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A Study of Orientation of Nuclear Methylation in Phenols and Naphthols

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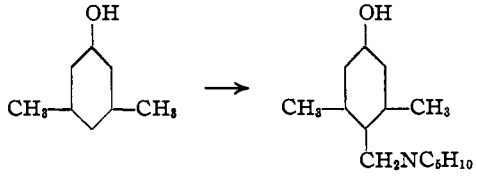
We described recently[1] a simple method for the introduction of one or more methyl groups into the nucleus of phenols, a method requiring merely treatment of the phenol with dimethylamine and formaldehyde and subsequent fission of the substituted benzylamine by catalytic high pressure hydrogenation.

In all reactions carried out at that time, we obtained only ortho substitution as proved by the structure of the methylated phenol formed. Indeed, the ease with which we were always able to purify these phenols indicated that they were substantially free of isomers or homologs which might have formed had any intramolecular rearrangements occurred during the hydrogenation, an unlikely possibility at best.

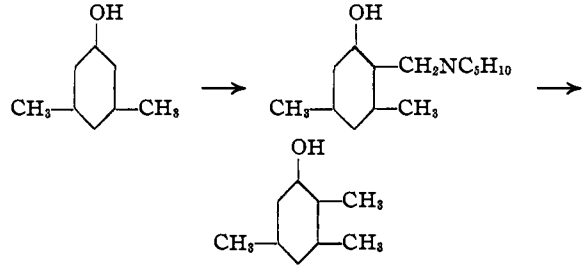
In 1906, Auwers and Dombrowski[2] prepared a number of analogously constituted benzylpiperidines by the action of piperidine and formaldehyde upon various phenols. They assumed that the piperidinomethyl groups entered the nucleus preferentially in the para position to the hydroxyl and that ortho substitution took place only when the para position was blocked. Thus, they formulated the reaction with 3,5-dimethylphenol to give a substituted piperidinomethyl derivative as follows



We already had prepared, in the course of our work, substituted benzylamines by using secondary amines other than dimethylamine; for example, 3,5-dimethylphenol formed a beautifully crystalline product with morpholine and formaldehyde which gave the same trimethylphenol on hydrogenolysis as did the dimethylaminomethyl derivative, namely, 2,3,5-trimethylphenol.

Although it appeared improbable that the use of piperidine instead of morpholine would bring about a different orientation in the product, this was not impossible; furthermore, if such were the case, we would have a desirable method of influencing the direction of nuclear methylation of phenols in which para and ortho positions are open.

We, therefore, prepared piperidinomethyl-3,5-dimethylphenol according to the directions given by Auwers and Dombrowski[2] and subjected it to hydrogenolysis. Again we obtained 2,3,5-trimethylphenol in accord with the steps indicated



Since this proved that the assumption of Auwers and Dombrowski had been erroneous in this particular case, we subjected additional piperidinomethyl phenols, for which they had assumed para substitution, to hydrogenolysis in order to ascertain whether or not this assumption was generally incorrect. In this way, we were able to prove that, although their assumption of para substitution was also wrong in the piperidinomethyl derivatives of *m*-cresol and of naphthol-1, it was correct in 4-piperidinomethyl-3-methyl-6-isopropylphenol and in 4-piperidinomethyl-2,5-dimethyl phenol. In addition, we subjected to hydrogenolysis some of the morpholinomethyl phenols described by Bruson[3] in order to determine their orientations. All of these methylations are summarized as follows

3-Methylphenol ⟶ 3,6-dimethylphenol
4-Methylphenol ⟶ 2,4-dimethylphenol
3,5-Dimethylphenol ⟶ 2,3,5-trimethylphenol
2,3,5-Trimethylphenol ⟶ 2,3,5,6-tetramethylphenol
2,5-Dimethylphenol ⟶ 2,4,5-trimethylphenol
3-Methyl-6-isopropylphenol ⟶ 3,4-dimethyl-6-isopropylphenol
Hydroquinone ⟶ 2,5-dimethylhydroquinone
Catechol ⟶ 2,4-dimethylcatechol
Naphthol-1 ⟶ 2-methylnaphthol-1
Naphthol-2 ⟶ 1-methylnaphthol-2

(1) Caldwell and Thompson, THIS JOURNAL, **61**, 765 (1939).
(2) Auwers and Dombrowski, *Ann.*, **344**, 285 (1906).
(3) H. Bruson, U. S. Patent 2,040,039 and 2,040,040 (May, 1936).

We have thus shown that, although para substitution does not occur preferentially, our surmise that ortho substitution would prove general is equally without foundation.

The formation of 3,4-dimethyl-6-isopropylphenol from 3-methyl-6-isopropylphenol is interesting when viewed in the light of what happens when this reaction is applied in two successive stages to 3,5-dimethylphenol. Attempts to introduce two dimethylaminomethyl or two morpholinomethyl groups into 3,5-dimethylphenol have not been successful in our hands; however, once we obtained 2,3,5-trimethylphenol we had no difficulty in converting it to 2,3,5,6-tetramethylphenol. Yet, to our surprise, we found that the piperidinomethyl group enters the para position in thymol. From this observation it appears that, although the ortho position is open, some factor other than a steric one causes preferential reaction in the para position. In view of the fact that 3,5-dimethylphenol had undergone successive methylations in the ortho positions, it seemed interesting to us to treat similarly 2,5-dimethylphenol, which differs from thymol only in having a methyl instead of an isopropyl group ortho to the hydroxyl. Here, too, substitution occurred in the para position although the ortho was as open as in 3,5-dimethylphenol or 2,3,5-trimethylphenol, and steric factors were alike.

Methylcarvacrol was prepared from carvacrol but has not been described in the literature. Its empirical formula has been proved by analysis and it is assumed that since carvacrol has a structure analogous to that of thymol and of 2,5-dimethylphenol, the methyl group enters para to the hydroxyl. The evidence at our disposal at this point, then, indicates that while the directional influences at play produce a single isomer, no simple prediction of orientation appears feasible, for comparatively slight changes in the constitution of the original phenol are, at times, sufficient to change the direction of the reaction.

An attempt was made to introduce an additional aminomethyl group into 2,5-dimethylhydroquinone and 3,4-dimethyl-6-isopropylphenol, in each of which an ortho position was still open, and into methylcarvacrol in which an ortho position was presumably open—at least an ortho or para position was certainly free. In none of these cases was any evidence of reaction obtained, and the original phenols were recovered and identified.

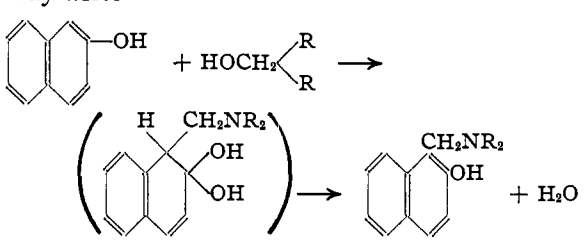
Again, 2,3,5,6-tetramethylphenol, in which only a para position is open, was submitted to the same treatment, but was recovered after giving no evidence of reaction.

The results obtained with catechol are particularly interesting in that one group entered the nucleus ortho to one hydroxyl while the other went into the para position with respect to the second hydroxyl. We have not been able to isolate, as yet, a product from catechol containing only one substituted aminomethyl group; hence, we cannot say whether the first substituent enters the ortho or para position, nor whether it does so exclusively in one way or to form a mixture of isomers. In any event, when disubstitution occurs, although both para positions as well as both ortho positions are free, the product formed indicates that one of each of these positions is involved.

In the naphthalene series we found that substitution took place with naphthol-2 in the position indicated by Auwers and Dombrowski, but not with naphthol-1. With the former, 1-methylnaphthol-2 was obtained in which an unhindered ortho position is still open. Therefore an attempt was made to introduce another piperidinomethyl group into this position, C_3. No evidence of reaction was obtained and the original material was recovered. Since steric factors do not seem to be involved, we believe that this observation properly may be regarded as additional evidence for the point of view[4] that the two ortho positions in naphthol-2 are not equivalent.

The reaction between a phenol, formaldehyde and a secondary amine apparently involves first the formation of a substituted aminomethanol which then reacts with the phenol, for we have not been able to obtain a substituted benzylamine by treating 2,6-dimethylol-4-methylphenol with morpholine.

Corresponding then to one formulation of the coupling of a diazo compound with naphthol-2, we may write



Experimental Part

The following piperidinomethyl phenols were made ac-

(4) Fieser and Lothrop, THIS JOURNAL, **57**, 1459 (1935).

cording to Auwers and Dombrowski,[5] the yields being essentially quantitative.

	M. P., °C. Obsd.	A. and D.
2-Piperidinomethyl-4-methylphenol	44.5–45.0	46
2-Piperidinomethyl-5-methylphenol	Oil	57
2-Piperidinomethyl-3,5-dimethylphenol	99	98.5
4-Piperidinomethyl-6-isopropyl-3-methylphenol	152–153	149.5
2-Piperidinomethyl-naphthol-1	137	133–134
1-Piperidinomethyl-naphthol-2	93–94	92–93
4-Piperidinomethyl-2,5-dimethyl	130–131	131.5–132.0
Piperidinomethylcarvacrol, (see text)	184–185	183

3,5-Dimorpholinomethyl Catechol.—One-quarter mole (27.5 g.) of practical catechol was mixed with 42 g. (0.5 mole) of morpholine and enough 95% alcohol added to keep the ingredients in solution; 45 ml. (0.5 mole) of formalin was added slowly and the mixture set aside. Crystals formed overnight and, after five days, were filtered off, giving a nearly quantitative yield; large, colorless prisms crystallized from 95% alcohol, m. p. 173–174°.

Anal. Calcd. for $C_{16}H_{24}O_4N_2$: N, 9.1. Found: N, 9.1.

2-Morpholinomethyl-3,5-dimethylphenol.—To one mole of technical 3,5-dimethylphenol were added one mole of morpholine and, then, while keeping the temperature between 25–35°, one mole of formaldehyde (as formalin) with vigorous stirring. On cooling in an ice-bath with continued agitation the product solidified in small aggregates which were filtered off and washed with water, giving an almost quantitative yield. Recrystallized from methyl alcohol, it melts at 96.5–97.0°.

Anal. Calcd. for $C_{13}H_{19}O_2N$: N, 6.3. Found: N, 6.3.

6-Morpholinomethyl-2,3,5-trimethylphenol.—Two and three-tenths grams of 2,3,5-trimethylphenol was treated with 5 g. of morpholine and 5 ml. of formalin and heated on the steam-bath for three hours. After adding some water, an oil formed which solidified on standing. Colorless needles crystallized from benzene: yield 70%; m. p. 78°.

Anal. Calcd. for $C_{19}H_{24}O_2N$: N, 5.88. Found: N, 5.81.

All hydrogenations were carried out in the following manner. The aminomethylphenol and copper chromite catalyst were placed in the copper liner of the high pressure hydrogenation apparatus and the dioxane solvent added. Under a pressure of 1500 lb. (102 atm.) and, with the rocker in motion, the electric heating element was adjusted so that in the course of one and one-half hours the temperature was 165°, at which it was kept constant for an additional hour and a half. Upon opening the bomb the odor of regenerated amine was quite noticeable. After filtering off the catalyst and removing the solvent, the mixture was acidified with hydrochloric acid and the phenol distilled with steam.

2,4-Dimethylphenol.—Eight and five-tenths grams of 2-piperidinomethyl-4-methylphenol, 1 g. of catalyst and 100 ml. of dioxane were hydrogenated. A colorless oil separated from the steam distillate and was extracted with ether, dried, and distilled: yield 1 g.; b. p. 205–206°. Jacobsen[6] gives b. p. 211.5° (corr.). The phenoxyacetic acid was made by condensing with monochloroacetic acid in 33% sodium hydroxide solution; m. p. 141°. Gluud and Breuer[7] give m. p. 141.6° for 2,4-dimethylphenoxyacetic acid.

2,5-Dimethylphenol.—Thirty-five grams of 2-piperidinomethyl-5-methylphenol, 5 g. of catalyst, and 200 ml. of dioxane were hydrogenated. Four grams of product solidified from the steam distillate and was crystallized from petroleum ether; m. p. 75°. Jacobsen[6] gives m. p. 74.5° for 2,5-dimethylphenol. A mixed melting point with an authentic sample showed no depression.

2,3,5-Trimethylphenol.—Eleven and five-tenths grams of 2-piperidinomethyl-3,5-dimethylphenol, 2 g. of catalyst, and 150 ml. of dioxane were hydrogenated. The white needles that crystallized from the steam distillate and also collected in the condenser were crystallized from petroleum ether; m. p. 93°; when mixed with an authentic sample of 2,3,5-trimethylphenol no depression of melting point occurred.

3,4-Dimethyl-6-isopropylphenol.—Eleven and five-tenths grams of 4-piperidinomethyl-3-methyl-6-isopropylphenol, 1.5 g. of catalyst, and 100 ml. of dioxane were hydrogenated. Six grams of product solidified from the steam distillate and, after crystallization from petroleum ether, the colorless needles melted at 70–71°; yield, 78%. Clemmensen[8] gives m. p. 70–71° for 3,4-dimethyl-6-isopropylphenol.

Methylcarvacrol.—Twenty grams of piperidinomethylcarvacrol, 2 g. of catalyst, and 200 ml. of dioxane were hydrogenated. An oil separated from the steam distillate and was extracted with ether. Distillation of the dried ether solution gave a colorless liquid which turned light brown on standing, b. p. 244–246°. The product became very viscous on cooling to −15°: yield 4 g., or 30%.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.5; H, 9.75. Found: C, 80.3; H, 9.70.

The phenoxyacetic acid derivative was made by condensing with monochloroacetic acid in the presence of 33% sodium hydroxide solution; colorless needles from benzene, m. p. 173°.

2-Methyl-1-hydroxynaphthalene.—Sixteen and one-tenth grams of 2-piperidinomethylnaphthol-1, 1.6 g. of catalyst, and 200 ml. of dioxane were hydrogenated. Two grams of product was volatile with steam; after crystallization from petroleum ether, fluffy needles were obtained, m. p. 61.5–62°; yield, 19%. Lesser[9] gives m. p. 62°.

1-Methyl-2-hydroxynaphthalene.—Fifteen grams of 1-piperidinomethyl-naphthol-2, 2 g. of catalyst, and 200 ml. of dioxane were hydrogenated. Two and eight-tenths

(5) Auwers and Dombrowski, *Ann.*, **344**, 280 (1906).

(6) Jacobsen, *Ber.*, **11**, 24 (1878).

(7) Gluud and Breuer, *Chem. Zentr.*, **90**, I, 626 (1919).

(8) Clemmensen, *Ber.*, **47**, 62 (1914).

(9) Lesser, *Ann.*, **402**, 8 (1914).

grams of substance was volatile with steam and after crystallization from petroleum ether melted at 107–108°. A sublimed portion melted at 109°. Betti and Mundici[10] give m. p. 110° for sublimed 1-methyl-2-hydroxynaphthalene. The acetate was found to melt at 65°; Betti and Mundici give m. p. 66°.

3,5-Dimethylcatechol.—Twenty-five grams of 3,5-dimorpholinomethylcatechol, 3 g. of catalyst, and 200 ml. of dioxane were hydrogenated. The product was not volatile with steam; it was therefore extracted three times with ether. The dried, ethereal solution gave, on distillation, 3 g. of colorless oil, b. p. 235–240°, which solidified on cooling to room temperature. Crystallization from petroleum ether–benzene mixture gave yellow needles, m. p. 73.5–74.0°; yield, 36%. Hodgkinson[11] gives m. p. 73–74°.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.6; H, 7.25. Found: C, 69.5; H, 7.25.

2,3,5,6-Tetramethylphenol.—Two and three-tenths grams of 2-morpholinomethyl-3,5,6-trimethylphenol, 0.5 g. of catalyst, and 50 ml. of dioxane were hydrogenated. Nine-tenths gram was volatile with steam and after crystallization from petroleum ether–benzene mixture melted at 117.5–118°. A sublimed portion melted at 118°. Jacobsen and Schnapauff[12] give m. p. 117°. Bromination in acetic acid gave the bromide, m. p. 117.5–118.5°. Jacobsen and Schnapauff give m. p. 118° for bromodurenol.

2,3,5-Trimethylphenol.—Twenty-five grams of 2-morpholinomethyl-3,5-dimethylphenol, 3 g. of catalyst, and 150 ml. of dioxane were hydrogenated. Four and five-tenths grams of product was volatile with steam and after crystallization from petroleum ether melted at 94°; yield, 29%.[1] The residual liquor from the steam distillation was filtered from a small amount of resinous material, and neutralized with sodium carbonate, giving a light brown precipitate weighing 15 g. After recrystallization from methyl alcohol, the melting point was 96–97° (2-morpholinomethyl-3,5-dimethylphenol). The yield, based on the amount of 2-morpholinomethyl-3,5-dimethylphenol converted, was 73%.

2,4,5-Trimethylphenol.—Six grams of 4-piperidinomethyl-2,5-dimethylphenol, 1 g. of catalyst, and 100 ml. of dioxane were hydrogenated. The product separated from the steam distillate and also in the condenser. Crystallization from petroleum ether gave needles, m. p. 70°. Auwers and Marwedel[13] give m. p. 70°. The yield, 0.8 g., was 21%.

Attempted Preparation of Certain Aminomethyl Derivatives.—As previously stated, we were unable to obtain aminomethyl derivatives of several phenols. As an example, we may record here our experience with 2-isopropyl-4,5-dimethylphenol: 1.6 g. (m. p. 70–71°) was mixed with equivalent amounts of piperidine and formalin in 75% alcohol. After standing for several days, no separation of oil or crystals occurred; the mixture then was acidified and, upon steam distillation, 1.2 g. of crystals, m. p. 70–71°, was recovered.

Summary

Although the formation of a substituted benzylamine from a phenol by the action of a secondary amine and formaldehyde occurs in such fashion that the ortho position generally is preferentially affected, contrary to the assumptions of Auwers and Dombrowski, nevertheless some factor or factors not always of a steric nature bring about para substitution in certain cases.

The failure of this reaction to take place with 1-methylnaphthol-2 is adduced as additional evidence bearing upon the nature of the two ortho positions and the disposition of the double bonds in naphthol-2.

A formulation of the reaction between a phenol, secondary amine and formaldehyde is suggested.

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(10) Betti and Mundici, *Gazz. chim. ital.*, **36**, II, 657 (1905).

(11) Hodgkinson and Limpach, *J. Chem. Soc.*, **63**, 108 (1893).

(12) Jacobsen and Schnapauff, *Ber.*, **18**, 2843 (1885).

(13) Auwers and Marwedel, *ibid.*, **28**, 2902 (1895).