[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORY, THE DOW CHEMICAL COMPANY]

Preparation of Hydroxyphenylalkanoic Acids by the Willgerodt Reaction

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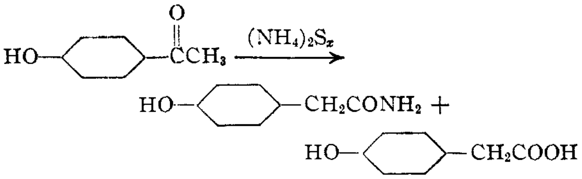
The present paper describes the preparation of *o*-, *m*- and *p*-hydroxyphenylacetic acids, β-*p*-hydroxyphenylpropionic acid, and *p*-hydroxyphenylacetamide by the Willgerodt–Kindler reaction.[3] For example, *p*-hydroxyacetophenone was heated with aqueous ammonium polysulfide and isopropanol in a steel bomb at about 150–300°, whereby a rearrangement occurred with conversion of the ketone into *p*-hydroxyphenylacetamide and a lesser amount of *p*-hydroxyphenylacetic acid. The amide then was hydrolyzed to the corresponding acid.



The significant new developments presented in this paper are: (a) the use of phenolic ketones (previously thought unsuitable), (b) the use of large quantities of ketone (up to 20 lb.) (previous efforts to use moderately large quantities in autoclaves were not very successful[3a,b]), and (c) the use of isopropanol as a solvent.

Experimental

***p*-Hydroxyphenylacetamide.**—A solution of 136 g. (1 mole) of *p*-hydroxyacetophenone in 470 g. of isopropanol was added to a solution of 83.3 g. (2.6 moles) of sulfur in 833 g. (5.3 moles) of 43% aqueous ammonium sulfide in a 2.5-liter steel rocker bomb, and the charge then heated twelve hours at 160° (pressure *ca.* 800 p.s.i.). At the end of the run the bomb was cooled and the contents boiled about three hours to remove ammonia, hydrogen sulfide, isopropanol and an oil. This solution, approximately 500 cc., was cooled, acidified to a *p*H of 7.0 employing acetic acid, treated with Norite and Filtercel, filtered, evaporated under reduced pressure to about 300 cc. volume, and cooled in an ice-bath. Crystals were filtered off and dried at 75°. Yield of crude product (m. p. 168–172°) was 102 g. or 67.5%. Recrystallization from water raised the m. p. to 172–174° (lit.,[4] 175°).

***p*-Hydroxyphenylacetic Acid.**—*p*-Hydroxyacetophenone was treated with ammonium polysulfide in the same weight amounts and molar proportions, and under the same conditions as given under *p*-hydroxyphenylacetamide, except that the time of heating was only nine hours.

After the boiling step, 3 moles of sodium hydroxide were added to the mixture which then was stirred a short while to extract acidic material, while cooling to room temperature. The alkaline solution was filtered to remove insoluble material and the filtrate refluxed six hours to complete the hydrolysis of the amide to the corresponding acid. After cooling, the solution was acidified with concentrated hydrochloric acid to a *p*H 1.0–1.5 (sulfur being precipitated along with some additional tar and a small quantity of black tarry oil), filtered, treated with charcoal at 70°, and filtered hot. To the solution at *p*H 1.5, there was added 125 g. of sodium chloride. The cooled solution was extracted three times with methyl ethyl ketone, and the combined ketone extracts dried with anhydrous sodium sulfate and filtered. Methyl ethyl ketone was removed under reduced pressure on a steam-bath, and the residue further dried three hours at 75°. The crude *p*-hydroxyphenylacetic acid weighed 95.5 g. (m. p. 140–147°), or a 62% yield. Recrystallized from water, the purified product had a m. p. of 145–147°.

Good results have been obtained in similar runs wherein the time of heating the bomb was as low as three hours. Other solvents, *i. e.*, dioxane, methanol, ethanol, *t*-butanol, 2-ethoxyethanol and diethyl ether have also been used, the yields varying from 27–63%. However, isopropanol is preferred because of its availability and low cost. Methanol has a disadvantage in that vile smelling sulfur compounds are formed from it. When no organic solvent was present in the charge, the yield of product was considerably lower. The intermediate *p*-hydroxyphenylacetamide can be hydrolyzed under either acidic or basic conditions.

***p*-Hydroxyphenylacetic Acid (Semiplant Run).**—A charge of 20 lb. of *p*-hydroxyacetophenone, 70 lb. of isopropanol, and ammonium polysulfide (from 121.5 lb. of aqueous 43% ammonium sulfide and 12.15 lb. of sulfur flowers) was heated twelve hours at 160° in a 40-gallon steel rotor bomb (max. gage pressure, 950 lb. p.s.i.). The cooled reaction mixture was pumped into a kettle and slowly warmed, hydrogen sulfide and ammonia gases being vented and aqueous isopropanol together with some oil being distilled out (liquid level in still was maintained by addition of water). To the cooled residual solution there was added 36.5 lb. of solid sodium hydroxide with additional cooling and the liquor then wheeled to remove solids. The filtrate was pumped back into the kettle and refluxed six hours to hydrolyze *p*-hydroxyphenylacetamide to *p*-hydroxyphenylacetic acid.

The cold hydrolysate was pumped into an enameled separator, acidified with concentrated hydrochloric acid to a *p*H of 1.5–2.0, settled, the liquor drained off from semi-sticky tar, and the acidified liquor pumped into a Pfaudler kettle. After treating with charcoal, it was extracted three times with methyl ethyl ketone to remove the product. The combined extracts were concentrated to about 8 gal. by flash distillation, and the concentrate then vacuum distilled until crystals formed on the edge of the boiling solution. The hot solution was poured into a 5-gallon enameled can, cooled to 10–15°, and the crystals removed by wheeling. A second crop was obtained from the mother liquor in the usual manner. Total yield of crude *p*-hydroxyphenylacetic acid was 45% (10 lb.).

***m*-Hydroxyphenylacetic Acid.**—A charge of 27.2 g. (0.2 mole) of *m*-hydroxyacetophenone, 166 g. (1.06 mole) of 43% aqueous ammonium sulfide, 16.6 g. (0.52 mole) of sulfur, and 94 g. of isopropanol was heated in a rotating 500-cc. cylindrical Pyrex glass bomb for twelve hours at 160°. The reaction mixture was worked up as described above. *m*-Hydroxyphenylacetic acid was obtained in a 41% crude yield. Recrystallized product had a m. p. 128.5–130° (from benzene–acetone mixture) (lit.,[5] 129°).

***o*-Hydroxyphenylacetic Acid.**—*o*-Hydroxyacetophenone was converted into *o*-hydroxyphenylacetic acid using the same weights and molar ratios of reactants, and under the same conditions as given under *p*-hydroxyphenylacetic

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(3) (a) Willgerodt and Scholtz, *J. prakt. Chem.*, [2] **81**, 382 (1910); (b) Fieser and Kilmer, THIS JOURNAL, **62**, 1354 (1940); (c) Schwenk and Bloch, *ibid.*, **64**, 3051 (1942); (d) King and McMillan, *ibid.*, **68**, 525, 632 (1946).

(4) Salkowski, *Ber.*, **22**, 2141 (1889).

(5) Robinson and Zaki, *J. Chem. Soc.*, 2412 (1927).

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°).

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.

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

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

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

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

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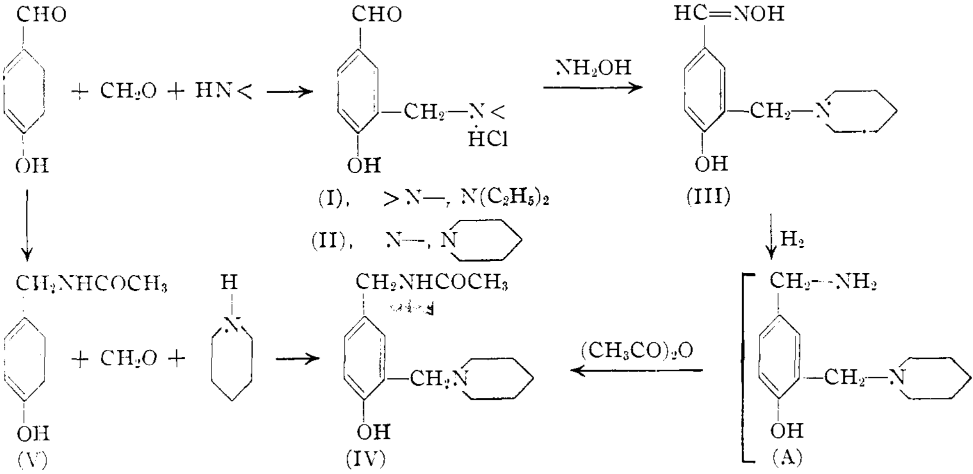
In an extension of a previous investigation dealing with the preparation of benzylamines and derivatives from aromatic aldehydes,[1] the possibility of obtaining certain N-substituted benzylamines and derivatives through the use of the Mannich reaction has been studied.

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.

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[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.