Chemical Reactivity of Myosmine

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It was previously reported that myosmine (I), 2-(3-pyridyl)-Δ^2-pyrroline, had been produced in fair yields by the pyrolysis of nicotine.[2] Since prior work on myosmine was limited to reactions selected to establish the structure of the alkaloid,[3,4] a more extensive investigation of its chemical reactivity has been undertaken in the present study. Particular attention has been directed to reduction products and to derivatives of 3-pyridyl-ω-aminopropyl ketone (II), the open chain hydrolytic product of myosmine.

Data previously reported on the hydrolysis of Δ^2-pyrrolines by water appear to be in disagreement. The reaction of 2-methyl-Δ^2-pyrroline with hydroxylamine, semicarbazide and phenylhydrazine in aqueous solution led Marz to conclude that an equilibrium existed between the cyclic form and the open chain primary amino ketone.[5] However, the several 1-methyl-2-alkyl-Δ^2-pyrrolines prepared and studied by Craig[6] apparently were not hydrolyzed by water, since no reaction took place with phenylhydrazine or semicarbazide. Basicity data obtained by Adams and Mahan[7] on a number of 1,2-dialkyl-Δ^2-pyrrolines supported the assumption "that only a single molecule" was involved in the titrations.

N-Alkyl-Δ^2-pyrrolines are generally not hydrolyzed in aqueous solution, whereas the corre-

(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) Woodward, Eisner and Haines, This Journal, **66**, 911 (1944).

(3) Späth, Wenusch and Zajic, *Ber.*, **69**, 393 (1936).

(4) Späth and Mamoli, *ibid.*, **69**, 757 (1936).

(5) Marz, Diss., Techn. Hochsch., München, 1913.

(6) Craig, This Journal, **55**, 295 (1933).

(7) Adams and Mahan, *ibid.*, **64**, 2588 (1942)

sponding secondary amines are readily susceptible to hydrolysis. Further evidence for this generalization was obtained in the present investigation. Myosmine reacted instantaneously with phenylhydrazine, hydroxylamine and semicarbazide to form carbonyl derivatives of the ω-aminoketone. The alkaloid also gave the correct nitrogen analytical value for one primary amino group by the Van Slyke procedure. N-Methylmyosmine, however, apparently underwent no hydrolytic ring cleavage, even on prolonged heating with concentrated acid or alkaline solutions.

Acceptance of modern electronic theories of organic reactions postulating that substitution of an alkyl group for hydrogen in a molecule produces an electronic displacement away from the substituent[8] may offer an explanation for the reactivity of Δ^2-pyrrolines under hydrolytic conditions. Electronic displacement away from the nitrogen of the N-alkyl group would impart a negative charge to the 2-carbon atom, which would in turn hinder the combination of hydroxyl ions with the 2-carbon atom. However, in view of the apparent ease of hydrolysis of N-alkyl-Δ^2-tetrahydropyridines,[9] the limitations of this explanation are obvious.

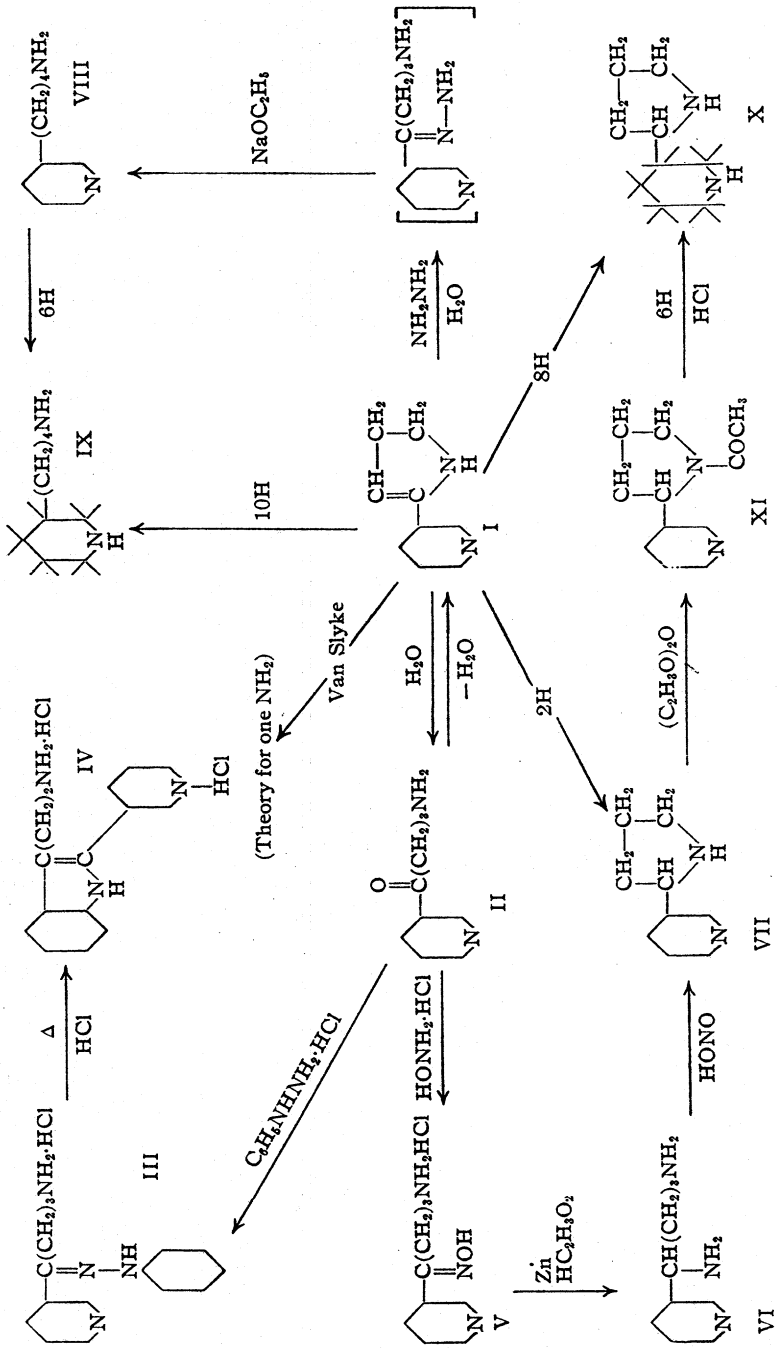
Reaction of myosmine with benzoic anhydride under anhydrous conditions yields the anticipated 2-(3-pyridyl)-N-benzoyl-Δ^2-pyrroline. If, however, 2-(3-pyridyl)-N-benzoyl-Δ^2-pyrroline stands in contact with a dilute acid solution, the product is the 3-pyridyl-ω-benzoylaminopropyl ketone previously reported by Späth.[3]

Nornicotine (VII), hexahydronornicotine (X), and octahydronornicotine (IX), were prepared by the reduction of myosmine. Evidence was obtained indicating that acylation of nornicotine protects the acetylated ring against cleavage on reduction.

The following new compounds were also prepared in the course of this investigation: 3-(1,4-diaminobutyl)-pyridine (VI), 3-(4-amino-butyl)-pyridine (VIII), and 2-(3-pyridyl)-3-(2-aminoethyl)-indole dihydrochloride (IV).

(8) Ingold, *Chem. Revs.*, **15**, 225 (1934).

(9) Lipp and Widnmann, *Ann.*, **409**, 79 (1915).



Experimental

All melting points are corrected unless otherwise noted.

3-Pyridyl-ω-aminopropyl Ketone Phenylhydrazone Hydrochloride (III).—A solution of 4.1 g. (0.0275 mole) of myosmine in 3 ml. of water was added to an equivalent amount of phenylhydrazine hydrochloride (3.9 g.) dissolved in the smallest amount of hot water. The mixture was cooled in an ice-bath and the precipitated product was dried in a vacuum desiccator; yield, 7.6 g. The phenylhydrazone hydrochloride was crystallized from absolute alcohol–petroleum ether mixture, m. p. 201.0–202.0°.

Anal. Calcd. for $C_{15}H_{19}N_4Cl$: Cl, 12.22. Found: Cl, 12.36.

Eighteen grams of the phenylhydrazone hydrochloride was dissolved in 200 ml. of 5 *N* HCl and the solution was evaporated to small volume. About 100 ml. of water was added and the solution was evaporated to small volume. This was repeated several times. The solution was finally evaporated to dryness, and the residue was recrystallized from 95% ethanol containing a small amount of acetone. To remove traces of contaminating salts, the hydrochloride was treated with excess sodium carbonate solution, and the mixture extracted with ether. The dried extract was evaporated to an oily residue. (Removal of the last traces of ether required reduced pressure.) The residue was treated with dry alcoholic hydrochloric acid, and the resulting hydrochloride was recrystallized from alcohol–acetone mixture, yield, 11.3 g., m. p., with dec., 323–325° (uncor.). The product was the expected **2-(3-pyridyl)-3-(2-aminoethyl)-indole dihydrochloride (IV).**

Anal. Calcd. for $C_{15}H_{17}N_3Cl_2$: C, 58.06; H, 5.48; Cl, 22.90. Found: C, 57.94; H, 5.54; Cl, 22.95.

To demonstrate the presence of a primary amino group in the hydrolytic product, a Van Slyke amino nitrogen determination was made on myosmine.

Anal. Calcd. for one amino nitrogen: 9.59 amino N. Found: N, 9.87.

3-Pyridyl-ω-aminopropyl Ketone Semicarbazone Hydrochloride.—To 1.2 g. of myosmine (0.0082 mole) dissolved in 3 ml. of absolute alcohol was added 0.92 g. of semicarbazide hydrochloride dissolved in the smallest amount of boiling 85% ethanol. The product formed slowly after long cooling: yield 1.5 g. The semicarbazone hydrochloride after recrystallization from 95% alcohol melted at 201.1–202.1°.

Anal. Calcd. for $C_{10}H_{16}N_5OCl$: Cl, 13.80. Found: Cl, 13.93.

3-Pyridyl-ω-aminopropyl Ketoxime Hydrochloride (V).—To 4.0 g. (0.0274 mole) of myosmine dissolved in 6 ml. of 95% ethanol was added an equivalent amount of hydroxylamine hydrochloride (1.9 g.) dissolved in the smallest amount of boiling 95% ethanol. The mixture was stirred while cooling, and the precipitated product after drying for one-half hour at 110° weighed 4.3 g. The ketoxime hydrochloride was crystallized from hot methyl alcohol to which petroleum ether had been added until it became turbid, m. p. 197.7–198.7°.

Anal. Calcd. for $C_9H_{14}N_3OCl$: N, 19.49; Cl, 16.47. Found: N, 19.87; Cl, 16.46.

Reduction of 3-Pyridyl-ω-aminopropyl Ketoxime Hydrochloride to 1-(3-Pyridyl)-1,4-diaminobutane (VI).—To 6.5 g. of the ketoxime hydrochloride dissolved in 150 ml. of 95% ethanol was added 45 ml. of glacial acetic acid. Fifty grams of zinc dust, in small portions, was added over a period of several hours. After standing overnight, the excess zinc was filtered off and washed with alcohol. To expel the alcohol and most of the acetic acid, the filtrate and washings were evaporated on the steam-bath to a thick sirup. A small amount of water was added, and the solution was evaporated again. The residue was taken up in several hundred ml. of water, and enough sodium hydroxide was added to dissolve any precipitate. The alkaline solution was extracted with ether, and the ether extract was dried over anhydrous sodium sulfate. Upon evaporation of the ether, the residual oil was vacuum distilled. The distillate (3.1 g.), b. p. 157–160° (6 mm.), n_D 1.5438 at 24°, formed a picrate; recrystallized from water, m. p. 207.2–208.4°. A portion of the distillate exposed to air for a few days formed a white solid, which could not be crystallized to a constant melting point. It was apparently a hydrate or carbonate and not an oxide, since its picrate was identical with that of its original distillate. The dibenzoyl derivative, recrystallized from 95% alcohol, melted at 173.6–174.8°.

Anal. Calcd. for $C_{23}H_{23}N_3O_2$: C, 73.99; H, 6.17; N, 11.26. Found: C, 73.96; H, 6.00; N, 11.71.

Cyclization of 1-(3-Pyridyl)-1,4-diaminobutane to *dl*-Nornicotine (VII).—To 0.5 g. of 1-(3-pyridyl)-1,4-diaminobutane dissolved in 25 ml. of concentrated hydrochloric acid was added 3 g. of sodium nitrite in small portions over a period of three to four hours. The insoluble salts were filtered off, and the filtrate was evaporated almost to dryness. The process was repeated after the addition of 5 ml. of concentrated hydrochloric acid. The residue was treated with excess sodium hydroxide and the solution was extracted with ether. The ether solution was extracted with dilute hydrochloric acid, and the acid extract was evaporated almost to dryness. Conversion of the residue to the picric acid derivative gave 0.4 g. of picrate melting at 193.0–194.0°. This compound was identical with *dl*-nornicotine picrate.

3-(4-Aminobutyl)-piperidine (Octahydronornicotine) (IX).—Ten grams of myosmine (0.069 mole) and 3.5 g. of hydrazine hydrate (0.07 mole) were dissolved in 20 ml. of absolute ethanol, and the mixture was refluxed for two hours. To this was added 6.6 g. of sodium ethylate, and the ethanol was distilled off by gradually raising the temperature (oil-bath) to 190°. The mixture was maintained at this temperature for two hours. Water was added after the mixture had cooled and the alcohol was distilled off. The alcoholic alkaline distillate was acidified, evaporated to dryness, and added to the distillation residue. The combined residues were made strongly alkaline and ether-extracted, and the ethereal solution was extracted with dilute hydrochloric acid. This solution was evaporated on the steam-bath to a sticky paste which was then washed with 95% ethanol. When the alcohol insoluble residue was mixed with myosmine hydrochloride, there was no depression of the melting point.

The washings were concentrated and converted to a picrate. Yield of picrate was 14.3 g., m. p. 180.5–181.5° after recrystallization from water. When it was mixed with myosmine picrate, the melting point was greatly depressed. The picrate was converted into the free base in the manner described previously. The base was distilled under reduced pressure, b. p. of **3-(4-aminobutyl)-pyridine (VIII)**, 104.5–105.5° (1.5 mm.); yield of product, 2.7 g., n_D 1.5200 at 25°. The free base was hygroscopic and did not give satisfactory analytical values. The benzenesulfonyl derivative was prepared (m. p. 112.5–113.5°).

Anal. of 3-(4-benzenesulfonamidobutyl)-pyridine. Calcd. for $C_{15}H_{18}N_2SO_2$: S, 11.03. Found: S, 11.31.

One and two-tenths grams of the base was dissolved in 25 ml. of water containing 2.0 ml. of concentrated hydrochloric acid and then hydrogenated, 0.1 g. of Adams platinum oxide being used as catalyst. The catalyst was filtered off, and the filtrate was evaporated to dryness on the steam-bath. The residue, recrystallized from absolute alcohol, melted at 228.8–230.0°. Yield of **3-(4-aminobutyl)-piperidine (IX) hydrochloride** was 0.8 g. A small portion converted to picrate melted at 118.5–119.5°. The free base obtained from the hydrochloride and distilled under reduced pressure gave a solid distillate, m. p. 41.0–42.3°.

The *p*-toluenesulfonyl derivative, made in the usual manner, when recrystallized from 70% ethanol, melted at 143.0–144.0°.

Anal. Calcd. for $C_{22}H_{32}N_2S_2O_4$: C, 59.48; H, 6.90; N, 6.03. Found: C, 59.67; H, 7.08; N, 5.93.

dl-Nornicotine (VII)

1. Catalytic Reduction.—To a solution of 5.0 g. of myosmine in 50 ml. of absolute ethanol was added 0.15 g. of palladous oxide catalyst, and the mixture was reduced with hydrogen at room temperature. The initial pressure was 50 lb. per sq. in., and hydrogen uptake ceased after an approximately equi-molar amount had been absorbed (two hours). The catalyst was filtered, 5 ml. of concentrated hydrochloric acid was added to the filtrate, and the solution was then concentrated to a thick sirup on the steam-bath. The *dl*-nornicotine was recovered as the picrate, formed by adding excess picric acid to the sirup. The resulting picrate after recrystallization from water melted at 193.0–194.0°. Yield of *dl*-nornicotine as picrate was 19.2 g., 93%.

2. **Reduction with Nascent Hydrogen.**—To a solution of 1.4 g. of myosmine in 60 ml. of 95% ethanol was added 25 ml. of glacial acetic acid. Eight grams of zinc dust was added in small portions over several hours, and the mixture was allowed to stand overnight. The unreacted zinc was filtered off and washed with 95% ethanol. The filtrate and washings were combined and concentrated to small volume on the steam-bath. A small amount of water was added, and the process was repeated. The sirupy residue was dissolved in 200 ml. of water, made strongly alkaline, and ether-extracted. The ether-extracted oil was converted to picrate in the usual manner. Yield of nornicotine picrate was 1.5 g. (27%).

Catalytic Reduction to Hexahydronornicotine (X) and Octahydronornicotine (IX).—Ten grams of myosmine (0.069 mole) was dissolved in 60 ml. of water. Thirteen ml. of concentrated hydrochloric acid (0.156 mole) and 1.5 g. of Pd charcoal (5% Pd) were added, and the mixture was subjected to catalytic hydrogenation at room temperature. Initial hydrogen pressure was 50 lb./sq. in. At the end of three hours the rate of hydrogen absorption dropped. One-tenth gram of Adams platinum oxide catalyst was added, and the reduction was continued. Hydrogen absorption ceased after about 0.27 mole of hydrogen had been taken up. The catalyst was filtered and washed with hot water. The filtrate and washings were combined, and to this mixture was added 30.5 g. of picric acid. The reaction mixture was heated to boiling, and sufficient water was added to complete solution. On chilling overnight, a mixture of picrates separated out; this was collected and fractionally crystallized from 95% ethanol. Twelve and eight-tenths grams of a picrate (m. p. 215–218°) separated out. The alcoholic filtrate was evaporated to dryness, and the residue was crystallized from water to yield 12.4 g. of an impure picrate melting at 111–118°. The latter was treated with an excess of 4 *N* hydrochloric acid and the precipitated picric acid was filtered off. The filtrate was extracted once with ether to remove traces of picric acid, and the solution was then made strongly alkaline and the liberated base extracted with ether. The ethereal solution was extracted with dilute hydrochloric acid, and the acid extract was evaporated to dryness on the steam-bath. The residue (2.3 g.) was recrystallized from absolute ethanol, m. p. 225.0–227.7°. The hydrochloride was converted into the picrate derivative, which, after recrystallization from water, melted at 118.0–119.0°. When mixed with a sample of 3-(4-aminobutyl)-piperidine dipicrate (obtained by catalytic reduction of the Wolff–Kishner reduction product from myosmine hydrazone) there was no depression of the melting point.

The 12.8 g. of picrate (m. p., 215–218°) was converted to the base hydrochloride in the same manner as that described for the picrate of the decahydro product. The residue obtained from the evaporation of the hydrochloric acid solution was fractionally crystallized from absolute ethanol. The hydrochloride which crystallized out (0.8 g.) melted at 300.0–302.0° (uncor.) with decomposition. A portion of this hydrochloride was converted to picrate, m. p. 224.8–225.8°.

The 0.8 g. of hydrochloride, dissolved in water, was optically inactive. The base was recovered from this solution by making it alkaline, extracting with ether, drying the extract, and evaporating the ether. The residual oil was distilled under reduced pressure (b. p. 133° at 26 mm.). The distillate (0.55 g.), which solidified in the receiver, seemed to take up water from the air to form a white powder. A picrate made from the hydrate melted at 224.5–225.5° and when it was mixed with the original picrate there was no depression of the melting point.

The benzenesulfonyl derivative recrystallized from 95% ethanol melted at 170.5–171.5°.

Anal. of dibenzenesulfonyl hexahydronornicotine. Calcd. for $C_{21}H_{26}N_2S_2O_4$: C, 58.06; H, 5.99; N, 6.45; S, 14.75. Found: C, 57.95; H, 6.14; N, 6.25; S, 14.92.

The alcoholic filtrate from the hydrochloride, m. p. 300.0–302.0°, was evaporated nearly to dryness, and the residue was treated with picric acid solution. The resulting picrate (2.5 g.) melted at 261–262° (uncor.). One and six-tenths grams was converted into the hydrochloride in the manner described previously. The hydrochloride obtained by evaporation of the hydrochloric acid solution did not solidify. Its aqueous solution was not optically active. The base was recovered from this solution in the usual manner and vacuum-distilled. The distillate (0.3 g.) solidified into white platelets. It also was hygroscopic, taking up water to form a white powder.

A benzenesulfonyl derivative of this material was prepared. It was recrystallized from 80% ethanol, m. p. 202.2–203.2°.

There are two asymmetric carbon atoms in hexahydronornicotine, so one would predict the occurrence of four enantiomorphs in the form of two optically inactive racemic modifications.

Anal. of dibenzenesulfonyl derivative of hexahydronornicotine. Calcd. for $C_{21}H_{26}N_2S_2O_4$: C, 58.06; H, 5.99; N, 6.45; S, 14.75. Found: C, 58.12; H, 5.91; N, 6.18; S, 14.65.

Catalytic Reduction of N-Acetyl-*dl*-nornicotine (XI).—N-Acetyl-*dl*-nornicotine (b. p. 154° (0.6 mm.), n_D 1.551 at 20°; picrate m. p. 158.5–159.5°)[10] was prepared by refluxing *dl*-nornicotine with excess acetic anhydride. To a solution of 6.3 g. (0.0332 mole) of N-acetyl-*dl*-nornicotine in 72 ml. of 5 *N* HCl was added 0.2 g. of Adams platinum oxide catalyst, and the mixture was reduced with hydrogen at room temperature. The initial pressure was 50 lb. per sq. in. Hydrogen uptake ceased after approximately 0.099 mole of gas had been absorbed (six hours). The catalyst was filtered off, and the filtrate was evaporated on the steam-bath to a sirupy residue. The residue was refluxed with 80 ml. of concentrated hydrochloric acid for five hours and again evaporated. The residue was treated with strong sodium hydroxide solution and ether-extracted. The ether solution was extracted with dilute hydrochloric acid. The acid extract was then evaporated to a sirup and stored overnight in a vacuum desiccator. The resulting white paste was suspended in 50 ml. of absolute ethanol, heated to boiling, cooled in ice, and filtered off. There was 2.1 g. of insoluble hydrochloride, m. p. 301–303° (dec. uncor.), which formed a picrate, m. p. 225–226°. When mixed with hexahydronornicotine hydrochloride and picrate, respectively (obtained by catalytic reduction of myosmine), there was no depression of the melting point.

The alcoholic filtrate was evaporated, and picric acid was added to the residue. After repeated recrystallization from ethanol–water mixture, there was 0.7 g. of picrate, m. p. 261–262°. When mixed with the isomeric hexahydronornicotine picrate melting at 261–262° (obtained by catalytic reduction of myosmine) there was no depression of the melting point.

No 3-(4-aminobutyl)-piperidine was found. Apparently the acetyl group on the pyrrolidyl nitrogen protects the ring from fission.

Benzoylation of Myosmine

N-Benzoyl-myosmine.—A mixture of 10.2 g. of myosmine (0.069 mole) and 20.4 g. of benzoic anhydride (0.09 mole) in a loosely stoppered flask was warmed on a steam-bath for three hours. The reaction mixture was cooled in an ice-bath, and 125 ml. of 1 *N* HCl was added. Benzoic acid was removed by filtration and ether-extraction of the acid filtrate. The filtrate was made strongly alkaline with sodium hydroxide and ether-extracted. The dried extract was evaporated, and the oil residue vacuum-distilled. A small fraction boiling below 172° at 0.15 mm. was discarded. The main fraction, 11.4 g., was a viscous yellow oil, boiling range 190–200° at 0.15 mm. Attempts to crystallize portions of this oil were unsuccessful; consequently it was converted to its picric acid derivative; yield, 13.8 g., m. p. after recrystallization from water, 201.5–202.5°.

Anal. Calcd. for $C_{22}H_{17}N_5O_8$: C, 55.11; H, 3.57; N, 14.61. Found: C, 54.83; H, 3.64; N, 14.82.

(10) v. Braun and Weiszbach, *Ber.*, **63**, 2018 (1930), report 151° as the m. p. of the picrate of N-acetyl-nornicotine.

3-Pyridyl-ω-benzamidopropyl Ketone.—A portion of the above picrate was treated with an excess of 6 *N* HCl, and the precipitated picric acid was filtered off. The acid filtrate was extracted with ether to remove traces of picric acid. The aqueous layer was chilled in ice, and enough sodium hydroxide was added to make the mixture just alkaline. The white precipitate, filtered off and crystallized from 40% ethanol, melted at 117.0–117.8° (yield 6.3 g.). The melting point and analytical result agree with those of the myosmine benzoylation product which Späth, Wenusch and Zajic[3] reported to be 3-pyridyl-ω-benzamidopropyl ketone. The picrate of this base melted at 151.0–152.0°. When mixed with the picrate of N-benzoylmyosmine, the melting point was depressed.

Anal. Calcd. for $C_{22}H_{19}N_5O_9$: C, 53.12; H, 3.82; N, 14.08. Found: C, 52.87; H, 4.14; N, 13.70.

The base also formed a hydrochloride melting at 195.0–196.0°.

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Summary

Myosmine hydrolyzes readily to 3-pyridyl-ω-aminopropyl ketone in aqueous solution, whereas N-methylmyosmine is resistant to hydrolysis.

Nornicotine, hexahydronornicotine and octahydronornicotine were prepared by the reduction of myosmine and by confirmatory syntheses. 3-(1,4-Diaminobutyl)-pyridine, 3-(4-aminobutyl)-pyridine, and 2-(3-pyridyl)-3-(2-aminoethyl)-indole dihydrochloride were also prepared.