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The Absolute Configuration of Valeroidine

The relative configurations[1] of the Tropa alkaloids, with the exception of dioscorine, as well as the absolute configuration of cocaine[2], have been determined, while the correlation of (−) valeroidine−obtained recently by total synthesis[3] also−with any of the optically active series still needs support. HUDSON's lactone rule[4] has been adopted to answer this question.

(+) Tropan-3 α · 6 β-diol 6-phenylurethane[5] has been resolved by means of D-tartric acid[3] and converted by thermolysis into the antipodes of 3 α · 6 β-dihydroxy-tropane[6]. The *laevo-rotatory* form, i.e. the alkamine of natural valeroidine, gave with ethyl iodoacetate (−) N_b-ethoxy-carbonylmethyl-3 α·6 β-dihydroxy-tropanium iodide[7] (m.p. 154° $[\alpha]_D^{20}$ = − 23·7°. Found: C, 38·6; H, 6·2; N, 3·6; J, 34·85. $C_{12}H_{22}O_4NJ$ requires C, 38·9; H, 5·9; N, 3·8; J, 34·25%) which could be cyclized spontaneously into the *dextro-rotatory* lactone of N_b-carboxymethyl-3 α·6 β- dihydroxytropanium iodide (m.p. 264° [corr., dec.], $[\alpha]_D^{20}$ = + 37·5°. Found: C, 37·4; H, 5·3; N, 4·3; J, 38·9. $C_{10}H_{17}O_3NJ$ requires C, 36·9; H, 5·0; N, 4·3; J, 39·0%).
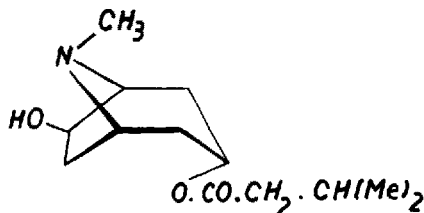
According to HUDSON's rule, which has been extended to δ-lactones[8]−and provided it holds true for *aza*-lactones also− one may conclude that the asymmetric, hydroxyl-bearing carbon no. 6 concerned belongs to the D_G-series. Since the free hydroxy acid cannot be isolated as it occurs often[9], owing to its extreme ten-

dency to lactonise, optical rotation of the ethyl *ester* salt has been compared with that of the lactone salt. Making use of the conventions outlined by CAHN, INGOLD, and PRELOG[10], valeroidine may be given the nomination of (3 R: 6 S) 3 α·6 β-dihydroxy-tropane-3-monoiso-valerate. Configurational correlation of (−) valeroidine with either D or L 3-oxo-proline is already in progress to provide conclusive evidence for the structure which has been assigned to this alkaloid.

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Zusammenfassung

Auf Grund der Laktonregel von HUDSON konnte dem (−)3α·6β-Dihydroxy-tropan und (−) Valeroidin eine absolute Konfiguration zugeschrieben werden.

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[2] E. HARDEGGER and E. OTT, Helv. chim. Acta *38*, 312 (1955).
[3] I. VINCZE, J. TÓTH, and G. FODOR, J. chem. Soc. *1957*, 1349.
[4] C. S. HUDSON, J. Amer. chem. Soc. *32*, 338 (1910). – P. A. LEVENE and H. S. SIMMES, J. biol. Chem. *68*, 737 (1926). – The same rule has been adopted recently to γ- and δ-hydroxyamino acids, e.g. δ-hydroxy-L-lysine by B. WITKOP. The manuscript of this paper, prior to being published in Exper. *12*, 372 (1956), has been kindly submitted to one of us (G. F.).
[5] G. FODOR, J. TÓTH, I. KOCZOR, and I. VINCZE, Chem. and Ind. *1955*, 1260.
[6] For direct resolution of 3 α · 6 β-tropandiol see G. FODOR and L. MÉSZÁROS, Research, London *5*, 534 (1952). – G. FODOR and Ö. KOVÁCS, J. chem. Soc. *1953*, 2341.
[7] For stereochemical notations of tropanes see G. FODOR, J. TÓTH, and I. VINCZE, J. chem. Soc. *1955*, 3504.
[8] P. A. LEVENE and H. S. SIMMES, J. biol. Chem. *68*, 737 (1926). The same rule has been adopted recently to γ- and δ-hydroxyamino acids, e.g. δ-hydroxy-L-lysine by B. WITKOP. The manuscript of this paper, prior to being published in Exper. *12*, 372 (1956), has been kindly submitted to one of us (G. F.).
[9] W. KLYNE, Chem. and Ind. *1954*, 1198.

Amido, Ureido and Urethano Neighbouring Group Participation

Substituted amide groups[1] provide powerful anchimeric[2] assistance to ionization. For example, benzamidoethyl *p*-toluenesulfonate (I) ionizes to oxazolinium salt in absolute ethanol at 25·0° with a first order rate constant[3], k_1, equal to 1·35 × 10^{-4} s^{-1}. While the rate is insensitive to sodium acetate, the inclusion of sodium ethoxide in the absolute alcohol gives rise to a much more rapid formation of oxazoline, obeying second order kinetics, the rate constant[4], k_2, being 0·727 s^{-1} mole^{-1} 1. Such a base-dependent cyclization mechanism had been previously discussed by WINSTEIN and BOSCHAN[5], and has more recently been demonstrated by HEINE *et al.* for the N⊖-5- and 0⊖-5-cyclizations[6] encountered with N-aryl-4-bromobutanamides[7] and N-2-bromoethylbenz-

[1] S. WINSTEIN and R. BOSCHAN, J. Amer. chem. Soc. *72*, 4669 (1950). – R. E. GLICK, Ph. D. Thesis, U.C.L.A. 1954. – H. W. HEINE, P. LOVE, and J. L. BOVE, J. Amer. chem. Soc. *77*, 5420 (1955). – H. W. HEINE, J. Amer. chem. Soc. *78*, 3708 (1956).
[2] S. WINSTEIN, C. R. LINDEGREN, H. MARSHALL, and L. L. INGRAHAM, J. Amer. chem. Soc. *75*, 147 (1953).
[3] R. E. GLICK, Ph. D. Thesis, U.C.L.A. 1954. – Neopentyl *p*-toluene-sulphonate has a solvolysis rate constant of 1·7 × 10^{-8} s^{-1} in ethanol at 75·0°. – S. WINSTEIN and H. MARSHALL, J. Amer. chem. Soc. *74*, 1120 (1952).
[4] R. E. GLICK, Ph. D. Thesis, U.C.L.A. 1954.
[5] S. WINSTEIN and R. BOSCHAN, J. Amer. chem. Soc. *72*, 4669 (1950).
[6] The symbolism X-*n* is employed, *X* representing the atom of the participating group which closes the ring and *n* denoting the ring size thus obtained. The minus sign in $X_\ominus$-*n* is used for the basic mechanism.
[7] H. W. HEINE, P. LOVE, and J. L. BOVE, J. Amer. chem. Soc. *77*, 5420 (1955).