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

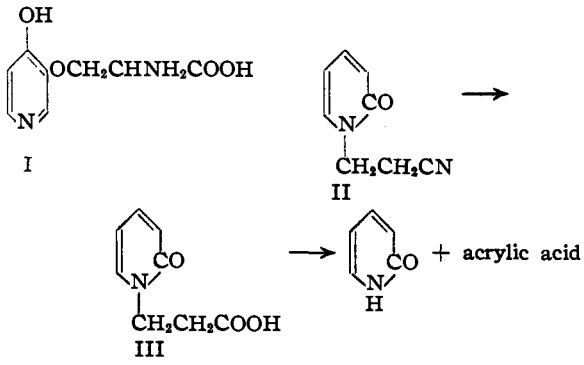
Leucenol, the active principle in *Leucaena glauca benth*, contains an amino acid side chain. It has been suggested that this may be attached to an oxygen of a hydroxyl group in a dihydroxypyridine or to the nitrogen of the same nucleus provided the dihydroxypyridine exists in its tautomeric form as 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 hydroxypyridine. 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).

Wibaut[2b] suggests replacing the name leucenol by leucaenine since the compound is an amino acid. This latter name is perhaps a better one but since either name, leucenol or leucaenine, is at best arbitrary, it seems inadvisable to make a change. The advantage of a change in name of this natural product is more than offset by the disadvantage of introducing two names for the same substance into the chemical literature.

Experimental

Sodium Salt of 2-Pyridone.—This was prepared by the method of Tschitschibabin.[7]

2-Pyridone.—The procedure through the diazotization was identical with that used for sodium pyridone. The diazotized solution of 52 g. of redistilled 2-aminopyridine was neutralized to litmus paper with strong aqueous sodium hydroxide and then evaporated practically to dryness on the steam-bath. The residue was ground and extracted with three 200-ml. portions of boiling acetone. The acetone solution was distilled at atmospheric pressure followed by concentration under diminished pressure on the steam bath to remove the last traces of water. The impure 2-pyridone was taken up in 500 ml. of hot acetone, filtered and cooled in an ice-bath. Tan-colored granular crystals separated; yield 42 g. (81%). For purification, it was recrystallized from acetone, m. p. 106–107° (cor.).

β-(N-2-Pyridone)-propionitrile.—The general method for cyanoethylation was used.[8,9] A mixture of 10 g. (0.105 mole) of 2-pyridone and 5.6 g. (0.105 mole) of acrylonitrile was warmed with approximately 0.1 g. of solid sodium hydroxide until the reaction started. An exothermic reaction occurred after which heating was continued on the steam cone for one-half hour. The resulting sirup was cooled in an ice-bath and the bottom of the flask scratched with a glass rod. An orange-colored solid formed. This was dissolved in 50 ml. of hot benzene and cooled in an ice-bath. Pale yellow needles separated; the yield was 14 g. (90%). The product was purified by boiling in benzene with activated charcoal; colorless needles, m. p. 93–94° (cor.).

Anal. Calcd. for $C_8H_8N_2O$: C, 64.87; H, 5.40; N, 18.9. Found: C, 64.84; H, 5.50; N, 18.3.

β-(N-2-Pyridone)-propionic acid.—A solution of 10 g. (0.675 mole) of the propionitrile in 50 ml. of water and 6 g. of concentrated sulfuric acid was refluxed for two hours. On standing overnight in a refrigerator, long flat white crystals formed. The yield was 8.0 g. (71%). On recrystallization from water, small white platelets were obtained, m. p. 176–178° (cor.). The product was sparingly soluble in cold water, very soluble in hot water and ethanol, but insoluble in acetone, ether, and benzene.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.21; H, 5.36; N, 8.34. Found: C, 57.64; H, 5.64; N, 8.56.

The same compound was prepared by a method somewhat similar to that for making N-alkyl-2-pyridones.[10] A mixture of 14 g. of the dihydrate of the sodium salt of 2-pyridone and 12 g. of β-chloropropionic acid was heated on a steam cone for three hours. On cooling, a tan-colored crystalline solid formed. This was heated with 50 ml. of absolute ethanol and filtered. The filtrate was concentrated to a thick sirup and 30 ml. of hot water added. Upon cooling in an ice-bath, fine white platelets crystallized. The crystals were filtered off and the filtrate further concentrated and cooled to yield a second crop. The combined yield was 15 g. (75%). The product was recrystallized from water, m. p. 176–178° (cor.). The melting point of the mixture of the product with that prepared by the hydrolysis of β-(N-2-pyridone)-propionitrile was 176–178° (cor.).

Pyrolysis of β-(N-2-Pyridone)-propionic acid.—A mixture of 3 g. of β-(N-2-pyridone)-propionic acid and 3 g. of zinc dust was placed in a small distilling flask. A small side-armed test-tube was used as a receiver and immersed in an ice-bath. The pressure in the distilling flask was reduced to 0.5 to 2 mm. and the flask then heated in a metal bath to 180–200° for two hours. A white solid which melted at room temperature sublimed into the receiving tube. This material boiled at 138° (745 mm.) (the b. p. of acrylic acid is 141–142° (760 mm.)) and had the characteristic odor of acrylic acid; yield 0.44 g. (34%). The pyrolysis residue was treated with dilute hydrochloric acid and after filtering and transference to a small flask the solution was made exactly neutral to litmus paper with dilute sodium hydroxide, evaporated to a moist residue, and extracted with 15 ml. of boiling acetone. This solution was mixed with an equal volume of acetone which had been saturated with picric acid, and set in an ice-bath for fifteen minutes. Yellow needles separated, m. p. 172–174° (cor.), giving a yield of 2.5 g. (43%). The melting point of a mixture of this product and of 2-pyridone picrate showed no depression.

The same reaction can be run satisfactorily without the presence of the zinc.

Cleavage of β-(N-2-Pyridone)-propionic Acid with Concentrated Alkali.—A mixture of 3.5 g. of β-(N-2-pyridone)-propionic acid and 25 ml. of 35% aqueous sodium hydroxide was heated on the steam cone for one-half hour. The mixture was cooled, made exactly neutral to litmus paper with dilute sulfuric acid and evaporated to a pasty mass. This was extracted twice with 25-ml. portions of boiling acetone and concentrated to a volume of 25 ml. Upon addition of 25 ml. of acetone saturated with picric acid followed by cooling in an ice-bath, yellow needles separated, m. p. 172–174° (cor.). The yield was 3.8 g. (56%). It proved to be 2-pyridone picrate.

Attempt to Cleave β-(N-2-Pyridone)-propionic Acid with Concentrated Hydrobromic Acid.—A mixture of 5.0 g. of β-(N-2-pyridone)-propionic acid and 50 ml. of 42% aqueous hydrobromic acid was refluxed for six hours. The volume was concentrated to 10 ml. and cooled. After adding 50 ml. of acetone, the mixture was cooled in an ice bath. Six grams (88%) of white granular crystals precipitated, m. p. 184–186°, which proved to be the hydrobromide of β-(N-2-pyridone)-propionic acid.

Anal. Calcd. for $C_8H_{10}O_3NBr$: C, 38.74; H, 4.04; N, 5.65; Br, 32.22. Found: C, 38.90; H, 4.19; N, 5.31; Br, 31.71.

About 2.0 g. of this material was dissolved in 10 ml. of water and made neutral to litmus with strong aqueous sodium hydroxide. Upon acidification with concentrated sulfuric acid small white platelets precipitated, m. p. 176–178°. The melting point of a mixture of this product and β-(N-2-pyridone)-propionic acid showed no depression.

N-*n*-Propyl-2-pyridone.—This was prepared by the method of Decker and Kaufmann.[11]

2-*n*-Propoxypyridine.—This was synthesized by the general method for obtaining O-ethers of hydroxypyridines.[12] In small pieces, 1.5 g. of sodium was added to 20 ml. of *n*-propyl alcohol under reflux. After all the sodium had reacted, 9.0 g. of 2-bromopyridine was added. A spontaneous reaction took place, after which heat was applied and the mixture refluxed for one hour. Water was added to the pasty mass sufficient just to dissolve the sodium bromide. The upper of the two layers was separated, dried over anhydrous magnesium sulfate and then distilled at atmospheric pressure. The yield of the product boiling at 179–182° (cor.) (760 mm.), $\alpha^{20}D$ 1.4914, was 62%.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.09; H, 8.03; N, 10.22. Found: C, 70.20; H, 8.05; N, 10.11.

(7) Tschitschibabin and Rjasanzew, *J. Russ. Phys.-Chem. Soc.*, **47**, 1580 (1915).

(8) British Patent 457,621, Dec. 2, 1936. Bruson, THIS JOURNAL, **64**, 2457 (1942).

(9) Rath, *Ann.*, **486**, 107 (1931).

(11) Decker and Kaufmann, *J. prakt. Chem.*, **84**, 425 (1911).

(12) Haitinger and Lieben, *Monatsh.*, **6**, 311 (1885).

Cleavage of 2-Propoxypyridine with Concentrated Hydrobromic Acid.—A mixture of 3.5 g. of 2-propoxypyridine and 100 ml. of 42% hydrobromic acid was refluxed for six hours. It was then concentrated by distillation to a volume of 10 ml. This was made neutral to litmus paper with concentrated sodium hydroxide solution and extracted with three 20-ml. portions of ether. The ether solution which should contain the starting material was evaporated. Only a negligible residue remained. The aqueous solution was evaporated to a moist residue and extracted once with 15 ml. of boiling acetone. To this was added a saturated solution of picric acid in 15 ml. of acetone. On cooling in an ice-bath for one hour, a solid mass of yellow needles formed, yield 5.1 g. (61%). The melting point was 171–174° (cor.), and the product proved to be 2-pyridone picrate.

Attempted Cleavage of N-*n*-Propyl-2-pyridone with Concentrated Hydrobromic Acid.—A mixture of 3.5 g. of N-*n*-propyl-2-pyridone and 100 ml. of 42% hydrobromic acid was refluxed for six hours. It was then concentrated by distillation to a volume of 10 ml. This was neutralized to litmus paper with concentrated sodium hydroxide solution and the two layers separated. The aqueous layer was extracted with three 20-ml. portions of isoamyl alcohol. The extracts were combined with the top layer, dried over anhydrous magnesium sulfate and distilled. The product boiling from 245–255° was collected. The recovery was 2.9 g. (82%). The aqueous layer was then treated in a manner similar to that mentioned under the cleavage of 2-propoxypyridine. No 2-pyridone picrate was obtained.

Summary

1. N-*n*-Propyl-2-pyridone and the *n*-propyl ether of 2-hydroxypyridine have been synthesized and subjected to the action of boiling hydrobromic acid. The former is unchanged but the latter is hydrolyzed to 2-pyridone.

2. β-(N-2-Pyridone)-propionic acid, a compound analogous to that proposed for leucenol, was prepared in two ways: (1) from sodium 2-pyridone and β-chloropropionic acid, (2) from sodium pyridone and acrylonitrile followed by hydrolysis. This propionic acid cleaves by pyrolysis to 2-pyridone and acrylic acid; it is unaffected by boiling with aqueous hydrobromic acid; it is cleaved by strong alkali to 2-pyridone.

3. The data presented above with those previously reported support the assumption that leucenol has its side chain attached to the nitrogen of a pyridone rather than to the oxygen of an hydroxypyridine.

URBANA, ILLINOIS RECEIVED FEBRUARY 8, 1947

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

On the Structure of Leucaenine (Leucaenol) from *Leucaena glauca* Bentham. II.

BY A. F. BICKEL[1]

On pyrolysis of leucaenine, an amino acid occurring in the tropical plant, *Leucaena glauca* Bentham, Adams, *et al.*,[2] obtained a dihydroxypyridine. Because the properties of this compound differed from those of all five known dihydroxypyridines reported in the literature, Adams, *et al.*,[2] assumed their compound to be the still-unknown 2,5-dihydroxypyridine. Wibaut and Kleipool,[3] and Bickel[4] proved that a compound obtained by Bickel and Wibaut[5] on degradative methylation (of leucaenine) is a derivative of 3,4-dihydroxypyridine. Hence it seemed very probable that the dihydroxypyridine isolated by Adams, *et al.*,[2] actually has the 3,4-structure. Experiments clearly demonstrating the identity of synthetic 3,4-dihydroxypyridine with the compound obtained on pyrolysis have now been completed. Both substances have the same melting point; the aqueous solutions of both are neutral to litmus, and give the same color reaction with ferric chloride; and both compounds react with acetic anhydride to form diacetates, which are also identical in all respects. These properties correspond closely with those reported by Adams, *et al.*[2]

3,4-Dihydroxypyridine was synthesized by hydrolysis of 3-methoxy-4-hydroxypyridine, using a method somewhat different from that described by Peratoner.[6]

The results obtained in the present investigation offer further support for assigning the 3,4-structure to leucaenine.[4]

Experimental

All melting points given are corrected.

3-Methoxy-4-hydroxypyridine was prepared by heating 3.02 g. of 3-methoxypyrone-4[4] with 125 cc. of 6% ammonia on the steam-bath for two hours.[7] The excess ammonia was then removed by evaporation on the steam-bath, the residue dissolved in water, and the solution boiled with Nuchar W. On cooling the filtrate, colorless crystals separated out. The product was filtered off and washed with a small quantity of ice-water. The air-dried trihydrate (yield, 2.92 g.; 68%) melted at 119° on rapid heating; Peratoner[7] gave m. p. 114°. Recrystallization from ethanol, and drying over phosphorus pentoxide, yielded 1.84 g. of 3-methoxy-4-hydroxypyridine, m. p., 180.5–181.5°. Peratoner[7] gave m. p. 173°.

Anal.[8] Calcd. for $C_6H_7O_2N$: C, 57.58; H, 5.64. Found: C, 57.62; H, 5.79.

3,4-Dihydroxypyridine. A. From 3-Methoxy-4-hydroxypyridine.—3-Methoxy-4-hydroxypyridine trihydrate (4.55 g.) was heated with 50 cc. of 38% hydrochloric acid in a sealed tube at 145° for five hours. The excess hydrochloric acid was removed by evaporation *in vacuo* and the residue was thoroughly dried in the vacuum desiccator over

(1) Visiting Fellow, Netherland-America Foundation.

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

(3) Wibaut and Kleipool, *Rec. trav. chim.*, **66**, 24 (1947); Wibaut, *Helv. Chim. Acta*, **29**, 1669 (1946).

(4) Bickel, THIS JOURNAL, **69**, 1801 (1947).

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

(6) Peratoner, *Gazz. chim. ital.*, **36**, I, 56 (1906).

(7) Peratoner, *ibid.*, **36**, I, 52 (1906).

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