REACTIONS OF
2-HYDROXY-3-BROMO-1,2,3,4-TETRAHYDROQUINOLIZINIUM BROMIDE

by

CLYDE EDWARD DAVIS

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Professor of Chemistry
In Charge of Major

Chairman of Department of Chemistry

Chairman of School Graduate Committee

Dean of Graduate School

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REATIONS OF
2-HYDROXY-3-BROMO-1,2,3,4-TETRAHYDROQUINOLIZINIUM BROMIDE

INTRODUCTION

The original object of this investigation was to study the reactions of 2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide with several nucleophilic reagents and to determine if different substituents could be placed at the two and/or three positions. The plan for placing different substituents at the three position was to prepare 3-bromo-3H,4H-quinolizinium bromide by dehydration of the cyclic alcohol (33, p. 21) followed by the reaction of this allylic bromide with various Grignard reagents. Further investigation of 3-bromo-3,4-dihydroquinolizinium bromide, reported as being purple crystals, also seemed necessary since other compounds of similar structure were reported as colorless (25, p. 22; 4, p. 1832-1836). It was thought that the cyclic ketone could be prepared by the oxidation of the 2-hydroxy group or by the cyclization of 1(α-pyridyl)-3-butene-2-one with bromine. Consideration was also given to the possibility that cyclization of 1(α-pyridyl)-3-butene-2-one might occur by the elimination of the bromine alpha to the carbonyl, thus forming a five membered pyrrocoline ring instead of the quinolizinium ion.
With basic reagents, 2-hydroxy-3-bromo-1,2,3,4-quinolizininium bromide, being a quaternary salt, would presumably undergo a Hofmann degradation. If the ring was opened by base, the possibility exists that recyclization could occur forming a five membered pyrrocoline ring. In basic or acidic medium the possibility of acid or base catalyzed dehydration occurring was also present. Recognizing that the 3-bromo group was a secondary bromide, this group should be quite reactive toward various amines and toward nucleophilic displacement.

Interest in this class of compounds stems from their occurrence in numerous natural alkaloids. Alkaloids such as lupinine possess the simple bicyclic quinolizine nucleus, while polycyclic ring structures incorporating the same nucleus are found in other bases of the lupin group (sparteine, matrine), the canadine alkaloids (berberine) and the ipecucuanha alkaloids (emetine). The basic quinolizine ring system is also a structural feature present in many of the compounds exhibiting high curariform activity (12, p. 285). It is also interesting that cytisine, a bitter, powerfully poisonous base, has been identified as a constituent of many legumes. Although there are to be found allusions to the cathartic and diuretic utility of cytisine, its general physiological properties do not render it
attractive for medicinal use (30, p. 4659-4670).

Wischmann prepared 1(2-pyridyl)-3-butene-2-ol (I) by condensing 2-picolyllithium with acrolein (33, p. 8-30). He found no oxotropic rearrangement to occur with this allylic alcohol on acid hydrolysis. Upon bromination in carbon tetrachloride 2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide (II) was isolated. Proof for the assigned structure of compound II was offered on the basis of: (1) ultraviolet peak at 266 m\(\mu\) (attributed as being characteristic of the tetrahydroquinolizinium cation by Boekelheide et al. (4, p. 1832-1836), (2) quantitative hydrogenation of compound II showed 3\(\frac{1}{2}\) moles of hydrogen were absorbed to give compound IV, and (3) compound II could be dehydrated to 3-bromo-3H,4H-quinolizinium bromide (III) which was reported as being a purple crystalline compound.

\[
\begin{align*}
\text{CH}_2\text{Li} & + \text{CH}_2=\text{CHCHO} \rightarrow \text{CH}_2\text{CH}=\text{CH}_2 \\
\text{Br}_2/\text{CCl}_4 & \rightarrow \text{Br}^-/\text{H}_2\text{SO}_4 \\
\text{Pt} & \rightarrow \text{Br}^-/\text{H}_2\text{SO}_4
\end{align*}
\]
Nash similarly condensed 2-picolyllithium with methacrolein and cyclized with bromine to give 2-hydroxy-3-methyl-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide. This cyclic alcohol was then dehydrated giving a compound which was not purple. Nash also reported that he was able to add hydrogen bromide across the double bond of 1-(2-pyridyl)-3-methyl-3-butene-2-ol hydrogen bromide (25, p. 9-30).

The first synthesis of simple dehydroquinolizinium compounds was in 1951 when Beaman condensed 2-picolyllithium with β-isopropoxyacrolein (2, p. 1002). However the yield of V was very low and the isolation presented difficulties.

\[ 2\text{-Py}:\text{CH}_2\text{Li} + \text{C}_3\text{H}_7\text{OCH}=\text{CHCHO} \rightarrow \text{V} \]

Richards and Stevens obtained the 2-ethyl-3-methyl homolog by substituting l-ethoxy-2-methyl-1-penten-3-one for β-isopropoxyacrolein (27, p. 905).

Boekelheide and Gall improved the above synthesis by substituting the more readily available β-ethoxy pro-pionaldehyde (4, p. 1832-1836). The condensate (VI) of
\( \beta \)-ethoxypropionaldehyde with picolylolithium was then cyclized to 2-hydroxy-1,2,3,4-tetrahydroquinolizinium iodide (VII) by using hydriodic acid then neutralizing with sodium carbonate.

\[
\text{2-Py} \text{CH}_2\text{Li} + \text{C}_2\text{H}_5\text{O(CH}_2\text{)}_2\text{CHO} \rightarrow \text{OH} \quad \text{N} \quad \text{CH}_2\text{CH(CH}_2\text{)}_2\text{OE}^+ \\
\text{VI}
\]

\[
\text{VI} \xrightarrow{\text{HI}} \text{Na}_2\text{CO}_3 \rightarrow \text{OH} \quad \text{N} \quad \text{CH}_2\text{CH(CH}_2\text{)}_2\text{OE}^+ \\
\text{VII}
\]

Compound VII was then dehydrated using acetic anhydride with a drop of concentrated sulfuric acid to VIII which in turn was dehydrogenated with palladium-charcoal catalyst to the dehydroquinolizinium cation (V).

\[
\text{VII} \xrightarrow{\text{Ac}_2\text{O} - \text{H}_2\text{O}} \text{OH} \quad \text{N} \quad \text{CH}_2\text{CH(CH}_2\text{)}_2\text{OE}^+ \\
\text{VIII} \xrightarrow{\text{Pd/C}} \text{X} \\
\text{V}
\]
Boekelheide and Ross later expanded on their original synthesis by using 2,6-lutidyllithium and β-ethoxypropionaldehyde to give the corresponding carbinol in 50% yield (6, p. 5691-5693). This carbinol was then cyclized with hydriodic acid to the 6-methyl homolog of VII which in turn was dehydrated and dehydrogenated. The yields of the dehydrogenation step were improved by using platinum catalyst in nitrobenzene to 42%. Boekelheide also reports dehydrogenation of 3H,4H-quinolizinium cation to go in poor yields with selenium dioxide, N-bromosuccimide and chloroanil. However 30% yields could be obtained by heating the picrates in butanol with a palladium-charcoal catalyst.

Glover and Jones prepared IX in 62% yield by condensing 2-cyanopyridine and 3-ethoxypropylmagnesium bromide (19, p. 1750-1754). Compound IX was cyclized with aqueous hydrobromic acid followed by boiling chloroform to give X in 73% yield. Dehydration of X then afforded dehydroquinolizinium picrate (V) in 96% yield (18, p. 3021-3028).
In later papers, Glover and Jones reported the synthesis of a number of substituted 1:2:3:4-tetrahydro-1-oxoquinolizinium bromides by using the appropriate aliphatic precursor (20, p. 1686-1691). When boiled in acetic anhydride these ketones were converted in high yields into the corresponding substituted dehydroquinolizinium salts.

Nesmeyanov and Rybenskaya improved the synthesis of 2-substituted dehydroquinolizinium salts (26, p. 6349d). The cyclic alcohols of type XI were obtained from the condensation of 2-picrolyllithium with β,β-dimethoxyethyl ketones followed by hydrobromic acid in 21-32% yields. Compound XI was then dehydrated to the 2-substituted dehydroquinolizinium salts.
Bradsher and Beavers have reported the synthesis of 7-methylnaphtho (1,2-a) quinolizinium bromide (XIII) and similar compounds by cycleodehydration of compound XII with aqueous hydrobromic acid (10, p. 2459-2462).

Diels et al. reported that pyridine reacts with dimethyl acetylenedicarboxylate in ether to yield tetramethyl pyridocoline-1,2,3,4-tetracarboxylate (XIV) (13, p. 16-49; 14, p. 103-150; 15, p. 87-128). Two other compounds were also isolated, a "red labile adduct" (XV) and "Kashimoto's compound" (XVI). The red product (XV) was found to be converted to the yellow compound (XIV) on crystallization from solvents; it could also be transformed into Kashimoto's compound (XVI) with mercuric acetate and acetic acid.
The proof of these structures was based mainly on the nature of the products obtained from oxidation. Hydrogen peroxide afforded α-picolinic acid N-oxide thus indicating that one point of attachment of acetylene-dicarboxylic ester was the 2-position of the pyridine ring (14, p. 103-150; 24, p. 1004-1009).

It was found that the stable adduct (XIV) could be converted to trimethyl pyrrocoline-1,2,3-tricarboxylate with bromine followed by hydrolysis or with nitric acid. Saponification and partial decarboxylation gave pyrrocoline-2-carboxylic acid (9, p. 672-674). Pyrolysis of the calcium salt of this acid afforded pyrrocoline.

Diels et al. claimed that when tetramethyl quinolizinetetracarboxylate (XIV) was reacted with nitric acid the intermediate XVII was detected. Upon addition of
water the hydroxyquinolizine (XVIII) was formed which in pyridine dehydrated forming the dehydroquinolizininium cation (Kashimoto's compound) (XVI) (14, p. 103-150).

\[
\begin{align*}
\text{XIV} & \xrightarrow{\text{HNO}_3} \text{XVII} \\
\text{XVII} & \xrightarrow{\text{H}_2\text{O}} \text{XVI} \\
\text{XVI} & \xleftarrow{\text{Pyr}} \text{XVIII}
\end{align*}
\]

Diels et al. reported that saponification and stepwise decarboxylation of XIV gave quinolizine (also named pyridocoline and pyrido-(1,2-a)-pyridine) (XIX) (13, p. 16-49; 14, p. 103-150). However in 1937, Diels and Schrum withdrew this claim (16, p. 68-86). They
found that the stepwise decarboxylation gave the isomeric 3-methyl-pyrrocoline (XX).

In 1954 Boekelheide et al. also attempted to obtain quinolizine by fusing 2-hydroxy-1,2,3,4-tetrahydroquinolizinium iodide with sodium acetate. However this attempt failed, giving only 2-(buta-1,3-dienyl)-pyridine (4, p. 1832-1836). At the present quinolizine itself has never been prepared.

However 4-ketoquinolizine (XXII) has been obtained by dehydrogenation of 4-ketoctahydroquinolizine (XXI) (28, p. 761). Boekelheide and Lodge have characterized this compound and published ultraviolet absorption data (5, p. 3682).
Preparation of pyridones by alkaline ferricyanide oxidation of quaternary salts derived from pyridine itself is well known (1, p. 165), yet the operation cannot be applied to \( \alpha \)-alkylpyridinium salts (XXIII) or to the simplest member of the tetrahydroquinolizinium salts (XXIV) (7, p. 162).
However the pyridones have been obtained in more complex polycyclic systems. Van Tamelen et al. were able to oxidize an intermediate (XXV) in their total synthesis of cytisine to the pyridone or cyclic amide (XXVI) with alkaline ferricyanide (30, p. 4659-4670).

\[ \phi-\text{CH}-\text{N} \rightarrow \text{Fe(CN)}_6^{3-} \rightarrow \phi-\text{CH}-\text{N} \]

The Japanese workers, Sagasawa et al., reported that 6,7-dihydrobenzoquinolizinium iodide (XXVII) would form the cyclic amide in basic solutions (XXVIII) (29, p. 10539g). With sodium hydroxide the change is instantaneous, while with weaker bases such as sodium carbonate, sodium bicarbonate and ammonium hydroxide, it was sluggish. The addition of sodium dithionate was found to accelerate the rate with the weak bases. The reaction could be reversed to give the quinolizinium ion by refluxing in phosphorous oxychloride.
Doering and Weil found that \( \gamma \)-(2-piperidyl) butyric acid can be cyclized to \( \alpha \)-norlupinone in a molecular still (17, p. 2461-2466).

Reduction in neutral solution of the 1,2,3,4-tetrahydroquinolizinium ion with platinum oxide is reported to go smoothly and in high yield to the corresponding octahydroquinolizine compound (13, p. 16-49; 4, p. 1832-1836).

Dehydration of hydroxyquinolizinidines affords the mixtures of the respective unsaturated compounds (24, p. 1017). The infrared and ultraviolet spectra have been found useful in determining the position of the double bonds (21, p. 439; 22, p. 437).

Since the occurrence of pyrrocolines in studies of the quinolizines and related compounds have been demonstrated, brief mention is made here of related
systems.

Pyrrocoline and all the known alkylpyrrocolines are either low melting solids or high boiling liquids volatile in steam, unstable in air and light. However, 2- or 5-phenyl pyrrocoline are stable solids and not volatile in steam.

All give colors in the pine splint test, characteristic of pyrrole, and colored melts on fusion with oxalic acid characteristic of indole. A third test is the treatment of pyrrocolines in dilute sulfuric acid with a crystal of sodium iodate, pyrrocoline and 7-methyl and 5-phenyl derivatives give deep blue indigo colors. Many pyrrocolines in solution or as vapors or solids show, in sunlight or under ultraviolet light, characteristic fluorescence.

Also similar to pyrrole and indole, pyrrocoline and its 7-methyl and 5-phenyl derivatives condense with aldehydes in alcoholic solutions to yield dipyrrocolinylmethanes, structures undetermined as of yet. These compounds tend to become blue in air while those prepared from pyrrocoline itself with simple ketones in acetic acid are stable compounds (8, p. 624-625).

Brand and Reuter reported the formation of pyrrocoline (XXX) in low yields by treatment of XXIX in strong aqueous sodium hydroxide solution (11, p. 1668-1678).
Boekelheide and Freely synthesized pyrrocoline (XXX) in 35% overall yield from XXXI (3, p. 589-592). The ultraviolet and infrared spectra of this pyrrocoline were also published.
Winterfield and Müller reported the cyclization of 1(2-pyridyl)-3-bromopropane (XXXII) by treatment with base then acid to yield XXXIII which was then hydrogenated to α-coniceine (XXXIV) (32, p. 4345).

Aromatic amides of pyrrocolinecarboxylic acid, useful for dyeing polyester fibers (particularly Dacron and cellulose acetate fibers) were prepared by Long and Boyle (23, p. 6633c). A mixture of methyl acetoacetic ester, pyridine, anhydrous ethanol and 2,3-dichloro-1,4-naphthoquinone were refluxed to give XXXV (R = CooMe). The ester was hydrolyzed to the acid which in turn was converted to the acid chloride. The acid chloride was reacted with paramethoxyaminobenzene or orthodichlorobenzene to give a deep violet dye (XXXVI) (23, p. 6633c).
XXXV

\[ R \text{CONHC}_6\text{H}_4\text{OMe} \]

XXXVI
FIGURE I. Compounds Prepared.

\[ \text{1(\text{\text{-PYRIDYL})-3-BUTENE-2-OL}} \]

\[ \text{Iodide} \]

\[ \text{Bromide} \]

\[ \text{Iodo-bromo-tetrahydroquinolizinium} \]

\[ \text{Iodo-bromo-tetrahydroquinolizinium} \]

\[ \text{Iodo-bromo-tetrahydroquinolizinium} \]
FIGURE 2. Compounds Prepared.

\[
\begin{align*}
\text{II} & \xrightarrow{\text{H}_2/\text{PtO}_2} \\
& \\
\text{2-hydroxy-3-bromoquinolizidine} & \text{hydrogen bromide} \\
\text{Compound IV} & \\
\text{2-acetoxy-3-bromoquinolizidine} & \text{hydrogen bromide} \\
\text{Compound V} & \\
\text{3-bromo-\textDelta^1-dehydro-quinolizidine} & \text{hydrogen bromide} \\
\text{Compound VII} & 
\end{align*}
\]
FIGURE 3. Base Reactions of Compound II.

\[
\begin{align*}
\text{Compound II} & \xrightarrow{\text{sublimation}} \text{Compound XI} \\
\text{Compound VIII (tan)} & \xrightarrow{\text{sublimation}} \text{Compound XI} \\
\text{Compound IX} & \xrightarrow{\text{H}^+} \text{Purple} \\
\text{Purple} & \xrightarrow{\text{HNO}_3, \text{Zn, HCl}} \text{Brown, \textit{"labile"}} \\
\text{Colorless} & \xrightarrow{\text{air}} \text{Green} \\
\text{Purple} & \xrightarrow{\text{air}} \text{Purple} \\
\end{align*}
\]
DISCUSSION

A. Starting Materials

1(α-pyridyl)-3-butene-2-ol was prepared by the condensation of 2-picolyllithium with acrolein following the procedure presented by Wischmann (33, p. 14-15). Phenyllithium was prepared by the reaction of monobromo-benzene with lithium metal in ethereal medium under a nitrogen atmosphere. Upon addition of 2-picoline, exchange of the lithium took place to give a blood red compound, 2-picolyllithium. At this point in the investigation, it was found that a nitrogen atmosphere was unnecessary since the refluxing ether provided a sufficiently inert atmosphere to prevent decomposition of the organolithium compounds. This same observation was found in Vogel (31, p. 1011-1012). The picolyllithium was cooled to 0°C or lower with a salt-ice bath and a theoretical amount of acrolein was added slowly. The lithium adduct was hydrolyzed with water and the ether layer separated. The ether extract was dried and distilled giving a light yellow oil which crystallized upon standing overnight. This oil had the same properties as described by Wischmann for the allylic alcohol. Since no ultraviolet data was reported for this compound, an
ultraviolet spectral scan was run.

2-Hydroxy-3-bromo-1,2,3,4-tetrahydroquinolinizinium bromide was prepared by bromination of 1(α-pyridyl)-3-buten-2-ol in carbon tetrachloride. The cyclic alcohol precipitated from solution as described by Wischmann (33, p. 20-21). Compound II was recrystallized from methanol. This quaternary ammonium salt was found to be very soluble in water, soluble in alcohol and glacial acetic acid and insoluble in chloroform, carbon tetrachloride, ether and acetone. In the course of this work it was found that 2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolinizinium bromide did not accurately obey Beer's Law between 1-10 ppm suggesting that an equilibrium might exist in solution. Conductometric experiments might shed more light on this possibility. Similar results were obtained for other quaternary salts of pyridine (1, p. 164).

B. Miscellaneous Reactions

To determine whether cyclization could occur with halogens other than bromine, 1(α-pyridyl)-3-buten-2-ol was reacted with iodine in carbon tetrachloride. A dark brown gum precipitated from solution, which on recrystallization from alcohol gave white crystals in low yield. The yield of the cyclic iodide was improved by dissolving compound I in an aqueous solution of 5% hydrogen peroxide
to which a theoretical volume of hydriodic acid was added. Upon concentration of the purple aqueous solution white plates were obtained. Recrystallization afforded a white solid which had u.v. peaks at 266 m/\mu and 226 m/\mu. Carbon-hydrogen and infrared analyses indicated cyclization had taken place.

Compound II was hydrogenated over platinum oxide to 2-hydroxy-3-bromoquinolizidine hydrogen bromide, compound IV (33, p. 21-22). Compound IV was dehydrated with acetic anhydride and a drop of concentrated sulfuric acid. The excess acetic anhydride was removed under vacuum and the remaining solid recrystallized from 100% ethanol-ether mixture. Carbon-hydrogen analysis indicated dehydration occurred presumably forming 3-bromo-\triangle'-dehydroquinolizidine hydrogen bromide. This compound was found to decolorize bromine water.

When compound IV was reacted with acetic anhydride without acid catalyst, the infrared spectrum showed a strong peak at 1740-1430 cm\(^{-1}\) indicating that the acetate ester (VII) was formed. No double bond peak was found. Carbon-hydrogen analysis also indicated the acetate was formed. Compound VII was found not to decolorize bromine water.

An aqueous solution of compound II was refluxed
with 47% hydriodic acid for 2 hours. Evaporation under vacuum afforded a glassy yellow solid which crystallized on standing. The crude yellow crystals were recrystallized from methanol to give a white compound. Ultraviolet scan showed a 228 m/μ peak. Carbon-hydrogen analysis indicated that the 2-hydroxy group had been replaced and the infrared spectra was found to be similar to compounds II and III.

C. Attempted Reactions of 2-Hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium Bromide

Following the procedure used by Wischmann for preparing 3-bromo-3,4-dihydroquinolizinium bromide (33, p. 21), the cyclic alcohol, compound II, was refluxed for 5-10 minutes with acetic anhydride with a drop of concentrated sulfuric acid. Purple crystals were obtained on recrystallization as described but with varying melting points, suggesting that impurities were present. The purple crystals were washed with acetone; the purple coloration was removed and only slightly colored crystals remained. After washing with acetone the melting point was raised to that of the cyclic alcohol and also the same u.v. peak at 266 m/μ. If dehydration had taken place as expected, there should have been a bathochromic shift since the double bond would have been in conjugation with the pyridine ring. This shift was observed by
Boekelheide et al. (4, p. 1832-1836) with the 3,4-dihydroquinolizinium ion. This same shift was also observed for 3-methyl-3-bromo-3,4-dihydroquinolizinium bromide* which gave a u.v. peak at 300 m\(\mu\). Another disconcerting fact was that if the dehydrated product was purple, this expected ionic salt should not be soluble in acetone and insoluble in water. Varying conditions of time and temperature only affected the amount of unreacted compound II recovered and the amounts of purple oil formed. Acetic anhydride alone gave a purple oil. Concentrated sulfuric acid and compound II reacted liberating bromine when heated; however when a u.v. was run on the solution a 266 m\(\mu\) was still observed with no indication of a bathochromic shift. Other attempts at dehydration such as refluxing in absolute alcohol for 48 hours to 3 days, and in absolute butanol for 1-3 hours, gave only purple solutions with 266 m\(\mu\) peaks. An acetone extract of the purple compound was evaporated and alcoholic solutions made of the residues. Spectrophotometric analysis showed broad absorption from 540-580 m\(\mu\) and a peak at 228 m\(\mu\) for the purple fractions. The purple fraction was found to decolorize bromine water

*We are grateful to Boyd Nash for furnishing an authentic sample of 3-methyl-3-bromo-3,4-dihydroquinolizinium bromide for u.v. analysis.
and form colorless solutions indicating double bonds were present.

The oxidation of the hydroxy group of compound II was also attempted. An Oppenheimer oxidation with aluminum isoproxide and excess acetone gave a purple oil from which no pure compound could be isolated. A second approach to the ketone was the preparation of 1(2-pyridyl)-3-butene-2-one (33, p. 18) and the attempted cyclization with bromine in carbon tetrachloride. A yellow-orange product precipitated from the carbon tetrachloride. This product turned blue-green upon addition of hot alcohol and liberated a pungent colorless gas resembling hydrogen bromide. On standing the blue-green solutions eventually turned purple.

Oxidation of the cyclic alcohol with 0.3 M nitric acid, concentrated nitric acid and 30% hydrogen peroxide in glacial acetic acid gave a yellow glassy solid which turned purple upon addition of hot alcohol. Ultraviolet spectral scan of aqueous solutions before the alcohol was added showed 266 m\(\mu\) peaks. The hydrogen peroxide oxidation product was washed with acetone; a white crystalline solid was obtained which infrared analysis showed to be the starting material. The acetone again contained the purple fraction. Oxidation of compound II with potassium dichromate and sulfuric acid also gave a
blue-green compound.

Compound II was refluxed with an alcoholic solution of ethyl orthoformate and pyridine for 2 hours to determine if this purple compound was analogous to the trimethincyanine dyes (1, p. 231). Seventy percent of the starting material was recovered which was normal for recrystallization of compound II from alcohol (u.v. peak at 266 m/\mu).

An interesting observation was made when the cyclic alcohol (II) was allowed to react with stannous chloride in aqueous hydrochloric acid. After heating the solution for 3 hours on a steam bath and allowing it to stand overnight, colorless plates formed. These crystals were insoluble in water, acetone, absolute alcohol and ether. However, they dissolved in concentrated hydrochloric acid to give a solution which on u.v. analysis had a 266 m/\mu peak. On neutralizing this strongly acid solution, at pH 2-3, the solution turned purple. Further neutralization gave a white precipitate at pH 12. Analysis of the white crystals in form of carbon-hydrogen gave an ash of 4.5% which indicated a complex was formed.

Various attempts were made to replace the 3-bromo group of compound II with amines. Compound II was refluxed in 95% ethanol with a theoretical amount of
aniline. The solution was observed to turn yellow, red and finally purple. In a second attempt, pyridine was refluxed with compound II. No observable change was noted; therefore methanol was added and then the solution darkened and finally turned purple. The purple-colored crystals were recovered which when washed with acetone lost the purple coloration. Ultraviolet scan and melting point determination indicated the crystals were compound II. Alterations were made on the above techniques by dissolving the amine in acetone and stirring with compound II. This technique gave quantitative recovery of compound II.

2-Hydroxy-3-bromo-1,2,3,4-tetrahydroquinolinizinium bromide crystals were added slowly to ether solution of phenyl magnesium bromide. Compound II reacted vigorously to give a red precipitate which was soluble in methanol and acetone, slightly soluble in carbon tetrachloride and insoluble in water. The red material was washed with ether several times and dissolved in acetone. Evaporation of the acetone solution afforded a red gum which thereafter was not soluble in acetone. The red gum was recrystallized from absolute ethanol to give a red solid which could not be identified at this time. The ether fraction was found to contain biphenyl.
D. Reactions with Nucleophilic Reagents

Compound II was reacted with various basic reagents to determine whether a Hofmann degradation or ring opening to a cyclic amide (29, p. 10539g) would occur. The following discussion refers to Figure 2.

An aqueous solution of ammoniacal silver oxide was prepared by a method outlined in Vogel (31, p. 328). The silver oxide was then added to an aqueous solution of compound II. A tan precipitate formed immediately which was filtered and dissolved in absolute ethanol. In an attempt to prepare a possible hydrochloride salt, anhydrous hydrogen chloride was bubbled into this alcoholic solution. The solution turned red and then slowly turned purple on standing.

In an attempt to form a more stable product of the base reaction of compound II, sodium ethoxide was substituted for silver oxide. Compound II was dissolved in absolute ethanol to which sodium ethoxide was added slowly. A white precipitate of sodium bromide formed leaving a red alcoholic solution. The solution was filtered and alcohol was removed by distillation. Distillation of the residue gave a small quantity of yellow oil having a pleasant ester-like odor. This oil was dissolved in absolute ethanol and treated with hydrogen
chloride. The solution turned blue-green from which white crystals were obtained. Bromination of this yellow liquid in water immediately gave a purple precipitate which turned light brown on further addition of bromine.

Aqueous solutions of compound II were found to give tan precipitates, compound VIII, with various bases. With 10% sodium hydroxide, a precipitate formed immediately; 10% sodium carbonate, a precipitate formed in 5-10 minutes; 10% sodium bicarbonate, precipitation was sluggish and incomplete; and 10% ammonium hydroxide, the precipitation was immediate. The freshly prepared water insoluble precipitate was found to be soluble in acetone, alcohols, chloroform, ether and carbon tetrachloride. Different colors were observed in these various solvents; acetone and alcohol solutions were red, chloroform and carbon tetrachloride were dark brown, and ether gave a light blue fluorescence which turned brown on further concentration. The carbon tetrachloride and ether solutions on exposure to air gave a purple precipitate. The other solutions and tan precipitate turned purple on standing in air. This tan precipitate behaved like a typical amine; it was soluble in acid and insoluble in base and it could be extracted with various non-polar solvents. The hydrochloride salt, compound X, could be precipitated from absolute ether with hydrogen chloride.
Attempted recrystallization from alcohol failed giving only the purple contaminated product. Other attempts at purification also failed for this compound was very labile, turning green immediately in air and finally purple. It was found that this hydrochloride could be stored under high vacuum for a short period of time. Immediate carbon-hydrogen analysis indicated that both the bromine atoms had been removed. Infrared analysis showed peaks in the region for conjugated double bonds, hydroxyl group and nitrogen.

In order to determine if the tan compound (VIII) was a cyclic amide similar to reactions encountered by Sugasawa et al. (29, p. 10539g), compound VIII was refluxed with phosphorus oxychloride for 2 hours. If the cyclic amide was formed the phosphorus oxychloride would expectedly regenerate the quinolizinum cation. However, the purple compound was formed and no indication of a 266 m peak in an ultraviolet scan was seen.

On sublimation of the basic precipitate of compound II a few white crystals were obtained in low yield. A very unique ultraviolet spectra was obtained from a 95% ethanol solution of these crystals. The peaks and fine structure were found to be identical to the u.v. curve published for pyrrocoline (3, p. 589-592). Other diagnostic tests were performed for the pyrrocoline ring
on the tan precipitate (8, p. 624-625). Oxalic fusion gave a purple colored melt; the pine splint test also gave a violet color. The tan compound was dissolved in dilute sulfuric acid and a crystal of sodium iodate added; a dark blue precipitate immediately formed.

Steam distillation of the tan precipitate gave a white emulsion which on ether extraction and evaporation of the ether gave a small residue of a yellow oil. An odor very similar to naphthalene was noted for this compound. However, only a small quantity of the tan precipitate distilled; the remaining tan material could not be identified at this time. This residue was found to have an ultraviolet spectra very similar to pyrrocoline but lacking much of the fine structure.

The tan solid or its solutions readily turned purple in air. The rate of formation of the purple compound (IX) was much faster when air was allowed to bubble into the various solutions of compound VIII. As mentioned before, sodium iodate also gave the purple compound. Nitric acid or potassium permanganate oxidation of compound II first, then treatment with sodium hydroxide gave an impure purple precipitate immediately which had a strong odor like naphthalene. Infrared analysis of the purple compound (IX) indicated conjugated double bonds with no carbonyl absorption. Hydrochloric acid
solution of this purple compound showed broad absorption from 540-580 m/μ and at 228 m/μ. Zinc and hydrochloric acid reduction of the purple compound which had been washed with ether gave a colorless solution with peaks at 300 m/μ, 266 m/μ and 228 m/μ and no 540-580 m/μ peak. This solution again turned purple on standing in the air. Nitric acid oxidation of the purple material gave a brown compound which had properties of an amine. This brown compound could not be isolated in a pure form for it darkened in air rapidly, giving only oils.

In this phase of the study, many of the products of the base reactions of compound II were so unstable that duplication of carbon-hydrogen analysis was not possible. The carbon-hydrogen percentages of the tan precipitate were found to increase with time and the amount of purple contaminant present. Infrared analysis was not entirely reliable because decomposition of the tan product in chloroform or carbon tetrachloride solutions took place in the infrared cells before complete scans could be made. Potassium bromide pellets were made on products immediately after they were prepared and stored under high vacuum. These pellets showed less tendency to decompose and complete scans could be made.
1(α-pyridyl)-3-butene-2-ol: To a dry three neck flask equipped with a dropping funnel, reflux condenser and calcium chloride drying tube and mechanical stirrer, 400 ml of absolute ether was added. Then 6.9 g (1 gram atom) of lithium, which had been pounded to thin sheets with a hammer, was introduced. A few milliliters of a solution containing 79 g (0.5 mole) bromobenzene in 100 ml of ether was added with the dropping funnel until the solution began to reflux. The flask was warmed if necessary to start the reaction, then the remaining bromobenzene was added at a rate sufficient to maintain refluxing. The mixture was stirred until the lithium was in solution. Forty-six grams of 2-picoline was added at a moderate rate to the phenyllithium solution and stirred for 1 hour in an ice bath. To the blood-red picolyllithium cooled in a salt-ice mixture to 0°C or lower, 35 g (0.63 mole) of acrolein in 50 ml of ether was added slowly. The yellow solid was then hydrolyzed with 200 ml of water, stirred for 30 minutes to 1 hour. The ether layer was separated and the aqueous layer extracted several times with fresh ether. The ether extracts were combined and the ether distilled. The oil was then transferred to a vacuum distillation apparatus.
The oil was distilled at atmospheric pressure until a temperature of nearly 100°C was obtained at which time a 1 mm pressure was secured with a high vacuum pump. A yellow oil was collected at 70-80°C/1 mm which crystallized on standing. Rapid distillation was found to minimize polymerization. The yellow crystals were washed with light petroleum ether to give white crystals, m.p. 40°C, yield 24-38%.

Ultraviolet peak at 260 m\(\mu\) in water.

2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide: In a 500 ml Erlenmeyer flask equipped with a magnetic stirrer and motor, 14.9 g (0.1 mole) of compound I was dissolved in 200-250 ml of carbon tetrachloride. From a separatory funnel a solution of 15.9 g (0.1 mole) of bromine was added slowly over 1-1½ hours with stirring to the above solution of compound I. A red-orange solid formed on the walls of the flask. The solvent was decanted; the solid washed with acetone and recrystallized from methanol. Norite was added if necessary to decolorize the product, m.p. 180-181°C, yield 65-70%.

**Anal.** Cal'd. for \(C_{9}H_{11}NOBr_{2}\): C, 34.9; H, 3.56.

**Found:** C, 34.98; H, 3.70.

2-hydroxy-3-iodo-1,2,3,4-tetrahydroquinolizinium iodide: One gram (0.00067 mole) of compound I was
dissolved in 50 ml of carbon tetrachloride in a flask equipped with magnetic stirrer and motor. A carbon tetrachloride solution of 1.7 g (0.00067 mole) iodine in 100 ml of solvent was added slowly to the above solution with stirring. A dark red gum precipitated which was washed with a small quantity of acetone and recrystallized from 95% ethanol and Norite. Yield of crude yellow crystals was 0.3 g (11%), m.p. 184-186°C.

Ultraviolet peak at 266 m\(\mu\) and 226 m\(\mu\) in water.

**Second method:** One gram of compound I was dissolved in 20-25 ml of water and 5 ml of 30% hydrogen peroxide added in a 50 ml Erlenmeyer flask equipped with magnetic stirrer. One ml of 47% hydriodic acid was added immediately and the mixture stirred. Iodine was liberated, then on further stirring and heating the iodine disappeared and aqueous solution was slightly purple colored. The aqueous solution was allowed to stand after which wite plates were observed. The white crystals were filtered and washed with acetone, then crystallized from methanol several times with filtering. The aqueous mother liquor was concentrated to give more white crystals, m.p. 195-196°C.

Ultraviolet peak at 266 m\(\mu\) and 226 m\(\mu\).

**Anal. Cal'd. for C\(_9\)H\(_{11}\)NO\(_2\):** C, 26.82; H, 2.75.

**Found:** C, 26.44; H, 2.93.
2-iodo-3-bromo-1,2,3,4-tetrahydroquinolinizinium bromide: One-half gram of compound II was refluxed with 5 ml of 47% hydriodic acid for 2 hours. The hydriodic acid was removed under vacuum leaving a glassy yellow solid which crystallized on standing. The crude yellow crystals were washed with acetone which removed the yellow coloration. The remaining solid was recrystallized from methanol to give a white crystalline compound, m.p. 184-185°C.

Ultraviolet peak at 228 m/λ.

Anal. Cal'd. for C_{9}H_{10}NIBr_{2}: C, 25.8; H, 2.41.
Found: C, 25.33; H, 2.62.

2-hydroxy-3-bromoquinolizidine hydrogen bromide:
Five grams of compound II was dissolved in 150 ml of absolute ethanol and placed in a Paar hydrogenation apparatus. Platinum oxide (0.5 g) (Adams catalyst) was added. The mixture was hydrogenated for 2 hours. Initial pressure was 40 psi. When the hydrogen ceased to be absorbed, the catalyst was removed by filtration, the filtrate concentrated and allowed to crystallize on ice mixture. Crystals were filtered and dried. Another crop of crystals could be obtained by further evaporation of the mother liquor. Yield 5.1 g, nearly quantitative; m.p. slow decomposition, 208-210°C.
3-bromo-Δ⁴-dehydroquinolizidine hydrogen bromide:
One gram of compound IV was dissolved in 5-7 ml of acetic anhydride by heating nearly to boiling. The solution was cooled slightly and 1 drop of concentrated sulfuric acid added. The mixture was heated under reflux apparatus protected from the atmosphere for 5-10 minutes. The excess acetic anhydride was removed by evaporation under vacuum. A slightly purple residue remained which was then washed with 5-10 ml of ethyl acetate and 5 ml of acetone. The white solid could be recrystallized from absolute ethanol to which a small quantity of absolute ether was added. The metallic-like crystals were filtered and washed with acetone, m.p. 205°C sublimes.


2-acetoxy-3-bromoquinolizidine hydrogen bromide:
One gram of compound IV was dissolved in 10 ml of acetic anhydride by heating on a steam bath. The mixture was allowed to stand overnight at room temperature, protected from the atmosphere. The acetic anhydride was evaporated under vacuum and the remaining pink crystals were recrystallized from absolute ethanol. The pink crystals were washed with acetone and again recrystallized from 100% ethanol, m.p. 215°C decomposes.
Anal. Cal'd. for $C_{11}H_{19}NO_2Br_2$: C, 37.0; H, 5.36.
Found: C, 37.07; H, 5.41.

Reaction of 2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide with sodium hydroxide: (a) One gram of 2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide was dissolved in 30 ml of distilled water. A 20% solution of sodium hydroxide was added slowly until no more precipitate formed. The precipitate was immediately transferred to a separatory funnel and extracted with 50 ml portions of reagent grade carbon tetrachloride several times.

The combined extracts were placed in a vacuum distillation apparatus and the carbon tetrachloride removed by vacuum distillation. The remaining tan solid was immediately dissolved in 30-50 ml of absolute ether and anhydrous hydrogen chloride added until no more precipitate formed. The ether was decanted from the light tan solid after which the solid was washed several times with anhydrous acetone. On contact with the atmosphere, this tan solid immediately turns green and eventually purple. However, the solid showed little tendency to react under acetone or under high vacuum in a desiccator. Attempted recrystallizations from alcohol and other solvents gave only purple solutions.
Evaporation of the acetone under vacuum gave a tan solid which was stored under vacuum until analysis could be made. A potassium bromide pellet was made for infrared analysis and a scan immediately run.

**Anal.** Cal’d. for $C_9H_{10}NOCl$: C, 58.87; H, 5.49. Found: C, 59.25; H, 5.96.

(b) The carbon tetrachloride extract from part (a) on standing in the atmosphere gave a purple precipitate. The purple compound was filtered and washed with several 10 ml portions of fresh carbon tetrachloride followed by absolute ether. The unreacted tan compound remained in solution, m.p. 230°C decomposed.

Ultraviolet in 0.1 N hydrochloric acid gave peaks at 540-580 m/$\mu$ and 232-228 m/$\mu$.

**Anal.** Found: C, 66.54; H, 5.92.

(c) The tan precipitate from aqueous sodium hydroxide, part (a), was filtered and washed with a large volume of distilled water. The solid was dissolved in absolute methanol then filtered again. The alcohol was evaporated and the procedure repeated using acetone as a solvent. The tan solid from the evaporation of the acetone was mixed with 1 g of oxalic acid in a porcelain dish. The mixture was fused giving a violet purple melt. A second portion of the tan solid was dissolved in 3 M sulfuric acid and a small crystal of
sodium iodate added; a dark purple precipitate immediately formed. A fresh sample of the tan compound was dissolved in absolute ethanol and a u.v. scan gave peaks at 350-360 m/μ, 293 m/μ, 286 m/μ and 236 m/μ; m.p. 120-125°C decomposes. Varying analyses in the form of carbon and hydrogen were obtained.

**Anal. Found:**
- C, 74.54; H, 5.16.
- C, 78.89; H, 5.80.
- C, 76.01; H, 5.75.
- C, 80.28; H, 5.96.

(d) One gram of the tan precipitate, freshly precipitated from base, was placed in a sublimation tube. A vacuum of 1 mm of mercury was secured and the temperature increased to 120-130°C. A white solid coated the upper portion of the tube after 5-10 minutes. Further sublimation gave no more product. The white solid was dissolved in absolute ethanol and u.v. analysis gave peaks at 350-360, 298, 293, 286, 280, 272 and 236 m/μ. This white compound turned to light brown oil on standing in contact with the atmosphere.
SUMMARY AND CONCLUSIONS

l(α-Pyridyl)-3-butene-2-ol was prepared by the condensation of 2-picolyllithium with acrolein as described by Wischmann (33, p. 14-15). This compound was found to have a maximum absorption peak at 260 m/.μ.

2-Hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide was prepared by the bromination of l(α-pyridyl)-3-butene-2-ol (33, p. 20-21). This cyclic alcohol (II) was found not to obey Beer's Law accurately between 1-10 ppm, suggesting that an equilibrium might exist in aqueous solutions.

Cyclization of l(α-pyridyl)-3-butene-2-ol was also found to occur with iodine to form 2-hydroxy-3-iodo-1,2,3,4-tetrahydroquinolizinum iodide. Better yields were obtained if the iodine was generated in the reaction mixture by oxidation of the iodide ion with hydrogen peroxide. Proof of structure was on the basis of: (1) maximum absorbance at 266 m/μ, (2) carbon-hydrogen analysis and (3) infrared absorption spectra similar to compound II.

When compound II was allowed to react with concentrated hydriodic acid, displacement of the 2-hydroxy group by iodine was thought to occur forming 2-iodo-3-bromo-1,2,3,4-tetrahydroquinolizinum bromide. This
structure was assigned on the basis of (1) infrared absorption spectra similar to compounds II and III, (2) carbon-hydrogen analysis.

Compound II was hydrogenated in the presence of platinum oxide to 2-hydroxy-3-bromoquinolizidine hydrogen bromide (33, p. 21-22). This compound IV was dehydrated with acetic anhydride and sulfuric acid to 3-bromo-Δ'-dehydroquinolizidine hydrogen bromide. The conclusion that dehydration had occurred was based on carbon-hydrogen analysis and that compound IV decolorized bromine water.

Compound IV was reacted with acetic anhydride alone to give 2-acetoxy-3-bromoquinolizidine hydrogen bromide (V). A strong peak at 1740-1730 cm⁻¹, characteristic of an ester carbonyl group, was found in the infrared absorption spectra of compound V. Carbon-hydrogen analysis also indicated the acetate ester was formed.

Various reactions were attempted for placing different substituents at the three and/or four positions of 2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizininium bromide. Attempted preparation of 3-bromo-3,4-dihydroquinolizininium bromide by dehydration of compound II with acetic anhydride and sulfuric acid gave a purple compound for which a structure could not be assigned at this time. The expected dehydrated compound was thought not to be
formed since no bathochromic shift from 266 m\(\mu\) to about 300 m\(\mu\) was observed. Carbon-hydrogen analysis also indicated that dehydration had not occurred.

Other reactions were attempted; however colored compounds were also obtained. It was evident that reactions other than those expected were occurring and the reaction of compound II with base was pursued. A tan compound (VIII) was obtained which was very labile; this compound turned purple in contact with the atmosphere. Attempted purification of this compound failed due to its unstable nature. However, sublimation of compound VIII gave a poor yield of white crystals which were found to give an absorption spectra identical to pyrrocoline. This evidence and qualitative tests indicated that the five membered ring could be formed from compound II. Compound VIII was found to behave like a typical amine, soluble in acid and non-polar solvents and insoluble in base and water. The hydrochloride could be precipitated from anhydrous ether.

The hydrochloride salt of compound VIII could be stored under vacuum for a short period of time and potassium bromide pellets could be made for infrared analysis. The infrared absorption spectra of compound X showed peaks for conjugated double bonds, hydroxyl group and nitrogen. However further evidence is necessary
before a structure can be drawn for this compound.

Oxidation of compound VIII or its hydrochloride salt (X) with air or sodium iodate gave a purple solid with properties identical to the other purple products obtained in this research. Compound IX showed maximum absorption at 228 m/\( \mu \) and 540-580 m/\( \mu \). This purple compound precipitated from ether and carbon tetrachloride solutions of compound VIII and could be obtained by sodium iodate oxidation of acid salts of compound VIII. Zinc and hydrochloric acid reduction of the purple compound IX was found to give a colorless solution with maximum absorption at 300 m/\( \mu \), 266 m/\( \mu \) and 228 m/\( \mu \). This colorless solution again turned purple in contact with the atmosphere. The possible existence of the quinolizine ring in these products cannot be ignored since the 266 m/\( \mu \) absorption peak, thought to be characteristic of the tetrahydroquinolizinium ion (4, p. 1832-1836) reappeared on acidic reduction of the purple compound. Diels et al. reported the hydrogenation in acid solution of tetramethyl quinolizinetetracarboxylate to yield the tetrahydro derivative (13, p. 103-150; 24, p. 1007). Similar results were also obtained by Boekelheide et al., who reported the reduction of 4-ketoquinolizine under acid conditions to give the tetrahydro compound (5, p. 3681-3682).


APPENDIX
APPARATUS USED

1. All melting points are uncorrected.

2. Ultraviolet data were obtained with a Beckman D.B. Spectrophotometer, O.S.U. #77051; #5856.
   (a) Cells used were 1 cm quartz cells manufactured by Beckman.

3. Infrared data were obtained from a Perkin-Elmer Model 21 infrared spectrophotometer.
   (a) Potassium bromide pellets were made of all samples analyzed by infrared.
FIGURE 4.
Plot of Absorbance versus Concentration for 2-Hydroxy-3-bromo-1,2,3,4-tetrahydroquinolinolizinium Bromide

![Graph showing a linear relationship between absorbance and concentration. The x-axis represents concentration in ppm ranging from 0 to 10, and the y-axis represents absorbance ranging from 0 to 0.2.](image-url)
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### TABLE II

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