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Abstract

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Synthesis of 3-Hydroxypyrrolidines and 3-Hydroxythiophane

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At the present time a large number of compounds containing the pyrrolidine ring are known. However, a number of functional derivatives of pyrrolidine still remain little studied. Thus 3-hydroxypyrrolidine, its homologues, and N-substituted 3-hydroxypyrrolidines have been studied very little. In the literature ([1–4]) only individual representatives of 3-hydroxypyrrolidines have been described, and the methods for obtaining them are, as a rule, different and specific for each compound.

In 1952 Yu. A. Arbuzov and L. I. Khmelnitskii ([5]) found a method for the synthesis of N-substituted 3-hydroxypyrrolidines by condensation of 1,4-dibromobutanol with primary amines. However, the method found is inconvenient because of the difficulty of obtaining 1,4-dibromobutanol and the insufficiently high yields of 3-hydroxypyrrolidines.

In 1955 V. Reppe and co-workers ([6]) described the preparation of 1-aryl-3-hydroxypyrrolidines by heating 1,2,4-trihydroxybutane with a mixture of a primary aromatic amine and its hydrochloride in an autoclave at 180–190°. However, the yields of 1-aryl-3-hydroxypyrrolidines were low.

It was of considerable interest to find a convenient method for the synthesis of 3-hydroxypyrrolidine and N-substituted 3-hydroxypyrrolidines, which was the main task of the present work.

It was natural to use for this purpose 1,4-dichlorobutanol, which we obtained in high yield by reduction of 1,4-dichlorobutanone with lithium aluminum hydride. The latter, in turn, is easily obtained in good yield by addition of chloroacetyl chloride to ethylene in the presence of aluminum chloride ([7,8]).

We have found that, on heating 1,4-dichlorobutanol with equimolecular amounts of primary amines in absolute alcohol in the presence of potash, N-substituted 3-hydroxypyrrolidines are formed in high yields. By this method we obtained 1-phenyl-3-hydroxypyrrolidine, 1-*p*-tolyl-3-hydroxypyrrolidine, 1-*p*-anisyl-3-hydroxypyrrolidine, 1-*n*-butyl-3-hydroxypyrrolidine, and 1-benzyl-3-hydroxypyrrolidine.

By catalytic debenzylation of 1-benzyl-3-hydroxypyrrolidine in the presence of palladium oxide we obtained 3-hydroxypyrrolidine in high yield. Until recently, 3-hydroxypyrrolidine had not been known, and only in 1957 was a brief communication by R. Kuhn ([9]) published in which the synthesis of 3-hydroxypyrrolidine was described. It should be noted that the method for obtaining 3-hydroxypyrrolidine developed by R. Kuhn is considerably more complicated than our method.

By condensation of 1,4-dichlorobutanol with sodium sulfide we obtained, in good yield, the previously unknown 3-hydroxythiophane.

Experimental Part

Preparation of 1,4-dichlorobutanol

Into a flask equipped with a stirrer, a dropping funnel, and a reflux condenser, the upper end of which was closed with a calcium chloride tube, was placed a solution of 70.5 g (0.5 mole) of freshly distilled 1,4-dichlorobutanone in 100 ml of abs. ether. The flask was placed in an ice bath, and, with stirring, a solution of 10 g (0.26 mole) of lithium aluminum hydride in 300 ml of abs. ether was added from the dropping funnel over the course of 4 hours. The reaction mixture was stirred under ice cooling for another hour, and then 120 ml of water and 200 ml of 10% sulfuric acid were successively added to it dropwise. After dissolution of the hydroxide precipitate, the ethereal layer was separated, and the aqueous layer was extracted repeatedly with ether. The combined ethereal solution was dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was fractionated in vacuo. There was obtained 51.7 g (72%) of 1,4-dichlorobutanol with the following constants: b.p. 95–98°/18 mm, d_4^{20} 1.2922, n_D^{20} 1.4882; MR_D 31.90; calculated for $C_4H_8OCl_2$ 31.93.

Found, %:	Cl	48.93
$C_4H_8OCl_2$. Calculated, %:	Cl	49.58

1,4-Dichlorobutanol is a colorless, viscous liquid with a characteristic odor. Literature data: b.p. 95–100°/18 mm ([6]).

Preparation of 3-hydroxypyrrolidines

The condensation of 1,4-dichlorobutanol with primary amines was carried out by us in the following manner. Into a flask equipped with a reflux condenser were placed 1,4-dichlorobutanol (1 mole), the primary amine (1 mole), abs. alcohol, and finely powdered dry potassium carbonate (1-1.5 moles). The flask was heated on a boiling water bath for 20–25 hours. The mixture was then cooled, the precipitate was filtered off and washed on the filter with abs. alcohol. The alcohol was distilled off, and the residue was fractionated in vacuo.

1-Phenyl-3-hydroxypyrrolidine. A mixture of 37 g (0.26 mole) of 1,4-dichlorobutanol, 24.2 g (0.26 mole) of aniline, 90 ml of abs. alcohol, and 54 g (0.39 mole) of potassium carbonate was heated for 20 hours. There was obtained 34.7 g (82%) of 1-phenyl-3-hydroxypyrrolidine with b.p. 134–137°/1 mm. The substance crystallizes already during distillation in the form of colorless fibers. M.p. 96–97°. Literature data: m.p. 96–97° (^{5}); b.p. 138–144°/1 mm (^{6}).

1-*p*-Tolyl-3-hydroxypyrrolidine. A mixture of 14.3 g (0.1 mole) of 1,4-dichlorobutanol, 10.7 g (0.1 mole) of *p*-toluidine, 40 ml of abs. alcohol, and 15 g (0.11 mole) of potassium carbonate was heated for 25 hours. There was obtained 14.5 g (82%) of 1-*p*-tolyl-3-hydroxypyrrolidine with b.p. 148–152°/1 mm. The substance crystallizes already during distillation in the form of colorless fibers. M.p. 85–86°. Literature data: m.p. 84–85° (^{5}).

1-*p*-Anisyl-3-hydroxypyrrolidine. A mixture of 15 g (0.105 mole) of 1,4-dichlorobutanol, 13 g (0.105 mole) of *p*-anisidine, 50 ml of abs. alcohol, and 22 g (0.16 mole) of potassium carbonate was heated for 25 hours. There was obtained 19.5 g (95%) of 1-*p*-anisyl-3-hydroxypyrrolidine with b.p. 164–166°/1 mm. The substance crystallizes already during distillation in the form of colorless fibers. M.p. 73–74°.

Found, %: C 68.30; H 8.11; N 7.46
$C_{11}H_{15}O_2N$. Calculated, %: C 68.37; H 7.82; N 7.25.

1-*n*-Butyl-3-hydroxypyrrolidine. A mixture of 11 g (0.077 mole) of 1,4-dichlorobutanol, 5.6 g (0.077 mole) of *n*-butylamine, 40 ml of abs. alcohol, and 16.2 g (0.12 mole) of potassium carbonate was heated for 20 hours. There was obtained 8.9 g (81%) of 1-*n*-butyl-3-hydroxypyrrolidine with the following constants: b.p. 84–

86°/3 mm, d_4^{20} 0.9425, n_D^{20} 1.4697; MR_D 42.37; calculated for $C_8H_{17}ON$ 42.41.

Found, %: C 66.80; H 12.12; N 9.88
$C_8H_{17}ON$. Calculated, %: C 67.08; H 11.96; N 9.98

Literature data: b.p. 120°/22 mm, n_D^{20} 1.4659 (^{3}).

Picrolonate of 1-*n*-butyl-3-hydroxypyrrolidine. A solution of 1.10 g (0.0077 mole) of 1-*n*-butyl-3-hydroxypyrrolidine in 30 ml of alcohol was added to a solution of 2.05 g (0.0077 mole) of picrolonic acid in 85 ml of alcohol. After 10 hr the yellow crystals that separated from the solution were filtered off and recrystallized from alcohol. 2.95 g (95%) of the picrolonate of 1-*n*-butyl-3-hydroxypyrrolidine was obtained, m.p. 167–169° (with decomposition). Bright-yellow needles. Literature data: m.p. 167.5–169.5° (with decomposition) (^{3}).

1-Benzyl-3-hydroxypyrrolidine. A mixture of 28.6 g (0.2 mole) of 1,4-dichlorobutanol, 21.4 g (0.2 mole) of benzylamine, 80 ml of abs. alcohol, and

41.4 g (0.3 mole) of potassium carbonate was heated for 25 hr. 27.8 g (79%) of 1-benzyl-3-hydroxypyrrolidine was obtained with the following constants: b.p. 138-141°/6.5 mm, d_4^{20} 1.0688, n_D^{20} 1.5528; MR_D 53.05; calculated for $C_{11}H_{15}ON$ 52.66.

Found, %:	C 74.72; H 8.77; N 7.89
$C_{11}H_{15}ON$. Calculated, %:	C 74.54; H 8.53; N 7.90

Colorless viscous liquid.

3,5-Dinitrobenzoate of 1-benzyl-3-hydroxypyrrolidine. A mixture of 3.31 g (0.019 mole) of 1-benzyl-3-hydroxypyrrolidine, 4.38 g (0.019 mole) of 3,5-dinitrobenzoyl chloride, and 8 ml of dry pyridine was heated on a boiling water bath for 15 min. To the cooled mixture was added 10% hydrochloric acid; the precipitate that separated was filtered off, washed with dilute hydrochloric acid and water, and recrystallized from methyl alcohol. 6.20 g (89%) of the 3,5-dinitrobenzoate of 1-benzyl-3-hydroxypyrrolidine was obtained, m.p. 227-228° (with decomposition). Shiny colorless needles.

Found, %:	N 11.25
$C_{18}H_{17}O_6N_3$. Calculated, %:	N 11.32

Catalytic debenzylation of 1-benzyl-3-hydroxypyrrolidine. 4.5 g (0.025 mole) of 1-benzyl-3-hydroxypyrrolidine was dissolved in 50 ml of abs. alcohol and hydrogenated at room temperature and ordinary pressure in the presence of 0.8 g of palladium oxide. Absorption of hydrogen ceased after 8 hr, 615 ml of hydrogen being absorbed (0°/760 mm). The catalyst was filtered off, the solvent was distilled off, and the residue was fractionated in vacuo. 1.9 g (86%) of 3-hydroxypyrrolidine was obtained, b.p. 102-104°/12 mm.

3-Hydroxypyrrolidine is a colorless, rather viscous liquid with a characteristic odor. Literature data: b.p. 102-103°/12 mm ([9]).

Picrolonate of 3-hydroxypyrrolidine. A solution of 0.5 g (0.0057 mole) of 3-hydroxypyrrolidine in 20 ml of alcohol was added to a solution of 1.50 g (0.0057 mole) of picrolonic acid in 40 ml of alcohol. After 10 hr the yellow crystals that separated from the solution were filtered off and recrystallized from alcohol. 1.80 g (90%) of the picrolonate of 3-hydroxypyrrolidine was obtained as yellow needles, m.p. 228-229° (with decomposition).

Found, %:	N 19.43
$C_{14}H_{17}O_6N_5$. Calculated, %:	N 19.88

Literature data: m.p. 228-230° (with decomposition) ([9]).

Preparation of 3-hydroxytetrahydrothiophene

In a flask equipped with a stirrer, dropping funnel, reflux condenser, and thermometer was placed a solution of 21.5 g (0.15 mole) of 1,4-dichlorobutanol in 200 ml of 50% alcohol. The solution was heated to 60°, and to it, with stirring, ...

with stirring over 40 min, a solution of 72 g (0.3 mole) of crystalline sodium sulfide in 100 ml of water was added. The introduction of the sodium sulfide solution was accompanied by heating of the reaction mixture, so that its temperature, without external heating, was maintained at about 60°. The reaction mixture was then heated with stirring on a boiling water bath for 4 hr. The mixture was cooled, and 20% hydrochloric acid was added to acid reaction to litmus. The alcohol was then distilled off in vacuo, and the residue was extracted repeatedly with ether. The combined ethereal solution was dried over anhydrous magnesium sulfate. The ether was distilled off, and the residue was fractionated in vacuo. This gave 11.6 g (74%) of 3-hydroxythiophane with the following constants: bp 84–85°/7 mm, d_4^{20} 1.1762, n_D^{20} 1.5427; MR_D 27.90; calculated for C_4H_8OS 28.07.

Found, %: C 46.03; H 7.68
C_4H_8OS. Calculated, %: C 46.12; H 7.74.

A rather viscous colorless liquid with a characteristic unpleasant odor.

Acetate of 3-hydroxythiophane. A mixture of 3.6 g (0.034 mole) of 3-hydroxythiophane and 7.2 g (0.092 mole) of acetyl chloride was boiled on a water bath for one hour. The excess acetyl chloride was distilled off, and the residue was distilled in vacuo. This gave 3.9 g (78%) of 3-hydroxythiophane acetate with the following constants: bp 82–83°/7 mm, d_4^{20} 1.1502, n_D^{20} 1.5003; MR_D 37.41; calculated for $C_6H_{10}O_2S$ 37.43.

Found, %: C 49.61; H 7.01
$C_6H_{10}O_2S$. Calculated, %: C 49.28; H 6.89

3,5-Dinitrobenzoate of 3-hydroxythiophane. A mixture of 2.07 g (0.02 mole) of 3-hydroxythiophane, 4.61 g (0.02 mole) of 3,5-dinitrobenzoyl chloride, and 8 ml of dry pyridine was heated on a boiling water bath for 15 min. The mixture was cooled, and 10% hydrochloric acid was added. The precipitate that separated was filtered off, washed with dilute hydrochloric acid and water, and recrystallized from methyl alcohol. This gave 5.7 g (95%) of 3-hydroxythiophane 3,5-dinitrobenzoate as lustrous plates with mp 121–121.5°.

Found, %: N 9.65
$C_{11}H_{10}O_6N_2S$. Calculated, %: N 9.39

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Note: Figure translations are in progress. See original paper for figures.