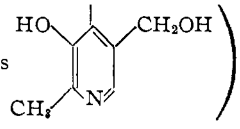
solubility tests indicated that *p*-hydroxybenzaldehyde 2,4-dinitrophenylhydrazone was the most soluble, and this is of the order of only 2–3 mg./ml. MeOH. The percentage isomerized was calculated as

$$\text{For } \underset{\text{I}}{\text{R—CH}_2\text{—N=CH—R}'} \longrightarrow \underset{\text{Ia}}{\text{R—CH=N—CH}_2\text{—R}'} \longrightarrow$$

$$\underset{\text{II}}{\text{R—CHO}} \longrightarrow \underset{\text{III}}{\text{R—CH=N—NH—Ph(NO}_2)_2}$$

$$\% = \frac{\text{Formula wt. (I)} \times \text{wt. of III in mg.} \times 100}{\text{Formula wt. (III)} \times \text{wt. of sample of I in mg.}}$$

The results (R' always



) are listed in Table III and Fig. 1.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

Infrared Diagnosis of the Hydrochlorides of Organic Bases. II.[1] The Structure of Myosmine

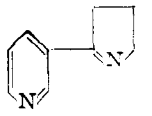
BY BERNHARD WITKOP

RECEIVED FEBRUARY 25, 1954

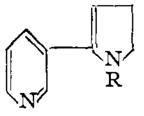
The alkaloid myosmine is particuarly suited for the demonstration of *ammonium* and *immenium* bands observed in the infrared spectrum on stepwise salt formation, which makes possible the exact assignment of these bands to the Δ^1-pyrroline and pyridine part of the molecule. The structure of myosmine as the free base or in the form of the two hydrochlorides is that of a Δ^1-pyrroline (I).

It has been shown in the preceding paper that hydrochlorides (or other salts) of tertiary bases, containing the element >C=N— isolated or in an aromatic system, in all simple cases display *immonium* bands in the region 4.5–5.5 μ which can be utilized for the characterization and structural elucidation of dibasic alkaloids.

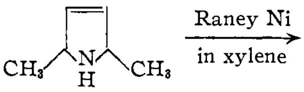
The application of this method to the location of the unsaturation in the pyrrolidine moiety of the tobacco alkaloid myosmine is an instructive example of the scope and usefulness of the method. Myosmine has hitherto been formulated as a Δ^2-pyrroline (IIb)[2] analogous to IIa, the structure favored for dihydronicotyrine ("N-methylmyosmine") by Wibaut and Beyerman.[3,4] It has now been found that myosmine as the free compound in the solid state, in solution,[5] and in the form of its mono- and dihydrochlorides is best expressed by the Δ^1-pyrroline structure (I). As Eddy and Eisner observed independently,[5] there is *no band in the NH region* in the infrared spectrum of myosmine (Fig. 1A). A strong band at 6.15 μ is characteristic of a >C=N— element conjugated with an aromatic system, thus ruling out structure II and the non-conjugated Δ^1-pyrroline. Δ^1-Pyrrolines with an unconjugated azomethine group show a strong band at 6.00 μ, Δ^2-pyrrolines exhibit the narrow and shorter band typical of >C=C< at approximately the same wave length.[6]



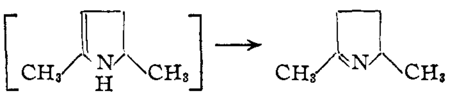
I



IIa, R = CH_3
IIb, R = H



III, picrate, m.p. 107°



IV

V, picrate 136°

The preferred position of the double bond in pyrrolines may depend largely on the position and nature of substituents. According to the report of the Raney nickel-catalyzed isomerization of a Δ^3- into a Δ^1-pyrroline (III → V), the Δ^2-tautomer (IV) in this case is very labile and not observed[6]; likewise, there is no evidence for the existence of a Δ^2-tautomer of myosmine. Other substituents apparently facilitate the reverse migration to a Δ^3-pyrroline.[7] There are probably no authentic secondary Δ^2-pyrrolines. In fact the alleged 2-methyl-[6] and 2-phenyl-Δ^2-pyrrolines[8] were shown to be Δ^1-pyrrolines by Zerewitinoff determinations.[9] The infrared diagnosis of such bases and their hydrochlorides should prove useful in further establishing their structure and any possible tautomerism.

The tertiary pyrrolidine nitrogen in nicotine (pK_B 6.15) and the tertiary pyrroline nitrogen in myosmine

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(1) Paper I in this series, B. Witkop, *Experientia*, **10**, Oct. (1954).

(2) *Cf.* L. Marion in "The Alkaloids," by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York, N. Y., 1950, Vol. 1, p. 255.

(3) J. P. Wibaut and H. C. Beyerman, *Rec. trav. chim.*, **70**, 977 (1951).

(4) M. L. Swain, A. Eisner, C. F. Woodward and B. A. Brice, THIS JOURNAL, **71**, 1341 (1949).

(5) C. R. Eddy and A. Eisner, *Anal. Chem.*, in press.

(6) G. G. Evans, THIS JOURNAL, **73**, 5230 (1951).

(7) J. W. Cornforth and A. J. Henry, *J. Chem. Soc.*, 597 (1952).

(8) S. Gabriel and J. Colman, *Ber.*, **41**, 519 (1908).

(9) P. M. Maginnity and J. B. Cloke, THIS JOURNAL, **73**, 49 (1951). It is probably safe to conclude that the homologous six-membered tetrahydropyridines, such as γ-coniceine and tetrahydro-α-picoline [A. Lipp and E. Widnmann, *Ber.*, **38**, 2471 (1905)] have to be formulated as Δ^1- and not as Δ^2-piperidines.

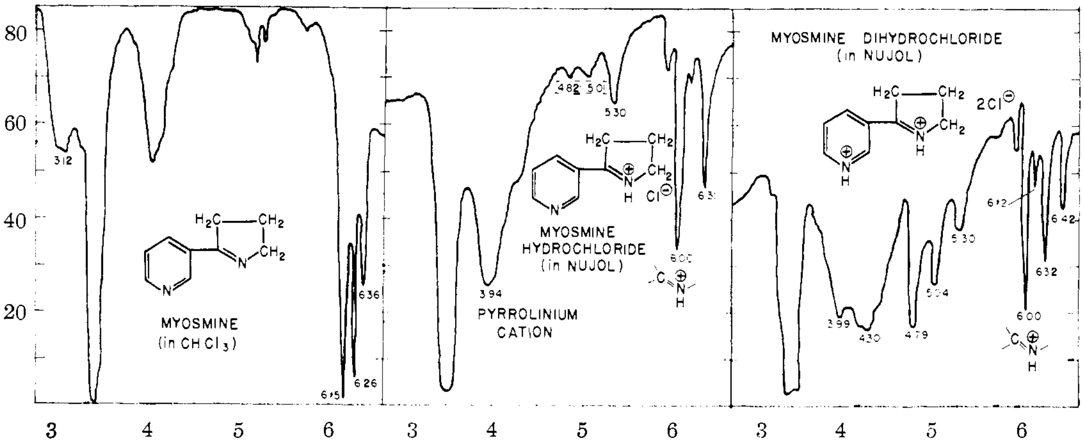

Fig. 1A.

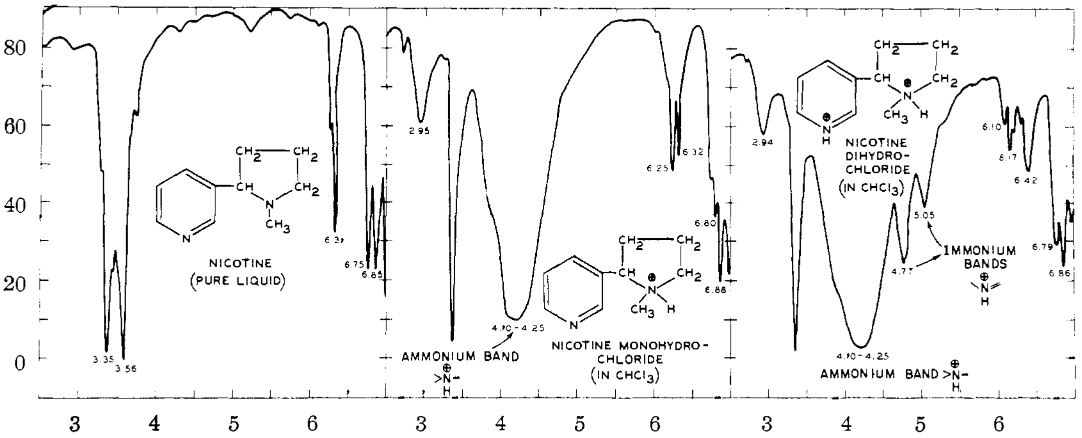

Fig. 1B.

Figs. 1A and 1B.—Infrared spectra of the mono- and dihydrochlorides of myosmine and nicotine (measured with a Perkin-Elmer double beam spectrophotometer model 21).

(pK_B estimated[10] at ~6.6) are both more strongly basic than the nitrogen in pyridine (pK_B 10.85). The monohydrochloride of myosmine in the solid state should also carry the proton at the pyrroline nitrogen, an expectation which is well borne out by the infrared spectrum (Fig. 1A) and the detailed analysis of the occurrence and position of the bands characteristic of: (i) *ammonium*, (ii) *immonium* and (iii) *free* and *protonated* azomethine groups (Table I). The assignments made for the monohydrochloride are confirmed and amplified by the new bands and shifts in the spectrum of the dihydrochloride (Fig. 1A, Table I) as well as by the comparison with the mono-[11] and dihydrochlorides[12] of nicotine (Fig. 1B).

The appearance of broad ammonium bands in saturated bases, and of ammonium *and* additional immonium bands in open or cyclic azomethines, is dependent on the presence of a proton at the nitrogen. Quaternary ammonium compounds (such as most of the crystalline alkaloids from calabash curare) show slight absorption in the ammonium region (4.37 μ for C-curarine-I chloride) and, when unsaturated (such as in cotarnine chloride),[13] no immonium bands. The complexes of saturated and unsaturated tertiary bases with Lewis acids (boron trifluoride, etc.) in anhydrous solvents do not show ammonium or immonium bands.

The hypsochromic shift in the ultraviolet spectrum of myosmine[4] observed on salt formation (266 → 262 mμ) is similar to that of 3-pyridyl methyl

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[10] *Cf.* L. C. Craig and R. M. Hixon, THIS JOURNAL, **53**, 4367 (1931). The titration of myosmine in aqueous solution with mineral acid would cause hydrolysis; *pK* values thus obtained would be those of 3-pyridyl ω-aminopropyl ketone [poikiline, A. Wenusch and R. Schöller, *Fachl. Mitt. österr. Tabak-Regie*, 1 (1936)]. Salt formation in absolute ether, however, proceeds with negligible hydrolysis as the very weak conjugated carbonyl (5.90μ) in myosmine mono- and dihydrochlorides indicates (Fig. 1A).

[11] Previously described as deliquescent crystals (no m.p., *cf. Beilstein*, [4] **23**, p. 114), it was found to melt at 126–128°. *Anal.* Calcd. for $C_{10}H_{14}N_2 \cdot HCl \cdot {}^1/_2H_2O$: C, 57.82; H, 7.61; N, 13.48. Found: C, 57.47; H, 8.01; N, 13.27.

[12] Previously described as deliquescent crystalline fibers (no m.p., *cf. Beilstein*, [4] **23**, 114), it was found to melt at 132–134°.

[13] Likewise, no immonium band is to be expected from the hydrochlorides of tautomeric tertiary enamines such as veatchine, garryine [K. Wiesner, S. K. Figdor, M. F. Bartlett and D. R. Henderson, *Can. J. Chem.*, **30**, 608 (1952)], δ-cevine [A. Stoll and E. Seebeck, *Helv. Chim. Acta*, **36**, 189 (1953)] or trimethylsolanocapsine [E. Schlittler and H. Uehlinger, *ibid.*, **35**, 2034 (1952)]. The salts of α,β-unsaturated tertiary enamines are derived from the imine form; the changes in the infrared spectrum associated with such a double bond shift serve as an excellent tool for the diagnosis of such enamines: N. J. Leonard and V. W. Gash, THIS JOURNAL, **76**, 2781 (1954). The hydrochlorides of the pyrolysis bases A and B from the pyrolysis of veatchine, as Dr. Wiesner kindly informs me, show strong immonium bands at 4.18^s, 4.56^m, 4.84^w and 513^m (Nujol mull).

TABLE I

ASSIGNMENTS OF CHARACTERISTIC BANDS IN THE INFRARED ABSORPTION SPECTRA OF MYOSMINE AND ITS TWO HYDROCHLORIDES

Compound	Ammonium bands of Δ^1-Pyrroline	Ammonium bands of Pyridine	Immonium bands of Δ^1-Pyrroline	Immonium bands of Pyridine	Azomethine group of Δ^1-Pyrroline	Azomethine group of Pyridine
Myosmine[a]	[4.07][b]		...	...	6.15[c]	6.26[d]
Myosmine monohydrochloride[e]	3.94[f]	...	5.30[g]	...	6.00[h]	6.31
Myosmine dihydrochloride[i]	3.99	4.30[k]	5.30	4.79[l] 5.04	6.00	6.12[m]

[a] A sample of this base, m.p. 45°, was kindly placed at my disposal by Dr. A. Eisner through the courtesy of Dr. B. A. Brice. [b] This slight but distinct band in the ammonium region is lacking in the spectrum of myosmine in carbon tetrachloride solution (C. R. Eddy and A. Eisner, *Anal. Chem.*, in press); it may be due to traces of HCl present in the solvent rather than to a possible zwitterionic form of Δ^2-myosmine. [c] As has been pointed out by Eddy and Eisner, ref. 5, this strong and characteristic $>C=N-$ band, together with the absence of bands in the NH region, clearly prove that myosmine is derived from a Δ^1- rather than Δ^2-pyrroline. [d] *Cf.* B. Witkop, *Experientia*, **10**, Oct. (1954), footnote 5. [e] The monohydrochloride was prepared by adding somewhat less than one equivalent of standardized ethereal hydrogen chloride solution to a solution of myosmine in ether; very hygroscopic microcrystalline colorless powder, subliming around 100° to glistening rods, m.p. 155–158° (clear melt). *Anal.* Calcd. for $C_9H_{10}N_2 \cdot HCl \cdot {}^2/_3H_2O$: C, 55.55; H, 6.38; N, 14.38; Cl, 18.28. Found: C, 55.58; H, 6.42; N, 14.81; Cl, 18.70. [f] The hydrochlorides of ethyl iminoacetate and cyclohexylidene aniline show ammonium bands at 4.97 and 4.90; 5.05 (B. Witkop, THIS JOURNAL, **76**, Unpubl. (1954); conjugation with aromatic rings, such as in indolenines, moves this band to 4.0–4.36. [g] Immonium bands at 5.30 and higher are only shown by the hydrochlorides of pyridines bearing substituents in the 4-position, *e.g.*, 8-picoline, 4-ethyl-, 4-isopropyl-, 4-*t*-butyl-, 4-benzylpyridine, etc. (B. Witkop, *Anal. Chem.*, in preparation). [h] The hypsochromic shift of this band produced by salt formation is highly characteristic of a conjugated or isolated $<C=\overset{\oplus}{N}H-$ group, *cf.* ref. *d.* [i] Prepared by adding an ethereal solution of myosmine to a solution of excess HCl in ether; microcrystalline colorless powder, subliming to stubby needles at 100° and higher, melting unsharply between 150 and 175°. *Anal.* Calcd. for $C_9H_{10}N_2 \cdot 2HCl$: C, 49.36; H, 5.52; N, 12.79. Found: C, 49.90; H, 5.39; N, 12.62. Both di- and monohydrochlorides are insoluble in chloroform. [k] No pyridine has been found so far whose hydrochloride shows a band below 4.0 in the ammonium band region. [l] These two bands are immonium bands of the pyridine ring as the comparison with the identical doublet in nicotine dihydrochloride (ref. *d*), at 4.77 and 5.04 μ shows (Fig. 1B). [m] The hypsochromic shift and the position of this band are very characteristic of a protonated pyridine (ref. *d*).

ketone (267 → 264 mμ) and dissimilar to the bathochromic shift of 3-vinylpyridine (278 → 287). With or without hydrolysis, this behavior is well explained by structure I. The name N-methylmyosmine for dihydronicotyrine[3] should be expunged from the literature.

The extension of the application of the immonium band method to the study of tautomeric pyrrolines and piperideines (anabaseine, anatabine, etc.) is being contemplated.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

Chemistry of Dihydroxyfumaric Acid[1]

BY SIDNEY GOODWIN AND BERNHARD WITKOP

RECEIVED APRIL 5, 1954

Infrared data on derivatives of dihydroxyfumaric acid are presented and discussed. Infrared evidence suggests that both dimethyl as well as diethyl ester A are derived from dihydroxyfumaric acid. The methanolysis and subsequent diazomethane esterification of diacetoxy- (II) and dibenzoyloxymaleic anhydride (XI) did not lead to isomers of dimethyl diacetoxy- (VII) and dibenzoyloxyfumarate (IX) but to trimethoxy derivatives (presumably VIII and XII). The colorless addition product (XV, dimethyl α-keto-α′-hydroperoxysuccinate) of ethereal hydrogen peroxide to dimethyl diketosuccinate (XIV) could not replace dihydroxyfumaric or ascorbic acid–hydrogen peroxide in the modified Wieland system.

The so-called dihydroxymaleic acid is in reality dihydroxyfumaric acid (I).[2–4] Interest in the mechanism of oxidation and isomerization of *cis*- and *trans*-enediols prompted us, some time ago, to attempt the preparation of *cis–trans* isomers in this series.[5] Table I summarizes reactions some of which have been described by Fenton[6] and recently repeated and reinterpreted by Hartree.[3]

The infrared data (Table I) add important material to the discussion of the complex picture of esterification of dihydroxyfumaric acid which itself shows the strong shifts (OH at 3.10, CO at 6.08)[7] expected from the strongly internally hydrogen-bonded structure I. The centrosymmetrical nature of the *trans*-structure I according to the rules of selection would not be expected to show any band for the $>C=C<$ element.[8] Compounds III, VIII, XII displaying bands in the $>C=C<$ region (5.9–6.1 μ) are apparently not centrosymmetrical, or, like VII, may need further investigation.

Fenton's ethyl ester A, obtained as one isomer in

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[1] Oxidation Mechanisms. XII. Preceding paper in this series: S. M. Goodwin, N. M. Johnson and B. Witkop, THIS JOURNAL, **75**, 4273 (1953). This paper was presented as part of a more comprehensive lecture on enediols at the Sixth Summer Seminar in the Chemistry of Natural Products at the University of New Brunswick, Fredericton, N.B., August 17–21, 1954.

[2] W. Franke and G. Brathuhn, *Ann.*, **487**, 1 (1931).

[3] E. F. Hartree, THIS JOURNAL, **75**, 6244 (1953).

[4] M. P. Gupta, *ibid.*, **75**, 6312 (1953).

[5] Examples of enediol derivatives which seem to have been isolated in *cis* and *trans* forms are 1,2-dimesitylacetylene glycol [R. C. Fuson, C. H. McKeever and J. Corse, *ibid.*, **62**, 600 (1940)] and triose reductone [H. v. Euler and H. Hasselquist, *Arkiv Kemi*, **3**, 405 (1951)].

[6] H. J. H. Fenton, *J. Chem. Soc.*, **65**, 899 (1894); **69**, 546 (1896); **73**, 78 (1898); **101**, 1570 (1912).

[7] The shift due to *external* hydrogen bonding of the usually dimeric carboxylic acids (measured as solid films) is smaller: maleic acid (dimerization sterically hindered to some degree) shows CO at 5.87 μ, fumaric acid at 5.95 [M. S. C. Flett, *J. Chem. Soc.*, 962 (1951)]. *Cf.* J. T. Harris, Jr., and M. E. Hobbs, THIS JOURNAL, **76**, 1419 (1954).

[8] See H. Gilman, "Organic Chemistry," J. Wiley and Sons, Inc., New York, 1953, p. 153; *cf.* the absence of the $>C=C<$ band in the similarly constituted molecule of α-pyridoine: W. Lüttke and H. Marsen, *Z. Elektrochem.* **57**, 680 (1953).