

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Indirect Phenol-Aldehyde Condensations

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Introduction

In the course of recent investigations of "blocked" phenol-aldehyde condensations³ it became necessary to repeat the work of M. Koebner⁴ on the condensation of *p*-cresol with its *o,o'*-dimethylol derivative.

M. Koebner condensed 168 g. (one mole) of dimethylol-*p*-cresol with 1000 g. (9.3 moles) of *p*-cresol in the presence of 20 ml. of concentrated hydrochloric acid. A crystalline condensation product (m. p. 215°) was obtained. Koebner assigned the molecular formula C₂₃H₂₄O₃, corresponding to a 2:1 condensation, and a "tri-nuclear" dibenzylphenol type of open-chain structure, which appears to be substantiated by quantitative carbon and hydrogen analyses and by a cryoscopic molecular weight determination.

Koebner's experiment was repeated using one-twentieth amounts. Thus, 8.4 g. of the dimethylol-*p*-cresol was condensed with 50 g. of *p*-cresol in the presence of 1 ml. of concentrated hydrochloric acid. Following the purification procedure as given by M. Koebner, the purified crystalline condensation product was then subjected to quantitative carbon and hydrogen analyses.⁵

It was found that Koebner's figures could not be duplicated. Also, cryoscopic molecular weight determinations, done according to Koebner,⁴ and also using phenol as the solvent, gave different values than those published by Koebner. (Found: 223 and 213, instead of 348.)

Realizing that phenol-aldehyde condensation products usually show a rather characteristic "retention effect"^{6a,6b} the product was acetylated, yielding a crystalline acetate in which this analytically confusing retention effect is absent. Analysis⁵ of this acetate (carbon, hydrogen, molecular

weight, and acetyl determination) checked for a 2:2 ratio of *p*-cresol with its dialcohol, and not for a 2:1 ratio as claimed by Koebner.

Since the original condensation product does not undergo diazotization reactions,⁷ and since an open-chain structure thus appears untenable (Koebner's open-chain formula has two ring positions available for diazotization) a cyclic structure becomes a definite possibility. Cyclic structures have previously been assigned to certain types of phenol-aldehyde condensation products by Raschig,^{6b} Niederl,^{6a} and Cheronis.⁸ Application of a similar cyclic structure to the *p*-cresol-*p*-cresol-dialcohol condensation product would be in full harmony with all analytical findings, both quantitative and qualitative.

In order to substantiate this more fully, dimethylol-*p*-cresol was also condensed with *p*-bromophenol in equimolar quantities and under identical reaction conditions. The resulting crystalline condensation product (m. p. 210° uncor.), which also did not undergo diazotization reactions, was then acetylated and the resulting crystalline acetate was subjected to quantitative carbon, hydrogen, and bromine analyses, as well as molecular weight determinations.⁵ Again, the values, which in this case, due to the introduction of a high atomic weight 'tracer' element (bromine), allow a much better differentiation, checked for a 2:2 ratio condensation product and not for a 2:1 molar ratio.

Finally, a "tri-nuclear" dibenzylphenol type of open-chain condensation product was actually prepared by condensing one mole of the same dimethylol-*p*-cresol with two moles of 2,4-xyleneol, a "blocked" phenol⁸ having only one ortho position open for reaction and thus being unable to undergo cyclization. The condensation product proved to be a low-melting solid whose crystalline acetate analyzed correctly for a 2:1 or linear open-chain condensation product, namely, 4-methyl-2,6-di-(2-hydroxy-3,5-di-methyl)benzylphenol-1.

From the experimental and analytical facts

(1) Original manuscript received March 20, 1942.

(2) Abstracted from Part II of the thesis submitted by John S. McCoy to the faculty of the Graduate School of New York University, in partial fulfillment for the degree of Doctor of Philosophy, April, 1942.

(3) J. B. Niederl and J. S. McCoy, *THIS JOURNAL*, **63**, 1731 (1941).

(4) M. Koebner, *Z. angew. Chem.*, **46**, 252 (1933).

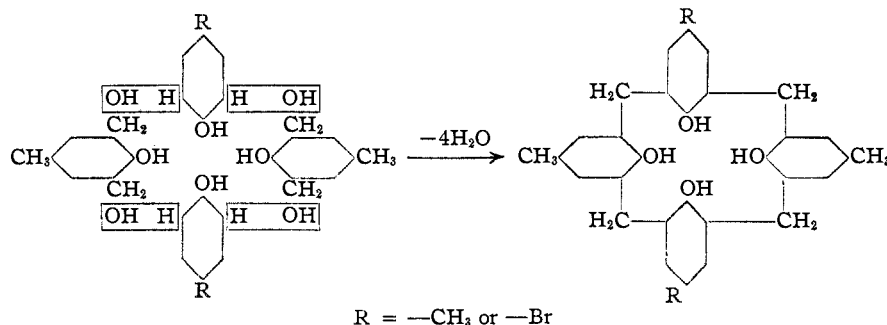
(5) J. B. Niederl and V. Niederl, "Micromethods of Quantitative Organic Analysis," Second edition, J. Wiley and Sons, New York, N. Y., 1942: (a) pp. 101-132; (b) pp. 48-49; (c) pp. 217-220.

(6) (a) J. B. Niederl and H. J. Vogel, *THIS JOURNAL*, **62**, 2512 (1940); (b) F. Raschig, *Z. angew. Chem.*, **25**, 1945 (1912).

(7) Shriner and Fuson, "Identification of Organic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1935, p. 30.

(8) N. D. Cheronis, "Semi-Micro and Macro Organic Chemistry," T. V. Crowell Co., New York, N. Y., 1942, p. 344.

enumerated above, it seems then that dimethylol-*p*-cresol condenses with *p*-cresol and with *p*-bromophenol to give crystalline condensation products which appear to possess a cyclic or tridimensional structure as given below



Experimental

Condensation of *p*-Cresol with 1,3,5-Trimethyl-1',2,3'-trihydroxybenzene.

Koebner's Method.⁴—Eight and four tenths grams of dimethylol-*p*-cresol, prepared according to Auwers,⁹ Ullmann and Brittner¹⁰ by condensing *p*-cresol with two mols of formaldehyde, was dissolved in 50 g. of *p*-cresol and placed in a 250 ml. Erlenmeyer flask. One ml. of concentrated hydrochloric acid was added. The temperature rose from 20 to 63° within one minute and then dropped to 55°. At the time of the drop in temperature, a white precipitate formed.

The solution was cooled to 20° and 50 ml. of petroleum ether added. The solution was allowed to stand overnight and then the precipitate was filtered off. The crystalline solid was recrystallized from glacial acetic acid and dried thoroughly in a vacuum desiccator over sodium hydroxide. The weight, after recrystallization, was 12 g., m. p. 215° (uncor.)¹¹

Equimolar Method.—One tenth of a mole (16.8 g.) of dimethylol-*p*-cresol was dissolved in 50 ml. of glacial acetic acid and 0.1 mole (10.8 g.) of *p*-cresol added. Dry hydrogen chloride gas was passed in until the solution was saturated. Seventeen grams of crystalline condensation product was obtained on standing. The product was recrystallized and dried as described above; m. p. 215° (uncor.); mixed m. p. with Koebner's product 215° (uncor.).

Anal. Calcd. for 2:2 condensation, C₂₂H₂₂O₄·H₂O: C, 77.35; H, 6.83; H₂O, 3.61. *Anal.* Calcd. for 2:1 condensation, C₂₂H₂₄O₃ (Koebner⁴): C, 79.31; H, 6.90. Found⁵: C, 77.54; H, 6.72^{5(a)}; H₂O, 3.31, 3.44.^{5(b)}

Acetate.—Fifteen grams of the above condensation product was refluxed with 75 ml. of acetic anhydride for two hours. The solution was poured into water and the crystalline precipitate filtered off and recrystallized from ethyl alcohol; m. p. 125° (uncor.).

Anal. Calcd. for 2:2 condensation, C₄₀H₄₀O₈: C, 74.07; H, 6.17; mol. wt., 648; for 2:1 condensation, C₂₀H₂₀O₄: C, 73.41; H, 6.33; mol. wt., 474. Found⁵: C, 73.85; H, 6.18^{5(a)}; mol. wt., 632.^{5(c)}

(9) K. Auwers, *Ber.*, **40**, 2532 (1907).

(10) Ullmann and Brittner, *ibid.*, **42**, 2540 (1909).

(11) German Patent 301,451 (1917).

Acetyl Determination.—A sample of the acetate, weighing 2.9314 g., was dissolved in a solution of 25 ml. of ethyl alcohol and 25 ml. of 5 *N* sodium hydroxide solution. The solution was refluxed for one hour and then the ethyl alcohol distilled off. After cooling, 75 ml. of 33% sulfuric acid was added. The solution was distilled, the distillate

being caught successively under the surface of 50-ml. portions of 0.1 *N* sodium hydroxide solution. This was continued until back-titrations of the alkali with 0.1 *N* hydrochloric acid showed no more acetic acid was being distilled over. The solid material left in the distilling flask was filtered off and recrystallized from ethyl alcohol. The

melting point and mixed melting point checked with the original condensation product.

Anal. 2.9314 g. of acetate neutralized 180.86 ml. of 0.1 *N* sodium hydroxide solution. Calcd. for 2:2 condensation, acetyl, 26.54; for 2:1 condensation, acetyl, 28.73. Found: acetyl, 26.54.

Condensation of *p*-Bromophenol with 1,3,5-Trimethyl-1',2,3'-trihydroxybenzene.—One tenth of a mole (16.8 g.) of dimethylol-*p*-cresol was dissolved in 50 ml. of glacial acetic acid and 0.1 mole (17.3 g.) of *p*-bromophenol added. Dry hydrogen chloride gas was passed in until the solution was saturated. No precipitate was obtained on standing, so the solution was poured into water. The precipitate was filtered off and recrystallized from ethyl alcohol; m. p. 210° (uncor.); yield, 29 g.

Acetate.—Ten grams of the above condensation product was refluxed with 50 ml. of acetic anhydride for two hours. The solution was poured into water and the white crystalline precipitate filtered off and recrystallized from ethyl alcohol; m. p. 111° (uncor.).

Anal. Calcd. for 2:2 condensation, C₃₃H₃₄O₈Br₂·C: 58.61; H, 4.37; Br, 20.56; mol. wt. 778; for 2:1 condensation, C₂₇H₂₄O₆Br₂: C, 53.64; H, 3.97; Br, 26.49; mol. wt. 604. Found⁵: C, 59.01; H, 4.62; Br, 20.11; mol. wt., 806.

Condensation of 2,4-Xylenol with 1,3,5-Trimethyl-1',2,3'-trihydroxybenzene.—Five one-hundredths of a mole (8.4 g.) of dimethylol-*p*-cresol was dissolved in 20 ml. of glacial acetic acid and 0.1 mole of 2,4-xylenol (12.2 g.) added. Dry hydrogen chloride gas was passed into the solution until it was saturated. On standing for one week, the solution had separated into two layers. The upper layer, consisting mostly of acetic acid, was decanted and the lower layer dissolved in ether, washed with water and dried over anhydrous sodium sulfate. The ether was evaporated and the residue taken up in ethyl alcohol. A white solid was obtained on diluting the ethyl alcohol solution with water; m. p. 116° (uncor.); yield, 15 g.

Acetate.—Two grams of the above condensation product was refluxed with acetic anhydride for two hours. The solution was poured into water and the white crystalline acetate filtered off and recrystallized from ethyl alcohol; m. p. 143° (uncor.).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 74.10; H, 6.77. Found: C, 74.03; H, 6.39.

Diazotization Experiments.—To a solution of 1 ml. of *o*-toluidine in 3 ml. of concentrated hydrochloric acid was added 5 ml. of water. The solution was cooled to 0° and 1 g. of sodium nitrite dissolved in 5 ml. of water added. Two ml. portions of this cold diazonium solution were added, respectively, to dilute sodium hydroxide solutions of each of the condensation products (0.1 g.). The solutions were then made acid. The tests were negative in each case. Control experiments were run, using *p*-cresol under the same conditions. In this case, a red precipitate was obtained.

Summary

Indirect phenol-aldehyde condensations were carried out with completely and partially blocked phenols.

When *o,o'*-dimethylol-*p*-cresol, a completely blocked phenol, was condensed with phenols having two ortho positions available for condensation, such as *p*-cresol and *p*-bromophenol, high-melting crystalline condensation products resulted, the acetates of which analyzed for a

2:2 condensation and not for a 2:1 condensation as previously suggested.

For purposes of comparison, a 2:1 condensation product was actually formed by condensing the same phenolic dialcohol with a "blocked" phenol, 2,4-xyleneol, unable to undergo cyclization. In contrast, the "linear" condensation product thus prepared proved to be a low-melting amorphous solid.

Thus, the analytical evidence presented in this paper does *not* support Koebner's postulations that phenol-aldehyde condensation products are of the linear type only, but rather favors a structural distinction between low-melting and high-melting types of condensation products. Thus, the lower-melting or "fusible" types appear to possess a "linear" structure, while for the high-melting types or "non-fusible" types, a "cyclic" structure appears to be in better harmony with actual analytical findings.

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RECEIVED DECEMBER 22, 1942

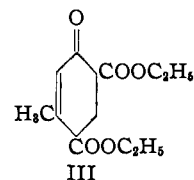
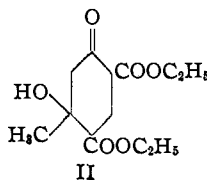
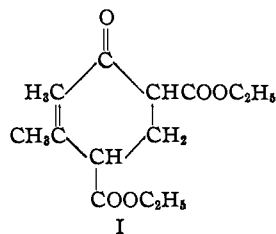
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Alkylation of 3-Methyl-4-carbethoxy-2-cyclohexen-1-one (Hagemann's Ester) and Related Substances

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In studies in the vitamin E series, it was of interest to investigate the introduction of perhydrogeranyl and other groups into the molecules of substituted cyclohexenones. The so-called Hagemann's ester (3-methyl-4-carbethoxy-2-cyclohexen-1-one, IV) appeared to be a promising starting material, and accordingly a study of its preparation and properties was undertaken. Knoevenagel and Klages² studied the condensation of acetoacetic ester with formalin (or trioxymethylene). They found that the condensation proceeded to completion under the influence of basic catalysts, and that it involved the sequence I, II and III. Rabe and Rahm³ found that the bis-acetoacetate I could be prepared without the use of a catalyst, but that a basic catalyst was necessary for conversion of I to the ketol II, which had been isolated previously, and which was readily con-

verted (even by steam distillation) into III by loss of water.⁴ When piperidine was used as the catalyst, considerable heat was evolved, and unless the reaction mixture was cooled efficiently, the direct product was the diester III.⁴ Hagemann⁵ first prepared the ester IV from aceto-



(1) Abstracted from a thesis by G. F. Rouault, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1942.

(2) Knoevenagel and Klages, *Ann.*, **281**, 94 (1894).

(3) Rabe and Rahm, *ibid.*, **322**, 10 (1904).

(4) Rabe and Elze, *ibid.*, **323**, 97 (1902).

(5) Hagemann, *Ber.*, **26**, 876 (1893).