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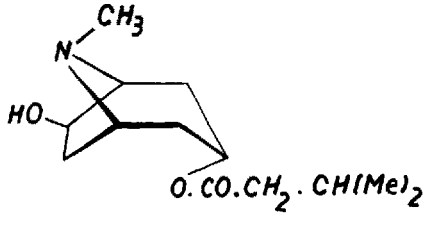
The Absolute Configuration of Valeroidine

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-3α · 6β-diol 6-phenylurethane[5] has been resolved by means of D-tartric acid[3] and converted by thermolysis into the antipodes of 3α · 6β-dihydroxy-tropane[6]. The *laevo-rotatory* form, i.e. the alkamine of natural valeroidine, gave with ethyl iodoacetate (−) N_b-ethoxy-carbonylmethyl-3α·6β-dihydroxy-tropanium iodide[7] (m.p. 154° $[\alpha]_D^{20} = -23{\cdot}7°$. 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-carboxy-methyl-3α·6β- dihydroxytropanium iodide (m.p. 264° [corr., dec.], $[\alpha]_D^{20} = +37{\cdot}5°$. 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-series. Since the free hydroxy acid cannot be isolated as it occurs often[9], owing to its extreme tendency 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*) 3α·6β-dihydroxy-tropane-3-monoiso-valeroate. 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.

[1] Summarized by G. FODOR, Exper. *11*, 129 (1955).

[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 3α · 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*, 304.

[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.

[10] R. S. CAHN, C. K. INGOLD, and V. PRELOG, Exper. *12*, 81 (1956).

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 $1{\cdot}35 \times 10^{-4}$ 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} l. 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 $N^{\ominus}$-5- and $O^{\ominus}$-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).

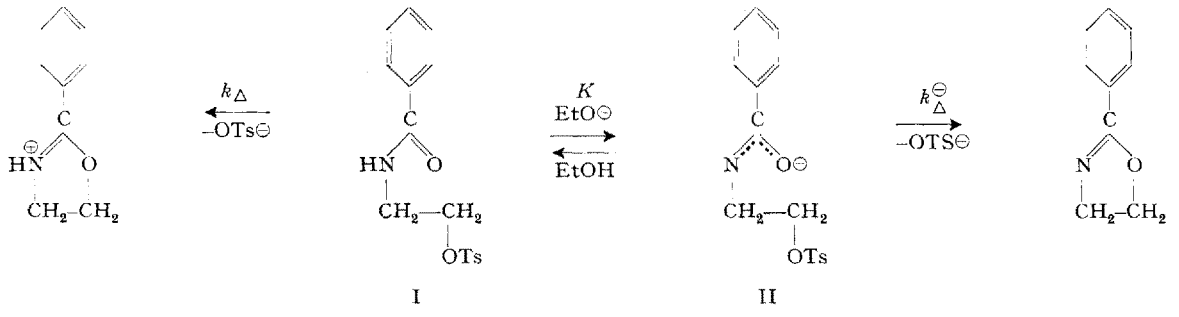
[3] R. E. GLICK, Ph. D. Thesis, U.C.L.A. 1954. – Neopentyl *p*-toluene-sulphonate has a solvolysis rate constant of $1{\cdot}7 \times 10^{-8}$ s^{-1} in ethanol at 75·0°. – S. WINSTEIN and H. MARSHALL, J. Amer. chem. Soc. *74*, 1120 (1952).

[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 $X_{\bigcirc}$-*n* is used for the basic mechanism.

[7] H. W. HEINE, P. LOVE, and J. L. BOVE, J. Amer. chem. Soc. *77*, 5420 (1955).



I II

amides[8]. The observed k_1 is equal to k_Δ, while the observed k_2 is evidently equal to $K\,k_\Delta^\ominus$, where K is the equilibrium constant for the neutralization of the substrate molecule I.

Because of recent interest in this area[9], we are prompted to report in summary form, the results of an investigation of the participation of some neighboring ureido and urethano groups. With the ureido neighboring group both neutral and basic mechanisms were again encountered, the latter being easily made dominant, as can be seen from Table I. With the compounds (IV) examined, we observed 0–5-closure to anilinooxazolines[10] under neutral conditions, and N⊖-5-closure to N-arylimidazolidones[10] in basic solution. With the urethano neighboring group, the duality of mechanism was again evident, the tendency toward the basic mechanism being even more pronounced. Thus, the solvolysis rate of 2-bromoethyl-N-α-naphthylurethane (VI) in 80% ethanol at 75·0° was increased substantially even by sodium acetate, and it was necessary to use a sodium acetate-acetic acid buffer to eliminate the contribution from the basic mechanism. The base-produced N⊖-5-cyclizations of the urethanes V–VII yield N-aryl-oxazolidones, and N⊖-6 cyclizations of X, XI yield N-aryl-oxazinid-2-ones[11]. In addition to the compounds of these types, not previously prepared and so indicated in Table I, both the 3-phenyl- and 3-α-naphthyl-*cis*-4,5-tetramethylene-oxazolid-2-ones were also obtained in the present work. Under neutral conditions, urethano group participation appears to give 0–5- and 0–6-closure, although the evidence is not unequivocal. Some rates and relative rates of the above processes are summarized in Table I (pag. 185).

Under neutral conditions, the sequence of neighboring groups in the order of decreasing k_Δ values is benzamido-ureido-urethano-acetoxy, even the last group being powerfully anchimeric[12]. As shown in Table II, the 0–5 ureido closures are accelerated by electron-releasing substituents in the phenyl ring and retarded by electron-attracting groups. It is of interest, also, that with the urethano-substituted bromides, 0–5-cyclization is 20 times as rapid as the corresponding 0–6 change.

The sequence of participating groups in order of decreasing values of k_2 is quite different from the one which obtains under neutral conditions, the differences arising mainly from the varying acidities of the compounds in question. The rate of N⊖-5-cyclization of ureido-substituted bromides is increased by electron-attracting substituents and decreased by electron-releasing substituents in the N-phenyl group (Table II).

Table II. – Effects of Phenyl Substituents on Reaction Rate

Closure Type	*p*-Cl *a*	*p*-NO_2 *a*	*p*-CH_3 *a*	*p*-OC_2H_5 *a*
0–5	0·65 *b*, 0·69 *c*	0·19 *c*	1·15 *c*, *d*	1·30 *c*
0⊖–5	2·00 *b*, *e*	8·00 *b*, *e*	–	–
N–5	0·63 *f*	–	–	1·2 *f*
N⊖–5	3·13 *e*, *f*, 5·18 *g*	87·0 *g*	0·56 *e*, *f*	0·75 *g*

a Rate relative to unsubstituted phenyl derivative; *b* 2-benzamido-1-ethyl-bromide in methanol[8] at 22·9°; *c* 2-phenylureido-1-ethyl bromides (IV) in 80% ethanol at 50°; *d* *o*-tolyl value; *e* Sodium methoxide as base[8]; *f* N-phenyl-4-bromobutanamide in absolute methanol at 22·9°[7]; *g* In absolute ethanol, plus sodium ethoxide, at 25·0°, with substituted (IV).

The effects of some types of methyl substitution on the alkyl portion of the substituted alkyl bromide or toluenesulfonate have been disclosed by the present work. Thus, the effect of 2,2-dimethyl substitution on rate of reaction of the 3-urethano-1-propyl bromide (X) is qualitatively, not quantitatively like the effect of β-methyl substitution on the usual S_n2 reactions of alkyl bromides with an external nucleophile. With the urethanopropyl bromide, β,β-dimethyl substitution reduces the rate of 0–6-closure by a factor of 75, and that of N⊖-6 by *ca.* 10^3 (Table I). The situation is qualitatively similar in the case of α-methyl substitution in benzamidoethyl *p*-toluenesulfonate[4] (I). Thus, an α-methyl group reduces the 0–5 rate by a factor of 4 and the 0⊖-5 rate by a factor of 12 in absolute ethanol at 25°. On the other hand, β-methyl substitution increases the 0–5 rate by a factor of 4·5.

It is interesting to note the net balance of electronic, conformational and other steric effects which determine the relative rates of 2-substituted-1-ethyl and *trans*-2-substituted-1-cyclohexyl derivatives. Thus, 2-benzamido-1-ethyl *p*-toluenesulfonate has an 0–5 rate 20 times that of the *trans*-2-benzamidocyclohexyl analog in absolute ethanol[4] at 50°. With the corresponding naphthylurethano bromides, the ethyl derivative (VI) displays an 0–5 rate *ca.* 10^3 times that of the cyclohexyl derivative in gl. acetic acid at 75°.

Because of the demonstrated large tendency toward participation in substitution processes displayed by such neighboring groups, and the availability of both neutral and basic mechanisms, often permitting a choice of either O- or N-closure, complex amide groups may be

[8] H. W. HEINE, J. Amer. chem. Soc. *78*, 3708 (1956).

[9] 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).

[10] J. P. PICARD and A. F. MCKAY, Can. J. Chem. *31*, 896 (1953).

[11] Compare J. S. PIERCE, J. Amer. chem. Soc. *50*, 241 (1928). – R. ADAMS and J. B. SEGUE, J. Amer. chem. Soc. *45*, 785 (1923). – J. S. PIERCE and R. ADAMS, J. Amer. chem. Soc. *45*, 790 (1923).

[12] S. WINSTEIN and R. BOSCHAN, J. Amer. chem. Soc. *72*, 4669 (1950). – R. E. GLICK, Ph. D. Thesis, U.C.L.A. 1954. – Compare S. WINSTEIN and R. ROBERTS, J. Amer. chem. Soc. *75*, 2297 (1953) and references therein.

Table I. – Summary of Rates and Relative Rates

	III	IV	V	VI	VII	VIII	IX	X	XI
$k_1{}^a \times 10^5$, s^{-1}	111·0 *b, c*	45·4 *d*	9·0	3·36	2·56	0·33 *e*	0,16 *e, f*	0·18 *g*	0·0023 *g*
Relative k_1	340	138	25	10	7·5	1	0·5	0·5	0·007
$k_2 \times 10^5$, s^{-1} mole^{-11}	13,000 *h, i*	1360 *h, k*	5·4 *m, l, o*	ca. $1{\cdot}2 \times 10^6$ *h, l*	$1{\cdot}5 \times 10^5$ *h, l*	0·89 *m, l, o*	—	$> 1 \times 10^5$ *h, l*	30·2 *m*
relative k_2	500	50	6*n*	5×10^4	5×10^3	1 *n*	—	$> 4 \times 10^3$	33 *n*

a At 50·0°, in 80·0% aqueous ethanol; *b* $6{\cdot}88 \times 10^{-5}$ s^{-1} at 25·0°; HEINE[8] reports $2{\cdot}36 \times 10^{-5}$ s^{-1} in absolute methanol at 22·9°; *c* 0–5-closure[13]; *d* 0–5-closure[10]; *e* Drifting rate constant, extrapolated to zero time; *f* 0–5-closure[12]; *g* Calculated from data at higher temperatures; *h* at 25·0° in absolute ethanol with ethoxide ion; *i* $O^{\ominus}$–5-closure[14]; *k* $N^{\ominus}$–5-closure[10], *l* $N^{\ominus}$–5-closure[11]; *m* At 25·0° in absolute methanol with methoxide ion; *n* Rough relative k_2 value in ethanol, obtained by multiplying k_2 in methanol by 30, this factor being derived from comparison of HEINE's data[8] and ours in the case of 2-benzamido-1-ethyl bromide; *o* These apparent second order constants are somewhat high because of incursion of as much as 1/4 or 1/3 of first order reaction at the concentrations employed.

[13] 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, J. Amer. chem. Soc. *78*, 3708 (1956).

[14] R. E. GLICK, Ph. D. Thesis, U.C.L.A. 1954. – H. W. HEINE, J. Amer. chem. Soc. *78*, 3708 (1956).

Table III. – Some Possibilities for Stereospecific Transformations

	Conversion	Participating Group
HO, OH (*)	0–5 → HO, OH	Acetoxy[12] / Urethano
	$N^{\ominus}$–5 → HO, NHAR	Urethano
NH_2, OH (*)	0–5 → NH_2, OH	Benzamido[5] / Ureido
	$N^{\ominus}$–5 → NH_2, NHAR	Ureido

important aids in stereospecific transformations. Table III illustrates schematically some of the possibilities, Walden inversion at the starred (*) reaction side being achieved *via* neighboring group participation and hydrolysis of the resultant product.

This work will be published in fuller detail elsewhere.

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Department of Chemistry University of California, Los Angeles, December 7, 1956.

Zusammenfassung

Bei der Ionisation eines 2-substituierten 1-Äthylhalogenides oder -toluolsulfonates mit Beteiligung benachbarter Amidgruppen handelt es sich entweder um eine Ionisation (Reaktionsgeschwindigkeitskonstante $k_{\triangle}$) mit Beteiligung der neutralen Amidgruppe, oder um eine Zyklisierung (Reaktionsgeschwindigkeitskonstante $k_{\triangle}^{\ominus}$), bei der die anionische Form der Amidgruppe beteiligt ist. Solche Zyklisierungen sind von der Basenkonzentration abhängig; die gemessene Reaktionsgeschwindigkeitskonstante k_2 ist gleich $K k_{\triangle}^{\bigcirc}$, wobei K die Gleichgewichtskonstante für die Neutralisation des Substratmoleküls ist. Unter neutralen Bedingungen in 80%igem Äthanol ist die beobachtete Sequenz für $k_{\triangle}$ Werte für verschiedene benachbarte Gruppen die folgende: Benzamido > Ureido > Urethano > Azetoxy, während in äthanolischer Natriumäthoxyd-Lösung die Sequenz die folgende ist: Urethano > Benzamido > Ureido.

Beweis des Steringerüstes von Ouabagenin[1]

Ouabagenin (I) ist zum ersten Male von MANNICH und SIEWERT[2] aus Ouabain (II) erhalten worden. Es besitzt die Formel $C_{23}H_{34}O_8$ und ist damit das sauerstoffreichste der bisher bekannten Cardenolide. Die Untersuchungen

[1] Glykoside und Aglykone, 178. Mitteilung.

[2] C. MANNICH und G. SIEWERT, Ber. dtsch. chem. Ges. *75*, 737 (1942).