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Covering the Period

May 31, 1963 - May 30, 1964

# The Investigation for Alternate Methods for the Synthesis of 3-Quinuclidinol and Other Azabicyclic Alcohols

(Security Classification)

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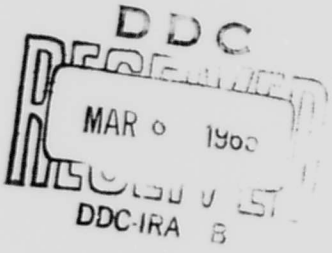
Final REPORT

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Title: The Investigation for Alternate Methods for the Synthesis of 3-Quinuclidinol and Other Azabicyclic Alcohols

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Date: June 25, 1964

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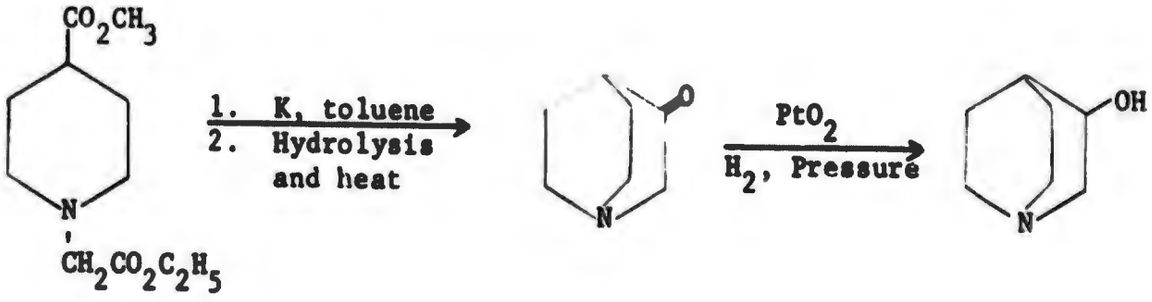
and Other Azabicyclic Alcohols

## I. Introduction

3-Quinuclidinol (III) was first prepared by Sternbach and Kaiser[1] using the scheme shown below. This procedure involves a




I II III

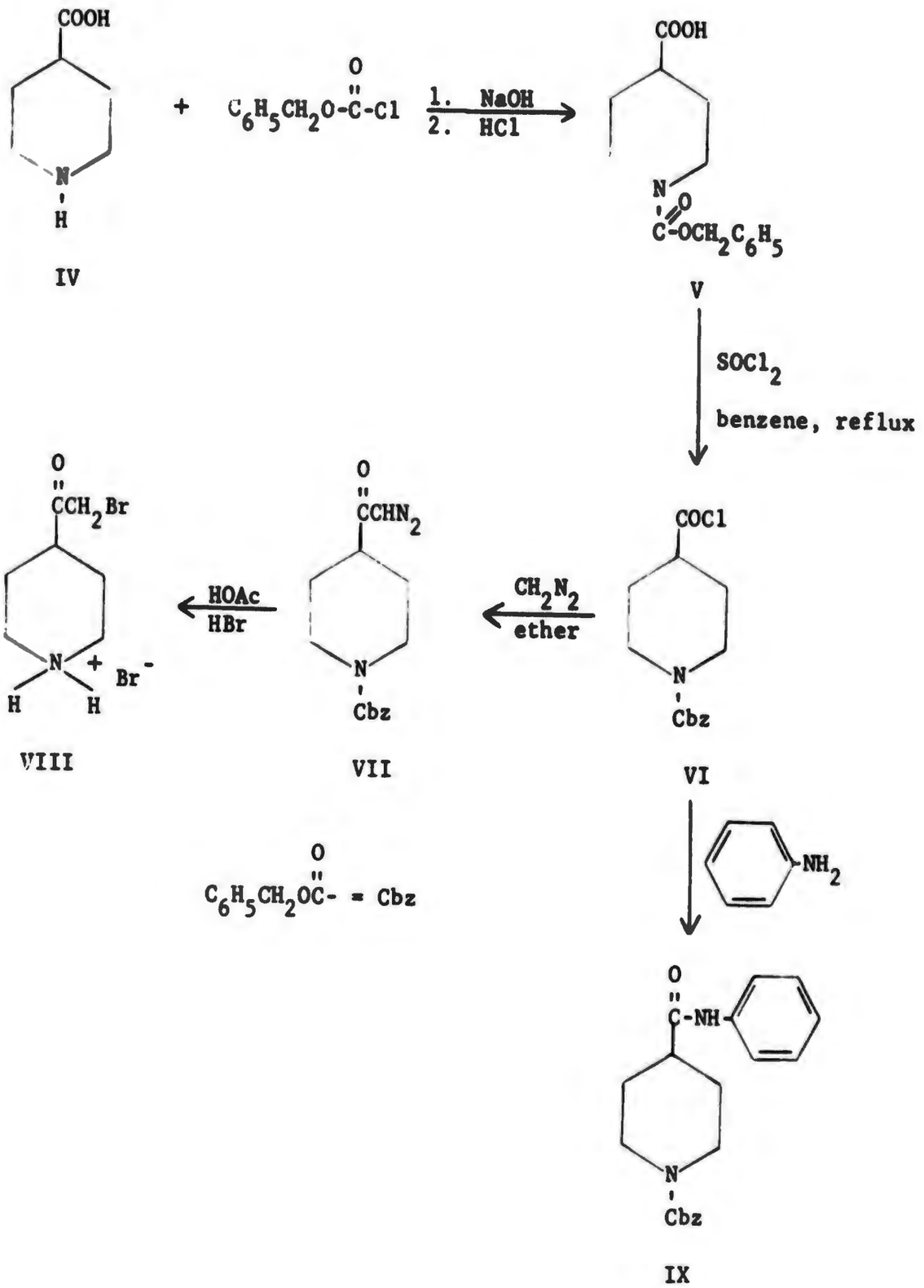
Dieckmann condensation of I to give 3-quinuclidinone (II). Experimentally this is a very difficult reaction to run and under the best conditions the yield of II obtained is low.

The following report comprises the research accomplished in an investigation to develop new methods, excluding the Dieckmann method, for the synthesis of 3-quinuclidinol.

## II. Research Accomplishments

### A. Attempted Preparation of 3-Quinuclidinol via 4-Bromoacetylpiperidine Hydrobromide (VIII)

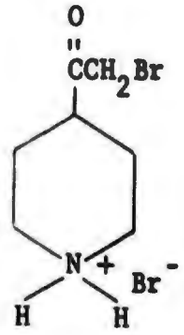
The $\alpha$-bromoketone (VIII) was regarded as a potential key intermediate in one of the possible routes leading to the preparation of 3-quinuclidinol. It was prepared in good yield by the following reactions.



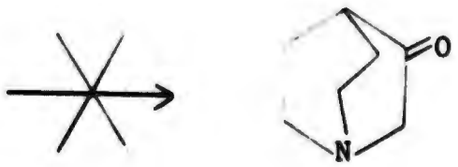

Treatment of isonipecotic acid (IV) with carbobenzyloxy chloride gave 1-carbobenzyloxypiperidine-4-carboxylic acid (V) as an oil in 90.5% yield. The infrared spectrum showed bands at 3500-2500 (bonded

acid -OH) and 1700-1685 cm.$^{-1}$ (acid and carbamate carbonyl). The crude 1-carbobenzyloxy-4-piperidinecarboxylic acid was used without further purification to prepare the acid chloride VI in 95% yield, which was also an oil. The infrared spectrum contained bands at 1795 (acid chloride carbonyl), and 1695 cm.$^{-1}$ (carbamate carbonyl). The oil was characterized as its anilide, obtained in 73% yield, m.p. 141.5-142.5°. The infrared spectrum showed bands at 3285 (N-H), 1695 (carbamate carbonyl) and 1655 and 1530 cm.$^{-1}$ (amide I and amide II bands). Treatment of VI with excess diazomethane gave the diazoketone (VII) as an oil in 97.6% yield. The infrared spectrum showed bands at 2112 ($-\overset{+}{N}\equiv\overset{-}{N}$), 1640 (ketone carbonyl adjacent to a diazo group) and 1695 cm.$^{-1}$ (carbamate carbonyl). Dissolving VII in an excess of acetic acid saturated with hydrogen bromide effected both conversion of the diazoketo group to the bromoacetyl group and decarbobenzyloxylation of the N-carbobenzyloxy group to give VIII in 64% yield, m.p. 153-155°. The infrared spectrum showed a band at 1728 cm.$^{-1}$ (carbonyl of a bromoacetyl group). The n.m.r. (nuclear magnetic resonance) spectrum showed two complex multiplets at 1.6-2.3 ($>C<^{-CH_2-}_{-CH_2-}$, 4.3 H) and 2.8-3.8 ($-CH_2-N-CH_2-$ and $>\overset{O}{\overset{\|}{C}}HC-$, 4.9 H) and a singlet at 4.38δ ($-\overset{O}{\overset{\|}{C}}CH_2Br$, 1.7 H).

However, various attempts, listed below, to convert the bromoketone (VIII) to 3-quinuclidinone (II) a precursor of 3-quinuclidinol (III) were unsuccessful.



VIII

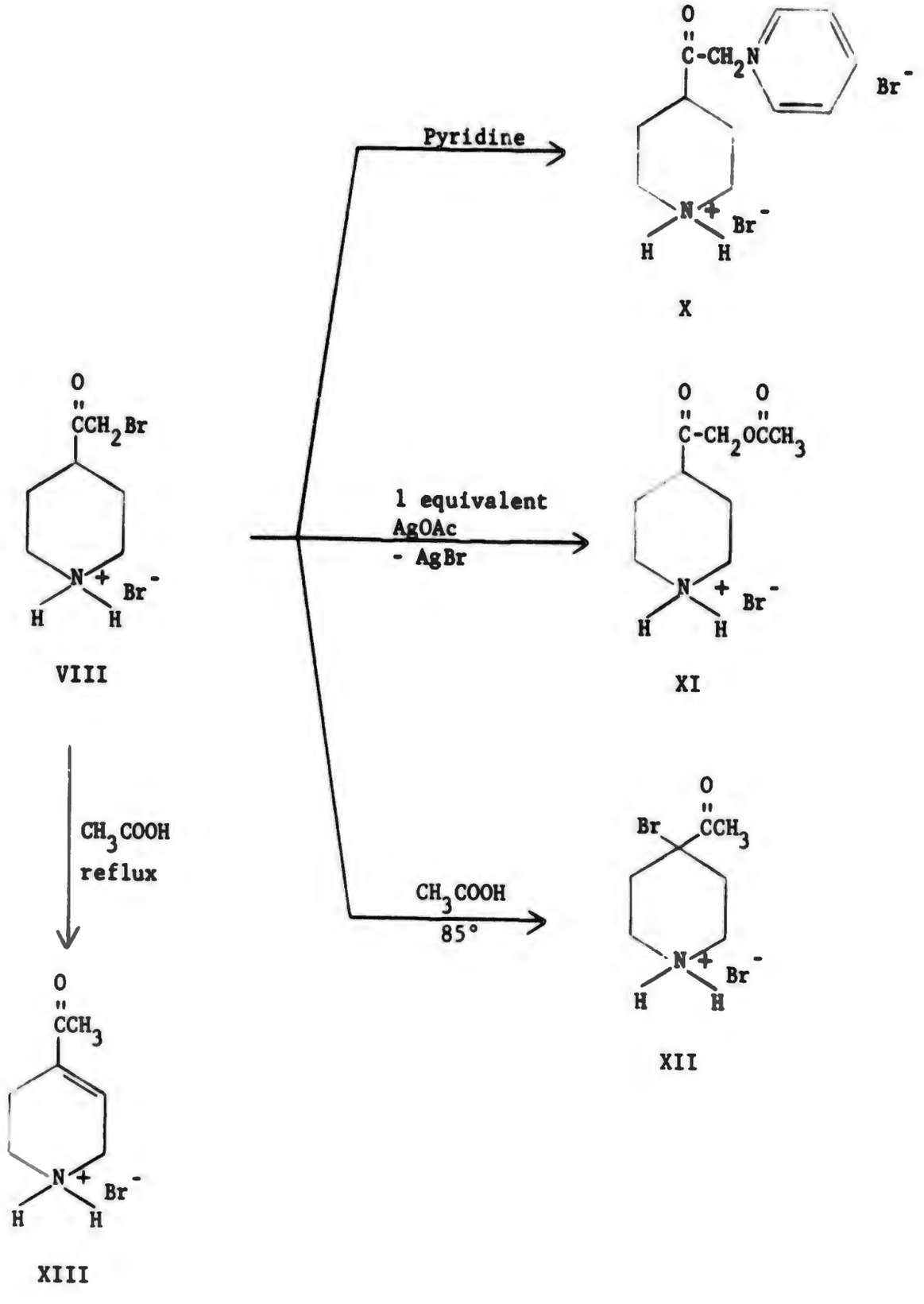


II

1. Sodium hydroxide in water.
2. Amberlite IRA-45 basic ion exchange resin in methanol.
3. Tri-isopropanolamine in water or chloroform.
4. Potassium tert-butoxide in tert-butyl alcohol.
5. Silver oxide in methanol.
6. Woelm basic alumina in methanol.
7. Sodium acetate in ethanol.

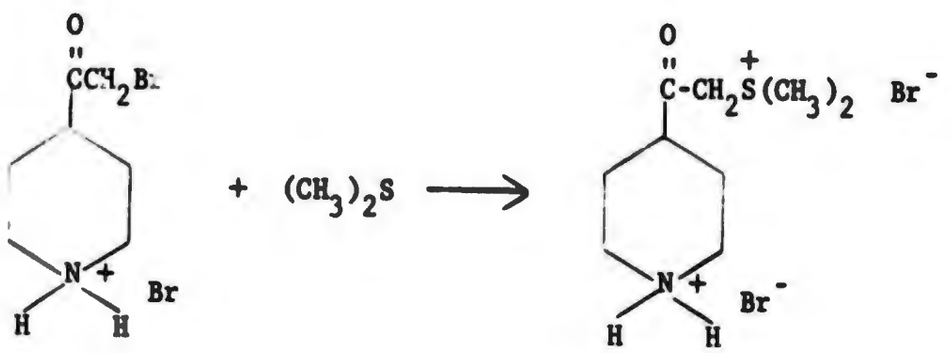
The details of each of the above reactions are given in the Experimental section.

In addition to the above reaction, which yielded no isolatable pure product, it was found that treatment of VIII with pyridine caused external displacement of the bromine to give the pyridinium salt (X), m.p. 240-242° in 93% yield. The infrared spectrum showed bands at 1732 (ketone adjacent to a $-CH_2-\overset{+}{N}$ group), and 1640 and 1494 $cm.^{-1}$ (pyridine ring stretching modes). The n.m.r. spectrum showed two very complex multiplets at 1.6-2.4 ($\begin{matrix} -CH_2- \\ C \\ -CH_2- \end{matrix}$, 4.2 H) and 2.8-3.8 ($\begin{matrix} -CH_2 \\ -CH_2 \end{matrix}\!\!>\overset{+}{N}$ and $\overset{O}{\overset{\|}{C}}HC-$, 5 H), a multiplet centered at 8.14 (β-pyridine protons, 1.9 H), and a multiplet centered at 8.65δ (α- and γ-pyridine protons, 3 H).


Pyridine
1 equivalent
AgOAc
- AgBr
CH3COOH
85°
CH3COOH
reflux
Br-
X
XI
XII
VIII
XIII

The protons due to the methylene group between the keto and 1-pyridyl group must either be masked by the HDO peak at 4.53δ or be acidic enough to exchange with the deuterium oxide. Treatment of VIII with silver acetate gave mostly an amorphous solid similar to the product isolated when VIII was treated with aqueous base, however, a 9.6% yield of the α-acetoxyketone XI was isolated, m.p. 137.5-139.8°. The infrared spectrum showed bands at 2800-2500 (peak typical of an amine hydrobromide), 1730 (ester carbonyl), 1712 (ketone carbonyl), and 1250 cm.$^{-1}$ (C-O). When VIII was warmed in acetic acid for seven days a 32% yield of the rearranged product, 4-acetyl-4-bromopiperidine hydrobromide (XII), m.p. 154-155°, was obtained. The infrared spectrum showed bands at 1702 (ketone carbonyl), and 1360 cm.$^{-1}$ ($CH_3\overset{O}{\overset{\|}{C}}-$). Since the carbonyl group is not shifted to higher frequency by the α-bromosubstituent, the C-Br and C=O bands must not be co-planar. Results similar to the above have been observed in steroids.[2] A $C_{20}$ carbonyl group has its frequency increased by 20 cm.$^{-1}$ by a bromine substitution at $C_{21}$, but the frequency remains unchanged when the bromine is substituted at $C_{17}\alpha$. The n.m.r. spectrum showed a multiplet centered at 2.4 ($-CH_2\diagdown\diagup C\diagup\diagdown CH_2-$, 3.6 H), a singlet at 2.65 ($CH_3\overset{O}{\overset{\|}{C}}-$, 3.3 H) and a multiplet centered at 3.45δ ($-CH_2\diagdown\diagup \overset{+}{N}\diagup\diagdown CH_2-$, 4 H). When VIII was refluxed in acetic acid the rearranged product XII that presumably formed first was dehydrohalogenated to give XIII, m.p. 160-163°. The infrared spectrum showed absorption at 1698 (conjugated ketone C=O), 1618 (C=C) and 1360 cm.$^{-1}$ ($CH_3\overset{O}{\overset{\|}{C}}-$). Treatment of VIII with dimethylsulfide yielded 4-dimethylsulfoniumacetyl-

piperidine bromide hydrobromide (XIV) in 59.5% yield. The infrared spectrum showed absorption at 2900-2400 (typical amine hydrobromide salt absorption) and 1710 cm.$^{-1}$ (ketone C=O). The n.m.r. spectrum showed a complex multiplet at 1.6-2.4 ($\left(\text{C}\begin{smallmatrix}\text{CH}_2\text{-}\\ \text{CH}_2\text{-}\end{smallmatrix}\right)$), a complex multiplet at 2.8-3.8 ($\left(\begin{smallmatrix}\text{-CH}_2\\ \text{-CH}_2\end{smallmatrix}\text{N}^+\right)$ and $\text{-C}\overset{\text{O}}{\overset{\|}{\text{H}}}$), and a sharp singlet appearing at 3.0δ ($CH_3$-S-). The protons due to the methylene group between the

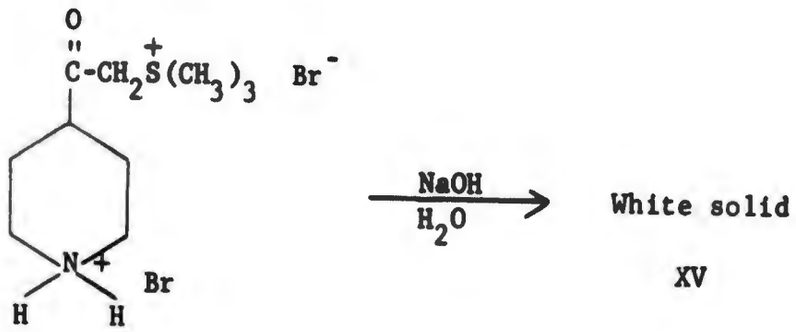



XIV

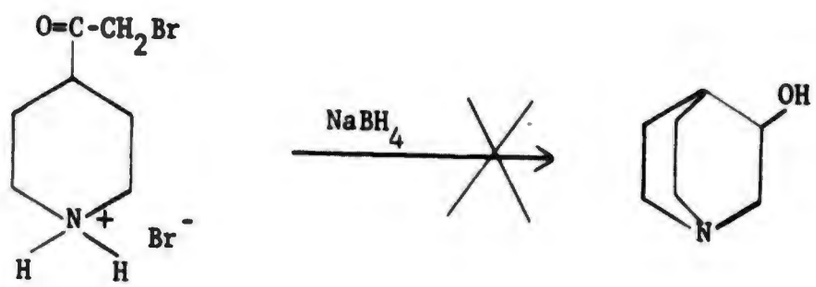
carbonyl and the sulfur must either be masked by the HDO peak at 4.53δ or be acidic enough to exchange with the deuterium oxide.

An attempt to prepare 3-quinuclidinone from X by treatment with dilute sodium hydroxide solution gave only a black gum. No pure product could be isolated from the gum. Treatment of XIV with dilute sodium hydroxide solution gave a solid which decomposed gradually at room temperature to a dark mass. A small amount of a white solid (XV) was isolated from the mass by sublimation, m.p. 131-135°. The infrared spectrum showed a carbonyl peak at 1708 cm.$^{-1}$. There was not enough of this solid to obtain an analysis. It was not investigated further.

Several attempts were made to form 3-quinuclidinol directly by the



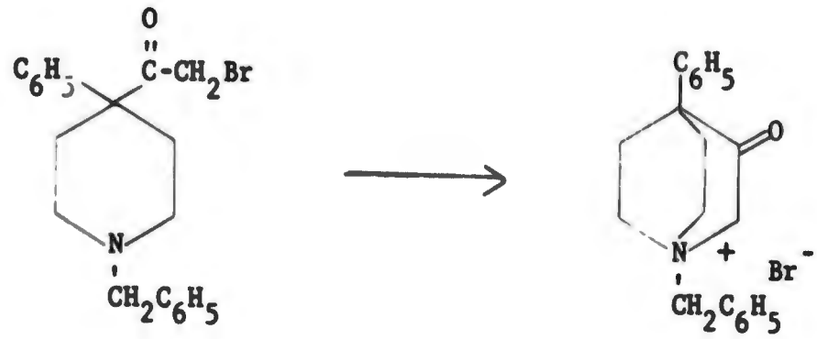

action of sodium borohydride on 4-bromoacetyl piperidine hydrobromide (VIII). The reaction was carried out using a mixture of 3:2, methanol: dioxane as solvent. In all cases an approximately ten fold excess of




sodium borohydride was used. When the reaction was run at a concentration of $2.6 \times 10^{-2}$ molar in bromoketone, thin layer chromatography (TLC) (2:2:1, butanol:water:acetic acid) indicated 3 products were formed in approximately equal amounts. One of these had an $R_f$ value identical to that of authentic 3-quinuclidinol. However, no 3-quinuclidinol could be isolated upon work-up by various procedures. When the concentration of bromoketone was reduced to about $1 \times 10^{-3}$ molar, TLC indicated that four products were formed. Only a very small amount of material with an $R_f$ similar to 3-quinuclidinol was observed. Similar results were obtained when the reduction was carried out in water.

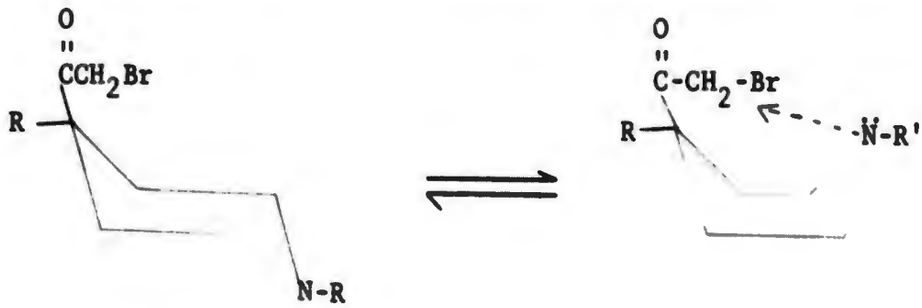
The resistance of 4-bromoacetylpiperidine hydrobromide to undergo

cyclization to 3-quinuclidinone is quite interesting since Perrine[3] found that 1-benzyl-4-bromoacetyl-4-phenylpiperidine (XVI) cyclizes readily to give 1-benzyl-4-phenylquinuclidinone bromide (XVII) in high yield.



XVI XVII

These results can be explained in the following way. In order for VIII or XVI to cyclize, the 4-bromoacetyl group and the pair of electrons on nitrogen would have to occupy axial positions (see figure XVIIIb).



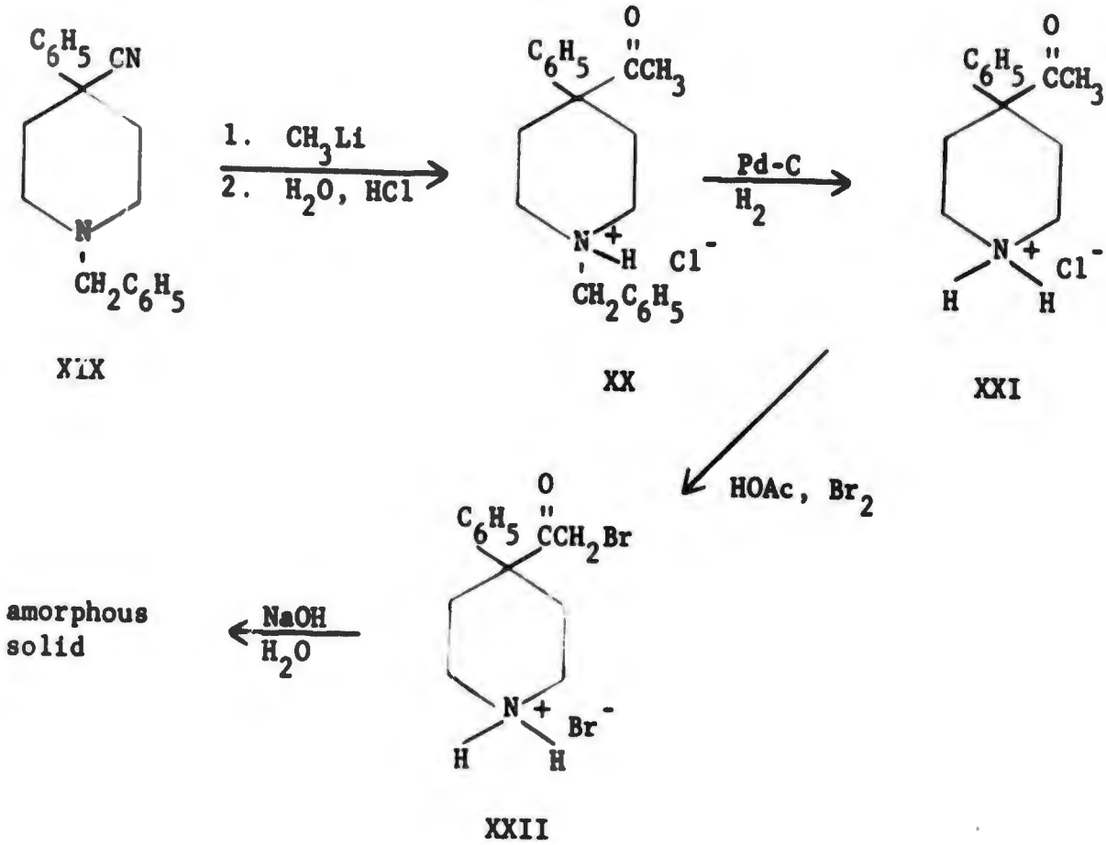
XVIIIa XVIIIb

R = H or $C_6H_5$

R' = H or $C_6H_5CH_2$-

Attainment of this reactive conformation is facilitated in the case of ketone XVI since the phenyl group in the form XVIIIb (R = $C_6H_5$) would then be equatorial.

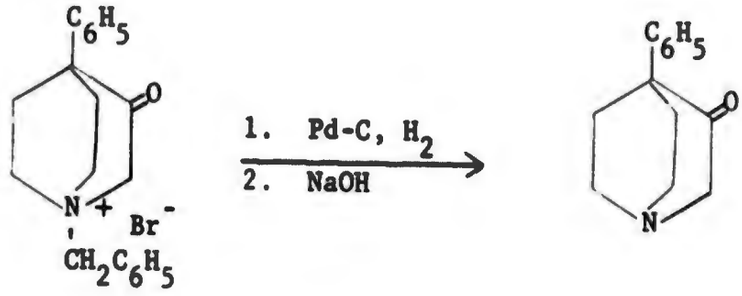
In order to check this explanation experimentally, 4-bromoacetyl-4-phenylpiperidine hydrobromide (XXII) was prepared by the scheme shown below. 4-Phenyl-4-acetylpiperidine hydrochloride (XXI) was prepared by




XIX XX XXI XXII

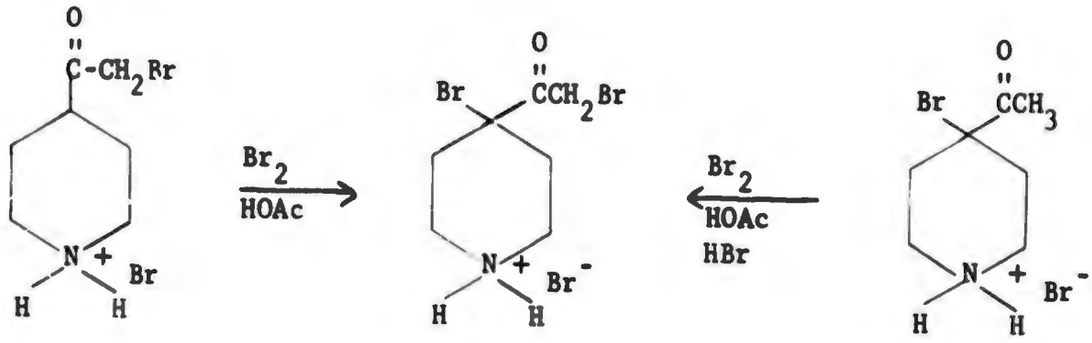
the procedure reported by Perrine.[3] Perrine reported that bromination of XXI gave only recovered starting material. However, we found that treatment of XXI with bromine in acetic acid gave a 91% yield of XXII, m.p. 202-206°. The infrared spectrum showed absorption at 1726 $cm.^{-1}$ (carbonyl of bromoacetyl group). The n.m.r. spectrum showed a multiplet at 2.40-2.78 ($-CH_2-C-CH_2-$, 4.0 H), a multiplet at 3.23-3.58 ($-CH_2-N^+-CH_2-$, 4.0 H), a singlet at 4.29 ($-\overset{O}{\overset{\|}{C}}CH_2Br$, 1.7 H) and a singlet at 7.55δ (aro-

matic protons, 5.2 H). Treatment of the 4-bromoacetyl-4-phenylpiperidine hydrobromide with aqueous sodium hydroxide did not, however, give 4-phenyl-3-quinuclidinone (XXIII). An amorphous solid was obtained. The infrared spectrum was quite different from that of an authentic sample of 4-phenyl-3-quinuclidinone XXIII prepared by the debenzylation of 1-benzyl-4-phenyl-3-quinuclidinone followed by neutralization.



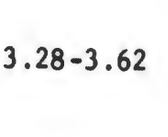

XVII XXIII

We also prepared 4-bromo-4-bromoacetylpiperidine hydrobromide XXIV by bromonation of either 4-bromoacetylpiperidine hydrobromide (VIII) or 4-bromo-4-acetylpiperidine hydrobromide (XII). The infrared spectrum of



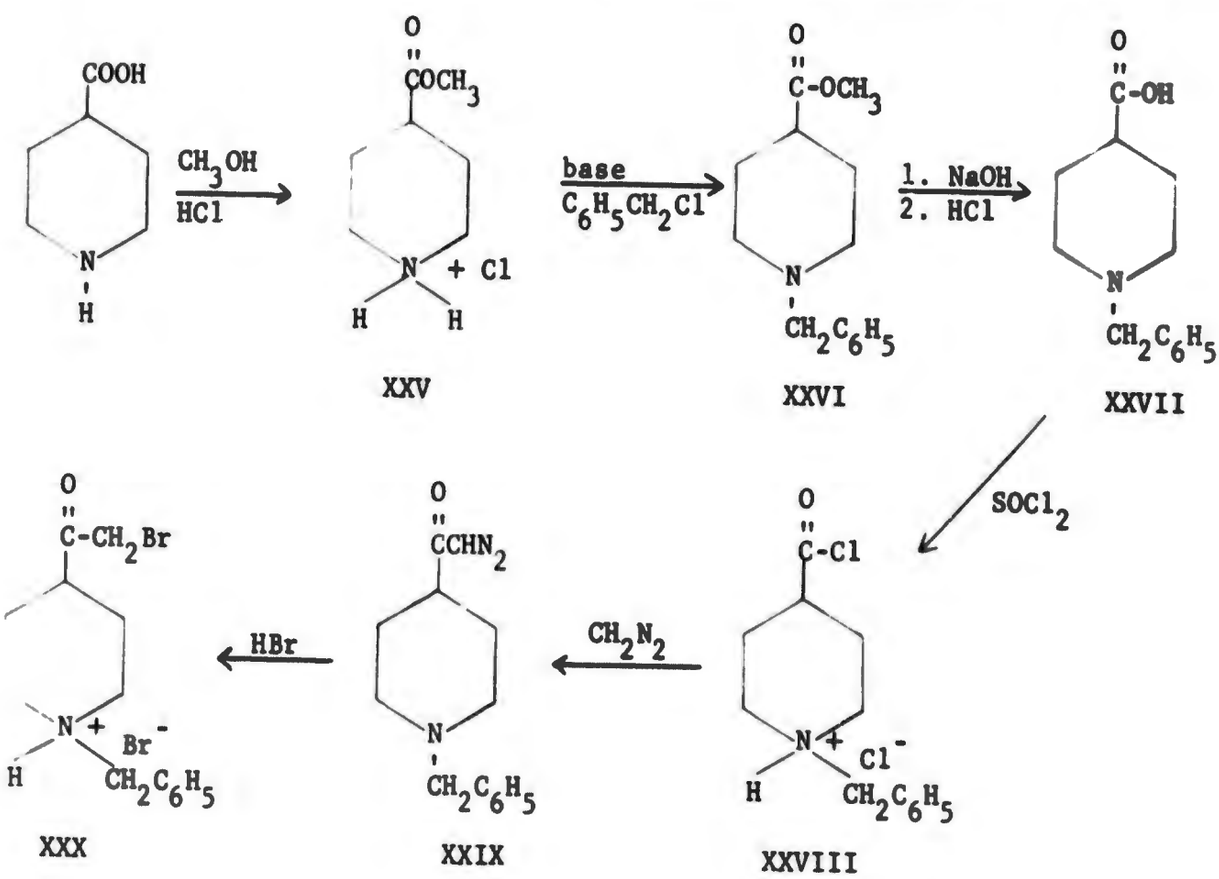

VIII XXIV XII

XXIV showed absorption at 1726 cm.$^{-1}$ (ketone C=O of a bromoacetyl group).

The n.m.r. spectrum showed a multiplet at 2.22-2.59 (  , 4. 1H), a multiplet at 3.28-3.62 (  , 4.1 H) and a singlet at 4.71δ ($\overset{O}{\overset{\|}{C}}-CH_2Br$, 1.9 H).

Treatment of XXIV with aqueous sodium hydroxide gave a polymeric material, m.p. >300°, similar to the one obtained when VIII was treated with aqueous sodium hydroxide.

The failure of XXII or XXIV as well as VIII to undergo a ring closure (compared with Perrine's case) may be due to excessive reactivity of these bromoketones or to the lack of a 1-benzyl substituent for axial stabilization of the nitrogen electron pair. In order to check this latter explanation we needed to prepare 1-benzyl-4-bromoacetylpiperidine hydrobromide (XXX) and subject it to the cyclization conditions. However, an effort to prepare XXX using the scheme shown below was unsuccessful.

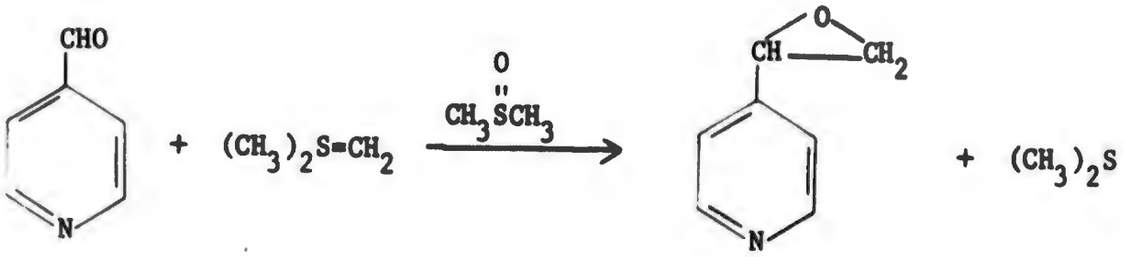


The methyl ester (XXVI) prepared by standard procedures was hydrolyzed to the acid XXVII, m.p. 168-170°. The infrared spectrum showed absorption at 3700-3200 (carboxylic acid -OH), 3080 and 3045 (aromatic C-H) and 1617 cm.$^{-1}$ (amino acid carbonyl). The n.m.r. spectrum showed a complex multiplet at 1.68-3.32 (all the ring protons, 8.9 H), a singlet at 3.87 (Ar-$CH_2$-N , 2.1 H), a singlet at 7.35 (aromatic protons, 5.1 H), and a singlet at 10.68 (-$\overset{O}{\overset{\|}{C}}$-OH, 0.94 H). Treatment of the acid with thionyl chloride gave a crude acid chloride. The infrared spectrum showed strong absorption at 1785 cm.$^{-1}$ (-$\overset{O}{\overset{\|}{C}}$-Cl). Addition of the acid chloride to an ethereal solution of diazomethane gave a crude diazoketone. The infrared spectrum showed absorption at 2100 (-$\overset{+}{N}\equiv N$) and 1700 and 1640 cm.$^{-1}$ (C=O). However, treatment of this diazoketone with hydrogen bromide in acetic acid did not give (XXX). A solid that analyzed for a higher bromine and lesser carbon content was obtained.

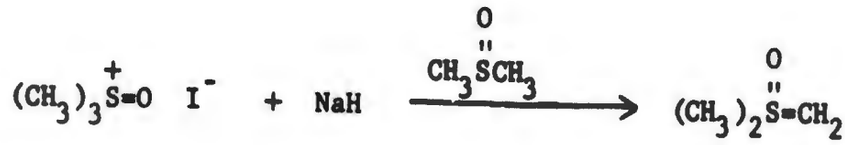
B. <u>Attempted Preparation of 3-Quinuclidinol via 4-Pyridylethylene Oxide</u>

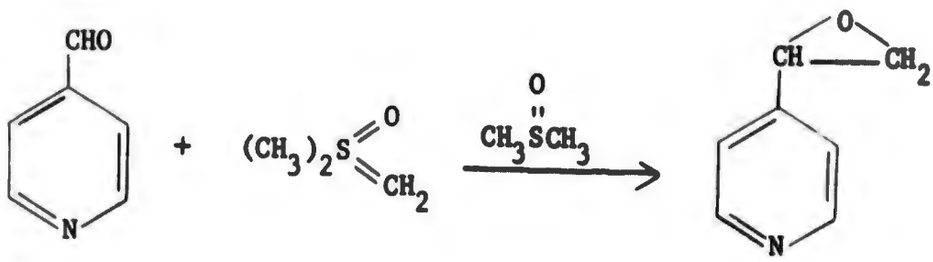
4-Pyridylethylene oxide (XXXI) was prepared by allowing pyridine-4-carboxaldehyde (XXXII) to react with dimethylsulfonium methylide[4] or with dimethylsulfoxonium methylide.[5]

$$(CH_3)_3S^+I^- + CH_3\overset{O}{\overset{\|}{S}}CH_2^-Na^+ \longrightarrow (CH_3)_2S{=}CH_2$$



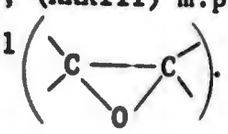

XXXII XXXI

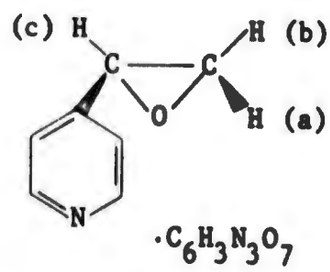




XXXII

XXXI

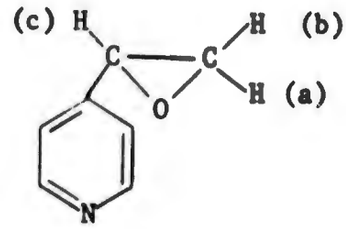
It was impossible to purify the crude product by vacuum distillation or preparative gas chromatography, therefore, the 4-pyridylethylene oxide was isolated and purified as its picrate, (XXXIII) m.p. 139-141°. The infrared spectrum shows a band at 875 cm.$^{-1}$  . The n.m.r. spectrum shows four quartets at 2.77 (a, 1.0 H), 3.12 (b, 1.0 H), and 3.87δ (c, 0.99 H) assigned as shown in XXXIII. The free 4-pyridyl-



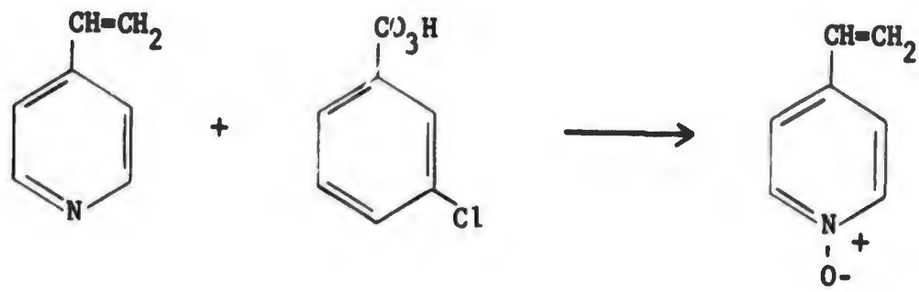
XXXIII

ethylene oxide was prepared by treating the picrate with aqueous sodium bicarbonate solution. The 4-pyridylethylene oxide decomposes slowly at room temperature and even decomposes at -10° to some extent. The infrared spectrum showed no C=O or S=O bonds and showed absorption at 1155,

1275 and 825 cm.$^{-1}$ (-CH$\overset{O}{\diagdown\diagup}$CH$_2$). The n.m.r. spectrum showed four quartets at 2.77 (a, 1.0 H), 3.20 (b, 1.0 H), and 3.85δ (c, 1.0 H) assigned as shown below.

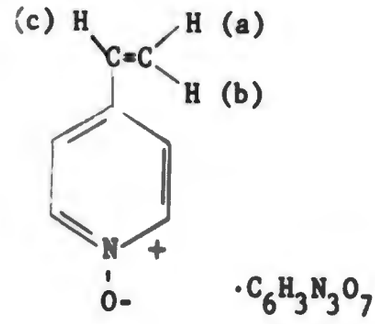



Attempts to prepare 4-pyridylethylene oxide by allowing 4-vinylpyridine to react with m-chloroperbenzoic acid yielded only 4-vinylpyridine N-oxide (XXXIV), isolated as its picrate. The n.m.r. spectrum

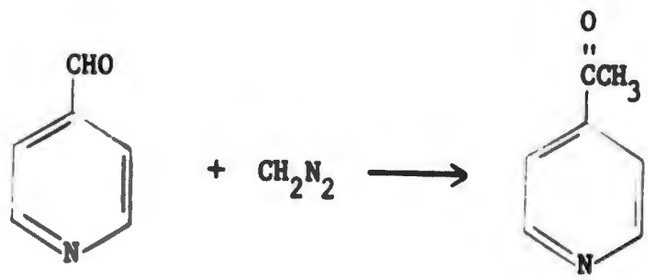



XXXIV

showed a doublet at 5.41, $J_{ac}$ = 10.5 cps (a, 1.0 H), a doublet at 5.89, $J_{bc}$ = 17.5 (b, 1.0 H), and a quartet at 6.70δ, $J_{cb}$ = 17.5 cps and $J_{ca}$ = 10.5 cps (c, 1.0 H) assigned as shown.

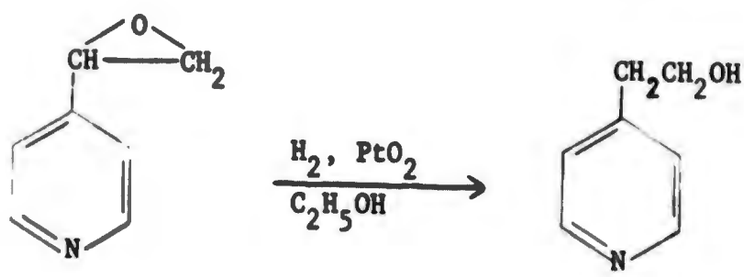



When pyridine-4-carboxaldehyde was treated with diazomethane, the major product isolated was 4-acetylpyridine (XXXV). Our initial plan




XXXV

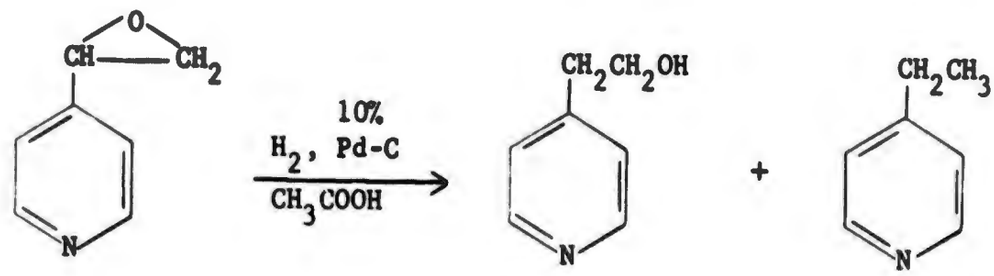
was reductive cyclization of 4-pyridylethylene oxide (XXXI) to 3-quinuclidinol, however, reduction of XXXI in ethanol using platinum oxide catalyst gave only 4-ethanolpyridine (XXXVI). G. N. Walker[6] reported that




XXXI XXXVI

supported palladium could often be employed more successfully than platinum oxide, in convenient low pressure hydrogenation of the acetate salts of

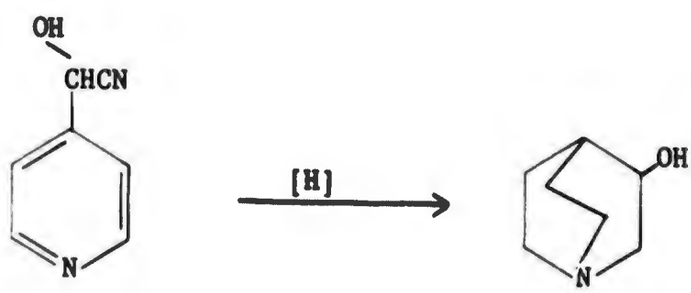
many pyridine compounds to the corresponding piperidines. However, reduction of 4-pyridylethylene oxide with 10% palladium-charcoal in glacial acetic acid gave a mixture of 4-ethanolpyridine and 4-ethylpyridine (XXXVII).




XXXVI XXXVII

C. <u>Attempted Preparation of 3-Quinuclidinol via Pyridine-4-Carboxaldehyde Cyanohydrin</u>

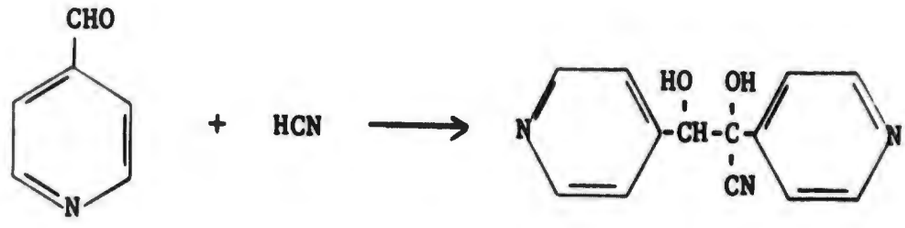
In this proposed synthesis of 3-quinuclidinol (III) we had hoped to prepare pyridine-4-carboxaldehyde cyanohydrin (XXXVIII) and reductively cyclize it to 3-quinuclidinol as shown below. However,




XXXVIII III

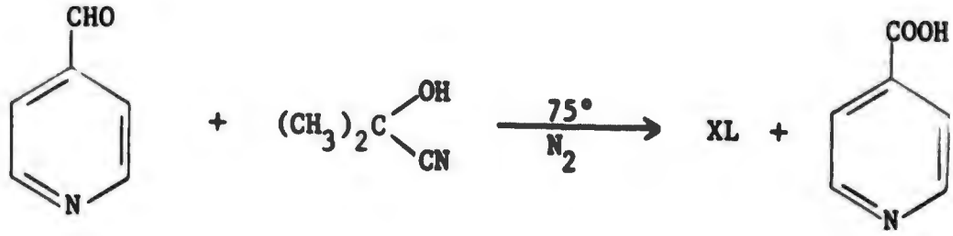
various attempts to prepare pyridine-4-carboxaldehyde cyanohydrin were unsuccessful. Mathes and W. Sauermilch[7] reported that they prepared XXXVIII by treating pyridine-4-carboxaldehyde with dry hydrogen cyanide.

An attempt to repeat this work by Dr. Arron and Dr. Miller at Edgewood Arsenal was unsuccessful. They obtained the condensation product XL, a product which Mathes and Sauermilch obtained when they treated pyridine-4-carboxaldehyde with aqueous potassium cyanide.

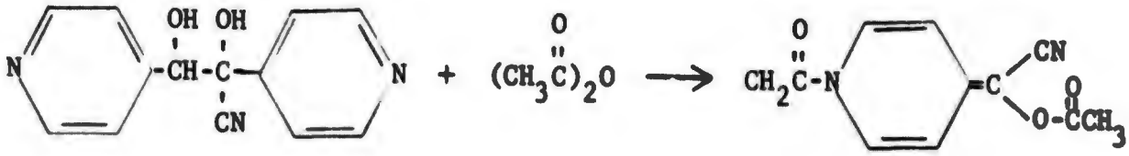


XL

In our efforts to prepare XXXVIII, we attempted an exchange reaction between acetone cyanohydrin and pyridine-4-carboxaldehyde. When equal molar amounts of these reactants were heated to 75°, under nitrogen, a mixture of XL and isonicotinic acid was obtained. The condensation product XL was identical to an authentic sample of XL prepared

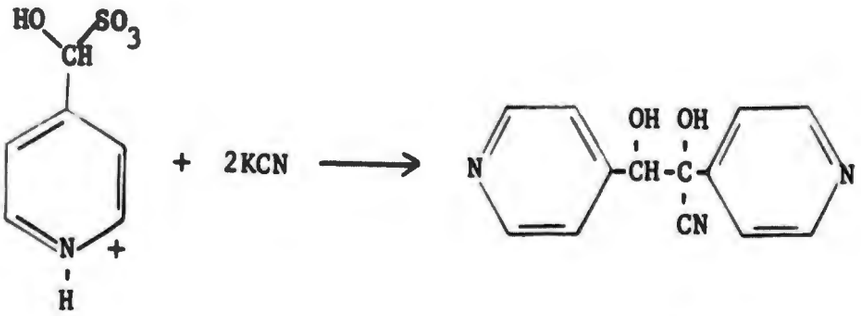


by the method of Mathes and Sauermilch.[7] Acetylation of XL gave the acetate XLI. The use of triethyl amine or potassium carbonate as



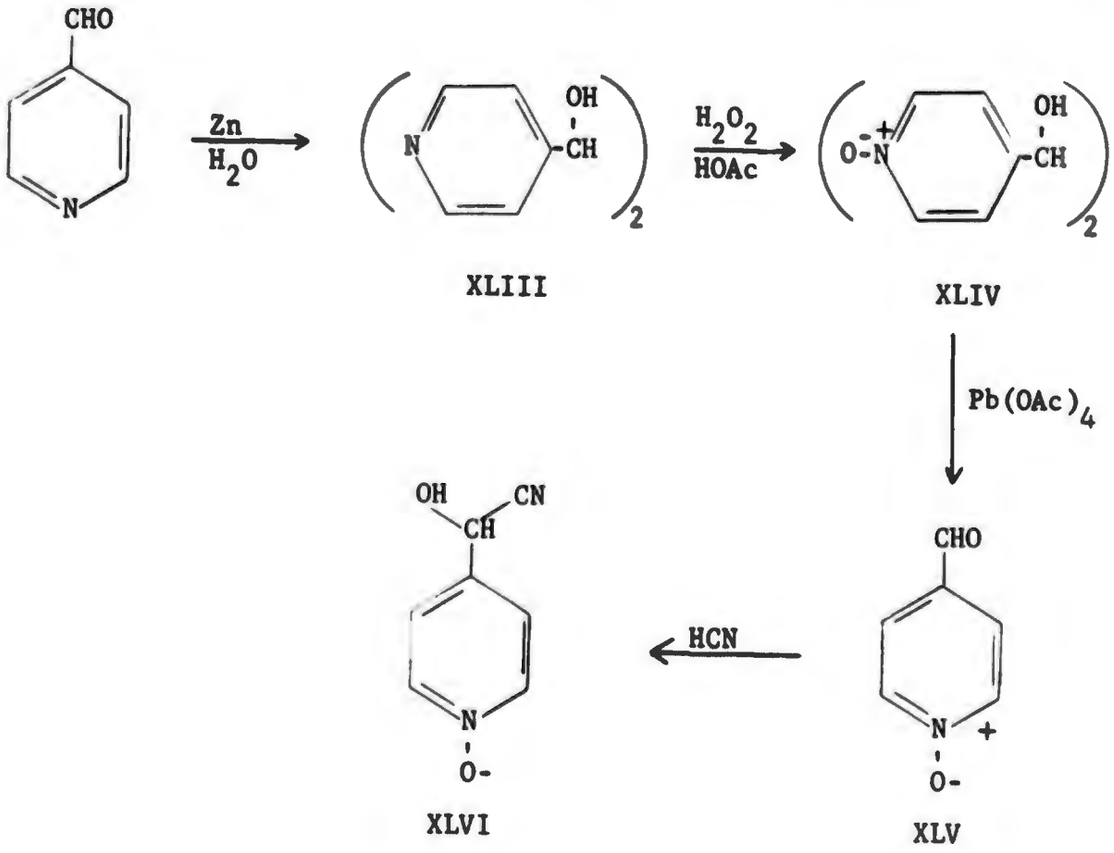
XLI

catalyst gave essentially the same results. When 4-pyridylhydroxy-methanesulfonic acid (XLII) prepared by the method of Rubtsov, Nikitskayo and Yanina,[8] was treated with potassium cyanide an almost quantitative yield of XL was obtained.



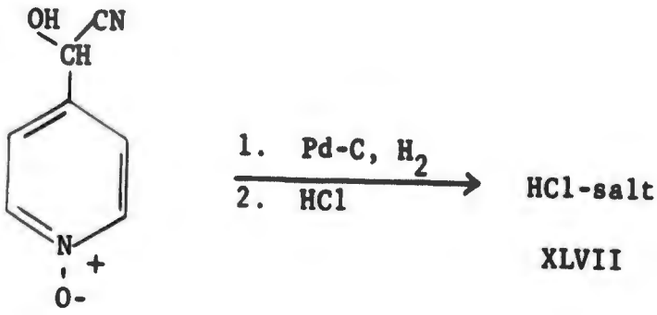
XLII XL

Since we were unable to prepare the cyanohydrin (XXXVIII), we turned our attention to the preparation of pyridine-4-carboxaldehyde cyanohydrin N-oxide which was reported by Mathes and Sauermilch.[9] Using the procedure reported by these authors shown below we obtained



XLIII XLIV XLVI XLV

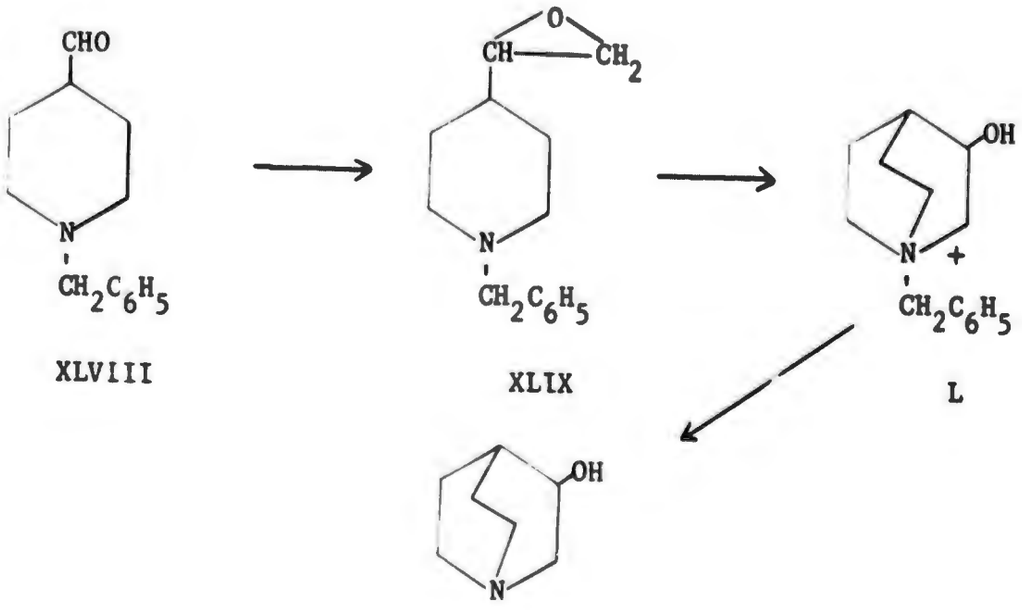
the desired pyridine-4-carboxaldehyde cyanohydrin N-oxide (XLVI) as a white powder, m.p. 118° (dec.). The infrared spectrum showed no aldehyde absorption peaks. Reduction of XLVI in acetic acid using 10% palladium on carbon catalyst using the condition reported by G. N. Walker[6] gave an oil. A TLC indicated that none of the desired 3-quinuclidinol was formed. The oil was converted to the hydrochloride (XLVII).




XLVII

D. <u>Attempted Preparation of 3-Quinuclidinol via 1-Benzylpiperidine-4-Carboxaldehyde</u>

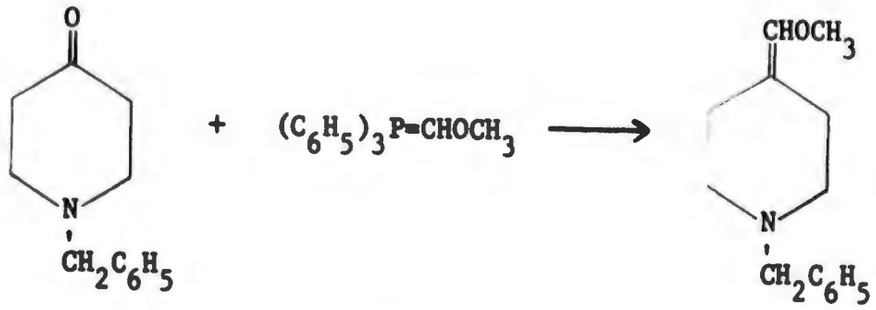
In our proposal P-63-1 we proposed to prepare 3-quinuclidinol from 1-benzylpiperidine-4-carboxaldehyde (XLVIII) as shown below.




XLVIII XLIX L

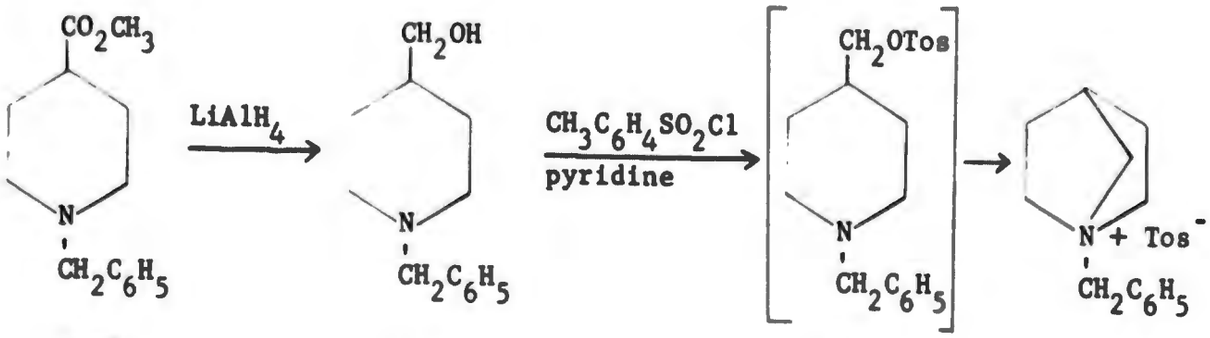
We did not have time to complete this phase of our investigation. Therefore, this section of the report will deal mostly with our attempts to prepare XLVIII.

We had hoped to prepare XLVIII from 1-benzyl-4-piperidone (LIII) prepared by the method of Grob and Brennusin,[10] by treatment with the Wittig reagent (LI), followed by acid hydrolysis of the enol ether (LII), in




LIII LI LII

one run a 30% yield of crude LII was obtained, b.p. 85-100° at 0.05 mm., $N_D^{25}$ = 1.5465. The infrared spectrum showed absorption at 3035 (aromatic C-H) and 1690 $cm.^{-1}$ (C=C-OR). Subsequent attempts to repeat this reaction resulted in recovery of the starting ketone.

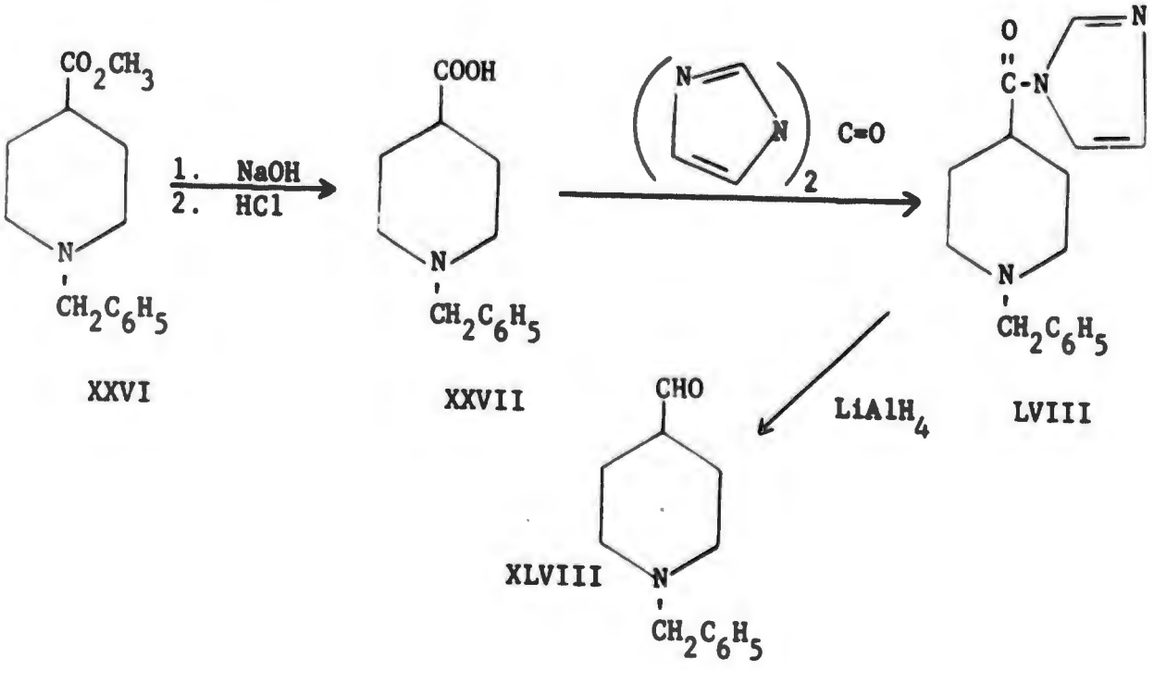



XXVI LIV LV LVI

In a separate attempt to prepare XLVIII the methyl ester XXVI was

reduced with lithium aluminum hydride to give an 84% yield of 1-benzyl-4-hydroxymethylpiperidine (LIV). The infrared spectrum showed a strong -OH peak at 3625 cm.$^{-1}$ and showed no ester peaks. We had hoped to convert LIV to the tosylate LV which could be oxidized to the desired aldehyde XLVIII by treatment of LV with dimethylsulfoxide according to the method of Kornblum.[11] However, treatment of the alcohol LIV with p-toluenesulfonyl chloride in pyridine gave a 56.4% yield of the cyclized product LVI, m.p. 170-171.5°. The infrared spectrum showed absorption at 1210 cm.$^{-1}$ ($SO_3^-$). The n.m.r. spectrum showed a multiplet at 1.26-2.43 with a sharp singlet pertruding at 2.31 ($-CH_2\diagdown\overset{+}{N}\diagup CH_2-$ and $CH_3Ar$, 7.4 H), a multiplet at 2.69 (H-C$\lessdot$, 1.1 H) a multiplet at 3.0-4.0 with a sharp singlet pertruding at 3.45 ($-CH_2\diagdown C\diagup CH_2-$ and bridgehead methylene, 6.1 H), a singlet at 4.81 ($ArCH_2$, 1.9 H), and a multiplet at 7.0-7.9δ (aromatic protons, 8.6 H).

A crude sample of 1-benzyl-piperidine-4-carboxaldehyde was prepared by the scheme shown below.



The methyl ester XXVI was hydrolyzed to 1-benzylpiperidine-4-carboxylic acid XXVII which was converted to the imidazolium compound (LVIII). Reduction of LVIII with lithium aluminum hydride gave a crude sample of the aldehyde XLVIII as an oil. Preparative gas chromatography gave a liquid that showed only one peak on VPC. The infrared spectrum showed absorption at 2665 and 2810 (aldehyde C-H) and 1718 $cm.^{-1}$ (aldehyde C=O).

## III. Experimental

The melting points were obtained on a Kofler hot-stage and are corrected. The boiling points are uncorrected. The infrared spectra were obtained using a Perkin-Elmer Model 221 spectrophotometer. The n.m.r. spectra were obtained using a Varian A-60 spectrometer with samples dissolved in either deuteriochloroform or pyridine (internal standard tetramethylsilane) or deuterium oxide [internal standard 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt]. Thin layer chromatograms were obtained using Silica Gel G as adsorbant. The gas chromatograms were obtained using a F & M Model 300 gas chromatograph.

Preparation of 1-Carbobenzyloxypiperidine-4-carboxylic Acid (V).--A solution of 12.9 g. (0.1 mole) of isonipecotic acid in 25 ml. of 4N sodium hydroxide (0.1 mole) was cooled in an ice bath and a total of 30 ml. of 4N sodium hydroxide (0.12 mole) and 18.7 g. (0.11 mole) of carbobenzyloxy chloride added alternatively thereto in 6 equal portions. After stirring for 30 minutes following the last addition, the reaction mixture was extracted with ether. The aqueous fraction was slowly acidified to congo red end point with 6N hydrochloric acid. An oil separated that was extracted with ethyl acetate. The extracts were dried and the solution concentrated under vacuum. After drying under vacuum overnight,

23.8 g., 90.5%, of 1-carbobenzyloxypiperidine-4-carboxylic acid was obtained, $\nu_{max}^{CH_2Cl_2}$ 3500-2500 (bonded acid -OH), and 1700-1685 cm.$^{-1}$ (acid and carbamate carbonyl). The oil was used without further purification for the preparation of the acid chloride (VI).

Preparation of 1-Carbobenzyloxypiperidine-4-carboxylic Acid Chloride (VI).--To a solution of crude 1-carbobenzyloxypiperidine-4-carboxylic acid 23.8 g. (0.0908 moles) from the previous experiment in 500 ml. of benzene (dried by azeotropic distillation) was added 35.70 g. (0.3 moles) of freshly distilled thionyl chloride and the solution was refluxed for 2 1/2 hrs. with the system protected from atmospheric moisture by a Drierite drying tube. The solvent and excess thionyl chloride were removed under reduced pressure (system protected from atmospheric moisture). The resulting oil was redissolved in dry benzene and concentrated to dryness under vacuum twice. The oil was dried under vacuum over sodium hydroxide pellets overnight to give 24.3 g. (95%) of 1-carbobenzyloxypiperidine-4-carboxylic acid chloride (VI), $\nu_{max}^{CH_2Cl_2}$ 1795 (acid chloride carbonyl), and 1695 cm.$^{-1}$ (carbamate carbonyl). The oil was used for the preparation of 1-carbobenzyloxy-4-diazoacetylpiperidine (VII) without further purification. The oil was characterized as its anilide (IX). Treatment of a portion of the oil with excess aniline in benzene afforded a 73% yield of the anilide (IX), m.p. 141.5-142.8°. An analytical sample, prepared by recrystallization from methanol and water, had m.p. 142-143.2°, $\nu_{max}^{CH_2Cl_2}$ 3285 (N-H), 1695 (carbamate carbonyl), and 1655 and 1530 cm.$^{-1}$ (amide I and amide II bands).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.56; N, 8.28. Found: C, 71.38; H, 6.42; N, 8.47.

Preparation of 1-Carbobenzyloxy-4-diazoacetylpiperidine (VII).--To an ice cooled, well stirred ethereal solution (500 ml.) of diazomethane [0.3-0.4 moles; prepared from 41.2 g. (0.4 moles) of N-nitrosomethylurea] was added dropwise 24.3 g. (0.086 moles) of crude 1-carbobenzyloxypiperidine-4-carboxylic acid chloride in 200 ml. of ether. After complete addition the reaction mixture was stirred for an additional 20 minutes. This was concentrated to a small volume (50 ml.) under vacuum and redissolved in ether and concentrated again. This was repeated until all the diazomethane was removed. After drying under vacuum overnight 24.2 g. (97.6%) of 1-carbobenzyloxy-4-diazoacetylpiperidine was obtained as a yellow oil, $\nu_{max}^{CH_2Cl_2}$ 2112 ($-\overset{+}{N}\equiv\overset{-}{N}$), 1640 (ketone carbonyl adjacent to a diazo group), and 1695 $cm.^{-1}$ (carbamate carbonyl). The crude oil was used for the preparation of 4-bromoacetylpiperidine hydrobromide (VIII) without further purification.

Preparation of 4-Bromoacetylpiperidine Hydrobromide (VIII).--To a solution of 24.2 g. (0.0842 moles) of 1-carbobenzyloxy-4-diazoacetylpiperidine (VII) in 50 ml. of acetic acid (distilled from potassium permanganate) cooled to 20° was added 99.7 ml. (27.9 g.; 0.345 moles) of a saturated solution of dry hydrogen bromide in acetic acid. The reaction flask was protected from atmospheric moisture by a Drierite drying tube. The hydrogen bromide addition effected the evolution of nitrogen and carbon dioxide gases. The orange colored reaction mixture was stirred for an additional 30 min. at 20°, 500 ml. of dry ether was added dropwise to the well stirred reaction mixture to precipitate the 4-bromoacetylpiperidine hydrobromide (VIII) as an orange colored solid. After drying 22.6 g. (93.5%) of solid was obtained. The solid was dis-

solved in methanol; treated with charcoal, and precipitated by the addition of ether to give 15.2 g. (64%) of the bromoketone (VIII), m.p. 153-155°. The analytical sample was prepared by recrystallization from methanol and ether, m.p. 153-155°, $\nu_{max}^{KBr}$ 1728 cm.$^{-1}$ (carbonyl of a bromoacetyl group). The n.m.r. spectrum ($D_2O$) showed two complex multiplets at 1.6-2.3 (>C<(-$CH_2$-)(-$CH_2$-), 4.3 H) and 2.8-3.8 (-$CH_2$-$\overset{+}{N}$-$CH_2$- and >C(H)-C(=O)-, 4.9 H) and a singlet at 4.38δ (-C(=O)-$CH_2$Br, 1.7 H).

Anal. Calcd. for $C_7H_{13}NOBr_2$: C, 29.29; H, 4.56; N, 4.88; Br, 55.69. Found: C, 29.46; H, 4.72; N, 4.87; Br, 55.46.

Treatment of VIII with Aqueous Sodium Hydroxide.--A 1.148 g. (0.004 mole) sample of VIII in 25 ml. of water and 0.008 moles of sodium hydroxide in 25 ml. of water were added from separate funnels dropwise and simultaneously to 250 ml. of water. The solution was concentrated by freeze drying to give a yellow oil. Extraction of the oil with isopropyl alcohol followed by concentration under vacuum gave 0.774 g. of a yellow oil. Sodium bromide 0.575 g. (70%) remained in the flask from the extraction. A TLC (methanol) and a gas chromatogram (XE-60) of the oil compared to the TLC and GLC of an authentic sample of 3-quinuclidinone indicated that none of the desired product was present. The infrared spectrum of the oil showed bands at 1720 cm.$^{-1}$ (ketone carbonyl) and 1630 cm.$^{-1}$ (-C(=O)-N<). All attempts to obtain a crystalline product from the oil failed. Essentially the same results were obtained when a dilute solution of the bromoketone was added to a dilute solution containing two equivalents of sodium hydroxide. An infrared spectrum of the oil obtained was essentially identical to the infrared spectrum above. Treatment of the oil with

methylene chloride gave a solid, m.p. softens at 120-130° but did not melt when heated to 300°. It gradually decomposed on heating.

When VIII was treated with one equivalent of sodium hydroxide in water none of the desired 3-quinuclidinone hydrobromide could be detected.

Treatment of the Bromoketone Hydrobromide (VIII) with Amberlite IR-45.--A 1.15 g. (0.004 mole) sample of VIII in 100 ml. of ethanol was allowed to stir for 5 hrs. with 5 g. of amberlite IR-45. The ion-exchange was separated by filtration and the filtrate concentrated in vacuo. The residue was dissolved in 3N hydrochloric acid and then concentrated under vacuum. Treatment of the residue with isopropyl alcohol gave a brown solid. The solid was completely insoluble in ethanol. The infrared spectrum showed a C=O peak at 1720 $cm.^{-1}$. An infrared spectrum of an authentic sample of 3-quinuclidinone hydrochloride showed a C=O peak at 1745 $cm.^{-1}$. Attempts to purify this solid were unsuccessful.

Treatment of the Bromoketone Hydrobromide (VIII) with Tri-isopropanolamine.--A 1.15 g. (0.004 mole) sample of VIII in 25 ml. of water and 7.31 ml. (0.008 mole) of 1.095 N tri-isopropanolamine in 25 ml. of water were added from separate funnels dropwise and simultaneously to 250 ml. of water. The reaction mixture was allowed to stir an additional 30 min. after the addition was complete. Concentration by freeze-drying gave an oil. Extraction of this oil with boiling Pet. ether or ethyl ether afforded none of the desired 3-quinuclidinone. A GLC (XE-60) of the oil compared to the GLC of an authentic sample of 3-quinuclidinone indicated that no 3-quinuclidinone was present in the oil.

Essentially the same results were obtained when a solution of VIII

was added to a dilute solution of 2 equivalents tri-isopropanolamine in water.

Treatment of the Bromoketone Hydrobromide (VIII) with Tri-isopropanolamine in Chloroform.--A 0.003 mole sample of VIII was placed in the thimble of a soxhlet setup. A chloroform solution containing 0.006 moles of tri-isopropanolamine was refluxed through the soxhlet for 2 days. However, the bromoketone hydrobromide VIII was so insoluble in hot chloroform that none of it was extracted.

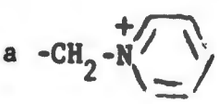
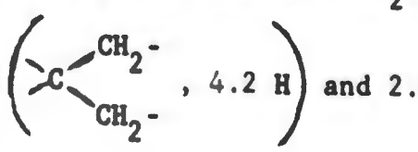
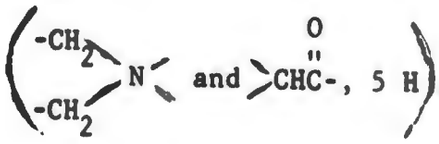
Treatment of the Bromoketone Hydrobromide (VIII) with Potassium tert-Butoxide in tert-Butyl Alcohol.--To a solution-suspension of 0.572 g. (0.002 mole) of the bromoketone hydrobromide VIII in tert-butyl alcohol was added 0.004 mole of potassium tert-butoxide. After stirring overnight the tert-butyl alcohol was concentrated by freeze drying. The remaining residue was extracted with ethanol. Concentration of the extract yielded 0.1415 g. of an oil. The infrared spectrum showed a C=O peak at 1710 $cm.^{-1}$. An infrared spectrum of 3-quinuclidinone showed a C=O peak at 1710 $cm.^{-1}$, however, the fingerprint region was quite different from the fingerprint region of the oil.

Treatment of the Bromoketone Hydrobromide (VIII) with Silver Oxide.--A 1.148 g. (0.004 mole) sample of VIII in 15 ml. of methanol was allowed to stir with 0.02 moles of freshly prepared silver oxide for 1 1/2 hrs. The silver oxide was separated by filtration. Concentration of the filtrate afforded 0.579 g. of an oil. A TLC ($CH_3OH$) and a VPC (XE-60) of this oil compared to the TLC and GLC of an authentic sample indicated that none of the desired 3-quinuclidinone was present.

Treatment of the Bromoketone Hydrobromide (VIII) with Alumina.--A 1.48 g. (0.004 mole) sample of VIII in 25 ml. of methanol was allowed

to stir with 10 g. of Woelm basic alumina for 5 hrs. The alumina was separated by filtration. Concentration of the filtrate gave a quantitative recovery of VIII.

Treatment of the Bromoketone Hydrobromide (VIII) with Sodium Acetate.--A 0.83 g. (0.003 mole) sample of VIII was dissolved in 25 ml. of ethanol and treated with 0.246 g. (0.003 mole) of sodium acetate. The solid that separated was filtered and dried. An infrared spectrum showed a C=O peak at 1720 $cm.^{-1}$. An infrared spectrum of an authentic sample of 3-quinuclidinone hydrochloride showed a C=O peak at 1745 $cm.^{-1}$. The solid was dissolved in as small amount of water as possible, and made basic with potassium hydroxide. However, no free base could be extracted with ether.

Treatment of the Bromoketone Hydrobromide (VIII) with Pyridine.--The bromoketone hydrobromide (VIII) (0.8316 g., 0.003 moles) was suspended in pyridine and allowed to stir at room temperature overnight. Filtration afforded a 92.8% yield of X, m.p. 234-236° (dec.). The analytical sample was prepared by recrystallization from methanol and ether, m.p. 240-242° (dec.), $\nu_{max}^{KBr}$ 3490 and 3445 (not assigned), 1732 (ketone C=O adjacent to a $-CH_2-\overset{+}{N}$  group), 1640 and 1494 $cm.^{-1}$ (pyridine ring stretching modes). The n.m.r. spectrum ($D_2O$) showed a very complex multiplet at 1.6-2.4  and 2.8-3.8  , a multiplet centered at 8.14 (β-pyridine protons, 1.9 H) and a multiplet centered at 8.65δ (α- and δ-pyridine

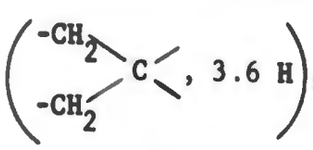
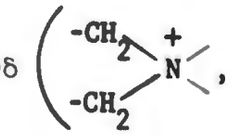
protons, 3 H). The protons due to the methylene group between the keto and 1-pyridyl group must be masked by the HDO peak at 4.53δ or be acidic enough to exchange with the deuterium oxide.

Anal. Calcd. for $C_{12}H_{18}Br_2N_2O$: C, 39.36; H, 4.95; N, 7.65; Br, 43.37. Found: C, 39.27; H, 5.22; N, 7.37; Br, 43.22.

Treatment of the Bromoketone Hydrobromide (VIII) with Silver Acetate.--To a solution of 1.148 g. (0.004 mole) of the bromoketone hydrobromide (VIII) in methanol was added 0.668 g. (0.004 mole) of silver acetate. After two hours the silver bromide was separated by filtration. Concentration of the filtrate afforded 1.15 g. of a brown solid, m.p. 295-310°. Recrystallization from methanol and ether afforded 0.44 g. of solid, m.p. decomposed over a wide range finally turning completely black at 310°. An infrared spectrum showed absorption at 1722 $cm.^{-1}$ (C=O) with a shoulder at 1745 $cm.^{-1}$. Attempts to purify the solid were unsuccessful. Addition of more ether to the filtrate afforded 0.102 g. (9.6%) of XI, m.p. 136.5-139°. The analytical sample was prepared by recrystallization from methanol and ether, m.p. 137.5-139.8°, $\nu_{max}^{KBr}$ 2800-2500 (bonds typical of an amine hydrobromide), 1730 (ester carbonyl), 1712 (ketone carbonyl), and 1250 $cm.^{-1}$ (C-O).

Anal. Calcd. for $C_9H_{16}NO_3Br$: C, 40.61; H, 6.06; N, 5.26; Br, 30.03. Found: C, 40.82; H, 6.02; N, 5.28; Br, 29.76.

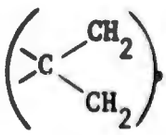
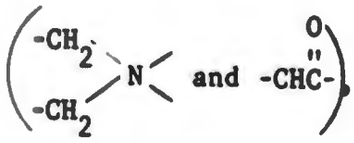
When this reaction was repeated in the absence of light only a trace of XI was obtained. The remainder of the product appeared to be polymeric. Treatment of VIII with two equivalents of silver acetate gave an oil, the infrared spectrum of which was quite different from the spectrum of an authentic sample of 3-quinuclidinone.

Treatment of the Bromoketone Hydrobromide (VIII) with Warm Acetic Acid.--The bromoketone hydrobromide VIII was dissolved in acetic acid, heated to 85° and allowed to remain at this temperature for seven days. The progress of the reaction was followed by the shift of a carbonyl peak at 1724 cm.$^{-1}$ in the starting bromoketone to 1702 cm.$^{-1}$ in the product. The reaction mixture was concentrated to dryness by freeze-drying. Recrystallization from ethanol and ether afforded a 32.2% yield of 4-acetyl-4-bromopiperidine hydrobromide (XII), m.p. 145-146.5°. The analytical sample, recrystallized from ethanol and ether had m.p. 154-155°, $\nu_{max}^{KBr}$ 1702 (ketone C=O) and 1360 cm.$^{-1}$ ($CH_3\overset{O}{\overset{\|}{C}}-$). The n.m.r. spectrum ($D_2O$) showed a multiplet centered at 2.4 (  , 3.6 H), a singlet at 2.65 ($CH_3\overset{O}{\overset{\|}{C}}-$, 3.3 H) and a multiplet centered at 3.45δ (  , 4 H).

Anal. Calcd. for $C_7H_{13}Br_2NO$; C, 29.29; H, 4.56. Found: C, 29.28; H, 4.62.

Treatment of the Bromoketone Hydrobromide (VIII) with Refluxing Acetic Acid.--The bromoketone hydrobromide (VIII) (0.574 g., 0.002 moles) was refluxed in acetic acid for 20 hrs. Considerable decomposition occurred. The acetic acid was concentrated by freeze-drying. The residue was dissolved in ethanol, treated with Norite and filtered. The addition of ether to the filtrate gave 0.059 g. (14.3%) of XIII. The analytical sample was prepared by recrystallization from ethanol and ether, m.p. 160-163°. $\nu_{CH_2Cl_2}^{KBr}$ 1698 (conjugated C=O), 1618 (C=C) and 1360 cm.$^{-1}$ ($CH_3\overset{O}{\overset{\|}{C}}C$).

Anal. Calcd. for $C_7H_{12}BrNO$: C, 40.79; H, 5.87; N, 6.80; Br, 38.78. Found: C, 40.17; H, 6.65; N, 6.57; Br, 38.38.

Preparation of 4-Dimethylsulfoniumacetylpiperidine Bromide Hydrobromide (XIV).--The bromoketone hydrobromide (VIII) (5.74 g., 0.02 moles) was suspended in 25 ml. of dimethylsulfide and allowed to stir overnight. The excess dimethylsulfide was allowed to evaporate under a stream of nitrog Crystallization of the remaining residue gave 4.11 g. (59.5%) of 4-dimethylsulfoniumacetylpiperidene bromide hydrobromide (XIV), m.p. 149-153°. The analytical sample prepared by further recrystallization from methanol had, m.p. 151-154°, $\nu_{max}^{KBr}$ 2900-2400 (bands typical of amine hydrobromide salt) and 1710 cm.$^{-1}$ (ketone carbonyl). The n.m.r. spectrum ($D_2O$) showed a complex multiplet at 1.6-2.4  a complex multiplet at 2.8-3.8  and a sharp singlet at 3.0δ ($CH_3$-S-). The peak due to the methylene protons between the ketone and sulfur must be masked by the HDO peak or be acidic enough to exchange with the deuterium oxide.

Anal. Calcd. for $C_9H_{19}NOSBr_2$: C, 30.94; H, 5.50; N, 4.01; S, 9.19; Br, 45.79. Found: C, 31.21; H, 5.49; N, 4.14; S, 9.02; Br, 46.04.

Treatment of X with Aqueous Sodium Hydroxide.--To a 3.35 g. (0.0089 mole) sample of X in 400 ml. of water was added dropwise 0.712 g. (0.178 mole) of sodium hydroxide in 200 ml. of water. The solution was concentrated by freeze-drying to give an oily solid. Extraction with isopropyl alcohol followed by concentration gave 2.09 g. of a black solid that could not be crystallized. The TLC and infrared spectrum of this material indicated that no 3-quinuclidinone was present.

Treatment of XIV with Aqueous Sodium Hydroxide.--A 1.397 g. (0.004 mole) sample of XIV in 25 ml. of water and 0.008 moles of sodium hydroxide in 25 ml. of water were added from separate funnels dropwise and simultaneously to 250 ml. of water. The reaction mixture was concentrated by freeze-drying to give an oil that gradually decomposed to a dark mass. A small amount of solid was sublimed from the mass, m.p. 131-135°. There was not a sufficient amount of this solid to obtain an elemental analysis.

Treatment of the Bromoketone Hydrobromide (VIII) with Sodium Borohydride in a Methanol Dioxane Mixture.--A 1.51 g. ($5.25 \times 10^{-3}$ mole) sample of 4-bromoacetyl piperidine hydrobromide (VIII) was dissolved in 200 ml. of a 2:3 mixture of methanol and dioxane and the solution cooled in an ice bath. Sodium borohydride (3.0 g., $8.0 \times 10^{-2}$ mole) was then added to the cooled solution. The reaction was allowed to proceed for 1.5 hrs. at ice bath temperature and was acidified with acetic acid. The solvent was removed, and the resulting solid was washed with methylene chloride. Removal of the solvent gave 1.2 g. of a gum which showed several spots by TLC. This gum was dissolved in 15 ml. of water. Approximately 5 g. of potassium hydroxide and 2 g. of potassium carbonate were added to this aqueous solution. The solution was extracted with several portions of hot benzene. Concentration of the extracts gave an oil which showed 3 spots on TLC (2:2:1, butanol:water:acetic acid) one of which had an $R_f$ value identical to that of 3-quinuclidinol. Attempts to isolate 3-quinuclidinol by formation of its picrate were unsuccessful.

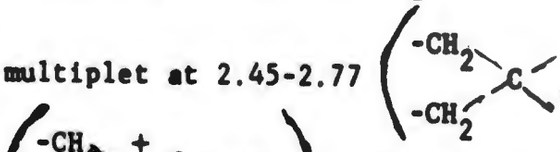
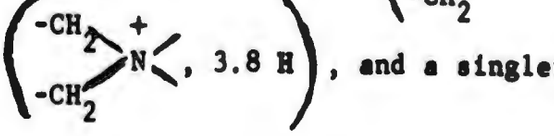
The reaction was also performed at lower concentration ($1 \times 10^{-3}$ molar) and at ambient temperature. Another variant in the work-up procedure was after the reaction was completed the solvent was removed without

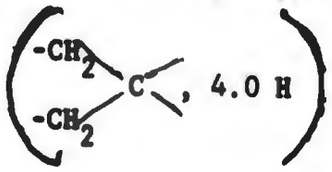
acidification. The resulting powder was then placed in a soxhlet and extracted with benzene. However in none of the experimental procedures described above was any 3-quinuclidinol isolated.

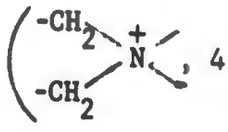
Treatment of VIII with Sodium Borohydride in Water.--To a cold solution of 1 g. of sodium borohydride in 3 ml. of 1N sodium hydroxide was added 1.148 g. (0.004 mole) of VIII in 2 ml. of water. The reaction mixture was allowed to warm to room temperature and remain for 6 hrs. The mixture was made strongly basic by the addition of sodium hydroxide pellets and then extracted with benzene. Concentration of the benzene extracts after drying, afforded 0.466 g. of an oil. An infrared spectrum showed no carbonyl absorption. The spectrum was quite different from a spectrum of an authentic sample of 3-quinuclidinol.

4-Acetyl-1-benzyl-4-phenylpiperidine Hydrochloride Hydrate (XX).--Using the method of Perrine,[3] a 15.67 g. (0.05 mole) sample of 1-benzyl-4-cyano-4-phenylpiperidine hydrochloride was converted to the base in benzene solution (100 ml.) by the addition of 100 ml. of 1N sodium hydroxide and stirring rapidly for twenty to thirty minutes. The benzene layer was washed with water and dried by azeotropic distillation. The dried benzene solution was added dropwise (nitrogen atmosphere) to 60 ml. (2.2 grams, 0.1 mole) of a 5.21% solution of methyl lithium in ether with stirring. The mixture was allowed to stand 2 days and decomposed with ice. The imine precipitated upon the addition of 6N hydrochloric acid to the orangic layer and was separated by filtration. The crude imine hydrochloride was hydrolyzed by refluxing with 1N hydrochloric acid to which enough ethanol had been added to facilitate solution for 4 hrs. and left at room temperature overnight. Upon cooling the solution in an ice bath, 11.15 g., 64%, of 4-acetyl-1-benzyl-4-phenylpiperidine hydrochloride hydrate was obtained,

m.p. 230-240°. Reported[3] m.p. 251-252°. $\nu_{max}^{KBr}$ 1712 (ketone C=O), 1603 and 1501 (aromatic), and 701 cm.$^{-1}$ (aromatic substitution peaks).

4-Acetyl-4-phenylpiperidine Hydrochloride (XXI).--Using the method of Perrine[3] a solution of 4.01 g. (0.011 mole) of 4-acetyl-1-benzyl-4-phenylpiperidine hydrochloride hydrate in 40 ml. of methanol and 9 ml. of water containing 1 ml. of 2.5N hydrochloric acid and 2 g. of 10% palladium-carbon catalyst was hydrogenated in the Parr hydrogenator until hydrogen ceased to be taken up. The catalyst was separated by filtration. Concentration of the filtrate afforded 2.05 g. (77.8%) of 4-acetyl-4-phenylpiperidine hydrochloride, m.p. 238-241°. Reported[3] m.p. 245°, $\nu_{max}^{KBr}$ 1712 cm.$^{-1}$ (ketone C=O). The n.m.r. spectrum ($D_2O$) showed a singlet at 2.17 ($CH_3\overset{O}{\overset{\|}{C}}$-, 3.2 H), a multiplet at 2.45-2.77 (  , 3.8 H), a multiplet at 3.27-3.60 (  , 3.8 H), and a singlet at 7.218 (aromatic protons, 5.0 H).

4-Bromoacetyl-4-phenylpiperidine Hydrobromide XXII.--To a solution of 2.25 g. (0.0094 mole) of 4-acetyl-4-phenylpiperidine hydrochloride in 30 ml. of acetic acid was added 0.55 ml. of bromine. The mixture was stirred overnight at room temperature. The resultant yellow solution was filtered. More product was obtained by the addition of ether to the filtrate, total yield 3.12 g. (91.3%), m.p. 201-207°. The analytical sample prepared by recrystallization from absolute ethanol had m.p. 202-206°. $\nu_{max}^{KBr}$ 1725 cm.$^{-1}$ (ketone carbonyl of a bromoacetyl group). The n.m.r. spectrum ($D_2O$) showed a multiplet at 2.40-2.78 (  , 4.0 H), a multiplet at 3.23-3.58

 , a singlet at 4.29 ($-\overset{O}{\overset{\|}{C}}-CH_2Br$, 1.7 H) and a singlet at 7.55δ (aromatic protons, 5.2 H).

Anal. Calcd. for $C_{13}H_{17}NOBr_2$: C, 43.00; H, 4.72; N, 3.86. Found: C, 42.70; H, 4.69; N, 3.94.

Attempted Preparation of 4-Phenyl-3-quinuclidinone (XXIII) from 4-Bromoacetyl-4-phenylquinuclidine Hydrobromide (XXII).--4-Bromoacetyl-4-phenylpiperidine hydrobromide (2.02 g., 0.0056 mole) was dissolved in 30 ml. of hot water. This solution was subjected to sudden cooling and 80 ml. of ether added. To this vigorously stirred, cooled solution, 25 ml. of 1 N sodium hydroxide was added. The organic layer was separated, dried and concentrated to give an amorphous solid. The infrared spectrum showed absorption at 1720 (C=O) and was quite different from the spectrum of an authentic sample of 4-phenyl-3-quinuclidinone prepared by reductive debenzylation of (XVII). See the following experiments.

1-Benzyl-4-bromoacetyl-4-phenylpiperidine Hydrobromide (XVI).--To a solution of 4.0 g. (0.0115 mole) of 4-acetyl-1-benzyl-4-phenylpiperidine hydrochloride hydrate in 30 ml. of acetic acid was added 0.63 ml. of bromine. After standing at room temperature for 3 days, the mixture was filtered. Ether was added to the filtrate to give more product, 3.39 g. (65.1%) total, m.p. 190-203°. Reported[3] m.p. 200°. $\nu_{max}^{KBr}$ 1730 $cm.^{-1}$ (ketone carbonyl), and 750 and 700 $cm.^{-1}$ (aromatic substitution peaks).

1-Benzyl-4-phenyl-3-quinuclidinone Bromide (XVII).--Using the procedure reported by Perring,[3] 1-benzyl-4-bromoacetyl-4-phenylpiperidine hydrobromide (3.47 g., 0.0077 mole) was dissolved in 250 ml. of hot water. The solution was subjected to sudden cooling and 100 ml. of ether added. To this solution was added 25 ml. of 1 N sodium hydroxide. The

solution was filtered to remove impurities and the ether layer was separated, dried and concentrated to give an oily solid. Acetone (50 ml.) was added to the mixture and left overnight. Filtration gave 2.0 g. (70.7%) of 1-benzyl-4-phenyl-3-quinuclidinone bromide, m.p. 265-272°. Reported[3] m.p. 290-295°. $\nu_{max}^{KBr}$ 1755 (ketone C=O adjacent to $\overset{+}{N}$), 1502 (aromatic stretching modes) and 702 cm.$^{-1}$ (aromatic substitution peaks).

Preparation of 4-Phenyl-3-quinuclidinone (XXIII) from 1-Benzyl-4-phenyl-3-quinuclidinone Bromide (XVII). A solution of 1.54 g. (0.0055 mole) of 1-benzyl-4-phenyl-3-quinuclidinone bromide in 35 ml. of methanol and 25 ml. of water containing 0.50 g. of 10% palladium-carbon catalyst was hydrogenated in a Parr hydrogenator until hydrogen ceased to be taken up. The catalyst was separated by filtration. Concentration of the filtrate afforded 1.05 g. (90.8%) of crude 4-phenyl-3-quinuclidinone hydrobromide, m.p. 276-279°. Reported[3] 285-287°. $\nu_{max}^{KBr}$ 2900-2400 (typical amine hydrobromide absorption), and 1755 (ketone C=O). Treatment of the hydrobromide with dilute sodium hydroxide gave the free base, 4-phenyl-3-quinuclidinone, m.p. 149-153°. Reported[3] m.p. 157-158°. The infrared spectrum showed absorption at 3025, 3065, 3085 (aromatic C-H) 2970-2860 (a number of C-H peaks), 1735 cm.$^{-1}$ (C=O) 1605, 1510 (aromatic stretching modes), and 770 and 700 cm.$^{-1}$ (aromatic substitution peaks).

Preparation of 4-Bromo-4-bromoacetylpiperidine Hydrobromide (XXIV) from VIII.--To a solution of 4.305 g. (0.015 mole) of VIII in 150 ml. of acetic acid was added 2.397 g. (0.015 mole) of bromine. The solution was allowed to stir overnight. Concentration of the solution by freeze-drying afforded an oily solid. Crystallization from methanol gave 2.8 g.

(51%) of XXIV, m.p. 151-153°. The analytical sample was prepared by recrystallization from methanol, m.p. 156-158°. $\nu_{max}^{Kbr}$ 1726 cm.$^{-1}$ (C=O). The n.m.r. spectrum ($D_2O$) showed a multiplet at 2.22-2.59 ($CH_2$, $CH_2$, $\overset{+}{N}$, 4.1 H), a multiplet at 3.28-3.62 ($CH_2$, $CH_2$, C, 4.1 H) and a singlet at 4.71δ ($-\overset{O}{\overset{\|}{C}}CH_2Br$, 1.9 H).

Anal. Calcd. for $C_7H_{12}NOBr_3$: C, 22.97; H, 3.31; N, 3.83; Br, 65.52. Found: C, 23.12; H, 3.37; N, 3.98; Br, 65.37.

Preparation of 4-Bromo-4-bromoacetylpiperidine Hydrobromide (XXIV) from XII.--To a solution of 0.574 g. (0.002 mole) of XII in 25 ml. of acetic acid saturated with dry hydrogen bromide was added 0.3197 g. (0.002 mole) of bromine in 3.2 ml. of acetic acid. The bromine was taken up immediately. The excess hydrogen bromide was expelled by passing nitrogen through the solution. The solution was concentrated by freeze-drying to give an orange solid. Recrystallization from methanol gave 0.3077 g. (42%) of 4-bromo-4-bromoacetylpiperidine hydrobromide, m.p. 153-153.5°. A mixture of this compound and XXIV obtained from the previous experiment melted at 153-155.5°. The infrared spectrum of the two compounds were identical.

Treatment of 4-Bromo-4-bromoacetyl-piperidine Hydrobromide with Aqueous Sodium Hydroxide.--To a solution of 2.26 g. (0.0062 mole) of 4-bromo-4-bromoacetylpiperidine hydrobromide in 200 ml. of water was added 12.4 ml. (0.0124 mole) of 1 N sodium hydroxide in 100 ml. of water. After the addition, the reaction mixture was concentrated by freeze-drying to give a solid. Extraction of this solid with isopropanol gave 0.955 g. of a polymeric solid m.p. >300° that gives a positive silver nitrate test for bromide. The infrared spectrum was very difuse showing no sharp

peaks. There was 1.7 g. of sodium bromide left from the isopropanol extraction.

Preparation of Piperidine-4-carboxylic Acid Methyl Ester Hydrochloride (XXV).--A stream of dry hydrogen chloride gas was passed through a suspension of 10 g. of piperidine-4-carboxylic acid in methanol at room temperature until all the solid dissolved. The solution was cooled in an ice bath and treatment continued until the solution was saturated. After standing 4 hrs. at room temperature, volatiles were removed under reduced pressure and the remaining solid was washed with ether and dried under vacuum over sodium hydroxide pellets. A 92.6% yield of XXV was obtained, m.p. 157-160°C. The analytical sample was prepared by recrystallization from methanol and ether, m.p. 161-164°. $\nu_{max}^{KBr}$ 1730 cm.$^{-1}$ (ester C=O).

Anal. Calcd. for $C_7H_{14}NO_2Cl$: C, 46.80; H, 7.85. Found: C, 46.49; H, 7.87.

Preparation of the Methyl Ester of 1-Benzylpiperidine-4-carboxylic Acid (XXVI).--To a sample of methyl isonipecotate hydrochloride (42.1 g., 0.234 mole) suspended in 300 ml. of methylene chloride was added 29.62 g. (0.234 mole) of benzyl chloride. To this mixture was added dropwise 109.21 g. (0.468 mole) of tri-isopropanolamine in 250 ml. of methylene chloride. The mixture was allowed to stir at room temperature overnight. The solution was concentrated, taken up in ether and washed with water. Concentration of the dried ether layer gave 48 g. of a liquid. Distillation under reduced pressure gave 28.6 g. (52%) of the methyl ester of 1-benzylpiperidine-4-carboxylic acid, b.p. 115° at 0.3 mm. $N_D^{25}$ 1.5049. $\nu_{max}^{KBr}$ 1735 cm.$^{-1}$ (C=O). The crude liquid was used to prepare 1-benzylpiperidine-4-carboxylic acid.

Preparation of 1-Benzylpiperidine-4-carboxylic Acid (XXVII).--To a solution of 28.5 g. (0.122 mole) of the methyl ester of 1-benzylpiperidine-4-carboxylic acid in a mixture of 360 ml. of dioxane (distilled from sodium) and 150 ml. of water was added 122 ml. of 1 N sodium hydroxide. The mixture was stirred for 20 hrs. then 122 ml. of 1 N hydrochloric acid was added. The solution was concentrated by freeze-drying to give a white solid which was extracted with hot isopropanol. The isopropanol extracts were concentrated to a small volume and cooled to give 19.2 g. (72%) of 1-benzylpiperidine-4-carboxylic acid, m.p. 168-170°. The analytical sample was prepared by recrystallization from the same solvent, m.p. 169-170.5°, $\nu_{max}^{KBr}$ 3700-3200 (carboxylic acid OH), 3080 and 3045 (aromatic C-H), and 1617 cm.$^{-1}$ (amino acid carbonyl). The n.m.r. spectrum showed a complex multiplet at 1.68-3.32 (all the ring protons, 8.9 H), a singlet at 3.87 ($ArCH_2N$ , 2.1 H), a singlet at 7.35 (aromatic protons, 5 H) and a singlet at 10.68 ($-\overset{O}{\overset{\|}{C}}-OH$, 0.94 H).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.88; N, 6.39. Found: C, 70.76; H, 7.83; N, 6.30.

The hydrochloride of this acid was prepared by bubbling dry hydrogen chloride gas into a benzene suspension of XXVII. This hydrochloride was too hydroscopic to obtain a good m.p. or analysis.

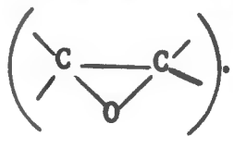
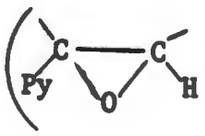
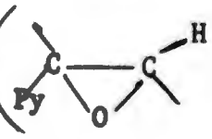
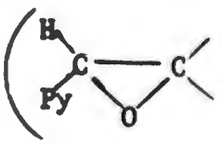
Attempted Preparation of 1-Benzyl-4-bromoacetylpiperidine Hydrobromide (XXX).--1-Benzylpiperidine-4-carboxylic acid hydrochloride (3.687 g., 0.014 mole) was dissolved in 20 ml. of thionyl chloride and refluxed for 2 hrs. Concentration under vacuum gave an oil. The infrared spectrum showed a strong peak at 1790 cm.$^{-1}$ ($-\overset{O}{\overset{\|}{C}}-Cl$). This oil was dissolved in 100 ml. of methylene chloride and added to a solution of 0.128 mole of diazomethane in ether. Concentration of the reaction mixture gave an

oily solid. The infrared spectrum showed absorption at 2100 ($-\overset{+}{N}\equiv N$), 1700 and 1640 cm.$^{-1}$ (C=O). This oil was dissolved in acetic acid saturated with hydrogen bromide. The excess hydrogen bromide was expelled by passing nitrogen through the solution. Concentration of the solution by freeze-drying gave an oil. Crystallization from methanol and ether gave 0.180 g. of a white solid, m.p. 163-165.5°. The analytical sample was prepared by recrystallization from the same solvent, m.p. 164-166.5°, $\nu_{max}^{KBr}$ 1735 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{14}H_{19}NO_2Br$: C, 44.58; H, 5.08; N, 3.71; Br, 42.38. Found: C, 36.84; H, 4.05; N, 3.41; Br, 51.43.

Preparation of Trimethylsulfonium Iodide.--The trimethylsulfonium iodide was prepared by the method of Emélesa and Heal.[12] To 24 g. (0.386 mole) of dimethylsulfide was added 56 g. (0.394 mole) of methyl iodide and the resulting solution was allowed to stir overnight. The solid mass obtained was recrystallized from absolute ethanol to give 57.9 g. (72%) of trimethylsulfonium iodide as white needles.

Preparation of 4-Pyridylethylene Oxide Picrate (XXXIII) Using Dimethylsulfonium Methylide.--Into a 2 l., 3-necked flask fitted with a mechanical stirrer, drying tube, and nitrogen inlet tube was placed 6.00 g. (0.25 mole) of 50% sodium hydride in mineral oil. The mineral oil was separated from the sodium hydride by washing with ether. To the sodium hydride was added 175 ml. of distilled dimethylsulfoxide and the stirred mixture was heated under nitrogen at 60° until hydrogen ceased to be evolved. The solution was diluted with 175 ml. of freshly distilled tetrahydrofuran and cooled in an ice-salt bath. To this cold solution was added rapidly a solution of 51 g. (0.25 mole) of trimethylsulfonium iodide in 200 ml. of dimethylsulfoxide. As soon as the tri-

methylsulfonium iodide was added, 21.4 g. (0.20 mole) of distilled pyridine-4-carboxaldehyde in 50 ml. of tetrahydrofuran was added rapidly. The reaction mixture was left at ice-bath temperature for 5 minutes, allowed to warm to room temperature, diluted with 800 ml. of water and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and then a saturated solution of picric acid in ether was added until no further precipitation occurred. The solid was filtered and dried to give 16.2 g. (23.1%) of crystals, m.p. 130-135°. The analytical sample was prepared by recrystallization from methanol, m.p. 139-141°, $\nu_{max}^{KBr}$ 875 cm.$^{-1}$ (  ). The n.m.r. spectrum (pyridine) showed a quartet at 2.77δ (  , cis to pyridine ring, 1.0 H), a quartet at 3.12δ (  , trans to pyridine ring, 1.0 H) and a quartet at 3.87δ (  , 0.99 H).

Anal. Calcd. for $C_{13}H_{10}N_4O_8$: C, 44.57; H, 2.87; N, 16.00. Found: C, 44.69; H, 2.94; N, 15.96.

In a separate run the ether extracts were concentrated to give 14.8 g. of a liquid that contained 4-pyridylethylene oxide and dimethyl sulfoxide as its major components. Attempts to purify this liquid by vacuum distillation or preparative gas chromatography were unsuccessful.

Preparation of Trimethylsulfoxonium Iodide.--Trimethylsulfoxonium iodide was prepared according to the method of Kuhn and Trischmann.[13] A solution of 32 g. (0.41 mole) of dimethylsulfoxide and 60 ml. of methyl iodide were allowed to reflux for 3 days. The solid that had

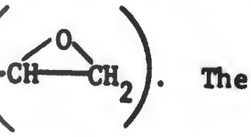
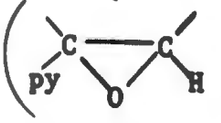
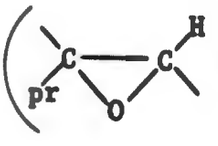
separated was filtered, washed with chloroform and recrystallized from water to give 26 g. of trimethylsulfoxonium iodide, m.p. 210-211°, reported[13] m.p. 200°. The filtrate was refluxed for 3 additional days, whereupon 12.9 g. more of product was obtained, m.p. 210°.

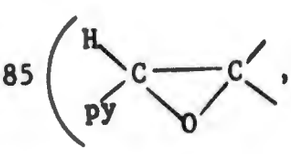
Preparation of Trimethylsulfoxonium Chloride.--Trimethylsulfoxonium chloride was prepared according to the method of Kuhn and Trischmann.[13] To a suspension-solution of 15.4 g. (0.07 mole) of trimethylsulfoxonium iodide in 250 ml. of water was added 15.05 g. (0.105 mole) of freshly prepared silver chloride and the mixture was stirred overnight. The silver iodide was separated by filtration and washed well with water. The filtrate was concentrated by freeze-drying. Recrystallization of the solid obtained from methanol and benzene gave 8.4 g. (93.4%) of trimethylsulfoxonium chloride, m.p. 230-234° with sublimation.

Preparation of 4-Pyridylethylene Oxide Picrate (XXXIII) Using Dimethylsulfoxonium Methylide.--Sodium hydride (2.65 g. of a 50% suspension in mineral oil, 0.055 mole) was placed in a 250 ml. 3-necked flask equipped with a mechanical stirrer, condenser fitted with a drying tube, and nitrogen inlet tube. Tetrahydrofuran (10 ml.) was added and the sodium hydride settled to the bottom. The tetrahydrofuran with the mineral dissolved was separated from the sodium hydride with an eye dropper. Tetrahydrofuran (50 ml.) and trimethylsulfoxonium chloride 7.07 g. (0.055 mole) were added and the mixture was refluxed for 4 1/2 hrs. At this time the reaction mixture had turned from grey to white. To the cooled mixture was added 5.35 g. (0.05 mole) of pyridine-4-carboxaldehyde in 20 ml. of tetrahydrofuran. After the addition, the reaction was left at room temperature for one hour and at 40-50° for one hour. The sodium chloride was separated by filtration. The filtrate

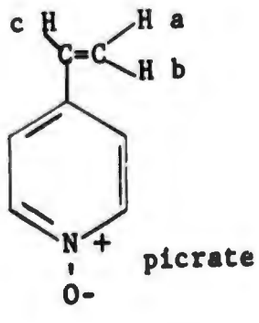
was diluted with ether and a saturated solution of picric acid in ether was added until no further precipitation occurred. The crude solid obtained was recrystallized from methanol to give 1.51 g. (8.6%) of 4-pyridylethylene oxide picrate, m.p. 134-137°. The infrared spectrum of the product was identical to the infrared spectrum of 4-pyridylethylene oxide picrate obtained by treating pyridine-4-carboxaldehyde with dimethylsulfonium methylide.

In a separate experiment, conducted on a 0.05 mole scale, pyridine-4-carboxaldehyde was treated with dimethylsulfoxonium methylide in dimethylsulfoxide. Distillation of the crude product gave 3.14 g. of a liquid that was mostly a mixture of dimethylsulfoxide and pyridine-4-carboxaldehyde. However, attempts to purify this liquid by preparative gas chromatography resulted in decomposition.

Generation of 4-Pyridylethylene Oxide (XXXI) from its Picrate.--A 7.00 g. (0.02 mole) sample of 4-pyridylethylene oxide picrate was suspended in 50 ml. of saturated sodium bicarbonate solution and 300 ml. of water was added to dissolve the sodium picrate. The aqueous solution was extracted 5 times with 75 ml. portions of ether. Concentration of the dried extracts afforded 2.09 g. of liquid. This liquid was extracted with ether leaving a dark oil. The ether extracts were concentrated to give 1.63 g. (76.2%) of a light yellow liquid. A VPC (DEGS) showed only one peak. An infrared spectrum ($CS_2$) showed absorption at 3075, 3055 (pyridine C-H), and 1275, 1155 and 822 $cm.^{-1}$  . The n.m.r. spectrum ($CDCl_3$) showed a quartet at 2.77  cis to pyridine ring, 1.0 H), a quartet at 3.20  trans to pyridine ring,

1.0 H), a quartet at 3.85 (  , 1.0 H), a quartet at 7.0 (β-pyridine protons, 2.3 H) and 8.68 (α-pyridine protons, 2.3 H).

Treatment of 4-Vinylpyridine with m-Chloroperbenzoic Acid.--To a cold solution of 1.06 g. (0.02 mole) of 4-vinylpyridine in chloroform was added 4.16 g. (0.04 mole) of 82.6% m-chloroperbenzoic acid. The mixture was allowed to warm to room temperature after the addition. The reaction was followed by titrating the iodine liberated on treating a small aliquot with sodium iodide with standard sodium thiosulfate solution. After 4 days all of the m-chloroperbenzoic acid had reacted. The m-chlorobenzoic acid that had precipitated during the reaction was separated by filtration. The filtrate was washed with a saturated sodium bicarbonate solution until the wash water was basic to litmus paper. The chloroform solution was dried over sodium sulfate and then treated with an ethereal solution of picric acid. The solid obtained was recrystallized from methanol to give 73.5% of 4-vinylpyridine N-oxide picrate (XXXIV), m.p. 158-162°. The analytical sample was prepared by recrystallization from methanol, m.p. 161-161.5°, $\nu_{max}^{KBr}$ 1215 (=N-O$^-$). The n.m.r. spectrum (pyridine) showed a doublet at 5.41, $J_{ac}$ = 10.5 c.p.s. (a, 1.0 H), a doublet at 5.89, $J_{ab}$ = 17.5 c.p.s. (b, 1.0 H), and a quartet at 6.70δ, $J_{cb}$ = 17.5 c.p.s. and $J_{ca}$ = 10.5 c.p.s. (c, 1.0 H) assigned as shown below.



picrate

Anal. Calcd. for $C_{13}H_{10}N_4O_8$: C, 44.57; H, 2.87; N, 16.00. Found: C, 44.56; H, 2.91; N, 16.11.

Treatment of pyridine-4-Carboxaldehyde with Diazomethane.--To a cold, stirred solution of 1.07 g. (0.01 mole) of pyridine-4-carboxaldehyde in 15 ml. of ether was added a solution of diazomethane prepared from 0.02 mole of N-nitrosomethylurea. After 5 days the solution was concentrated to afford 1.36 g. of a yellow liquid. A VPC (DEGS) showed that all but a very small amount of the pyridine-4-carboxaldehyde had reacted. In addition, the VPC showed one major peak and 3 smaller peaks. The major component was separated from the mixture by preparative gas chromatography. A 0.21 g. fraction was collected that showed only one peak on a VPC chromatogram (DEGS), equal in retention time to an authentic sample of 4-acetylpyridine (XXXV). The infrared spectrum was identical to the infrared spectrum of authentic 4-acetylpyridine. Treatment of the liquid with an ethereal solution of picric acid yielded 4-acetylpyridine picrate, m.p. 128-130°. Reported[14] m.p. 129.5-130°.

Reduction of 4-Pyridylethylene Oxide Using Platinum Oxide Catalyst in Ethanol.--4-Pyridylethylene oxide (1.21 g., 0.01 mole) in 80 ml. of ethanol containing 0.50 g. of platinum oxide was reduced at 2-3 atm. until hydrogen ceased to be taken up. Concentration of filtered solution gave 1.15 g. (93.5%) of 4-ethanolpyridine XXXVI. A VPC (DEGS) showed only one peak equal in retention time to an authentic sample of 4-ethanolpyridine. The infrared spectrum was identical to the infrared spectrum of an authentic sample of 4-ethanolpyridine. Conversion to the picrate gave 2.44 g. (69.5%) of picrate, m.p. 125-130°. Recrystallization from ethanol gave crystals, m.p. 128-131°. Reported[15] m.p. 134-135°. A mixture of this compound with an authentic sample of 4-ethanolpyridine, m.p. 128-131° was

not depressed.

Reduction of 4-Pyridylethylene Oxide using 10% Palladium on Charcoal as Catalyst in Acetic Acid.--4-Pyridylethylene oxide (1.21 g., 0.01 mole) in 100 ml. of acetic acid containing 0.500 g. of 10% palladium-charcoal was reduced at 2-3 atm. until hydrogen ceased to be taken up. The catalyst was separated by filtration and 2.6 g. of picric acid was added to the filtrate. Concentration of the filtrate by freeze-drying gave 3.9 g. of a yellow solid. Recrystallization from ethanol gave 2.8 g. of crystals, m.p. 125-136°. A 1.5 g. sample of the picrate was added to 10 ml. of a saturated sodium bicarbonate solution and enough water was added to dissolve the sodium picrate. The solution was extracted with ether four times. The extracts were dried over anhydrous potassium carbonate. Concentration gave 0.163 g. of 4-ethylpyridine. A VPC (DEGS) showed only one major peak identical in retention time to an authentic sample of 4-ethylpyridine (XXXVII). The infrared spectrum was identical to the infrared spectrum of 4-ethylpyridine. Treatment with picric acid in ether gave 0.33 g. of 4-ethylpyridine picrate. Recrystallization from methanol gave crystals, m.p. 155-160°. Reported[16] 169-170°. The infrared spectrum of this picrate was identical to the infrared spectrum of an authentic sample of 4-ethylpyridine picrate.

The aqueous solution above was extracted with methylene chloride. Concentration of the dried extracts gave 0.155 g. of 4-ethanolpyridine. The VPC (DEGS) retention time and infrared spectrum were identical to that of an authentic sample. Treatment with picric acid in ether gave 0.298 g. of 4-ethanolpyridine picrate, m.p. 127-133°. Reported[15] m.p. 134-135°. The infrared spectrum was identical to an authentic sample of 4-ethanolpyridine picrate.

Treatment of Pyridine-4-carboxaldehyde with Acetone Cyanohydrin.--A solution of 10.7 g. (0.1 mole) of freshly distilled pyridine-4-carboxaldehyde and 10.2 g. (0.12 mole) of acetone cyanohydrin was heated to 75° while $N_2$ was passed through the solution. When the solution reached 75° the contents of the flask solidified. Heating was continued for 15 min. and the reaction mixture was then allowed to cool. The solid was washed with warm ether and with hot ethyl acetate. After drying, 5.64 g. of solid was obtained. An infrared spectrum indicated that the solid was a mixture of XL and isonicotinic acid. The solid was washed in turn with 1 N sodium hydroxide and water, then dried to give 2.7 g. (21.6%) of XL. An infrared spectrum of this solid was identical to the spectrum of an authentic sample of XL prepared by the method of Mathes and Sauermilch.[7] Acetylation of this compound yielded XLI, m.p. 156-159°. Reported[7] m.p. 163°. Concentration of the above ether gave 5.4 g. of recovered acetone cyanohydrin. Concentration of the ethyl acetate gave an oil that could not be crystallized.

In a separate run conducted in the same manner, an 18% yield of isonicotinic acid was obtained by recrystallizing the crude reaction mixture from methanol.

The use of triethylamine or potassium carbonate as catalyst gave similar results.

Treatment of Pyridine-4-carboxaldehyde Hydrochloride with Acetone-Cyanohydrin.--When a mixture of 4.26 g. (0.07 mole) of pyridine-4-carboxaldehyde hydrochloride and 8 ml. of acetonecyanohydrin were allowed to stir together for 24 hrs., a quantitative recovery of the hydrochloride was obtained.

Preparation of 4-Pyridylhydroxymethanesulfonic Acid (XLII).--To a solution of 0.1 mole of crude pyridine-4-carboxaldehyde in toluene was added 40 ml. of saturated sodium meta-bisulfite solution. A solid formed in the aqueous layer. The mixture was cooled to 0° and the liquid decanted from the solid. The solid was washed from the flask with ethanol and washed with ether. Recrystallization from water afforded 9.77 g. (51.5%) of white crystals, m.p. 202-203° with sublimation. Reported[17] m.p. 218° with sublimation, $\nu_{max}^{KBr}$ 3700-2500, (OH, NH, CH) 1640, 1612 (pyridine) and 1030, 1260 ($SO_3^-$).

Treatment of 4-Pyridylhydroxymethanesulfonic Acid with Two Equivalents of Potassium Cyanide.--A mixture of 0.945 g. (0.005 mole) of XLII and 0.650 g. (0.01 mole) of potassium cyanide in 40 ml. of water were allowed to react overnight. Filtration of the solid that had precipitated afforded 0.75 g. (90%) of XL, m.p. 146-152°. Reported[7] m.p. 144-146°. The infrared spectrum was identical to the infrared spectrum of an authentic sample of XL.

Preparation of 1,2-Bis-(4-pyridyl)-1,2-ethanediol Trihydrate (XLIII).--Using the procedure reported by Mathes and Sauermilch,[9] a mixture of 25 g. of pyridine-4-carboxaldehyde, 100 ml. of water and 12 g. of zinc dust were stirred together at 70-80° for two days. The zinc dust was separated by filtration. After cooling, 6.11 g. of d,l-1,2-bis-(4-pyridyl)-1,2-ethanediol trihydrate was obtained, m.p. 173-178°. Reported[9] m.p. 178°. The zinc dust was washed with the filtrate. After cooling an additional 3.19 g. of product was obtained, m.p. 174-178°. Total yield was 9.3 g. (33.9%). No attempt was made to isolate the meso-1,2-bis(4-pyridyl)-1,2-ethanediol trihydrate (XLIII).

Preparation of d,l-1,2-Bis-(4-pyridyl)-1,2-ethanediol bis N-Oxide Monohydrate (XLIV).--Using the procedure of Mathes and Sauermilch,[9] to a solution of 3.38 g. (0.0124 mole) of d,l-1,2-bis(4-pyridyl)-1,2-ethandiol trihydrate in 16.5 ml. of acetic acid was added 3.8 g. of 30% hydrogen peroxide. The solution was stirred at 45 ± 5° for three days. The solution was concentrated under vacuum leaving a white solid which was washed with hot acetonitrile. After drying 3.0 g. (91%) of d,l-1,2-bis-4-(pyridyl)-1,2-ethandiol bis-N-oxide monohydrate was obtained m.p. 193-198°, reported[9] m.p. 200°. In other runs the yield varied from 50-98%.

Preparation of Pyridine-4-carboxaldehyde N-Oxide (XLV).--Using the procedure of Mathes and Sauermilch,[9] a suspension of 11.8 g. of lead tetraacetate and 5.91 g. (0.022 mole) of d,l-1,2-bis-4-(pyridyl)-1,2-ethanediol bis N-oxide monohydrate in 50 ml. of chloroform was stirred for 60 min. Sodium carbonate was added until the solution was weakly basic. The mixture was filtered and the residue washed with chloroform. Concentration of the solution gave a solid which on recrystallization from benzene gave 2.27 g. (84%) of 4-pyridine-carboxaldehyde N-oxide, m.p. 148-152°. Reported[4] m.p. 152°.

Preparation of Pyridine-4-carboxaldehyde N-Oxide Cyanohydrin (XLVI).--Dry hydrogen cyanide gas was passed into a flask cooled in an ice bath and protected from moisture containing 2.27 g. (0.0184 mole) of pyridine-4-carboxaldehyde N-oxide. The ice bath was removed and the excess hydrogen cyanide was allowed to evaporate, to give 2.69 g. (97.6%) of pyridine-4-carboxaldehyde N-oxide cyanohydrin, m.p. 118° (Dec.). The infrared spectrum showed no aldehyde absorption peaks.

Reduction of Pyridine-4-carboxaldehyde N-Oxide Cyanohydrin (XLVI).--Pyridine-4-carboxaldehyde N-oxide cyanohydrin (2.49 g., 0.0166 mole) in 100 ml. of acetic acid (distilled from potassium permanganate) containing 1.2 g. of 10% palladium on carbon catalyst was hydrogenated in a Parr hydrogenator at 2-3 atms. The temperature was gradually increased during the reduction to 73° and held until hydrogen ceased to be taken up. The reduction mixture was allowed to cool to room temperature and the catalyst was separated by filtration. Concentration of the filtrate by freeze-drying gave an oil. A TLC (butanol-water-acetic acid, 2-2-1) indicated that no 3-quinuclidinol was present. The oil was dissolved in an ethanolic hydrogen chloride solution. Concentration gave 3.0 g. of an amine hydrochloride. The infrared spectrum of this hydrochloride was quite different from the spectrum of an authentic sample of 3-quinuclidinol hydrochloride. Attempts to crystallized the oil were unsuccessful.

Preparation of Di-(β-carbethoxyethyl)-benzylamine.--Using the method of C. A. Grob and P. Brenneisin,[10] 200 g. (2 mole) of ethyl acrylate in 250 ml. of absolute alcohol was added to 107 g. (1 mole) of benzyl amine in 200 ml. of absolute alcohol. Immediately after the addition a vapor phase chromatogram (5% carbowax 20 M) indicated that all of the benzyl amine had reacted. Two new peaks were present in addition to the alcohol peak. The area under the first peak due to mono-addition product ($C_6H_5CH_2NHCH_2CH_2CO_2Et$) was eleven times larger than the area under the slower moving peak due to the desired product. After standing 18 days at room temperature the area under the second peak was 10 times as large as that under the first peak. Work-up afforded 333 g. (108%) of crude product. An IR showed no N-H absorption but showed a strong C=O peak at 1730 $cm.^{-1}$. Since this compound was characterized by Grob, it was used

in crude form in the following experiment.

Preparation of 1-Benzyl-4-piperidone.--Di-(β-carbethoxyethyl)-benzyl amine (0.867 mole) was converted to 1-benzyl-4-piperidone by the procedure reported by C. A. Grob and P. Brenneisin[10] using a slight excess of sodium hydride in refluxing benzene to effect ring closure followed by treatment with dilute hydrochloric acid and heat to give hydrolysis and decarboxylation. Distillation of the crude product under reduced pressure afforded 132.3 g. of 1-benzyl-4-piperidone, b.p. 105-107° at .05-.1 mm. Hg., $N_D^{25}$ 1.5369. An infrared spectrum showed a strong C=O peak at 1712 $cm.^{-1}$.

Preparation of Triphenylmethoxymethylphosphonium Chloride.--The phosphonium chloride was prepared by the method of U. Schöllkopf.[18] A mixture of 0.167 mole of triphenyl phosphine, 85 ml. of benzene and 0.169 mole of methyl chloromethyl ether was heated at 40-60° for 72 hrs. A thin layer chromatogram (cyclohexane) showed that unreacted triphenylphosphine was present and a VPC (5% carbowax 20 M) showed that unreacted methyl chloromethyl ether was also present. After 95 hrs. total reaction time only a faint spot was observable for triphenyl phosphine on TLC. Filtration, washing with ether and recrystallization from a chloroform and ethyl acetate mixture afforded 49.7 g., 86.1% yield, m.p. 190-192.5°. Reported,[2] m.p. 201-202°. The n.m.r. spectrum ($CDCl_3$) showed a singlet at 3.67 ($CH_3O$-, 3.0 H), a doublet at 5.82 (P-$CH_2$-O, 2.0 H), and a multiplet at 7.76δ (aromatic protons, 15 H).

Preparation of the Enol Ether (LII).--Triphenylmethoxymethylphosphonium chloride (13.7 g., 0.04 mole) was suspended in 140 ml. of ether (distilled from lithium aluminum hydride). The system was protected from atmospheric moisture by a calcium chloride drying tube. An ethereal solu-

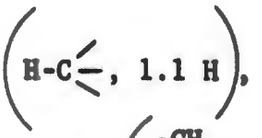
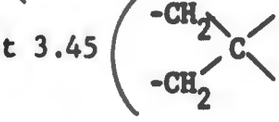
tion of phenyl lithium (20.75 ml. of 1.93 N, 0.04 mole) was added dropwise to the stirred suspension under nitrogen. At first the mixture turned yellow, but on slight warming the mixture turned dark red. To the cooled reaction mixture was added 3.79 g. (0.02 mole) of 1-benzyl-4-piperidone in 40 ml. of ether and the mixture was refluxed for 4 hrs. Acetone (2.4 g., 0.04 mole + 4%) was added to the reaction mixture to destroy the excess Wittig reagents. After heating for 1/2 hr. the mixture was allowed to cool and filtered. Concentration of the filtrate afforded a dark oil. Distillation under reduced pressure through a 4" vigreaux column gave 1.32 g., 30.6% of LII, b.p. 85-100°. $N_D^{25}$ = 1.5465, $\nu_{max}^{KBr}$ 3035 (aromatic C-H) and 1690 cm.$^{-1}$ (C=C-OR).

Several attempts to repeat this reaction were unsuccessful.

Preparation of 1-Benzyl-4-hydroxymethylpiperidine (LIV).--A 9.9 g. (0.0423 mole) sample of the undistilled methyl ester of 1-benzylpiperidine-4-carboxylic acid in 100 ml. of ether was added to a suspension-solution of 1.605 g. (0.0423 mole) of lithium aluminum hydride in 50 ml. of dry ether. After the addition the reaction mixture was refluxed for 1 1/4 hrs. The mixture was allowed to cool, the excess lithium aluminum hydride was decomposed by the addition of water and then 200 ml. of a 20% potassium sodium tartrate solution was added. The ether layer was separated and the aqueous layer extracted with three 50 ml. portions of ether. The ether layer and washings were combined and dried over anhydrous sodium sulfate. Concentration of the ether gave 7.3 g. (84%) of crude 1-benzyl-4-hydroxymethylpiperidine (LIV) as an oil. The infrared spectrum showed a strong -OH peak at 3625 cm.$^{-1}$.

This oil was used to prepare LVI without further purification.

Treatment of 1-Benzyl-4-hydroxymethylpiperidine with p-Toluene-

sulfonyl Chloride in Pyridine.--To a ice-cooled solution of 1 g. (0.0048 mole) of 1-benzyl-4-hydroxymethylpiperidine in 10 ml. of pyridine was added 1.83 g. (0.0096 mole) of p-toluenesulfonyl chloride portionwise. Upon the first addition the solution turns yellow. As more p-toluenesulfonyl chloride was added the solution turned orange and finally red. After 3 1/2 hrs. the reaction mixture was diluted with 75 ml. of chloroform. Then 10 ml. of a saturated solution of sodium bicarbonate was added. Solid sodium bicarbonate was added until bubbles ceased to be evolved. The chloroform layer was washed with water, dried over sodium sulfate and concentrated under vacuum to give a rust colored solid. Recrystallization from acetone gave 0.972 g. (56.4%) of LVI, m.p. 170-171.5°. The analytical sample prepared by further recrystallization from acetone had m.p. 170.5-172°. $\nu_{max}^{KBr}$ 1200 ($SO_3^-$) 780 cm.$^{-1}$ (aromatic substitution peak). The n.m.r. spectrum showed a multiplet at 1.26-2.43 with a sharp singlet pertruding at 2.31  and $CH_3$-Ar, 7.4 H), a multiplet at 2.69  , 1.1 H), a multiplet at 3.0-4.0 with a sharp singlet pertruding at 3.45  and bridgehead methylene, 6.1 H), a singlet at 4.81 ($ArCH_2$-, 1.9 H) and a multiplet at 7.0-7.98 (aromatic protons, 8.6 H).

Preparation of 1-Benzylpiperidine-4-carboxaldehyde (XLVIII).--A 0.01 mole sample of 1-benzylpiperidine-4-carboxylic acid and N,N$^1$-carbonyldiimidazole in 50 ml. of tetrahydrofuran (distilled from lithium aluminum hydride) was refluxed for 1 1/2 hrs. The solution was concentrated to 2/3 its original volume and transferred to a 3-necked flask.

To this solution, cooled to -20° was added dropwise under nitrogen, 90 ml. of 0.055 molar lithium aluminum hydride in ether. After 1/2 hr., 4 ml. of water was added and the solution allowed to warm to room temperature. The reaction mixture was diluted with 200 ml. of 20% sodium potassium tartrate solution and extracted with ether. After drying over sodium sulfate the ether extracts were concentrated to afford 1.4 g. of an oil. An infrared spectrum showed absorption at 2765 and 2815 (aldehyde C-H) and 1725 $cm.^{-1}$ (aldehyde C=O). Attempts to crystallize the oil were unsuccessful. By subjecting the oil to preparative gas chromatography, a 0.45 g. sample of the aldehyde was obtained that showed only one peak on a VPC (SE-30) chromatogram. An infrared spectrum showed peaks at 2765 and 2810 (aldehyde C-H) and 1718 $cm.^{-1}$ (C=O).

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