This checks with the reported boiling point in the literature.[6] The yield was 0.5 g. (40.5%). There was not enough to purify further.

*Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.08; H, 7.96. Found: C, 73.71; H, 8.09.

The aqueous solution which was extracted with ether contained the hexahydrobenzoic acid. This solution was acidified with dilute sulfuric acid, then extracted three times with 15-cc. portions of ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether mixture was then filtered and the ether was evaporated to leave an unpleasant smelling oil. This oil was dried in a vacuum desiccator at 3 mm. pressure overnight. It was then treated with 1 cc. of thionyl chloride and heated under reflux for thirty minutes. The reaction mixture was cooled and a solution of 1 g. of aniline in 25 cc. of dry benzene was added. The mixture was then warmed on the steam cone for fifteen minutes. The mixture was cooled and filtered. The filtrate was washed successively with 2 cc. of water, 5 cc. of 5% hydrochloric acid, 5 cc. of 5% sodium hydroxide and finally 2 cc. of water. The benzene solution after drying over calcium chloride was evaporated to leave white plates melting at 137°. These were recrystallized twice from benzene to give a melting point of 142°. This checks with the melting point of the anilide of hexahydrobenzoic acid as given in the literature.[10]

**Phenylurethan of Dihydrotubanol.**—A mixture of 0.1 g. of dihydrotubanol and 0.5 cc. of phenylisocyanate was heated in a sealed Pyrex glass tube for seventeen hours. At the end of this time, a small crystalline precipitate had formed in the bottom of the tube. The reaction tube was then broken and the reaction mixture was washed out with a 1:1 mixture of benzene and ligroin. Upon slow evaporation of the benzene high-boiling petroleum ether solution, white prisms of the urethan precipitated. These were filtered, washed with cold ligroin and recrystallized from the benzene ligroin mixture. The yield of urethan was 0.12 g. The melting point was 137°.

*Anal.* Calcd. for $C_{18}H_{19}O_3N$: N, 4.72. Found: N, 4.93.

## Summary

Catalytic reduction of 2-isopropylidine-4-hydroxycoumaran-3-one with platinum and hydrogen yields the 2-isopropyl derivative but in the presence of a trace of hydrochloric acid complete reduction to the substituted hexahydrocoumaran took place.

Dihydrotubanol has been synthesized by reducing the benzoate of 2-isopropylidine-4-hydroxycoumaran-3-one to the hexahydrobenzoate of dihydrotubanol followed by hydrolysis.

URBANA, ILLINOIS RECEIVED MAY 23, 1941

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[10] Ref. 9, p. 182.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, UNITED STATES PUBLIC HEALTH SERVICE]

# Preparation of 4-Aminobenzenephosphonic Acid (Phosphanilic Acid)*

BY HUGO BAUER

The chemotherapeutic properties of organic phosphorus compounds hitherto have not been investigated. Preliminary studies[1] indicated that active phosphorus compounds with comparatively low toxicity can be obtained. Bis-(4-dimethylaminophenyl)-hydroxyphosphine,[2] $[(CH_3)_2NC_6H_4]_2POH$, showed activity against streptococcal infections in mice equal to that of sulfanilamide. In the course of chemotherapeutic studies an attempt has been made to obtain benzene phosphorus derivatives containing a free primary amino group in the para position. The present report deals with the preparation of 4-aminobenzenephosphonic acid for which the name phosphanilic acid is suggested by analogy with sulfanilic and arsanilic acids.

D. R. Nijk[3] made an unsuccessful attempt to prepare phosphanilic acid by the reaction of ammonium hydroxide with 4-chlorobenzenephosphonic acid[4] in the presence of copper powder at 150°. H. Erlenmeyer and E. Berger,[5] who followed the procedure of Nijk, determined the quantity of phosphanilic acid present in the mixture of acids by titration with nitrite, but did not report the yield.

In the present investigation the maximum yield of phosphanilic acid that could be obtained with the use of copper powder was 5–15%. However, the substitution of freshly precipitated cuprous oxide for copper powder increased the yield to 60–63%. The action of cuprous oxide apparently is not exclusively catalytic. To secure a good yield, it was necessary to use one mole of cuprous

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[1] H. Bauer and S. M. Rosenthal, *Pub. Health Repts.*, **54**, 2093 (1939).

[2] Bourneuf, *Bull. soc. chim. Mém.*, [4] **33**, 1808 (1923); H. Raudnitz, *Ber.*, **60**, 743 (1927).

[3] D. R. Nijk, *Rec. trav. chim.*, **41**, 461 (1922).

[4] A. Michaelis, *Ann.*, **293**, 193 (1897).

[5] H. Erlenmeyer and E. Berger, *Biochem. Z.*, **255**, 429 (1932).

oxide to each mole of phosphonic acid, the copper obviously taking part as a chemical reactant.

## Experimental

**4-Chlorobenzenephosphonic Acid.**—The compound was prepared by the procedure of Michaelis[4] with the exception that the reaction mixture was maintained at about 50° during chlorination of 4-chlorobenzenedichlorophosphine to prevent crystallization of 4-chlorobenzenetetrachlorophosphine before completion of the reaction. After the chlorination mixture had been mixed with ice water, the crude 4-chlorobenzenephosphonic acid thus produced was purified by recrystallization from ethyl acetate; m. p. 188° (uncor.). Michaelis reported melting point of 184–185°.

4-Chlorobenzenephosphonic acid in aqueous solution yields a precipitate of a magnesium salt upon being heated with magnesia mixture. This reaction is analogous to the formation of the slightly soluble magnesium salts of the arsonic acids.

Crystals of an acid ammonium salt were obtained by the addition of hydrochloric acid to a solution of 4-chlorobenzenephosphonic acid in ammonium hydroxide until the solution was acid to congo red. The crystals are moderately soluble in water, readily soluble in hot alcohol.

*Anal.* Calcd. for $[ClC_6H_4PO(OH)_2]_2NH_3$: Cl, 17.64; P, 15.43; $NH_3$, 4.24. Found: Cl, 17.68; P, 15.68; $NH_3$, 4.12.

This acid ammonium salt, containing a small amount of phosphanilic acid, was always obtained in following the procedure of Nijk,[3] when the ammoniacal copper-free solution of the reaction products was acidified with hydrochloric acid. After extraction of the acid ammonium salt with hot alcohol, the phosphanilic acid remained in a yield of 5–15%. The acid ammonium salt of 4-chlorobenzenephosphonic acid was not reported by Nijk.

**Phosphanilic Acid.**—To 100 cc. of 28% ammonium hydroxide in a Pyrex glass tube, cooled in ice, were added 6 g. of crude 4-chlorobenzenephosphonic acid and 4.5 g. of freshly prepared cuprous oxide. After the tube had been sealed, the mixture was kept at 150° for five hours during which the cuprous oxide dissolved completely to yield a blue solution. The copper was precipitated from the combined contents of eight tubes by hydrogen sulfide, the solution was then warmed and the copper sulfide removed by filtration. The filtrate was concentrated on the water-bath until crystallization started, a few drops of ammonium hydroxide were added and the solution filtered hot. After being acidified to congo red by the addition of 25% hydrochloric acid, the precipitate was filtered, washed with cold water, and extracted with hot alcohol to remove some of the previously described acid ammonium salt of 4-chlorobenzenephosphonic acid. The yield of crude phosphanilic acid was about 27 g., or 62%.

For purification, 50 g. of the crude product was suspended in 300 cc. of water and 200 cc. of 36% hydrochloric acid added. The dark solution was stirred with charcoal until the filtrate was colorless. After filtering, about 220 cc. of 10 *N* sodium hydroxide was added, the reaction remaining distinctly acid to congo red paper. The phosphanilic acid separated as a sandy crystalline powder from the warm solution. After cooling, the product was filtered, washed with water, then with alcohol, and dried on the water-bath. The yield was 47 g. The pure substance is colorless, but the preparations often show a yellowish tint. When rapidly heated it melts at 245° (uncor.) with decomposition, solidifies and melts again at about 285° to a dark blue liquid.

*Anal.* Calcd. for $C_6H_8O_3NP$: P, 17.92. Found: P, 17.94. Assay with 0.1 *N* nitrite: 101%.

Phosphanilic acid is very sparingly soluble in water; insoluble or sparingly soluble in the usual organic solvents. It is soluble in solutions of alkali hydroxides and carbonates, of sodium hydrogen carbonate and sodium acetate. It is easily soluble in 5 *N* hydrochloric acid, difficultly in dilute hydrochloric acid, sparingly soluble in dilute acetic acid. The diazotized compound couples with $\beta$-naphthol to yield a red dye. With magnesia mixture, no precipitate occurs at ordinary temperature, but, when heated, a white precipitate of a magnesium salt of phosphanilic acid is formed.

**N-Acetylphosphanilic Acid.**—To a suspension of phosphanilic acid in water was added sufficient sodium hydrogen carbonate to dissolve the compound. The solution was shaken with acetic anhydride until a test with dimethylaminobenzaldehyde showed the absence of the primary amino group. Upon addition of hydrochloric acid, colorless leaflets separated in almost quantitative yield; m. p. 229° with decomposition. For analysis the substance was crystallized from alcohol and dried in the vacuum oven at 100°.

*Anal.* Calcd. for $C_8H_{10}O_4NP$: P, 14.41. Found: P, 14.43.

Deacetylation was carried out by boiling with 5 *N* hydrochloric acid for fifteen minutes. Upon neutralization with sodium hydrogen carbonate, the free phosphanilic acid was recovered in quantitative yield and in a pure state; m. p. 245° (dec.).

## Summary

The preparation of 4-aminobenzenephosphonic acid or phosphanilic acid has been performed by heating 4-chlorobenzenephosphonic acid with concentrated ammonium hydroxide to 150°, using cuprous oxide as a catalyst. An acetyl derivative has been prepared.

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