moved by a hot water-bath and the resulting product purified by the conventional means of vacuum distillation, steam distillation or crystallization.

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## Some Nuclearly Substituted Catechols and their Acid Dissociation Constants

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RECEIVED FEBRUARY 17, 1953

In the course of other work, the acid dissociation constants in water of certain nuclearly substituted catechols were required. Such values of the constants[1,2] as appeared in the literature were open to question, so that it was decided to determine them for the entire group. In the preparation of the catechols, difficulties unmentioned by previous authors were encountered, which made it desirable to report some of the synthetic procedures in detail.

The attempt to make 4-nitrocatechol according to Benedikt[3] led, at first, to the isolation of a dinitro derivative, identified *via* its dimethyl ether as 3,4-dinitrocatechol. Reduction in the quantity of nitrosating reagents permitted the desired 4-nitrocatechol to be obtained. Nitration of catechol in ether solution,[4] to produce a mixture of 3- and 4-nitrocatechols, gave evidence of a threshold concentration of reagents, below which no reaction could take place; such a phenomenon has been described by Halberstadt, Hughes and Ingold.[5] After several unsuccessful attempts to isolate 3,4-dihydroxybenzophenone according to the method of Rosenmund and Lohfert,[6] the authors were furnished by Dr. Joseph Corse with a satisfactory modification of that method.[7]

### Experimental and Results

**3,4-Dinitrocatechol.**—A solution of sodium nitrite (16 g., 0.24 mole) and catechol (4.0 g., 0.036 mole) in water (150 ml.) was mixed with sufficient ice to bring the temperature down to 0°. In the course of 3–5 minutes, 75 ml. of 2.5 *M* $H_2SO_4$ (0.19 mole) was added, along with more ice and with shaking. The solution was then extracted with ether in two portions (150 and 75 ml.). The combined ether extract was twice washed with 100 ml. of water, dried briefly over anhydrous sodium sulfate and evaporated quickly at room temperature under a stream of nitrogen. When the ether had been removed, the oily residue was left under vacuum until it had crystallized; it was then extracted with xylene at 100° and the crystalline product that separated from the cooled xylene solution was collected, washed with petroleum ether and air-dried. This material was recrystallized twice from 15% ethanol–water (8–11 ml./g.), care being taken not to exceed the temperature required for solution. The air-dried dihydrate thus obtained in 24% yield lost two moles of water on drying for several hours at 59° and a pressure of 8 mm. The anhydrous compound was somewhat hygroscopic (m.p. 147–148°).

*Anal.* Calcd. for $C_6H_4O_6N_2$: C, 36.0; H, 2.0; N, 14.0; mol. wt., 200. Found: C, 35.2; H, 2.39; N, 13.4; mol. wt. (Rast), 197.

In 1 *N* aqueous HCl this compound showed an absorption maximum at 352 mμ, $\epsilon$ 7.1 $\times 10^3$, and a minimum at 266 mμ.

**3,4-Dinitroveratrole.**—Anhydrous 3,4-dinitrocatechol (0.45 g., 0.00225 mole) was mixed with methyl sulfate (0.60 ml., 0.0063 mole) and 1.09 *N* NaOH (4.8 ml., 0.0052 mole) and subjected to vigorous shaking and gentle heating for about five minutes at which time the initially red color of the aqueous phase had been nearly discharged. Additional NaOH solution (3.1 ml., 0.0034 mole) caused reappearance of the red color, which persisted on further heating and shaking. A solid phase soon appeared to take the place of the liquid methyl sulfate layer. The mixture was cooled and extracted with ether. The ether layer was extracted with several portions of a dilute aqueous NaOH solution until the aqueous phase was colorless, then washed twice with water and dried over $Na_2SO_4$. Evaporation of the ether left a white residue which was recrystallized from methanol–water. The product so obtained was isolated and dried with a stream of air (m.p. 90.5°). Of the four possible dinitroveratroles, all of which are known,[8] only the 3,4-isomer has the m.p. found.

**4-Nitrocatechol.**[3]—A solution of sodium nitrite (5.5 g., 0.08 mole) and catechol (4.0 g., 0.036 mole) in water (150 ml.) was mixed with sufficient ice to bring the temperature down to 0°. In the course of 3–5 minutes, 25 ml. of 2.5 *M* $H_2SO_4$ (0.063 mole) was added, along with more ice and with shaking. The solution was then extracted with ether in two portions (150 and 75 ml.). The combined ether extract was twice washed with 100 ml. of water, dried briefly over anhydrous sodium sulfate and evaporated quickly at room temperature under a stream of nitrogen. The residue was subjected to vacuum sublimation at a pressure of 6 mm. The first small fraction, somewhat oily, was removed at a bath temperature of 100–150° and probably consisted mostly of 3,4-dinitrocatechol. The second fraction, removed at a bath temperature of 160–190°, was nearly pure 4-nitrocatechol (m.p. 172–174°); its weight was 1.63 g. (29% yield). When somewhat greater amounts of sodium nitrite (8.25 g., 0.12 mole) and sulfuric acid (37.5 ml., 0.09 mole) were used a yield of 2.11 g. (37%) of 4-nitrocatechol was obtained.

**3- and 4-Nitrocatechol.**—Previous authors[4] treated a solution of 10 g. of catechol in 500 ml. of ether with 4 ml. of fuming nitric acid, allowed the resulting solution to stand 24 hours, washed the ether solution with water and proceeded with the isolation of 3- and 4-nitrocatechol. The present authors recovered mostly catechol by this procedure. Neither refluxing nor addition of water induced the reaction when the recommended quantity of ether was employed, but distillation of a portion of the ether prior to washing with water caused the desired reaction to take place. When the amount of ether was reduced to 250 ml. the reaction proceeded rapidly and the products were isolated; when 375 ml. of ether was employed, the reaction proceeded in three out of the four times it was tried. When 375 ml. of ether was used, isolation was carried out by evaporation of the washed ether solution, vacuum sublimation of the residue (bath temperature being raised gradually from 100 to 200°), and continuous extraction of the sublimate with 30–60° petroleum ether. The petroleum ether-soluble fraction consisted of nearly pure (m.p. 84°, reported 86°) 3-nitrocatechol, while the residue, consisting mostly of 4-nitrocatechol, was purified (m.p. 176°, reported 174°) by recrystallization from water. The yield of impure mononitrocatechols was approximately 65–70%, the product consisting of 56–62% 3-nitrocatechol and 38–44% 4-nitrocatechol. Variation of the temperature of reaction did not produce significant difference in the ratio of the 3- to 4-isomer. Spectral absorption maxima for 4-nitrocatechol in 1 *M* aqueous HCl occurred at 240 and 346 mμ, while the 3-isomer showed a single maximum at 298 mμ. Isobestic points for the first dissociation of 4-nitrocatechol were found at 229, 252, 280 and 370 mμ, while those of 3-nitrocatechol were found at 268 and 320 mμ.

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(7) Private communication from Dr. Joseph W. Corse of the Western Regional Research Laboratory, Albany, California. A sample of this material was kindly made available to us by Dr. Corse.

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TABLE I
ACID DISSOCIATION CONSTANTS

| Compound | $K_1$ | $K_2$ | Melting point, °C. Lit. | Found |
|---|---|---|---|---|
| 3-Nitrocatechol | $2.2 \times 10^{-7}$ | ........ | 86 | 84 |
| 4-Nitrocatechol | $1.3 \times 10^{-7}$ | ........ | 174 | 176 |
| 3,4-Dinitrocatechol | $4.1 \times 10^{-5}$ | $5.4 \times 10^{-9}$ | ..... | 147–148 |
| Protocatechualdehyde[13] | $4.4 \times 10^{-8}$ | ........ | 153–154 | 152 |
| Protocatechualdoxime[14] | $2.1 \times 10^{-9}$ | ........ | 157 | 156 |
| Protocatechunitrile[14] | $1.9 \times 10^{-8}$ | ........ | 156 | 156 |
| 3,4-Dihydroxybenzophenone | $1.8 \times 10^{-8}$ | ........ | 145[6] | 147–148 |
| 3-Methoxycatechol[15] | $5.3 \times 10^{-10}$ | ........ | ..... | ..... |
| 3-Methylcatechol | $5.3 \times 10^{-10}$ | ........ | 45, 47, 68 | 58–62 |

**3,4-Dihydroxybenzophenone.**[7]—Sixty-five grams of catechol dibenzoate, 185 ml. of nitrobenzene and 56 g. of anhydrous aluminum chloride were heated on the steam-bath for six hours. Ice and hydrochloric acid were then added, and, after the decomposition was complete, the nitrobenzene was steam distilled. The remaining solution was chilled and the solid material collected, dried and dissolved in 400 ml. of methanol. The resulting solution was saturated with anhydrous hydrogen chloride, and refluxed for 3.5 hours. Methanol was removed on the steam-bath, water was added to the residue, and the mixture was steam distilled to remove methyl benzoate. The residual mixture was boiled, enough water was introduced to effect solution, and decolorizing charcoal was added. After being boiled for several minutes, the solution was filtered and chilled. The product was collected and recrystallized four times from hot water. The resulting colorless crystalline material melted at 147–148°, and showed no melting point depression when mixed with an authentic specimen.[7] The substance appeared to contain a small amount of water of crystallization, which was not determined exactly.

**3-Methylcatechol.**—Orthovanillin was reduced[9] to 2-hydroxy-3-methoxytoluene in 45% yield. The latter was converted to 3-methylcatechol by the de Vries[10] demethylation procedure. The viscous oil obtained by distillation (130–139° (20 mm.)) of the crude product solidified on standing in the refrigerator. Vacuum sublimation at 0.8 mm. gave a white substance melting at 58–62°. The melting point has been reported[11] as 45, 47 and 68°. The compound gave a negative test for aldehydes with 2,4-dinitrophenylhydrazine.

Dissociation constants were obtained by potentiometric titration[12] of $10^{-3}$ *M* solutions of the substances in question with 0.02 *N* NaOH at 25° against a Beckman Model G *p*H meter. In each case the dissociation constant was an average of values calculated from data near the mid-point of the titration (Table I). The figures for the last three compounds are only approximate, since the titration curves were poor.

Spectrophotometric data were determined on the Beckman Model DU spectrophotometer at $2 \times 10^{-4}$ *M* concentrations. From some of these data it was possible to calculate[16] dissociation constants in confirmation of the potentiometrically derived values. Thus, 4-nitrocatechol in 1.25 *M* HCl and in 0.04 *M* phosphate buffers, had extinction coefficients at 430 mμ of 200, $1.0 \times 10^4$ and $1.375 \times 10^4$ at *p*H's 0.11, 7.1 and 8.0, which yield a value of $1.8 \times 10^{-7}$ for the apparent dissociation constant. The constant for 3-nitrocatechol has been derived similarly.[16]

## Discussion

The dissociation constants of several of the present group of compounds have been determined in 40% dioxane–water by Corse and Ingraham[17] and show excellent qualitative agreement with the present results, especially when the difference in the dielectric constants of the media is considered. The present values for 3- and 4-nitrocatechol are significantly lower than those found by Gilbert, Laxton and Prideaux[1]; no evident reason can be shown for this discrepancy. The value found for protocatechualdehyde is of the same order of magnitude as that of Pauly, *et al.*[2]

**Acknowledgment.**—The authors wish to acknowledge the technical assistance of Dr. Robert W. Rosenthal, Miss Mary Demek, Mr. Thomas Parr and Privates First Class Peter Hlinka and Vyto Adomaitis. The microanalyses of 3,4-dinitrocatechol were performed by Mr. C. A. Rush of Chemical and Radiological Laboratories, Army Chemical Center, Maryland.

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## Substitution Reactions of 2- and 3-Methylthianaphthene

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RECEIVED FEBRUARY 26, 1953

The nitration of 2-methylthianaphthene gave a mononitro derivative in 48% yield. This was shown to be the 2-methyl-3-nitrothianaphthene by reduction and acetylation to 2-methyl-3-acetaminothianaphthene which was desulfurized by the useful technique of Mozingo[2] with Raney nickel catalyst to form 1-acetamino-1-phenylpropane. This last compound was identical with an authentic sample.

Bromination of 2-methylthianaphthene gave 2-methyl-3-bromothianaphthene in 88% yield. The structure of the product was proved by conversion through the Grignard reagent to 2-methyl-3-thianaphthenecarboxylic acid which was desulfurized as above to the known α-phenylbutyric acid. The 2-methyl-3-thianaphthenecarboxylic acid was identical in melting point with an acid obtained by Gaertner[3] and shown to be 2-methyl-3-thianaphthenecarboxylic acid by oxidation to 2,3-thianaphthenedicarboxylic acid.

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