[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

New Syntheses of Myosmine

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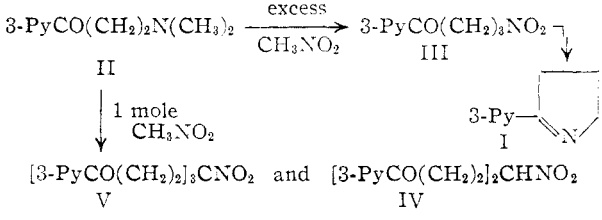
Treatment of 1-(3-pyridyl)-3-dimethylaminopropanone-1 with nitromethane gave 1-(3-pyridyl)-4-nitrobutanone-1 which could be hydrogenated to myosmine. Another route to myosmine, although less rewarding, led from methyl nicotinylacetate *via* methyl α-(2-phthalimidoethyl)-nicotinylacetate. The condensation with N-(2-bromoethyl)-phthalimide furnished three additional compounds, one a quaternary salt of methyl nicotinylacetate, and two unsaturated isomers which appear to be O-alkylation products.

In the course of studies concerning the metabolic fate of nicotine and related tobacco alkaloids[2] it became necessary to develop syntheses of the ring skeleton of such compounds which would permit labeling positions 4′ and 5′ of their azole moiety. This article reports two syntheses of myosmine (2-(3-pyridyl)-1-pyrroline (I) in which carbon atoms 5′ and eventually 4′ are incorporated in the molecule at a late stage of the synthetic sequence. Since myosmine has been hydrogenated to (±)-nornicotine[3] and this compound has been converted to nicotine by several methods, the syntheses of myosmine presented below also open a path to these alkaloids with selectively labeled positions.

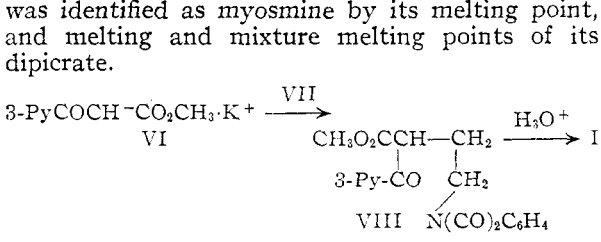
Myosmine was isolated from tobacco smoke[4] and synthesized[5] by Späth. As a Δ^1-pyrroline derivative[6,7] it is hydrolyzed easily, and ketonic and N-acyl derivatives of 4-amino-1-(3-pyridyl)-1-butanone are isolated from various reactions of myosmine in the presence of water.[3] It has been suggested[8] that in aqueous solution myosmine and 4-amino-1-(3-pyridyl)-1-butanone ("poikiline")[9] are in equilibrium although most of the material is in the cyclic form. The dissociation constant would have to be much greater than found[8] if the compound were present essentially as an amino ketone; the infrared spectrum of myosmine dipicrate which had been prepared in water solution shows a weak carbonyl band,[10] but in chloroform myosmine exhibits no carbonyl absorption.[6,7]

The first of the two new syntheses was to lead to myosmine with C-5′ introduced toward the end of the synthesis in a simple manner. It started from 1-(3-pyridyl)-3-dimethylaminopropanone-1 hydrochloride (II) which was prepared from 3-acetylpyridine, formaldehyde and dimethylammonium chloride.[11] Nucleophilic reaction with a large (seven-molar) excess of nitromethane in the presence of sodium methoxide gave a 50–60% yield of 1-(3-pyridyl)-4-nitrobutanone-1 (III) plus about 10% of 1,7-bis-(3-pyridyl)-4-nitro-1,7-heptanedione (IV). The two products were separated by chromatography. When only one mole of nitromethane was used, the main product (70%) was tris-(3-pyridyl-γ-propionyl)-nitromethane (V).[12] Hydrogenation of III in ethanol in the presence of Raney nickel catalyst furnished myosmine in yields of 80–90%.



Reduction of 1-(3-pyridyl)-4-nitrobutanone-1 with iron and water containing one equivalent of sulfuric acid gave a colorless hygroscopic solid, which contained no carbonyl group and could not be converted to myosmine. The analysis of its picrate corresponded to a base $C_9H_{10}N_2O$. This compound has not been investigated further.

The second synthesis was designed to permit labeling of myosmine at C-4′ and C-5′. For this purpose, potassium methyl nicotinylacetate (VI) was condensed with N-(2-bromoethyl)-phthalimide (VII) in boiling dimethylformamide solution, and the alkali-soluble fraction of the mixture of reaction products containing methyl α-(2-phthalimidoethyl)-nicotinylacetate (VIII) was hydrolyzed and decarboxylated with hydrochloric acid. The product was identified as myosmine by its melting point, and melting and mixture melting points of its dipicrate.



Surprisingly, VIII was formed only in small amounts, although similar carbon alkylations involving ethyl nicotinylacetate and alkyl halides proceed in good yields.[13] Three other products besides VIII were isolated from our condensation. The principal product, m.p. 144°, was obtained in a yield of 20–25%. It was an alkali-insoluble iso-

(1) Consiglio Nazionale delle Ricerche-Italia Fellow, 1955. American Tobacco Co. Fellow, 1956.

(2) See R. N. Castle and A. Burger, *J. Am. Pharm. Assoc.*, **43**, 163 (1954), for additional references.

(3) P. G. Haines, A. Eisner and C. F. Woodward, THIS JOURNAL, **67**, 1258 (1945).

(4) E. Späth, A. Wenusch and E. Zajic, *Ber.*, **69**, 393 (1936).

(5) E. Späth and L. Mamoli, *ibid.*, **69**, 757 (1936).

(6) C. R. Eddy and A. Eisner, *Anal. Chem.*, **26**, 1428 (1954).

(7) B. Witkop, THIS JOURNAL, **76**, 5597 (1954).

(8) C. O. Badgett, A. Eisner and H. A. Walens, *ibid.*, **74**, 4096 (1952).

(9) A. Wenusch, *Z. Lebensm. Untersuch. Forsch.*, **88**, 629 (1948); *C. A.*, **43**, 4345 (1949).

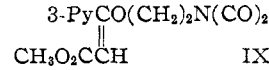
(10) Private communication, Dr. C. H. Rayburn, American Tobacco Co.

(11) J. M. Snell and S. M. McElvain, THIS JOURNAL, **56**, 1612 (1936).

(12) B. Reichert and H. Posemann, *Arch. Pharm.*, **275**, 67 (1937), observed a similar course for the reaction of 1-(3-phenyl)-3-dimethylaminopropanone-1 with nitromethane.

(13) S. Sugasawa, T. Tatsuno and T. Kamiya, *Pharm. Bull. (Japan)*, **2**, 39 (1954).

mer of VIII and, by its acid cleavage to 3-acetylpyridine, revealed itself as a β-phthalimidoethyl enol ether of methyl nicotinylacetate (IX). Al-



IX

though adequate examples of O-alkylation of saturated β-keto esters may be found in the literature,[14,15] no similar cases have been recorded for β-keto esters containing such strongly electrophilic groups as pyridine. The presence of this ring and the consequent relative stabilization of the enolate ion of the keto ester may account for the prevalence of O-alkylation in the present case, although condensation of ethyl nicotinylacetate with ethyl bromoacetate furnishes ethyl α-nicotinylsuccinate in satisfactory amounts.[13]

When the enol ether IX was warmed with dilute hydrochloric acid, 3-acetylpyridine was formed as well as an alkali-insoluble isomer of IX, m.p. 181°. The same material X has also been separated from crude IX in minute amounts, and is formed quantitatively when the hydrochloride of IX is heated above its melting point for a short time. It appears to be a geometrical isomer of IX. Reduction of either IX or X should have given the same substance but we have been unable to effect saturation of their double bonds.

The fourth product (XI) from the condensation of methyl nicotinylacetate with N-(2-bromoethyl)-phthalimide was isolated by washing the alkaline reaction mixture with ether and neutralizing it with acetic acid. Chloroform extraction removed XI as well as VIII from which XI was separated by its insolubility in ether. It was readily soluble in water; its composition ($C_{19}H_{18}N_2O_6$) suggests the quaternary structure XI, 1-(2-phthalimidoethyl)-3-(methyl carboxyacetyl)-pyridinium hydroxide.

Acknowledgment.—We wish to thank Dr. C. H. Rayburn of the American Tobacco Company for valuable suggestions, and for samples of myosmine. The Cancer Chemotherapy National Service Center made available 3-acetylpyridine used in this research.

Experimental[16]

Condensation of 1-(3-Pyridyl)-3-dimethylaminopropanone-1 with Nitromethane.—(a) A solution of 2.97 g. (0.055 mole) of sodium methoxide in 100 ml. of methanol was added gradually to a stirred solution of 10.7 g. (0.05 mole) of 1-(3-pyridyl)-3-dimethylaminopropanone-1 hydrochloride[11] and 21.36 g. (0.35 mole) of nitromethane in 60 ml. of methanol. The mixture was heated to boiling, and about 10 ml. of methanol was distilled off slowly over a period of 15 minutes in order to remove dimethylamine. The solvent and excess nitromethane were then removed under reduced pressure, the residue was taken up in 100 ml. of water containing a few drops of 10% sodium hydroxide solution, and the mixture was allowed to stand for ten minutes at 4°. A little tris-(3-pyridyl-γ-propionyl)-nitromethane which had formed separated and was filtered off. The filtrate was acidified with acetic acid and the precipitated brown oil extracted into chloroform. The extract was dried over sodium sulfate, cleared with Norite, and the solvent was distilled. The dark oily residue was dissolved in 75 ml. of dry ethyl acetate, filtered from resins, and the filtrate was chromatographed on alumina. Elution with ethyl acetate gave 5.4 g. of 1-(3-pyridyl)-4-nitrobutanone-1 in the first four 45-ml. fractions. About 0.3 g. of bis-(3-pyridyl-γ-propionyl)-nitromethane (IV) was eluted pure with additional ethyl acetate, but since this proved too slow a total of 1 g. of less pure product was eluted with a 1:1 mixture of ethyl acetate and ethanol.

1-(3-Pyridyl)-4-nitrobutanone-1 crystallized on cooling and addition of ether as plates, m.p. 32–32.5°. It was soluble in acids and alkali. Its **picrate** crystallized from ethanol, m.p. 112°.

Anal. Calcd. for $C_{15}H_{13}N_5O_{10}$: C, 42.56; H, 3.09. Found: C, 42.59; H, 3.09.

The colorless **hydrochloride** crystallized from dry ethanol–ether; m.p. 143–143.5°. It turned brown on standing after several days.

Anal. Calcd. for $C_9H_{11}ClN_2O_3$: C, 46.86; H, 4.81. Found: C, 46.10; H, 4.79.

1,7-Bis-(3-pyridyl)-4-nitro-1,7-heptanedione (IV) was recrystallized from ethyl acetate. The colorless needles melted at 154–155°. The compound was amphoteric.

Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.24. Found: C, 62.20; H, 5.45.

(b) The condensation was carried out as described under (a), but with 3.05 g. (0.05 mole) of nitromethane, and the mixture was heated for 30 minutes and worked up. The residue did not dissolve appreciably in dilute sodium hydroxide solution. It solidified on standing and stirring. **Tris-(3-pyridyl-γ-propionyl)-nitromethane** (6 g., 70%) was filtered, washed with water, and recrystallized from ethanol. The colorless crystals melted at 180°.

Anal. Calcd. for $C_{25}H_{24}N_4O_5$: C, 65.21; H, 5.25. Found: C, 65.22; H, 5.28.

Neither the hydrochloride nor the picrate was crystalline. From the alkaline filtrate 2 g. (25%) of bis-(3-pyridyl-γ-propionyl)-nitromethane was obtained by neutralization, extraction and chromatography (see a).

Myosmine.—A solution of 0.6 g. of 1-(3-pyridyl)-4-nitrobutanone-1 in 30 ml. of dry ethanol was hydrogenated with Raney nickel catalyst under 2 atm. of hydrogen at 30° for seven hours, the catalyst was filtered, and 0.5 g. of a pale brown oil was obtained when the solvent was removed. It crystallized but was converted to a dipicrate in ethanol solution. This salt (yield 80%) melted at 182–183° and did not depress the melting point of an authentic sample of myosmine dipicrate (m.p. 182–183°).[2]

A yellow **monopicrate** obtained by mixing equivalent amounts of the base and picric acid in ether solution, melted at 175.5–176° after crystallization from ethanol.

Anal. Calcd. for $C_{15}H_{13}N_5O_7$: C, 48.00; H, 3.49. Found: C, 48.06; H, 3.95.

A hydrochloride salt of our synthetic myosmine melted at 173–177°. After two to three days in a closed vessel, the melting point of the sample had dropped to 168–170°. A mixture melting point with authentic myosmine dihydrochloride (m.p. 158–175°)[5] was 160–175°.

Reduction of 1-(3-Pyridyl)-4-nitrobutanone-1 with Iron and Water.—A solution of 2 g. of 1-(3-pyridyl)-4-nitrobutanone-1 in 50 ml. of water containing enough sulfuric acid to produce *p*H 4 was added dropwise, over a period of 45 minutes, to a boiling stirred suspension of 3 g. of iron filings in 5 ml. of water. After boiling for another hour, the iron was filtered, washed with water, and the filtrate was extracted with chloroform. The dried extract was distilled, the residue (1.2 g.) was triturated with ether, and the resulting solid recrystallized from ether. The highly hygroscopic material melted at 91–92°, and was not analyzed.

The picrate crystallized from ethanol, m.p. 164–166°. It depressed the melting point of myosmine picrate.

Anal. Calcd. for $C_9H_{10}N_2O \cdot C_6H_3N_3O_7$: C, 46.04; H 3.35. Found: C, 46.09; H, 3.38.

Methyl Nicotinylacetate.—This ester was prepared by the general method recommended for the ethyl ester[17] using methyl nicotinate. The colorless compound, b.p. 128–129° (1 mm.), crystallized from ligroin, m.p. 42°.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06. Found: C, 60.62; H, 5.19.

(14) J. L. Simonsen and R. Storey, *J. Chem. Soc.*, **95**, 2106 (1909).

(15) J. C. Sheehan and C. E. Mumaw, THIS JOURNAL, **72**, 2127 (1950).

(16) All melting points are corrected. Microanalyses by Miss Barbara Williamson.

(17) F. M. Strong and S. M. McElvain, THIS JOURNAL, **55**, 816 (1933).

The hydrochloride crystallized from absolute ethanol, m.p. 154–155°.

Anal. Calcd. for $C_9H_9NO_3 \cdot HCl$: C, 50.13; H, 4.67. Found: C, 50.49; H, 4.44.

The picrate crystallized from ethanol, m.p. 146.5–147°.

Anal. Calcd. for $C_9H_9NO_3 \cdot C_6H_3N_3O_7$: C, 44.12; H, 2.96. Found: C, 44.26; H, 3.01.

Condensation of Methyl Nicotinylacetate and N-(2-Bromoethylphthalimide).—A solution of 23.5 g. of N-(2-bromoethylphthalimide) in 15 ml. of freshly fractionated dimethylformamide was added to a near-boiling stirred mixture of 20 g. of dry potassium methyl nicotinylacetate and 40 ml. of dimethylformamide. As soon as the mixture began to reflux, external heating was interrupted since spontaneous ebullition continued for about four minutes. After a total heating time of eight minutes, the brown mixture was cooled, precipitated potassium bromide was filtered, and the filtrate poured into a mixture of 300 ml. of water and 50 ml. of 6 *N* hydrochloric acid. A large amount of insoluble material precipitated. The acid solution was decanted, cleared by ether extraction, and made alkaline with sodium hydroxide solution. After standing at 4° overnight, 7 g. of a semi-solid was filtered and recrystallized from ethanol. The colorless crystals (IX) melted at 144°.

Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58. Found: C, 64.54; H, 4.29.

The colorless hydrochloride of IX, prepared in ethereal solution, melted at 145–146° but lost hydrogen chloride readily on recrystallization from ethanol reverting to the base (m.p. 144°). The molten salt resolidified at 152–155°, and then melted again at 190–195°. This salt, the hydrochloride of X, also lost hydrogen chloride on recrystallization from ethanol. The conversion of IX to X was effected best by heating the hydrochloride of m.p. 145–146° at 150–160° for two to three minutes. The molten mass was cooled, dissolved in dilute hydrochloric acid, and the new base X precipitated with sodium carbonate solution. After recrystallization from ethanol it melted at 181°.

Anal. Calcd. for $C_{19}N_{16}N_2O_5$: C, 64.77; H, 4.58. Found: C, 64.69; H, 4.66.

The same compound (X) also was obtained in small yield by tedious fractional crystallization of the ethanolic mother liquors of IX. Its m.p. (181°) was not depressed by a sample prepared by isomerization of the hydrochlorides above.

1-(2-Phthalimidoethyl)-3-(methyl carboxyacetyl)-pyridinium Hydroxide (XI).—The aqueous alkaline filtrate of IX (*vide supra*) was neutralized with acetic acid, the precipitated brown oil was extracted into chloroform, and the dried extract was concentrated. Ether was added to the residue and the mixture was cooled at 4° until crystals separated. They were washed with ethyl acetate to remove adherent oil, and recrystallized from ethanol–ether. The water-soluble salt melted at 137–138°.

Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90. Found: C, 61.58; H, 4.98.

Methyl α-(2-Phthalimidoethyl)-nicotinylacetate (VIII).—The chloroform–ether mother liquors of the quaternary salt XI were evaporated to dryness, the residue was dissolved in ethyl acetate, the solution was decanted from dark insoluble material, and chromatographed over activated alumina using benzene as an eluent. The colorless product isolated from the first fractions melted at 159–160.5°, after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58. Found: C, 64.80; H, 4.68.

Myosmine from VIII.—Since the yield of pure VIII was to small for further work, crude VIII of m.p. 125–140° and its oily, carbonate-soluble mother liquors were refluxed with 6 *N* hydrochloric acid for six hours. The acid solution was evaporated to dryness under reduced pressure, the bases were liberated and extracted into chloroform. Part of the oily residue[18] from the chloroform extract was converted to a picrate which was crystallized from ethanol and from water. It melted at 183° and did not depress the melting point of an authentic sample of myosmine dipicrate.

Anal. Calcd. for $C_{21}H_{16}N_8O_{14}$: C, 41.74; H, 2.67. Found: C, 41.09; H, 2.88.

(18) Fractionation of the oily base gave some 3-acetylpyridine (picrate, m.p. 132–133°, hydrochloride, m.p. 176–177°). The higher boiling fraction was myosmine.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

γ-Pyrones by Isomerizaton. Substituted 3,5-Dibenzyl-4H-pyran-4-ones

BY NELSON J. LEONARD AND DEBABRATA CHOUDHURY

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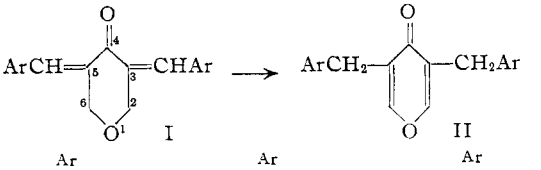
The isomerization of substituted 3,5-dibenzylidenetetrahydro-4H-pyran-4-ones to the correspondingly substituted 3,5-dibenzyl-4H-pyran-4-ones has been effected in boiling diethylene glycol solution using palladium-on-charcoal. The average rate of isoaromatization leading to γ-pyrones appears to be slower than that of the corresponding reaction leading to similarly constituted γ-pyridones and faster than that leading to the tropolones. A series of substituted 3,5-dibenzylidenetetrahydro-4H-1-thiapyran-4-ones were synthesized and were found to resist isoaromatization to the corresponding γ-thiapyrones.

As a second general illustration of heterocyclic aromatization using a glycol solvent and palladium-on-charcoal, we turned to the conversion of substituted 3,5-dibenzylidenetetrahydro-4H-pyran-4-ones (I) to the corresponding 3,5-dibenzyl-4H-pyran-4-ones (II). The first general application to the heterocyclic series, the isoaromatization of 1-methyl-3,5-dibenzylidene-4-piperidones to 1-methyl-3,5-dibenzyl-4-pyridones,[1] was based on aromatizations of isocyclic types to 2,6-dibenzylphenols[2] and 3,7-dibenzyltropolones.[3,4] The preparation of the substituted 3,5-dibenzylidenetetrahydro-4H-pyran-4-ones (I) was effected by condensation of the appropriate aldehyde with tetrahydro-4H-pyran-4-one using piperidine acetate in ethanol.[1] These conditions were found to be gen-



a, C_6H_5 e, p-$C_2H_5OC_6H_4$ i, m-$CH_3C_6H_4$
b, p-$CH_3C_6H_4$ f, 3′,4′-$(CH_3O)_2C_6H_3$ j, p-$(CH_3)_2NC_6H_4$
c, p-$(CH_3)_2CHC_6H_4$ g, 3′,4′-$CH_2O_2C_6H_3$ k, p-$NO_2C_6H_4$
d, p-$CH_3OC_6H_4$ h, 2′,3′-$(CH_3O)_2C_6H_3$ l, 1′-$C_{10}H_7$

(1) N. J. Leonard and D. M. Locke, THIS JOURNAL, **77**, 1852 (1955).

(2) E. C. Horning, *J. Org. Chem.*, **10**, 263 (1945).

(3) N. J. Leonard and J. W. Berry, THIS JOURNAL, **75**, 4989 (1953).

(4) N. J. Leonard and G. C. Robinson, *ibid.*, **75**, 2143 (1953).