When bis-(2-hydroxy-3-methyl-5-*t*-butyl benzyl) ether was treated with oleic acid in place of the methylolphenol, the same chroman acid 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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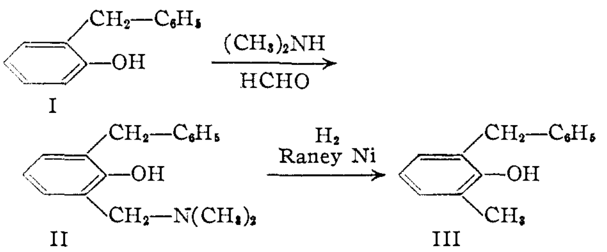
In continuing our investigation of the chemistry of the benzylphenols, we turned our attention to the Mannich reaction, since it is well known that many phenols react with formaldehyde and amines with ease.[2] The reaction of 2-benzylphenol (I) with formaldehyde and dimethylamine proceeded smoothly, 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 substitution[3]; 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-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.

### Experimental[5]

**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 *p*H 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.; $n^{25}_D$ 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 $C_{20}H_{16}N_2O_5$: 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°.

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(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).

(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.

**2-Benzyl-4-chloro-6-dimethylaminomethylphenol.**—Using 219 g. (1.0 mole) of 2-benzyl-4-chlorophenol, 190 ml. of aqueous dimethylamine and 80 ml. of formalin, the Mannich reaction was carried out as above. On neutralization of the acid extracts, the Mannich base separated as a solid. It was extracted into benzene (its solubility in ether was very low), and the benzene solution dried by shaking with saturated sodium chloride and filtering through anhydrous sodium sulfate. The benzene was evaporated and the crude product crystallized from methanol, giving 209 g. (76% yield) of 2-benzyl-4-chloro-6-dimethylaminomethylphenol, m.p. 84.5–86.5°. Repeated recrystallization from methanol sharpened the m.p. to 85.5–86.5°.

*Anal.* Calcd. for $C_{16}H_{18}ClNO$: C, 69.7; H, 6.6. Found: C, 69.7; H, 6.7.

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# The Acidity Constant, Solubility Product and Solubility of Dithioöxamide[1]

BY RUTH POWERS YAFFE AND ADOLF F. VOIGT

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Dithioöxamide, frequently called rubeanic acid, is a well-known complexing agent of the platinum group metals. It is readily soluble in alkaline solutions and forms salts which have been called rubeanates. Although the acidic behavior of dithiooxamide is well known, no determination of its acidity constant has been reported.

The method followed for this determination was the potentiometric titration procedure for acids of limited solubility given by Back and Steenberg.[2]

The potentiometric titrations were made with a Beckman Model G *p*H meter equipped with a #1190-E High *p*H Glass Electrode. A known quantity of dithioöxamide was dissolved in a known excess volume of standard base. This solution was then titrated with a standard acid. At the beginning of the titration the weak acid was in the form of its soluble salt in a slight excess of base. After this excess base was neutralized, a known concentration, $C_s$, of titrating acid was added and the *p*H measured. This process was repeated with about five additions of acid before flocculation occurred. From each of these measurements a value of $pK_a$ was calculated by means of equation (1)

$$pK_a = pH + \log \left\{ \frac{C_s + C_{OH} - C_H}{C_a + C_H - C_s - C_{OH}} \right\} + \frac{0.5\sqrt{\mu}}{1 + \sqrt{\mu}} \tag{1}$$

where $C_a$ is the total concentration of the weak acid [HA + A⁻]. The titration was continued through the stage of flocculation, about five more measurements being obtained before salting out of the dithioöxamide at the reference electrode caused the results to be inconsistent. These data were used in equation (2) to calculate the solubility product.

$$pK_{sp} = pH - \log \{ C_a + C_H - C_s - C_{OH} \} + \frac{0.5\sqrt{\mu}}{1 + \sqrt{\mu}} \tag{2}$$

The solubility of the acid is given by the relation

$$S = K_{sp}/K_a \tag{3}$$

It was found that the dithioöxamide behaved as a monobasic acid. Equations (1) and (2) give the thermodynamic constants since they contain an expression for the activity coefficient of the acid ion, and the hydrogen ion activity is determined directly. The values of $\mu$ used in the equations were calculated for each point and were approximately 0.01. In each titration, 5 or 6 individual determinations of $K_a$, $K_{sp}$ and $S$ were obtained. In all, five complete titrations were carried out. The over-all averages of these 25 to 30 determinations and their standard deviations are: for the acidity constant, $K_a$, $(1.28 \pm 0.04) \times 10^{-11}$, for the solubility product, $K_{sp}$, $(3.94 \pm 0.12) \times 10^{-14}$ and for the solubility, $S$, $(3.07 \pm 0.04) \times 10^{-3}$ mole per liter.

In addition to these thermodynamic constants, the non-thermodynamic constants at an ionic strength of 1.0 were desired. Sodium perchlorate, made by dissolving sodium carbonate in perchloric acid, was used as the inert electrolyte. Three complete titrations were made, and the results averaged. The non-thermodynamic constants may be summarized as follows: $k_a = (3.78 \pm 0.04) \times 10^{-11}$; $k_{sp} = (6.27 \pm 0.14) \times 10^{-14}$; $s = (1.66 \pm 0.03) \times 10^{-3}$ mole per liter.

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[1] Contribution No. 171 from the Institute for Atomic Research and the Department of Chemistry, Iowa State College, Ames, Iowa. Work performed in the Ames Laboratory of the Atomic Energy Commission.

[2] E. Back and B. Steenberg, *Acta Chem. Scand.*, **4**, 810 (1950).

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# NEW COMPOUNDS

## Derivatives of *p*-Aminosalicylic Acid[1,2]

Two derivatives of *p*-aminosalicylic acid have been prepared.

**Methyl N-(2-Hydroxyethyl)-*p*-aminosalicylate.**—To a vigorously stirred solution of 33.4 g. (0.2 mole) of methyl *p*-aminosalicylate (prepared from commercial *p*-aminosalicylic acid[3]) and 700 ml. of anhydrous ether in a one-liter flask surrounded by an ice-bath were added simultaneously over a period of 30 minutes 61 ml. (0.1 mole) of a 10% solution of ethylene oxide in anhydrous ether and 40 ml. of a 2% solution of boron trifluoride etherate in anhydrous ether. After two hours of additional stirring, the ice-bath was removed and stirring continued for 30 minutes. The mixture was then heated at reflux temperature for one hour, transferred to a separatory funnel and extracted quickly with three 150-ml. portions of 10% sodium hydroxide solution. The extracts were combined, treated with carbon dioxide, and filtered at intervals to obtain the precipitate in several fractions. These were dried in a vacuum desiccator, dissolved in anhydrous ether, filtered from any carbonates, and the ether evaporated. Each fraction was a mixture of methyl *p*-aminosalicylate (I) and methyl N-(2-hydroxyethyl)-*p*-aminosalicylate (II), the latter being present in increasing proportions in successive fractions. By fractional sublimation at 0.02–0.05 mm. pressure 24.1 g. of I and 2.9 g. (37%) of II were obtained. From a mixture of benzene and petroleum ether II was obtained as a white crystalline solid, m.p. 90°.

*Anal.* Calcd. for $C_{10}H_{13}NO_4$: N, 6.63. Found: N, 6.53.

**N-(2-Hydroxyethyl)-*p*-aminosalicylic Acid.**—In a pear-shaped 25-ml. flask a mixture of 0.75 g. (0.0036 mole) of methyl N-(2-hydroxyethyl)-*p*-aminosalicylate and 4.27 ml. (0.0106 mole) of 10% sodium hydroxide solution were re-

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[1] From the M. S. thesis of E. Kenneth Brakebill, June, 1951.

[2] This work was supported in part by a Research Corporation Grant-in-Aid.

[3] J. J. Schaefer and Leonard Doub, THIS JOURNAL, **71**, 3564 (1949).