

The ether was removed by distillation leaving a residue of crude dihexylmethylmalonic acid amounting to 59.6 g., which partially crystallized on standing.

To this crude material, dissolved in 95 ml. of absolute ether, was added dropwise 29.2 g. (0.183 mole) of bromine as the reaction mixture was stirred and heated under reflux over a period of 45 minutes. After the addition of bromine was complete, the reaction mixture was heated for an additional one-half hour. The mixture was cooled to room temperature, and 70 ml. of water was added dropwise. The ether layer was separated, and without drying the ether was removed by distillation leaving a residue of crude bromodihexylmethylmalonic acid. This was decarboxylated by heating at 135–145° in an oil-bath for 90 minutes. The material was then heated *in vacuo* at the same temperature for an additional hour to remove volatile substances. The residue which amounted to 57.2 g. was dissolved in 200 ml. of hexane. The solution was warmed, treated with 5 g. of Darco and filtered. The hexane was removed under reduced pressure. The crude product obtained was an orange-colored oil, yield 54.2 g. (92%).

β , β -Dihexylalanine.—In the glass liner of a high pressure bomb was placed 5.0 g. (0.016 mole) of the crude bromo-acid dissolved in 30 ml. of absolute ethanol. This was cooled in a Dry Ice–Cellosolve mixture and 5.1 g. (0.30 mole) of liquid ammonia was added with stirring. The reaction mixture was heated in the bomb to 130° over a period of seven hours and then allowed to cool overnight. The contents were removed, and a light, amber solution was obtained. The ethanol and excess ammonia were then removed under reduced pressure. When about half of the ethanolic ammonia had been removed, a voluminous, white precipitate began to form. This precipitate was removed by filtration and washed thoroughly with anhydrous ether. The crude material was of a spongy consistency, m.p. 211–223°, yield 2.6 g. A sample for analysis was recrystallized twice from 50% aqueous acetic acid. The material sintered at 215° and melted at 222–223° (cor.).

Anal. Calcd. for $C_{16}H_{33}NO_2$: C, 69.99; H, 12.14; N, 5.44. Found: C, 70.05; H, 12.05; N, 5.42.

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The Reaction of a *p*-Substituted *o*-Methylolphenol with Oleic Acid

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The heat reaction of *o*-hydroxymethyl phenols with unsaturated compounds has been found by K. Hultzschi¹ to result in the formation of chroman rings in the case of simple unsaturates such as styrene. Many other authors² join Hultzschi in assuming that the same formation of chromans takes place in reaction with drying oils, but no definite proof of this has been advanced. Others assume a reaction of unspecified nature between the methylol groups and "active methylene hydrogen,"³ or a transesterification accompanied by reaction with polyunsaturated centers only,⁴ or with formation of

(1) K. Hultzschi, *J. prakt. Chem.*, **158**, 275 (1941).

(2) J. I. Cunneen, E. H. Farmer and H. P. Koch, *J. Chem. Soc.*, 472 (1943); H. S. Lilley, *Paint Technology*, **11**, 179 (1946).

(3) H. Honel, *J. Oil, Colour Chem. Assoc.*, **21**, 247 (1938); British Patent 334,572 (1929).

(4) T. P. Hilditch and C. J. Smith, *J. Soc. Chem. Ind.*, **54**, 111 T (1935).

methylene bridges.⁵ Some authors⁶ dispute the fact that a reaction takes place with a drying oil at all.

To avoid complications this reaction was investigated using monofunctional reagents. Being conveniently available, the *o*-methylol derivative of *p*-*t*-butyl-*o*-cresol and oleic acid or its methyl ester were employed.

When these two reagents, the latter in large excess, were heated together to 180° for 3–4 hr. in a slow stream of dry CO₂, a reaction took place with the evolution of almost exactly one mole of water per mole of methylol phenol used. No evolution of formaldehyde could be detected. After removal of excess oleic acid and volatile self-condensation products of the methylolphenol by vacuum distillation, a residue greater than the original amount of methylolphenol used remained. This residue was shown by potentiometric titration and esterification to contain a considerable amount of carboxylic acid groups, though only a very small amount of oleic acid could be recovered from it by extraction with alkali. Contrary to the assertion of Hultzschi,¹ the extraction with alkali yielded no high molecular weight acids. The carboxyl groups must be bound to some molecule other and presumably larger than oleic acid, which yields water insoluble soaps.

By the use of a Duolite A-2 anion exchange resin column, the residue could be separated into three fractions, two of which evidently resulted from self-condensation of the methylolphenol. The larger of these latter fractions was neutral, had an

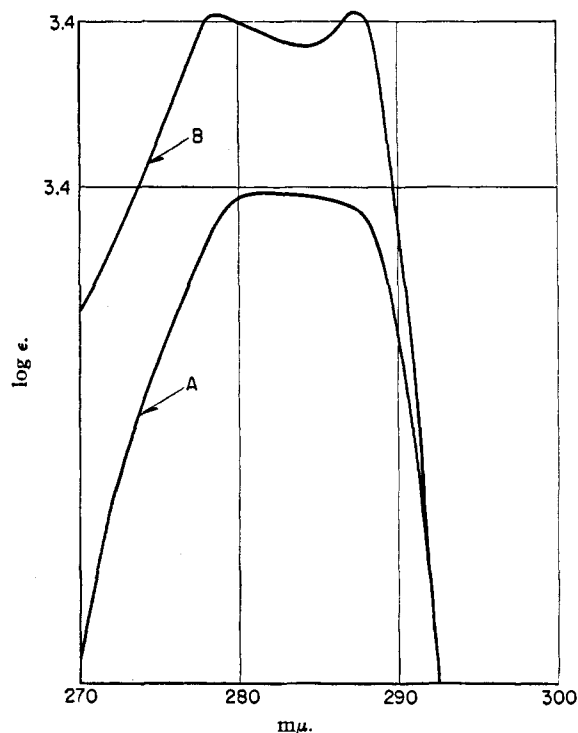


Fig. 1.—Ultraviolet spectra of 2-methyl-4-*t*-butyl-6-methylolphenol (A) and the corresponding chroman ester (B).

(5) S. Van der Meer, *Rec. trav. chim.*, **63**, 147, 157 (1944).

(6) K. H. Dold, *Schweiz. Arch. angew. Wiss., Tech.*, **3**, 287, 325 (1937); *Farben-Z.*, **44**, 1034 (1939); W. E. Wornum, *Chem. Ind.*, **66**, 995 (1937).

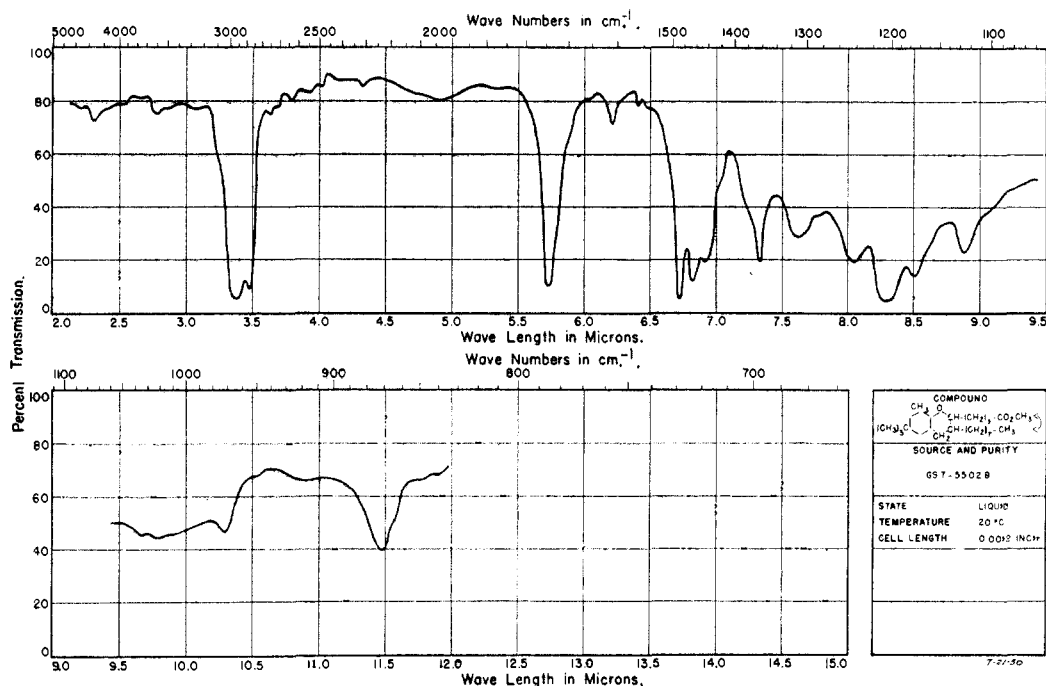


Fig. 2.—Infrared spectrum of the chroman ester.

approximate molecular weight of 560, and contained only about 1.0–1.7% hydroxyl groups; the second fraction, recovered in very small amount, was weakly acid, apparently due to a phenolic hydroxyl content of 3.6%, and had a molecular weight of approximately 680. It may be noted that both of these fractions have a molecular weight higher than can be accounted for by current theories on the self-condensation of monofunctional methylolphenols and a hydroxyl content so low as to be accounted for only by almost exclusive formation of quinone methide. The third fraction obtained was a carboxylic acid, the methyl ester of which could be further purified by distillation (b.p. 207–210° (0.05 mm.)). It was later found that the same substance could be isolated by direct esterification and vacuum distillation of the original residue, though the free acid seems to decompose when distilled under the same conditions. The ester thus recovered had a molecule weight of 460–465, and the acid obtained from it by saponification had an acid equivalent weight of 454–455. The substance contains no reactive double bonds, no free hydroxyl groups, and no active hydrogen (in the ester). The ultraviolet spectrum (Fig. 1) shows a peak with two maxima, at 279.5 and 287 $m\mu$, respectively, typical of chroman spectra.⁷ The infrared spectrum (Fig. 2) shows no indication of hydroxyl groups. The ultimate analysis of the ester indicates an empirical formula of $\text{C}_{21}\text{H}_{32}\text{O}_3$.

On this evidence it is concluded that the substance isolated is a chroman acid IIIa or IIb (or its ester) formed from the methylol phenol and oleic acid (or methyl oleate) by reactions AB (Fig. 3). No decision has been made between formulas IIa and IIb, and, in fact, both are probably represented in the product since the position directing carboxyl group is too far from the double bond in oleic acid

to have a strong directive influence. The intermediate substance I is formulated as a monomeric quinone methide to bring out the resemblance to a Diels–Alder reaction, even though such quinone methides are only known in the form of unreactive dimers or trimers. Even as a transient state I is not intended to represent actual structure.

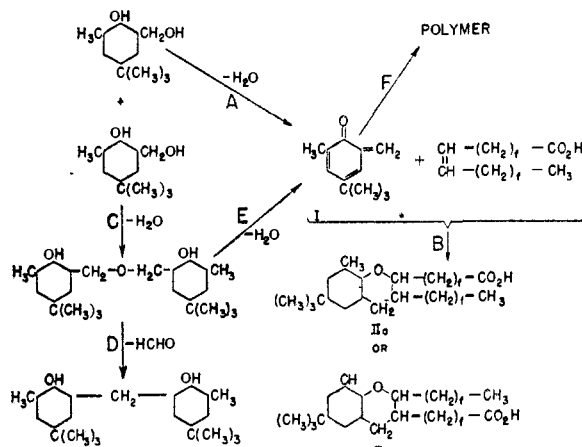


Fig. 3.

Reaction D, which plays a large part in self-reinification when the methylolphenol is heated by itself or in a neutral, non-reactive oil (transformer oil or Nujol), does not take place at all in presence of oleic acid in excess. No accurate method for simultaneous determination of water and formaldehyde in the gas stream emerging from such a reaction mixture could be devised so far. But qualitative tests showed that in presence of oleic acid no formaldehyde was evolved up to 230° bath temperature.

In presence of oleic acid (or methyl oleate) virtually all of the methylolphenol present must react

(7) T. J. Webb, et al., *J. Org. Chem.*, **4**, 386 (1939).

via AB, CEB, AF or CEF, since a water evolution of one mole per mole of methylol phenol can be accounted for in no other way. Corroborating this is the fact that the neutral self-resinification product of the methylolphenol isolated had a molecular weight corresponding to 3-4 methylolphenol units and a very low hydroxyl content. *o*-Quinone methide polymers are known to contain no free hydroxyl groups.⁸ The products of reactions C and D obviously have a high free hydroxyl content and a molecular weight less than twice that of the original methylphenol. No further investigations as to the nature of the neutral polymer formed were made.

Esterification or transesterification of the methylol or phenolic hydroxyl by the fatty acid can play only a very minor role in the reaction, since saponification of either the neutral or the entire higher molecular weight residue increases its carboxyl and hydroxyl content only very slightly.

The amount of chroman acid recovered indicates that under the conditions used 35-45 mole-% of the methylolphenol reacts with oleic acid to form chroman.

As indicated by reaction EB, the corresponding dibenzyl ether can undergo the reaction to form a chroman as well as the methylolphenol. The molar yields of chroman acid using the dibenzyl ether as the starting material were approximately the same as those with methylolphenol. Correspondingly less water was evolved in the reaction.

Experimental

2-Hydroxymethyl-4-*t*-butyl-6-methylphenol was prepared by treating *p*-*t*-butyl-*o*-cresol (Dow Chemical Company) with somewhat more than a molar proportion of 37% aqueous formaldehyde in presence of the stoichiometric amount of sodium hydroxide. The product was recrystallized from hexane-benzene.

Chroman Reaction.—Charges of 10 g. (0.0515 mole) of the dry methylolphenol were powdered and heated with 70 g. (0.0248 mole) of oleic acid (Eimer and Amend No. A-216) in a flask immersed in a wax-bath. A slow stream of CO₂ (approx. 0.2-0.3 l./min.) was dried by passing through tubes of CaCl₂ and Drierite, then bubbled through the reaction mixture. The emergent gas stream was passed first through a U-tube filled with glass wool and immersed in a beaker of boiling water to catch entrained oil, then through a weighed U-tube filled with Drierite. The change in weight of the Drierite U-tube was taken as water evolved in reaction. The methylolphenol dissolves in the charge at about 100°, thereafter the temperature was quickly raised to 170-180° and held there for 3-5 hr. on various runs, then raised to 220-230° for a final 1/4 hr. In four quantitative runs 0.97-1.10, av. 1.01 moles of water was evolved per mole of methylolphenol; test with chromotropic acid showed no evolution of formaldehyde.

Oleic acid was removed from the reaction products by distillation in a modified "collar still"⁹ up to a bath temperature of 280° at 1.5 mm. The distillate contains besides oleic acid a small amount of aldehyde tentatively identified as 2-hydroxy-3-methyl-5-*t*-butylbenzaldehyde and small amounts of other distillable self-condensation products of the methylol phenol not yet identified.

The residue of distillation (13.5-15.0 g.) has an acid equiv. wt. of 570-650 and contains very little oleic acid, which can be removed by extraction with 2% sodium hydroxide. The residue was dissolved in dry petroleum ether and poured on a column (200 × 35 mm.) of Duolite A-2 anion exchange resin (Chemical Products Co.) which had previously been ground to 35-200 mesh, treated to obtain the basic form, and

dried.¹⁰ A dark brown fraction washed through with the petroleum ether, which was put through until the effluent contained no more substance. The substance washed through with petroleum ether usually amounted to approx. 10% of the total charge. It was a very sticky, dark grease, nearly neutral (acid equiv. wt. 5,000-30,000), and contained very few hydroxyl groups (1.0-1.7% OH). The molecular weight in benzene by the Menzies-Wright ebullioscopic method was determined as 564, though due to the difficult nature of the substance this value is probably low.

When the neutral fraction had been washed through, the acid fraction was eluted with sufficient 2% sodium hydroxide in methanol to make the effluent alkaline, washing thereafter with methanol until no more substances came through and the effluent was neutral. This left the column ready for the next run. The acid fraction thus obtained (acid equiv. wt. av. 485-90) was esterified by refluxing with absolute methanol containing 0.1-0.3% concd. sulfuric acid, recovered and put through the Duolite column again in petroleum ether. The run-through in petroleum ether now contained reasonably pure chroman ester (ester of IIa or IIb), with a saponification equiv. of 460-465. Elution with alkali produced a small amount of a fraction containing acid groups, apparently phenolic hydroxyls, (3.6% hydroxyl; OH equiv. wt. 470). This fraction had an ebullioscopic molecular weight of 676 and an acid equiv. wt. of 680. Neither of these values is probably very accurate, since the nature of the substance as a tacky resin made it hard to add definite amounts in the mol. wt. determination, and the acidity titrated appears to be largely or entirely due to the acid hydroxyls, which makes the end-point indefinite.

The chroman ester obtained in 35-45% yield could be further slightly purified by repeated distillation in vacuum, b.p. 204-208° (0.04-0.05 mm.). Still further purification was achieved by chromatography of the ester on aluminum oxide in petroleum ether. The pure ester is washed down the column with further petroleum ether and isolated from the portion of the run-through taken before the first visible (yellowish) band reaches the end of the column. It is a pale yellowish oil, slightly less mobile than oleic acid. Molecular weight was determined ebullioscopically in benzene by the modified Menzies-Wright method,¹¹ using a hypodermic syringe as a weight buret to deliver substance.

Anal. Calcd. for C₂₈H₃₂O₃; mol. wt., 472.73; C, 78.76; H, 11.09. Found: mol. wt., 460, 465; C, 78.80, 78.79; H, 10.96, 11.00.

The ester was saponified with alcoholic potassium hydroxide, and the acid recovered and dried in vacuum.

Anal. Calcd. for C₂₀H₂₀O₃; acid equiv. wt., 458.7. Found: acid equiv. wt., 454, 455.

The ultraviolet spectrum of the ester (Fig. 1) was taken in cyclohexane purified over silica gel, showing maxima at 279.5 and 287 mμ agreeing with other chroman spectra.⁷ The infrared spectrum of the ester (without solvent, 0.001 inch cell) (Fig. 2) shows no absorption due to free hydroxyl groups. No hydrogen is evolved on treatment of the ester with lithium aluminum hydride in *n*-butyl ether soln., showing the absence of active hydrogen. The ester takes up bromine very slowly from carbon tetrachloride soln., apparently chiefly by substitution or ring fission. Quantitative catalytic hydrogenation, using Adams Pt-catalyst, showed a hydrogen consumption varying with conditions but corresponding to only a few per cent. of the theoretical value for one double bond per molecule, probably due to hydrogenolysis or to some residual impurity.

When the chroman reaction was run under the same conditions but using methyl oleate as the unsaturated component only 0.80-0.90 mole of H₂O were evolved per mole of methylol phenol used. In this case the distillation of volatile components from the residue was carried to 255° bath temp. at 1.5-2.0 mm., the methyl oleate distilling at 155-170°. The same chroman acid (as methyl ester) was formed as above, but in slightly lower yield, corresponding to 30-40 mole % of the methylolphenol used. At the same time a somewhat larger proportion of free, phenolic hydroxyl groups was found in the neutral fraction of the distillation residue. Reaction here evidently does not go as completely *via* the quinone methide as in presence of oleic acid.

(8) K. Fries and E. Brandes, *Ann.*, **542**, 48 (1939); K. Fries and K. Kann, *ibid.*, **353**, 335 (1907).

(9) K. Hickman and W. Weyerts, *THIS JOURNAL*, **52**, 4712 (1930).

(10) D. A. Robinson and G. F. Mills, *Ind. Eng. Chem.*, **41**, 2221 (1949).

(11) W. E. Hanson and J. R. Bowman, *Anal. Chem.*, **11**, 440 (1939).

When bis-(2-hydroxy-3-methyl-5-*t*-butyl benzyl) ether was treated with oleic acid in place of the methylolphenol, the same chroman was produced in approximately the same molar yield, based on hydroxybenzyl residues. In this case also the maximum possible amount of water is evolved, one mole per mole of dibenzyl ether.

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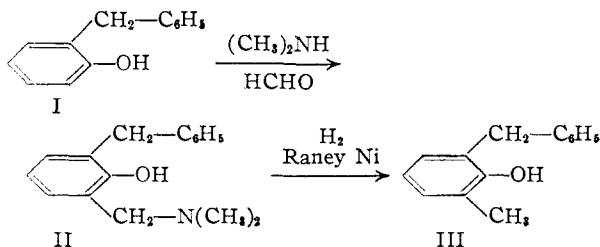
2-Benzylphenol Derivatives. VII.¹ Mannich Bases

BY WILLIAM B. WHEATLEY AND LEE C. CHENEY

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In continuing our investigation of the chemistry of the benzylphenols, we turned our attention to the Mannich reaction, since it is well known that many phenols react with formaldehyde and amines with ease.² The reaction of 2-benzylphenol (I) with formaldehyde and dimethylamine proceeded smoothly, but distillation of the resulting phenolic Mannich base was not satisfactory.³ Decomposition accompanied the distillation, resulting in a low yield of distilled product and a large black residue.

The Mannich reaction with 2-benzylphenol could yield any or all of three products: the 4- or the 6-dimethylaminomethyl-2-benzylphenol or 4,6-bis-(dimethylaminomethyl)-2-benzylphenol. By using formaldehyde and dimethylamine just equivalent to the 2-benzylphenol, we hoped to keep the amount of the 4,6-disubstituted product at a minimum. By analogy with the results reported for *o*-cresol and *o*-phenylphenol, we assumed the entering dimethylaminomethyl group would occupy the 6-position. Dimethylamine and formaldehyde react with *o*-cresol exclusively by ortho substitution³; diethylamine and formaldehyde react with *o*-phenylphenol to give a mixture of ortho and para isomers in a ratio of approximately 3:1.⁴ Hydrogenolysis of the Mannich base prepared from 2-benzylphenol gave 2-benzyl-6-methylphenol, indicating that the product obtained possesses structure II. It is possible, of course, that the undistillable residue contained appreciable amounts of the isomeric 2-benzyl-4-dimethylaminomethylphenol.



The Mannich reaction with 2-benzyl-4-chlorophenol gave the expected product, 2-benzyl-4-

(1) For the preceding paper in this series, see W. B. Wheatley, *et al.*, *THIS JOURNAL*, **72**, 5575 (1950).

(2) F. F. Blicke, in R. Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 303 ff.

(3) Distillation of the Mannich bases obtained from *o*-cresol was reported to be accompanied by considerable decomposition (R. B. Carlin and H. P. Landerl, *THIS JOURNAL*, **72**, 2762 (1950)).

(4) J. H. Burckhalter, *ibid.*, **72**, 5309 (1950). See also W. T. Caldwell and T. R. Thompson, *ibid.*, **61**, 765, 2354 (1939); E. L. Eliel, *ibid.*, **73**, 43 (1951).

chloro-6-dimethylaminomethylphenol, in 76% yield (the best yield obtained in several experiments with 2-benzylphenol was 36%). This greatly increased yield of isolated product may be because this Mannich base was purified by crystallization instead of by distillation, as well as the fact that in this case there is no possibility for isomer formation or disubstitution.

The authors are indebted to Mr. Richard M. Downing for the analyses reported herein, and to Mrs. Nancy Jones for technical assistance.

Experimental⁵

2-Benzyl-6-dimethylaminomethylphenol (II).—To a stirred solution of 92.1 g. (0.5 mole) of 2-benzylphenol (I) in 300 ml. of 95% ethanol was added 95 ml. of 25% aqueous dimethylamine, followed by 40 ml. of 37% formalin. A slight evolution of heat was observed. After 50 ml. of water was added, the solution was heated on the steam-bath for one hour. The reaction mixture was homogeneous at first but separated into two layers soon after heating was begun. The lower layer was withdrawn and the upper layer diluted with a liter of water. This solution was extracted twice with ether and the ether extracts added to the original lower layer. The ether solution was extracted three times with 6 *N* hydrochloric acid. The combined acid extracts were neutralized with sodium bicarbonate (to pH 7 or 8) and the oil which separated extracted into ether. The ether extracts were shaken with saturated sodium chloride and filtered through anhydrous sodium sulfate. Distillation afforded 43.4 g. (36% yield) of II, b.p. 155–160° at 2.5 mm.; n_D^{20} 1.5712. Decomposition prevented further distillation, leaving a large black residue.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.6; H, 7.9; N, 5.8. Found: C, 80.3; H, 7.8; N, 5.9.

Proof of Structure of II.—Twelve grams of the Mannich base obtained from 2-benzylphenol was dissolved in 75 ml. of methanol and shaken for seven hours at 50° with Raney nickel (12 g. of the wet paste) under an initial hydrogen pressure of 52 p.s.i. The cooled reaction mixture was filtered and the filtrate evaporated under reduced pressure. The residual oil was taken up in 100 ml. of ether and extracted with two 25-ml. portions of 6 *N* hydrochloric acid. The ether layer was shaken with saturated sodium chloride and filtered through anhydrous sodium sulfate. On distillation there was obtained 5.7 g. (58% yield) of a colorless oil, b.p. 127–128° at 2 mm., which spontaneously solidified. Two recrystallizations from Skellysolve B (petroleum ether, b.p. 60–71°) gave colorless crystals of III, m.p. 48.0–50.0°. A mixture of III and an authentic sample of 2-benzyl-6-methylphenol, which was prepared by benzylation of *o*-cresol,⁶ likewise melted at 48.0–50.0°. Had the isomeric 2-benzyl-4-dimethylaminomethylphenol been the product isolated from the Mannich reaction with I, hydrogenolysis would have given 2-benzyl-4-methylphenol. This phenol is reported to be an oil,⁷ an observation which we verified. As further evidence for the structure assigned to III, derivatives were prepared. Under identical conditions, III and the authentic 2-benzyl-6-methylphenol did not react with phenyl isocyanate, while 2-benzyl-4-methylphenol gave the known phenylurethan.⁷ 2,4-Dinitrophenyl ethers of all three phenols were readily prepared.⁸ The ether of the authentic 2-benzyl-6-methylphenol melted at 109.0–110.5° (recrystallized from 95% ethanol).

Anal. Calcd. for $C_{20}H_{18}N_2O_5$: C, 65.9; H, 4.4. Found: C, 66.3; H, 4.5.

The ether of III, even after repeated recrystallization, melted slightly lower, 105.0–107.0°. A mixture of these, however, melted at 105.0–108.0°. The ether of authentic 2-benzyl-4-methylphenol melted at 110.0–112.5°; a mixture of it with the ether of III melted at 86.0–98.0°.

(5) Melting points are corrected.

(6) P. Schorigin, *Ber.*, **58**, 2028 (1925).

(7) L. Claisen, F. Kremers, F. Roth and E. Tietz, *Ann.*, **442**, 210 (1925).

(8) S. M. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945, p. 248.