[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY,[1] PHILADELPHIA 18, PA.]

Identification of Pseudo-oxynicotine and its Conversion to N-Methylmyosmine

BY PAUL G. HAINES[2] AND ABNER EISNER

Pseudo-oxynicotine was first described by Pinner and Wolfenstein[3] who prepared it by heating oxynicotine (I) with hydrochloric acid in a sealed tube maintained at 140°. These authors assigned no structure to the compound and made no structural determinations other than elementary analyses. By following their procedure a 12% yield of pure product is obtained. A small amount of nicotine is also formed in the reaction. If an attempt is made to avoid the use of a sealed tube by refluxing with hydrobromic acid, the yield is reduced to 5%.

The ultraviolet absorption spectrum of pseudo-oxynicotine (Fig. 1) showed maxima at 223 mμ (ϵ_M = 6,000) and 263 mμ (ϵ_M = 5,230) in 0.1 *N* hydrochloric acid suggesting the presence of a pyridyl ketone structure. Preparation of 3-pyridyl 3-methylaminopropyl ketone dihydrochloride (II) by acid reflux of 1-methyl-3-nicotinoyl-2-pyrrolidone (V)[4] yielded in several steps a hydrochloride melting with decomposition at 196–198°. The melting point of a mixture with pseudo-oxynicotine dihydrochloride was not depressed. Likewise the mercuric chloride and picrate derivatives from each of the two sources were identical. The picrate is of particular interest. The preparation of a picrate from the amino ketone hydrochloride (II) by addition to aqueous picric acid solution produces a picrate melting at 128–130° which analyzes as $C_{22}H_{20}N_8O_{15}$. If this picrate is crystallized from absolute methanol the melting point becomes 158–160° and it analyzes as $C_{22}H_{18}N_8O_{14}$ and is thus assumed to be the dipicrate of N-methylmyosmine (IV) while the former would appear to be the picrate of III. The aminoketone hydrochloride (II) forms a 2,4-dinitrophenylhydrazone; attempts to obtain a styphnate result in an oily product. Upon alkalizing an aqueous solution of II, chloroform extracting and distilling, N-methylmyosmine (IV) is obtained. The free base rapidly undergoes polymerization to a viscous brown oil which then yields an oily picrate.

N-Methylmyosmine, like myosmine,[5] formed no azeotrope with water when a freshly prepared aqueous solution was distilled through a helices packed fractionating column.

Attempts to prepare N-methylmyosmine by methylation of myosmine with methyl iodide or methyl sulfate under various conditions produced only resin.

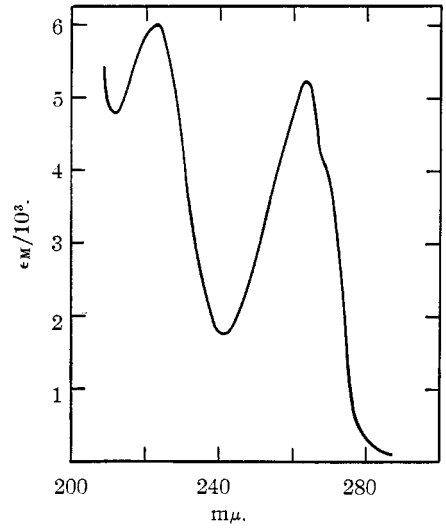
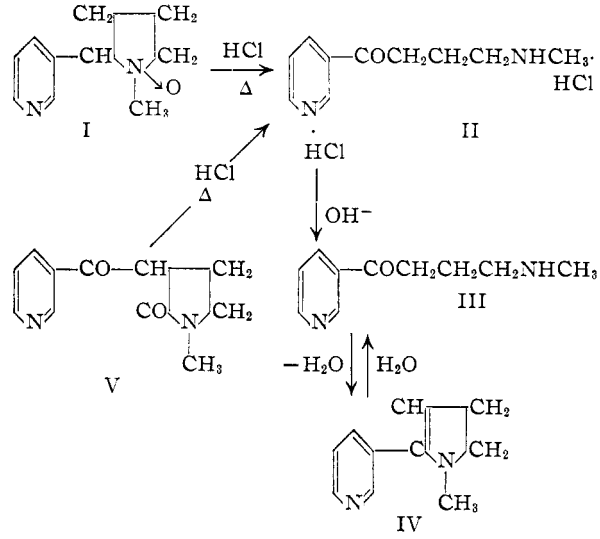


Fig. 1.—Ultraviolet absorption spectrum of 3-pyridyl-3-methylaminopropyl ketone dihydrochloride in 0.1 *N* hydrochloric acid.



Späth, Wibaut and Kesztler[4] have reported that the N-methylmyosmine picrate produced from the base obtained by hydrolysis of 1-methyl-3-nicotinoyl-2-pyrrolidone was identical with the picrate obtained from the dihydronicotyrine produced by zinc–acid reduction of nicotyrine according to the procedure of Wibaut and Hackmann.[6] We have prepared a quantity of dihydronicotyrine picrate (m. p. 159–161°) by reduction of nic-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) Present address: Pennsylvania Salt Company, Whitemarsh Laboratory, Philadelphia 18, Pennsylvania.

(3) Pinner and Wolfenstein, *Ber.*, **25**, 1428 (1892).

(4) Späth, Wibaut and Kesztler, *ibid.*, **71**, 100 (1938), and Späth and Bretschneider, *ibid.*, **61**, 327 (1928), used hydrochloric acid in a sealed tube for this reaction.

(5) Haines, Eisner and Woodward, THIS JOURNAL, **67**, 1258 (1945); Woodward, Eisner and Haines, *ibid.*, **66**, 911 (1944).

(6) Wibaut and Hackmann, *Rec. trav. chim.*, **51**, 1157 (1932).

otyrine according to the method of Wibaut and Hackmann. A mixture of N-methylmyosmine picrate (IV picrate, m. p. 158–160°) with dihydronicotyrine picrate (m. p. 159–161°) had a melting point of 140–145° indicating that they are not identical. A styphnate prepared from dihydronicotyrine melted at 198–200° with decomposition. Recent ultraviolet spectroscopic examination[7] of dihydronicotyrine has shown no evidence of a double bond in a position of conjugation with the pyridine ring. If the double bond is not in a position of conjugation with the pyridine ring the carbon atom to which the pyridine is attached is asymmetric. An attempted resolution of dihydronicotyrine by Osterhuis and Wibaut[8] yielded a material of very small optical activity. If the double bond were located in the 4,5-position of the dihydropyrrole ring facile hydrolysis to an aminoaldehyde and consequent reaction with 2,4-dinitrophenylhydrazine would be expected. We have not been able to obtain a 2,4-dinitrophenylhydrazone by the reaction of this reagent with dihydronicotyrine. Thus it would appear that the double bond is in the 3,4-position in the dihydropyrrole ring of dihydronicotyrine.

In view of the difference between our results and those of Späth, Wibaut and Kesztler[4] several treatments with acid and alkali were conducted to determine if isomerism of dihydronicotyrine into N-methylmyosmine (IV) could be observed. A solution of dihydronicotyrine in dilute aqueous alkali remained unchanged after a month at room temperature but refluxing the dihydronicotyrine with a solution of sodium hydroxide in ethylene glycol produced a crude material from which nicotine picrate could be isolated. The nicotine probably is formed by disproportionation, a reaction previously observed for dihydronicotyrine under different conditions.[6] A twelve hour reflux of dihydronicotyrine with concentrated hydrobromic acid followed by treatment with picric acid gave a picrate mixture melting at 150–175° which could not be purified by crystallization. No clear-cut evidence of isomerism of dihydronicotyrine into N-methylmyosmine was found.

Experimental

Pseudo-oxynicotine Dihydrochloride (II).—Preparation of this compound by the method of Pinner and Wolffenstein[3] gave a 12% yield of product which melted at 196–198° with sintering and decomposition (lit.[3] reports 192°). Heating under reflux with concentrated hydrobromic acid instead of hydrochloric acid in a sealed tube gave a 5% yield. Addition of a portion of II to excess aqueous picric acid solution produced a picrate melting at 128–130°. Crystallization from water did not change this melting point.

Anal. Calcd. for $C_{22}H_{20}N_8O_{15}$: C, 41.51; H, 3.15; N, 17.61. Found: C, 41.50; H, 3.42; N, 17.64.

Crystallization from absolute methanol yielded a picrate melting at 158–160°.

Anal. Calcd. for $C_{22}H_{18}N_8O_{14}$: C, 42.72; H, 2.91; N, 18.12. Found: C, 42.90; H, 3.04; N, 18.13.

Addition of an aqueous solution of II to excess aqueous solution of mercuric chloride gave white crystals melting at 211–213° (lit.[3] reports 212°).

3-Pyridyl 3-Methylaminopropyl Ketone Dihydrochloride (II).—This compound was prepared by hydrolysis of 1-methyl-3-nicotinoyl-2-pyrrolidone (V) prepared by reaction of ethyl nicotinate with 1-methyl-2-pyrrolidone as described by Späth and Bretschneider.[4]

A solution of 6.5 g. of 1-methyl-3-nicotinoyl-2-pyrrolidone in 25 ml. of concentrated hydrobromic acid was refluxed for eight hours. After addition of 100 ml. of water the solution was made strongly alkaline with sodium hydroxide while externally cooling. The alkaline solution was extracted with chloroform. The chloroform extract was extracted with aqueous hydrochloric acid and this acid extract was distilled to dryness at reduced pressure while heating on a hot water-bath. The white crystalline residue was crystallized from absolute ethanol with addition of an equal volume of Skellysolve B[9] while cooling. After drying at 100° for one-half hour there was 4.3 g. of white crystals (II). They melted at 196–198° and the melting point of a mixture with pseudo-oxynicotine dihydrochloride was not depressed. The picrate when crystallized from water melted at 128–130° and if crystallized from absolute methanol melted at 158–160°. The mercuric chloride derivative melted at 211–213°. These derivatives showed no depression of melting point when each was mixed with the like derivative prepared from pseudo-oxynicotine dihydrochloride.

An attempt to prepare a styphnate of II gave an oily product.

When an aqueous solution of II was made alkaline with excess magnesium oxide (forming the equilibrium mixture of III $\rightleftarrows$ IV) and distilled through an eighteen inch long helices packed fractionation column, the distillate was neutral showing that N-methylmyosmine (IV) does not form an azeotrope with water.

A solution of 0.4 g. of II and 0.4 g. of 2,4-dinitrophenylhydrazine in 33 ml. of 95% ethanol was heated to boiling on the steam-bath. Six-tenths of a ml. of concentrated hydrochloric acid was added and the solution was gently boiled for fifteen minutes. Cooling to room temperature produced an orange-colored 2,4-dinitrophenylhydrazone derivative which, after crystallization from 95% ethanol, melted at 224–225°.

Anal. Calcd. for $C_{16}H_{19}N_6O_4Cl$: C, 48.67; H, 4.82; N, 21.29; Cl, 9.00. Found: C, 48.78; H, 4.94; N, 20.65; Cl, 9.21.

N-Methylmyosmine.—A solution of 4.4 g. of II in 20 ml. of water was made strongly alkaline with sodium hydroxide and thrice extracted with 20-ml. portions of chloroform. After drying overnight with anhydrous sodium carbonate, the carbonate was filtered off and the chloroform was distilled off on the steam-bath at slightly reduced pressure. The oil residue distilled at 126–129° at 20 mm. There was 1.3 g. of pale yellow distillate and a fairly large non-distillable residue which solidified to a black solid upon cooling. Addition of aqueous picric acid to a few drops of distillate dissolved in water yielded a picrate melting at 128–130° which changed to a picrate melting at 158–160° upon crystallizing from absolute methanol. The melting point of a mixture with the picrate from II (m. p. 158–160°) was not depressed.

After standing several days in the refrigerator the distillate became very viscous and dark brown-colored. It now produced a somewhat oily picrate which could not be crystallized to constant melting point. N-Methylmyosmine appears to polymerize readily.

Reduction of 3,2′-Nicotyrine to Dihydronicotyrine.—This reduction as described by Wibaut and Hackmann[6] did not yield the anticipated compound.[4] While rapidly stirring and ice-bath cooling, a solution of 29.4 g. of 3,2′-nicotyrine in 360 ml. of 6 *N* hydrochloric acid was treated with 50 g. of zinc dust in small portions during one and

(7) Swain, Eisner, Woodward and Brice, THIS JOURNAL, **71**, 1341 (1949).

(8) Osterhuis and Wibaut, *Rec. trav. chim.*, **55**, 727 (1936).

(9) The mention of specific brands here and in other parts of the paper should not be construed as an endorsement or recommendation of these brands over others not tested.

three-quarter hours at a rate such that the temperature of the solution was maintained at 20–25°. At the time of the first addition of zinc about 0.1 g. of cupric acetate was added. After addition of the last portion of zinc, 80 ml. of concentrated hydrochloric acid was added and the temperature was then maintained at 32–35° while stirring for the next two and one-half hours. While cooling, enough sodium hydroxide was added to redissolve the initially precipitated zinc hydroxide. A small amount of water was added to dissolve precipitated sodium chloride. The alkaline solution was thrice extracted with chloroform. The chloroform extracts were combined and dried overnight with anhydrous sodium carbonate. After filtering off the carbonate and distilling off the chloroform, the oil residue was distilled to yield 17.0 g. of colorless distillate (b. p. 122–130° at 15 mm.).

Addition of a portion of the distillate to excess aqueous picric acid gave a picrate melting at 158–160° after crystallization from methanol or water. The melting point of a mixture with N-methylmyosmine picrate (IV picrate) was 140–145°. The melting point of a mixture with dihydrometanicotine picrate[10] was 145–152°. The remainder of the base was purified through the picrate and then reconverted to the base (b. p. 124° at 20 mm.). Addition of a small amount of the dihydronicotyrine to excess alcoholic styphnic acid solution gave yellow crystals of a styphnate which melted with decomposition at 198–200°. Treatment of 0.2 g. of the dihydronicotyrine with 0.2 g. of 2,4-dinitrophenylhydrazine in hot alcohol solution containing a little concentrated hydrochloric acid produced no derivative. Upon concentrating and cooling only 2,4-dinitrophenylhydrazine precipitated.

Alkali Treatment of Dihydronicotyrine.—When 0.1 g. of dihydronicotyrine was dissolved in 20 ml. of dilute aqueous sodium hydroxide solution and allowed to stand for one month the picrate obtained from it at the end of that time was still that of unchanged dihydronicotyrine.

A solution of 0.2 g. of dihydronicotyrine in 20 ml. of ethylene glycol containing one pellet of sodium hydroxide was refluxed for seven hours. After diluting with 8 ml. of water the solution was acidified by addition of a few drops of concentrated hydrochloric acid. A picrate was formed by adding excess aqueous picric acid. After crystallizing from water the picrate melted at 215–218°. The melting point of a mixture with nicotine picrate was 218–220°. Concentration of the filtrate from the picrate crystallization gave only a gummy picrate.

Acid Treatment of Dihydronicotyrine.—A solution of 0.1 g. of dihydronicotyrine in 20 ml. of concentrated hydrobromic acid was refluxed for twelve hours. After evaporating on the steam-bath to a viscous sirup it was added to excess aqueous picric acid solution. The picrate, after repeated crystallization from water and from alcohol, had a melting range of 150–175°. The melting point of a mixture with dihydronicotyrine picrate was 155–165°. Mixture with nicotyrine picrate gave a melting point of 142–150°. The melting point of a mixture with N-methylmyosmine picrate (IV picrate) was 140–150°.

Acknowledgment.—The authors are indebted to Ruth Brand and Jane Dixon for the elemental analyses, to Leopold Weil of this laboratory for the ultraviolet absorption spectrum and to the Cliffs–Dow Chemical Company, Marquette, Michigan for a generous sample of pyrrolidone-2.

Summary

Pseudo-oxynicotine dihydrochloride was identified as 3-pyridyl 3-methylaminopropyl ketone dihydrochloride which upon alkalization and distillation yielded 1-methyl-2-(3-pyridyl)-2-pyrroline (N-methylmyosmine).

Contrary to a previous report the zinc-acid reduction of 3,2′-nicotyrine did not produce N-methylmyosmine but produced a dihydronicotyrine of uncertain structure.

N-Methylmyosmine underwent ready polymerization upon standing while dihydronicotyrine did not.

Though acid and alkali did have some effect upon dihydronicotyrine at elevated temperatures no clear-cut evidence of isomerism of dihydronicotyrine into N-methylmyosmine was found.

(10) Wibaut and Gitsels, *Rec. trav. chim.*, **52**, 303 (1933).

PHILADELPHIA 18, PA. RECEIVED AUGUST 12, 1949

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE AMERICAN TOBACCO COMPANY]

Rearrangement of Nicotine Oxide

BY C. H. RAYBURN, W. R. HARLAN AND H. R. HANMER

Two isomers of nicotine oxide were described by Pinner and Wolffenstein[1] and Pinner,[2] who named them pseudo-oxynicotine and nicotone. Pseudo-oxynicotine has been identified as 3-pyridyl 3-methylaminopropyl ketone by Haines and Eisner.[3]

Nicotine oxide (I) was pyrolyzed to an isomeric, volatile base by heating *in vacuo* to 200°. The dipicrate melted at 184° when first prepared, agreeing with the melting point of nicotone dipicrate,[2] though further purification raised the melting point to 194–195°. The similarity in method of preparation and properties of the compounds indicates that the base is identical with Pinner's nicotone.

That this base is 2-methyl-6-(3-pyridyl)-tetrahydro-1,2-oxazine (II) is shown by its conversion to 3-pyridyl 3-methylaminopropyl ketone (III) by heating with hydrochloric acid, and by its reduction to 4-methylamino-1-(3-pyridyl)-1-butanol (IV). The structure of IV was proven by dehydration to a mixture of nicotine (V) and metanicotine (VI).

The melting points of the dipicrate and the mercuric chloride derivatives differentiate II from its isomer, 3-pyridyl 3-methylaminopropyl ketone.[3] Tests for aldehyde and ketone groups with II gave negative results. The ultraviolet absorption spectrum in 0.1 *N* hydrochloric acid (Fig. 1) showed only one maximum, at 257.5 mμ, (ϵ_M = 5,600) and was almost identical with that of nicotine oxide (ϵ_M = 5,677 at 257.5 mμ). The

(1) Pinner and Wolffenstein, *Ber.*, **25**, 1428 (1892).
(2) Pinner, *ibid.*, **28**, 456 (1895).
(3) Haines and Eisner, THIS JOURNAL, **72**, 1719 (1950).