due recrystallized from 60–70° petroleum ether. The glycol crystallized as glistening colorless plates, m.p. 99.0–99.5°. It sublimed readily *in vacuo* at room temperature, or on heating several degrees below its melting point at atmospheric pressure.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.82; H, 12.41. Found: C, 65.82; H, 12.35.

cis-Octene-3[10] was prepared by the hydrogenation of octyne-3 in methanol at 2–3 atm. pressure over the Lindlar catalyst[11]; b.p. 118–119° (reported[10] b.p. 122.3°).

threo-Octane-3,4-diol.—*cis*-Octene-3 (2.0 g.) was stirred at room temperature for 36 hours with 10 g. of 30% hydrogen peroxide and 20 g. of 98% formic acid. The bulk of the formic acid and water was removed by warming under reduced pressure, and the residue was stirred with dilute potassium hydroxide in 50% aqueous methanol for 24 hours. The methanol was removed under reduced pressure, the residue diluted with water, then extracted with ether. After washing with water, drying over magnesium sulfate, and evaporating the solvent, the residue was distilled through a small Vigreux column. The glycol was collected at 260° (bath temperature); it could not be induced to crystallize. The infrared spectrum showed distinct differences from that of the Hofmann diol.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.90; H, 12.33.

erythro-Octane-3,4-diol.—A cold solution of 0.22 g. of *cis*-octene-3 in 5 ml. of anhydrous ether was treated with a solution of 0.5 g. of osmium tetroxide in 10 ml. of ether, and kept in the dark for 142 hours. The mixture was evaporated to dryness under reduced pressure and the residue taken up in 75 ml. of ethanol. A solution of 5 g. of sodium sulfite in 25 ml. of water was added, the mixture refluxed for three hours, and freed of osmium by filtration through a sintered glass funnel. The precipitate was washed well with ethanol, and the combined filtrates evaporated under reduced pressure to remove the alcohol. The residue was diluted with water, then extracted twice with ether, twice with chloroform. The extracts were washed with water, dried and evaporated, leaving a solid residue; after two recrystallizations from 60–70° petroleum ether it melted at 98.0–98.2°.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 66.04; H, 12.27.

A mixture of the *erythro*-diol and the Hofmann glycol melted at 99.0–99.5°, and their infrared spectra were indistinguishable.

NOTE ADDED IN PROOF.—Since this manuscript was submitted, the same assignment of configuration has been reached independently by J. Sicher and M. Tichy, *Chemistry and Industry*, 16 (1958).

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Stereochemistry of the Hemlock Alkaloids. II. Pseudoconhydrine[1]

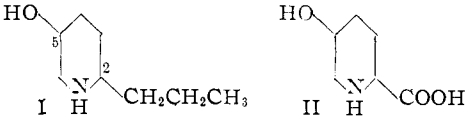
BY RICHARD K. HILL

RECEIVED NOVEMBER 5, 1957

1-Dimethylaminoöctanol-2 was prepared from octene-1,2-oxide and dimethylamine, and resolved through the dibenzoyltartrate. Hofmann degradation of the *l*-base gave *d*-octene-1,2-oxide, which was reduced to *d*-octanol-2. This sequence of reactions completes the correlation of the *l*-amine to L-glyceraldehyde, and establishes the absolute configuration of the hydroxyl of the hemlock alkaloid ψ-conhydrine as that of D-glyceraldehyde. The biogenetic implications of this result are discussed, and the substituents of ψ-conhydrine are shown to have a *trans* orientation.

Introduction

The stereochemistry of conhydrine having been determined,[2] ψ-conhydrine (I) is the only member of the hemlock alkaloids whose configuration remains unknown. Pseudoconhydrine belongs to a small group of β-hydroxypiperidine alkaloids, along



with carpaine[3] and febrifugine.[4] While most piperidine alkaloids are believed to owe their biogenetic origin to lysine[5] (see Fig. 1), the source of the hydroxyl in the members of this group is unknown. One possibility is that ψ-conhydrine is formed from the natural amino-acid δ-hydroxylysine by the same process which the plant uses to convert lysine to coniine, retaining the hydroxyl group throughout the synthesis. An observation that might be taken as support for this hypothesis is the isolation[6] of a cyclization product of δ-hydroxylysine, 5-hydroxypipecolic acid (II), from dates. A second possibility is Robinson's suggestion[5] of an oriented oxidation beta to the nitrogen atom. It is not implausible that a biogenetic intermediate such as III or IV could undergo oxidation at a position activated by the C=N double bond.

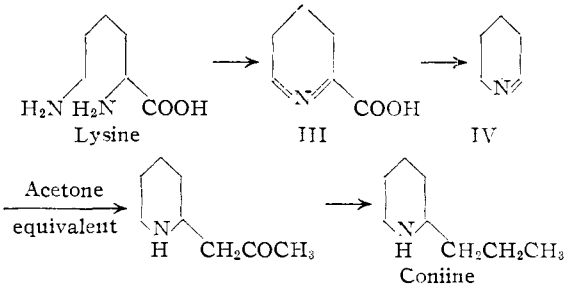


Fig. 1.—Biogenesis of coniine.

The determination of the absolute configuration of the hydroxyl of ψ-conhydrine, and its relation to that of δ-hydroxylysine, might help to decide between these two possibilities, and is an added incentive for investigating the stereochemistry of ψ-conhydrine. In fact, determination of the ab-

(1) Presented at the 132nd Meeting of the American Chemical Society, New York, N. Y., September, 1957.

(2) R. K. Hill, THIS JOURNAL, **80**, 1609 (1958).

(3) H. Rapoport, H. D. Baldridge, Jr., and E. L. Volcheck, Jr., *ibid.*, **75**, 5290 (1953).

(4) B. R. Baker, R. E. Schaub, F. J. McEvoy and J. H. Williams, *J. Org. Chem.*, **17**, 132 (1952).

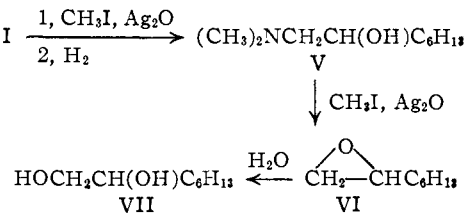
(5) R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, London, 1955, p. 64. Robinson's hypothesis that the piperidine ring of coniine is derived from lysine has been confirmed recently by the tracer experiments of Prof. E. Leete, U. C. L. A. (private communication from Prof. Leete).

(6) B. Witkop and C. M. Foltz, THIS JOURNAL, **79**, 197 (1957).

solute configuration at C-5 appeared to be a convenient way of establishing the orientation of the two substituents. The method used in determining the configuration of conhydrine[2] is not applicable to ψ-conhydrine, since no degradation products are known which still contain both asymmetric carbon atoms, but the principle used by Neuberger[7] in his determination of the configuration of hydroxyproline can be used to advantage here. In this method, the relative orientation of two substituents is established by showing the absolute configuration of each. The absolute configuration at C-2 of ψ-conhydrine is known to be that of D-serine, since dehydration, followed by reduction, gives *d*-coniine,[8] while conhydrine, a member of the natural series at C-2,[2] yields *l*-coniine on treatment with hydriodic acid and subsequent hydrogenation.[9] It remains, then, to show the absolute configuration at C-5.

Discussion

Some years ago, Späth and his co-workers[8] converted ψ-conhydrine, by Hofmann degradation, to a series of compounds containing only the C-5 asymmetric carbon. Hofmann elimination of ψ-conhydrine, followed by catalytic hydrogenation of the olefin formed, yielded *d*-dimethylamino-1-octanol-2 (V). A second Hofmann gave *l*-octene-1,2-oxide (VI), which was hydrolyzed to the active octane-1,2-diol (VII). The stereochemical problem, then, can be reduced to relating one of these degradation products to glyceraldehyde.

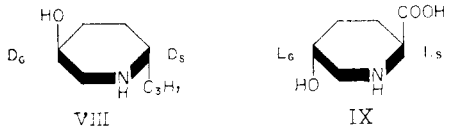


The unavailability of ψ-conhydrine necessitated finding another source for these active compounds. *d,l*-Octene-1,2-oxide, prepared by perbenzoic acid oxidation of octene-1, reacted with dimethylamine to give, in high yield, the racemic amino-alcohol V. The attack of the basic reagent at the less hindered epoxide carbon is in accord with previous experience.[10] Although the base did not form crystalline salts with tartaric or camphorsulfonic acids, it readily did so with *l*-dibenzoyltartaric acid. The salt was purified by repeated crystallization from alcohol to yield a single diastereoisomer, from which the pure *l*-base was regenerated. Its rotation was slightly higher in magnitude than that reported by Späth for the *d*-isomer.

Hofmann elimination yielded pure *d*-octene-1,2-oxide, whose infrared spectrum was identical with that of the *d,l*-oxide, and revealed no trace of octanone-2. Finally, the active oxide was reduced with lithium aluminum hydride to *d*-octanol-2. The reduction of the racemic oxide to octanol-2 had been reported by Hickinbottom[11] and was confirmed in this Laboratory; the identity of the active octanol was established by comparison of its acid phthalate with an authentic sample.

d-Octanol-2 has been related[12] to *d*-butanol-2, which is known, from the extensive work of Levene,[13] to belong to the L-series. The above sequence of reactions, none of which has affected the asymmetric carbon, thus completes the correlation of *l*-dimethylamino-1-octanol-2 to L-glyceraldehyde, and consequently C-5 of ψ-conhydrine has the D-glyceraldehyde configuration. The hydroxyl group is thus not related to that of natural δ-hydroxylysine, which appears to have the L_G configration,[14] but has the opposite configuration. This finding weakens the argument for biogenetic conversion of natural δ-hydroxylysine to ψ-conhydrine.

Finally, knowing the absolute configuration of both substituents, it is possible to assign the *trans* orientation (VIII) to them. It is a striking fact that, although the substituents are *trans* in both ψ-conhydrine and 5-hydroxypipecolic acid[6] (IX), these two natural products of such structural similarity differ in absolute configuration at both centers of asymmetry.



Acknowledgments.—The author gratefully acknowledges the interest and helpful comments of Dr. Bernhard Witkop, and also the assistance of Roger S. Kaufman in carrying out preliminary work on this problem for his senior thesis at Princeton University, 1956.

Experimental

Melting points were taken by capillary, and are uncorrected. Rotations were measured on a Model 200 Rudolph photoelectric polarimeter; it is a pleasure to thank Prof. Walter Kauzmann for the use of this instrument.

d,l-**Octene-1,2-oxide** was prepared by the perbenzoic acid oxidation[11] of octene-1. It distilled at 65° (15 mm.); boiling points recorded in the literature are 62.5–63° (17 mm.),[11] 61° (15 mm.)[15] and 71–73° (27 mm.).[16]

d,l-**Dimethylamino-1-octanol-2.**—Octene-1,2-oxide (20.5 g.) was heated with 20 ml. of anhydrous dimethylamine at 125° in a sealed bomb for 36 hours. The product was taken up in dilute hydrochloric acid and washed with ether, then made alkaline with ammonium hydroxide, saturated with ammonium chloride, and extracted with ether. The extracts were washed with water, dried over sodium carbonate, and concentrated. The residual base distilled at 111–112° (18 mm.), and weighed 23.6 g. (85%).

Anal. Calcd. for $C_{10}H_{23}NO$: C, 69.30; H, 13.38; N, 8.09. Found: C, 69.43; H, 13.66; N, 7.81.

l-**Dimethylamino-1-octanol-2 Dibenzoyltartrate.**—A solution of 23.6 g. of amino-alcohol in 30 ml. of ethanol was added to a warm solution of 48.8 g. of *l*-dibenzoyltartaric acid in 100 ml. of ethanol. Crystallization began within a few

(7) A. Neuberger, *Adv. in Protein Chem.*, **4**, 325 (1948).

(8) E. Späth, F. Kuffner and L. Ensfellner, *Ber.*, **66**, 591 (1933).

(9) K. Loffler and G. Friedrich, *ibid.*, **42**, 107 (1909).

(10) S. Winstein and R. B. Henderson, Chapter 1 in "Heterocyclic Compounds," Vol. 1, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 32–33.

(11) W. J. Hickinbottom and D. R. Hogg, *J. Chem. Soc.*, 4200 (1954).

(12) W. E. Doering and R. W. Young, THIS JOURNAL, **74**, 2997 (1952).

(13) P. Levene, A. Walti and H. Haller, *J. Biol. Chem.*, **71**, 465 (1926).

(14) B. Witkop, *Experientia*, **12**, 372 (1956).

(15) D. Swern, G. N. Billen and J. T. Scanlan, THIS JOURNAL, **68**, 1504 (1946).

(16) W. D. Emmons and A. S. Pagano, *ibid.*, **77**, 89 (1955).

minutes; after cooling for several hours the crystals were filtered and washed with a little ethanol. The solid (59 g.) was recrystallized four times from ethanol, using 20 ml. of solvent per gram of salt. It then weighed 22.1 g. (61.2%) and had a constant melting point of 158.5–159°, $[\alpha]^{21}D$ −87.5° (*c* 4.375 in pyridine).

Anal. Calcd. for $C_{28}H_{37}O_9N$: C, 63.26; H, 7.02; N, 2.63. Found: C, 63.22; H, 7.11; N, 2.59.

***l*-Dimethylamino-1-octanol-2.**—A suspension of the resolved dibenzoyltartrate (21.9 g.) in 100 ml. of water was treated with 50 ml. of 2 *N* potassium hydroxide, saturated with sodium chloride, and extracted with ether. The extracts were washed with saturated salt solution, dried over potassium hydroxide pellets, and evaporated. The residue was taken up in benzene and distilled; the base was collected at 115–117° (23 mm.) and weighed 5.0 g. (70%), $[\alpha]^{21}D$ −15.3° (neat). The *d*-base is reported[8] to boil at 99–100.5° (11 mm.), with $[\alpha]D$ +12.2°.

Anal. Calcd. for $C_{10}H_{23}NO$: C, 69.30; H, 13.38; N, 8.09. Found: C, 69.19; H, 13.44; N, 8.33.

***d*-Octene-1,2-oxide.**—Excess methyl iodide was added to an ethereal solution of the *l*-amine. An exothermic reaction resulted in an immediate precipitate. After standing overnight, the colorless methiodide was collected and washed with ether. An aqueous solution of 8.1 g. of methiodide was converted to the quaternary hydroxide by passing it through a column of 15 g. of Amberlite IRA-400 resin on the hydroxide cycle and eluting the column with water until the washings were neutral. The eluates were evaporated almost to dryness under reduced pressure below 60°.

The residue was heated at atmospheric pressure; trimethylamine was evolved and an oily liquid steam distilled with the water present. More water was added in small portions and heating continued until no more organic material distilled. The distillate, collected in an ice-bath, was extracted with ether, and the extracts dried over magnesium sulfate and concentrated. Distillation of the residue yielded 1.61 g. (49%) of colorless epoxide, b.p. 60–62° (15 mm.), $[\alpha]^{21}D$ +14.5° (*c* 3.62 in ethanol). Späth reports, for the *l*-oxide,[8] b.p. 60–70° (17 mm.), $[\alpha]^{17}D$ −12.2°. The infrared spectrum of the *d*-oxide was identical with that of the *d,l*-oxide, and showed no evidence of any ketonic product.

Anal. Calcd. for $C_8H_{16}O$: C, 74.92; H, 12.59. Found: C, 74.76; H, 12.32.

***d*-Octanol-2.**—To a stirred, refluxing solution of 1.5 g. of lithium aluminum hydride in 100 ml. of ether was added dropwise a solution of 1.0 g. of *d*-octene-1,2-oxide in 50 ml. of ether. Reflux and stirring were continued for three hours, the mixture cooled and treated cautiously with saturated salt solution, and enough dilute hydrochloric acid added to dissolve the salts. After separating the layers, the aqueous layer was extracted several times with ether. The combined ethereal solutions were washed with water, dried over magnesium sulfate, and concentrated. The residue distilled at 80–82° (17 mm.), and weighed 0.88 g. (86%), $[\alpha]^{21}D$ +10.1° (*c* 5.575 in ethanol); lit.[17] b.p. 86° (20 mm.). $[\alpha]^{17}D$ +9.9°. The infrared spectrum was identical with that of authentic *d,l*-octanol-2.

The acid phthalate, crystallized once from aqueous acetic acid, melted at 74.5–75°, alone or mixed with an authentic sample of *d*-octanol-2-phthalate; lit.[17] m.p. 75°.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.20; H, 7.92.

(17) J. Kenyon, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 418.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

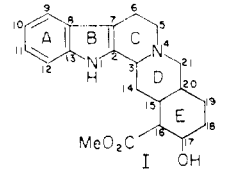
Oxidation–Reduction Studies in the Realm of Indole Alkaloids[1,2]

BY ERNEST WENKERT AND D. K. ROYCHAUDHURI

RECEIVED OCTOBER 21, 1957

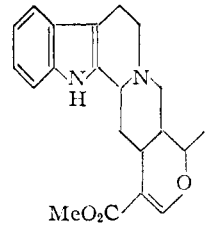
Palladium–maleic acid dehydrogenation is shown to be a general method for the oxidation of ring C of various indole alkaloids and their derivatives. Relative rate data for this process can be used as a diagnostic tool for determination of the stereochemistry of alkaloid ring skeletons. Catalytic hydrogenation and sodium borohydride reduction of tetradehydro compounds lead mainly to *normal* and *allo* products. Reduction–oxidation investigations on sempervirine are described. An infrared spectrophotometric method for the determination of the steric configuration of C-3 in indole alkaloids is presented.

As part of a study of the steric interrelationships of indole alkaloids it was of interest to devise a method of general applicability for the elucidation of the stereochemistry of the ring skeletons of the yohimbine- (I), ajmalicine- (II) and corynantheine-type (III) natural products.

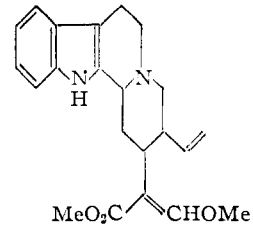


I

The vast body of experimental data in the field of indole alkaloids reveals several procedures for ascertaining the C-3 configuration, albeit a few of these await a test of universality. Catalytic hydrogenation at *p*H 10 of two tetradehydro compounds (IV) of D/E *trans* ring juncture, tetradehydroyohimbine[3] and tetradehydroyohimbane,[4] has yielded *normal* (V) products while hydrogenation of



II



III

d,l-tetradehydroalloyohimbane, a compound of D/E *cis* ring juncture, led to an *allo* (VI) compound.[5] Sodium borohydride reduction of a few

(1) For preliminary communications of this work see (a) E. Wenkert and D. K. Roychaudhuri, THIS JOURNAL, **78**, 6417 (1956); (b) **79**, 1519 (1957).

(2) Part of this research was presented to the 17th Midwest Regional Meeting of the American Chemical Society, November 8–9, 1956, Ames, Iowa.

(3) B. Witkop, *Ann.*, **554**, 83 (1943).

(4) M.-M. Janot, R. Goutarel, A. LeHir, M. Amin and V. Prelog, *Bull. soc. chim. France*, 1085 (1952).

(5) A. LeHir, M.-M. Janot and R. Goutarel, *ibid.*, 1027 (1953).