Tetrahedron Letters No. 9, pp. 357-360, 1962. Pergamon Press Ltd. Printed in Great Britain.

STRUCTURE OF THE ALKALOID CASIMIROEDINE

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(Received 31 March 1962)

CASIMIROEDINE[1] ($C_{21}H_{27}N_3O_6$)[2,3] has been shown[4] to contain the N-cinnamoyl-N-methyl histamine moiety attached to a $C_6H_{10}O_5$ fragment which contains four acylable hydroxyl groups[2,3] and is probably a sugar.[4] The base casimidine ($C_{12}H_{21}N_3O_5$), of which casimiroedine is either the _trans_ or _cis_ cinnamic acid amide, contains this $C_6H_{10}O_5$ fragment and the N-methyl histamine residue. We report jointly here the results of a further organic chemical study of casimidine and a single-crystal X-ray diffraction study of the dihydrochloride of casimidine.

The chemical evidence in addition to that previously reported was obtained by acetylation (acetic anhydride-pyridine, assumed to acetylate

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* The X-ray studies were supported by the National Institutes of Health and the Air Force Office of Scientific Research. We also thank Dr. Yoshiro Kainuma, Mr. Paul Simpson and Mr. Robert Dobrott for assistance with the experiments and computations.

** The organic chemical studies (part XXXIV in the series "Alkaloid Studies") were performed at Wayne State University under Grant No. H-2574 from the National Heart Institute of the National Institutes of Health.

[1] F.B. Power and T. Callan, _J. Chem. Soc._ 1993 (1911).

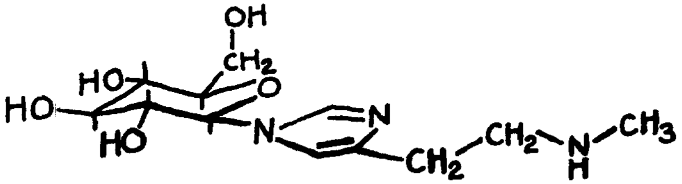
[2] A. Aebi, _Helv. Chim. Acta_ **39**, 1495 (1956).

[3] C. Djerassi, J. Herrán, H.N. Khastgir, B. Riniker and J. Romo, _J. Org. Chem._ **21**, 1510 (1956).

[4] C. Djerassi, C. Bankiewicz, A.L. Kapoor and B. Riniker, _Tetrahedron_ **2**, 168a (1958).

completely) of casimidine at 25° followed by cleavage for 1.5 hr at 40° in a solution of 7 parts of 40 per cent aqueous hydrobromic acid to 3 parts of acetic acid and 5 parts of methylene chloride. The resulting bromo sugar was extracted with methylene chloride and then hydrolysed with silver carbonate.[5] Acetylation of the crude product and chromatography gave 28 per cent of β-D-glucose penta-acetate [m.p. 130°-131°, $[\alpha]_D^{25}$ + 3° ($CHCl_3$)], which was shown to be identical with an authentic sample by comparison of mixture melting point, infrared spectral and X-ray powder diffraction data. These conditions, which are assumed not to alter the identity of the sugar residue as glucose, suggest an N-glycoside linkage, but leave open the three questions of the configuration of the anomeric center (α vs. β), a five- vs. a six-membered sugar ring, and which nitrogen of the histamine ring is bonded to the sugar. Thus the organic chemical evidence shows that casimiroedine is one of a number of possible N-D-glucosides of N-cinnamoyl-N-methylhistamine.

The crystallographic study of casimidine dihydrochloride established independently the glucose residue, except for absolute configuration, and showed further that β-glucose, having all 5 H atoms of the six-membered ring in the axial configuration, is attached by an equatorial bond to the histamine ring at the N atom further from the $CH_2CH_2NHCH_3$ group.



The dihydrochloride has the space group $\underline{P}2_12_12_1$, and unit cell dimensions $\underline{a}$ = 27.81, $\underline{b}$ = 10.76 and $\underline{c}$ = 5.76 A. The readily located Cl atoms, which

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[5] See B.R. Baker, J.P. Joseph and R.E. Schaub, J. Amer. Chem. Soc. 77, 5905 (1955).

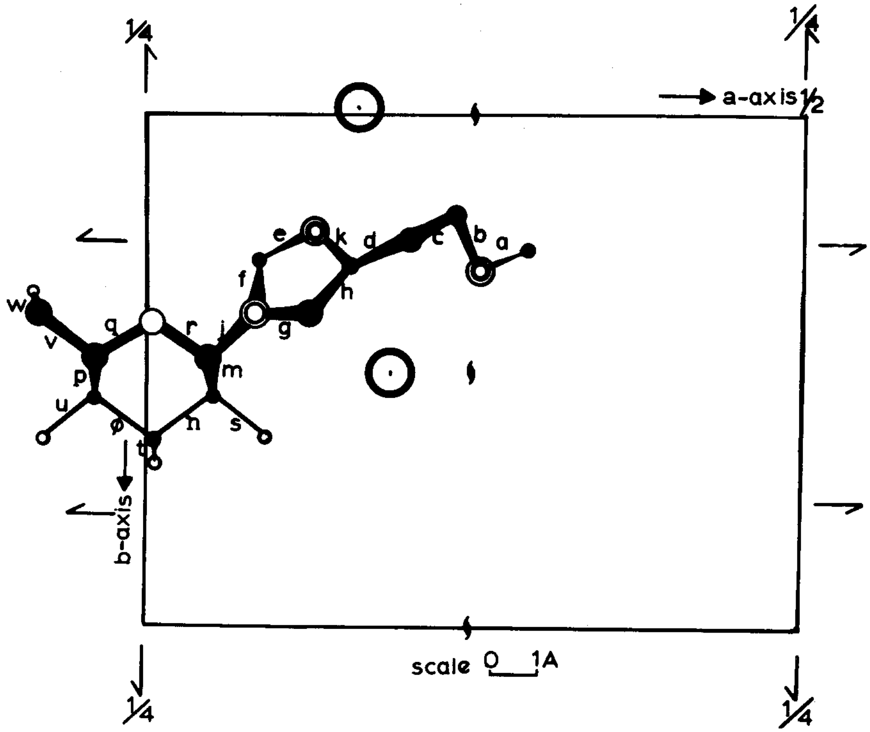

FIG. 1

Relation of one $C_{12}H_{23}N_3O_5^{+2}.2Cl^-$ to symmetry elements of the unit cell. Bond distances are a = 1.53, b = 1.52, c = 1.49, d = 1.51, e = 1.35, f = 1.39, g = 1.40, h = 1.34, i = 1.41, k = 1.40, m = 1.48, n = 1.53, ø = 1.58, p = 1.58, q = 1.46, r = 1.43, s = 1.43, t = 1.46, u = 1.37, v = 1.48 and w = 1.41 Å, all ± 0.03 to 0.04 Å. Bond angles characterizing the histamine ring are gi = 128°, fi = 124°, gf = 108° about a planar N, and ef = 105°, ek = 113°, hk = 104°, gh = 111°, dk = 120° and dh = 136°. Largest circles are Cl, single circles are O, double circles are N and solid circles are C atoms. The z coordinates are 0.817 and 0.814 (center of Fig. 1) for Cl atoms, 0.025 for N of the NMe, 0.100 for the NH^+ of the ring, 0.185 for the N attached to β-glucose and 0.169 for the O of the β-glucose ring.

unfortunately form a very nearly centrosymmetric array, were of little help in the structure determination. Chemical assumptions which were made in the discovery of the correct trial structure were atoms of equal scattering power in expected geometries of C,N or O atoms of N-methylhistamine and only the six atoms of the chair-like ring of the sugar residue. All other atoms, including most H atoms, as well as the chemical identity of all C,N and O atoms were found from the X-ray data without chemical assumptions. The final agreement factor, $\underline{R} = \Sigma||\underline{F}_o| - |\underline{F}_c||/\Sigma|\underline{F}_o| = 0.12$ for the 1036 observed reflections. All bonds from C atoms of the β-glucose ring to OH, CH_2OH or the N atom of the histamine ring are of the equatorial type and hence all axial bonds are of the C-H type. The most interesting stereochemical aspects of the previously undescribed geometrical structure of the histamine ring are the values of the external bond angles, and the fact that the N atom attached to β-glucose forms coplanar bonds. Finally, the $CH_2CH_2\overset{+}{N}H_2CH_3$ chain is unexpectedly not in the extended form, but is distorted. Nevertheless the observed configuration of this chain preserves the staggered configurations about single bonds. The system of hydrogen bonding, to be described in full later, is consistent with the assumptions of one NH_2^+ group and one NH^+ group in this dihydrochloride of casimidine, and that the N atom attached to the β-glucose is not protonated. These results therefore establish the structure of casimidine.

Taken together, the available organic chemical and X-ray evidence therefore complete the structure of casimiroedine except for the question of trans or cis configuration of the cinnamoyl group.