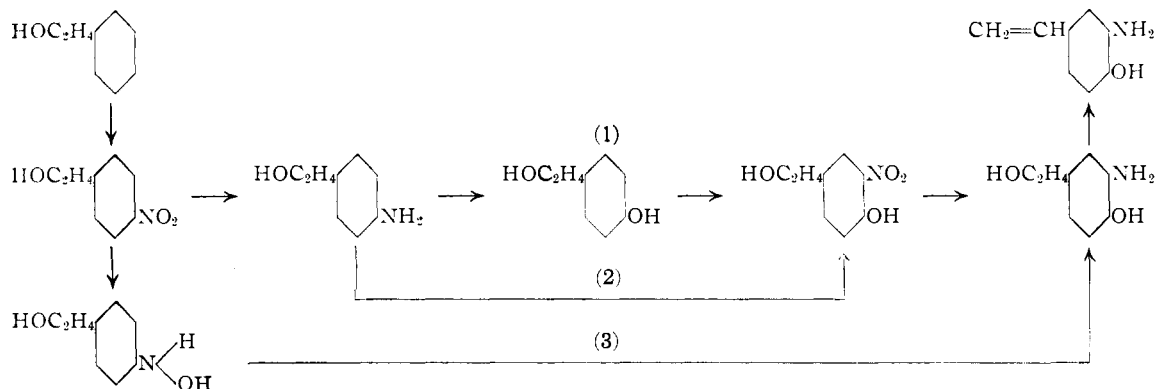


[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

The Synthesis of β -(3-Amino-4-hydroxyphenyl)-ethanol; 3-AminotyrosolBY HENRY M. WOODBURN AND CALVIN F. STUNTZ^{1,2}

Our desire for a substituted styrene in which the substituent groups might enter into chelate ring structures with metals, led to the formulation of a scheme of synthesis for 3-amino-4-hydroxystyrene. The complete objective was not attained since unusual difficulties surround the preparation of a styrene containing both an acidic and a basic group. However, a possible parent compound, β -(3-amino-4-hydroxyphenyl)-ethanol, hereafter designated as 3-aminotyrosol, was produced. Its synthesis is described in this paper, together with certain observations arising from our unsuccessful attempts to convert the ethanol to the styrene.

The successful preparation, by Sabetay and Mintsou,³ of *p*-aminostyrene, by distilling β -(4-aminophenyl)-ethanol over potassium hydroxide, influenced our choice of 3-aminotyrosol as a logical intermediate for the synthesis of 3-amino-4-hydroxystyrene. The following scheme presented itself as a reasonable mode of procedure. Routes 2 and 3 were investigated first since, if successful, they would shorten the process appreciably.



4-Nitrophenylethanol was prepared in essentially the way described by Ferber.⁴ We were unable to duplicate his reported yield of 76%, however, a series of four nitrations giving pure material not exceeding 49.5%.

Several methods of reducing the nitro compound were tried, including Ferber's method of zinc dust in boiling calcium chloride solution, tin and hydrochloric acid, stannous chloride, and catalytic hydrogenation, as well as zinc and ammonium chloride which it was hoped might give the hydroxylamine. The latter was completely unsuccessful, resulting instead in the formation of a waxy par-

affin-like material which was almost nitrogen and oxygen free.

Of the other methods, catalytic reduction at 3-4 atmospheres using a platinum black catalyst was most successful (over 90% yield of aminophenylethanol) although the stannous chloride method was a close second (88% yield). Ferber's method gave a 61% yield (Ferber reported 90%), while with tin and hydrochloric acid a 41% yield was accompanied by appreciable amounts of wax closely resembling that obtained from neutral reduction.

The most attractive synthetic route having been eliminated by the failure of the zinc-ammonium chloride reduction, an intensive study of the conversion of aminophenylethanol in one step to nitrohydroxyphenylethanol was undertaken. Diazotization using an excess of sodium nitrite in sulfuric acid solution proved to be the most successful, resulting in a 50% yield of 3-nitrotyrosol (3-nitro-4-hydroxyphenylethanol). The pure compound was a canary-yellow solid melting

sharply at 56°. Details of the less desirable diazotization in nitric acid are included in the experimental section of this paper.

Reduction of 3-nitrotyrosol to 3-aminotyrosol was accomplished by catalytic hydrogenation. Considerable difficulty was encountered from inactive and poisoned catalysts, both nickel and platinum. This was overcome by the use of scrupulously clean reaction bottles and charcoal treatment of the alcoholic solutions of the nitrohydroxy compound prior to reduction. Purification of the material was accomplished by vacuum sublimation after it had been proved that none of the common solvents was suitable for recrystallization nor could it be salted out of its hydrochloric acid solution.

The sublimed material was nearly white in color and melted with decomposition at 131-135° to a red-brown liquid. A determination of its solubil-

(1) From a thesis submitted by Calvin F. Stuntz in partial fulfillment of the requirements for the Ph.D. degree, University of Buffalo, August, 1946.

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(3) Sabetay and Mintsou, *Bull. soc. chim.*, **45**, 842 (1929).

(4) Ferber, *Ber.*, **62**, 183 (1929).

ity at 25° gave 1.79 g. per 100 ml. of water, 0.78 g. per 100 ml. of ether. Analysis for carbon, hydrogen and nitrogen confirmed the identity of the compound.

A sodium hydrosulfide reduction which had been very successful in parallel experiments on nitroresol proved unsuited to 3-nitrotyrosol.

The conversion of 3-aminotyrosol to 3-amino-4-hydroxystyrene was attacked from two angles, first, the elimination of water from the alcohol and second, the elimination of hydrogen bromide from the hydrobromide of β -(3-amino-4-hydroxyphenyl)-ethyl bromide.

Dehydration in the conventional manner by distilling the ethanol with potassium hydroxide was out of the question because of the presence of the hydroxy group which would form a non-volatile phenolate. It was hoped, however, that after heating with an excess of alkali at fusion temperature or below, the desired product could be recovered from the mixture by solution in water and neutralization with carbon dioxide. Sodium hydroxide was chosen because of its lower melting point and the higher solubility of its bicarbonate.

From only one of three experiments was any product worth investigating obtained. In that case the yield was but 11% and the analytical data poor.

Sabetay⁵ reported that good yields of styrene were obtained from β -phenylethanol by passage over heated "porosite." In a more recent paper, Mowry, Renoll and Huber⁶ described the preparation of a large number of substituted styrenes by the vapor phase dehydration of the corresponding phenylmethylcarbinols. Accordingly an apparatus was constructed to permit 3-aminotyrosol to be sublimed *in vacuo* through a column of heated alumina. The experiments were completely unsuccessful, resulting only in the decomposition of the starting material.

3-Aminotyrosol was converted by reaction with hydrogen bromide to the hydrobromide of β -(3-amino-4-hydroxyphenyl)-ethyl bromide and elimination of hydrogen bromide attempted by the use of sodium ethylate⁷ and of alcoholic potassium hydroxide. In each case the sole product was a small amount of tan solid which gave analytical data for carbon and hydrogen too low for 3-amino-4-hydroxystyrene. Similarly unsatisfactory results attended the use of β -(4-aminophenyl)-ethyl bromide which was investigated in an attempt to work out a satisfactory conversion to styrene.

Experimental

β -(4-Nitrophenyl)-ethanol.— β -Phenylethanol was esterified by the slow addition of a slight excess of acetyl chloride followed by heating to reflux under an air condenser to remove hydrogen chloride and excess acetyl chloride. The ester (413 g.) was added slowly and with rapid stirring to 1650 ml. of fuming nitric acid (sp. gr. 1.5) contained in a 2000-ml. beaker surrounded by an acetone-

chloroform Dry Ice mixture maintained at -50° by frequent addition of Dry Ice. The temperature of the contents remained between -15 and -20° during the addition and for one-half hour thereafter. The reaction product was then poured over crushed ice, extracted with ether and the extracts washed with water, 20% potassium carbonate solution and again with water. After drying over anhydrous magnesium sulfate the ether was distilled off on a steam-bath.

The nitrated ester was converted to the alcohol by refluxing for three hours with 800 ml. of methanol containing 2% hydrogen chloride. Methyl acetate and excess methanol were removed under gentle vacuum on a steam-bath. The residual oil became almost black during the heating.

To separate the para from the ortho isomer, a small portion of the oil was crystallized from 30% alcohol following the procedure of Sabetay and Mintsou⁸ and the crystals so formed used to seed the main portion of the liquid which had meanwhile been cooled to -10°. The thick slush of crystals was filtered on a Buchner funnel using a thin sheet-rubber dam to free the solid more completely of residual oil. At this stage the crystals were nearly white and pure enough for further use without recrystallization. The yield was 208 g. or 49.5%.

Carbon tetrachloride proved to be the best solvent for recrystallization when this was desired. About 300 ml. of solvent for 10 g. of the solid was needed and the temperature of the saturated solution could not go above 55°. Under these conditions, the ortho impurity separated as an oil which floated on the surface while the para isomer crystallized on the walls and bottom of the container as white needles melting at 62°.

β -(4-Aminophenyl)-ethanol from Nitrophenylethanol:
(a) **By Catalytic Hydrogenation.**—Most consistent results were obtained by the use of a platinum catalyst prepared according to the method of Adams, Vorhees and Shriner⁹ although nickel catalysts prepared according to Adkins⁹ gave satisfactory yields if proper precautions were observed.

To the hydrogenation bottle containing 15 g. of 4-nitrophenylethanol in 150 ml. of 95% alcohol was added 0.1 g. of platinum catalyst. The initial hydrogen pressure was 50 pounds. After an induction period of five minutes, the catalyst darkened, the pressure began to drop and the bottle became very warm. After ten minutes it was so hot that the shaker had to be stopped to moderate the reaction. With alternate periods of agitation and quiet the reaction was continued until the pressure leveled off at 28 pounds. The drop in pressure corresponded to the absorption of 0.27 mole of hydrogen, a quantitative reaction.

The catalyst was separated by filtration, the alcohol distilled off rapidly under vacuum and the solid recrystallized from toluene. An 85% yield, 10.5 g. of crystals melting 107-108° was obtained.

The best product resulted when it was worked up immediately after the reduction since the amino compound darkened considerably on standing in alcohol solution more than a few hours. After recrystallization the solid was nearly white and perfectly stable, showing no discoloration after one year.

Reductions with a nickel catalyst gave erratic results until the practice was adopted of washing the bottles with chromic acid cleaning solution prior to each use. With this precaution, yields of 80-90% could be expected.

(b) **By Stannous Chloride.**—Five grams of 4-nitrophenylethanol was added in small portions to 55 ml. of a solution made from 50 g. of stannous chloride in 100 ml. of concentrated hydrochloric acid. Strong sodium hydroxide solution was added until the precipitated tin hydroxide had redissolved. As the solution cooled a white solid separated, which was filtered off, dried, and extracted with

(8) Adams, Vorhees and Shriner. "Organic Syntheses." Coll. Vol. I, 1941, p. 463.

(9) Adkins. "Reactions of Hydrogen over Copper-Chromium Oxide and Nickel Catalysts." The University of Wisconsin Press, Madison, Wisconsin, 1937, p. 20.

(5) Sabetay, *Bull. soc. chim.*, **45**, 89 (1929).

(6) Mowry, Renoll and Huber. *THIS JOURNAL*, **68**, 1105 (1946).

(7) Skell and Hauser, *ibid.*, **67**, 1661 (1945).

hot toluene. White crystals melting at 107–108° after recrystallization from carbon tetrachloride resulted, the weight being 3.6 g. or an 88% yield.

(c) **By Tin and Hydrochloric Acid.**—Five grams of 4-nitrophenylethanol, 10 g. of granular tin, and 100 ml. of 6 *N* hydrochloric acid were shaken together until all of the nitro compound had disappeared. After the excess tin had dissolved, the solution was cooled to 0° and sodium hydroxide solution added to liberate the amine. A large amount of tin hydroxide precipitated which redissolved only slightly with excess alkali. Consequently, the mixture was made acid again with hydrochloric acid. An oil soon separated which solidified on cooling to a wax weighing about 1 g. Analysis of the wax gave 85.4% carbon, 14.6% hydrogen, a total of 100% indicating that the wax was a hydrocarbon.

The solution from which the wax was removed was neutralized with sodium carbonate, heated to boiling, and filtered. Ether extraction of the filtrate gave a red solution. Red crystals remained after evaporation of the ether. Recrystallization from hot alcohol gave 1.7 g. of tan crystals melting 107–108° (41% yield).

(d) **By Zinc Dust and Calcium Chloride.**—Ferber's procedure⁴ was followed exactly. The product was in the form of red-brown massive crystals instead of white needles expected. Recrystallization from carbon tetrachloride gave pale yellow needles melting at 107–108°. The yield was 61%.

Reduction of Nitrophenylethanol by Zinc and Ammonium Chloride.—To a mixture of 1.23 g. (0.023 mole) of ammonium chloride, 60 ml. of water and 3.34 g. (0.02 mole) of 4-nitrophenylethanol, was added 3.56 g. (0.05 mole) of 92% zinc dust in small portions over a period of twenty minutes. The temperature was maintained at 10–15°. The nitroalcohol gradually disappeared and a heavy gray precipitate formed which was filtered and washed with hot water. Both filtrate and washings deposited small amounts of orange-yellow crystals. The washings in addition deposited a waxy solid resembling paraffin.

The original filtrate was acidified with 50 ml. of 1:1 sulfuric acid, diluted to 200 ml., and boiled for fifteen minutes in the hope of converting any substituted hydroxylamine present to the aminophenol. On cooling, a layer of oil formed which hardened to a wax, weighing over 3 g. It was insoluble in water, ether, and acetone, but soluble in benzene. Treatment with hot aqueous sodium hydroxide had no effect other than to melt the wax. Combustion analysis gave 82.1% carbon and 13.8% hydrogen.

β -(3-Nitro-4-hydroxyphenyl)-ethanol, 3-Nitrotyrosol:
(a) **Diazotization with Excess Sodium Nitrite and Sulfuric Acid.**—To a cold solution of 24.6 g. (0.18 mole) of 4-aminophenyl ethanol in 300 ml. of water and 50 ml. of concentrated sulfuric acid was slowly added a solution of 50 g. (0.725 mole) of sodium nitrite in 200 ml. of water keeping the temperature below 5°. This mixture was then added as rapidly as possible to a solution of 50 ml. of concentrated sulfuric acid in 1000 ml. of water, previously heated to 80°. By keeping a Fisher burner under the beaker this could be accomplished in four to five minutes without allowing the temperature to fall below 75°.

The clear red solution resulting was immediately cooled by packing the beaker in ice. The solution became cloudy and a small amount of oily material separated. Using the apparatus described by Hossfeld¹⁰ the entire mixture was extracted with 800 ml. of ether until the liquid delivered from the large flask was very pale yellow. This required three to four hours. The product was extracted from the ether by 10% sodium carbonate, this extract heated to 80° with decolorizing carbon, filtered and cooled to 0°. Concentrated hydrochloric acid was added drop by drop and the nitrotyrosol separated in solid form. (In some runs an oil started to form but strong cooling, vigorous agitation, or seeding, caused it to crystallize.)

Fifteen grams of yellow microcrystalline material, m. p. 53.5–55°, a 50% yield, was obtained. A small sample

purified by vacuum sublimation melted sharply at 56°.

Anal. Calcd. for $C_8H_9O_4N$: C, 52.4; H, 4.95. Found: C, 52.2; H, 4.95.

Tests showed the substance to be soluble in methanol, ethanol, chloroform, and glacial acetic acid, hot benzene, toluene and carbon tetrachloride, insoluble in ligroin or petroleum ether. At 25° 1.28 g. dissolved in 100 ml. of water.

It was essential that the steps in the procedure up to and including the ether extraction be carried out in one day. When the acid solution was allowed to stand overnight there was considerable tar formation and lower yields.

(b) **Diazotization in Nitric Acid Solution.**—A solution of 24.6 g. (0.18 mole) of 4-aminophenylethanol in 250 ml. of water and 50 ml. (0.80 mole) of concentrated nitric acid was diazotized at 0° by the slow addition of a solution of 13 g. (0.19 mole) of sodium nitrite in 50 ml. of water. The resulting mixture was then added to a solution of 10 ml. of concentrated sulfuric acid in 250 ml. of water, previously heated to 80°, at such a rate that the temperature could be maintained at 75–80°. The temperature was held at this point for one hour, after which the mixture was cooled, made strongly alkaline with sodium hydroxide and extracted with ether to remove alkali-insoluble impurities. Acidification of the alkaline solution with hydrochloric acid produced a small amount of gummy black tar. The entire mixture was extracted with ether, the tar being only partially soluble, after which a solution of 10% sodium carbonate was used to remove the product from the ether. Careful addition of hydrochloric acid caused the separation of an oil which soon solidified. Considerable orange-yellow solid had formed by the time the solution was acid. Twelve grams of dirty-yellow product melting between 52 and 58° was obtained. This represented a yield of 37%.

β -(3-Amino-4-hydroxyphenyl)-ethanol, 3-Aminotyrosol.—A solution of 14.2 g. of 3-nitrotyrosol in 150 ml. of ethanol was shaken for thirty minutes with activated charcoal and filtered into a reaction bottle which had been cleaned with chromic acid cleaning solution and thoroughly rinsed with water and alcohol. About 0.05 g. of platinum catalyst, prepared as above, was added and the reduction started at 50 pounds hydrogen pressure. After a short time the pressure dropped rapidly, reaching 31.5 pounds in forty-five minutes. This corresponded to a quantitative absorption of hydrogen.

After filtering off the catalyst, the alcohol was quickly evaporated by applying the full vacuum of a water aspirator and swirling the flask under a stream of hot water. The amine remained as a light tan solid which could easily be scraped out and dried in a vacuum desiccator. If the solution was left standing for more than a few hours, or if the alcohol was removed by ordinary distillation, a dark-colored, sticky product was obtained.

The solid was purified by sublimation using an apparatus similar to that described by Morton, Mahoney and Richardson¹¹ except that a wad of glass wool replaced the glass cloth suggested. About sixteen hours was required to complete the sublimation of 20 g. of crude material. The product was nearly white, hard and dense or in massive crystals depending on the rate of sublimation. It melted with decomposition between 131° and 135°. At 25°, 1.79 g. dissolved in 100 ml. of ether.

Anal. Calcd. for $C_8H_{11}O_2N$: C, 62.7; H, 7.24; N, 9.15. Found: C, 62.7; H, 7.19; N, 9.02.

Hydrobromide of β -(3-Amino-4-hydroxyphenyl)-ethyl Bromide.—Five grams of 3-aminotyrosol dissolved in a mixture of 10 ml. of freshly distilled constant-boiling hydrobromic acid and 40 ml. of water was treated with hydrogen bromide gas until its composition approximated that of constant-boiling acid. The mixture was heated at 115–125° for five hours, the color becoming black in the meantime, and cooled overnight. The crystalline precipitate was filtered on a sintered glass filter, washed twice with

(10) Hossfeld, *Ind. Eng. Chem., Anal. Ed.*, **14**, 118 (1942).

(11) Morton, Mahoney and Richardson, *ibid.*, **11**, 460 (1939).

ice-cold hydrobromic acid and dried *in vacuo* over solid sodium hydroxide. A 66% yield (6.5 g.) of light gray material was obtained.

Anal. Calcd. for $C_8H_{10}ONBr \cdot HBr$: C, 32.4; H, 3.73; Br, 53.8. Found: C, 32.7; H, 3.79; Br, 54.6.

Attempted Synthesis of 3-Amino-4-hydroxystyrene:
(a) **By Elimination of Water from 3-Aminotyrosol.**—(1) With aqueous sodium hydroxide: One gram of 3-aminotyrosol, 1.5 g. of sodium hydroxide, and 3 ml. of water were heated slowly in a nickel crucible to 300° where the temperature was held for twenty minutes. After cooling, the contents of the crucible were dissolved in water and saturated with carbon dioxide. Without filtering, the mixture was extracted with ether, the extract dried, clarified with charcoal and evaporated. Only a trace of thick tarry material remained.

(2) **By fusion with sodium hydroxide:** One gram of 3-aminotyrosol and 1 g. of crushed sodium hydroxide pellets were heated together in a Pyrex test-tube immersed in a fused salt-bath. The final temperature of 300° was held for one half hour. After cooling and dissolving the mass in water the solution was saturated with carbon dioxide, the fluffy precipitate filtered off, washed with water and dried *in vacuo*. It was light gray in color, insoluble in water, benzene and carbon tetrachloride, but soluble in alcohol. The weight was only 0.1 g., an 11% yield if it represented the desired aminohydroxystyrene.

Anal. Calcd. for C_8H_9ON : C, 71.1; H, 6.71. Found: C, 69.0; H, 6.86.

(3) **By sublimation over hot alumina:** An apparatus was constructed to allow aminotyrosol, vaporized at low pressure, to be carried by a stream of nitrogen admitted by a capillary leak through a column of granular activated alumina ("Hydralo") heated to 350°. Results indicated that the aminotyrosol had decomposed and deposited a carbonaceous residue on the alumina.

(b) **By Elimination of Hydrogen Bromide from β -(3-Amino-4-hydroxyphenyl)-ethyl Bromide (I).**—(1) With sodium ethylate: Three modifications of a procedure in which (I) was treated with sodium ethylate solution were examined. While sodium bromide was definitely produced, no product analyzing higher than 68% carbon could be obtained. Aminohydroxystyrene contains 71.1% carbon.

(2) With alcoholic potassium hydroxide: Two experiments in which (I) was treated with potassium hydroxide gave a product analyzing only 67% carbon.

Attempted Conversion of β -(4-Aminophenyl)-ethyl Bromide to 4-Aminostyrene.—The hydrobromide of β -(4-aminophenyl)-ethyl bromide was prepared by dissolv-

ing 2.5 g. of 4-aminophenylethanol in 25 ml. of constant-boiling hydrobromic acid and refluxing four hours. White crystals melting at 199–201° were obtained.

Anal. Calcd. for $C_8H_{10}NBr \cdot HBr$: C, 34.2; H, 3.95. Found: C, 33.8; H, 3.95.

Two grams of the above in 20 ml. of absolute alcohol was mixed with 1.35 g. of potassium hydroxide in 15 ml. of alcohol. After twenty-four hours the potassium bromide was removed, the solution saturated with carbon dioxide and filtered, and the alcohol evaporated *in vacuo* at room temperature. A viscous yellow liquid remained.

4-Aminostyrene should be easily purified by vacuum distillation but half of the viscous liquid gave only 2–3 drops of distillate at 1 mm. up to 250°. This analyzed C, 70.7; H, 8.92. Aminostyrene contains 80.6% C, 7.61% H. The other half of the viscous liquid hardened to a glassy solid in a few days. Analysis gave C, 71.0; H, 7.65.

3-Amino-4-hydroxytoluene, 3-Aminocresol.—Ten grams of 3-nitro-4-hydroxytoluene in 200 ml. of water and 50 ml. of concentrated ammonium hydroxide was added slowly to a solution of 75 g. of sodium hydrosulfite in 300 ml. of water. After a few minutes white flaky crystals appeared and the red color of the solution turned to pale yellow. Without filtering, the entire mixture was extracted with ether. The extract, dried, treated with charcoal and evaporated gave 6.5 g. (81% yield) of light tan crystals, melting 134–135°.

Attempts to reduce the nitrocresol by sodium sulfide or sodium hydroxide and hydrogen sulfide, by phenylhydrazine, and by catalytic hydrogenation were unsuccessful.

Acknowledgment is made to Dr. Groves H. Cartledge at whose suggestion this work was initiated.

Summary

1. Satisfactory methods for the synthesis of the following new compounds have been worked out and are described: β -(3-nitro-4-hydroxyphenyl)-ethanol, β -(3-amino-4-hydroxyphenyl)-ethanol, the hydrobromide of β -(3-amino-4-hydroxyphenyl)-ethyl bromide, and the hydrobromide of β -(4-aminophenyl)-ethyl bromide.

2. Unsuccessful attempts to prepare 3-amino-4-hydroxystyrene are noted.

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Some Metal Compounds of Aminocresol and Aminotyrosol

BY CALVIN F. STUNTZ^{1,2} AND HENRY M. WOODBURN

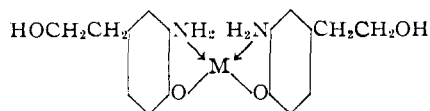
In the course of work involving 3-amino-4-hydroxytoluene and β -(3-amino-4-hydroxyphenyl)-ethanol,³ referred to hereafter as aminocresol and aminotyrosol, respectively, it was desired to prepare salts of these compounds with certain divalent metals. Since the amino and hydroxyl groups are ortho to one another, it

(1) Abstracted from a portion of a thesis submitted in partial fulfillment of the requirements for the Ph.D. degree at the University of Buffalo, August, 1948.

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(3) For the synthesis of this compound, see Woodburn and Stuntz, *THIS JOURNAL*, **72**, 1361 (1950).

might be expected that chelate ring compounds of the inner complex type would be formed, one metal atom combining with two organic molecules, replacing the hydroxyl hydrogens and forming coordinate bonds with the amino nitrogen



Compounds of this general structure have been reported by Hieber and Schnackig,⁴ who pre-

(4) Hieber and Schnackig, *Z. anorg. allgem. Chem.*, **226**, 209 (1936).