Experimental

A suspension of 0.12 g. of capaurimine in a small volume of ethanol was treated with an excess of an ethereal solution of diazoethane and the mixture set aside until the alkaloid had completely dissolved and the evolution of nitrogen had ceased. The solvents were then evaporated and the amorphous residue dissolved in a small volume of dilute hydrochloric acid. The solution was treated with sodium bicarbonate until the turbidity was just permanent. The cooled mixture was treated with an aqueous solution of potassium permanganate until the color of the latter persisted for two hours. A slight excess of the oxidant was destroyed with a little methanol and the heated solution filtered. The filtrate was then acidified with hydrochloric acid and exhausted with ether. The residue from the ether extract was dissolved in dilute ammonia and a small amount of oxalic acid precipitated by adding calcium chloride. The filtrate from the calcium oxalate was acidified and again exhausted with ether. The residue from the latter was sublimed from a small tube, the sublimate of mixed anhydrides dissolved in ethanol, and treated with an excess of ethylamine. The mixture was evaporated to dryness, heated to 200° for several minutes and then sublimed *very* slowly *in vacuo* at 1 mm. from a small tube in an air-bath. A small forerun of liquid material was discarded. The temperature of the air-bath was then raised to 135°. In the course of about three hours there was obtained a small amount of crystalline sublimate which when washed with pentane and recrystallized from the same solvent, melted at 84°.[6] When this was admixed with varying amounts of N-ethyl-3-ethoxy-4-methoxy-phthalimide[5] (m. p. 91°) the mixture invariably melted above 84°. A mixture containing approximately equal amounts melted at 86°. There was insufficient to admit of further purification.

A second fraction of distillate was obtained when the temperature of the air-bath was raised to 150°. The semi-solid product was extracted with several successive portions of pentane, the solvent removed from the extract and the residue recrystallized twice from hot water. The colorless fine needles thus obtained melted not quite sharply at 73° and admixture with a specimen of N-ethyl-3-ethoxy-4,5-dimethoxyphthalimide (m. p. 76°) raised this melting point by one degree. It may be added that the separation of these imides is possible primarily because the trialkoxy derivative is respectively less volatile and more soluble in pentane than the dialkoxy compound.

Summary

The constitution of capaurimine has been determined. It is a dihydroxytrimethoxytetrahydroprotoberberine.

(6) All melting points are corrected.

GUELPH, ONTARIO RECEIVED MARCH 19, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE]

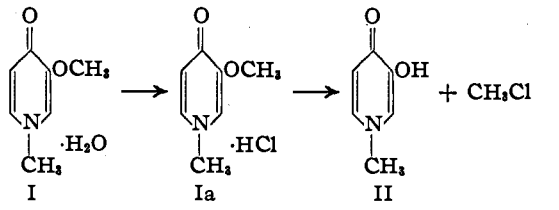
On the Structure of Leucaenine (Leucaenol) from *Leucaena Glauca* Bentham. I.

BY A. F. BICKEL[1]

Leucaenine is an amino acid obtained from the leaves and seeds of the tropical plant, *Leucaena glauca* Bentham. On methylation of leucaenine with dimethyl sulfate in alkaline medium, Bickel and Wibaut[2] obtained a decomposition product, $C_7H_{11}O_3N$(I), to which the structure of a methoxy-oxo-dihydropyridine N-hydroxymethylate was assigned. By heating the "chloro derivative" of I, ($C_7H_{10}O_2NCl$) (Ia), methyl chloride was split off and an N-methylhydroxypyridone, $C_6H_7O_2N$ (II), was formed. The N-methyl-3-hydroxypyridone-4 synthesized by Wibaut and Kleipool[3] proved to be identical with II. According to Bickel and Wibaut, therefore, I should be 4-methoxy-3-oxo-2,3-dihydropyridine N-hydroxymethylate.

In the present investigation, however, it has been shown that I is N-methyl-3-methoxypyridone-4 monohydrate; this compound has now been synthesized by heating together 3-methoxypyrone-4 and methylamine, in aqueous solution. It proved to be identical with I. This result was confirmed by identity of the picrates prepared from I and from the synthetic product, respectively.

The structures of both I and II being now definitely established, the conversion of I into II may be represented by the formulas



I and Ia may also be represented as 3-methoxy-4-hydroxypyridine N-hydroxymethylate and N-chloromethylate, respectively. The pyridone formula, however, accounts more readily for the addition by I of one molecule of bromine, as well as for the fact that a molecule of water may be removed from I by drying over phosphorus pentoxide at 80° (1 mm.). At first sight, the mechanism whereby methyl chloride splits off is not quite clear. In order to elucidate the course of this reaction, N-*ethyl*-3-methoxypyridone-4 was synthesized from 3-methoxypyrone-4 and ethylamine; this compound, prepared under conditions similar to those used for I, does *not* form a hydrate, thus providing further proof that I has the pyridone structure. The hydrochloride of N-ethyl-3-methoxypyridone-4, when heated, yielded N-ethyl-3-hydroxypyridone-4, thus indicating that, in the conversion of Ia into II, the methyl group attached to nitrogen does not wander. These processes, therefore, must be regarded as *intramolecular* reactions of the methoxy group with the

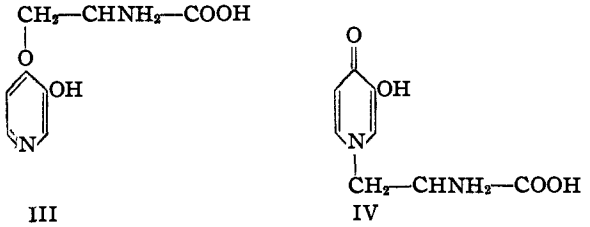
(1) Visiting Fellow, Netherland-America Foundation.

(2) Bickel and Wibaut, *Rec. trav. chim.*, **65**, 65 (1946).

(3) Wibaut and Kleipool, *ibid.*, **66**, 24. (1947). Wibaut, *Helv. Chim. Acta*, **29**, 1069 (1946).

bound hydrochloric acid. It was found that demethylation could also be performed by heating I with aqueous hydrochloric acid in a sealed tube.

From the results obtained in the present investigation, it is obvious that the structural formula of leucaenine proposed by Bickel and Wibaut[2] cannot be correct. Leucaenine must be considered as either β-[4-(3-hydroxypyridyl)-oxy]-α-aminopropionic acid (III) or β-[N-(3-hydroxypyridone-4)]-α-aminopropionic acid (IV).



On pyrolysis of leucaenine, Adams, *et al.*,[4] obtained a dihydroxypyridine to which they tentatively assigned the 2,5-structure. Since it has been shown by Wibaut and Kleipool,[3] as well as in the present investigation, that on degradative methylation of leucaenine a derivative of 3,4-dihydroxypyridine is formed, the dihydroxypyridine isolated by Adams, *et al.*,[4] very probably has the 3,4-structure. The latter authors have also found that leucaenine is unaffected by refluxing with 48% hydrobromic acid or constant-boiling hydriodic acid, and, therefore, prefer a pyridone structure.

Consequently, Formula IV appears to offer the most satisfactory explanation of all the experimental facts now known.

Experimental

All melting points given are corrected.

3-Hydroxypyrone-4 ("pyromeconic acid") was prepared by pyrolysis of meconic acid.[5] Fifteen-gram portions of dehydrated meconic acid in a small flask were heated in a metal-bath, the temperature of which was gradually increased from 240 to 340° during three hours. The distillate solidified to a brown crystalline mass; it was dried in the vacuum desiccator over phosphorus pentoxide and then sublimed at 115° (20 mm.) giving colorless crystals. Average yield was 4.45 g. (53%); m. p., 117.5–119.5°.

3-Methoxypyrone-4 ("methyl ester of pyromeconic acid") was synthesized by the action of diazomethane on 3-hydroxypyrone-4.[6] A large excess of an ether solution of diazomethane was added to 3.2 g. of pyromeconic acid, and the mixture allowed to stand at 0° for several hours. As the reaction proceeded, brownish crystals of the reaction product separated out. As soon as a test sample of the solution showed no red color with ferric chloride, the ether was removed on a water-bath. The brown residue was sublimed at 135° (20 mm.). On repetition of the sublimation, colorless crystals were obtained. Yield was 2.7 g. (76%); m. p., 94.5–95.5°. Peratoner[6] gave m. p. 85°.

Anal.[7] Calcd. for $C_6H_6O_3$: C, 57.12; H, 4.80. Found: C, 57.25; H, 4.95.

(4) Adams, Cristol, Anderson and Albert, THIS JOURNAL, 67, 89 (1945).

(5) See, among others, (a) Ihlée, *Ann.*, 188, 32 (1877); (b) Peratoner, *Gass. chim. ital.*, 24, II, 75 (1894); (c) Borsche, *Ber.*, 49, 544 (1916).

(6) Peratoner, *Gass. chim. ital.*, 36, I, 15 (1906).

(7) The microanalyses were carried out by Mr. G. L. Stragand of the University of Pittsburgh.

N-Methyl-3-methoxypyridone-4 monohydrate was prepared by heating 0.5 g. of 3-methoxypyrone-4 in 28 cc. of a 10% aqueous solution of methylamine on the steam-bath for two hours. The brown solution obtained was evaporated on the steam-bath and the resulting sirup thoroughly dried in a vacuum desiccator over potassium hydroxide and sulfuric acid, giving brownish crystals. These were dissolved in boiling amyl acetate and the solution decanted from a trace of impurity. After cooling, ether was added to the solution and the mixture kept in the refrigerator overnight, giving slightly brown-colored crystals which were filtered off and washed with ether; yield was 0.59 g. (94%). Recrystallization was performed from toluene (yield, 0.46 g.), gave m. p. 91.5–92.5°; mixture melting point with I obtained from leucaenine, 91.5–92.5°.

Anal. Calcd. for $C_7H_{11}O_3N$: C, 53.47; H, 7.07; N, 8.91; H_2O, 11.47. Found: C, 53.71, 53.97; H, 7.06, 7.19; N, 9.21; H_2O, 11.01.

The picrate was prepared by adding a small excess of picric acid dissolved in ethanol to a solution of 50 mg. of N-methyl-3-methoxypyridone-4 monohydrate in 1 cc. of ethanol. Recrystallization was performed from the same solvent, m. p. 215–216°; mixed melting point with the picrate prepared starting from leucaenine, 215–216°.

Anal. Calcd. for $C_7H_9O_2N \cdot C_6H_2(NO_2)_3OH$: N, 15.21. Found: N, 15.31.

N-Methyl-3-hydroxypyridone-4.—N-Methyl-3-methoxypyridone-4 monohydrate (0.45 g.) was heated with 10 cc. of 38% hydrochloric acid in a sealed tube at 145° for four hours. The excess hydrochloric acid was removed by evaporation on a steam-bath to dryness. The brown crystalline residue was dissolved in water and neutralized with sodium carbonate. After evaporation, and drying in a vacuum desiccator, the solid was sublimed at 160° (20 mm.), giving 0.24 g. of a colorless, crystalline sublimate (yield, 67%). This was recrystallized twice from ethanol, m. p. 226–228° with decomposition; mixed melting point with II obtained from leucaenine, 226–228°.

Anal. Calcd. for $C_6H_7O_2N$: C, 57.58; H, 5.64; N, 11.20. Found: C, 57.71; H, 5.65; N, 11.14.

N-Ethyl-3-methoxypyridone-4 was synthesized by heating 0.73 g. of 3-methoxypyrone-4 and 63 cc. of a 10% aqueous solution of ethylamine on the steam-bath for two hours. The excess ethylamine was then removed by evaporation on the steam-bath, the residue dissolved in water and the solution boiled with Nuchar W. The colorless filtrate was re-evaporated and the residue thoroughly dried in the vacuum desiccator over potassium hydroxide and sulfuric acid. The crystals obtained were recrystallized by dissolving in boiling toluene, cooling and adding petroleum ether to opalescence. Yield was 0.65 g. (74%); no color with ferric chloride; m. p., 100.0–101.5°.

Anal. Calcd. for $C_8H_{11}O_2N$: C, 62.71; H, 7.24; N, 9.15. Found: C, 62.48; H, 6.88; N, 9.48.

N-Ethyl-3-methoxypyridone-4 Hydrochloride.—A solution of 0.55 g. of N-ethyl-3-methoxypyridone-4 in 2 cc. of anhydrous methanol was saturated with dry hydrogen chloride at 0°. Methanol and excess hydrogen chloride were removed in the vacuum desiccator over potassium hydroxide and sulfuric acid. The resulting solid was recrystallized from ethanol. Yield was 0.59 g. (87%); m. p., 150–152°.

Anal. Calcd. for $C_8H_{12}O_2NCl$: C, 50.64; H, 6.38. Found: C, 50.44, 50.16; H, 6.43, 6.33.

N-Ethyl-3-hydroxypyridone-4.—A suspension of 0.25 g. of the hydrochloride in 2.5 cc. of dry nitrobenzene was heated in a 25-cc. beaker. At the boiling point of the nitrobenzene, evolution of gas occurred, while the solid dissolved. After boiling for (at least) five minutes the liquid was cooled, slightly brown-colored crystals separating out. These were filtered off, washed with ether, and sublimed at 150° (20 mm.). Yield was 0.11 g. (60%). In an aqueous solution of a test sample, no precipitate of

silver chloride was obtained on adding silver nitrate; with ferric chloride an intense violet color resulted. The sublimate was recrystallized from ethanol, m. p. 169.5–171.5°.

Anal. Calcd. for $C_7H_9O_2N$: C, 60.40; H, 6.52; N, 10.07. Found: C, 60.36; H, 6.22; N, 10.15.

Acknowledgment.—The author expresses his gratitude to Dr. E. R. Weidlein, Director of Mellon Institute, for enabling him to carry out this investigation, and to Dr. Leonard H. Cretcher for his interest and encouragement. He also thanks Professor J. P. Wibaut, of the University of Amsterdam, Holland, for his kindness in presenting him with a considerable quantity of leucaenine.

Summary

A compound, $C_7H_{11}O_3N$ (I), obtained on alkaline methylation of *leucaenine* has been proved by synthesis to be N-methyl-3-methoxypyridone-4 monohydrate.

A new reaction mechanism has been proposed for the demethylation which occurs on heating the hydrochloride obtained from I.

PITTSBURGH 13, PA. RECEIVED JANUARY 23, 1947

[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Structure of Leucenol. II.

BY ROGER ADAMS AND V. V. JONES

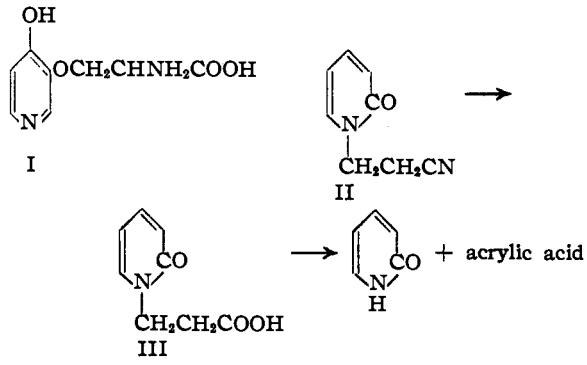
Leucenol, the active principle in *Leucaena glauca benth*, contains an amino acid side chain. It has been suggested that this may be attached to an oxygen of a hydroxyl group in a dihydroxypyridine or to the nitrogen of the same nucleus provided the dihydroxypyridine exists in its tautomeric form as a hydroxypyridone. In a previous paper[1] the conclusion was reached that the nitrogen attachment was to be preferred since neither boiling concentrated hydrobromic nor hydriodic acids cleaved the side chain in leucenol. Wibaut,[2] however, could explain more satisfactorily his degradations of leucenol on the basis of the side chain attached to oxygen. Further experiments have now been completed which serve as supplementary evidence that the side chain is attached to nitrogen.

N-*n*-Propyl-2-pyridone, β-(N-2-pyridone)-propionic acid and the *n*-propyl ether of 2-hydroxypyridine were synthesized and subjected to the action of boiling hydrobromic acid. The first two were recovered unchanged whereas the third one was degraded to 2-pyridone. Peratoner and Tamburello[3] found that hydriodic acid converts 3-methoxy-4-pyridone to 3-hydroxy-4-pyridone and Haitinger and Lieber[4] report the failure of N-methyl-2-pyridone to react with hydriodic acid.

Leucenol gives a blue color with Folin reagent[5] which is characteristic of a 3-hydroxypyridine, whereas this reagent gives no color with a 2- or 4-hydroxypyridine. A N-substituted pyridone with a 3-hydroxyl substituent might be expected to give the same color reactions as a 3-hydroxypyridine since chemical and physical data[6] indicate that N-alkylpyridones are resonance hybrids between the pyridone and the zwitterion structures, the latter of which have a pyridine-like nucleus. N-Methyl-3-hydroxy-4-pyridone has been tested and does give a blue color with Folin reagent.

Wibaut[2] treated leucenol with concentrated alkali and dimethyl sulfate and isolated a pyridone derivative. It has now been demonstrated that β-(N-2-pyridone)-propionic acid (III) readily cleaves with concentrated alkali to 2-pyridone and, moreover, pyrolyzes to 2-pyridone, thus resembling the pyrolysis of leucenol to a hydroxypyridone. It is obvious that a pyridone residue attached through nitrogen to the β-position of a propionic acid undergoes decomposition at high temperatures or with alkali with formation of a pyridone and hence this type of structure may be present in leucenol.

These experimental facts render unlikely the structure (I) proposed by Wibaut with the side chain attached to oxygen and favors the nitrogen attachment as previously suggested in the report from this Laboratory.[1]



2-Pyridone adds to acrylonitrile in the presence of alkali with formation of β-(N-2-pyridone)-propionitrile (II) which is readily hydrolyzed to the corresponding propionic acid (III). This same acid was also prepared directly from sodium pyridone and β-chloropropionic acid.

(1) Adams, Cristol, Anderson and Albert, THIS JOURNAL, **67**, 89 (1945).

(2) (a) Bickel and Wibaut, *Rec. trav. chim.*, **65**, 65 (1946); (b) Wibaut, *Helv. Chim. Acta*, **29**, 1669 (1946).

(3) Peratoner and Tamburello, *Gass. chim. ital.*, **36**, I, 56 (1906).

(4) Haitinger and Lieber, *Monatsh.*, **6**, 311 (1885).

(5) Kuhn and Wendt, *Ber.*, **72**, 305 (1939).

(6) Arndt and Kalischek,. *ibid*, **63**, 587 (1930): 2963 (1930).