96. *A New General Method for the Preparation of* o*-Hydroxy-aldehydes from Phenols and Hexamethylenetetramine.*

By James C. Duff.

The preparation of sixteen phenolic aldehydes from phenols is described, including two new dialdehydes. The phenol is heated with hexamethylenetetramine in anhydrous glycerol in the presence of glyceroboric acid. Diluted sulphuric acid is then added, and the mixture steam-distilled, giving the *o*-hydroxy-aldehyde free from unchanged phenol. The probable mechanism of the reaction is indicated.

Salicylic acid and β-naphthol react with hexamethylenetetramine in anhydrous acetic acid at 100° and the products, on hydrolysis with hydrochloric acid, yield respectively 3- and 5-aldehydosalicylic acid and 2-hydroxy-1-naphthaldehyde (Duff and Bills, J., 1934, 1305). Later experiments showed that phenol and the cresols when submitted to the same reaction yield small amounts of *o*-hydroxy-aldehydes, separated by steam-distillation. A search for an anhydrous acid medium more suitable than acetic acid led to experiments with glycerol and boric acid. It was necessary to avoid formation of water, as this would produce formaldehyde from the hexamethylenetetramine. A suitable anhydrous acid medium consisting of glyceroboric acid in anhydrous glycerol was prepared by heating excess of glycerol with boric acid at 170° until free from water. In the resulting liquid the phenol was heated with hexamethylenetetramine, in most cases at temperatures between 150° and 160°. The dark brown, viscous liquid so obtained was mixed with diluted sulphuric acid and distilled in steam. Fourteen phenols were used and in every case the distillate contained an *o*-hydroxy-aldehyde.

In comparing this new method with the Reimer–Tiemann method, the following features may be noted. (1) The new method is quicker and in some cases gives a higher yield of aldehyde. (2) It is unnecessary to use sodium bisulphite, as there is no unchanged phenol in the distillate, an important point in the cases of thymol and carvacrol, both of which yield aldehydes which do not combine with sodium bisulphite. (3) The diluted glycerol mixture at the steam-distillation stage can be heated to 120—130° while steam is passing through it, to facilitate separation of the volatile aldehyde. On the other hand, no *p*-hydroxy-aldehydes could be separated from the residual material in the distillation flask.

In no case was it found possible to separate an intermediate compound which could account for the formation of an aldehyde by the hydrolysing action of the sulphuric acid. It is suggested that the reaction caused by the glyceroboric acid may be

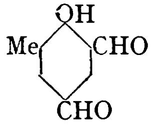
$$3RH + C_6H_{12}N_4 \longrightarrow NH_3 + 3R{\cdot}CH_2{\cdot}N{:}CH_2 \text{ (RH = the phenol)}$$

followed by isomerisation and hydrolysis :

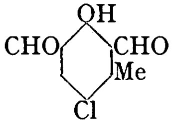
$$R{\cdot}CH_2{\cdot}N{:}CH_2 \longrightarrow R{\cdot}CH{:}N{\cdot}CH_3 \xrightarrow{H_2O} R{\cdot}CHO + CH_3{\cdot}NH_2$$

This view receives support from a reaction described by Sommelet (*Compt. rend.*, 1913, **157**, 854), who heated benzyl chloride and hexamethylenetetramine in aqueous-alcoholic solution and obtained a good yield of benzaldehyde. To account for this, Sommelet presumed the formation of $C_6H_5{\cdot}CH_2{\cdot}N{:}CH_2$, isomerising to $C_6H_5{\cdot}CH{:}N{\cdot}CH_3$. In all the preparations described below, methylamine was detected in strong concentration when the residual liquid after steam-distillation was rendered alkaline with sodium hydroxide.

All the phenols examined yielded the expected *o*-hydroxy-aldehydes and two new dialdehydes were obtained in addition. In both cases separation from the monoaldehyde was easily effected. *o*-Cresol yielded 3 : *5-dialdehydo-*o*-cresol* (I) and 6-chloro-*m*-cresol yielded *6-chloro-2 : 4-dialdehydo-*m*-cresol* (II). These dialdehydes do not form in the Reimer–Tiemann reaction. 2-Chloro-*m*-5-xylenol yielded a new aldehyde, *2-chloro-4-aldehydo-*m*-5-xylenol* (III).



(I.)



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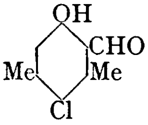

(III.)

EXPERIMENTAL.

All the aldehydes recorded below formed yellow solutions in aqueous sodium hydroxide and a yellow colour with aqueous ammonia, their *o*-hydroxy-aldehyde character thus being confirmed. All, except the aldehydes from thymol and carvacrol, formed addition compounds with sodium bisulphite. As far as possible comparison was made with authentic specimens and identity confirmed by mixed m. p. of the aldehydes or of their derivatives.

Method of Preparation.—Glycerol (150 g.) and boric acid (35 g.) were heated for 30 minutes at 170° (thermometer in the liquid) to expel all water; then, at 170°, hexamethylenetetramine (25 g.) was added. The mixture was stirred and brought to 160°, the phenol (25 g.) added without delay, and the temperature maintained at 150—155° during 15 minutes' stirring. The thick brown liquid was left to cool to 110°, a solution of concentrated sulphuric acid (30 ml.) in water (100 ml.) added, and the whole boiled in a current of steam. The liquid aldehydes obtained merely required drying and distilling for purification. The solid aldehydes were practically pure when collected, the only separation required being in the case of the two solid aldehydes obtained from 6-chloro-*m*-cresol (see below).

In earlier experiments the reaction was carried out at 100° instead of at 150°, but the time required was usually at least 3 hours and the yield of aldehyde in most cases was lower.

After the separation of the aldehydes mentioned below, the acid liquid left in the distillation flask, when made alkaline with aqueous sodium hydroxide, yielded a large proportion of resinous matter, most of which was soluble in sodium hydroxide solution, in which a definite compound has not yet been identified.

In the following table the m. p.'s are also mixed m. p.'s.

Phenol used (25 g.).	Aldehyde obtained.	M. p. or b. p.	Yield, g.	Derivative.
Phenol	Salicylaldehyde	B. p. 197°	5	Phenylhydrazone, m. p. 142°
o-Cresol	2-Hydroxy-*m*-tolualdehyde	B. p. 208	4·5	Phenylhydrazone, m. p. 97
m-Cresol	3-Hydroxy-*p*-tolualdehyde	M. p. 60	5	Phenylhydrazone, m. p. 161
p-Cresol	4-Hydroxy-*m*-tolualdehyde	M. p. 56	8·5	Phenylhydrazone, m. p. 149
o-Chlorophenol	3-Chloro-2-hydroxybenzaldehyde	M. p. 54	2	
p-Chlorophenol	5-Chloro-2-hydroxybenzaldehyde	M. p. 99	5·5	Oxime, m. p. 128
2 : 4-Dichlorophenol	3 : 5-Dichloro-2-hydroxybenzaldehyde	M. p. 95	2	Oxime, m. p. 195
m-5-Xylenol	4-Aldehydo-*m*-5-xylenol	M. p. 49	5	Oxime, m. p. 130
4-Hydroxydiphenyl	4-Hydroxy-3-aldehydodiphenyl	M. p. 102	7·5	Phenylhydrazone, m. p. 210
β-Naphthol	2-Hydroxy-1-naphthaldehyde	M. p. 82	8	Oxime, m. p. 157
Carvacrol	*o*-Carvacrolaldehyde	B. p. 130/15 mm.	7·5	Semicarbazone, m. p. 180
Thymol	*o*-Thymolaldehyde	B. p. 130/15 mm.	5	Semicarbazone, m. p. 198

In the aldehyde preparation from *o*-cresol, after all the liquid 2-hydroxy-*m*-tolualdehyde had passed over in the steam, there followed on prolonged distillation 1·5 g. of colourless minute needles, identified as 3 : *5-dialdehydo-*o*-cresol* (I), m. p. 123° (Found : C, 65·6; H, 4·9. $C_9H_8O_3$ requires C, 65·9; H, 4·9%). The *dioxime* had m. p. 199° (Found : N, 14·5. $C_9H_{10}O_3N_2$ requires N, 14·4%). The dialdehyde gave a yellow solution in aqueous sodium hydroxide solution and formed an addition compound with sodium bisulphite which was soluble in the bisulphite solution.

6-Chloro-*m*-cresol (25 g.) yielded 7·5 g. of a mixture of two aldehydes. Crystallisation from 75 ml. of 80% alcohol gave 4 g. of colourless minute needles, identified as *6-chloro-*2 : *4-dialdehydo-*m-*cresol* (II), m. p. 113° (Found : C, 54·2; H, 3·6; Cl, 17·4. $C_9H_7O_3Cl$ requires C, 54·4; H, 3·5; Cl, 17·9%). The *dioxime* was obtained in small colourless plates, m. p. 148° (Found : N, 12·7. $C_9H_9O_3N_2Cl$ requires N, 12·3%). After (II) had been separated, the alcoholic filtrate was diluted with water (2 vols.) and yielded 2·5 g. of 6-chloro-4-aldehydo-*m*-cresol in pale yellow crystals, m. p. and mixed m. p. 68°. When the preparation was carried out at 100° for 4 hours, the yields of the dialdehyde (II) and the monaldehyde were respectively 3·5 g. and 2·5 g. from 25 g. of the cresol. The Reimer–Tiemann reaction, carried out with 6-chloro-*m*-cresol (25 g.), sodium hydroxide (30 g.), water (150 ml.), and chloroform (35 g.), yielded 9 g. of 6-chloro-4-aldehydo-*m*-cresol, m. p. 68°, but no dialdehyde.

2-Chloro-*m*-5-xylenol (25 g.) yielded 8 g. of *2-chloro-4-aldehydo-*m*-5-xylenol* (III) in minute colourless crystals, m. p. 96° (Found : C, 58·2; H, 5·0; Cl, 19·0. $C_9H_9O_2Cl$ requires C, 58·5; H, 4·9; Cl, 19·2%). The *oxime* had m. p. 197° (Found : N, 7·4. $C_9H_{10}O_2NCl$ requires N, 7·0%). The Reimer–Tiemann method, carried out with 2-chloro-*m*-5-xylenol (25 g.), chloroform (35 g.), sodium hydroxide (30 g.), and water (200 ml.), gave only 3 g. of the aldehyde, which was separated with difficulty from the large proportion of unchanged xylenol.

Bell and Kenyon (J., 1926, 3047) prepared the aldehyde from 4-hydroxydiphenyl (see Table) by the Reimer–Tiemann method, but did not separate it by steam-distillation.

The aldehyde obtained from β-naphthol distils in steam rather slowly. The method of preparation using hexamethylenetetramine in glacial acetic acid (Duff and Bills, *loc. cit.*) is a more convenient method in this case.

o-Carvacrolaldehyde (2-hydroxy-3-methyl-6-*iso*propylbenzaldehyde) is a pale yellow oil. It was obtained by the Reimer–Tiemann reaction by Lustig (*Ber.*, 1886, **19**, 14) but not purified by distillation. Bell and Henry (J., 1928, 2221) found that the aldehyde was formed from carvacrol by the Gattermann reaction, but only separated the semicarbazone in a pure state. They also (*loc. cit.*) submitted carvacrol to the Reimer–Tiemann reaction and obtained the aldehyde mixed with unchanged carvacrol. The new method of preparation gives the aldehyde in almost pure condition, confirmed by distillation under 15 mm. pressure. The semicarbazone is the same as that obtained by Bell and Henry, m. p. 180°. The *phenylhydrazone* has m. p. 150° (Found : N, 10·6. $C_{17}H_{20}ON_2$ requires N, 10·4%).

o-Thymolaldehyde (2-hydroxy-6-methyl-3-*iso*propylbenzaldehyde) obtained by the new method of preparation is practically free from unchanged thymol. Distillation at 15 mm. pressure yields a pale yellow oil. The *oxime*, obtained in colourless plates, has m. p. 123° (Found : N, 7·6. $C_{11}H_{15}O_2N$ requires N, 7·3%). By the formation of a semicarbazone Bell and Henry (*loc. cit.*) showed that some *o*-aldehyde is produced by the Gattermann method from thymol. Kobek (*Ber.*, 1883, **16**, 2104) applied the Reimer–Tiemann reaction to thymol, but reported only the formation of a *p*-aldehyde and dialdehyde. The present author submitted 25 g. of thymol to the Reimer–Tiemann reaction. About 7 g. of oil were obtained by steam-distillation in the usual way. It contained unchanged thymol and the aldehyde was only separated in the form of its semicarbazone.

The fact that neither *o*-thymolaldehyde nor *o*-carvacrolaldehyde forms an addition compound with sodium bisulphite prevents separation of the aldehyde in the usual way.

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