# Tetrahydropyridines[1]

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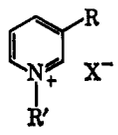
A variety of β-acylpyridines and their N-alkyl salts are converted into 3-acyl-2-piperideines on palladium-catalyzed hydrogenation. Condensation of some of the products with indole derivatives are described. The nature of the ions produced on exposure of the tetrahydropyridines to protic acids and the isolation of protic salts are discussed. Attempts of the base-promoted isomerization of 3-piperideines into their $\Delta^2$ isomers are portrayed.

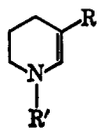
Much of our work on alkaloid synthesis in recent years has featured the utilization of tetrahydropyridines (piperideines) in acid-induced transformations into polyheterocyclic substances. The usual methods of preparation of the starting compounds consisted of hydride reduction and catalytic hydrogenation of pyridine derivatives. In view of the novelty of the hydrogenation procedure and its great potential in organochemical synthesis its scope required investigation. The latter and some of the chemistry of the reduction products, 2- and 3-piperideines, form the subject of the present communication.

**2-Piperideines.**—The syntheses of eburnamonine[3] and some yohimboid and corynanthoid alkaloid models[4] featured as pivotal reaction the conversion of 1-alkyl-3-acylpyridinium salts into 1-alkyl-3-acyl-2-piperideines by palladium-induced hydrogenation in the presence of triethylamine.[5] The intervening years since the discovery of the unusual reduction[6] have seen its use in the synthesis of a large variety of 2-piperideines some of which are presented herewith.

Hydrogenation of the salts Ia–k by the aforementioned procedure yielded 2-piperideines IIa–k, respectively, in good yield. Predictably, variation of the



I

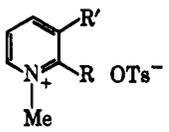


II

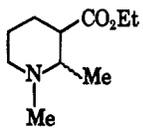
a, R = Ac; R′ = β-[3-(2-methylindolyl)]ethyl
b, R = CHO; R′ = β-[3-(2-methylindolyl)]ethyl
c, R = $CO_2Me$; R′ = β-[3-(2-methylindolyl)]ethyl
d, R = $CO_2$-t-Bu; R′ = β-[3-(2-methylindolyl)]ethyl
e, R = Ac; R′ = $(CH_2)_2OH$
f, R = Ac; R′ = $CH_2OMe$
g, R = $COCH_2CO_2Me$; R′ = Me
h, R = Ac; R′ = Me
i, R = $CO_2Me$; R′ = Me
j, R = $CONH_2$; R′ = Me
k, R = CN; R′ = Me
l, R = $CH_2CO_2Me$; R′ = β-(3-indolyl)ethyl
m, R = $CH_2CO_2Me$; R′ = Me

nitrogen substituent had no effect on the course of the reduction. More importantly, a broad spectrum of 3-acyl and related substituents, including aldehydo and cyano[7] functions and a β-keto ester moiety, survived the reaction. These observations revealed that the reaction possesses extraordinary flexibility.

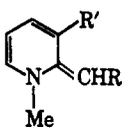
While our previous work[4] had shown that 4,5-dialkylated 1-alkyl-3-acylpyridinium salts underwent hydrogenation to the tetrahydro stage without complications, reduction of a 2-alkylated pyridinium salt now yielded an anomalous result. Hydrogenation of IIIa produced the piperidine IV exclusively. However the formation of a deep red color upon the addition of triethylamine to the alcohol solution of the salt IIIa prior to hydrogenation afforded the clue needed for interpretation of the unexpected course of reduction. If it be assumed that the base had converted the salt at least in part into the chromophore Va and that the latter be the substance undergoing reduction, no facile path would be available during the hydrogenation process for unmasking the vinylogous amide moiety[3] responsible for the early stoppage of the reduction in all previous cases.



IIIa, R = Me; R′ = $CO_2Et$
b, R = $CH_2CO_2Me$; R′ = H



IV



Va, R = H; R′ = $CO_2Et$
b, R = $CO_2Me$; R′ = H

The above anomaly suggested that it may be possible to reduce N-alkyl salts of 2-pyridylacetic esters, pyridine derivatives having no β-acyl function at all, to the tetrahydro state, since in basic solution such salts would be expected to be in equilibrium with substances of structure type Vb. As a test of this hypothesis 1-methyl-2-carbomethoxymethylpyridinium tosylate (IIIb) was hydrogenated in sodium methoxide solution. Both the piperidine derivative VI and the vinylogous urethane VII proved to be the products of the reaction.[8] Thus it appears that hydrogenation of any aromatic nucleus capable of

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(2) (a) Van Leer Visiting Fellow, Weizmann Institute of Science, April–July 1965; (b) Public Health Service Predoctoral Fellow, 1963–1966.

(3) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580, 5810 (1965).

(4) E. Wenkert, K. G. Dave, and F. Haglid, *ibid.*, **87**, 5461 (1965).

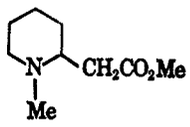
(5) For similar observations see (a) C. A. Grob and F. Ostermayer, *Helv. Chim. Acta*, **45**, 1119 (1962); (b) R. E. Lyle, G. H. Warner, and D. A. Nelson, *Bol. Soc. Quim. Peru*, **31** (3), 89 (1965); *Chem. Abstr.*, **64**, 19,548 (1966).

(6) The first example, the hydrogenation of 1-[β-(3-indolyl)ethyl]-3-acetylpyridinium bromide,[3] was presented by E. W. for the first time at the 17th National Organic Chemistry Symposium of the American Chemical Society at Bloomington, Ind., June 26–29, 1961.

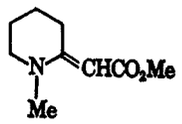
(7) Hydrogenation of 1,5-dimethyl-3-cyanopyridinium bromide in aqueous, carbonate-containing solution over Adams catalyst has yielded 1,5-dimethyl-1,4,5,6-tetrahydronicotinamide: Professor Lyle, personal communication (1966); R. E. Lyle and S. E. Mallett, "The Partial Hydrogenation of Pyridines," presented at the Conference on Catalytic Hydrogenation and Analogous Pressure Reactions sponsored by the New York Academy of Sciences, New York, N. Y., June 20–22, 1966.

(8) *Cf.* the hydrogenation of 1-benzyl-2-phenacylidene-3,4,5,6-tetradehydropiperidine over Raney nickel: B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 118 (1955).

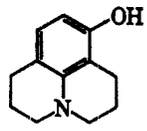
unmasking a stable vinylogous amide unit during the reduction is potentially prone to stoppage at an earlier than hexahydro stage. An intriguing recent example is the formation of IX on hydrogenation of the aminophenol VIII[9] over Raney nickel.



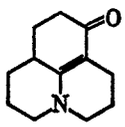
VI



VII

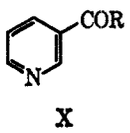


VIII

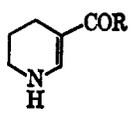


IX

Midway in our hydrogenation study the conversion of β-acetylpyridine (Xa) into its tetrahydro derivative (XIa) on palladium-induced hydrogenation was reported.[10] In view of the immediate relevancy of this discovery to our study a brief investigation of the generality of this reduction was instituted. Hydrogenation nicotinaldehyde (Xb), methyl and *t*-butyl nicotinates (Xc and d, respectively)[4] and nicotinamide (Xe) yielded the 2-piperideines XIb–e, respectively.[11–13] The products were readily N-acylable, *e.g.*, XIIa and b.

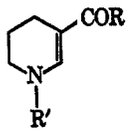


X



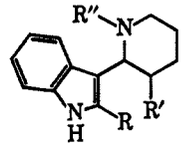
XI

a, R = Me
b, R = H
c, R = OMe
d, R = O-*t*-Bu
e, R = $NH_2$



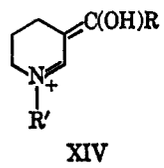
XIIa, R = Me; R′ = Ac
b, R = OMe; R′ = β-indolylacetyl

The synthesis of 2-piperideines II and XI made available a large number of substances for acid-catalyzed condensation with nucleophilic substrates. The preparation of the indolylpiperidines XIIIa and b by the condensation of indole with XId and its N-methyl derivative, respectively, under decarbalkoxylation conditions has already been described.[4] Acid treatments of indole with IIi and with XIc and of methyl α-indolylacetate with the same tetrahydropyridines yielded the esters XIIIc,[14] d, e, and f, respectively. By contrast, all attempts of condensing indoles with 2-piperideines (II and XI) containing aldehydic or ketonic-3-acyl groups failed. Conditions under which 3-carbalkoxy derivatives had undergone condensation led to recovery of starting material, while more stringent acid conditions yielded intractable tars.

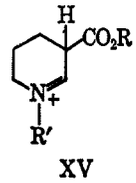


XIIIa, R = R′ = R″ = H
b, R = R′ = H; R″ = Me
c, R = H; R′ = $CO_2Me$; R″ = Me
d, R = R″ = H; R′ = $CO_2Me$
e, R = $CH_2CO_2Me$; R′ = $CO_2Me$; R″ = Me
f, R = $CH_2CO_2Me$; R′ = $CO_2Me$; R″ = H

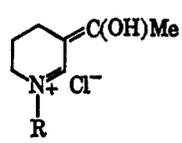
The divergent behavior of the various vinylogous amides in acid medium appeared to reflect the nature of their protonated species. Aldehydo and keto compounds would be expected to exist as O-protonated salts of general structure type XIV,[15] whereas esters should prefer C protonation, *e.g.*, XV.[16] An ultraviolet spectral study of two tetrahydropyridines lent credence to this view. Whereas acid interaction of the keto system IIh, $\lambda_{max}^{HOAc}$ 312 mμ (log ε 4.35), enhanced its absorption characteristics, $\lambda_{max}^{HCl-HOAc}$ 303 mμ (log ε 4.44), the chromophore of the ester IIi, $\lambda_{max}^{HOAc}$ 298 mμ (log ε 4.29), was totally destroyed. Some O-protic salts, the hydrochloride XVIa and b, could be isolated in crystalline form. In view of the stabilization of the vinylogous amide moiety by O protonation and its serious destabilization by C protonation, the intermediacy of XIV and XV in the acid-promoted condensations of indoles with aldehydo–keto systems and esters, respectively, is in accord with the aforementioned experimental findings.[17]



XIV



XV



XVIa, R = $(CH_2)_2OH$
b, R = Me

(9) Z. Valenta, P. Deslongchamps, R. Ellison, and K. Wiesner, *J. Am. Chem. Soc.*, **86**, 2533 (1964).

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

(11) Further examples of this hydrogenation process have recently been reported: P. M. Quan and L. D. Quinn, *ibid.*, **31**, 2487 (1966).

(12) The transformation of 3-acetylquinoline into its 1,4-dihydro derivative on hydrogenation over Raney nickel represents an early case of the reduction under consideration: R. B. Woodward and E. C. Kornfeld, *J. Am. Chem. Soc.*, **70**, 2508 (1948).

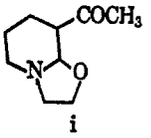
(13) In an early attempt of explaining the details of the hydrogenation of 1-alkyl-3-acylpyridinium salts it was assumed that triethylamine liberates alkoxide whose products of addition to the pyridine nucleus undergo hydrogenation. In view of the ease of reduction of N-unsubstituted β-acylpyridines in the absence of base the latter's function in the hydrogenation of the salts is probably to act merely as a neutralizing agent of the liberated acid.

(14) Some time after our synthesis of XIIIc its formation from an interaction of indole and IIi was described by J. C. Powers, *J. Org. Chem.*, **30**, 2534 (1965). As a consequence it is omitted from the Experimental Section.

(15) *Cf. inter alia* N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959); H. E. A. Kramer and R. Gompper, *Tetrahedron Letters*, 969 (1963); G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **30**, 1407 (1965).

(16) *Cf.* reference in footnote 14.

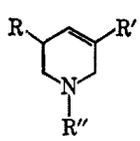
(17) The integrity of XVIa in solution and its refusal to undergo cyclization into i, in contrast to the behavior of its deacetyl analog, constitutes another illustration of the inertness of the vinylogous amide system containing a 3-ketonic function toward nucleophiles: N. J. Leonard and W. K. Musker, *J. Am. Chem. Soc.*, **82**, 5148 (1960).



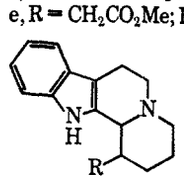
i

**3-Piperideines.**—N-Alkylpyridinium salts undergo facile transformation into 3-piperideines on sodium borohydride reduction.[18] Were it possible to isomerize the double bond in these tetrahydropyridines, a new, simple method of preparation of the useful 2-piperideines would be on hand.[19] In view of the reported base-induced transformation of dimethylallylamine into dimethylpropenylamine[20] and on the assumption of greater stability of an enamino unit than an allylamino function also in cyclic compounds, a study of the interconversion of 3- and 2-piperideines was undertaken.

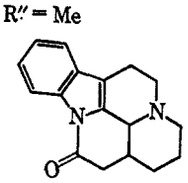
It was hoped to affect the alteration of 1-[β-(3-indolyl)ethyl]-3-piperideine (XVIIa)[18b] into its 2-piperideine isomer by treatment with potassium *t*-butoxide in dimethyl sulfoxide and to establish the presence of the anticipatedly unstable product by its acid-induced conversion into the indoloquinolizidine XVIIIa. However base treatment of XVIIa under a variety of conditions produced no change. This curious result was open to two possible interpretations; either 3-piperideines were preferred at equilibrium contrary to expectation or equilibrium had not been reached under the conditions of the new method of isomerization of isolated double bonds.[21,22] It was decided to seek differentiation between these rationales in a more classical system, XVIIb. Double bond isomerization and acid-catalyzed cyclization was expected to lead to XVIIIb or desethyleburnamonine (XIX).



XVIIa, R = R′ = H; R″ = β-(3-indolyl)ethyl
b, R = H; R′ = $CH_2CO_2Me$; R″ = β-(3-indolyl)ethyl
c, R = $CHCO_2Me$; R′ = H; R″ = β-(3-indolyl)ethyl
d, R = H; R′ = $CH_2CO_2Me$; R″ = Me
e, R = $CH_2CO_2Me$; R′ = H; R″ = Me

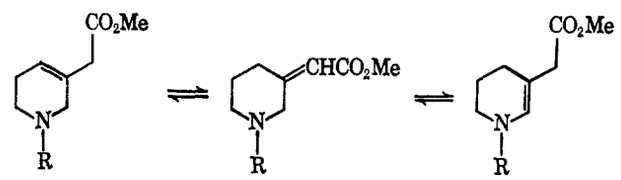


XVIIIa, R = H
b, R = $CH_2CO_2Me$



XIX

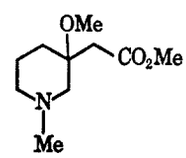
Synthesis of the amino ester XVIIb proceeded along the following path: interaction of methyl homonicotinate and tryptophyl bromide, sodium borohydride reduction of the salt II, and separation of XVIIb from its double bond isomer XVIIc. In analogy with the classical studies of Kon and Linstead[23] on the equilibration of 1-cyclohexenylacetyl and cyclohexylideneacetyl systems it was assumed that sodium methoxide treatment of XVIIb would set up an equilibrium between it, the exocyclic double bond isomers and the desired enamine III (*vide infra*). However exposure of XVIIb to sodium methoxide in methanol solution followed by treatment with acid yielded no tetracyclic (XVIIIb) or pentacyclic (XIX) compounds. As a consequence of this second disappointing result it was decided to study the interconversion of structurally simple representatives of the following triad, *i.e.*, the N-methyl derivatives.



*cis* and *trans*
XX

The two allylamines were synthesized in the following manner. Sodium borohydride reduction of methyl homonicotinate methiodide (Im) yielded a mixture of XVIId and XVIIe which could be separated. Condensation of 1-methyl-3-piperidone[24] with trimethyl phosphonoacetate under the influence of base[25] produced the geometric isomer mixture XX (R = Me).[26] In the face of several thwarted attempts of preparing the enamine IIm a study of the based-induced isomerization of only the allyl amines was executed.

Interaction of sodium methoxide with XVIId or with XX (R = Me) in methanol solution under a variety of conditions yielded mixtures of XVIId, XX (R = Me), and XXI. No enamine IIm was ever detected. The optimum conditions for the highest material balance and lowest product variance involved refluxing the methanol solutions for 2 hr. Under these circumstances XVIId produced a 77% yield of a mixture consisting of 90% XVIId, 10% XX (R = Me), and less than 1% XXI, while XX (R = Me) led to a 80% yield of products embracing 61% XVIId, 10% XX (R = Me), and 29% XXI. Whereas the



XXI

ratio of endocyclic to exocyclic products resembled the equilibrium value in the cyclohexane series,[23] the interfering methanol addition reaction and the lack of 100% material recovery prevented assessment of the actual equilibrium position. However the results indicated clearly that the base-promoted conversion of 3-piperideines into 2-piperideines under customary equilibrating conditions is impossible because of either

(18) *Inter alia*, *cf.* (a) J. J. Panouse, *Bull. Soc. Chim. France*, 60 (1953); (b) E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Am. Chem. Soc.*, **84**, 3732 (1962).

(19) A. Jackson and J. A. Joule, *Chem. Commun.*, 459 (1967), have reported an interesting example of isomerization, the conversion of 1-methyl-4-(α-indolecarbonyl)-3-piperideine into 1-methyl-4-(α-indolecarbonyl)-2-piperideine.

(20) C. C. Price and W. H. Snyder, *Tetrahedron Letters*, 69 (1962).

(21) For a review of olefin isomerization see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 175–210.

(22) At the time of this study only limited details of the isomerization of olefins by *t*-butoxide/dimethyl sulfoxide had appeared; reference in footnote 20; A. Schriesheim, R. J. Muller, and C. A. Rowe, Jr., *J. Am. Chem. Soc.*, **84**, 3164 (1962), and references therein.

(23) C. K. Ingold, *Ann. Rept. Progr. Chem.* (Chem. Soc. London), **24**, 109 (1927).

(24) S. M. McElvain and J. F. Vozza, *J. Am. Chem. Soc.*, **71**, 896 (1949).

(25) *Cf.* W. S. Wadsworth, Jr., and W. D. Emmons, *ibid.*, **83**, 1733 (1961).

(26) No attempt was made to separate or otherwise differentiate between the *cis* and *trans* compounds. Their 1:1 mixture was considered one constituent of the triad.

an abnormally low rate of formation of the 2-piperideine or its surprisingly lower stability.

## Experimental Section[27]

**Tetrahydropyridines IIa–k.**—A mixture of 1.2 g of β-acetylpyridine and 2.4 g of α-methyltryptophyl bromide[28] in 4 ml of methanol was heated at 60° under nitrogen for 15 min. Crystallization of the precipitate from methanol yielded 3.2 g of yellow needles of Ia (X = Br): mp 262–263°; infrared spectrum (Nujol) NH 2.93 (m), 3.15 (m), C=O 5.90 (s), C=C 6.14 (m), 6.34 μ (m).

*Anal.* Calcd for $C_{18}H_{19}ON_2Br$: N, 7.80. Found: N, 7.61.

A mixture of 0.5 g of 10% palladium–charcoal and 0.7 ml of triethylamine in 50 ml of methanol was saturated with hydrogen. A suspension of 1.8 g of Ia in 60 ml of methanol was added and the mixture hydrogenated at room temperature and atmospheric pressure. Upon cessation of hydrogen uptake the catalyst was filtered and washed with ethanol. The combined filtrate and washing were evaporated to dryness and any absorbed water was removed azeotropically by distillation from benzene. The dry residue was mixed with benzene and triethylamine hydrobromide precipitate was filtered. The filtrate was passed through a short alumina column and evaporated under vacuum. Crystallization of the residue yielded 1.34 g of needles of IIa: mp 166–167°; infrared (Nujol) NH 3.13 (m), C=O and C=C 6.18 (s), 6.44 μ (s); ultraviolet $\lambda_{max}^{EtOH}$ 317 mμ (ε 23,750), $\lambda_{max}^{EtOH-HCl}$ 296 mμ (ε 20,250); the pmr spectrum showed three-proton singlets at 1.69 (indolyl Me), 2.27 (acetyl Me), and a one-proton singlet at 6.77 ppm (olefinic H).

*Anal.* Calcd for $C_{18}H_{22}ON_2$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.72; H, 7.72; N, 10.03.

A mixture of 1.0 g of nicotinaldehyde and 2.3 g of α-methyltryptophyl bromide[28] in 6 ml of methanol was heated at 60° under nitrogen for 3 hr. The solvent was evaporated under vacuum and the residue extracted several times with hot water. The extract was filtered through Norit and the filtrate treated with saturated sodium perchlorate solution. Crystallization of the precipitate from water gave 2.8 g of yellow-orange needles of Ib (X = $ClO_4$): mp *ca.* 300° (blackening at 248–250°); infrared spectrum (Nujol) NH 3.03 (m), C=O 5.86 (s), C=C 6.13 (m), 6.31 μ (m).

*Anal.* Calcd for $C_{17}H_{17}O_5N_2Cl$: C, 55.91; H, 4.66; N, 7.67. Found: C, 55.82; H, 4.66; N, 7.44.

Hydrogenation of 1.9 g of Ib under the above reaction conditions and work-up led to a product whose crystallization from benzene yielded 1.2 g of IIb: mp 180–182°; infrared (Nujol) NH 3.18 (m), C=O and C=C 6.26 μ (s); ultraviolet $\lambda_{max}^{EtOH}$ 304 mμ (ε 29,250), $\lambda_{max}^{EtOH-HCl}$ 284 mμ (ε 27,750), $\lambda_{shoulder}^{EtOH-HCl}$ 295 mμ (ε 25,230); the pmr spectra showed a three-proton singlet at 2.27 (Me) and one-proton singlets at 6.51 (olefinic H), 8.43 ppm (aldehydic H).

*Anal.* Calcd for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.51; N, 10.52. Found: C, 76.00; H, 7.52; N, 10.52.

A mixture of 1.3 g of methyl nicotinate and 2.3 g of α-methyltryptophyl bromide[28] in 4 ml of methanol was heated at 60° under nitrogen for 15 min. Crystallization of the precipitate from methanol afforded 3.2 g of yellow needles of Ic (X = Br): mp 189–191°; infrared spectrum (Nujol) NH 2.90 (m), 3.15 (m), C=O 5.80 (s), C=C 6.14 (m), 6.31 (m), 6.41 μ (w).

Hydrogenation of 1.85 g of Ic under the above reaction conditions and work-up yielded a product whose crystallization from ether led to 1.45 g of IIc: mp 106–107°; infrared (Nujol) NH 3.10 (m), C=O and C=C 6.06 (s), 6.20 μ (s); ultraviolet $\lambda_{max}^{EtOH}$ 296 mμ (ε 28,750), $\lambda_{max}^{EtOH-HCl}$ 287 mμ (ε 6750); the pmr spectrum showed three-proton singlets at 2.28 (C—Me), 3.62 (O—Me) and a one-proton singlet at 7.24 ppm (olefinic H).

*Anal.* Calcd for $C_{18}H_{22}O_2N_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.44; H, 7.29; N, 9.30.

A mixture of 3.7 g of *t*-butyl nicotinate and 4.3 g of α-methyltryptophyl bromide[28] in 10 ml of methanol was stirred over nitrogen at room temperature for 24 hr. The solvent was evaporated under vacuum and the residue stirred under dry ether. Filtration and drying of the precipitate yielded 6.9 g of yellow salt whose crystallization from methanol–ether gave crystals of Id (X = Br), mp 156–157°.

*Anal.* Calcd for $C_{21}H_{25}O_2N_2Br$: Br, 19.20. Found: Br, 19.57.

Hydrogenation of 3.5 g of Id under the above reaction conditions and work-up yielded 2.4 g of a solid whose crystallization from cyclohexane led to IId: mp 152–154°; infrared spectrum (KBr) NH 3.05 (m), C=O and C=C 6.09 (s), 6.23 μ (s).

*Anal.* Calcd for $C_{21}H_{28}O_2N_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.16; H, 8.24; N, 8.10.

A mixture of 2.00 g of β-acetylpyridine and 1.88 g of β-bromoethanol in 100 ml of xylene was stirred at 120° for 3 hr. The solvent was decanted from the separated oil and the latter was washed several times with ether and dried under vacuum. Whereas the pale yellow oil (Ie, X = Br) (3.20 g; infrared spectrum (neat) OH *ca.* 3.0 (m, broad), C=O, 5.88 (s), C=C 6.14 (s), 6.31 μ (m)) solidified on standing for 1 week, the solid was hygroscopic and hard to handle and hence was used directly in the next reaction.

Hydrogenation of 1.4 g of Ie under the above reaction conditions and work-up yielded an oil which solidified on standing. Crystallization from benzene-hexane yielded 0.28 g of needles of IIe: mp 79–80°; infrared (Nujol) OH 3.09 (m), C=O and C=C 6.16 (s), 6.46 μ (s); ultraviolet $\lambda_{max}^{EtOH}$ 311 mμ (ε 29,000); $\lambda_{max}^{EtOH-HCl}$ 305 mμ (ε 28,800); the pmr spectrum showed a three-proton singlet at 2.08 (Me), a four-proton multiplet at 3.0–3.4 (aminomethylenes), a two-proton multiplet at 3.6–3.9 (hydroxymethylene), a one-proton singlet at 7.37 ppm (olefinic H).

*Anal.* Calcd for $C_9H_{15}O_2N$: C, 63.90; H, 8.86; N, 8.26. Found: C, 63.97; H, 8.94; N, 8.02.

A benzene solution of IIe was saturated with dry hydrogen chloride gas and then kept at 0° for 24 hr. The solvent was decanted and the remaining solid crystallized from methanol–ether yielding needles of XVIa: mp 142–144°; infrared spectrum (Nujol) OH 3.00 (m), double bond 6.23 μ (s).

*Anal.* Calcd for $C_9H_{16}O_2NCl$: C, 52.81; H, 7.82; N, 6.84. Found: C, 53.07; H, 7.88; N, 6.77.

A mixture of 1.29 g of β-acetylpyridine and 1.29 g of methyl chloromethyl ether in 10 ml of acetone was refluxed for 10 hr. The cooled mixture was filtered and the hygroscopic solid (If, X = Cl) (1.81 g; infrared spectrum (Nujol) C=O 5.90 (s), C=C 6.15 (s), 6.30 μ (w)) used in the next reaction without further purification.

Hydrogenation of 1.50 g of If under the above reaction conditions and work-up led to an oil whose distillation (bath temperature 125–130° (0.3 mm)) yielded 0.99 g of liquid IIf: infrared (neat) C=O and C=C 6.25 μ (s); the pmr spectrum showed three-proton singlets at 2.16 (C—Me), 3.30 (O—Me), a two-proton singlet at 4.51 ($NCH_2O$), a one-proton singlet at 7.37 ppm (olefinic H).

*Anal.* Calcd for $C_9H_{15}O_2N$: C, 63.91; H, 8.88; N, 8.28. Found: C, 64.10; H, 9.15; N, 7.98.

A mixture of 1.00 g of methyl nicotinylacetate and 2.03 g of methyl *p*-toluenesulfonate in 10 ml of benzene was refluxed for 3 hr. The cooled mixture was filtered and the crystalline salt Ig (X = OTs), 2.23 g, used in the next reaction without further purification.

Hydrogenation of 2.23 g of Ig under the above reaction conditions and work-up produced an oil which crystallized gradually upon standing at 0° and whose distillation (bath temperature 127–130° (0.075 mm)) yielded 0.90 g of IIg: infrared (neat) C=O 5.76 (s), C=O and C=C 6.14 (s), 6.35 μ (s); the pmr spectrum showed three-proton singlets at 3.00 (N—Me), 3.68 (O—Me) and two-proton singlets at 3.50 (diacylmethylene), 7.28 ppm (olefinic H).

*Anal.* Calcd for $C_{10}H_{15}O_3N$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.87; H, 7.82; N, 7.29.

A mixture of 3.0 g of β-acetylpyridine methiodide (Ih, X = I)[29] and 7 g of freshly prepared silver chloride in 80 ml of methanol was stirred at room temperature for 2 hr. The solid was filtered and washed with methanol. The combined filtrate and washings were concentrated and then hydrogenated under the above reaction conditions and work-up. This led to an oil whose distillation (bath temperature 130–135° (0.2 mm)) yielded 1.1 g of liquid IIh: infrared (neat) C=O and C=C 6.14

(27) Melting points were determined on a Reichert micro hot stage and are uncorrected. Proton magnetic resonance spectra of deuteriochloroform solutions with tetramethylsilane acting as internal standard were recorded on a Varian A-60 spectrometer.

(28) I. I. Grandberg, N. N. Kost, and A. P. Terent'ev, *J. Gen. Chem. USSR*, **27**, 3338 (1957).

(29) M. R. Lamborg, R. M. Burton, and N. O. Kaplan, *J. Am. Chem. Soc.*, **79**, 6173 (1957), and references cited therein.

(s), 6.35 $\mu$ (s); ultraviolet $\lambda_{max}^{EtOH}$ 315 m$\mu$ ($\epsilon$ 31,300), $\lambda_{max}^{EtOH-HCl}$ 305 m$\mu$ ($\epsilon$ 30,300); the pmr spectrum showed three-proton singlets at 2.09 (C—Me), 3.03 (N—Me) and a one-proton singlet at 7.32 ppm (olefinic H).

*Anal.* Calcd for $C_8H_{13}ON$: C, 68.91; H, 9.35; N, 10.07. Found: C, 69.12; H, 9.17; N, 10.32.

An ether solution of IIh was saturated with dry hydrogen chloride gas and kept at 0° for 1 week. The solvent was decanted and the solid residue crystallized from methanol–ether yielding needles of XVIb: mp 88–90°; infrared spectrum (Nujol) OH 3.12 (m), double bond 6.20 $\mu$ (s). Drying for three days under vacuum (0.05 mm) destroyed the crystalline form and produced a powder, mp 145–147°.

*Anal.* Calcd for $C_8H_{14}ONCl$: N, 7.97. Found: N, 7.72.

Methyl nicotinate methiodide (Ii, X = I),[29,30] 9.86 g, was converted into its methochloride as above and hydrogenated under the above reaction conditions and work-up. This produced an oil whose distillation afforded 4.12 g of liquid IIi: bp 75–76° (0.2 mm); infrared (neat) C=O 5.94 (s), C=O and C=C 6.21 $\mu$ (s); ultraviolet $\lambda_{max}^{EtOH}$ 296 m$\mu$ ($\epsilon$ 22, 500), $\lambda_{max}^{EtOH-HCl}$ 295 m$\mu$ (low intensity); the pmr spectrum showed three-proton singlets at 2.90 (N—Me), 3.62 (O—Me) and a one-proton singlet at 7.28 ppm (olefinic H).

Hydrogenation of 1.68 g of nicotinamide methochloride (Ij, X = I),[29,31] under the above reaction conditions and work-up yielded a solid whose crystallization from ethyl acetate gave 0.96 g of needles of IIj: mp 118–120°; infrared (Nujol) NH 3.00 (m), 3.20 (m), C=O 5.95 (m), 6.12 (s), C=C 6.42 (s), 6.47 $\mu$ (s); ultraviolet $\lambda_{max}^{EtOH}$ 297 m$\mu$ ($\epsilon$ 27,600); $\lambda_{max}^{EtOH-HCl}$ 310 m$\mu$ ($\epsilon$ 22,600); the pmr spectrum showed a three-proton singlet at 2.88 (Me) and a one-proton singlet at 7.26 ppm (olefinic H).

*Anal.* Calcd for $C_7H_{12}ON_2$: C, 60.00; H, 8.57; N, 20.00. Found: C, 60.10; H, 8.70; N, 20.24.

Nicotinonitrile methiodide (Ik, X = I),[29,32] 3.00 g, was converted into its methochloride by the above procedure and hydrogenated under the above reaction conditions and work-up. This yielded an oil whose distillation (bath temperature 125–130° (0.2 mm)) gave 0.84 g of liquid IIk:[32] infrared (neat)[32] C≡N 4.60 (s), C=C 6.16 $\mu$ (s); ultraviolet[32] $\lambda_{max}^{EtOH}$ 277.5 m$\mu$ ($\epsilon$ 18,400); the pmr spectrum showed a three-proton singlet at 2.90 (Me) and a one-proton triplet at 6.72 ppm ($J$ = ~0.7 cps) (olefinic H).

**Piperidines IV, VI, and VII.**—A mixture of 6.70 g of ethyl 2-methylnicotinate[33] and 8.40 g of methyl *p*-toluenesulfonate in 150 ml of benzene was refluxed for 12 hr. The solvent was removed under vacuum and the solid residue washed with ether and dried under vacuum. It (IIIa), 10.9 g, was used in the next reaction without further purification.

Hydrogenation of 5.97 g of ethyl 2-methylnicotinate methotosylate (IIIa) under the above reaction conditions and work-up produced an oil whose benzene solution was passed through a short alumina column and whose subsequent distillation (bath temperature 75–80° (0.15 mm)) yielded 2.78 g of ethyl 1,2-dimethylnipecotate (IV, probably *cis*):[34] infrared ($CCl_4$) C=O 5.79 $\mu$ (s); the pmr spectrum showed a three-proton doublet at 0.89 ($J$ = 7.0 cps) (C—Me), a three-proton triplet at 1.21 ($J$ = 7.0 cps) (ethoxy Me), a three-proton singlet at 2.28 (N—Me), and a two-proton quartet at 4.09 ppm ($J$ = 7.0 cps) (ethoxy methylene).

*Anal.* Calcd for $C_{10}H_{19}O_2N$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.65; H, 10.34; N, 7.76.

A mixture of 15.1 g of methyl 2-pyridylacetate and 18.6 g of methyl *p*-toluenesulfonate was heated under nitrogen at 65° for 24 hr. The resultant solid was washed with copious amounts of ether and filtered. Crystallization of the precipitate, 31.2 g, from ethanol–benzene yielded white plates of IIIb: mp 139–141°; infrared spectrum (Nujol) C=O 5.74 (s), C=C 6.14 (m), 6.34 $\mu$ (m).

*Anal.* Calcd for $C_{16}H_{19}O_5NS$: N, 4.36. Found: N, 4.11.

A mixture of 16.9 g of IIIb, sodium methoxide (from 1.15 g of sodium) and 3 g of 10% palladium–charcoal in 300 ml of methanol was hydrogenated under 45 psi. The usual work-up yielded an oil whose distillation produced 5.1 g of methyl 1-methyl-2-piperidylacetate (VI) (infrared ($CCl_4$) C=O 5.74 $\mu$ (s); the pmr spectrum showed three-proton singlets at 2.22 (N—Me) and 3.65 ppm (O—Me)) and 2.1 g of methyl 1-methyl-2-piperidylideneacetate (VII) (infrared ($CHCl_3$) C=O 5.96 (s), C=C 6.40 $\mu$ (s); the pmr spectrum showed three-proton singlets at 2.77 (N—Me), 3.55 (O—Me), and a one-proton singlet at 4.51 ppm (olefinic H)). (No study of improvement of the yield of VII was undertaken.)

*Anal.* Calcd for $C_9H_{15}O_2N$: C, 64.07; H, 8.89; N, 8.23. Found: C, 64.03; H, 8.82; N, 8.44.

**Tetrahydropyridines XI and Their Derivatives XII.**—A mixture of 4.00 g of nicotinaldehyde (Xb) and 400 mg of 10% palladium–charcoal in 40 ml of methanol was hydrogenated at room temperature and a pressure of 45 psi. Upon cessation of hydrogen uptake the catalyst was filtered and the filtrate concentrated under reduced pressure. Distillation of the residual oil yielded 1.89 g of $\beta$-hydroxymethylpyridine, bp 73–74° (0.75 mm), and 1.10 g of 1,4,5,6-tetrahydronicotinaldehyde (XIb) (bath temperature 140–147° (0.05 mm)) which solidified on standing: mp 62–64° (without crystallization); infrared (neat) NH 3.13 (m), C=O and C=C 6.32 $\mu$ (s); the pmr spectrum showed a two-proton multiplet at 1.6–2.0 (C-5 methylene), 2.1–2.5 (C-4 methylene), 3.2–3.5 (C-6 methylene), a one-proton doublet at 7.21 ($J$ = 7.0 cps) (olefinic H), and a one-proton singlet at 8.74 ppm (aldehydic H).

*Anal.* Calcd $C_6H_9ON$: C, 64.85; H, 8.16; N, 12.60. Found: C, 64.94; H, 8.32; N, 12.70.

A mixture of 5.00 g of methyl nicotinate (Xc) and 600 mg of 5% palladium–charcoal in 100 ml of methanol was hydrogenated at 50 psi and room temperature. After a 2-mole hydrogen uptake at the end of 5 hr the mixture was filtered and evaporated. The residual oil, 5.00 g (gas phase chromatography on a Pye Argon apparatus 4 ft × ⅛ in. column of 25% silicone SE-30 on 60–80 mesh Gaschrom P, column temperature 182°, inlet pressure 15 psi; 6% methyl hexahydronicotinate, retention time 0.38 relative to XIc), was distilled yielding methyl 1,4,5,6-tetrahydronicotinate (XIc): bp 93–95° (0.25 mm); low-melting solid on standing; infrared (neat) NH 3.00 (s), C=O 5.99 (s), C=O and C=C 6.21 $\mu$ (s); the pmr spectrum showed two-proton multiplets at 1.6–2.0 (C-5 methylene), 2.1–2.5 (C-4 methylene), 3.0–3.3 (C-6 methylene), a three-proton singlet at 3.63 (O—Me), and a one-proton doublet at 7.46 ppm ($J$ = 6.5 cps) (olefinic H).

*Anal.* Calcd for $C_7H_{11}O_2N$: C, 59.57; H, 7.80; N, 9.93. Found: C, 59.61; H, 7.71; N, 9.74.

A solution of 1.30 g of $\beta$-indolylacetyl chloride[35] and 800 mg of XIc in 15 ml of pyridine was kept at room temperature for 24 hr. The solvent was removed below 40° under reduced pressure and the residue treated with water and ethyl acetate and extracted with benzene. The extract was washed with sodium bicarbonate and water and dried over sodium sulfate. Evaporation under vacuum yielded 1.71 g of a brown syrup whose filtration through an alumina column and crystallization from methanol yielded 472 mg of XIIb: mp 177.5–178.5°; infrared spectrum (KBr) NH 3.02 (m), C=O 5.88 (s), 5.98 (s), C=C 6.12 $\mu$ (s).

*Anal.* Calcd for $C_{17}H_{18}O_3N_2$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.40; H, 6.01; N, 9.20.

A mixture of 12.2 g of nicotinamide (Xe) and 2.0 g of 10% palladium–charcoal in 150 ml of ethanol was hydrogenated at 45 psi and room temperature. Upon cessation of hydrogen uptake at the end of *ca.* 36 hr the mixture was filtered and evaporated. Crystallization of the solid residue from ethanol yielded 11.7 g of 1,4,5,6-tetrahydronicotinamide (XIe):[11] mp 203–205°; infrared spectrum (Nujol) NH 3.01 (s), 3.10 (m), C=O and C=C 6.08 (m), 6.16 $\mu$ (s).

*Anal.* Calcd for $C_6H_{10}O_2N$: C, 57.12; H, 7.99; N, 22.21. Found: C, 56.99; H, 7.93; N, 22.00.

A solution of 3.39 g of 3-acetyl-1,4,5,6-tetrahydropyridine (XIa)[10] and 3.50 g of acetic anhydride in 10 ml of pyridine was kept at room temperature for 3 days. The solvent and excess reagent were removed under vacuum. A benzene solution of the residual oil was washed with 10% potassium carbonate solution and evaporated. Distillation of the residue yielded 3.65 g of 1,3-diacetyl-1,4,5,6-tetrahydropyridine (XIIa): bp 153–155° (2.8 mm); infrared (neat) C=O 5.94 (s), 6.05 (s), C=O and C=C 6.20 $\mu$ (s); the pmr spectrum showed a six-

(30) Y. Hukusima, *J. Chem. Soc. Japan*, **61**, 121 (1940).

(31) P. Karrer, G. Schwarzenbach, F. Benz, and U. Solmssen, *Helv. Chim. Acta*, **19**, 811 (1936).

(32) K. Schenker and J. Druey, *ibid.*, **42**, 1960 (1959).

(33) P. Baumgarten and A. Dornow, *Ber.*, **72B**, 563 (1939).

(34) *Cf.* N. F. Albertson, *J. Am. Chem. Soc.*, **74**, 2594 (1950).

(35) E. Shaw and D. W. Wooley, *J. Biol. Chem.*, **203**, 979 (1953).

proton singlet at 2.31 (methyls) and a two-proton multiplet at 3.5–3.8 ppm (C-6 methylene).

*Anal.* Calcd for $C_9H_{13}O_2N$: C, 64.67; H, 7.78; N, 8.38. Found: C, 64.66; H, 7.86; N, 8.18.

**β-Indolylpiperidines XIII.**—A mixture of 1.08 g of indole, 1.70 g of XIc, and 1 ml of concentrated hydrochloric acid in 50 ml of glacial acetic acid was allowed to stand at room temperature for 20 hr. The solution was concentrated to a syrup under vacuum and below 40°. The residue was dissolved in water and extracted with ethyl acetate. The aqueous solution was cooled and made alkaline with potassium carbonate solution. The mixture was extracted with ethyl acetate and the extract washed with water and dried over anhydrous potassium carbonate. Evaporation of the solvent, chromatography of the residue, 2.32 g, on alumina (activity I) and elution with benzene produced 1.23 g of a syrup which solidified on trituration with ether–petroleum ether (bp 40–50°). Crystallization from hexane–ether yielded 1.05 g of methyl *trans*-2-(β-indolyl)nipecotate (XIIId): mp 103–104°; infrared (KBr) NH 3.00 (m), C=O 5.78 (s), C=C 6.18 (w), 6.45 μ (w); the pmr spectrum showed a three-proton singlet at 3.25 (O—Me) and one-proton doublets at 4.15 ($J$ = 10.0 cps) (C-2 methine), 6.86 ppm ($J$ = 2.5 cps) (indolyl α-H).

*Anal.* Calcd for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.67; H, 7.05; N, 10.73.

A solution of 100 mg of methyl α-indolylacetate, 106 mg of methyl 1-methyl-1,4,5,6-tetrahydronicotinate (IIi) and two drops of concentrated hydrochloric acid in 3 ml of glacial acetic acid was kept at room temperature for 4 hr. The solvent was evaporated under vacuum and below 60°. The residue was treated with 10% hydrochloric acid solution and extracted with benzene. The extract led to the recovery of 33 mg of methyl α-indolylacetate. The aqueous solution was filtered through Norit and made alkaline by the slow addition of solid potassium carbonate. The mixture was extracted with benzene and the extract washed with water and dried over sodium sulfate. The solvent was evaporated and the residual gum, 140 mg, was chromatographed on neutral alumina (activity I). Benzene and ether elutions yielded 42 mg of unreacted IIi, while elution with 1:1 ether–chloroform afforded 43 mg of a glass which solidified on standing. Crystallization from hexane gave 34 mg of methyl 1-methyl-2-(α-carbomethoxymethyl-β-indolyl)nipecotate (XIIIe): mp 112–114°; infrared (Nujol) NH 2.99 (m), C=O 5.82 (s), 5.85 μ (s); the pmr spectrum showed three-proton singlets at 1.98 (N—Me), 3.22 (O—Me), 3.72 (O—Me) and a two-proton singlet at 3.93 ppm (α-indolyl methylene).

*Anal.* Calcd for $C_{19}H_{24}O_4N_2$: C, 66.27; H, 6.97; N, 8.13. Found: C, 65.74; H, 7.03; N, 7.94.

A mixture of 1.28 g of methyl α-indolylacetate, 1.24 g of methyl 1,4,5,6-tetrahydronicotinate (XIc), and 0.5 ml of concentrated hydrochloric acid in 20 ml of acetic acid was kept at room temperature for 20 hr. The solvent was evaporated under vacuum and below 40°. The residue was dissolved in water and extracted with ethyl acetate for the removal of all nonbasic products. The cooled, aqueous solution was made alkaline with saturated potassium carbonate solution and extracted with ethyl acetate. The extract was washed with water, dried over potassium carbonate, and evaporated. Chromatography of the residue, 2.27 g, on alumina (activity I) and elution with benzene yielded 1.02 g of syrup whose crystallization from ether–petroleum ether gave 0.99 g of colorless prisms of methyl *trans*-2-(α-carbomethoxymethyl-β-indolyl)-nipecotate (XIIIf): mp 137–138°; infrared (KBr) C=O 5.80 (s), 5.83 μ (s); the pmr spectrum showed three-proton singlets at 3.25 (O—Me), 3.68 (O—Me), a two-proton singlet at 3.68 (α-indolyl methylene), and a one-proton doublet at 4.07 ppm ($J$ = 10.0 cps) (C-2 methine).[36]

*Anal.* Calcd for $C_{15}H_{22}O_4N_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.61; H, 6.75; N, 8.61.

**3-Piperideines XVII.**—A mixture of 3.58 g of methyl homonicotinate and 2.60 g of tryptophyl bromide[37] was heated at 80° under nitrogen for 45 hr. The solid product was washed with ether yielding 3.72 g of crystalline solid and crystallized from ether–methanol. The salt II (X = Br), mp 162–164°, was converted into II (X = $ClO_4 \cdot H_2O$): mp 156–160° (crystallization from water); infrared spectrum (Nujol) NH 2.92 (m), C=O 5.82 (s), C=C 6.06 μ (w).

*Anal.* Calcd for $C_{18}H_{19}O_6N_2Cl \cdot H_2O$: C, 52.50; H, 5.14; N, 6.81. Found: C, 52.61; H, 4.96; N, 7.10.

A solution of 4.00 g of II (X = Br) and 1.00 g of sodium borohydride in 100 ml of methanol was kept under nitrogen at room temperature for 15 min. Water, 200 ml, was added and the mixture left standing for another 30 min. The mixture was saturated with sodium chloride and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. Chromatography of the residue, 3.36 g, on silica gel and elution with ethyl acetate led to 250 mg of liquid methyl 1-[β-(3-indolyl)ethyl]-1,2,3,6-tetrahydrohomonicotinate (XVIIc): infrared (neat) NH 2.95 (m), C=O 5.78 (s), C=C 6.17 μ (w); the pmr spectrum showed a three-proton singlet at 3.65 (O—Me), a two-proton broad singlet at 5.69 (olefinic Hs), and a one-proton doublet at 6.90 ppm (α-indolyl H).

*Anal.* Calcd for $C_{18}H_{22}O_2N_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.62; H, 7.70; N, 9.68.

Subsequent chromatography fractions yielded 2.30 g of liquid methyl 1-[β-(3-indolyl)ethyl]-1,2,5,6-tetrahydrohomonicotinate (XVIIb): infrared (neat) NH 2.95 (m), C=O 5.78 (s), C=C 6.17 μ (w); the pmr spectrum showed a three-proton singlet at 3.62 (O—Me), a one-proton multiplet at 5.5–5.8 (olefinic H), and a one-proton doublet at 6.86 ppm (α-indolyl H).

*Anal.* Calcd for $C_{18}H_{22}O_2N_2$: C, 72.46; H, 7.43. Found: C, 72.46; H, 7.49.

A mixture of 15.0 g of methyl homonicotinate and excess methyl iodide was left standing under nitrogen for 15 hr. The excess methyl iodide was evaporated under vacuum and the solid residue washed with ether and dried. Crystallization of the solid from ether–methanol yielded 28.5 g of methyl homonicotinate methiodide (Im, X = I): mp 96°; infrared spectrum (Nujol) C=O 5.79 (s), C=C 6.11 μ (w).

*Anal.* Calcd for $C_9H_{12}O_2NI$: C, 36.86; H, 4.09; N, 4.77. Found: C, 36.93; H, 4.05; N, 4.62.

A mixture of 6.00 g of methyl homonicotinate methiodide (Im, X = I) and 1.30 g of sodium borohydride in 40 ml of methanol was kept under nitrogen at room temperature for 0.5 hr. Water (40 ml) was added and the mixture left standing for another 0.5 hr. It then was saturated with sodium chloride and extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and evaporated. Distillation of the residue yielded 2.60 g of a liquid mixture of XVIId and XVIIe, bp 69° (0.6 mm). A thin layer chromatogram on silica gel G (3:2, chloroform–methanol) revealed two spots, while gas phase chromatography (gpc) (F & M Model 500 chromatograph, 10 ft × 0.25 in column of 20% Apiezon L on WAW, column temperature 200°, flow rate 50 cc/min) showed the mixture to consist of 19% XVIIe (retention time 163 sec) and 81% of XVIId (retention time 177 sec). The mixture was separated by gpc (Aerograph Autoprep Model A-700 chromatograph, 10 ft × 0.375 in column of 30% Apiezon L on Chromosorb P, column temperature 198°, flow rate 150 cc/min). Treatment of the first fraction, a liquid (XVIIe) (the pmr spectrum showed three-proton singlets at 2.30 (N—Me), 3.68 (O—Me) and a two-proton doublet at 5.65 ppm ($J$ = 2.0 cps) (olefinic Hs)), with a saturated solution of picric acid in 95% ethanol and crystallization of the resultant solid from ethanol produced XVIIe picrate: mp 114–117.5°; infrared spectrum (Nujol) $NH^+$ 3.7 (m, broad), C=O 5.80 (s), C=C 6.10 (s), 6.14 (s), 6.17 (s), 6.21 μ (s).

*Anal.* Calcd for $C_{15}H_{18}O_9N_4$: C, 45.23; H, 4.55; N, 14.07. Found: C, 45.37; H, 4.77; N, 13.96.

Treatment of the second fraction, a liquid (XVIId) (the infrared spectrum (neat) showed C=O at 5.76 μ (s); the pmr spectrum showed three-proton singlets at 2.33 (N—Me), 3.68 (O—Me) and a one-proton multiplet at 5.61 ppm (olefinic H)), with a saturated solution of picric acid in 95% ethanol and crystallization of the product from ethanol yielded XVIId picrate: mp 89–91°; infrared spectrum (Nujol) $NH^+$ 3.7 (m), C=O 5.79 (s), C=C 6.10 (s), 6.14 (s), 6.17 (s), 6.21 μ (s).

*Anal.* Calcd for $C_{15}H_{18}O_9N_4$: C, 45.23; H, 4.55; N, 14.07. Found: C, 45.19; H, 4.41; N, 13.88.

**Piperidines XX (R = Me) and XXI.**—Trimethyl phosphonoacetate, 4.80 g, was added dropwise to a slurry of 1.05 g of

(36) Both XIIId and XIIIf were converted into N-acylpiperidines. Chloroacetylation yielded XIII (R = H, R′ = $CO_2Me$, R″ = $ClCH_2CO$), mp 147–151°, with an infrared spectrum (KBr) of NH 3.03 (m), C=O 5.75 (s), 6.09 (s), 6.15 (s), 6.22 μ (s), and XIII (R = $CH_2CO_2Me$, R′ = $CO_2Me$, R″ = $ClCH_2CO$), mp 160–163°, with an infrared spectrum (KBr) of NH 3.05 (m), C=O 5.79 (s), 6.10 μ (s), respectively. Acetylation of XIIIf produced XIII (R=$CH_2CO_2Me$, R′ = $CO_2Me$, R″ = Ac), mp 170°.

(37) T. Hoshino and K. Shimodaira, *Ann.*, **520**, 19 (1935).

sodium hydride in 100 ml of 1,2-dimethoxyethane kept at a temperature below 10°. Upon cessation of gas evolution, 1-methyl-3-piperidone, liberated from 4.08 g of its hydrochloride,[24] was added dropwise to the mixture still below 10°. The mixture then was stirred at 0° for 5 min and at room temperature for 1.3 hr. Saturated brine solution (80 ml) was added and the homogeneous solution extracted exhaustively with ether. The extract was dried over sodium sulfate and evaporated. Distillation of the residue gave 3.10 g of liquid methyl 1-methyl-3-carbomethoxymethylenepiperidine (XX, R = Me): bp 71–72° (0.5 mm); infrared (neat) C=O 5.83 (s), C=C 6.06 μ (s); ultraviolet $\lambda_{max}^{EtOH}$ 214 mμ (ε 15,500); the pmr spectrum showed two three-proton singlets at 2.23 and 2.26 (N—Me of both stereoisomers), a three-proton singlet at 3.62 (O—Me), and a one-proton multiplet at 5.62 (olefinic H); gpc (F & M Model 500, *vide supra*) retention time 223 sec. Its treatment with a saturated solution of picric acid in 95% ethanol and crystallization of the product from ethanol yielded yellow needles of XX (R = Me) picrate: mp 148°; infrared spectrum (Nujol) $NH^+$ 3.7 (m, broad), C=O 5.87 (s), C=C 6.03 (m), 6.14 (s), 6.21 μ (s).

*Anal.* Calcd for $C_{15}H_{18}O_9N_4$: C, 45.23; H, 4.55; N, 14.07. Found: C, 45.39; H, 4.84; N, 14.16.

The product mixture from the sodium methoxide treatment of XX (R = Me) (*vide infra*) was treated with a saturated solution of picric acid in 95% ethanol. Repeated fractional crystallization of the mixture of solids from ethanol separated the highest melting picrate. The latter was decomposed in 10% sodium hydroxide solution and the free base taken up in methylene chloride. The organic solution was dried over sodium sulfate and evaporated. The liquid product, methyl 1-methyl-3-methoxyhomonipecotate (XXI) (the infrared spectrum (neat) showed C=O at 5.70 μ (s); the pmr spectrum showed three-proton singlets at 2.25 (N—Me), 3.29 (ether O—Me), 3.69 (ester O—Me) and a two-proton singlet at 2.58 ppm (exocyclic methylene)), was reconverted to its picric acid derivative: mp 180–181°; infrared spectrum (Nujol) $NH^+$ 3.7 (m), C=O 5.78 (s), C=C 6.10 (s), 6.14 (s), 6.17 (s), 6.21 μ (s).

*Anal.* Calcd for $C_{16}H_{22}O_{10}N_4$: C, 44.65; H, 5.15; N, 13.02. Found: C, 44.67; H, 5.13; N, 12.96.

**Interconversion of XVIId and XVIIe.**—With high material recovery as a constant goal a variety of conditions of the reaction of each of the esters with sodium methoxide in methanol was tested (changes in concentration of ester and of base, in temperature and in time). The reactions were monitored and the product ratios determined by pmr and gpc methods (*vide supra*). The best reaction conditions were found to be the following. The ester was added to a *ca.* 1% sodium methoxide (*ca.* 65 mole %) solution in methanol and the mixture refluxed under nitrogen for 2 hr. Water was added to the cooled solution and the mixture extracted with methylene chloride. The extract was dried over sodium sulfate and evaporated under vacuum. The residual oil then was analyzed for product content.

**Registry No.**—Ia, 14997-23-0; Ib, 14996-82-8; Ic, 15083-66-6; Id, 14996-83-9; Il, 14996-84-0; If, 14996-85-1; Ig, 14996-86-2; Il (X = Br), 14996-87-3; Il (X = $ClO_4$), 14996-88-4; Im, 14996-89-5; IIa, 14996-90-8; IIb, 14996-91-9; IIc, 14996-92-0; IId, 14996-93-1; IIe, 14996-94-2; IIf, 14996-95-3; IIg, 15077-09-5; IIk, 14996-96-4; IIi, 14996-97-5; IIj, 14996-98-6; IIk, 14996-99-7; IIIb, 14997-00-3; IV, 14997-01-4; VI, 14997-02-5; VII, 14997-03-6; XIb, 14997-04-7; XIc, 14997-05-8; XIe, 7032-11-3; XIIa, 14997-07-0; XIIb, 15083-67-7; XIIId, 14997-08-1; XIIIe, 14997-09-2; XIIIf, 14997-10-5; XIII (R = H, R′ = $CO_2Me$, R″ = Cl = $CH_2CO$), 14996-76-0; XIII (R = $CH_2CO_2Me$, R′ = $CO_2Me$, R″ = $ClCH_2$-CO), 15076-94-5; XIII (R = $CH_2CO_2Me$, R′ = $CO_2Me$, R″ = Ac), 14996-77-1; XVIa, 14997-11-6; XVIb, 14997-12-7; XVIIb, 14997-13-8; XVIIc, 14997-14-9; XVIId, 14997-15-0; XVIId picrate, 14997-16-1; XVIIe picrate, 14997-17-2; XX (*trans*), 14997-18-3; XX (*trans*) picrate, 14997-19-4; XX (*cis*), 14997-21-8; XX (*cis*) picrate, 14997-22-9; XXI, 15077-10-8; XXI picrate, 14997-20-7; β-hydroxymethylpyridine, 586-98-1.

# The Kinetics of *syn–anti* Conversions of 2,4-Dinitrophenylhydrazones[1]

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The kinetics of bromination of alkylidene 2,4-dinitrophenylhydrazones (DNPs) (giving the corresponding alkylhydrazidic bromides) were studied using an electrometric technique to follow the low (*ca.* $10^{-5}$ *M*) bromine concentrations involved. The reaction was zero order in bromine. It was also insensitive to variation in the halogenating species (as between, *e.g.*, bromine, tribromide ion, and chlorine). The first-order rate constants for the reactions of eight alkylidene DNPs were correlated by the Taft equation with $\delta = +0.49$; *i.e.*, the rate of internal hydrazone change measured was dependent only on the size of the alkyl group involved. This was interpreted in terms of rate-determining *syn–anti* isomerism. Consistent with this proposal, bromination of N-(2,4-dinitrophenyl)-2-pyrazoline, which is a model for the *anti* isomer of the DNP, was a rapid second-order reaction. The preparation of a DNP with an asymmetric center α to the bromination site was achieved and its bromination occurred with essentially complete retention of optical activity. This, together with some chemical evidence, makes ene–hydrazine formation as the slow step unlikely (although this may be the rate-determining step with ketone DNPs). Rate data implied that N,N-disubstituted hydrazones, which are widely reported as being inactive toward electrophilic attack, should be brominated, though at a much reduced rate. An N,N-disubstituted hydrazidic bromide has been isolated for the first time from the bromination of one of the appropriate hydrazones and was readily converted into the corresponding hydrazide. We regard normal electrophilic substitution of arylidene (or alkylidene)hydrazones as SE2′ reactions and the corresponding reactions of N,N-disubstituted hydrazones as SE2 processes. The hydrolysis of the eight alkylhydrazidic bromides isolated (by bromination of the alkylidene DNPs), together with some of their reactions with nucleophiles, are also described.

Although 2,4-dinitrophenylhydrazine has been widely recommended as a reagent for the characterization of carbonyl compounds, its use for the formation of derivatives of simple aldehydes has been restricted because of the often widely differing melting points reported for these compounds. These differences in melting points have been variously ascribed to the coexistence of two (or more) isomeric forms of the hydrazones involving either geometric isomers (*syn* and *anti*) about the azomethine bond (—C=N—) or

(1) Some of the results reported here have been presented in communication form: A. F. Hegarty and F. L. Scott, *Chem. Commun.*, 521 (1967).