# 133. *Nuclear Methylation of 3 : 5-Dimethylphenol.*

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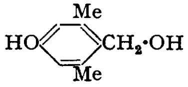
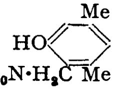
The nuclear methylation of 3 : 5-dimethylphenol, involving its treatment with formaldehyde and calcium hydroxide and subsequent dry distillation, yields pentamethylphenol in addition to durenol. The action of formaldehyde on 3 : 5-dimethylphenol and durenol in alkaline conditions has been systematically reinvestigated. It is confirmed that 3 : 5-dimethylphenol forms in presence of sodium hydroxide 3 : 5-dimethyl-4-hydroxymethylphenol, whereas it is known to yield with formaldehyde and piperidine 3 : 5-dimethyl-2-piperidinomethylphenol. In contrast to earlier claims, durenol reacts with formaldehyde in alkaline conditions. The reaction products are discussed.

Recently, a method for the exhaustive nuclear methylation of phenols has been described (Barclay, Burawoy, and Thomson, *J.*, 1944, 400), the phenol being treated with formaldehyde and calcium hydroxide and the mixture subjected to dry distillation, and the process being then repeated on the distillate. When applying this method to 3 : 5-dimethylphenol, a good yield (30%) of 2 : 3 : 5 : 6-tetramethylphenol (durenol) was obtained. This was erroneously thought to be the final product of the methylation, and it was concluded that durenol does not react with formaldehyde in alkaline conditions. This did not appear surprising since Caldwell and Thompson (*J. Amer. Chem. Soc.*, 1939, **61**, 765, 2354) had earlier reported that durenol does not react with formaldehyde and a secondary amine, and Megson (*Trans. Faraday Soc.*, 1936, **32**, 336), by distilling the condensation product of 3 : 5-dimethylphenol with formaldehyde in acid conditions, had identified some durenol but no pentamethylphenol in the distillate.

This also led to the erroneous conclusion that 3 : 5-dimethylphenol itself does not react with formaldehyde in the *p*-position to the phenolic hydroxyl group, in contrast to Auwers's claim (*Ber.*, 1907, **40**, 2524) that the 3 : 5-dimethyl-*x*-hydroxymethylphenol obtained from 3 : 5-dimethylphenol with one mole of formaldehyde in presence of sodium hydroxide is the 4-derivative (I). Again, this doubt appeared to be justified since Auwers and Dombrowski's claim (*Annalen*, 1906, **344**, 280) that the product obtained from 3 : 5-dimethylphenol with formaldehyde and piperidine is 3 : 5-dimethyl-4-piperidinomethylphenol was already shown to be incorrect by Caldwell and Thompson (*loc. cit.*). These authors subjected this product to catalytic reduction and obtained 2 : 3 : 5-trimethylphenol, establishing it to be 3 : 5-dimethyl-2-piperidinomethylphenol (II). Moreover, treatment of 3 : 5-dimethylphenol with hexamethylenetetramine was known to yield only 2-hydroxy-4 : 6-dimethylbenzaldehyde (Duff, *J.*, 1941, 547).

(I.)



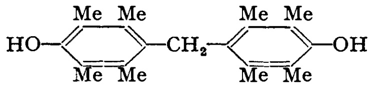


(II.)

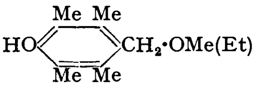
Reinvestigating the nuclear methylation of 3 : 5-dimethylphenol, we observed that in addition to durenol a small amount of pentamethylphenol is formed which increases in subsequent dry distillations. Yields of about 2, 5, and 8% of pentamethylphenol are obtained after 1, 2, and 3 dry distillations respectively. The formation of pentamethylphenol clearly indicated that chemical attack has at some stage occurred in the *p*-position to the phenolic hydroxyl group, necessitating a reinvestigation of the action of formaldehyde on durenol and 3 : 5-dimethylphenol in alkaline conditions. We have found that :

(i) Durenol reacts with formaldehyde in alkaline conditions to yield bishydroxydurylmethane (III). This condensation does not occur very readily in the presence of calcium hydroxide or an equivalent amount of sodium hydroxide, *i.e.*, the usual conditions for phenol–formaldehyde condensations, but requires a considerable excess of both sodium hydroxide and formaldehyde to be complete. No hydroxymethyldurenol can be isolated under these conditions. The properties of (III) are the subject of the following communication.

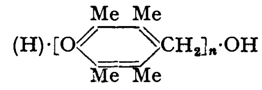
(ii) 4-Methoxymethyl- and 4-ethoxymethyl-durenol (IV) are obtained by carrying out the condensation in methyl or ethyl alcohol respectively at room temperature. These substances are alkali-soluble and rather unstable. They are easily converted by heating with aqueous



(III.)



(IV.)



(V.)

alkali into (III), and with traces of an acid into a high-melting substance which is almost insoluble in all solvents and in alkali. It is probably a dimer or polymer anhydrohydroxymethyldurenol (V). Dry distillation of the alkoxymethyldurenols in presence of calcium hydroxide affords a 35% yield of pentamethylphenol in addition to a small amount of durenol.

(iii) Durenol reacts with formaldehyde and piperidine, yielding the crystalline 4-piperidinomethyldurenol. Again, this condensation is very slow under the usual conditions, *i.e.*, in alcoholic solution with only one mole each of formaldehyde and piperidine, which accounts for Caldwell and Thompson's failure to obtain it. It proceeds readily when piperidine is used as solvent in place of alcohol, *i.e.*, in stronger alkaline conditions. The slow rate of the reaction should be mainly due to the low acidity of durenol, the phenoxide ion being, undoubtedly, the reactant in such condensations, although steric hindrance by the methyl groups as a contributory factor cannot be exlcuded. When heated with aqueous alkali, piperidinomethyldurenol is converted into (III), whereas boiling concentrated hydrochloric acid does not affect it.

(iv) The substance obtained from 3 : 5-dimethylphenol with 1 mole of formaldehyde and sodium hydroxide is, in agreement with Auwers's claim, the 4-hydroxymethyl derivative (I), since oxidation of its methyl ether and of the known 4-methoxy-2 : 6-dimethylbenzaldehyde yields the same 4-methoxy-2 : 6-dimethylbenzoic acid. It is noteworthy that 3 : 5-dimethylphenol reacts with formaldehyde and sodium hydroxide in the 4-position in contrast to its reaction with formaldehyde and piperidine (as well as with hexamethylenetetramine), when attack occurs in the 2-position. Our experiments do not allow a decision whether this different behaviour is a function of the different pH or is due to a steric effect being operative in the formaldehyde–amine condensation, but not in the formaldehyde condensation.

(v) Although the possibility cannot be excluded that the 4-methyl group in pentamethylphenol is introduced to a very small degree at an earlier stage of the nuclear methylation of 3 : 5-dimethylphenol, we have ascertained that durenol itself is converted into pentamethylphenol when treated with formaldehyde and calcium hydroxide and dry distilled, the yield improving with an increasing amount of formaldehyde.

## EXPERIMENTAL.

*Exhaustive Nuclear Methylation of* 3 : 5-*Dimethylphenol.*—3 : 5-Dimethylphenol (244 g.) was thoroughly mixed with calcium hydroxide (" Limbux ") (244 g.). Formaldehyde (225 c.c. of 40% solution) was added gradually with mixing and cooling. After 24 hours, the mixture was distilled at low temperatures to remove water and unchanged 3 : 5-dimethylphenol, and, subsequently, dry distilled. The distillate (180 g.), " Limbux " (180 g.), and formaldehyde (150 c.c.) were again mixed and distilled. The process was repeated with the mixture consisting of the second distillate (150 g.), " Limbux " (150 g.), and formaldehyde (100 c.c.). Fractionation of the final distillate, consisting mainly of durenol (b. p. 250°; m. p. 117—118°) and pentamethylphenol (b. p. 267°; m. p. 129°), yielded : 240—250°, 6 g.; 250—260°, 34 g.; 260—265°, 19 g.; 265—275°, 23 g.; 275—285°, 12 g.; residue, 7 g. Treatment with formaldehyde and sodium hydroxide and subsequent steam distillation yielded pure pentamethylphenol, 20 g. After only 1 and 2 dry distillations, 7 and 13 g. of pentamethylphenol were respectively obtained.

*Bishydroxydurylmethane* (III).—To a warm solution of durenol (10 g.) in 10% sodium hydroxide (150 c.c.), 40% formaldehyde (50 c.c.) was added. After reaction had ceased, the mixture was acidified, and the *compound* was collected in almost quantitative yield; colourless needles (from ethyl alcohol), m. p. 213—214° (Found : C, 80·4; H, 9·2. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%). Heating with acetic anhydride and a drop of concentrated sulphuric acid yielded *bisacetoxydurylmethane*, colourless needles (from glacial acetic acid), m. p. 218° (Found : C, 76·2; H, 7·9. $C_{25}H_{32}O_4$ requires C, 75·7; H, 8·1%).

*Ethoxymethyldurenol.*—To durenol (2 g.) in ethyl alcohol (100 c.c.), 40% formaldehyde (8 c.c.) and sodium hydroxide (2·5 c.c. of 10% solution) were added with cooling. After 3 days, the solution was carefully neutralised with acetic acid, and the precipitate was collected; colourless needles (from alcohol), m. p. 98° [Found : C, 75·1; H, 9·6; OEt (Zeisel), 21·1. $C_{13}H_{20}O_2$ requires C, 74·9; H, 9·7; OEt, 21·6%]. The *compound* was soluble in sodium hydroxide solution, and was very sensitive to heat in presence of traces of acids and alkalis.

*Ethoxymethyldurenyl Benzoate.*—This *compound* formed colourless needles (from alcohol), m. p. 143° (Found : C, 77·4; H, 8·1; OEt, 13·8. $C_{20}H_{24}O_3$ requires C, 76·8; H, 7·8; OEt, 14·4%).

*Action of Alkali and Traces of Acid on Ethoxymethyldurenol.*—(*a*) The phenol (0·5 g.) dissolved in 10% sodium hydroxide (20 c.c.) was heated for a few minutes; pure bishydroxydurylmethane then separated. (*b*) A suspension of the phenol (1 g.) in water containing a trace of acetic or hydrochloric acid was boiled for a few minutes; the oil then solidified. After cooling, the precipitate was collected; it was colourless, had m. p. 256—260°, and was almost insoluble in all common solvents and in alkali. It was converted into bishydroxydurylmethane by being heated with methyl alcohol and a small amount of concentrated hydrochloric acid until solution was complete. No further investigation was carried out in view to the difficulty of its purification.

*Dry Distillation of Ethoxymethyldurenol.*—A mixture of the phenol (5 g.) and " Limbux " (5 g.) was dry distilled. The distillate, consisting of durenol and pentamethylphenol (2·4 g.), was treated with formaldehyde and alkali and steam-distilled. Yield : pentamethylphenol, 1·4 g.; bishydroxydurylmethane, 0·6 g.

*Methoxymethyldurenol.*—This was prepared as above, but in methyl-alcoholic solution. The *compound* formed needles (from alcohol), m. p. 112° (Found : OMe, 15·3. $C_{12}H_{18}O_2$ requires OMe, 15·9%), with properties similar to those of ethoxymethyldurenol.

*Piperidinomethyldurenol.*—To a solution of durenol (10 g.) in piperidine (40 c.c.), 40% formaldehyde

(20 c.c.) was added with cooling. After 4 days, the solution was diluted with water and extracted with ether. After washing, drying ($Na_2SO_4$), and removal of the ether, an oil (containing formaldehyde–piperidine condensation products) was removed at 118—127°/18—20 mm. The residue (15 g.) solidified on cooling, and was crystallised from alcohol. It formed needles, m. p. 130—131°, soluble in dilute mineral acids (Found: N, 6·0. $C_{16}H_{25}ON$ requires N, 5·7%). It was converted into pure bishydroxydurylmethane by being heated for a short time with a 10% sodium hydroxide solution, but was recovered unchanged after boiling with hydrochloric acid.

3 : 5-*Dimethyl*-4-*hydroxymethylanisole*.—A solution of 3 : 5-dimethyl-4-hydroxymethylphenol (Auwers, *Ber.*, 1907, **40**, 2524) (5 g.) in 10% sodium hydroxide (20 c.c.) was shaken with methyl sulphate (4 c.c.); the *anisole* then separated as colourless needles (from light petroleum), m. p. 71° (Found: OMe, 18·2. $C_{10}H_{14}O_2$ requires OMe, 18·7%).

4-*Methoxy*-2 : 6-*dimethylbenzoic Acid*.—To a solution of 3 : 5-dimethyl-4-hydroxymethylanisole (2·3 g.) in acetone (80 c.c.), potassium permanganate (2·9 g.) in water (100 c.c.) was slowly added at 40—50°. After filtration and removal of acetone, the aqueous solution was neutralised with hydrochloric acid and the precipitate collected; the *compound* formed colourless needles (from ligroin), m. p. 144—146° (Found: OMe, 16·8. $C_{10}H_{12}O_3$ requires OMe, 17·2%). 4-Methoxy-2 : 6-dimethylbenzaldehyde, m. p. 47—48° (Auwers and Borsche, *Ber.*, 1915, **48**, 1713, give m. p. 45—47°), was oxidised as above. The product obtained was identical with the former acid.

*Nuclear Methylation of Durenol*.—A mixture of durenol (6 g.), calcium hydroxide (6 g.), and 40% formaldehyde (35 c.c.) was left for 20 hours, and then dry distilled. The distillate was treated with formaldehyde and alkali, and steam distilled. Yield: pentamethylphenol, 1·2 g.; bishydroxydurylmethane, 4·5 g.

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