washed with hot water. The combined washing and filtrate were acidified ($pH \sim 0$) with hydrochloric acid and extracted with ether to remove the benzoic acid. Then the solution was adjusted to pH 4 and was continuously extracted with ether for 12 hours. Evaporation of the ether, sublimation

(70° (0.05 mm.)) of the residue and crystallization of the sublimate from hexane gave 5-ethylpicolinic acid, m.p. 107–109°.

BERKELEY, CALIFORNIA

Stereochemistry of the Hemlock Alkaloids. I. Conhydrine

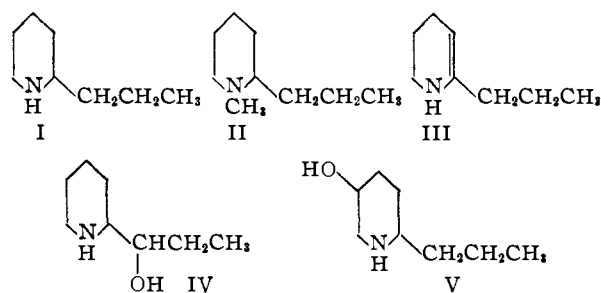## BY RICHARD K. HILL

The stereochemistry of the hydroxylated hemlock alkaloid, conhydrine, has been determined. d,l-Conhydrine was degraded by Hofmann elimination to 5,6-epoxyoctene-1, which was hydrolyzed and hydrogenated to an octane-3,4-diol. This product was identified by synthesis as the *erythro* isomer, establishing the *erythro* configuration for the alkaloid.

Introduction

The poisonous properties of the common hemlock, *Conium maculatum*, have been recognized since antiquity, and the extracts were used in ancient Greece for the execution of criminals. This historic stimulus led to an early investigation of the toxic principle. Coniine, the major alkaloid, was soon shown[1] to be 2-n-propylpiperidine (I); it was the first alkaloid ever synthesized.[2] It is accompanied by four congeners of the same skeleton: N-methylconiine (II), γ-coniceine (III), and two hydroxy derivatives, conhydrine (IV) and pseudo-


conhydrine (V). The structure proof of this group of alkaloids was completed in 1933 by Späth's work on the Hofmann degradation of these latter two bases,[3] and was followed, some years later, by their synthesis.[4] Despite the extensive research, both degradative and synthetic, on the structure and reactions of the conhydrines, the question of their stereochemistry remains unanswered. This and the following communication describe the elucidation of the configurations of conhydrine and pseudoconhydrine.

Discussion

In 1933, Späth and Adler[3a] confirmed the position of the hydroxyl group in conhydrine by an elegant application of the Hofmann elimination. The Hofmann reaction on N-methylconhydrine methiodide (VI), taking the course typical of β-

hydroxyamines,[5] produced the epoxy-amine VII. A second Hofmann converted this to a mixture of the unsaturated epoxide IX and its hydrolysis product X. The glycol was reduced to an octane-3,4-diol XI; all of these compounds retained optical activity.
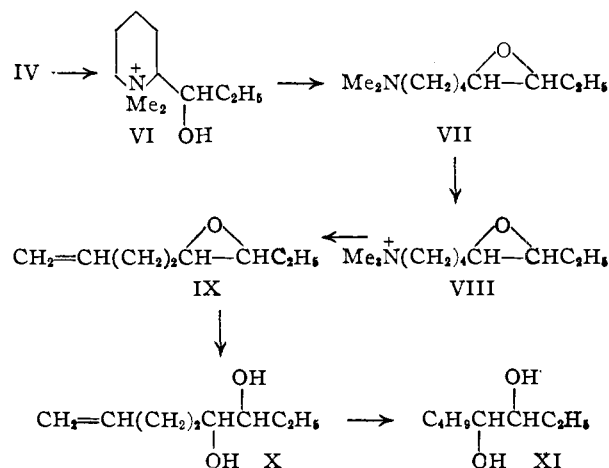
It can be seen that, with our present understanding of the stereochemical course of the reactions used by Späth, the configuration of conhydrine could be deduced from the knowledge of the configuration of the glycol XI. Accordingly, the synthesis of both isomeric glycols and a repetition of the Hofmann degradation were undertaken. Because of the unavailability of the alkaloid, and to avoid the necessity for optical resolutions, all reactions were carried out with racemic compounds.

Formation of ethyl-(2-piperidyl)-carbinol by reduction of ethyl-(2-pyridyl) ketone, either catalytically[4a,6] or chemically,[7] or of ethyl-(2-pyridyl)-carbinol,[8] yields an almost equimolar mixture of both possible diastereomers, so that it is impossible to assign the configuration to either. Galinovsky and Mulley,[4a] however, have shown that the higher-melting isomer (m.p. 100°) represents racemic con-

(1) A. Ladenburg, *Ber.*, **18**, 1587 (1885).

(2) A. Ladenburg, *ibid.*, **19**, 439 (1886).

(3) (a) E. Späth and E. Adler, *Monatsh.*, **63**, 127 (1933); (b) E. Späth, F. Kuffner and L. Ensfellner, *Ber.*, **66**, 591 (1933).

(4) (a) F. Galinovsky and H. Mulley, *Monatsh.*, **79**, 426 (1948); (b) F. Sorm and J. Sicher, *Coll. Csech. Chem. Comm.*, **14**, 331 (1949); (c) L. Marion and W. F. Cockburn, THIS JOURNAL, **71**, 3402 (1949); (d) W. Gruber and K. Schlogl, *Monatsh.*, **80**, 499 (1949).

(5) (a) 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. 13–14. (b) Some examples from the field of natural products are listed by B. Witkop and C. M. Foltz, THIS JOURNAL, **79**, 197 (1957).

(6) K. Hess, *Ber.*, **53**, 129 (1920).

(7) C. Engler and F. W. Bauer, *ibid.*, **24**, 2530 (1891).

(8) L. Lautenschlager and A. G. T. Onsager, *ibid.*, **51**, 602 (1918).

hydrine by resolving this base and demonstrating the identity of the dextrorotatory compound with the natural product.

d,l-Conhydrine was therefore synthesized and subjected to the same series of reactions used by Späth on the natural isomer. The procedure of Weinstock and Boekelheide,[9] employing a basic ion-exchange resin to prepare quaternary hydroxides, was utilized in the Hofmann eliminations. The mixture of epoxide and glycol resulting from the second Hofmann was not separated, but hydrolyzed with aqueous perchloric acid to the solid diol (X). Catalytic hydrogenation gave a beautifully crystalline octane-3,4-diol, m.p. 99° (XI).

The synthesis of pure samples of the unknown *threo* and *erythro* isomers of octane-3,4-diol was accomplished in the following manner. *cis*-Octene-3[10] was prepared by stereospecific hydrogenation of octyne-3 with the Lindlar catalyst.[11] Treatment of this olefin with performic acid, a reagent known to result in *trans* hydroxylation,[12] gave *threo*-octane-3,4-diol, while osmium tetroxide, a *cis* hydroxylating agent,[13] yielded the *erythro* isomer. The *threo*-diol proved to be a liquid which could not be induced to crystallize, but the *erythro* isomer was a crystalline solid, m.p. 98°. The large difference in melting points of these glycols is not unexpected; the two isomers of heptane-3,4-diol[14] are a solid of m.p. 96° and a liquid; the isomeric nonane-4,5-diols[14] are a solid melting at 125° and a liquid; and *meso*- and *d,l*-octane-4,5-diol melt at 124° and 28°, respectively.[15]

The identity of the Hofmann glycol with the *erythro* octanediol was demonstrated by mixed melting point determination and comparison of infrared spectra. This knowledge makes it possible to assign configurations to the other compounds of this series. Hydrolysis of epoxides is known to take place with inversion of configuration,[16] so that compounds VII, VIII and IX are *trans*-epoxides. The formation of epoxides from β-hydroxyamines is also accompanied by inversion at the carbon bearing the nitrogen atom,[5] and consequently the alkaloid must have the *erythro* configuration.

IV   VII, R = (CH₂)₄NMe₂   XI
            IX, R = (CH₂)₂CH=CH₂
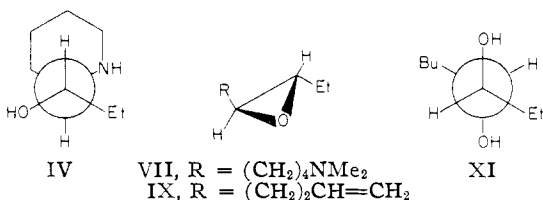
(9) J. Weinstock and V. Boekelheide, THIS JOURNAL, **75**, 2546 (1953).

(10) K. N. Campbell and L. T. Eby, *ibid.*, **63**, 216 (1941).

(11) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(12) D. Swern, in "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, Chapter 7.

(13) R. Criegee, *Ann.*, **522**, 75 (1936).

(14) J. S. Pierce and R. Adams, THIS JOURNAL, **47**, 1098 (1925).

(15) W. G. Young, L. Levanas and Z. Jasaitis, *ibid.*, **58**, 2274 (1936).

(16) For example, see (a) D. Swern, *ibid.*, **70**, 1235 (1948); (b) H. J. Lucas, M. J. Schlatter and R. C. Jones, *ibid.*, **63**, 22 (1941), and earlier papers by Lucas; (c) J. Boeseken, *Rec. trav. chim.*, **47**, 683 (1928). The only reported cases of retention of configuration during acid-catalyzed hydrolysis occur with epoxides carrying a substituent which can stabilize an intermediate carbonium ion, *e.g.*, phenyl, see (d) J. H. Brewster, THIS JOURNAL, **78**, 4061 (1956); (e) D. Y. Curtin, A. Bradley and Y. G. Hendrickson, *ibid.*, **78**, 4064 (1956); and allyl, *cf.* (f) R. G. Kadesch, *ibid.*, **68**, 41 (1946).

Finally, the absolute configuration may be assigned on the basis of the oxidation of conhydrine to *l*-pipecolic acid,[17] which is known, by its relation to L-aspartic acid (through the amino-acid baikaian[18]), to belong to the natural L-series. Conhydrine thus has the absolute configuration depicted in the Fischer projection XII.

$$C_2H_5$$
$$HO{-}|{-}H$$
$$HN{-}|{-}H$$
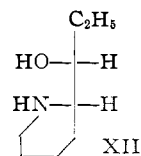
XII

Experimental

Ethyl-(2-pyridyl)-carbinol[8] was prepared in 50% yield by the addition of ethylmagnesium iodide to 2-pyridinecarboxaldehyde; b.p. 113–117° (18 mm.) (reported b.p. 135° (49 mm.),[8] 112–113° (13 mm.[19])).

Ethyl-(2-piperidyl)-carbinol (*d,l*-conhydrine) was prepared by hydrogenation of the foregoing base with platinum in acetic acid.[6] After recrystallization from ether, the colorless needles melted[20] at 99.5–100° (reported m.p.[6] 98–99°, m.p.[4a] 100°, m.p.[8,21] 99–100°).

Hofmann Degradation of *d,l*-Conhydrine.—A solution of 3.0 g. of *d,l*-conhydrine in 15 ml. of methanol was treated with 8 g. of methyl iodide, and the mildly exothermic reaction moderated by cooling. Powdered potassium hydroxide (1.0 g.) was added and the mixture kept in the refrigerator for 4 hours. More potassium hydroxide (0.5 g.) was added, with 5 g. of methyl iodide, and the mixture kept overnight. The methiodide (VI) was filtered and washed with a little ether. After recrystallization from methanol, it melted at 182–183° (lit.[19] m.p. 179°).

A solution of the methiodide in 30 ml. of water was converted to the quaternary hydroxide by passing through a column of 20 g. of Amberlite IRA-400 resin on the hydroxide cycle, and eluting with water until the washings were neutral. The aqueous solution was concentrated on a rotary evaporator below 50° to 4–5 ml. The residue was heated at atmospheric pressure until an oily liquid distilled. Small portions of water were added and heating continued until no more organic liquid steam distilled with the water. The distillate was saturated with salt and extracted with ether. The ethereal extracts, after washing with saturated salt solution and drying, were concentrated to 25 ml. and treated with methyl iodide. After standing overnight, the methiodide (VIII) of 1-dimethylamino-5,6-epoxyoctane was collected and washed with ether; yield 2.05 g. (31%). A sample was recrystallized from ether–methanol for analysis; m.p. 116.5–117.5°.

Anal. Calcd. for C₁₁H₂₄NOI: C, 42.18; H, 7.72; N, 4.47. Found: C, 42.07; H, 7.57; N, 4.38.

Octene-1-diol-5,6.—The preceding methiodide was subjected to a second Hofmann elimination under the conditions already described. The steam distillate was acidified with a few drops of 70% perchloric acid, swirled at room temperature for an hour, then warmed at 50–60° for 30 min., until the epoxide odor disappeared. The solution was neutralized with sodium bicarbonate and saturated with salt, then extracted four times with ether. The extracts were washed with a little water, dried over magnesium sulfate, and evaporated. The solid residue was recrystallized from 60–70° petroleum ether, yielding 0.30 g. (33%) of colorless glycol, m.p. 78–79°.

Anal. Calcd. for C₈H₁₆O₂: C, 66.63; H, 11.18. Found: C, 66.63; H, 11.17.

Octane-3,4-diol.—The unsaturated glycol (195 mg.) was hydrogenated over prereduced platinum at atmospheric pressure in 20 ml. of methanol, quickly absorbing 34.3 ml. of hydrogen (calcd. 32.5 ml.). The catalyst was removed by filtration, the filtrate carefully evaporated, and the resi

(17) R. Willstätter, *Ber.*, **34**, 3166 (1901).

(18) F. King, T. King and R. Warwick, *J. Chem. Soc.*, 3590 (1950).

(19) K. Hess and R. Grau, *Ann.*, **441**, 101 (1925).

(20) Melting points were taken on a hot-stage microscope and are uncorrected.

(21) K. Hess, *Ber.*, **52**, 964 (1919).

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


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

BY RICHARD K. HILL

1-Dimethylaminoöctanol-2 was prepared from octene-1,2-oxide and dimethylamine, and resolved through the dibenzoyl-tartrate. 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
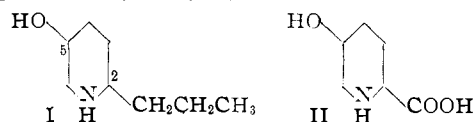
with carpaine[3] and febrifugine.[4] While most piperidine alkaloids are believed to owe their biogenetic origin to lysine[5] (see Fig. 1), the source of the hydroxyl in the members of this group is unknown. One possibility is that ψ-conhydrine is formed from the natural amino-acid δ-hydroxylysine by the same process which the plant uses to convert lysine to coniine, retaining the hydroxyl

(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).

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.
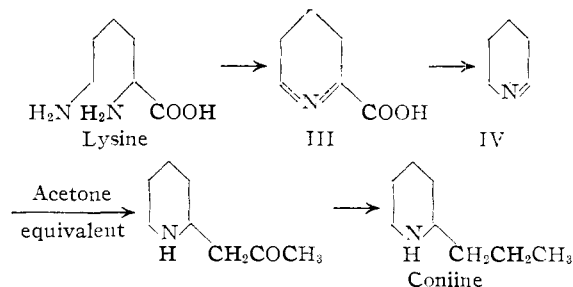

Fig. 1.—Biogenesis of coniine.

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-

(6) B. Witkop and C. M. Foltz. THIS JOURNAL, **79**, 192 (1957).