

4. This type of condensation is being extended to meta and para alkylated phenols and polyhydroxyphenols with ketones in order to check the

influence of the substituent group of the benzene ring in its different positions.

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RECEIVED NOVEMBER 8, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

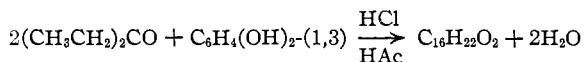
Simultaneous Multiple Alkylation of Phenols. The Synthesis of a Phenolic Coumarane Involving the Condensation of Diethyl Ketone with Resorcinol

BY JOSEPH B. NIEDERL AND VICTOR NIEDERL

Theoretical

In continuation of the studies of the condensations of carbonyl compounds with phenols, the condensation of diethyl ketone with resorcinol was investigated. In this condensation a new phenomenon was encountered, namely, the simultaneous di-alkylation of a phenol, regardless of the mole ratio of the reactants employed.

The empirical formula of the crystalline and non-polymeric condensation product obtained in quantitative yields by condensing diethyl ketone with resorcinol in glacial acetic acid solution in the presence of dry hydrogen chloride, corresponds to an addition of two molecules of diethyl ketone to the resorcinol followed by the elimination of two molecules of water as follows



This fact then adds to the already reported condensation systems of the mole ratios 1 : 1 (one mole phenol and one mole carbonyl compound),¹ 2 : 1 (two moles of phenol and one mole of carbonyl compound),² 2 : 3 (two moles of phenol and three moles of carbonyl compound),³ and now a condensation system involving a mole ratio of 1 : 2 (one mole of phenol and two moles of carbonyl compound). Thus it becomes apparent that the nature of the end-product is influenced not only by the type of carbonyl compound employed, but also by the type of phenol used in the condensations. This influence exerts itself particularly through the position of the second substituent in the benzene ring, *i. e.*, whether it is

ortho, meta or para to the hydroxyl group. The nature of the catalyst used in these condensations appears only to influence the yield but not the course of the reaction nor the type of condensation product obtained.⁴

Elucidation of the Structural Formula

Although the empirical formula of the crystalline condensation product suggests immediately a dipentenylresorcinol, structure proof work, however, revealed that there is only one free phenolic hydroxyl group present in the compound (formation of a monoacetate (IV) and a monophenyl urethan (V)) and that there is only one double bond in the compound, as evidenced by the formation of a tribromide (VI) from the free phenolic coumarane (III) (treatment of an aqueous solution of the phenol with excess bromine water) and a dibromide (VII) from the acetate (IV) (addition of an excess of bromine in carbon tetrachloride to a solution of the acetate in the same solvent). All this then suggests ring formation between one of the phenolic hydroxyl groups and one of the pentenyl radicals leading to the formation of a coumarane type of compound as has been observed in related condensation systems.⁵

Summarily, the reaction mechanism then would involve first the addition of the two molecules of diethyl ketone to resorcinol with the formation of an intermediate and under the given reaction conditions unstable phenol-dihydrin (I), which upon the loss of two molecules of water would give the dipentenylresorcinol (II). Then under the influence of dry hydrogen chloride, ring closure between one of the pentenyl groups and one of the phenolic hydroxyl groups appears to ensue with the formation of a phenolic coumarane (III), as follows

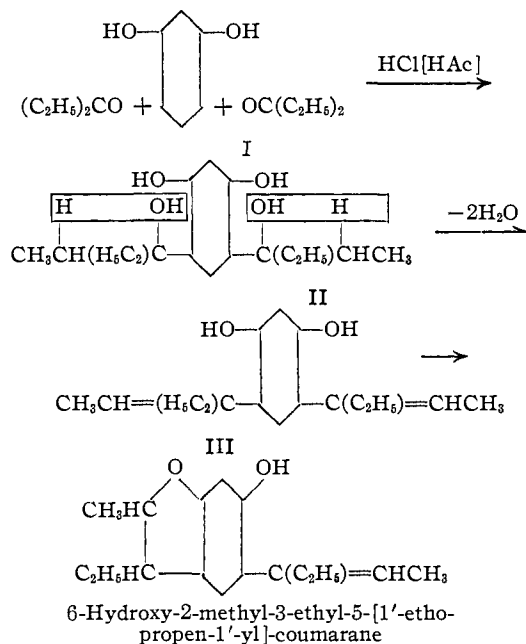
(1) E. Fischer, *Ber.*, **27**, 1355 (1894); Niederl and co-workers, *THIS JOURNAL*, **58**, 657 (1936); **59**, 1113 (1937).

(2) McGreal, Niederl and Niederl, *ibid.*, **61**, 345 (1939); Lunjak, *J. Russ. Phys.-Chem. Soc.*, **36**, 303 (1904); Dianin, *ibid.*, **23**, 492 (1891); Claus and Trauer, *Ber.*, **19**, 3009 (1886); Zincke and Grueters, *Ann.*, **343**, 85 (1905); Zincke, *ibid.*, **363**, 255 (1908).

(3) J. B. Niederl, *THIS JOURNAL*, **50**, 2230 (1928); *Monatsh.*, **60**, 150 (1932); Niederl and Casty, *THIS JOURNAL*, **51**, 1038 (1929).

(4) J. B. Niederl, *Ind. Eng. Chem.*, **30**, 1269 (1938).

(5) Niederl and Storch, *THIS JOURNAL*, **55**, 4549 (1933); Jordau, German Patent, 501,723 (1926).



Experimental

Condensation Method.—One-half mole (55 g.) of resorcinol and 1 mole (86 g.) of diethyl ketone were dissolved in 100 cc. of glacial acetic acid and placed in a 1-liter 2-necked round-bottomed flask. The flask was provided with a reflux condenser and a gas inlet tube reaching to the bottom of the reaction vessel. Dry hydrochloric acid gas was passed into the reaction mixture at room temperature for four hours and then the flask was well stoppered and left standing at room temperature until the entire reaction mixture had completely solidified, which occurred after about forty-eight hours. Warm water, about 60°, was added to the reaction mixture, the flask shaken to break up the crystalline mass and the crystals filtered off under suction in a Büchner funnel. The condensation product was washed repeatedly with warm water and dried. It was recrystallized from dilute acetic acid (80%) until the product was white. The mother liquor was diluted with water and the additional crystals recrystallized. The product was well washed with warm water, filtered off and dried in a vacuum desiccator over phosphorus pentoxide. The compound is soluble in Claisen solution (cryptophenol),⁶ yield 105 g. The pure product melted at 134–135° (uncorr.).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 78.05; H, 8.95; mol. wt., 246. Found: C, 78.19; H, 9.05; mol. wt., 243, 249. The molecular weight determination was performed cryoscopically according to K. Rast.⁷

Derivatives

Acetate (IV).—Fifty grams of the above condensation product was dissolved in 250 cc. of acetic anhydride, the

(6) L. Claisen, *Ann.*, **418**, 96 (1919); **442**, 210 (1925); J. B. Niederl, *Ind. Eng. Chem.*, **30**, 1272 (1938).

(7) K. Rast, as described in: J. B. Niederl and V. Niederl, "Micromethods of Quantitative Organic Elementary Analysis," J. Wiley and Sons, Inc., New York, N. Y., 1938, p. 175.

solution placed in a ground-glass joint apparatus and refluxed for four hours. Then the acetic anhydride was distilled off and the residue fractionally distilled under reduced pressure. The fraction boiling between 150 and 160° at 4 mm. was collected and redistilled in vacuum. Almost all of it distilled over at 157–158° and 4 mm. as a water-clear oil which crystallized in needles upon standing for several days. The compound is insoluble in Claisen solution and adds one mole equivalent of bromine: yield 48 g.; m. p. 42° (uncorr.); b. p. 158° (4 mm.) (uncorr.).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.00; H, 8.33. Found: C, 74.99; H, 8.28.

Phenylurethan (V).—To 1 g. of perfectly dry condensation product which was placed in a test-tube was added an excess of phenyl isocyanate (2 g.), the test-tube sealed and heated in the water-bath for three hours, by which time crystal formation was observed. The test-tube was left standing at room temperature until the entire reaction material had become crystalline. It was opened and the crystals placed on a porous tile. Upon recrystallization from petroleum the substance melted at 155–156° (uncorr.).

Anal. Calcd. for $C_{23}H_{27}NO_3$: C, 75.20; H, 7.36; N, 4.35. Found: C, 75.30; H, 7.42; N, 4.29.

Tribromide (VI).—One gram of substance was boiled with 2 liters of distilled water until most of it had dissolved, the solution was filtered and permitted to cool. Bromine water was added in excess with repeated shaking and the solution left standing for twenty-four hours, during which time the bromine derivative precipitated out. It was filtered off, washed well with distilled water, placed on a porous tile, recrystallized from 80% ethyl alcohol and dried in a vacuum desiccator; m. p. 165° (uncorr.).

Anal. Calcd. for $C_{18}H_{21}O_2Br_3$: C, 39.51; H, 4.52; Br, 49.38. Found: C, 39.27; H, 40.40; Br, 49.50.

Dibromide (VII).—One-twentieth mole (14.4 g.) of the acetate (IV) was dissolved in 50 cc. of carbon tetrachloride, the solution placed in a 250-cc. Erlenmeyer flask and cooled to -10° in an ice-salt mixture. An excess of bromine dissolved in carbon tetrachloride was added dropwise and the reaction vessel repeatedly shaken. After completion of the addition of bromine the carbon tetrachloride was removed by distillation under reduced pressure. The residue was dissolved in ether and transferred to an evaporating dish. After standing for several days the dibromide crystallized; it was placed on porous tile to dry and the recrystallized twice from diisobutylene; m. p. 168–170° (uncorr.).

Anal. Calcd. for $C_{18}H_{24}O_2Br_2$: C, 48.21; H, 5.35; Br, 35.71. Found: C, 48.20; H, 5.64; Br, 35.30.

The authors desire to express their appreciation to Reed and Carrick, Jersey City, N. J., for fellowship grants.

Summary

Systematic investigation in the condensations of carbonyl compounds with phenols led to the discovery of simultaneous double alkylation of phenols irrespective of the mole ratios of the re-

actants. The condensation system diethyl ketone-resorcinol was studied, leading to the direct synthesis of a crystalline, non-polymeric phenolic

coumarane, the structure of which was proved.

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RECEIVED NOVEMBER 30, 1938

[CONTRIBUTION FROM THE BUREAU OF CHEMISTRY AND SOILS, UNITED STATES DEPARTMENT OF AGRICULTURE]

Isoguanine from the Croton Bean

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Naturally occurring isoguanine was first isolated by Cherbuliez and Bernhard from the croton bean (*Croton tiglium* L.). It occurs as the aglycone fragment of the glycoside 2-oxy-6-aminopurine-*d*-ribose.¹

We confirmed the observation of E. Fischer² and Cherbuliez and Bernhard¹ that isoguanine, unlike guanine,³ is apparently not convertible to xanthine by reaction with nitrous acid. Xanthine was obtained from natural isoguanine in good yield, however, by the action of hydrochloric acid⁴ and this reaction affords an unusual example of the deamination of a compound resistant to the action of nitrous acid.

The conversion of naturally occurring isoguanine to xanthine is confirmation for its accepted structure, 2-oxy-6-aminopurine.

Isoguanine has been found to crystallize from water in large rosetts, containing one and one-half molecules of water of crystallization. The optical properties of the substance were kindly determined by George L. Keenan of the Food and Drug Administration.

Experimental

Isolation of Isoguanine.—The crotonoside was extracted from ground, unshelled croton beans (*Croton tiglium* L.) with methanol and isolated by the method of Cherbuliez and Bernhard.¹ The purified riboside was hydrolyzed by heating on the water-bath with 100 parts of 0.1 *N* sulfuric acid for four hours. The crude sulfate which separated on cooling was purified by recrystallizations from 5% sulfuric acid after charcoal decolorization. The amorphous base was obtained by dissolving 5 g. of the sulfate ($C_6H_8ON_6$)₂H₂SO₄·H₂O in 75 ml. of 1 *N* sodium hydroxide. To the solution was added 10 ml. of glacial acetic acid and 100 ml. of water. The precipitated base was filtered off, washed with water, and dried in vacuum over phosphorus pentoxide; yield 3.4 g.

(1) E. Cherbuliez and K. Bernhard, *Helv. Chim. Acta*, **15**, 464 and 978 (1932); cf. Spies and Drake, *THIS JOURNAL*, **57**, 774 (1935).

(2) E. Fischer, *Ber.*, **30**, 2247 (1897).

(3) Strecker, *Ann.*, **118**, 167 (1861); E. Fischer, *ibid.*, **215**, 309 (1882).

(4) E. Fischer, *Ber.*, **43**, 805 (1910), used hydrochloric acid to deaminate guanine.

Crystallization of Isoguanine Hydrate.—One gram of pure isoguanine was dissolved in 37 ml. of 0.33 *N* sodium hydroxide. The alkaline solution was filtered into 2 liters of distilled water, heated to 65°. Twenty milliliters of glacial acetic acid was added to the hot solution, which was allowed to cool slowly to room temperature. After six hours, the clear solution was placed in the refrigerator at 5°. The solution was still clear after twenty-four hours but on the third day crystallization had commenced. After twelve days, the crystals were filtered off and washed with a little water. The crystals attained a length up to 4 mm.; yield 0.61 g. The solubility of isoguanine (calculated on basis of the anhydride) is approximately 0.21 mg./ml. at 5° in water containing about 1% acetic acid.

*Anal.*⁵ Calcd. for $C_6H_8ON_6 \cdot 1.5H_2O$: C, 33.71; H, 4.53; N, 39.32; H₂O, 15.17. Found: C, 34.5, 34.4; H, 4.31, 4.37; N, 39.5, 39.5; H₂O (dried in vacuum at 110°), 14.71, 14.62. Calcd. for $C_6H_8ON_6$: C, 39.74; H, 3.34; N, 46.36. Found: C, 39.5, 39.4; H, 3.31, 3.30; N, 46.2, 46.2.

Microscopical examination of the crystals ($C_6H_8ON_6 \cdot 1.5H_2O$) in ordinary light showed them to consist largely of colorless rods, usually terminated by a plane at right angles, also narrower needle-like forms. The refractive indices are as follows: n_α 1.516; n_β indt.; $n_\gamma > 1.734$ (immersion method). An intermediate index value n 1.734 (methylene iodide) occasionally is shown on very slender rods when the long dimension is oriented perpendicular to the vibration plane of the lower nicol (crosswise). n_α is the most commonly occurring index and is always shown on the rods when their long dimension lies parallel to the vibration plane of the lower nicol (lengthwise). The maximum index value is always shown crosswise on the rods. The double refraction is extremely strong ($n_\gamma - n_\alpha = > 0.218$). With crossed nicols, the extinction is straight and the sign of the elongation is negative. Anomalous interference colors, consisting of peculiar and characteristic blues and purples, are quite significant for the substance with cross nicols. The rods invariably extinguish sharply. The compound apparently crystallizes in the orthorhombic system.

Xanthine from 2-Oxy-6-aminopurine.—Two grams of anhydrous isoguanine was refluxed with 200 ml. of 25% hydrochloric acid (starting concentration) for forty-seven hours. The hydrochloric acid was evaporated on the steam-bath and the residue was washed with 50 ml. of

(5) The author is indebted to Thomas H. Harris, Jr., for the microanalytical determinations reported in this paper.