Arch. Pharm. (Weinheim) *316*, 688–690 (1983)

Synthesis of Cimetidine

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Eingegangen am 6. Juli 1982

A simple and economical synthesis of cimetidine is described. It is based on the reaction of 4-halomethyl-5-methylimidazole with *N*-cyano-*N'*-methyl-*N''*-(2-mercaptoethyl)guanidine in water-ethanol at pH 9.0 ± 0.3. Pure crystalline cimetidine is obtained in about 75 % yield.

Synthese von Cimetidin

Eine einfache und ökonomische Synthese von Cimetidin wird beschrieben. Die Synthese basiert auf der Reaktion von 4-Halomethyl-5-methylimidazol mit N-Cyano-N'-methyl-N''-(2-mercaptoethyl)guanidin in verd. Methanol bei pH 9,0 ± 0,3. Reines, kristallines Cimetidin wird in einer Ausbeute von etwa 75 % erhalten.

Several methods have been described in the patent literature[1–6] for the synthesis of cimetidine **(3)**, a new H_2-receptor antagonist used for the treatment of duodenal ulcer. These methods[4–6], which are based on the reaction of 4-chloromethyl-5-methylimidazole **(1a)** with N-cyano-N'-methyl-N''-(2-mercaptoethyl)guanidine **(2)**, are, however, of no practical value for the production of cimetidine on an industrial scale, because they require tedious solvent evaporations and several crystallizations and/or chromatographic purification procedures. This reaction has been carried out in dry organic solvents, such as ethanol[4], DMF[5] or DMSO[6], in the presence of sodium ethoxide.

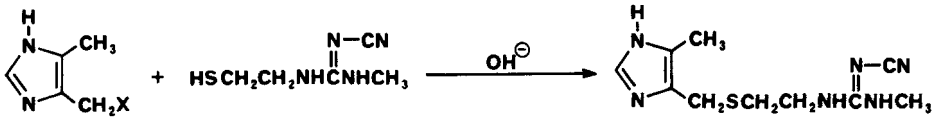
We have found by TLC that, besides cimetidine, varying amounts of impurities are formed in this reaction. Generally, crude cimetidine is obtained as a semisolid mass which is difficult to crystallize. We found unexpectedly that pure crystalline cimetidine is formed in a simple way if 4-halomethyl-5-methyl-imidazole (**1a** or **1b**) is reacted with **2** in water or in an aqueous medium at a strictly controlled pH of 9.0 ± 0.3 at room temperature. It is unnecessary to isolate the extremely readily oxidized intermediate **2**, and the solution can be used immediately for reaction with **1**.

Pure cimetidine crystallizes slowly out of the reaction mixture on cooling, giving a good yield (about 75 %). A mixture of water-methanol (5:1) was found to be the best solvent in this reaction. Most of the impurities remain in the mother liquor. In basic conditions the compounds **1a** and **1b** are very unstable and hydrolyze rapidly into 4-hydroxymethyl-5-methylimidazole. But at pH 9.0 the velocity of the reaction of **1a** or **1b** with the thiol anion of **2** is considerably faster than with a hydroxide ion. However, small amounts of 4-hydroxymethyl-5-methylimidazole are found in the crude product in addition to the disulfide of **2**. These impurities can easily be removed by dissolving the crude product in an equal amount of dilute hydrochloric or acetic acid at pH 5.5.–6.0, treating the solution with

0365-6233/83/0808–0688 $ 02.50/0

charcoal and adding concentrated ammonia (or sodium hydroxide) to the filtrate to reach pH 9.0, whereupon very pure crystalline cimetidine is obtained.

The method presented here offers an easy and economical alternative for the production of cimetidine on an industrial scale.



1a : X = Cl **2** **3**
1b : X = Br

Experimental part

MP: Kofler block, uncorr. *Elemental analyses:* Mikroanalytisches Laboratorium, West Germany, by Dr. Ilse Beetz. *^{1}H-NMR spectra:* Perkin Elmer R 12A spectrometer, TMS int. stand.

4-Chloromethyl-5-methylimidazole hydrochloride (1a)

To a boiling suspension of 148.5 g (1 mole) 4-hydroxymethyl-5-methylimidazole hydrochloride in 450 ml 99.5 % ethanol, 220 ml (3 moles) thionylchloride was added gradually. The mixture was refluxed for 1 h and cooled to –5 to –10 °C for 20 h. The product was washed with cold ethanol and dried. Yield 134 g (82 %), mp 218–220 °C. $C_5H_8Cl_2N_2$ (167.05) Calcd. C 35.9 H 4.83 Cl 42.4 N 16.8 Found C 36.1 H 4.95 Cl 42.2 N 16.6. ^{1}1H-NMR ($CDCl_3$/DMSO-d_6): δ (ppm) = 2.40 (s, 3H); 4.83 (s, 2H); 9.00 (s, 1H); 13.8 (2H).

4-Bromomethyl-5-methylimidazole hydrobromide (1b)

A mixture of 82 g (1 mole) 5-methylimidazole and 35 g paraformaldehyde in 1000 ml 48 % hydrobromic acid was refluxed for 1 h. The solution was evaporated under reduced pressure and the residue crystallized from ethanol. Yield 245 g (96 %), mp 200–204 °C. $C_5H_8Br_2N_2$ (255.97) Calcd. C 23.5 H 3.15 Br 62.4 N 10.9 Found C 23.3 H 3.25 Br 62.2 N 11.1. ^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ (ppm) = 2.35 (s, 3H); 4.73 (s, 2H); 9.15 (s, 1H); 13.9 (2H).

N-Cyano-N'-methyl-N''-(2-mercaptoethyl)guanidine (2)

A solution of 102 g (0.9 mole) cysteamine hydrochloride, 116 g (0.9 mole) N-cyano-N,S-dimethyl-isothiourea, 200 ml methanol, and 144 g (1.8 moles) 50 % NaOH in 700 ml water was refluxed for 1 h under nitrogen. The solution was used immediately for the next step.

N-Cyano-N'-methyl-N''-2-(5-methyl-4-imidazolylmethyl-thio)ethylguanidine-cimetidine (3)

The above solution containing about 0.9 mole of N-cyano-N'-methyl-N''-(2-mercaptoethyl) guanidine was cooled to 20 °C and the pH adjusted to 9.0 with conc. hydrochloric acid. To this solution was added a solution containing 150 g (0.9 mole) 4-chloromethyl-5-methylimidazole hydrochloride (or 230 g of 4-bromomethyl-5-methylimidazole hydrobromide) and 30 ml of conc. hydrochloric acid in 120 ml water with stirring at room temp. under nitrogen. During the addition, the pH of the solution was adjusted to 9.0 ± 0.3 with 50 % NaOH (a total of about 144 g). After addition, the solution was seeded with cimetidine crystals and stirred for 20 h at 0 °C. The crystalline product was washed with cold water and dried. Yield 170 g (75 %), mp 141–143 °C.

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Arch. Pharm. (Weinheim) *316,* 690–694 (1983)

Some New Piperazino Derivatives as Antiparkinson and Anticonvulsant Agents

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Eingegangen am 6. Juli 1982

The piperazino derivatives **1–7** were synthesized and evaluated for their antiparkinson activity on oxotremorine-induced tremors and reserpine-induced rigidity. The same compounds were screened for their anticonvulsant activity. Compounds **1, 3, 4** and **5** showed promising antiparkinson activity. Maximum activity (10 mg/kg i.p.) was exhibited by compound **3**. Its antiparkinson profile is better than that of L-dopa (100 mg/kg i.p.) and that of bromocriptine (10 mg/kg i.p.). Compounds **2, 3** and **4** were 90, 80 and 80 % protective against MES.

Einige neue Piperazin-Derivate als Antiparkinsonmittel und als Antikonvulsiva

Die Piperazin-Derivate **1–7** wurden synthetisiert und auf ihre Antiparkinson-Aktivität gegenüber einem oxotremorininduzierten Tremor und reserpininduzierter Starrheit geprüft. Diese Verbindungen wurden auch auf ihre anticonvulsive Wirkung geprüft. Die Verbindungen **1, 3, 4** und **5** der Serie haben eine vielversprechende Antiparkinson-Aktivität. Die Verbindung **3** hat die größte Aktivität (10 mg/kg i.p.). Ihre Antiparkinson-Aktivität ist besser als die von L-dopa (100 mg/kg i.p.) und Bromocriptin (10 mg/kg i.p.). Die Verbindungen **2, 3** und **4** zeigten 90, 80 und 80 % Schutz vor Elektroschock.

Piperazine derivatives, besides other CNS activities, also possess marked antiparkinsonian activity[1–6]. Amino acids are the precursors of the biogenic amines and are beneficial in the therapy of parkinsonism[7–10]. In our search for antiparkinsonian compounds, it was thought worthwhile to synthesize some new piperazino derivatives of amino acids and to evaluate them for their antiparkinsonian, anticonvulsant and other CNS activities.

0365-6233/83/0808-0690 $ 02.50/0