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THE SYNTHESIS OF ZAPOTIDINE

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Abstract—A three step synthesis of the alkaloid zapotidine (I) is described. Histamine (II) was cyclized to imidazo[1,5-c]tetrahydropyrimidine-5-one (III) with carbonyl diimidazole. LAH reduction of III gave N^{α}-methylhistamine (IV), which was cyclized with thiocarbonyl diimidazole to I.

ZAPOTIDINE (I), one of the few known sulfur-containing alkaloids, is a minor constituent of the seeds of the Mexican tree *Casimiroa edulis* La Llave *et* Lej. (Rutaceae). It was isolated in 0·0014% yield by Kincl *et al.*[1] in 1956 and its structure was determined by Mechoulam *et al.*[2] in 1961. Zapotidine is unusual in several respects. It possesses a ring system that has not been encountered previously in a natural product and moreover it is exceedingly rare for a thiourea derivative to occur in Nature.[3]

The constituents of *C. edulis* are of pharmacological interest. In 1651 Francisco Hernandez[4] reported that the fruit known as Zapote blanco (meaning "white fruit") possessed hypnotic properties and was toxic. This claim has been refuted;[5] later publications have indicated however that the seeds are indeed hypnotic, sedative and hypotensive. The low yield in which zapotidine has been isolated from the plant has precluded a pharmacological investigation.

In view of the unusual structure and possible pharmacological activity it seemed of interest to synthesize zapotidine.

A number of synthetic routes leading to a suitable imidazotetrahydropyrimidine system can be envisaged. We decided on the approach described in this paper for the following reasons.

(a) Zapotidine can be viewed as a N^{α}-methylhistamine derivative in which the nitrogen on the side chain and one of the ring nitrogens has been joined through a thiocarbonyl bridge. This is not an arbitrary dissection of the molecule. Within the Rutaceae numerous species contain imidazole alkaloids.[7] Moreover, in *C. edulis* itself two additional alkaloids are derived from histamine: N^{α}, N^{α}-dimethylhistamine (V)[8]

[1] F. A. Kincl, J. Romo, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4163 (1956).
[2] R. Mechoulam, F. Sondheimer, A. Melera and F. A. Kincl, *J. Amer. Chem. Soc.* **83**, 2022 (1961).
[3] See M. G. Ettlinger and J. E. Hodgkins, *J. Org. Chem.* **21**, 204 (1956).
[4] F. Hernandez, *Rerum medicarum Novae Hispaniae thesaurus*, Lib III; p. 89. Rome Italy (1651).
[5] F. B. Power and T. Callan, *J. Chem. Soc.* **99**, 1993 (1911); *Proc. Chem. Soc.* **27**, 257 (1911); *Pharm. J.* **87**, 623 (1911).
[6] J. de Lille, *An. Inst. Biol., Mex.* **5**, 45 (1934); E. Ramirez and M. D. Rivero, *Rev. Mensual Med., Mex.* **9**, 1 (1936); *Farmacopea Mexicana* (6th Edition) p. 423 (1952); See also J. F. Morton, *Econ. Bot.* **16**, 288 (1962).
[7] H. G. Boit, *Ergebnisse der Alkaloid-Chemie bis* 1960 p. 750. Akademie-Verlag, Berlin (1961); J. R. Price in *Chemical Plant Taxonomy* (Edited by T. Swain) p. 429. Academic Press, London (1963).
[8] R. T. Major and F. Dursch, *J. Org. Chem.* **23**, 1564 (1958); J. S. L. Ling, S. Y. Pan and F. A. Hochstein, *J. Pharmacol. Exptl. Ther.* **122**, 44 A (1958).

and casimiroedine (VI).[9] It has been suggested that zapotidine might arise by cyclization of a hypothetical histamine-derived isothiocyanate (VII), followed by methylation.[10] Although ring closures of this type are yet unprecedented in naturally derived compounds, closely related cyclizations, such as the formation of the antithyroid factor goitrin, (—) 5-vinyl-2-oxazolidinethione (VIII) from the isothiocyanate IX, have been repeatedly observed.[11]

(b) From a practical point of view, it is simpler to start from an imidazole ring and to attach it to a tetrahydropyrimidine ring than *vice versa*.

Therefore, both on practical grounds and from a desire to follow (in a very general way) the suggested natural route we chose the following synthetic scheme: The reaction between histamine (II) and carbonyl diimidazole[12] gave imidazo[1,5-c]-tetrahydropyrimidine-5-one (III) m.p. 218–219°, in 60% yield. Compound III has previously been prepared by Schlögl[13] via a different route. Reduction of III with LAH in tetrahydrofuran gave N^{α}-methylhistamine (IV)[2,13,14] in 62% yield. This reaction is a modification of a published procedure.[13] The dipicrate of IV was identified (mixture m.p., IR comparison) with the dipicrates of authentic samples prepared both by degradation of zapotidine[2] and by a previously described, considerably less facile synthesis.[14] The reaction between N^{α}-methylhistamine (IV) and thiocarbonyl diimidazole[15] gave zapotidine in 60% yield. The synthetic zapotidine was identical with the natural product.

The reaction between N^{α}-methylhistamine and carbonyl diimidazole yielded the urea derivative (X), which was shown to be identical (mixture m.p., IR comparison) with the same compound obtained from zapotidine upon boiling with ethanolic silver nitrate solution with gradual addition of aqueous sodium hydroxide.[2]

Preliminary pharmacological tests have shown that zapotidine is toxic (L.D. 50 in mice ca. 50 mg/kg on intraperitoneal administration). No effect on the autonomic nervous system was noted. Central nervous system effects were observed near the toxic level of the compound, and therefore it is not planned to investigate the nature of these effects further. Zapotidine failed to show *in vitro* action against *Strep. pyogenes*, *Staph. aureus*, *Protens mirabilis*, *Pseud. aeroginosa*, *Salm. typhimurium* and *M. tuberculosis*.[16]

[9] C. D. Djerassi, C. Bankiewicz, A. L. Kapoor and B. Riniker, *Tetrahedron* **2**, 168a (1958); S. Raman, J. Reddy, W. N. Lipscomb, A. L. Kapoor and C. Djerassi, *Tetrahedron Letters* 357 (1962); S. Raman, J. Reddy and W. N. Lipscomb, *Acta Cryst.* **16**, 364 (1963).

[10] This suggestion was made to us by Professor A. Kjær, The Royal Veterinary and Agricultural College, Copenhagen, to whom we would like to express our thanks. He has also pointed out, however, that the failure to recognize isothiocyanate-producing glucosides in *C. edulis* makes this hypothesis rather tenuous.

[11] A. Kjær, R. Gmelin and R. B. Jensen, *Acta Chem. Scand.* **10**, 432 (1956); O. E. Schultz and W. Wagner, *Arch. Pharmaz.* **289**/61 597 (1956). For a review see A. Kjær in *Fortschritte der Chemie Organischer Naturstoffe* (Edited by L. Zechmiester) Vol. 18; p. 123 (1960).

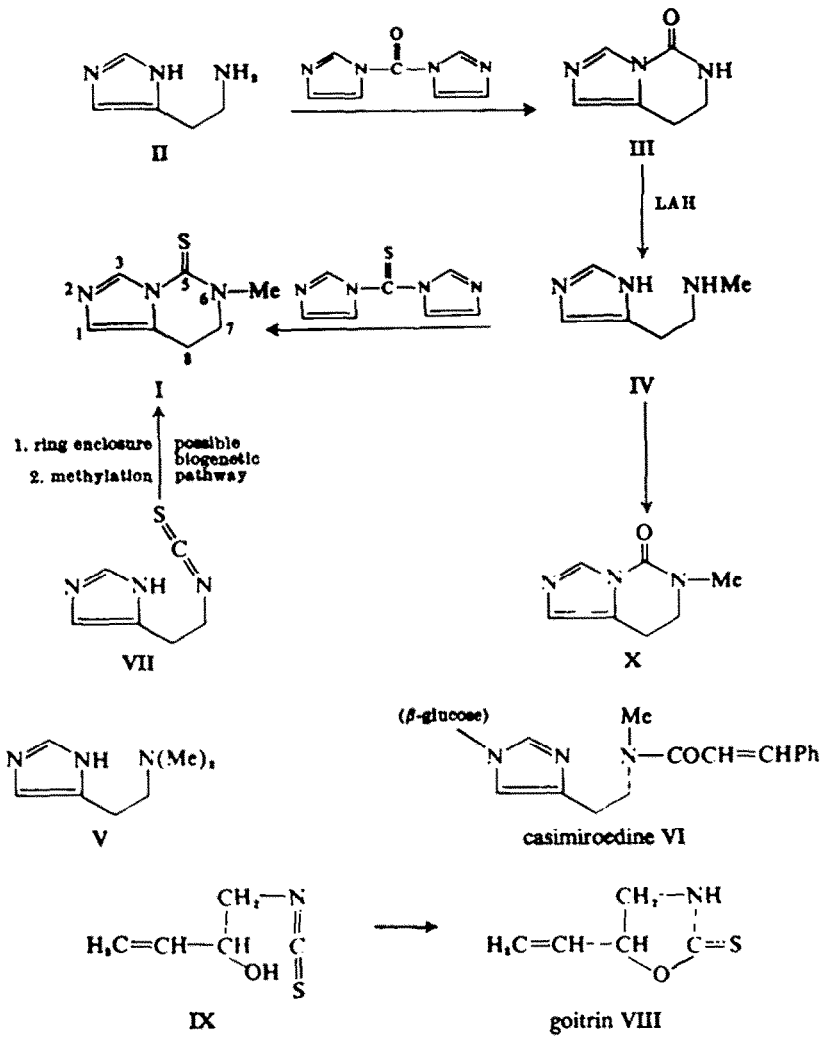
[12] H. A. Staab, *Liebigs Ann.* **609**, 75 (1957).

[13] K. Schlögl and H. Woidich, *Monatsh.* **87**, 679 (1956).

[14] B. Garforth and F. L. Pyman, *J. Chem. Soc.* 489 (1935).

[15] H. A. Staab and K. Wendel, *Angew. Chem.* **73**, 26 (1961); W. Ried and B. M. Beck, *Liebigs Ann.* **646**, 96 (1961); H. A. Staab and G. Walther, *Ibid.* **657**, 98 (1962); E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.* **85**, 2677 (1963).

[16] The pharmacological tests were done by the staff of the Research Laboratories, Parke, Davis & Co., Ann Arbor, Michigan, to whom we would like to express our thanks.



EXPERIMENTAL

Imidazo[1,5-c]*tetrahydropyrimidine-5-one*(III). An intimate mixture of histamine (1 g) and carbonyl diimidazole (2 g) was heated slowly to 120°. After the mixture had melted, crystals began to separate from the sol. The mixture was stirred for 1 hr at 100°. The imidazole obtained from the reacted carbonyl diimidazole was removed by sublimation from the solid mixture at 70°/1 mm. The residue was crystallized from EtOH giving 518 mg of III, m.p. 218–219°. From the mother liquors an additional 220 mg of slightly less pure material, m.p. 210–214° were obtained, total yield: 60%. The UV and IR data are identical with those reported for the same compound, m.p. 221–222°, prepared via a different route. The NMR spectrum in $(CD_3)_2SO$ + $CDCl_3$) showed peaks at 7·9 ppm (C-3 proton), 6·75 ppm (C-1 proton), 3·35 ppm (C-7 protons), and 2·85 ppm (C-8 protons). This spectrum is very similar to that reported for the corresponding N-methyl compound X[3].

N^{α}-*methylhistamine* (IV). The method described is a modification of the one used by Schlögl.[18] Compound III (411 mg) was added to a suspension of LAH (400 mg) in dry THF (25 ml). The reaction mixture was boiled under reflux for 2 hr. The excess reagent was destroyed with AcOEt and then sat Na_2SO_4aq was added. The clear sol obtained was filtered from the solid residue and evaporated. A portion of the oil obtained (233 mg; yield, 62%) was used for the preparation of a

crystalline dipicrate, m.p. 187–188°, identical (mixture m.p. IR comparison) with an authentic sample (m.p. 187–180°).[3,4] The oily N^{α}-methylhistamin was used in the next step without further purification.

Zapotidine (I)

Thiocarbonyl diimidazole (350 mg) was added to a sol of N^{α}-methylhistamin (210 mg) in THF. The reaction was left overnight and the THF was decanted from a small amount of oily residue. The THF was evaporated and the material obtained was dissolved in ether and water. The ester sol was concentrated and the crystals obtained were recrystallized from ether giving 155 mg zapotidine which was identified (mixture m.p., IR comparsion) with an authentic sample.

6-*Methylimidazo*[1,5-c]*tetrahydropyrimidine-5-one* (X). N^{α}-methylhistamine (1 g) and carbonyl diimidazol (1 g) in THF (30 ml) were left overnight. The solvent was evaporated and the oily residue was dissolved in chf and water. The water layer was extracted 5 times with chf, which was then dried and evaporated. The residue was crystallized with ether giving 720 mg X (60% yield), identified (mixture m.p., IR comparison) with an authentic sample.[5]