

NENCKI'S REACTION WITH CRESOLS

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NENCKI'S reaction which involves the condensation of an organic acid and a phenol in the presence of anhydrous zinc chloride¹ does not appear to have been studied in any detail with reference to cresols. Of the three cresols only with *m*-cresol the reaction was tried using propionic and butyric acids, and 4-acyl derivatives were produced.²

The condensation of *o*- and *p*-cresols with acetic, propionic and butyric acids has now been studied according to the conditions of Nencki's reaction. So also the interaction between *m*-cresol and acetic acid has been tried to complete the series. In the latter case 4-acetyl-*m*-cresol has been obtained. With *o*-cresol both *o*- and *p*-substituted derivatives have been produced in different proportions, while with *p*-cresol only the 5-acyl derivative is the product. In all the cases the yields vary with the duration of heating and each reaction has its optimum period for the maximum yield.

It may be noted that in the above condensations the yields produced are lower than those obtained by the isomerization of the corresponding phenol esters according to Fries reaction.

EXPERIMENTAL

m-Cresol was condensed with acetic acid and *o*- and *p*-cresols with acetic, propionic and butyric acids according to the following general procedure:—The cresol (10 g.) was added to the appropriate acid (10 c.c.) in which anhydrous zinc chloride (10 g.) had been dissolved previously by heating. The mixture was then heated under reflux for different periods of time. After the heating was over, it was cooled, treated with 100 c.c. of 50 per cent. hydrochloric acid and left overnight. On extraction with ether an oily product mixed with some resin was obtained. When this mixture was subjected to steam distillation, a part passed over along with steam, while the rest remained in the distillation flask. The volatile portion consisted of a mixture of some unreacted original phenol and a ketone, and their separation was effected by taking advantage of the fact that when the mixture was dissolved in hot 5 N sodium hydroxide and cooled, the ketone separated as the sodium salt in pale-yellow crystals. The latter on decompo-

sition with dilute hydrochloric acid regenerated the ketone, which could be purified by distillation under reduced pressure.

The nonvolatile residue remaining after the steam distillation contained another isomeric ketone in some cases. Wherever it was formed, it was isolated by extraction with ether and purified by crystallization from either hot water or dilute alcohol.

It may be noted that the steam-volatile ketones contained the ketonic group in *ortho* position to the hydroxyl and produced the characteristic colours on treatment with ferric chloride. They are mostly liquids at the ordinary temperature.

Condensation of m-cresol with acetic acid

Only the steam-volatile ketone was produced in this case. It boiled at 126°/20 mm. and at 245° at atmospheric pressure. It was identified as 2-hydroxy-4-methylacetophenone, since it formed the semicarbazone and the oxime melting at 214° and 132° respectively. The variation of the yields of the ketone with the duration of heating is given below:—

TABLE I

Sl. No.	Duration of heating	Yield of 4-acetyl-m-cresol (2-hydroxy-4-methylacetophenone)
1	5 minutes	Nil
2	1 hour	15%
3	3 hours	20%
4	4 „	22%
5	6 „	25%
6	7 „	Much resinification

Condensation of o-cresol

(a) *With acetic acid.*—Two ketones, *viz.*, 2-hydroxy-3-methylacetophenone (b.p. 106°–07°/10 mm.; semicarbazone, m.p. 228°; phenyl hydrazone, m.p. 122°) and 4-hydroxy-3-methylacetophenone (m.p. 104°; oxime, m.p. 93°–94°)³ were obtained.

(b) *With propionic acid.*—2-Hydroxy-3-methylpropiophenone (b.p. 127°–29°/15 mm.; semicarbazone, m.p. 202°) and 4-hydroxy-3-methylpropiophenone (m.p. 83°–84°; 2:4-dinitrophenyl hydrazone, m.p. 238°⁴) were obtained.

(c) *With butyric acid.*—2-Hydroxy-3-methylbutyrophenone (b.p. 142°–43°/10 mm.; oxime, m.p. 87°–88°; phenyl hydrazone, m.p. 157°–58°) and 4-hydroxy-3-methylbutyrophenone (m.p. 132°–33°; phenyl hydrazone, m.p. 110°) were formed. Some difficulty was experienced in the preparation of the oxime and phenyl hydrazone derivatives of the 2-hydroxy-3-methylbutyrophenone. However, the ketone reacted with 2:4-dinitrophenylhydrazine very readily to produce the 2:4-dinitrophenylhydrazone. For the condensation, it (1 g.) was treated with dinitrophenylhydrazine (1 g.) dissolved in concentrated sulphuric acid (2 c.c.) and refluxed after the addition of 15 c.c. of alcohol on a water-bath for half an hour. The derivative crystallized out from acetic acid as brick-red, narrow rectangular plates, and melted at 190°–92° (Found: C, 56.36; H, 4.81; $C_{17}H_{18}O_5N_4$ requires C, 56.98; H, 5.03%).

In all the above condensations the yields varied with the duration of heating and the results are given below:—

TABLE II

Duration of heating	With acetic acid		With propionic acid		With butyric acid	
	2-Hydroxy-3-methylacetophenone	4-Hydroxy-3-methylacetophenone	2-Hydroxy-3-methylpropiofenone	4-Hydroxy-3-methylpropiofenone	2-Hydroxy-3-methylbutyrophenone	4-Hydroxy-3-methylbutyrophenone
5 minutes ..	5%	10%	4%	11%	Nil	8%
15 "	12.5%	8.5%
30 "	25%	6%
1 hour ..	15%	8%	21%	3%	5%	10.5%
1.5 hours	14%	2%
2 " ..	20%	5%	8%	4.5%
4 "	4%	2%

Condensation of p-cresol with acetic, propionic and butyric acids

p-Cresol underwent condensation with acetic, propionic and butyric acids yielding respectively 6-hydroxy-3-methylacetophenone (m.p. 50°; oxime, m.p. 145°; semicarbazone, m.p. 211°–12°), 6-hydroxy-3-methylpropiofenone (b.p. 153°/40 mm.; phenylhydrazone, m.p. 146°; oxime, m.p. 134°–35°) and 6-hydroxy-3-methylbutyrophenone (b.p. 132°/15 mm.; oxime, 96°–97°; semicarbazone, m.p. 188–89°). The yields of the different ketones obtained when the reaction mixtures were heated for different times are recorded below:—

TABLE III

Duration of heating	With acetic acid	With propionic acid	With butyric acid
	6-Hydroxy-3-methyl acetophenone	6-Hydroxy-3-methyl propiophenone	6-Hydroxy-3-methyl butyrophenone
5 minutes ..	2%
15 "	27%	15%
1 hour ..	10%	55%	24%
2 hours ..	14%	50%	27%
3 " ..	12%
4 " ..	Much resinification	35%	24%
5 "	18%

SUMMARY

The condensation of cresols with acetic, propionic and butyric acids was tried under conditions of Nencki's reaction employing anhydrous zinc chloride as the condensing agent. Only *o*-cresol gave rise to both the *ortho*- and *para*-substituted derivatives, while the *m*- and the *p*-cresols produced only the *ortho*-substituted products. The yields varied with the duration of heating.

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