Weighed samples of the *p*-toluenesulfonates were dissolved in 50.0 ml of magnesium-dried ethanol, which was then divided into 6-ml aliquots and sealed into ampoules. The ampoules were placed in a constant-temperature bath (±0.01°). The rates were followed by withdrawing the sealed ampoules at the specified time interval, quenching the reaction by cooling in a Dry Ice–acetone bath, and titration of a 5.0-ml aliquot with standard sodium hydroxide.

The rate constants were obtained for each titration point using the formula ln $[a(a - x)] = kt$, where a = concentration of tosylate at time t_0 and x = concentration of sulfonic acid at time t. The infinite titer method was used to obtain a and $a - x$. The ΔH^* was obtained from a plot of ln K_r *vs.* $1/T$°K. The ΔS^*, at 50.20°, was calculated from the formula ln K_r = ln $RT/Nh - \Delta H^*/RT + \Delta S^*/R$.

The results are summarized in Table II.

1,4,5,6-Tetrahydropyridines from Catalytic Reduction of Nicotinoyl Derivatives and Their Ring Opening with Hydrazine

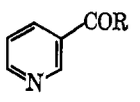
P. M. QUAN AND LOUIS D. QUIN[1]

Department of Chemistry, Duke University, Durham, North Carolina

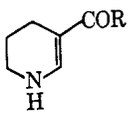
Received January 3, 1966

Pyridines with a carbonyl function (exemplified by ketones, an ester, and an amide) in the 3 position can be hydrogenated to the corresponding 1,4,5,6-tetrahydropyridine derivatives in good yield. The alkaloid myosmine (IV), possibly through a preliminary ring opening to a ketone (V), also gives such a derivative. 1,4,5,6-Tetrahydronicotinamide, as well as the corresponding ethyl ester, reacts with hydrazine to give a product of ring opening, 4-(3-aminopropyl)-2-pyrazolin-5-one. The net conversion of a nicotinic acid derivative to a pyrazolone represents a potentially useful means for the degradation of the pyridine ring in biosynthetic studies.

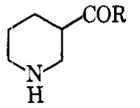
Ethyl γ-hydroxy-γ-(3-pyridyl)butyrate was needed in some synthetic studies, and an attempt was made to prepare it by catalytically reducing the ketone function of ethyl β-nicotinoylpropionate (Ia). However, with a palladium–carbon catalyst, 2 moles of hydrogen were absorbed, giving a product still containing a keto group. The infrared and ultraviolet spectra failed to show the characteristic pyridine bands and suggested that the keto grouping was conjugated. The tetrahydropyridine structure IIa was suspected and this was confirmed by the nmr spectrum. A similar result was obtained on attempted reductive amination, with benzylamine, of ethyl nicotinoylacetate (Ib); the ketone group was unattacked and the amide IIb was isolated. At about the same time, Freifelder[2,2a] reported the reduc-



Ia, R = CH_2CH_2COOEt
b, R = CH_2COOEt
c, R = OEt
d, R = NH_2



IIa, R = CH_2CH_2COOEt
b, R = $CH_2CONHCH_2C_6H_5$
c, R = OEt
d, R = NH_2



IIIc, R = OEt
d, R = NH_2

tion of 3-acetylpyridine to a similar tetrahydropyridine and it appeared that the pyridine ring is particularly susceptible to this mode of reduction if a 3-keto function is present. The products are examples of "vinylogous amides;" they show carbonyl stretching absorption in the infrared at much lower frequencies than would be expected for simple unsaturated ketones, and have the intense ultraviolet absorption near 300 mμ now well established for compounds of this type.[2,3]

Δ^2-Tetrahydropyridines unsubstituted on nitrogen have rarely been prepared,[4] and several alkaloids thought to contain this moiety have recently been reassigned to the corresponding Δ^1 structure.[5] Since the double bond in the Δ^1 compounds is readily reduced, considerable stabilization must be present in the Δ^2 compounds through interaction between keto and amino groups to account for the preservation of the double bond under reductive conditions. This suggested that such stabilization might be provided by other functions involving carbonyl groups. Thus, the infrared spectra of β-amino-α,β-unsaturated esters suggest this effect, since the carbonyl group absorbs at unusually low frequencies.[6] We therefore examined the catalytic reduction of ethyl nicotinate (Ic) and nicotinamide (Id) and found that in each case yields greater than 70% of the apparently unreported tetrahydro derivative (IIc and IId) could be isolated. The reactions were allowed to proceed until no hydrogen absorption was observable. The small quantities of the piperidines (IIIc and IIId) which were isolated apparently did not, therefore, arise from further reduction of the tetrahydro products, a phenomenon noted previously,[2] unless this reduction occurred on particularly active sites of the catalyst which became poisoned by the piperidines when produced. Both ethyl nicotinate[7]

(1) To whom inquiries may be addressed.

(2) M. Freifelder, *J. Org. Chem.*, **29**, 2895 (1964).

(2a) NOTE ADDED IN PROOF.—E. Wenkert, K. G. Dave, and F. Haglid [*J. Am. Chem. Soc.*, **87**, 5461 (1965)] have now demonstrated the similar partial reduction of *t*-butyl nicotonate.

(3) (a) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *ibid.*, **71**, 3337 (1949); (b) N. F. Albertson, *ibid.*, **74**, 249 (1952); (c) J. Weinstein and G. M. Wyman, *J. Org. Chem.*, **23**, 1618 (1958); (d) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965); (e) R. B. Woodward and E. C. Kornfeld, *ibid.*, **70**, 2508 (1948).

(4) M. F. Grundon and B. E. Reynolds, *J. Chem. Soc.*, 2445 (1964).

(5) *E.g.*, Myosmine, B. Witkop and T. W. Beiler, *J. Am. Chem. Soc.*, **76**, 5589 (1954); C. R. Eddy and A. Eisner, *Anal. Chem.*, **26**, 1428 (1954); γ-coniceine, K. H. Bückel and F. Korte, *Ber.*, **95**, 2460 (1962); anabaseine, H. Kamimura and I. Yamamoto, *Agr. Biol. Chem.* (Tokyo), **27**, 450 (1963).

(6) (a) C. A. Grob, *Helv. Chim. Acta*, **33**, 1787 (1950); (b) C. A. Grob and F. Ostermeyer, *ibid.*, **45**, 1119 (1962); (c) N. A. Nelson, K. O. Gelotte, Y. Tamura, H. B. Sinclair, J. M. Schuck, V. J. Bauer, and R. W. White, *J. Org. Chem.*, **26**, 2599 (1961); (d) G. N. Walker and R. N. Beaver, *ibid.*, **26**, 4441 (1961); (e) J. C. Powers, *ibid.*, **30**, 2535 (1965).

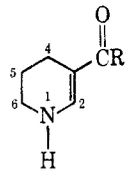
(7) S. M. McElvain and R. Adams, *J. Am. Chem. Soc.*, **45**, 2738 (1923).

and nicotinamide[8] have previously been hydrogenated to the corresponding piperidines (IIIc and IIId) with platinum catalysts in acid solutions, a combination much favored for reduction of pyridine systems since it obviates catalyst poisoning.[9] Using these conditions, we then observed the tetrahydronicotinamide (IId) to be readily reduced to nipecotamide (IIId).

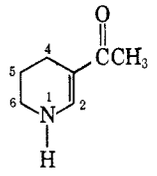
It has been reported[10] that in 50% aqueous acetic acid, with a palladium catalyst, 5′-methylmyosmine gave after absorption of 1 mole of hydrogen a compound of λ_{max} 318 mμ, considered likely to be a dihydropyridine. Using the more accessible alkaloid, myosmine (IV), under these conditions we have isolated in 30% yield a rather unstable solid, similar to that above,[10] with a proton count in the nmr spectrum indicating that 2 moles of hydrogen had been absorbed. The similarity of this spectrum with those of the tetrahydropyridines (see Table I) allows formulation of

TABLE I

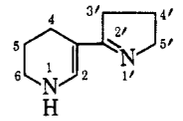
PROTON CHEMICAL SHIFTS IN 1,4,5,6-TETRAHYDROPYRIDINES[a]



IIa–d



IIe



VI

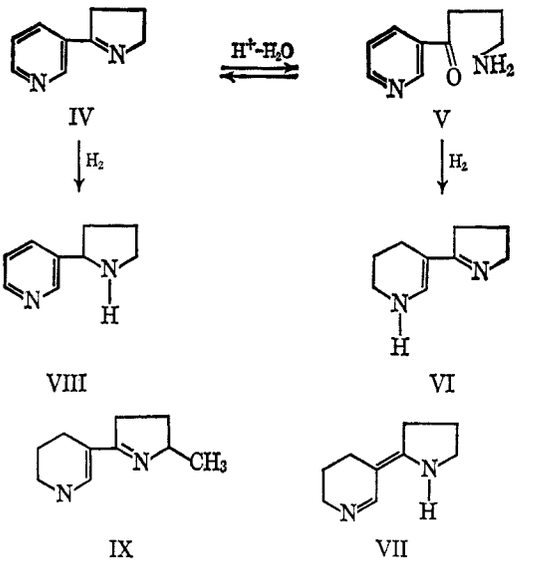
	Shift (δ, ppm; TMS = 0.0)				
Compd	H-1	H-2	H-4	H-5	H-6
IIa	6.00 (b)	7.79 (d)	2.42 (t)	1.87 (m)	3.32 (m)
IIb	6.02 (b)	7.47 (d)	2.29 (t)	1.72 (m)	3.10 (m)
IIc	5.04 (b)	7.46 (d)	2.31 (t)	1.80 (m)	3.19 (m)
IId[b]	...	7.89 (s)	2.66 (t)	2.27 (m)	3.60 (t)
IIe[c]	7.12 (b)	7.48 (d)	2.28 (t)	1.77 (m)	3.23 (t)
VI[d]	4.64 (bs)	6.80 (s)	2.47 (m)[e]	1.84 (m)[f]	3.21 (t)

[a] The intensities of the resonances correspond to the number of protons required by the formulas. Unless otherwise stated the solvent was deuteriochloroform; s = singlet, d = doublet, t = triplet, b = broad, m = multiplet. [b] Deuterium oxide solution, in which H-1 is replaced by D. In water solution, the H-2 signal is a doublet and the H-6 signal is a multiplet. [c] From data of Freifelder,[2] using CCl_4 as solvent. The H-5 value is approximated from the statement "multiple peaks of which three at 101, 106, and 111 cps stand out." [d] H-5′, δ 3.83 (t). [e] Combined with H-3′. [f] Combined with H-4′.

this compound as VI, although the possibility of isomerization to VII having occurred cannot be completely eliminated. The fact that H-2 does not couple with the adjacent NH group as in the other compounds of the series IIa–d is probably due to a greater degree of exchange in this more basic (less amidelike) nitrogen function. H-1 thus absorbs further upfield than in the other cases. The position of the maximum in the ultraviolet spectrum (317 mμ) is almost the same as that of the reduction product of 5′-methylmyosmine,[10] and this raises some question on the assignment of the latter product as a dihydro pyridine. It may in fact be the 1,4,5,6-tetrahydro derivative (IX); the discrepancy in ϵ_{max} (VI, 33,700; the 5′-methyl derivative, 11,600) may be explained by the impure state of the specimen of the 5′-methyl compound, which was not analyzed.

When the reduction of myosmine was attempted in neutral ethanol with the same catalyst, only 1 mole of

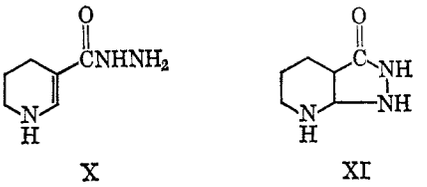
SCHEME I



hydrogen was absorbed to give, as has been described,[11] a virtually quantitative yield of nornicotine (VIII) (Scheme I). There is considerable evidence to show[11] that in aqueous acid solution myosmine exists in equilibrium with the open-chain amino ketone (V). It is likely that in the hydrogenation we conducted in aqueous acetic acid solution this is the species actually reduced, and subsequent ring closure leads to the product VI. The result of the reduction in neutral ethanol solution, where myosmine may remain largely in the cyclic form IV, and the failure in our hands also of 3-cyanopyridine to yield more than trace amounts of a tetrahydropyridine on hydrogenation (as judged by the ultraviolet absorption of the crude product), indicate that carbon–nitrogen multiple bonds are too readily reduced to allow partial reductions of the type obtained with a carbonyl function.

Proton resonances in the tetrahydropyridine rings of the compounds discussed are given in Table I, and in general are in agreement with Freifelder's results.[2]

The tetrahydropyridines IIc and IId are potentially valuable as synthetic intermediates in that they are produced in high yield from cheap, readily available materials. Furthermore, the reactivity predictable from consideration of these compounds as enamines would suggest that facile ring opening might occur, and that a useful new process for degradation of the pyridine ring might be achievable. In fact, such a ring opening has been accomplished by treatment with hydrazine. A crystalline solid (A) resulted in high yield from reaction of either ester IIc or amide IId with hydrazine. While its analysis indicated that the expected displacement of ethoxy or amino, respectively, had occurred, its properties were clearly not those of the hydrazide X or of a ring-closed isomer of the hydrazide (XI). Thus,



X XI

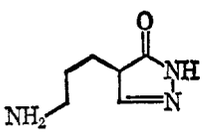
(8) H. H. Fox, *J. Org. Chem.*, **17**, 542 (1952).

(9) M. Freifelder *Advan. Catalysis*, **14**, 203 (1963).

(10) I. Yamamoto and H. Kamimura, *Agr. Biol. Chem.* (Tokyo), **27**, 445 (1963).

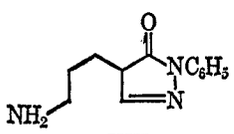
(11) P. G. Haines, A. Eisner, and C. F. Woodward, *J. Am. Chem. Soc.*, **67**, 1258 (1945).

the ultraviolet spectrum [λ_{max} 237 mμ (ϵ 5800)] eliminated structure X, whose spectrum should contain the strong absorption at longer wavelength characteristic of the other 3-acyl-1,4,5,6-tetrahydropyridines (II). Also, compound A failed to undergo hydrogenation to a piperidine under conditions effective for reducing IId to nipecotamide. Compound A did, however, react with nitrous acid with gas evolution, a result not in accord with either X or XI. From its nmr spectrum (D_2O solution), A was seen to have three methylenes (2.27, 2.80, 3.41 ppm) as in the starting compounds. The spectrum also showed a single vinyl proton (7.69 ppm) and structure XI is conclusively eliminated. The only other conceivable isomeric structure is the 5-pyrazolone (XII),[12] which might be looked upon as resulting from attack of the NH_2 group of X at the 2 position of the ring with displacement of the enamine nitrogen. Such a ring closure is not without precedent; β-alkoxy and β-alkylthio groups in α,β-unsaturated esters are displaced on reaction with hydrazine to form pyrazolones,[13] and β-arylamino groups of α,β-unsaturated ketones are displaced to form pyrazoles.[14] The 5-pyrazolone formulation XII is compatible with the nmr spectrum and the other facts stated for compound A; the ultraviolet absorption is similar to that for other 5-pyrazolones.[13] The infrared spectrum also supported the pyrazolone structure, showing bands associable with the dipolar ion character of these compounds.[13] Strong bands spread over the region 3150–2330 and a peak at 2180 cm^{-1} are similar to absorptions reported by de Stevens, *et al.*,[15] from a study of 5-pyrazolones containing no substituents on the nitrogen atoms. These absorptions were attributed to $-NH^+$ bonds of zwitterionic forms. Such pyrazolones fail to show the strong absorption of the carbonyl of a cyclic amide (1700–1690 cm^{-1}), and show instead absorptions at lower frequency for $C-O^-$ or $C{=}N^+H$. In the spectrum of XII, true carbonyl absorption is absent; there is a peak at 1670 cm^{-1}, but its intensity is quite low.



XII

Phenylhydrazine also gave a product with amide IId which can be assigned the 5-pyrazolone structure XIII; its properties resembled those of XII. The phenyl group is assumed to occupy the 1 position as is customary in 5-pyrazolones synthesized by condensations with phenylhydrazine.[13]



XIII

These reactions thus constitute a new method for rupturing the pyridine ring and may find use in particular in biosynthetic studies on the pyridine ring of certain alkaloids and of nicotinic acid. There is considerable activity in this area at present, and since 1963, three methods have been reported for converting the pyridine ring in nicotinic acid, as derived from oxidation of nicotine[16,17] or anabasine,[18] into a form amenable to degradation for location of labeled carbon atoms. The pyrazolones XII and XIII have functionality at positions 2, 3, and 6 of the original pyridine ring and it appears possible that these compounds can form the basis for degradations revealing the location of labels.

Experimental Section[19]

Catalytic Hydrogenations.—Unless otherwise stated, catalytic hydrogenations were conducted at room temperature under 2–4 atm of hydrogen in a Parr apparatus. The catalyst was 10% palladium on carbon (used as obtained from Matheson Coleman and Bell Co.). For quantities of reactant less than 4 g, an atmospheric pressure apparatus was used, with agitation by magnetic stirring.

Ethyl γ-3-(1,4,5,6-Tetrahydropyridyl)-γ-oxobutyrate (IIa).—A solution of 5.0 g of ethyl β-nicotinoylpropionate (Ia)[20] in 50 ml of 95% ethanol was hydrogenated with 0.35 g of catalyst for 7 hr. The solution was filtered and the solvent was evaporated. Addition of a mixture of pentane and ether (60:40) to the oily residue gave 2.51 g (50%) of white crystals. These were collected and recrystallized from pentane–ether: mp 81–83°; $\lambda_{max}^{95\%\ EtOH}$ 302 mμ (ϵ 26,000); ν_{max}^{KBr} 3280 (NH), 1731 (ester), 1575, 1512 cm^{-1}; $\nu_{max}^{CHCl_3}$ 3460 (NH), 1723 (ester), 1597 cm^{-1}.

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.63; H, 8.13; N, 6.87.

β-3-(1,4,5,6-Tetrahydropyridyl)-β-oxo-N-benzylpropionamide (IIb).—Ethyl nicotinoylacetate (Ib,[21] 1.93 g, 0.01 mole), benzylamine (1.18 g, 0.01 mole), and *p*-toluenesulfonic acid (0.02 g) were dissolved in 15 ml of benzene, and the solution was heated under reflux for 15 hr. The solvent was evaporated, and the residue was dissolved in 20 ml of 95% ethanol. The solution was hydrogenated in the presence of 50 mg of catalyst for 25 hr, when uptake of gas had ceased. The solution was filtered and the solvent evaporated to give an oil which crystallized from 10 ml of benzene. The crystals (0.70 g, 27% yield) were collected and recrystallized from a benzene–ethanol mixture as colorless spines, mp 151–153°, $\lambda_{max}^{95\%\ EtOH}$ 304 mμ (ϵ 27,000).

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.93; H, 7.17; N, 10.82.

Ethyl 1,4,5,6-Tetrahydronicotinate (IIc).—A solution of 16.0 g of ethyl nicotinate (Ic)[22] in 50 ml of 95% ethanol was hydrogenated in the presence of 0.50 g of catalyst for 36 hr, when uptake of gas had ceased. The solution was filtered and the solvent evaporated to give a pale yellow oil (A). This was dissolved in ether and extracted with several small portions of 2% hydrochloric acid to remove any of the basic Ic or IIIc present. The ether solution was then dried with sodium carbonate and concentrated to a yellow oil (12.8 g) which was distilled fairly rapidly (bp 121° at 0.05 mm). There was obtained 11.93 g (74%) of a colorless, pleasant-smelling oil, which set on standing to a white solid. The solid could be stored indefinitely in the dark in a nitrogen-filled container at 0°. It became yellow and oily on

(12) Tautomerism in the 5-pyrazolone family makes the assignment of the exact structure difficult. By convention, the 2-pyrazolin-5-one formula is used here without implication that no other tautomeric structure is involved. See ref 13.

(13) R. H. Wiley and P. Wiley, "The Chemistry of Heterocyclic Compounds," Vol. 20, Part I, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapters 1 and 2.

(14) F. B. Dains and E. W. Brown, *J. Am. Chem. Soc.*, **31**, 1148 (1909); F. B. Dains and J. Alin, *Univ. Kansas Sci. Bull.*, **18**, 627 (1928).

(15) G. de Stevens, A. Halmandaris, P. Wenk, and L. Dorfman, *J. Am. Chem. Soc.*, **81**, 6292 (1959).

(16) D. R. Christman and R. F. Dawson, *Biochemistry*, **2**, 182 (1963).

(17) K. S. Yang, R. K. Gholson, and G. R. Waller, *J. Am. Chem. Soc.*, **87**, 4184 (1965).

(18) E. Leete and A. R. Friedman, *ibid.*, **86**, 1224 (1964).

(19) Melting points are uncorrected and were taken with a Mel-Temp apparatus. Nmr spectra were recorded with a Varian A-60 instrument, and tetramethylsilane was used as an internal standard with chloroform solutions, and as an external standard with other solvents.

(20) (a) S. Sugasawa, T. Tatsuno, and T. Kamiya, *Pharm. Bull.* (Tokyo), **2**, 39 (1954); (b) F. Zymalkowski and B. Trenktrog, *Arch. Pharm.*, **292**, 9 (1959).

(21) H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **70**, 2755 (1948).

(22) M. C. Kloetzel and F. L. Chubb, *ibid.*, **79**, 4226 (1957).

exposure to the atmosphere for a few hours. It had mp 30–33°; $\lambda_{max}^{95\% EtOH}$ 286 mμ (ε 21,000); ν_{max}^{film} 3280 (NH), 1660, 1607 (vs) cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.19; H, 8.70; N, 8.92.

The crude product (A) had ϵ_{max} 18,500 at 286 mμ, indicating an 85–90% yield of the product (IIc). Careful fractional distillation at this stage through a spinning-band column did remove a lower boiling side product (IIIc) in 12% yield but resulted in considerable polymerization of IIc in the still to a brittle glass.

Compound IIIc had bp 52° at 0.5 mm [lit.[7] (for ethyl nipecotate) bp 102–104° at 7.0 mm] and showed the nmr and infrared spectra expected for this compound.

1,4,5,6-Tetrahydronicotinamide (IId).—A solution of 35 g of nicotinamide (Id) in 120 ml of 80% ethanol was hydrogenated with 1.0 g of catalyst until no further gas was absorbed (70 hr). Precipitation of the product during this time did not affect the yield. The solution was filtered and the catalyst was washed with hot ethanol. Filtrate and washings were combined and evaporated until crystals began to appear. The solution was then refrigerated, whereupon 20.2 g of white crystals, mp 204–207° dec (unimproved by further recrystallization) was deposited. The mother liquor was concentrated and then triturated with chloroform, when a second crop (4.5 g), mp 200–205° dec, was obtained (total yield, 71%): $\lambda_{max}^{95\% EtOH}$ 287 mμ (ε 19,500), ν_{max}^{KBr} 1628 and 1510 cm^{-1} (both complex).

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 56.98; H, 7.93; N, 22.24.

The chloroform solution described above was concentrated to a yellow oil which solidified on drying *in vacuo* to a hygroscopic solid, mp 80–90°. This material was distilled through a warmed condenser (bp 130° at 0.05 mm) to give an oil which solidified in the receiver to a hygroscopic white solid (6.7 g, 19%), mp 100–105° [lit. (for nipecotamide) bp 149–160° at 0.3–0.5 mm,[23] mp 111–112°[8]]. As described for nipecotamide (IIId), the compound gave a picrate, mp 193–196° (lit.[23] mp 193.5–194.5°), and an oxalate, mp 199–201° dec (lit.[8] mp 203–205° dec).

1-Acetyl-1,4,5,6-tetrahydronicotinamide.[24]—Tetrahydronicotinamide (IId, 2.00 g) was heated for 15 min on the steam bath with 5 ml of acetic anhydride. The solution was cooled and diluted with 10 ml of ether. The precipitated solid was collected and recrystallized from water: yield 2.05 g, mp 206–209°. The nmr spectrum (in deuterated dimethyl sulfoxide at 60°, external TMS) provided proof of attachment of the acetyl group to the ring nitrogen; H-2 appeared as a singlet (8.2 ppm) as a result of removal of H-1 (*cf.* with IId, Table I).

Anal. Calcd for $C_8H_{12}N_2O_2$: C, 17.13; H, 7.19; N, 16.66. Found: C, 57.09; H, 7.38; N, 16.47.

Hydrogenation of 1,4,5,6-Tetrahydronicotinamide (IId).—A solution of 300 mg of IId in 8 ml of 95% ethanol was adjusted to pH 2 with 10% hydrochloric acid and hydrogenated in the presence of 30 mg of platinum oxide catalyst, prereduced in 5 ml of ethanol. Uptake of hydrogen ceased after 1 hr when 1 mole of gas had been absorbed. The solution was filtered and brought to pH 9 with 40% potassium hydroxide solution. The precipitated potassium chloride was collected by filtration, and the filtrate was evaporated to give a yellow oil which solidified on drying *in vacuo*. The solid (245 mg), which had an infrared spectrum virtually identical with that of nipecotamide (IIId) from the preparation of IId, was dissolved in 10 ml of absolute ethanol, and the solution was filtered. Treatment of this solution with ethanolic picric acid gave a picrate (281 mg) which was recrystallized from ethanol–benzene. It had mp 192–195°, undepressed on admixture with the nipecotamide picrate prepared previously.

Hydrogenation of Myosmine (IV) in Acid Solution.—Myosmine was prepared by pyrolysis of nicotine at 550–600° as described by Haines, Eisner, and Woodward.[25] A solution of myosmine (220 mg) dissolved in 5 ml of 50% aqueous acetic acid (v/v) was hydrogenated using 30 mg of equilibrated catalyst. After 75 min, when 1.65 moles of hydrogen/mole of myosmine had been absorbed, a sharp decrease in the rate occurred (a phenomenon observed each time the experiment was carried out). Only after 240 min was 2 moles absorbed. The solution was filtered, cooled in ice–salt, and made strongly basic with cold 40% potassium hydroxide solution, when a white solid was precipitated. This was collected at 0° and washed with a few drops of cold concentrated ammonium hydroxide. After drying *in vacuo* the solid was rapidly transferred to a piece of glass tubing (sealed at one end) and was sublimed at 80–100° under 0.1-mm pressure. The hard white sublimate (VI, 72 mg, 33% yield) had mp 104–124° dec, and became yellow and oily on exposure to the atmosphere for 1 hr. It had $\lambda_{max}^{95\% EtOH}$ 317 mμ (ε 33,700); ν_{max}^{KBr} 3220 (NH), 1638, 1590, 1560 cm^{-1}.

Anal. Calcd for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65. Found: C, 71.22; H, 9.31; N, 18.29.

Hydrogenation of Myosmine in Neutral Solution.—A solution of myosmine (250 mg) in 10 ml of 95% ethanol was hydrogenated in the presence of 20 mg of equilibrated catalyst. Uptake of gas ceased after 100 min when 1.10 moles had been absorbed. The solution was filtered and the solvent was evaporated in a stream of nitrogen, and finally *in vacuo*, to give a colorless oil (250 mg) which had an infrared spectrum corresponding to that of an authentic sample of nornicotine (VIII). Gas chromatography on a polypropylene glycol 1025 column, as described previously,[26] gave only one peak with retention volume and area equal to those obtained by injection of the same quantity of the authentic sample.

4-(3-Aminopropyl)-2-pyrazolin-5-one (XII).—A solution of 6.00 g of IId in 20 ml of 36% hydrazine hydrate and 5 ml of ethanol was heated under reflux on a steam bath for 90 min. The solution was diluted with 10 ml of ethanol and allowed to crystallize at 0° for 2 days. The solid was collected and washed with ethanol: yield 6.21 g (93%), mp 223–227° dec. The analytical sample was recrystallized from water–ethanol: mp 226–228° dec; $\lambda_{max}^{95\% EtOH}$ 237 mμ (ε 5800); ν_{max}^{KBr} 3150–2330 (almost continuous), 2180, 1670 (medium), 1570 (medium) cm^{-1}; nmr (D_2O), 2.27 (2 H, m), 2.80 (2 H, t), 3.41 (2 H, t) (side-chain methylene groups), 7.69 (1 H, s) (C-3 ring proton) ppm.

Anal. Calcd for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.76. Found: C, 50.91; H, 7.89; N, 29.49.

By a similar procedure the same compound could be prepared from the ester IIc in 87% yield.

1-Phenyl-4-(3-aminopropyl)-2-pyrazolin-5-one (XIII).—A solution of 2.00 g of IIc and 4.0 g of phenylhydrazine in 15 ml of water was heated under reflux for 7 hr. The solvent was evaporated, and the residual oil was dissolved in ethanol and treated with ether until the solution was just cloudy. The product then crystallized slowly with 1 mole of ethanol of crystallization (estimated by nmr), which was lost below the melting point (171–176°). The yield was 3.37 g (81%). Two recrystallizations from 1-butanol–ethyl acetate gave the analytical sample: mp 176–178.5°; $\lambda_{max}^{95\% EtOH}$ 252 mμ (ε 14,900); ν_{max}^{KBr} 3150–2330, 2180, 1590, 1560 (medium) cm^{-1}; nmr (D_2O), 2.46 (2 H, m), 3.00 (2 H, t), 3.58 (2 H, t) (side-chain methylene groups), 8.15 (6 H, m) (phenyl group and C-3 ring proton) ppm. The compound was slightly sensitive to light.

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.35; H, 6.96; N, 19.34. Found: C, 66.17; H, 7.06; N, 19.18.

Acknowledgments.—The authors are indebted to the American Tobacco Company for its generous support of this work. They are also pleased to acknowledge the preliminary work of Dr. T. K. B. Karns, who first isolated the partial reduction products of Ia and Ib.

(23) R. H. Reitsema and J. A. Hunter, *J. Am. Chem. Soc.*, **71**, 1680 (1949).

(24) Freifelder[2] reported that it was not possible to acetylate 3-acetyl-1,4,5,6-tetrahydropyridine, but conditions used were not stated.

(25) C. F. Woodward, P. G. Haines, and A. Eisner, *J. Am. Chem. Soc.*, **66**, 911 (1944).

(26) L. D. Quin, *J. Org. Chem.*, **24**, 911 (1959).