acid, except that the charge was heated for eight hours at 155–158°. There were obtained 123 g. of crude *o*-hydroxyphenylacetic acid (m. p. 135–142°) equal to an 81% crude yield. Recrystallized product had a m. p. 145–147° (from benzene–acetone mixture) (lit.,[6] 146–147°).

The identity of the *o*-hydroxyphenylacetic acid was further confirmed by its conversion into the corresponding lactone upon distillation.

β-(*p*-Hydroxyphenyl)-propionic Acid.—A charge of 125 g. (0.833 mole) of *p*-hydroxypropiophenone, 693 g. (4.39 moles) of 43% aqueous ammonium sulfide solution, 69.3 g. (2.17 moles) of sulfur, and 574 g. of dioxane was heated twelve hours at 160° in a rocker bomb. The reaction product was worked up as above except that the intermediate amide was hydrolyzed in the presence of hydrochloric acid.

β-(*p*-Hydroxyphenyl)-propionic acid was obtained thereby in 41.5% crude yield (57.4 g.). When recrystallized the m. p. was 128.5–129.5° (lit.,[7] 128–130°).

(6) Barnes and McElvain, THIS JOURNAL, **59**, 2350 (1937).

(7) Hlasiwetz, *J. prakt. Chem.*, [1] **67**, 110 (1856).

MIDLAND, MICH. RECEIVED JUNE 21, 1946

Summary

Hydroxyphenyl methyl and ethyl ketones were treated with ammonium polysulfide (Willgerodt reaction) to yield hydroxyphenylacetamides and β-(*p*-hydroxyphenyl)-propionamide, respectively, in good yields. On hydrolysis, the amides yielded the corresponding acids.

A procedure suitable for large scale production of *p*-hydroxyphenylacetic acid was developed.

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Mannich Reaction with *p*-Hydroxybenzaldehyde and N-(*p*-Hydroxybenzyl)-acetamide

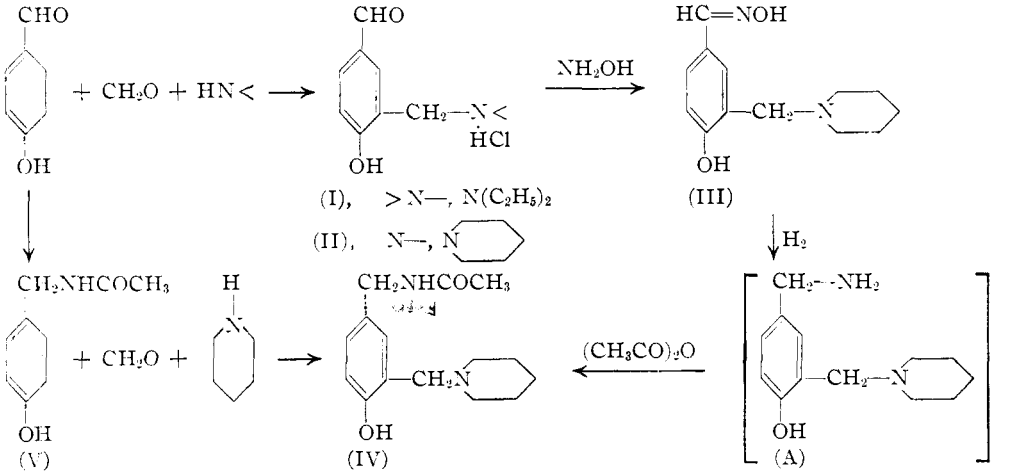
BY NORMAN H. CROMWELL

In an extension of a previous investigation dealing with the preparation of benzylamines and derivatives from aromatic aldehydes,[1] the possibility of obtaining certain N-substituted benzylamines and derivatives through the use of the Mannich reaction has been studied.

It has been known for some time that the hydroxyl group on the benzene nucleus activates the hydrogen in the ortho and para positions sufficiently to allow such compounds to undergo the Mannich reaction with formaldehyde and secondary amines.[2] It therefore appeared likely that *p*-hydroxybenzaldehyde would take part in such reactions, provided the secondary amine did not engage in a competing reaction with the aldehyde group, ($RCHO + 2\,HNR_2 \rightarrow RCH(NR_2)_2 + H_2O$).

When *p*-hydroxybenzaldehyde was heated in an open flask in absolute alcohol solution with an equivalent amount of a previously prepared solution of the assumed active agent $C_2H_5O—CH_2—N<$, in which $—N<$ was the diethylamino group and the piperidino group, respectively, a 41% yield of 4-hydroxy-3-(diethylaminomethyl)-benzaldehyde (I) and a 64% yield of 4-hydroxy-3-(piperidinomethyl)-benzaldehyde (II) resulted, and were isolated as their hydrochlorides.

In order that other derivatives to be used as intermediates in the synthesis of products for chemotherapeutic testing might be obtained, the possibility of converting the aldehyde group into the amino methyl group was investigated. These aldehydes (I) and (II) formed both phenylhydrazones and oximes, readily. The oxime (III) of (II) was reduced with hydrogen at four atmospheres and Raney nickel catalyst in the presence of concd.



(1) Cromwell and Hoeksema, THIS JOURNAL, **67**, 1658 (1945).

(2) "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 311.

ammonium hydroxide. The resulting diamine (A) was not isolated, but was converted into 4-hydroxy-3-(piperidinomethyl)-N-acetylbenzyl amine (IV) by treatment of the crude product with acetic anhydride. Attempts to reduce (III) by various other catalytic procedures, such as with palladinized charcoal in absolute alcohol and sulfuric acid solution or in absolute alcohol and dry hydrogen chloride solution, or with platinum oxide in acetic anhydride solution failed.

Since the yield of (IV) from (III) was only 9.8%, it seemed advisable to attempt an alternative synthesis. An excellent method for preparing N-(*p*-hydroxybenzyl)-acetamide (V) by dissolving *p*-hydroxybenzylamine[3] in pure acetic anhydride and filtering off the product was developed. The amide (V) underwent the Mannich reaction readily with formaldehyde and piperidine to give a 61% yield of (IV). The fact that (IV) was obtained starting from either (V) or (II) indicated the piperidino methyl group to have entered the same relative position in both *p*-hydroxybenzaldehyde and (V) during the Mannich reaction. In accordance with previous investigations[2] this position is assumed to be the position ortho to the phenolic hydroxyl group.

Acknowledgment.—The author appreciates very much a research grant from Parke, Davis and Company of Detroit, Michigan, which made this investigation possible.

Experimental[4]

Reaction of *p*-Hydroxybenzaldehyde with Formaldehyde and Secondary Amines

(a) **4-Hydroxy-3-(diethylaminomethyl)-benzaldehyde Hydrochloride** (I).—A mixture of 24.4 g. (0.2 mole) of *p*-hydroxybenzaldehyde, 40 ml. of absolute alcohol and 50 ml. of a stock solution[5] containing approximately 0.2 mole of $C_2H_5O\text{-}CH_2N(C_2H_5)_2$ was heated on the steam-bath without reflux for four hours. The thick mixture was mixed with 200 ml. of ether and shaken with a large amount of anhydrous calcium sulfate. The dry ether solution was cooled and dry hydrogen chloride gas passed in to give a pink gummy precipitate. This product was crystallized by dissolving in warm absolute alcohol and then adding twice this volume of ethyl acetate and a small amount of dry ether. A pale, pink crystalline product resulted, wt. 20 g. (41% yield), m. p. 163–166° dec. This product[1] gave a purple color with ferric chloride solution and was soluble in water.

Anal. Calcd. for $C_{12}H_{18}NO_2Cl$: Cl^-, 14.55; N, 5.75. Found: Cl^-, 14.80; N, 5.89.

This aldehyde (I) would not form a solid oxime, but readily gave a solid **phenylhydrazone** with phenylhydrazine in 95% alcohol containing a drop of acetic acid, m. p. 78–80°.

(3) Holly and Cope, THIS JOURNAL, **66**, 1879 (1944).

(4) The micro-Kjeldahl nitrogen analyses were carried out by the Research Laboratories of Parke, Davis and Company, Detroit, Michigan.

(5) A stock solution was prepared by adding slowly 33 g. (1 mole active CH_2O) of paraformaldehyde to a solution of absolute alcohol and 85 g. (1 mole) of piperidine. Enough absolute alcohol was added to the mixture to bring the volume to 250 ml. Thus 25 ml. of this solution contained approximately 0.1 mole of the active reagent ($C_2H_5OCH_2NC_5H_{10}$). This solution was stored in the ice chest and withdrawn as needed. A four molar stock solution of $C_2H_5O\text{-}CH_2N(C_2H_5)_2$ was prepared in the same way.

Anal. Calcd. for $C_{18}H_{23}N_3O$: C, 72.69; H, 7.79. Found: C, 72.67; H, 7.90.

(b) **4-Hydroxy-3-(piperidinomethyl)-benzaldehyde Hydrochloride** (II).—A mixture of 48.8 g. (0.4 mole) of *p*-hydroxybenzaldehyde, 100 ml. of absolute alcohol and 100 ml. of the stock solution[5] containing approximately 0.4 mole of $C_2H_5OCH_2NC_5H_{10}$ was heated on the steam-bath without reflux for four hours and under vacuum for one-half hour. The residual gummy product was dissolved in ether, this solution was shaken twice with a saturated sodium chloride solution, and the ether layer dried over anhydrous calcium sulfate. Dry hydrogen chloride gas was passed into the solution to give 79 g. of a pale-pink, crystalline product. This hydrochloride was recrystallized by dissolving in 500 ml. of hot 60% alcohol-water solution and then adding 125 ml. of ethyl acetate and 750 ml. of dry ether. A colorless, crystalline product resulted, m. p. 240–245° dec., wt. 65 g. (64% yield). This aldehyde (II) was very water soluble and gave a purple color with ferric chloride solution.

Anal. Calcd. for $C_{13}H_{18}NO_2Cl$: Cl^-, 13.87; N, 5.48. Found: Cl^-, 14.18; N, 5.31.

The oxime (III) **of** (II) was prepared by adding 20 g. of (II) to a solution of 8.0 g. of hydroxylamine hydrochloride in 50 ml. of water, followed by the addition of 11 g. of sodium carbonate dissolved in 25 ml. of water. To this mixture was added 25 ml. of 95% alcohol. The reaction mixture was heated on the steam-bath for ten minutes and then cooled to precipitate colorless crystals, m. p. 131–147°, wt. 16 g. (87% yield).

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.60; H, 7.74. Found: C, 66.62, H, 7.90.

This oxime (III) was undoubtedly a mixture of the two possible geometrical isomers. It was rather readily hydrolyzed to the starting aldehyde when alcohol-water solutions of it were warmed. Several careful recrystallizations of the reaction product gave as the higher melting isomer, colorless crystals, m. p. 143–148°.

4-Hydroxy-3-(piperidinomethyl)-N-acetylbenzylamine (IV) **from the Oxime** (III).—Ten grams of the oxime (III) was dissolved in a mixture of 100 ml. of alcohol and 20 ml. of concentrated ammonium hydroxide. This solution was shaken with hydrogen at room temperature under 60 lb./sq. in. pressure in the presence of Raney nickel catalyst. A small amount of heat was developed and the theoretical amount of hydrogen was taken up in twenty-five minutes. The catalyst was filtered off and the solvent evaporated under vacuum from a water-bath to leave a thick, dark oil which could not be crystallized.

The oily product was dissolved in ether and the solution washed several times with water and dried with Drierite. Evaporation of this solution left 5.0 g. of a dark oil which was mixed with 20 ml. of acetic anhydride. Considerable heat was developed by the solution, which after ten minutes was poured into 50 ml. of water containing 25 g. of potassium carbonate. The precipitated oil was extracted with chloroform and the solution dried with Drierite and evaporated to leave 6.3 g. of a brown, thick oil that refused to crystallize.

The oily acetylation product was slowly dissolved in a solution of 70 ml. of 10% sodium hydroxide and 10 ml. of absolute alcohol by warming on a steam-bath. The cooled, orange-colored solution was first made acid to congo red with concentrated hydrochloric acid, and then basic with solid sodium carbonate. From the gummy semi-solid precipitate, 1.1 g. (9.8% yield) of (IV), m. p. 122–125° was obtained by careful crystallization from 40% alcohol solutions.

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: N, 10.66. Found: N, 10.24.

N-(*p*-Hydroxybenzyl)-acetamide (V).—To 160 ml. of pure acetic anhydride was added 40 g. of *p*-hydroxybenzylamine,[3] in three minutes, with shaking. All of the solid amine dissolved and heat was developed. The clear solution was immediately placed in an ice-bath whereupon white crystals deposited to form a solid mass. A 200 ml.

mixture of 50% dry ether and 50% petroleum ether (b. p. 60–70°) was added to the mixture and the colorless crystals filtered onto a Büchner funnel having a sintered glass plate, and washed with a mixture of 50% ether and 50% petroleum ether. The product was vacuum dried, wt. 39 g. (73% yield), m. p. 134–136°.[6]

Reaction of (V) with Piperidine and Formaldehyde to Give (IV).—A mixture of 16.5 g. (0.1 mole) of the amide (V), 30 ml. of absolute alcohol and 25 ml. of the stock solution[5] containing approximately 0.1 mole of $C_2H_5OCH_2NC_5H_{10}$ was heated on the steam-bath for two hours without reflux. The remaining solvent was removed by vacuum distillation from a water-bath. On standing in the ice chest overnight the residual mass partially solidified and was readily recrystallized from 30% alcohol to give 16 g. (61% yield) of colorless crystals, m. p. 123–125°, identical with the amide (IV). Further recrystallization did not change the m. p. This product (IV) was soluble in both dilute sodium hydroxide and dilute hydrochloric acid and gave a pale yellow-green color with ferric chloride solution.

A similar experiment using the stock solution[5] containing $C_2H_5O\text{-}CH_2N(C_2H_5)_2$ gave a product which would not crystallize, and which gave only an oily hydrochloride.

(6) Kelferich Günther and Winkler, *Ann.*, **508**, 192 (1934).

Summary

p-Hydroxybenzaldehyde and N-(*p*-hydroxybenzyl)-acetamide both readily undergo the Mannich reaction with formaldehyde and secondary amines. The substituted amino methyl group enters the same relative position on the benzene ring in both compounds.

LINCOLN, NEBRASKA RECEIVED JULY 30, 1946

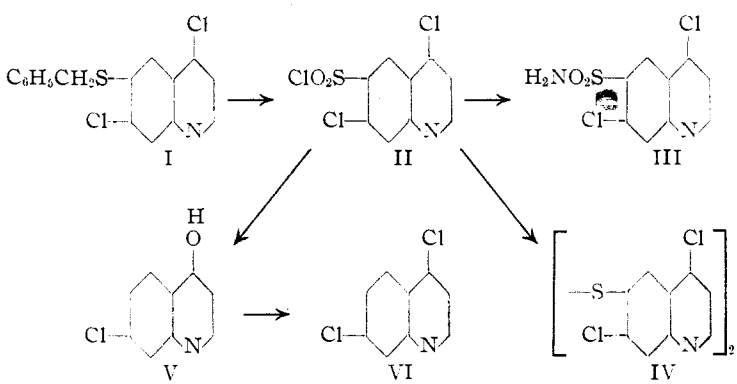
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Cleavage of Organic Sulfides with Chlorine[1]

BY ROBERT H. BAKER, R. M. DODSON[2] AND BYRON RIEGEL

In connection with the antimalarial program a synthesis of 4,7-dichloro-6-quinolinesulfonamide, III, and bis-(4,7-dichloro-6-quinolyl) disulfide, IV, was desired. Attempts to prepare these compounds by means of the ethoxymethylenemalonic ester (EMME) synthesis on bis-(4-amino-2-chlorophenyl) disulfide were unsuccessful.[3] The condensation of EMME and the aminodisulfide and the necessary ring-closure were successfully accomplished, but the decarboxylation of the resulting bis-(3-carboxy-4-hydroxy-7-chloro-6-quinolyl) disulfide could not be effected. Since the EMME synthesis on sulfanilamide was also unsuccessful, any approach analogous to this was excluded. The low temperature sulfonation of 4,7-dichloroquinoline was not attempted because of the fact that the sulfonic acid group enters both 4- and 7-chloroquinoline at the 8 position.[4,5] The high temperature reaction used by Georgievics[6] to prepare 6-quinolinesulfonic acid failed when applied to the dichloroquinoline because excessive decomposition occurred upon heating with sulfuric acid at 300°.

It was finally decided to synthesize 4,7-dichloro-6-benzylthioquinoline, I, by means of the EMME synthesis on 4-benzylthio-3-chloroaniline and then to cleave the sulfide, I, by one of the better known methods. Zincke and Rose[7] have reported the cleavage of 4-methylthio-3-nitrotoluene with chlorine in wet acetic acid with the resulting formation of 3-nitrotoluene-4-sulfonyl chloride. More recently, Lee and Dougherty[8] have cleaved and oxidized dibutyl and dibenzyl sulfides to the corresponding alkylsulfonyl chlorides and alkyl chlorides by the same method.



The oxidative cleavage of 4,7-dichloro-6-benzylthioquinoline, I, with chlorine in acetic acid resulted in the formation of 4,7-dichloro-6-quinolinesulfonyl chloride, II. The sulfonyl chloride was then converted to the desired sulfonamide, III; the over-all yield from I was 67%. The sulfonyl chloride, II, was also reduced by means of stannous chloride and hydrochloric acid to the mercaptan which in turn was oxidized by means of sodium hypoiodite to the desired bis-(4,7-dichloro-6-quinolyl) disulfide, IV.

The structure of 4,7-dichloro-6-benzylthioquinoline had been surmised by analogy with the products of other EMME syntheses.[3] Since the posi-

(1) Part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Northwestern University.

(2) National Research Council Predoctoral Fellow, 1946–1947.

(3) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson and R. H. Baker, THIS JOURNAL, **68**, 1264 (1946).

(4) B. Riegel, G. R. Lappin, C. J. Albisetti, Jr., B. H. Adelson, R. M. Dodson, L. G. Ginger and R. H. Baker, *ibid.*, **68**, 1229 (1946).

(5) A. Claus and R. Kayser, *J. prakt. Chem.*, **156**, 270 (1893).

(6) G. Georgievics, *Monatsh.*, **8**, 577 (1888).

(7) Th. Zincke and H. Rose, *Ann.*, **406**, 127 (1914).

(8) S. W. Lee and G. Dougherty, *J. Org. Chem.*, **5**, 81 (1940).