, **66**, 1515) (0.058 mole in 50 c.c. of ether) was run into a solution of 4-bromo-2 : 6-di-(2-hydroxy-3 : 5-dimethylbenzyl)-phenol (5 g.) in ether (250 c.c.), and the solution was kept for 17 hr., carboxylated by pouring on to solid carbon dioxide, acidified, and extracted with ether. The ethereal solution was washed with water and extracted with 10% aqueous sodium carbonate. 4-Hydroxy-3 : 5-di-(2-hydroxy-3 : 5-dimethylbenzyl)benzoic acid, obtained on acidification, was recrystallised from glacial acetic acid, then having m. p. 243—245° (0.95 g.) (Found : C, 73.4; H, 6.3. $C_{25}H_{26}O_5$ requires C, 73.8; H, 6.4%). The acid (0.3 g.), in dry ether (180 c.c.), was added to lithium aluminium hydride (1 g.) in a small amount of the same solvent during 5 min. and the mixture was heated under reflux for an hour. The excess of lithium aluminium hydride was decomposed with wet ether, the mixture acidified with dilute sulphuric acid, and the ethereal layer washed with aqueous sodium carbonate. On evaporation of ether and recrystallisation from methanol, the hydroxymethyl derivative was obtained in needles (0.06 g.), m. p. 170—171° (Found : C, 76.7; H, 7.1. Calc. for $C_{25}H_{28}O_4$: C, 76.8; H, 7.2%). A mixture of this (0.03 g.) and 2 : 4 : 1-xylenol (1.3 g.) with a trace of hydrochloric acid was heated for 16 hr. The residue (m. p. 176—179°) obtained after removal of excess of xylenol in steam, on recrystallisation from benzene, furnished 2 : 4 : 6-tri-(2-hydroxy-3 : 5-dimethylbenzyl)phenol, m. p. 182—183° undepressed by admixture with that prepared from 2 : 4 : 6-trisacetoxymethylphenyl acetate.

Reaction of 2 : 4 : 6-Trisacetoxymethylphenol with p-Cresol.—2 : 4 : 6-Tri-(2-hydroxy-5-methylbenzyl)phenol was prepared by heating a mixture of 2 : 4 : 6-trisacetoxymethylphenyl acetate (10 g.) with *p*-cresol (250 g.) and concentrated hydrochloric acid (10 c.c.) on a water-bath for 6 hr. The product (10 g.) obtained by neutralisation with sodium carbonate and removal of excess of cresol in steam, followed by crystallisation from toluene, had m. p. 179—182°. On recrystallisation this furnished 2 : 4 : 6-tri-(2-hydroxy-5-methylbenzyl)phenol in prisms, m. p. 182.5—184.5° [Found : C, 79.1; H, 6.6%; *M* (micro-Rast), 423. Calc. for $C_{30}H_{30}O_4$: C, 79.3; H, 6.6%; *M*, 454]. In an experiment in which 2 : 4 : 6-trisacetoxymethylphenyl acetate (3.9 g.) was heated with *p*-cresol (100 g.) in the presence of toluene-*p*-sulphonic acid (0.15 g.) and the excess of cresol was removed in steam, white flakes (0.1 g.; m. p. 156—158°) later collected in the condenser. After recrystallisation from benzene-light petroleum these had m. p. 165.5—167° undepressed on admixture with 2 : 7-dimethylxanthen [Found : C, 85.1; H, 6.6%; *M* (micro-Rast), 212. Calc. for $C_{15}H_{14}O$: C, 85.7; H, 6.7%; *M*, 210]. In two further similar experiments the residues remaining after removal of *p*-cresol were substantially greater than that required for simple condensation. On evaporative high-vacuum distillation ($150—190^{\circ}/10^{-4}$ mm.) these furnished yields upwards of 20% (calc. on weight of residue) of 2 : 2'-dihydroxy-5 : 5'-dimethyldiphenylmethane which after recrystallisation from benzene-light petroleum had m. p. and mixed m. p. 124—125°.

Reaction of 2 : 4 : 6-Tri-(2-hydroxy-5-methylbenzyl)phenol with p-Cresol.—(a) It was first ascertained that the tetranuclear Novolak was stable under the conditions of evaporative distillation: 0.1076 g. of a specimen whose m. p. had been raised to 186—187° by repeated recrystallisation was distilled at 10^{-4} mm. at a rate of 0.02 g. per hr. with a furnace temperature of 200—220°, and 0.1014 g. was recovered as a crystalline distillate, m. p. 189—191.5°, which did not depress the m. p. of the original specimen.

(b) 2 : 4 : 6-Tri-(2-hydroxy-5-methylbenzyl)phenol (1 g.), *p*-cresol (15 g.), and hydrochloric

acid (0.05 c.c.) were heated for 17 hr., *p*-cresol removed in steam, the residue extracted with ethyl acetate, and the material recovered from this subjected to evaporative distillation (3 hr. at 170—180°). The distillate, after recrystallisation from light petroleum and thereafter from aqueous acetic acid, furnished 2 : 4'-*dihydroxy-5-methyldiphenylmethane*, m. p. 133—135° which was undepressed by admixture with the specimen prepared from *p*-hydroxybenzyl alcohol and *p*-cresol (Found : C, 78.7; H, 6.8. $C_{14}H_{14}O_2$ requires C, 78.5; H, 6.5%). In a similar experiment in which the tetranuclear Novolak (5 g.) was heated with *p*-cresol (75 g.) and hydrochloric acid (0.25 c.c.) for 17 hr., the distillate on recrystallisation from aqueous acetic acid and thereafter from light petroleum furnished 2 : 2'-*dihydroxy-5 : 5'-dimethyldiphenylmethane* (0.05 g.), m. p. and mixed m. p. 125°. The mother-liquors furnished a small amount of 2 : 4'-*dihydroxy-5-methyldiphenylmethane*.

(c) A mixture of *p*-hydroxybenzyl alcohol (5 g.), *p*-cresol (50 g.), and toluene-*p*-sulphonic acid (0.1 g.) was heated on a water-bath overnight, then neutralised, and excess of cresol removed in steam. The product was distilled at 0.1 mm. (bath temp. 220—250°) and thereafter recrystallised from aqueous acetic acid, 2 : 4'-*dihydroxy-5-methyldiphenylmethane* being obtained (2.5 g.), m. p. 135—136° (Found : C, 78.1; H, 6.2%).

2 : 4 : 6-*Tri-(2-hydroxy-5-methylbenzyl)phenol* was prepared in 88% yield by heating 2 : 4 : 6-*trihydroxymethylphenol* (4 g.) with *p*-cresol (200 g.) and toluene-*p*-sulphonic acid (0.2 g.) on a water-bath for 4 hr. Excess of *p*-cresol was removed in steam after addition of 2 c.c. of 0.5*N*-sodium hydroxide. On recrystallisation from toluene 8.7 g. of the tetranuclear Novolak were obtained, having m. p. 180—182°. Further recrystallisation raised this m. p. to 183—184°.

2 : 4 : 6-*Tri-(5-bromo-2-hydroxybenzyl)phenol*.—(i) A mixture of 2 : 4 : 6-*trisacetoxymethylphenyl acetate* (1 g.), *p*-bromophenol (23 g.), and concentrated hydrochloric acid (1 c.c.) was heated on a water-bath for 5½ hr. After removal of excess of *p*-bromophenol in steam, the aqueous layer deposited crystalline material (0.25 g.), m. p. 192—194°, which on recrystallisation from ethylene dichloride-light petroleum furnished 2 : 4 : 6-*tri-(5-bromo-2-hydroxybenzyl)phenol* in small light pink crystals, m. p. 197—199° (Found : C, 49.5; H, 3.4; Br, 36.6. $C_{27}H_{21}O_4Br_3$ requires C, 49.9; H, 3.2; Br, 37.0%). No crystalline material could be isolated from the resinous residue obtained from distillation in steam. (ii) 2 : 4 : 6-*Trishydroxymethylphenol* (1 g.), *p*-bromophenol (10 g.), and hydrochloric acid (0.1 c.c.) were heated on a water-bath for 1½ hr., the excess of *p*-bromophenol was removed in steam, and the residue was extracted with benzene. On precipitation with light petroleum, 2 : 4 : 6-*tri-(5-bromo-2-hydroxybenzyl)phenol* was obtained (0.25 g.), having m. p. 195°, undepressed on admixture with the specimen previously obtained.

2 : 4 : 6-*Tri-(4-hydroxy-3 : 5-dimethylbenzyl)phenol*, prepared from 2 : 4 : 6-*trisacetoxymethylphenyl acetate* and 2 : 6 : 1-*xylolol* as for the 2'-hydroxy-3' : 5'-dimethyl derivative, separated from toluene-light petroleum in deep yellow crystals, m. p. 168—170°. Repeated recrystallisation raised the m. p. to 177—179° but failed to free the substance from colour (Found : C, 80.4; H, 7.3%). By evaporative distillation (225—265°/10⁻⁴ mm.) the tetranuclear Novolak was obtained as an almost colourless crystalline deposit, m. p. 177—180° [Found : C, 80.2; H, 7.3; *M* (micro-Rast), 440. $C_{33}H_{36}O_4$ requires C, 79.8; H, 7.3%; *M*, 496].

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