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Studies on the Azasteroids and Related Compounds. V.[1] Syntheses of Isomeric Ethyl 3-Methoxy-2-piperidineacetates and 4-Methoxy-1,2,3,4,4a,5,7,8,9,10-Decahydro-6*H*-benzo[*c*]-quinolizin-6-ones

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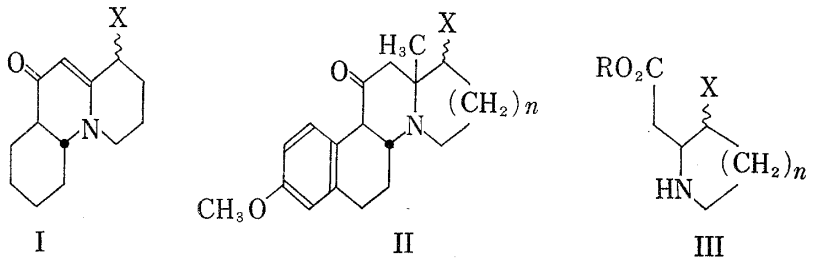
The lactim ether (XXII), prepared from 3-methoxy-2-piperidone (XXI) by the action of Meerwein reagent, condensed smoothly with benzyl cyanoacetate to give the Cope product (XXIII), which underwent debenzylation and decarboxylation, followed by sodium borohydride reduction and alcoholysis, yielding a mixture of ethyl *cis*- and *trans*-3-methoxy-2-piperidineacetates (XXIX). Cyclodehydration of XXIX with cyclohexanone afforded the vinylogous amides (XXX).

In the previous paper,[1] we have described the unsuccessful bromination, acetoxylation or hydroxylation of the vinylogous amide (Ia) to the 4-substituted benzo[*c*]quinolizine derivatives (Ib) and pointed the neccessity of preparation of the compounds (II; n=1 or 2), 3-substituted 2-piperidine- or 2-pyrrolidineacetates (III) as the starting materials.



I II III

a : X=H b : X=Br, OH, or OAc n=1 or 2

Chart 1

In the present paper, we describe the preparation of the compound (III) and their cyclodehydration with cyclohexanone.

Attempted Synthesis of Ethyl 3-Acetoxy-2-pyrrolidineacetate

In order to synthesize ethyl 3-acetoxy-2-pyrrolidineacetate (XI), we first prepared 3-acetoxy-2-pyrrolidylidene-α-bromoacetonitrile (X) from 2-pyrrolidone.

2-Pyrrolidone was treated with Meerwein reagent in chloroform to afford the lactim ether (IV), which was followed by the Cope reaction with benzyl cyanoacetate in benzene to give benzyl 2-pyrrolidylidenecyanoacetate (V) in good yield. The benzyl ester (V) then underwent debenzylation with 10% palladium on charcoal in hydrogen atmosphere, followed by decarboxylation to give 2-pyrrolidylideneacetonitrile (VI). Now, we planned to introduce an oxygen function into C-3 position of the pyrrolidine ring first by preparing the 3-bromide, followed by solvolysis with silver acetate. Bromination of the unsaturated nitrile (VI) with an equimolar amount of N-bromosuccinimide in carbon tetrachloride afforded the side-chain brominated compounds (VII) in good yield, whereas no ring-brominated product

1) Part IV: Z. Horii, K. Morikawa, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **17**, 846 (1969).

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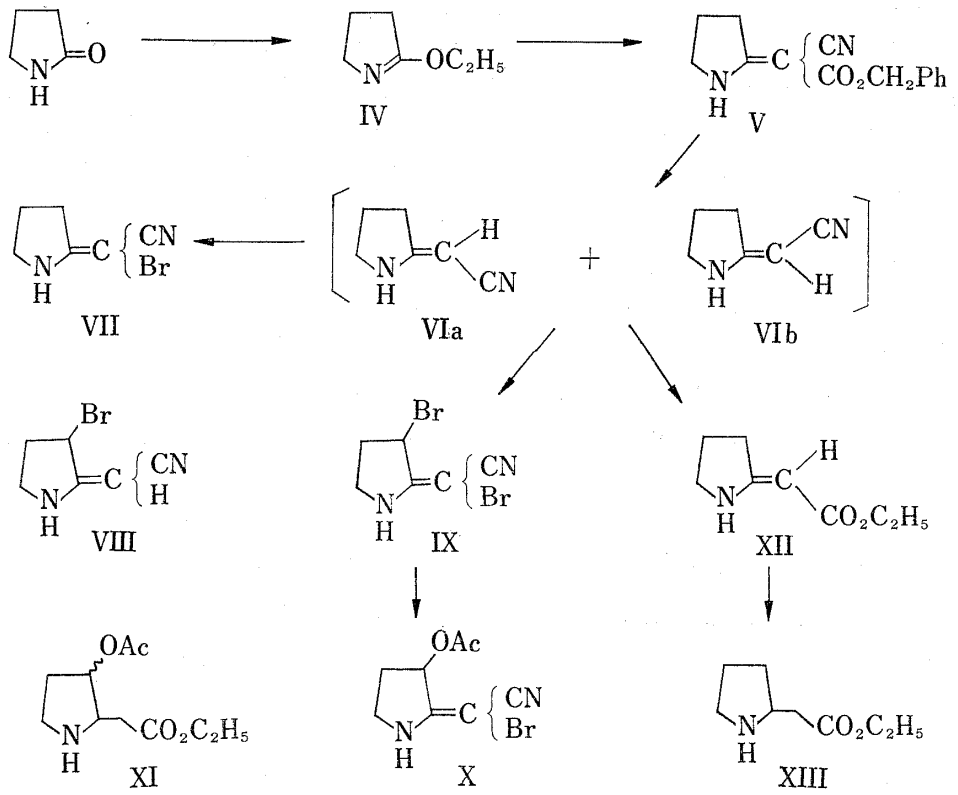

Chart 2

(VIII)could be isolated. On the other hand, when treated with two equivalent amount of N-bromosuccinimide, VI was converted into the dibromide (IX) bearing a bromine atom in the ring, in 66% yield, which was warmed with silver acetate in glacial acetic acid to afford 3-acetoxy-2-pyrrolidylidene-α-bromoacetonitrile (X) in only small amount, not enough to carry out the following sequence of reactions to XI.

However, the unsaturated nitrile (VI) underwent alcoholysis in absolute alcohol to ethyl 2-pyrrolidylideneacetate (XII), which was hydrogenated with Adams catalyst to give ethyl 2-pyrrolidineacetate (XIII).[3]

The structures of products (V, VI, VII, IX, X, XII) were determined from inspection of their infrared (IR) and nuclear magnetic resonance (NMR) spectra. The IR spectrum of the compound (V) showed sharp absorptions at 2180, 1670 and 1590 cm^{-1}, due to an unsaturated nitrile and an enaminoester grouping.[4] The compounds (VI, VII, IX, and X) showed absorptions due to an unsaturated nitrile grouping at 2190—2170 cm^{-1} [5] and a carbon–carbon double bond at 1640—1615 cm^{-1}, respectively, and the compound (X) showed an absorption due to an acetoxyl group at 1740 cm^{-1}. The enaminoester (XII) had two absorptions at 1665 and 1595 cm^{-1}, characteristic for an enaminoester grouping. The NMR spectrum of VI showed two singlet signals at τ 6.03 and 6.31, each corresponding to half a proton, which are assignable to an olefinic proton and thus suggested that the compound (VI) exists as an 1:1 mixture of isomeric VIa and VIb. The compound (V) gave two spots on thin-layer chromatography (TLC) which showed V existing as an isomeric mixture as in VI. While, the compound (IX and X) exhibited no signal corresponding to an olefinic proton in their NMR spectra. The signal due to C-3 ring proton in the compound (IX and X) appeared

3) R. Adams, S. Miyano, and M.D. Nair, *J. Am. Chem. Soc.*, **83**, 3323 (1961); G. Clemo, W.M. Morgan, and R. Raper, *J. Chem. Soc.*, **1935**, 1743.
4) R. Huisgen, K. Herbig, A. Siegel, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).
5) S. Baldwin, *J. Org. Chem.*, **26**, 3288 (1961).

at τ 4.98 and 4.15, each for one proton, as quartet, respectively. Thus, it could be concluded that bromination on VI occurred first at the side chain, followed by C-3 ring position.

In the NMR spectrum of the compound (XII), a signal due to an olefinic proton appeared as a sharp singlet at τ 5.47, indicating XII as being homogeneous and a signal due to a proton on nitrogen appeared in abnormally lower field (τ 2.10), suggesting the existence of intramolecular hydrogen bonding.[4] Therefore, the compound (XII) should be represented by the structure XII. The compound (XIII) was identified with the authentic sample prepared by the method described in literature.[3]

Preparation of Isomeric Ethyl 3-Methoxy-2-piperidineacetates and Their Cyclodehydration with Cyclohexanone

In order to prepare 3-substituted 2-piperidineacetates, we first attempted the synthesis of ethyl 3-carbethoxy-2-piperidineacetate (XIX) from ethyl 2-oxo-3-piperidinecarboxylate[6] (XIV).

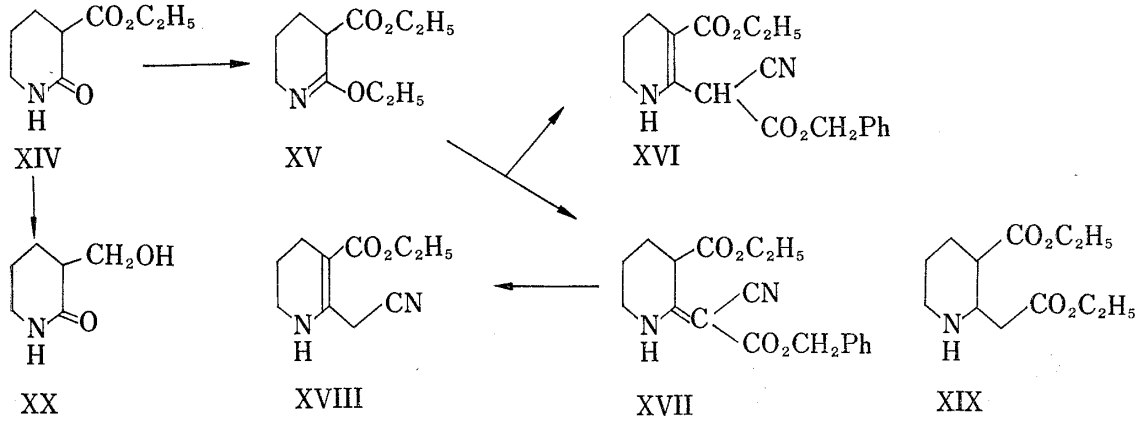

Chart 3

The compound (XIV) was treated with Meerwein reagent in chloroform to afford the lactim ether (XV)[7] in good yield. The Cope reaction of XV with benzyl cyanoactete in benzene, toluene, or xylene gave the compound (XIV) even after longer refluxing. The compound (XV) was then heated with benzyl cyanoacetate in *p*-cymene for 5 hr to afford the piperidylidenecyanoacetate (XVII) in low yield, accompanying with a very small amount of tetrahydropyridylcyanoacetate (XVI). The piperidylidenecyanoacetate (XVII) was treated with 10% palladium on charcoal in hydrogen atmosphere, followed by decarboxylation to give the 2-cyanomethyl derivative (XVIII) in good yield. The low yield of the Cope product (XVII) from the lactim ether (XV) could be ascribed mainly to two factors working on XV; that is, the steric and the electrostatic factors of the neighbering carbethoxyl group, both of which would hinder the access of the cyanoacetate molecule toward the lactim ether.

Therefore to get rid of these two factors, it was neccessary to convert the carbethoxyl group at C-3 in the compound (XIV) into a smaller and inactive group.

Preparation of the 2-hydroxymethyl derivative (XX) by reduction with sodium borohydride or lithium aluminum hydride in order to lower the electrostatic effect of the ester group was not promising due to poor yield. So, we chose 3-methoxy-2-piperidone (XXI), which has been prepared by Baker and coworkers,[8] and from which 3-methoxy-2-piperidineacetic acid esters were prepared as follows.

6) N.F. Albertson and J.L. Fillmann, *J. Am. Chem. Soc.*, **71**, 281 (1949).
7) R.G. Glushkov and O.Y. Magidson, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, **1965** (2), 240 [*C.A.*, **63**, 13259b (1965)].
8) B.R. Baker, R.E. Schaub, F.J. MeEvoy, and J.H. Williams, *J. Org. Chem.*, **17**, 132 (1952).

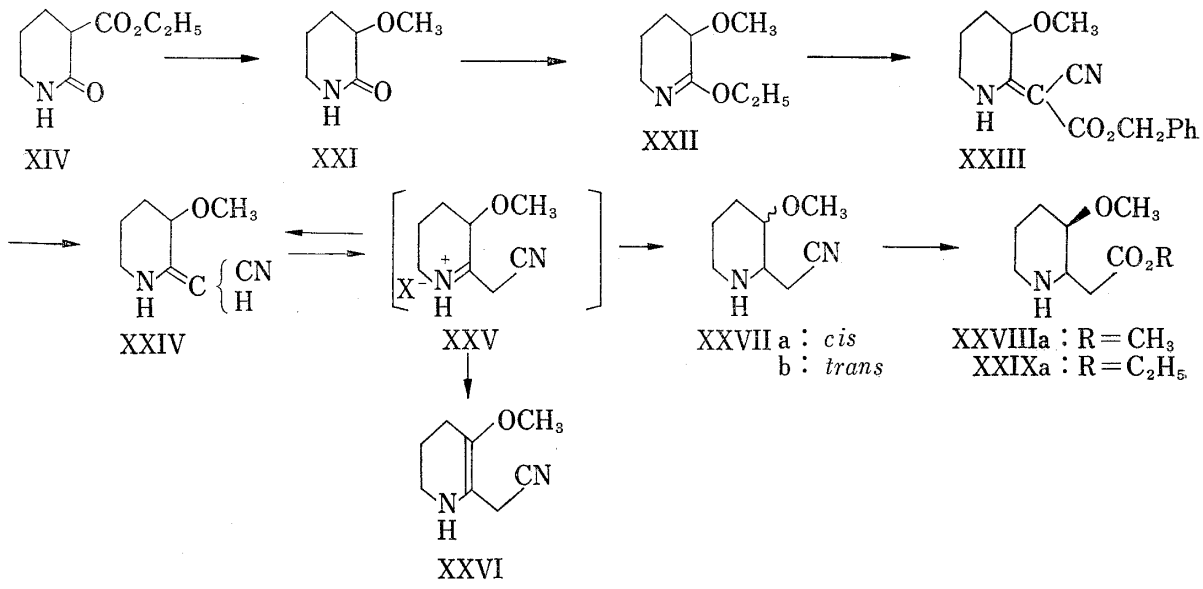

Chart 4

3-Methoxy-2-piperidone (XXI) was treated with Meerwein reagent in methylene chloride to afford the lactim ether (XXII) in 58% yield, which was condensed readily with benzyl cyanoacetate in toluene to give the piperidylidenecyanoacetate (XXIII) in 75% yield. The ester (XXIII) was hydrogenated with 10% palladium on charcoal, followed by decarboxylation to afford 3-methoxy-2-piperidylideneacetonitrile (XXIV) in high yield. The hydrochloride or perchlorate (XXV; X=Cl or ClO_4) of XXIV was reduced with sodium borohydride in aqueous methanol to the saturated nitrile (XXVII) in 30—40% yield, accompanying with small amount of the isomer (XXVI) of the compound (XXIV). On the other hand, the unsaturated nitrile (XXIV) was reduced smoothly with sodium borohydride and 40% sulfuric acid in aqueous methanol to afford XXVII in 70% yield in one step. The saturated nitrile (XXVII) thus obtained was found to be an isomeric mixture of the *cis*- (XXVIIa) and *trans*-nitriles (XXVIIb), each of which was separated by column chromatography as single product, the former being the main component.

In these reduction of XXIV, two forms (XXVa′ and XXVb′) for the intermediate could be considered. The former would be more preferable than the latter because of the presence of severe steric interaction between the cyanomethyl group at C-2 and the methoxyl group at C-3 in the latter form. The attack of the reducing agent in XXVa′ would be more preferably occur from the back side of the axial methoxyl group than from the same side, thus the *cis*-isomer (XXVIIa′) being obtained as the main product (Fig. 1).

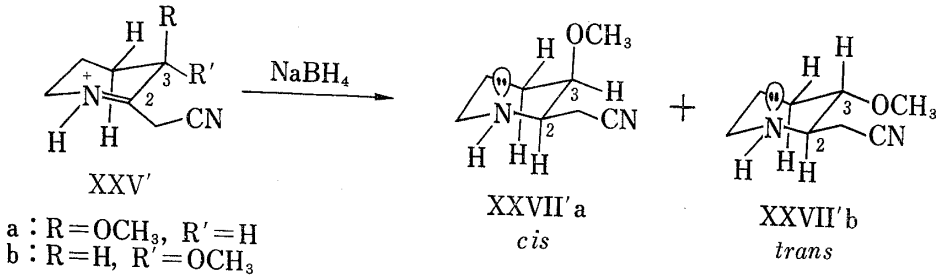

Fig. 1

The *cis*-saturated nitrile was readily esterified to the *cis*-esters (XXVIIIa and XXIXa). The *cis*-ethyl ester (XXIXa) was refluxed with excess of cyclohexanone in the presence of *p*-toluenesulfonic acid, followed by prolonged heating in ethylene glycol to afford the vinylogous amide (XXXa) in 52% yield, which was homogeneous on TLC. On the other hand, a mixture

of *cis*- and *trans*-ethyl esters (XXIXa and XXIXb), obtained by alcoholysis of a mixture of *cis*- and *trans*-nitriles (XXVIIa and XXVIIb), was similarly treated with cyclohexanone to afford a mixture of the vinylogous amides (XXXa and XXXb) in 62% yield, which showed two spots on TLC. Each of these vinylogous amides was separated as a single product by column chromatography.

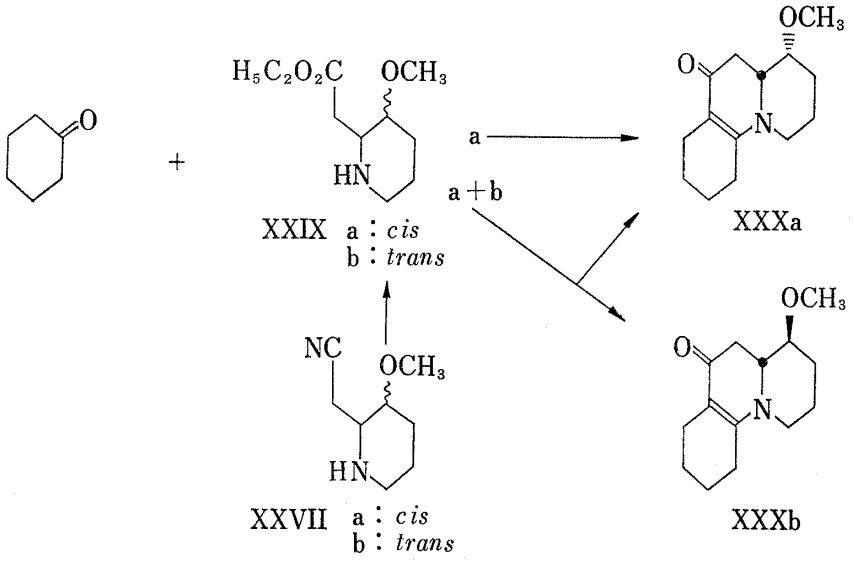

Chart 5

The structures of these products (XV—XXX) were determined or suggested from their IR and NMR spectra. In the IR spectra, both XVI and XVII showed absorptions at about 1730 cm^{-1} due to an ester group and at about 1650 and 1610 cm^{-1} due to an enaminoester grouping. On the other hand, a sharp absorption due to an unsaturated nitrile grouping appeared at 2203 cm^{-1} in the IR spectrum of XVII. However, XVI exhibited no visible peak at around 2300—2150 cm^{-1} in IR region. The IR spectrum of XVIII showed absorptions at 1665 and 1600 cm^{-1} corresponding to an enaminoester grouping and a weak peak at 2247 cm^{-1} due to a saturated nitrile group, and the NMR spectrum of XVIII showed a singlet signal at τ 5.98 (2H), assignable to methylene proton of the cyanomethyl group and no signal due to an olefinic proton.

The compound (XXIII) exhibited IR absorption at 2193 cm^{-1} attributable to an unsaturated nitrile grouping and at 1653 and 1608 cm^{-1} due to an enaminoester grouping. The IR spectrum of XXIV showed sharp peaks at 2180 and 1608 cm^{-1} assignable to an unsaturated nitrile and a carbon–carbon double bond groupings, respectively. On the other hand, the compound (XXVI) had weak absorptions at 2230 and 1668 cm^{-1} due to a saturated nitrile and an unsaturated double bond groups. A proton on nitrogen in the NMR spectra of XVII and XXIII appeared in the very low field (τ −0.15 and 0.09) as a broad singlet peak, showing the presence of the hydrogen bonding with ester carbonyl group[4] respectively, and the NMR spectrum of XXIV exhibited a proton on nitrogen normally at τ 4.82 and an olefinic proton at τ 5.94 as a singlet.

Both *cis*- and *trans*-saturated nitriles (XXVIIa and XXVIIb) showed IR absorption at 2225 cm^{-1} due to a saturated nitrile. The IR spectra of the esters (XXVIIIa and XXIXa) had an absorption at about 1720 cm^{-1} attributable to an ester group. The compounds (XXXa and XXXb) showed two strong peaks at 1620—1550 cm^{-1} region, characteristic for a vinylogous amide grouping[9] in their IR spectra.

9) Z. Horii, C. Iwata, I. Ninomiya, N. Imamura, M. Ito, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **12**, 1405, (1964); Z. Horii, K. Morikawa, I. Ninomiya, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **14**, 1399 (1966).

The stereochemistries of *cis*- and *trans*-nitriles (XXVIIa and XXVIIb), *cis*-esters (XXVIIIa and XXIXa), and the vinylogous amides (XXXa and XXXb) were suggested upon inspection of their NMR spectra. In the NMR spectra of the compounds (XXVIIa, XXVIIIa or XXIXa), a signal due to C-3 equatorial proton commonly at τ 7.00, 6.85 or 6.84 as multiplets with a half width of 8 cps, which suggested that the methoxyl group at C-3 was axially oriented in these compounds. Since it could not be thought that both side chains at C-2 and C-3 axially oriented, so it could be concluded that these compounds (XXVIIa, XXVIIIa, and XXIXa) would have the *cis*-forms with the axial methoxyl group at C-3 and the equatorial side chain at C-2.

On the other hand, in the NMR spectrum of XXVIIb, a signal due to C-3 proton appeared at τ 7.20 as triplet of doublets (J=12 and 4 cps), which showed that the axial C-3 proton was coupled with two adjacent axial protons and one adjacent equatorial proton. Accordingly, the structure of XXVIIb would be represented by XXVIIb' (Fig. 1).

The NMR spectrum of XXXa showed multiplet signal with a half width of 8 cps at 6.75 due to C-4 equatorial proton. On the other hand, XXXb had signal at τ 6.92 as triplet of doublets (J=12 and 5 cps) assignable to C-4 axial proton, which was coupled with two adjacent axial protons and one equatorial proton. These facts suggested that the compounds (XXXa and XXXb) would be represented by structures (XXXa' and XXXb') respectively, and the conclusion drawn from the above IR and NMR spectra was in accord with the assignment of the structure of the ethyl ester (XXIXa). Thus the intermediates from the ethyl ester (XXIXa or XXIXb) to the vinylogous amides (XXXa or XXXb) would be represented by structure (XXXIa or XXXIb).

XXX' XXXI

a : R=H,R'=OCH_3
b : R=OCH_3,R'=H

Fig. 2

Experimental[10]

5-Ethoxy-3,4-dihydro-2*H*-pyrrole (IV)——To a suspension of Meerwein reagent, prepared from BF_3·ethirate (273 g) and epichlorohydrin (133 g) in anhydrous ether (500 ml), in dry $CHCl_3$ (700 ml), was added 2-pyrrolidone (125 g) in dry $CHCl_3$ (200 ml), stirred at R.T. for 1 hr and allowed to stand overnight. After the excess of the reagent was decomposed with 50% K_2CO_3, the $CHCl_3$ layer was separated and dried. Evaporation of $CHCl_3$ gave pale brown volatile oil, which was distilled, to afford a volatile colorless liquid, bp 50—60° (15 mmHg). Yield, 65 g (40%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (–N=C<), 1030 (O–Et).

Benzyl 2-Pyrrolidylidenecyanoacetate (V)——The lactim ether (IV; 15 g), benzyl cyanoacetate (5 g) and triethylamine (2 ml) were dissolved in dry benzene (200 ml) and refluxed for 15 hr. Evaporation of the solvent afforded pale brown solid, which was recrystallized from *n*-hexane to give V, as colorless needles, mp 125—126°. Yield, 24.5 g (76%). *Anal.* Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.59; H, 5.91; N, 11.60. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (>NH), 2180 (>–CN), 1670, 1590 (–N–C=C–CO_2 CH_2Ph).

2-Pyrrolidylideneacetonitrile (VI)——The compound (V: 970 mg) was shaken with 10% Pd–C in EtOH (25 ml) and piperidine (0.5 ml) in a H_2 atmosphere. After completion of H_2 uptake (105 ml), the catalyst and the solvent were removed to give colorless crystal (VI), bp 140—150° (1.5 mmHg), mp 74—75° (from *n*-hexane). Yield, 430 mg. *Anal.* Calcd. for $C_6H_8N_2$: C, 66.64; H, 7.46; N, 25.91. Found: C, 66.61; H, 7.37; N, 25.81. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3344, 3300 (>NH), 2174 (=C–CN), 1615 (–C=C–). NMR τ ($CDCl_3$): 6.03 (s, 0.5H, >C=CH–), 6.31 (s, 0.5H, >C=CH–), 4.40 (broad s, 1H, >NH).

Bromination of 2-Pyrrolidylideneacetonitril (VI) with NBS——a) With One Molar Equivalent of NBS: A mixture of VI (350 mg, 3.25 mmoles), NBS (520 mg, 2.92 mmoles), and dibenzoylperoxide (10 mg) in CCl_4 was refluxed for 3 hr in N_2 stream. The hot reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo* to give almost colorless solid (610 mg), which was chromatographed on silicagel (12 g).

10) All melting points and boiling points are uncorrected. The NMR spectra were taken in $CDCl_3$ on Hitachi Perkin–Elmer H-60 type Spectrometer at 60 Mc., tetramethylsilane as internal reference.

The elution with $CHCl_3$ (100 ml) gave 2-pyrrolidylidene-α-bromoacetonitrile (VII) as colorless needles, mp 150.5—151.5° from benzene–*n*-hexane. Yield, 420 mg (70%). *Anal.* Calcd. for $C_6H_7N_2Br$: C, 38.53; H, 3.77; N, 14.98. Found: C, 38.45; H, 3.69; N, 14.99. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (>NH), 2170 (>–CN), 1624 (–C=C–). NMR τ ($CDCl_3$): 4.60 (broad s, 1H, >N–H), 6.30—6.40 (three peaks, 2H, $-CH_2-NH-$), 7.05—7.31 (four peaks, 2H, $-CH_2-C=C<$), 7.55—7.95 (four peaks, 2H, $-CH_2-CH_2-CH_2-$).

b) With Two Molar Equivalents of NBS: A mixture of VI (216 mg, 2.00 mmoles), NBS (776 mg, 4.35 mmoles) and dibenzoylperoxide (20 mg) was refluxed in CCl_4 (20 ml) for 4 hr. After succinimide was filtered off, the filtrate was evaporated to dryness to afford dark brown semi-solid (520 mg), which was purified by chromatography on silicagel (10.0 g). The elution with $CHCl_3$ (90 ml) gave almost colorless fine prisms, 3-bromo-2-pyrrolidylidene-α-bromoacetonitrile (IX), mp 123.5—125.5° from benzene–*n*-hexane. Yield, 350 mg (66%). *Anal.* Calcd. for $C_6H_6N_2Br_2$: C, 27.69; H, 2.27; N, 10.53. Found: C, 27.73; H, 2.26; N, 10.62. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (>NH), 2190 (>–CN), 1632 (–C=C–). NMR τ ($CDCl_3$): 4.50 (broad s, 1H, >NH), 4.98 (q, 1H, –CHBr–), 6.05—6.55 (many peaks, 2H, $-CH_2-NH-$), 7.10—7.65 (many peaks, 2H, $-CH_2-CH_2-CHBr-$).

Reaction of IX with Silver Acetate in AcOH——A mixture of IX (1.07 g, 4.02 mmoles) and silver acetate (0.70 g, 4.26 mmoles) in AcOH (20 ml) was stirred at R.T. for 8 hr, allowed to stand overnight and refluxed for 10 min. After removing AcOH, was added 10% aq. Na_2CO_3 (50 ml) and extracted with $CHCl_3$ (150 ml). Evaporation of $CHCl_3$ afforded dark brown pasty residue (0.27 g), which was chromatographed on silica-gel (7 g). Elution with $CHCl_3$ (150 ml) gave almost colorless crystals, 3-acetoxy-2-pyrrolidylidene-α-bromoacetonitrile (X), mp 119—120.5°, from benzene–*n*-hexane. Yield, 0.14 g (14%). *Anal.* Calcd. for $C_8H_9O_2N_2Br$: C, 39.22; H, 3.70; N, 11.44. Found: C, 39.76; H, 3.55; N, 11.74. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360 (>NH), 2180 (>–CN), 1740 (–O–$COCH_3$), 1640 (–C=C–). NMR τ ($CDCl_3$): 4.15 (q, 1H, >CH–OAc), 4.33 (broad s, 1H, >NH).

Ethanolysis of VI——A solution of VI (324 mg) in abs. EtOH (10 ml) was saturated with dry HCl gas under ice-cooling and then refluxed for 30 min. After evaporation of the solvent, to the residue was added $CHCl_3$ (50 ml) and K_2CO_3 paste prepared from K_2CO_3 (10 g) and H_2O (5 ml). After the resulting mixture was warmed on a steam bath for a minute and shaken well, the inorganic salt was filtered off. Evaporation of the $CHCl_3$ afforded pale brown semi-solid (290 mg), which was chromatographed on silica-gel. Elution with $CHCl_3$ (150 ml) gave colorless solid (200 mg, 43%), ethyl 2-pyrrolidylideneacetate (XII), which was sublimed at 70—80° under 40—50 mmHg, mp 63.0—63.5°. *Anal.* Calcd. for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.59; H, 8.19; N, 9.14. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (NH), 1665, 1595 (N–C=C–CO_2Et). NMR τ ($CDCl_3$): 2.10 (broad s, 1H, >NH), 5.47 (s, 1H, >C=CH–), 5.90 (q, 2H, $-OCH_2CH_3$), 6.3—6.6 (three peaks, 2H, $>N-CH_2-CH_2-$), 7.2—7.6 (three peaks, 2H, $-CH_2-C=C<$), 7.8—8.3 (multiplet, 2H, $>N-CH_2-CH_2-CH_2-$), 8.74 (t, 3H, $-CH_2-CH_3$).

Hydrogenation of XII with PtO_2——The compound (XII: 120 mg) was hydrogenated in AcOH (15 ml) with PtO_2 (25 mg) in H_2 stream. The catalyst and solvent were removed. Neutralization with K_2CO_3 paste, extraction with $CHCl_3$ (70 ml) afforded pale brown oil (125 mg), which was distilled *in vacuo* to give colorless oil, bp 130—135° (bath temp.) (20 mmHg), ethyl 2-pyrrolidineacetate (XIII), identical with the authentic sample[3] prepared alternatively throughout the range of IR spectra. Yield, 110 mg (91%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (>NH), 1725 (–CO_2Et).

3-Carbethoxy-2-ethoxy-3,4,5,6-tetrahydropyridine[7] (XV)——A solution of 3-carbethoxy-2-piperidone[6] (XIV: 20 g) in CH_2Cl_2 (50 ml) was added to a CH_2Cl_2 (200 ml) solution of Meerwein reagent prepared from BF_3·ethirate (46 g) and epichlorohydrin (22.5 g) and the resulting solution was stirred at R.T. for several hours and then allowed to stand overnight. After decomposing the excess of Meerwein reagent with 50% K_2CO_3, the CH_2Cl_2 layer was separated, dried and evaporated to give the oily residue, which was distilled *in vacuo* to give colorless oil, 3-carbethoxy-2-ethoxy-3,4,5,6-tetrahydropyridine[7] (XV), bp 90—92° (5 mmHg). Yield, 18 g (78%). IR ν_{max}^{EtOH} cm^{-1}: 1730 (–CO_2Et), 1670 (>C=N–), 1035 (=C–OEt).

Cope Reaction of XV with Benzyl Cyanoacetate——A solution of XV (4.0 g), benzyl cyanoacetate (3.0 g) and $AcONH_4$ (0.3 g) in *p*-cymene (20 ml) was refluxed for 5 hr. After evaporation of *p*-cymene under reduced pressure, the oily residue was chromatographed on alumina (120 g). The first elution with benzene (1 liter) afforded colorless leaflets, benzyl 3-carbethoxy-2-piperidylidenecyanoacetate (XVII), mp 107—108° from *n*-hexane–benzene. Yield, 1.0 g (13%). *Anal.* Calcd. for $C_{18}H_{20}O_4N_2$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.76; H, 6.11; N, 8.36. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3155, 3096 (NH), 2203 (=C–CN), 1730 (–CH–CO_2Et), 1662, 1613 (>C=C–CO_2CH_2Ph). NMR τ ($CDCl_3$): −0.15 (broad s, 1H, >NH), 4.85 (s, 2H, $-OCH_2Ph$), 5.80 (q, 2H, $-OCH_2CH_3$), 8.73 (t, 3H, $-OCH_2CH_3$). The second elution with $CHCl_3$ (300 ml) afforded benzyl 3-carbethoxy-1,4,5,6-tetrahydro-2-pyridylcyanoacetate (XVI), 0.19 g (3%), which was recrystallized from benzene–*n*-hexane to give colorless needles, mp 161.5—163.5°. *Anal.* Calcd. for $C_{18}H_{20}O_4N_2$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.98; H, 6.08; N, 8.43. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 (NH), 1735 (–CO_2CH_2Ph), 1640, 1608 (–C=C–CO_2Et). NMR τ ($CDCl_3$): 4.83 (s, 2H, $-OCH_2Ph$), 5.35 (broad s, 1H, –NH–), 6.20 (q, 2H, $-OCH_2CH_3$), 6.71 (m, 2H, $-CH_2NH-$), 6.10 (s, 1H, =C–CH<(CN, CO)). The third elution with $CHCl_3$ (600 ml)

gave semi-solid, (1.30 g, 36%), 3-carbethoxy-2-piperidone (XIV). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1670.

3-Carbethoxy-1,4,5,6-tetrahydro-2-pyridylacetonitrile (XVIII)——The compound (XVII; 328 mg) in EtOH (10 ml) containing a few drops of piperidine was shaken with 10% Pd-C (350 mg) in H_2 stream at R.T. under atmospheric pressure. After 32 ml of H_2 was absorbed, the catalyst and solvent were removed to give colorless crystal (210 mg), which was recrystallized from benzene–*n*-hexane to give colorless needles (XVIII), mp 93—95°. Yield, 170 mg (88%). *Anal.* Calcd. for $C_{10}H_{14}O_2N_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 62.00; H, 7.31; N, 14.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425 (>NH), 2247 (–CH_2–CN), 1665, 1600 (–N–C=C–CO_2Et). NMR τ ($CDCl_3$): 5.24 (broad, s, 1H, >NH), 5.88 (q, 2H, –O$CH_2$$CH_3$), 5.98 (s, 2H, =C–$CH_2$CN).

Reduction of Ethyl 2-Oxo-3-piperidinecarboxylate (XIV)——a) With $NaBH_4$: To a solution of XIV (5.0 g) in MeOH (80 ml) was added $NaBH_4$ (5.0 g) and refluxed for 7 hr on a steam bath. A small amount of conc. HCl was added to the reaction mixture, and further refluxed for 30 min. After cool, the inorganic salt and solvent were removed to give the oily residue, which was treated with 10% Na_2CO_3 (60 ml) and extracted with $CHCl_3$ (40 ml × 5). The organic extract was washed with brine, dried and evaporated to afford colorless pasty residue which was distilled *in vacuo*, giving colorless crystal, 3-hydroxymethyl-2-piperidone (XIX), bp 160—170° (0.01 mmHg), mp 79—80.5° from benzene–*n*-hexane. Yield, 450 mg (12%). *Anal.* Calcd. for $C_6H_{11}O_2N$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.88; H, 8.48; N, 10.77. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3401, 3320, 3247 (>NH and –OH), 1677, 1653 (>N–CO–). NMR τ ($CDCl_3$): 5.72 (m, 1H, –CH_2–OH), 6.69 (t, 2H, >CH–CH_2–OH), 7.52 (m, 1H, >CH–CH_2–OH).

b) With $LiAlH_4$: To a solution of XIV (3.43 g) in anhydrous ether (100 ml) was added a suspension of $LiAlH_4$ (0.76 g) in anhydrous ether (50 ml) at −40——35° under dry ice–acetone cooling. After adding $LiAlH_4$, stirring was continued at the same temperature for 4.5 hr. And then AcOEt (50 ml) and H_2O (20 ml) were added and stirred well. The organic layer was separated and aqueous layer was shaken with AcOEt (50 ml × 4). The combined organic layer was washed with brine and dried. Evaporation of the solvent gave almost colorless viscous residue (1.18 g), which was chromatographed on alumina (20 ml). The first elution with $CHCl_3$ (200 ml) gave semi-solid (0.82 g, 24%), the starting material (XIV). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1670. The second elution with EtOH (100 ml) gave colorless crystals, (XIX: 0.24 g, 9%), mp 77—79.5°, which was identical with the sample obtained from a) by comparison of their IR spectra. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3401, 3320, 3247, 1677, 1653.

3-Methoxy-2-piperidone (XXI)——According to the method described by Baker and coworkers,[8] XIV was chlorinated with SO_2Cl_2, followed by treatment with NaOMe in anhydrous MeOH to give 3-carbethoxy-3-methoxy-2-piperidone in overall 70% yield, which was then hydrolyzed with KOH in aq. MeOH followed by decarboxylation to XXI, in 70—80% yield, bp 100—110° (0.1 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320, 3170 (>NH), 1670 (–CO–N<).

2-Ethoxy-3-methoxy-3,4,5,6-tetrahydropyridine (XXII)——A mixture of XXI (5.5 g) and Meerwein reagent (15.6 g) in anhydrous $CHCl_3$ (200 ml) was stirred at R.T. for 5 hr and allowed to stand overnight. After decomposing the excess of reagent with 50% K_2CO_3, the $CHCl_3$ layer was separated, dried and evaporated. The oily residue thus obtained was distilled *in vacuo*. The lower boiling fraction, bp 120—125° (4 mmHg), gave 2-ethoxy-3-methoxy-3,4,5,6-tetrahydropyridine (XXII). Yield, 4.28 g (58%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1667 (>C=N–), 1036 (=C–OEt). The higher boiling fraction, bp 110—140° (0.1 mmHg), recovered the starting material (XXI), 1.45 g (26%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320, 3170, 1670.

Benzyl 3-Methoxy-2-piperidylidenecyanoacetate (XXIII)——a) From the Lactim Ether (XXII): A solution of XXII (3.77 g, 24.2 mmoles), benzyl cyanoacetate (4.32 g, 24.2 mmoles) and $AcONH_4$ (0.7 g) in dry toluene (100 ml) was refluxed for 7 hr. After evaporating toluene, the lower boiling substances were distilled off *in vacuo* at 5 mmHg. The dark brown pasty residue was chromatographed on alumina (100 g). The first elution with benzene (1 liter) and the second elution with a 1:1 mixture of benzene–$CHCl_3$ gave 5.15 g (75%) of pale yellow viscous oil, benzyl 3-methoxy-2-piperidylidenecyanoacetate (XXIII), bp 170—180° (0.01 mmHg). *Anal.* Calcd. for $C_{16}H_{18}O_3N$; C, 67.11; H, 6.34; N, 9.78. Found: C, 66.86; H, 6.24; N, 9.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3247, 3175 (NH), 2193 (=C–CN), 1653, 1608 (>N–C=C–CO_2CH_2Ph). NMR τ ($CDCl_3$): 0.09 (broad s, 1H, >NH), 4.82 (s, 2H, –OCH_2Ph), 5.73 (t, 1H, –CH_2–CH–OCH_3), 6.51(s, 3H,–OCH_3).

b) From XXI: A solution of 3-methoxy-2-piperidone (XXI) (10.55 g, 0.09 mole) and Meerwein reagent (34.0 g, 0.179 mole) in CH_2Cl_2 (180 ml) was stirred at R.T. for 5 hr and allowed to stand overnight. The K_2CO_3 paste prepared from K_2CO_3 (100 g) in H_2O (50 ml) was portionwise added under ice–water cooling. Inorganic salt was removed and washed with CH_2Cl_2. The combined organic layer was gently evaporated to afford reddish-brown oil, 2-ethoxy-3-methoxy-3,4,5,6-tetrahydropyridine (XXII, 12.75 g). The crude lactim ether (XXII) thus obtained was dissolved in anhydrous toluene (50 ml), and was added benzyl cyanoacetate (12.50 g, 0.072 mole) and $AcONH_4$ (1.5 g). The resulting solution was heated under reflux for 8.5 hr. After the solvent and some low boiling substances were removed *in vacuo*, the residue (15.9 g) was chromatographed on alumina (100 g). Elution with benzene (1.3 liter) gave viscous oil, benzyl 3-methoxy-2-piperidylidenecyanoacetate (XXIII), 170—180° (0.01 mmHg). Yield, 12.24 g (46% from XXI). R $\nu_{max}^{CHCl_3}$ cm^{-1}: 3247, 3175, 2193, 1653, 1608.

3-Methoxy-2-piperidylideneacetonitrile (XXIV)——A solution of benzyl 3-methoxy-2-piperidylidenecyanoacetate (XXIII; 5.15 g) in MeOH (100 ml) was shaken with 10% Pd-C (1.00 g) at R.T. in H_2 stream.

After completion of H_2 absorption (460 ml), the catalyst and the solvent were removed, giving the yellow oily residue, which was distilled *in vacuo* to almost colorless oil, 3-methoxy-2-piperidylideneacetonitrile (XXIV, 2.48 g, 90.5%), bp 120—140° (0.1 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3344 (NH), 2181 (=C–CN), 1608 (–C=C–). *Anal.* Calcd. for $C_8H_{12}ON_2$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.63; H, 7.83; N, 18.16. NMR τ ($CDCl_3$): 5.94 (s, 1H, >C=CH–), 6.62 (s, 3H, –OCH_3), 4.82 (broad s, 1H, >NH).

Reduction of 3-Methoxy-2-piperidylideneacetonitrile (XXIV) with $NaBH_4$——a) Via the Hydrochloride (XXV: X=Cl): A solution of XXIV (600 mg) in anhydrous ether(30 ml) was saturated with dry HCl gas under ice cooling. Ether was evaporated to dryness *in vacuo* to give the residue, which was dissolved in MeOH (40 ml) and was added portionwise $NaBH_4$ (1.10 g) under ice–water cooling. Stirring was continued for 1 hr at R.T. After adding H_2O (50 ml), the mixture was stirred further for 20 min and then extracted with $CHCl_3$ (30 ml×5). Drying and evaporating the $CHCl_3$ extract afforded the oily residue, which was distilled, collecting a fraction boiling at 110—120° (3 mmHg) as colorless oil (0.41 g), which was chromatographed on silica–gel (10 g). The first elution with $CHCl_3$ (300 ml) gave 3-methoxy-1,4,5,6-tetrahydro-2-pyridylacetonitrile (XXVI, 90 mg (15%)). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3280 (>NH), 2230 (–CH_2CN), 1668 (–C=C–). Picrate: mp 176—178.5° (decomp.) from MeOH. *Anal.* Calcd. for $C_{14}H_{15}O_8N_5$: C, 44.10; H, 3.97; N, 18.37. Found: C, 44.31; H, 3.90; N, 18.54. The second elution with $CHCl_3$ (150 ml) gave a mixture of *cis*- and *trans*-3-methoxy-2-piperidineacetonitriles (XXVIIa and XXVIIb) (270 mg, 45%). IR ν_{max}^{film} cm^{-1}: 3270 (>NH), 2225 (–CN). Picrate: mp 220—227° (decomp.).

b) Via the Perchlorate (XXV, X=ClO_4): To a solution of XXIV in 70% MeOH was added a calculated amount of 70% $HClO_4$ followed by $NaBH_4$ and stirred at R.T. for 1 hr. Worked up as above was obtained a mixture of *cis*- and *trans*-3-methoxy-2-piperidineacetonitriles (XXVIIa and XXVIIb) (200 mg) from the first $CHCl_3$ elution, and the *cis*-isomer (810 mg, 37%) from the latter elution. IR ν_{max}^{film} cm^{-1}: 3270 (NH), 2225 (–CH_2CN). Picrate: mp 234—236° (decomp.) from MeOH. *Anal.* Calcd. for $C_{14}H_{17}O_8N_5$: C, 43.86; H, 4.47; N, 18.27. Found: C, 43.96; H, 4.39; N, 18.39. NMR τ ($CDCl_3$): 6.63 (s, 3H, –OCH_3), 7.00 (m, W1/2=8 cps, 1H, >CH–OCH_3), 7.46 (d, 2H, >CH–CH_2–CN), 8.40 (s, 1H, >NH).

c) Direct Reduction: To a solution of XXIV (2.0 g) in 75% MeOH (25 ml) was added $NaBH_4$ (3.5 g) and 50% MeOH (50 ml) at once and followed by dropwise addition of 40% H_2SO_4 (16 ml) under ice cooling, while the temperature being maintained below 20°. After completion of H_2SO_4 addition, 10% NaOH (50 ml) was added and the resulting mixture was extracted with $CHCl_3$ (500 ml). The extract was washed with brine, dried and evaporated to give an oily residue (1.50 g), which was chromatographed on silica–gel (30 g). The first elution with $CHCl_3$ (350 ml) gave the starting material (200 mg, 10%). The second elution with $CHCl_3$ (500 ml) afforded a mixture of *cis*- and *trans*-nitriles (XXVIIa and XXVIIb) (280 mg). The third elution with $CHCl_3$ (1.3 liter) and the fourth elution with $CHCl_3$–EtOH (9:1) (600 ml) gave 1.05 g (53%) of *cis*-isomer (XXVIIa). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3270 (NH), 2225 (CN). Picrate: mp 234—236°. A fraction of a mixture of *cis*- and *trans*-isomers obtained above was rechromatographed on silica–gel and obtained *trans*-3-methoxy-2-piperidineacetonitrile (XXVIIb) (180 mg, 9%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3270 (NH), 2225 (–CH_2-CN). NMR τ ($CDCl_3$): 6.66 (s, 3H, –OCH_3), 7.20 (t-d, J=12 and 4 cps, 1H, >CH–OCH_3), 7.33 (d, 2H, >CH–CH_2CN), 8.37 (s, 1H, –NH). Picrate: mp 177—178.5° (decomp.) from EtOH. *Anal.* Calcd. for $C_{14}H_{17}O_8N_5$: C, 43.86; H, 4.47; N, 18.27. Found: C, 43.90; H, 4.52; N, 18.26.

Alcoholysis of *cis*-3-Methoxy-2-piperidineacetonitrile (XXVIIa)——a) In abs. MeOH: A solution of XXVIIa (290 mg) in anhydrous MeOH (20 ml) was saturated with dry HCl gas under ice cooling and then warmed at 40—45° for 1.5 hr. MeOH was eva porated under reduced pressure at 30—40°. After neutralizing with 50% K_2CO_3, $CHCl_3$ extraction, upon distillation, afforded colorless oil, methyl *cis*-3-methoxy-2-piperidineacetate (XXVIIIa: 340 mg, 96%), bp 110—125° (5 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 1720 (–CO_2Me). NMR τ ($CDCl_3$): 6.68 (s, 3H, >CH–OCH_3), 6.85 (m, W1/2=8 cps, 1H, >CH–OCH_3), 7.48 (d, 2H, >CH–CH_2–CO_2Me), 8.09 (s, 1H, >NH). Picrate: mp 151.5—153.0° (decomp.) from EtOH. *Anal.* Calcd. for $C_{15}H_{20}O_{10}N_4$: C, 43.27; H, 4.84; N, 13.46. Found: C, 43.57; H, 4.74; N, 13.41.

b) In abs. EtOH: To a solution of XXVIIa (460 mg) in abs. EtOH (30 ml) was saturated with dry HCl gas under ice cooling and then warmed at 50—60° for 2 hr. Worked up as usual was obtained, upon distillation *in vacuo*, colorless oil, ethyl *cis*-3-methoxy-2-piperidineacetate (XXIXa; 450 mg, 75%), bp 110—120° (5 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330, 1718. NMR τ ($CDCl_3$): 6.67 (s, 3H, >OCH_3), 6.84 (m, W1/2 =8 cps, 1H, >CH–OCH_3), 7.50 (d, 2H, >CH–CH_2–CO_2Et), 7.88 (s, 1H, >NH). *Anal.* Calcd. for $C_{16}H_{22}O_{10}N_4$: C, 44.65; H, 5.15; N, 13.02. Found: C, 44.75; H, 5.05; N, 13.21.

Reaction of Ethyl *cis*-3-Methoxy-2-piperidineacetate (XXIXa) with Cyclohexanone——A solution of XXIXa (100 mg) and cyclohexanone (3 ml) was refluxed in the presence of a few crystals of *p*-TsOH in N_2 stream for 12.5 hr. After evaporating excess cyclohexanone *in vacuo*, ethylene glycol (10 ml) was added to the above residue and refluxed for 11 hr. After cool, the reaction mixture was poured onto ice–water (50 ml), and extracted with $CHCl_3$ (100 ml). The extract was washed with H_2O, dried and evaporated to give the viscous oily residue, which was chromatographed on alumina (2.0 g). The first elution with benzene (100 ml) afforded a viscous oil (50 mg), mostly cyclohexanone containing a trace of vinylogous amide (XXXa). The second elution with benzene (50 ml) and the third elution with $CHCl_3$ (100 ml) afforded semi–solid, 4α-methoxy-1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo[*c*]quinolizin-6-one (XXXa), bp 140—150° (0.01 mmHg).

Yield, 60 mg (52%). *Anal.* Calcd. for $C_{14}H_{21}O_2N$: C, 71.45; H, 9.00; N, 5.90. Found: C, 71.05; H, 9.10; N, 5.67. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1560 (>N–C=C–C=O). NMR τ ($CDCl_3$): 6.16 (d-m, 1H, C_{1eq}–H), 6.63 (s, 3H, –O$\underline{CH_3}$), 6.75 (m, W1/2=8 cps, 1H, C_4–H).

Mixture of Ethyl *cis*- and *trans*-3-Methoxy-2-piperidineacetates (XXIXa and XXIXb)——To a solution of the perchlorate (XXV, X=ClO_4), prepared from XXIV (1.35 g), in 70% MeOH (150 ml) was added $NaBH_4$ (4.5 g) under ice cooling, and stirred at R.T. for 1 hr. Worked up as above was obtained a mixture of *cis*- and *trans*-saturated nitriles (XXVIIa and XXVIIb; 690 mg, 51%). IR ν_{max}^{film} cm^{-1}: 3270, 2225. Alcoholysis of a mixture of isomeric nitriles (690 mg) in abs. EtOH was carried out as above and afforded a mixture of *cis*- and *trans*-ethyl esters (XXIXa and XXIXb), 700 mg (78%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330, 1718.

Reaction of a Mixture of isomeric Ethyl *cis*- and *trans*-3-Methoxy-2-piperidineacetates (XXIXa and XXIXb) with Cyclohexanone——A solution of an isomeric mixture of XXIXa and XXIXb (700 mg) in cyclohexanone (6 ml) in the presence of a few crystals of *p*-TsOH was refluxed for 14 hr and then, upon replacing excess cyclohexanone with ethylene glycol (15 ml), refluxed further 7 hr. Upon treated as described above, a crude oily product (1.3 g) was obtained, which was then chromatographed on alumina (150 ml). From the second elution with benzene was obtained a very viscous oil, a mixture of 4α- and 4β-methoxydecahydro-6*H*-benzo[*c*]quinolizin-6-one (XXXa and XXXb). Yield, 370 mg (46%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620—1615, 1560—1550. And from the following elution with $CHCl_3$ was obtained semi-solid (XXXa). Yield, 190 mg (24%), identified with the sample obtained the foregoing experiment. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1560. Rechromatography of a fraction of a mixture of isomeric XXXa and XXXb on silica-gel (1 g). The first elution with $CHCl_3$ (50 ml) gave XXXa (190 mg, 24%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1560. The second elution with $CHCl_3$ (250 ml) gave semi-solid, 4β-methoxy-1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo[*c*]quinolizin-6-one (XXXb), bp 140—150° (0.01 mmHg). Yield, 80 mg (10%). *Anal.* Calcd. for $C_{14}H_{21}O_2N$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.26; H, 8.94; N, 6.21. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615, 1550. NMR τ ($CDCl_3$): 6.18 (d-m, 1H, C_{1eq}–H), 6.64 (s, 3H, –O$\underline{CH_3}$), 6.92 (t-d, J=12 and 5 cps, 1H, C_4–H).