aminobutyrolactone hydrobromide in 100 ml. of water was added 4.62 g. of sodium bicarbonate. The resulting solution was allowed to stand overnight at room temperature. No precipitate had formed at this time so the solution was evaporated on a steam-bath to yield a thick semi-crystalline sirup. This sirup was dissolved in 18 ml. of water and the resulting solution was diluted with 100 ml. of absolute ethanol and let stand overnight in a refrigerator. The crystalline product was collected on a filter, washed with absolute alcohol, and was air dried; yield, 5.0 g.; m. p., 160–163° dec. An additional 0.6 g. of product having the same melting point was obtained by reworking the mother liquors.

The combined fractions were recrystallized by dissolving them in 20 ml. of hot water, adding 40 ml. of absolute ethanol, and allowing the solution to stand for several days in a refrigerator; 0.7 g. of flat parallelograms, m. p. 197–200°, was obtained. This compound gave a negative ninhydrin test and a mixed melting point with *meso*-homoserine diketopiperazine (m. p. 200–202°) showed no depression.

Anal. Calcd. for $C_8H_{14}O_4N_2$: N, 13.86. Found: N, 13.61.

The filtrate from this compound was diluted with 20 ml. of absolute ethanol and was allowed to stand in a refrigerator several more days: 1.4 g. of well formed flat needles was obtained, m. p. 183–185° dec. This compound gave a strongly positive ninhydrin test and a mixed melting point with DL-homoserine (m. p. 186–187°) showed no depression.

Anal. Calcd. for $C_4H_9O_3N$: N, 11.76. Found: N, 11.75.

A solution of homoserine in water was evaporated to dryness on a steam-bath in the same manner as in the above experiment. After it was redissolved in water an amino nitrogen determination showed that no loss in amino nitrogen had occurred, hence no diketopiperazine had formed under the conditions used.

The Optical Rotation of L-Homoserine and L-α-Aminobutyrolactone.—Rotation was measured using a 2-dm. tube and monochromatic light from a sodium vapor lamp. A 1% solution of homoserine was used in aqueous solutions containing varying amounts of acid and alkali; a 1.53% solution of α-aminobutyrolactone hydrobromide (equimolar with the 1% solution of homoserine) was used in a corresponding manner. The proper ratios of acid and alkali to the compounds were obtained by previously preparing standardized solutions containing the correct amounts of acid or alkali. The finely powdered compounds were dissolved in the solvent, placed in a polarimeter tube and the rotations of the solutions were measured as quickly as possible and thereafter at intervals. In cases where rapid mutarotation occurred the rotations at zero time were estimated by extrapolation. All rotations were measured at 25 ± 3°; there is no measurable error over this amount of variation in temperature due to a temperature coefficient for these compounds.

The results of the experiments are shown graphically in Figs. 1, 2 and 3.

Summary

The relationships between homoserine, its lactone and its diketopiperazine have been studied.

In basic and in neutral aqueous solution homoserine itself is stable and does not transform into either its lactone or diketopiperazine. In acidic solution homoserine is in equilibrium with its lactone; increasing amounts of the lactone are present in more strongly acid solutions.

In basic solution the lactone ring of α-aminobutyrolactone is opened to form homoserine; in solutions containing 1 mole or more of acid per mole of lactone the lactone is in equilibrium with homoserine. In dilute neutral solution the lactone ring opens to form homoserine and in dilute solutions containing less than 1 mole of acid per mole of lactone the lactone is in equilibrium with homoserine; in more concentrated neutral and slightly acidic solutions a mixture of homoserine and its diketopiperazine is formed.

SALT LAKE CITY, UTAH RECEIVED APRIL 18, 1949

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

The Synthesis of Pseudoconhydrine[1]

BY LÉO MARION AND WILLIAM F. COCKBURN

Pseudoconhydrine, one of the Hemlock group of alkaloids, occurs in the common hemlock, *Conium maculatum* L., along with coniine, N-methylconiine, γ-coniceine and conhydrine. It was discovered in the residues from the isolation of coniine and found to be an isomer of conhydrine, with the empirical formula $C_8H_{17}ON$.[2] Further investigation showed the base, like conhydrine itself, to be an hydroxyconiine,[3] while a study of the exhaustive methylation demonstrated that the hydroxyl group occupies position 5 of the piperidine nucleus.[4] Pseudoconhydrine is thus 5 - hydroxy - 2 - *n* - propylpiperidine[4] (VI), a structure now confirmed by the total synthesis of the alkaloid, the resolution of the synthetic base into its optical isomers and the preparation of derivatives.

Attempts to sulfonate conyrine (2-propylpyridine) in the 5-position with oleum and a mercury catalyst were largely unsuccessful, apparently owing to oxidation of the propyl side-chain, with the formation of tarry by-products. A small amount of impure material was isolated, but the method was not considered sufficiently profitable and was abandoned. The following scheme, however, proved successful.

2-Methylpyridine-5-sulfonic acid (I) was obtained by sulfonation of α-picoline[5] and converted to 5-hydroxy-2-methylpyridine (II) by potash fusion.[6] Addition of ethereal diazomethane to an aqueous–methanolic solution of II yielded the

(1) Published as National Research Council Bull. No. 2002.

(2) A. Ladenburg and G. Adam, *Ber.*, **24**, 1671 (1891).

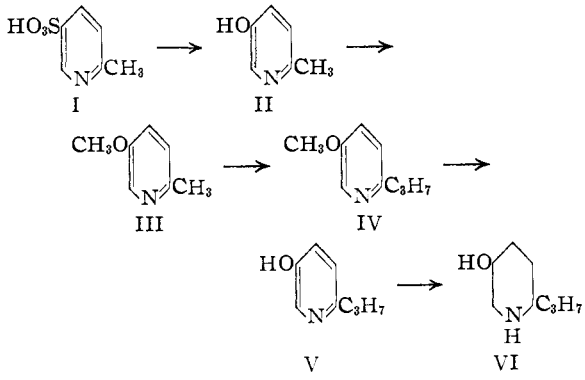
(3) K. Löffler, *ibid.*, **42**, 116, 960 (1909).

(4) E. Späth, F. Kuffner and L. Ensfellner, *ibid.*, **66**, 591 (1933).

(5) S. M. McElvain and M. A. Goese, THIS JOURNAL, **65**, 2233 (1943).

(6) O. Wulff, U. S. Patent 1,880,645; *C. A.*, **27**, 518 (1933).

methyl ether (III) which was condensed with ethyl chloride in the presence of freshly prepared



potassamide to give 5-methoxy-2-propylpyridine (IV). Although the yield for this last reaction was only 22% for a single run, most of the unchanged α-picoline derivative could be recovered in a pure state and recycled, raising the "conversion" to 66%. A similar experiment employing phenyllithium as condensing agent gave only a 5% yield of the desired compound contaminated with other material, while sodium triphenylmethide failed to effect any conversion at all. Demethylation of IV was brought about by refluxing with 48% hydrobromic acid in glacial acetic acid, and the resulting phenolic compound (V) hydrogenated at 50 lb. pressure in presence of Adams catalyst. The hydrogenation product (VI) was obtained as a yellowish semi-crystalline mixture, fairly readily separable by vacuum distillation into approximately equal amounts of a white crystalline solid and a colorless oil. These are presumably the two racemic diastereomers to be expected on the basis of the two asymmetric carbon atoms in the molecule of pseudoconhydrine. The solid isomer, like the natural alkaloid, appears to hydrate very readily, and was dried by vacuum-sublimation at 70° (0.05 mm.) being then pure, m. p. 91.5–92°. Since the natural alkaloid melts at 105–106°, it seemed probable that this isomer was racemic pseudoconhydrine.

This compound, like synthetic conhydrine,[7] failed to form a crystalline salt with *d*-tartaric acid, and was therefore resolved with the optically active 6,6′-dinitro-2,2′-diphenic acids[8–10] into *l*- and *d*-pseudoconhydrine. Measurement of the optical activity gave $[\alpha]^{26}D$ − 10.75° and $[\alpha]^{23}D$ + 11.09° for the *l*- and *d*- isomers, respectively, the latter value being in excellent agreement with the values of +10.98 and +11.06° recorded for the natural alkaloid.[2] The melting points of the free base, 105–106°, the hydrochloride, 214–215°, and the N-benzoyl derivative, 131–132°, also correspond to those obtained by Löffler[3] and Späth[4] for the natural product and the corresponding derivatives, and identity is assumed.

Acknowledgment.—The authors wish to acknowledge with thanks their indebtedness to the Goldsmiths' Company of London, England, for the award of a Travelling Fellowship to one of them (W. F. C.).

Experimental

2-Methylpyridine-5-sulfonic Acid (I).—α-Picoline was sulfonated with oleum in presence of a mercury catalyst as described by McElvain and Goese.[5] The free sulfonic acid was obtained as a tan-colored crystalline solid, m. p. 334–338° (uncor.).[11] McElvain reports this as 338–341° (cor.); yield 54%.

5-Hydroxy-2-methylpyridine (II).—The free sulfonic acid (I) was fused with excess potassium hydroxide in a nickel crucible, with some iron filings as catalyst.[6] After cooling, the melt was dissolved in water and partly neutralized with hydrochloric acid, neutralization being completed with carbon dioxide. The precipitated phenolic compound was filtered off, dried in a desiccator, and extracted with ether in a Soxhlet. The aqueous mother liquors were also extracted overnight in a liquid–liquid extractor, and the two extracts combined and concentrated. The crude 5-hydroxy-2-methylpyridine which crystallized was purified by sublimation in a large Pyrex tube at 130° (0.1 mm.) being obtained as an almost white crystalline solid m. p. 167–169°. This is reported as 164–166°.[6] It gave a red color with aqueous ferric chloride.

Anal. Calcd. for C_6H_7ON: C, 66.06; H, 6.46. Found: C, 66.22, 66.34; H, 6.40, 6.30.

5-Methoxy-2-methylpyridine (III).—Ten grams (0.10 mole) of 5-hydroxy-2-methylpyridine was dissolved in 150 ml. of methanol containing 10% of water, and the solution chilled in an ice–salt-bath. A solution of 11.0 g. (0.26 mole) of diazomethane in 300 ml. of ether was added slowly with swirling from a dropping funnel, the stem of which projected below the surface of the liquid. A brisk effervescence accompanied the addition, which was interrupted several times in order to boil off the accumulated ether. If the latter procedure, which serves to keep the polarity of the solution at a maximum, was omitted, or more nearly equivalent quantities of phenol and methylating agent employed, the yield of methyl ether was much lower, although a greater recovery of unchanged phenol was possible. After being allowed to stand in the ice-box overnight, the methanol solution was acidified with hydrochloric acid, and most of the ether and methanol removed by concentration on the steam-bath. The resulting sirup was diluted with water and the solution exhausted with ether. It was then alkalized with sodium hydroxide pellets, and again extracted with ether. This second extract was dried over potassium hydroxide pellets, the ether removed by distillation, and the residual oil vacuum distilled. The product was a colorless oil, b. p. 43–45° (1 mm.) or 188–189° (760 mm.), $n^{25}D$ 1.5088.

Anal. Calcd. for C_7H_9ON: C, 68.28; H, 7.36. Found: C, 68.30, 68.37; H, 7.17, 7.35.

The maximum yield obtained was 40%, but some of the phenol was recoverable, the amount depending on the exact procedure followed.

5-Methoxy-2-propylpyridine (IV).—Potassium (5 g., 0.128 atom) was converted to potassamide in liquid ammonia (80 ml.) with ferric nitrate (0.2 g.) as catalyst. The reaction was carried out in a 100-ml. three-necked, ground-glass flask equipped with a stirrer and a cold-finger Dry Ice condenser with nitrogen inlet, while the third neck was closed with a stopper and used for the addition of reagents. When all the metal had been converted to amide, the ammonia was allowed to evaporate past the

(7) C. Engler and F. W. Bauer, *Ber.*, **27**, 1775 (1894).
(8) E. Späth and F. Kesztler, *ibid.*, **69**, 2725 (1936); **70**, 70 (1937).
(9) F. Galinovsky and H. Mulley, *Monatsh.*, **79**, 427 (1948).
(10) A. W. Ingersoll and J. R. Little, THIS JOURNAL, **56**, 2123 (1934).
(11) All melting points are corrected, unless otherwise stated.

loose stopper, the last traces being driven off by warming under nitrogen in a water-bath. The solid cake of potassamide was carefully broken up with a spatula in a strong stream of nitrogen, and the cold-finger filled with Dry Ice. Ten grams (0.081 mole) of 5-methoxy-2-methylpyridine was added, and allowed to stir for fifteen minutes, during which time the solution developed a deep purplish-red color. To the mixture was added 9.5 ml. (0.135 mole) of ethyl chloride from a cooled graduated pipet in 0.3-ml. portions at five-minute intervals, the condenser being kept cold by fresh additions of Dry Ice. After several hours, the flask was immersed in an ice-bath and stirring continued overnight. The ice-bath was then removed, fresh Dry Ice added to the condenser, and stirring continued at room temperature for a further ten hours. The total reaction time was thirty hours.

About 40 ml. of ether was added to the mixture, and the unreacted potassamide decomposed by the cautious addition of water from a dropping funnel. The ether layer was separated, extracted thoroughly with dilute hydrochloric acid, and the acid extract combined with the acidified aqueous portion of the reaction mixture. The combined solutions were repeatedly extracted with ether to remove non-basic impurities, alkalized with sodium hydroxide, and again extracted with ether. This second extract was dried with potassium carbonate, the ether removed by distillation and the residue vacuum distilled in a Vigreux-Claisen flask. The product was a water-white oil with a penetrating odor reminiscent of oil of aniseed, b. p. 60–61° (0.7 mm.). The yield was 2.6 g. (22%), 67% of the starting material being recovered.

The analysis results were slightly low, presumably due to the presence of unchanged 5-methoxy-2-methylpyridine, so the product of several runs was carefully fractionated at about 1 mm. pressure in a column (23 cm. long and 1 cm. dia.) packed with wire gauze, and equipped with a heated jacket and Whitmore and Lux still-head.[12] Two sharp fractions were obtained at 37–40° and 60–62°, corresponding to unchanged starting material and the desired product, respectively.

Anal. Calcd. for $C_9H_{13}ON$: C, 71.48; H, 8.66. Found: C, 71.45, 71.48, 71.50; H, 8.87, 8.76, 8.63; $n^{25}D$ 1.5012.

Treatment with the theoretical amount of picric acid in methanol gave a picrate in pale greenish-yellow needles, m. p. 113–114°.

Anal. Calcd. for $C_9H_{13}ON \cdot C_6H_3O_7N_3$: C, 47.37; H, 4.24. Found: C, 47.47, 47.67; H, 4.24, 4.30.

5-Hydroxy-2-propylpyridine (V).—For the demethylation, 4.30 g. (0.028 mole) of 5-methoxy-2-propylpyridine was refluxed for ninety hours with 200 ml. of glacial acetic acid containing 90 ml. of 48% hydrobromic acid. After cooling, the solution was diluted with its own volume of water and extracted four times with twice its own volume of ether. It was then basified with sodium hydroxide pellets and extracted with ether again. This extract yielded 0.13 g. of starting material (3%).

The aqueous solution was made just acid with concentrated hydrochloric acid, then basified with excess ammonium hydroxide, and the solution extracted continuously overnight with ether. The extract was dried with Drierite and concentrated to 10 ml. on the steam-bath. A white crystalline solid separated on cooling, and a further quantity could be obtained from the mother liquors by slow and repeated addition of petroleum ether (b. p. 50–60°). The product was readily purified by crystallization from ether–petroleum ether, being obtained as a white crystalline solid m. p. 93–93.5°. It is much more soluble in ether than 5-hydroxy-2-methylpyridine, and like the latter gives a deep red color with aqueous ferric chloride.

(12) F. C. Whitmore and A. R. Lux, THIS JOURNAL, **54**, 3448 (1932).

Anal. Calcd. for $C_8H_{11}ON$: C, 70.06; H, 8.08. Found: C, 70.01, 70.20; H, 7.84, 7.93.

The final yield was 2.60 g. (66%).

5-Hydroxy-2-propylpiperidine (VI).—One gram (0.0073 mole) of 5-hydroxy-2-propylpyridine was hydrogenated at 44 lb. pressure in 50 ml. of glacial acetic acid containing 250 mg. of Adams catalyst, the reaction time being sixteen hours. The solution was diluted with its own volume of water, filtered from the catalyst, acidified with 5 ml. of concentrated hydrochloric acid, and most of the acetic acid removed by ether extraction. The solution was basified with sodium hydroxide and extracted continuously overnight with ether. The extract was dried with potassium carbonate, and the ether removed by distillation, leaving a yellow oil which partially crystallized on cooling. The mixture had a pleasant sweetish smell reminiscent of crushed leaves. Yield was 1.008 g. (96%).

***dl*-Pseudoconhydrine.**—A bulb was blown in the end of a 30-cm. length of 12 mm. Pyrex tubing, and an ether solution of 1 g. of 5-hydroxy-2-propylpiperidine introduced into it. The ether was removed at the water-pump, and the residue slowly vacuum distilled from an air-bath, the portion of the tube outside the bath being wrapped with asbestos to provide a temperature gradient. The compound distilled at 70–75° (0.1 mm.) giving white crystals in the hotter part of the tube, and a colorless oil in the cooler part, the two being separated by breaking the tube between the fractions. The solid could be crystallized from ethyl acetate–petroleum ether in fine felted needles, but still had a diffuse melting point, probably due to hydrate formation. It was again sublimed *in vacuo*, being obtained in feathery white needles, m. p. 91.5–92°. It gave no color with aqueous ferric chloride, and depressed the melting point of 5-hydroxy-2-propylpyridine by over 50°.

Anal. Calcd. for $C_8H_{17}ON$: C, 67.11; H, 11.96. Found: C, 67.30, 67.24; H, 11.71, 11.76.

***l*- and *d*-Pseudoconhydrine.**—For the resolution, 0.685 g. of the racemic base was treated with 1.590 g. of *d*-6,6′-dinitro-2,2′-diphenic acid in 30 ml. of hot water. On cooling, 0.854 g. of yellow crystals separated. These were recrystallized from water nine times, giving 0.132 g. of salt, m. p. 238–240° (dec.).

Anal. Calcd. for $C_8H_{17}ON \cdot C_{14}H_8O_8N_2$: C, 55.56; H, 5.30. Found: C, 55.49, 55.35; H, 5.06, 5.14.

The free base was liberated and distilled at 70° (0.05 mm.) being obtained in feathery white crystals m. p. 105–106° (in vacuum tube); $[\alpha]^{26}D$ −10.75° (c = 1.675 in absolute ethanol). The hydrochloride was prepared and crystallized from methanol–acetone in silvery-white needles, m. p. 214–215°.

The free base was recovered from the mother liquors of the above resolution and treated with *l*-6,6′-dinitro-2,2′-diphenic acid. The same treatment as above yielded *d*-pseudoconhydrine m. p. 105–106°; $[\alpha]^{28}D$ +11.09° (c = 1.715 in absolute ethanol).

Treatment with 1 mole of benzoyl chloride in ether solution yielded the N-benzoyl derivative, which was recrystallized from ether in white nodules, m. p. 131–132°.

Summary

1. The structure assigned to pseudoconhydrine has been confirmed by a total synthesis of the alkaloid from α-picoline.

2. The 5-hydroxy-2-propylpiperidine so obtained has been separated by fractional distillation into two racemic diastereomers, of which the solid isomer has been resolved into its optical antipodes by means of its salts with the optically active 6,6′-dinitro-2,2′-diphenic acids.

OTTAWA, CANADA RECEIVED MAY 23, 1949