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2-Hydroxyhistamine and 2-Methoxyhistamine, their Synthesis and Certain Properties

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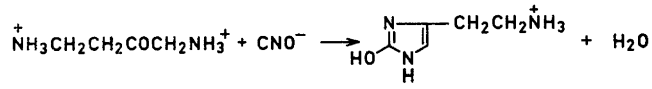
1. An improved method for the preparation of 1,4-diaminobutan-2-one dihydrochloride from histamine is described.
2. 2-Hydroxyhistamine hydrochloride has been obtained in about 65 % yield by reacting 1,4-diamino-butan-2-one with cyanate at pH 5 and 20°. 2-Methoxyhistamine dihydrochloride has been prepared from methyl(iso)cyanate in a similar manner.
3. Preliminary results from an investigation of the tautomeric properties of 2-hydroxyhistamine are presented.

Although a large number of derivatives of histamine are known (see, *e.g.* Ref. 1), 2-hydroxyhistamine appears not to have been synthesized.

The introduction of a hydroxy group into aromatic, physiologically active amines causes, in some cases, marked changes in the physiological properties of the parent compounds, for example, in tryptamine. 2-Hydroxyhistamine would therefore be expected to be of potential pharmacological interest. This compound has now been synthesized and a preliminary investigation of its properties has been undertaken.

Of the possible synthetic routes for the preparation of substituted imidazole rings, the condensation of a ketodiamine with cyanate was chosen for the synthesis of 2-hydroxyhistamine:[2]



Although this type of condensation is normally a simple one, several difficulties were encountered in this case. A successful synthesis was attained, however, but only under rigidly controlled conditions.

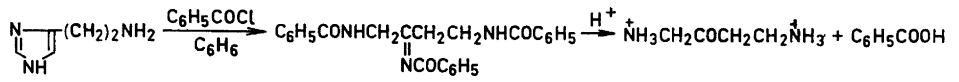
Preparation of 1,4-diamino-butan-2-one. Several methods for the synthesis of this compound have already been reported, and two published paths for its preparation have been investigated during these studies. Fraser and Raphael [3] recently described the preparation of 1,4-diamino-butan-2-one from commercially available but-2-yne-1,4-diol:

$$HOCH_2C{\equiv}CCH_2OH \xrightarrow[2.\ C_6H_4(CO)_2NK]{1.\ SOCl_2} C_6H_4(CO)_2NH_2CC{\equiv}CCH_2N(CO)_2C_6H_4 \xrightarrow{Hg^{2+}}$$

$$\rightarrow C_6H_4(CO)_2NCH_2COCH_2CH_2N(CO)_2C_6H_4 \xrightarrow{HCl} \overset{+}{N}H_3CH_2COCH_2CH_2\overset{+}{N}H_3$$

This method is claimed by the authors to give a high yield. The use of the above procedure in this laboratory on a larger scale than that originally reported resulted in considerably lowered yields. Also, the method is very time-consuming. The most serious drawback is, however, that the last step involving the hydrolysis of the phthalimido compound does not proceed smoothly and that only a relatively low yield of pure diaminoketone could be obtained.

A more convenient method for the preparation of the diamino-ketone on a laboratory scale is to use histamine as a starting material.[4,5] Upon benzoylation, the imidazole ring is cleaved and the resulting benzoyl derivative can easily be hydrolyzed to the desired amino-ketone. Several improvements of this method were made during the present investigation. For instance,



the presence of benzene in the benzoylation step greatly accelerates the rate of benzoylation of histamine, partly by causing a more effective emulsification of the benzoyl chloride layer in the water phase during agitation, partly by slightly dissolving histamine. The benzoylation reaction appears to occur mainly in the benzene droplets.

The condensation step. In the preliminary report,[2] a pH of 7.0 was chosen for the condensation between 1,4-diamino-butan-2-one and potassium cyanate. Paper chromatographic investigations later revealed that the reaction is faster in slightly acidic solution and a pH of 5.0 was found suitable. In more acidic solution there is a considerable decomposition of cyanic acid resulting in a lower yield of 2-hydroxyhistamine.

In addition to greater speed, fewer by-products are formed at pH 5.0 than at pH 7.0.

The best molar ratio cyanate/1,4-diamino-butan-2-one was found to be slightly above 1. Paper chromatography showed that some diamine was left unreacted under these circumstances. An increase of the amount of cyanate caused all the diamine to react but at the same time the yield of 2-hydroxyhistamine was lowered, due to the carbamylation of the aminoethyl group.

Isolation of 2-hydroxyhistamine from the reaction mixture. The isolation of pure 2-hydroxyhistamine hydrochloride from the reaction mixture proved to be a difficult task. The compound readily dissolves in water, and attempted precipitation procedures with the use of organic solvents constantly yielded products that were contaminated by inorganic salts. No solvent was found that was suitable for recrystallisation of 2-hydroxyhistamine hydrochloride. The compound is not absorbed on Dowex 2 (OH^-), nor is it quantitatively absorbed on weakly acidic ion exchange resins like Amberlite IRC 50 (H^+). It could not be separated from sodium and potassium ions by the use of Dowex 50 (H^+). Attempts were also made to extract the free form of 2-hydroxy-

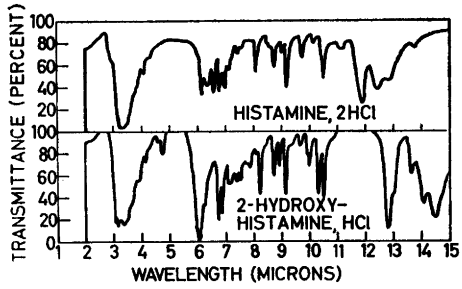


Fig. 1. Infra-red absorption spectra of histamine dihydrochloride and 2-hydroxyhistamine hydrochloride (KBr pellets).

histamine with organic solvents. The partition coefficient is not favorable, for instance, with butanol.

The method finally adopted consisted of isolation of the 2-hydroxyhistamine as a picrate followed by decomposition on Dowex 1 (Cl^-). This resin absorbs the picrate ion quantitatively whereas 2-hydroxyhistamine passes through as the hydrochloride salt.

Synthesis of 2-methoxyhistamine. This compound was prepared by the action of methyl(iso)cyanate (prepared *in situ* from methyl iodide and silver cyanate) on 1,4-diamino-butan-2-one. No attempt has as yet been made to determine optimal conditions for this reaction.

Tautomeric properties of 2-hydroxyhistamine. The infrared spectrum of the compound herein designated 2-hydroxyhistamine shows absorption peaks at 3.06 and 3.14 μ, which are probably due to NH absorption from the —NHCONH— grouping of the tautomer 4(5)-aminoethyl-2(3H)-imidazolone. This is supported by the fact that *sym*-diphenyl urea also shows this absorption. Furthermore strong carbonyl stretching absorption occurs at 6.05 μ. (Fig. 1).

However, the spectrum also shows relatively strong absorption at 7.52 and 8.23 μ indicating the presence of phenolic hydroxyl groups. These bands are lacking in the infra-red spectra of histamine dihydrochloride and 2-methoxyhistamine dihydrochloride.

At present it is difficult to judge which tautomeric form of the compound is the predominating one. However, preliminary nuclear magnetic resonance studies indicate that it is the enolic form.

EXPERIMENTAL

Paper chromatography was carried out using Whatman No. 1 paper and 2-propanol:conc. ammonia (8:2) as the solvent. After drying the papers were sprayed with a fresh solution of Echtblausalz B, (4,4′-bis(2-methoxybenzenediazonium chloride), Merck Co.), 0.1 % in water. 2-Hydroxyhistamine gives almost immediately a red spot at $R_F = 0.45$.

2-Benzoylimino-1,4-dibenzamido-butane. 30 g (0.2 mole) of histamine dihydrochloride was added to an ice cold solution of 114 g (2.85 mole) of sodium hydroxide in 750 ml of water. 150 ml of benzene and 150 ml (1.3 mole) of benzoylchloride were added. The reaction mixture was vigorously stirred for 4 h, with cooling on an ice bath. The mixture was filtered, and the precipitate was washed with water. Yield 83.8 g (100 %), m.p. 188—190°. (Ref. 4 gives m.p. 191°).

1,4-Dibenzamido-butan-2-one. 82.0 g of 2-benzoylimino-1,4-dibenzamido-butane were refluxed in a mixture of 1350 ml of ethanol and 150 ml of conc. hydrochloric acid for

2.3 h. The solution was evaporated to about 150 ml and poured into 3000 ml of water. The precipitate was filtered off and was washed with water and then ether. Yield 37.9 (63 %), m.p. 156–157°. (Ref. 4 gives m.p. 158–159°).

2,4-Diamino-butan-2-one dihydrochloride. 37.9 g of 1,4-dibenzamido-butan-2-one were refluxed in 300 ml of conc. hydrochloric acid for 3 h, after which time another 120 ml of conc. hydrochloric acid were added. The refluxing was continued for 2 h and the solution was evaporated to dryness in vacuum in a rotating evaporator (bath temperature about 50°). The substance was thoroughly washed with ether and then acetone. Yield: 17.2 g (81 %), m.p. 222–223° (Ref. 4 gives m.p. 221°). (Found: N 16.2; Cl 39.9. Calc. for $NH_2CH_2CH_2COCH_2NH_2,2HCl$ (175): N 16.0; Cl 40.6).

2-Hydroxyhistamine. 0.87 g (5 mmole) of 2,4-amino-butan-2-one dihydrochloride was dissolved in 15 ml of water. The solution was adjusted to pH 5.0 with 1 M sodium hydroxide. 0.47 g (5.75 mmole) of potassium cyanate dissolved in 10 ml of water was added, followed by 1 M acetic acid to pH 5.0. The solution was stirred for 3 h and then 1.72 g (7.5 mmole) of picric acid was dissolved therein with warming. The picrate that precipitated upon cooling was recrystallized from 20 ml of water. 1.90–2.02 g of picrate, m.p. 205–215° (decomp.), was obtained. Elementary analysis indicated it to be a mixture of the mono- and dipicrates of 2-hydroxyhistamine. The picrate was dissolved in boiling water and passed through a column of Dowex 1 (Cl^-), 50–100 Mesh, (about 1.8 × 25 cm²) while still hot. The column was washed with hot water until the effluent was free of substance diazotizable with Echtblausalz B. The solution of 2-hydroxyhistamine hydrochloride was evaporated to dryness in vacuum in a rotating evaporator (bath temperature about 50°). Brown impurities were removed by slurrying the substance with 20 ml of methanol for 30 min. After filtration 0.51–0.54 g (62–66 %) of 2-hydroxyhistamine hydrochloride, decomposing at 227–230° was obtained. (Found: C 36.9; H 6.1; N 25.8. Calc. for $C_6H_{10}N_3ClO$ (163.6): C 36.8; H 6.1; N 25.7).

2-Methoxyhistamine. To a stirred suspension of silver cyanate (3.0 g, 20 mmole) in 20 ml of dimethyl formamide was added 1.5 ml (28 mmole) of methyl iodide. The mixture was stirred at 20° for 30 min, and then 3.5 g (20 mmole) of 1,4-diamino-butan-2-one dihydrochloride and 10 ml of water were added. After 2 h of stirring at 20°, an additional 60 ml of water was added and the precipitated silver iodide was filtered off.

To the remaining solution 13.6 g (60 mmole) of picric acid were added and the mixture was heated to boiling. The solution was allowed to cool slowly and the precipitate was recrystallized once from water.

The picrate (4.8 g, m.p. 207–208°) was dissolved in boiling water and passed through a column (1.5 × 35 cm²) of Dowex 1 (Cl^-), that previously had been treated with hot water. The column was washed with hot water until the eluate was free of diazotizable substance. The effluent was evaporated to dryness in a rotating vacuum dryer using a bath temperature of about 50°. Brown impurities were removed by slurrying with 30 ml methanol for 1 h. 0.85 g (17 %) of 2-methoxyhistamine dihydrochloride dihydrate, m.p. 208–210° (decomp.), were thus obtained. (Found: C 28.5; H 6.7; N 16.6; Cl 28.1. Calc for $C_6H_{11}N_3O,2HCl,2H_2O$ (250.1): C 28.8; H 6.8; N 16.8; Cl 28.3).

Addendum. Recently Keller *et al.*[6] state that they have obtained 4-β-aminoethyl-2-imidazolone hydrochloride, m.p. 255°, by heating 1,4-diamino-butan-2-one dihydrochloride with potassium cyanate. Experimental details (or the yield) were not given. The compound mentioned by these authors is obviously not identical with the one described in this paper; (m.p. 227–230° decomp.).

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