yield the unchanged compound (m.p. 240–250°) soluble in dilute alkali.

(ii) A mixture of the quinoline (0.2 g.), phosphorus oxychloride (4 c.c.), and phosphorus pentachloride (0.3 g.) was kept at 120° for 1.5 hr., cooled, and poured onto ice. After making ammoniacal, the tan-colored product was removed and triturated with dilute alkali when it all dissolved. Acidification of the alkaline solution with acetic acid gave unchanged material m.p. 215–248°; colorless needles from dilute ethanol, m.p. and m.m.p. 250–251°.

2-Phenyl-6-methyl-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5, X = 6-CH_3) formed as colorless feathery crystals, m.p. 263–264° (lit.,[1,2] m.p. 255°; 263°).

Anal. Calcd. for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 5.17%.

2-Phenyl-8-methyl-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5, X = 8-CH_3) formed colorless needles, m.p. 211–212° (lit.[1] m.p. 215°) which gave a claret coloration with alcoholic ferric chloride. The same base resulted on employment of ethyl β-amino-α-(*N*-*o*-tolylbenzimidoyl)crotonate (Va. R = C_6H_5, X = 2-CH_3) in the reaction.

Anal. Calcd. for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 5.15%.

The quinoline was recovered unchanged after warming with phosphorus oxychloride on the water bath for 1 hr.

The *pyrazole* was obtained as colorless silky needles, m.p. 140–141°, insoluble in hot 10% sodium hydroxide.

Anal. Calcd. for $C_{24}H_{19}N_3$: N, 12.03. Found: N, 12.13%.

2-Phenyl-6,8-dimethyl-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5, X = 6,8-diCH_3). The methyl and ethyl crotonates (V and Va; R = C_6H_5, X = 2,4-diCH_3) both yielded the same quinoline as colorless crystals, m.p. 216–217°, which gave a claret coloration with ferric chloride. The base was recovered unchanged after heating with phosphorus oxychloride on the water-bath for 1 hr.

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84. Found: C, 78.12; H, 5.63%.

The *pyrazole* was obtained as colorless feathery crystals, m.p. 160–161°.

Anal. Calcd. for $C_{25}H_{21}N_3$: N, 11.57. Found: N, 11.70%.

2-Phenyl-6-methoxy-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5, X = 6-OCH_3). The crude product from methyl β-amino-α-(*N*-*p*-anisylbenzimidoyl)crotonate (V. R = C_6H_5, X = 4-OCH_3) was recrystallized twice from dilute ethanol (charcoal) and obtained as colorless plates m.p. 290–292° (lit,[1] m.p. 270°).

Anal. Calcd. for $C_{18}H_{15}NO_3$: N, 4.78. Found: N, 4.99%. The *pyrazole* crystallized from dilute ethanol as colorless needles, m.p. 192–194°.

2-o-Tolyl-3-acetyl-4-hydroxyquinoline (II. R = *o*-$C_6H_4CH_3$, X = H). Methyl β-amino-α-(*N*-phenyl-*o*-toluimidoyl)crotonate (V. R = *o*-$C_6H_4CH_3$, X = H) yielded the quinoline as colorless crystals m.p. 256–257° (lit,[2] m.p. 251–252°) which showed no coloration with ferric chloride.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.05. Found: C, 77.50; H, 5.44; N, 5.20%.

2-p-Tolyl-3-acetyl-4-hydroxyquinoline (II. R = *p*-$C_6H_4CH_3$, X = H). The base was obtained as colorless shining plates m.p. 239–240° (lit,[2] not melted at 297°) and showed no coloration with ferric chloride.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.05. Found: C, 77.37; H, 5.54; N, 5.10%.

The *dinitrophenylhydrazone* had m.p. 284–286° dec. (lit,[2] not melted at 300°). The *pyrazole*, colorless feathery needles, m.p. 185°, was insoluble in alkali.

Anal. Calcd. for $C_{24}H_{19}N_3$: N, 12.03. Found: N, 12.11%.

Action of polyphosphoric acid on methyl β-amino-α-(N-methylbenzimidoyl)crotonate (VI. X = Me). The ester (1 g.) and polyphosphoric acid (6 g.) were stirred and heated at 170° for 15 min. during which period effervescence occurred. After cooling somewhat, water was added to the orange solution when benzoylacetone (0.2 g.; m.p. 52–56°) separated; colorless crystals from dilute ethanol, m.p. and m.m.p. with authentic benzoylacetone 56–57°. The acid filtrate on making alkaline deposited a small amount of a yellow base (m.p. 135–158°, soluble in dilute acid to give a yellow solution, and not further investigated) and contained acetophenone. Methyl β-amino-α-(*N*-ethylbenzimidoyl)-crotonate (VI. X = C_2H_5) similarly yielded benzoylacetone, some yellow base and acetophenone.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Quinolizinium Salts. I. Synthesis of 2-Hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium Bromide

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A two-step method for preparing tetrahydroquinolizinium salts has been devised. This method involves the condensation of certain α,β-unsaturated aldehydes with 2-picolyllithium and subsequent cyclization by the addition of bromine to the unsaturated alcohol. The alcohol formed in the initial step does not undergo the typical allylic rearrangement seen in many α,β-unsaturated alcohols in acidic solution. This method overcomes many of the difficulties involved in former syntheses and makes possible the preparation of a number of potentially useful therapeutic agents.

The hydroxyoctahydroquinolizines and hydroxytetrahydroquinolizinium compounds are of potential therapeutic value because of their similarity in structure to other therapeutic agents and because the octahydroquinolizine ring is present in a number of physiologically active alkaloids such as the Lupine, Sparteine, Reserpine, Yohimbine, Veratrine, and Berberine alkaloids. To date only a few references to these compounds having physiological activity have been reported. Soine[3] has prepared

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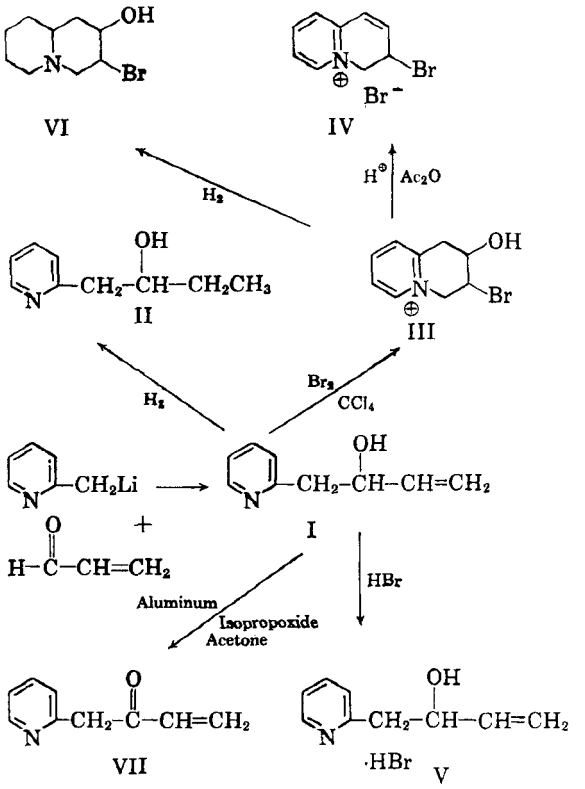
esters of the 1-, 2- and 3-hydroxyoctahydroquinolizines which had some spasmolytic activity and the quaternary salts also had ganglionic blocking activity. Other esters, ethers, and amine derivatives of the 2-hydroxyoctahydroquinolizines have been prepared which had a variety of different physiological activities, none of which was particularly significant.[4-6] Therefore, it was decided to prepare the quinolizinium analogs to determine their activity.

Previous workers have synthesized the quinolizinium ring by a variety of methods. Boekelheide[7] first synthesized the 2-hydroxy compound using a procedure analogous to one used by Beaman.[8] This method consisted of condensing β-ethoxypropionaldehyde with 2-picolyllithium and subsequent cyclization of the compound by cleaving the ether with hydriodic acid. This method has the disadvantage that pure starting materials are difficult to obtain, and cleavage of the ether many times destroys the product.

Glover and Jones[9] have prepared several ketoquinolizinium compounds by the condensation of 2-cyanopyridine with the appropriate Grignard reagent of a β-halogenated ether and subsequent cleavage of the ether to form the cyclized product. Here again, starting materials are not easily obtained, and it is very difficult to reduce the ketone to the alcohol.

Richards and Stevens[10] have prepared 3-hydroxyquinolizinium derivatives by condensation of various β-ketoaldehydeacetals and subsequent cyclization by hydrolysis of the acetal. This method produces impure products in poor yields and starting materials are not easily prepared.

Our procedure involves the condensation of readily available acrolein or other α,β-unsaturated aldehydes with 2-picolyllithium and subsequent cyclization of the amino alcohol (I) by the addition of bromine to the double bond to form the 2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide (III). Other workers have reported reactions similar to the first step with picolyllithium[11] and other organolithium compounds such as isobutenyllithium[12] and *cis*-propenyllithium,[13] but



this is the first cyclization reaction of this type reported.

The initial condensation, after acid hydrolysis of the lithium intermediate, produced a yellow oil which crystallized after standing. Braude[12-13] has reported the allylic rearrangement of similar compounds under acidic conditions; therefore, it was thought that the acid hydrolysis of the condensation product had caused the secondary alcohol to rearrange to the more stable primary alcohol, producing the change in physical properties. However, the same product was obtained when a procedure was used in which no acid was involved in the reaction. Further studies such as the reduction of the isolated double bond to form a known compound (II), ozonolysis and infrared data indicated that the secondary alcohol remained unchanged.

This is surprising since it is known that most α,β-unsaturated secondary alcohols readily rearrange in acidic solution, to form the primary alcohol. As the rearrangement depends on the initial formation of a carbonium ion, it is postulated that the presence of the basic nitrogen in the ring prevents carbonium ion formation and the subsequent rearrangement. Further studies are being performed to determine whether this postulation is correct.

The cyclization reaction is also rather surprising, as Glover and Jones[9] reported that it was necessary to treat an analogous δ-alkylbromopyridine with

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boiling chloroform to cause cyclization to take place. As our cyclization step involved no such application of heat, there is no danger of decomposed products.

Dehydration, according to the procedure of Boekelheide[7] produced a crystalline purple compound which was not further characterized but which gave the proper carbon-hydrogen analysis for 3-bromo-3,4-dihydroquinolizinium bromide (IV). When this compound was placed in a basic solution, it became colorless and the purple color was regenerated with acid. The same type of product was obtained if the alcohol (III) was oxidized to the ketone. This phenomenon may be compared to the analogous reactions of the acridizinium ion.[14] Further studies are being performed to determine the exact nature of the color reaction.

Preliminary pharmacological studies indicate that hydroxybromoquinolizinium bromide has hypotensive properties. The position of the bromine in the ring should make possible the further synthesis of many potentially active compounds. In addition, the reaction could also be used as a method of preparing tricyclic-*N*-bridgehead rings, bicyclic rings, etc., from simpler compounds. It is also a better method for preparing the octahydroquinolizinium compounds since fewer steps are involved.

EXPERIMENTAL

1-(α-Pyridyl)-3-butene-2-ol (I) was prepared following the procedure used by Walter[15] for preparing 1-(α-pyridyl)-2-propanol. From 35 g. (0.63 mole) of acrolein there was obtained 20 g. (27%) of a yellow oil, b.p. 76–80° at 1 mm. Using a slightly different hydrolysis procedure—*i.e.*, 200 ml. of water—instead of the hydrochloric acid–water mixture, 25 g. (34%) was obtained. After cooling, the oil crystallized and after recrystallization from petroleum ether, white crystals were obtained, m.p. 36°.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.4; H, 7.37. Found: C, 72.2; H, 7.40.

Two grams of the purified alcohol was added to 3 ml. of phenyl isocyanate. The reaction mixture was warmed on a steam bath for 10 min. and then cooled to 0°. The crystalline product was then filtered and recrystallized from carbon tetrachloride. A light tan compound resulted, m.p. 104–105°.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 71.6; H, 5.95. Found: C, 71.8; H, 5.91.

Ozonolysis of the alcohol according to the procedure of Long[16] and subsequent preparation of the dimedone derivative yielded a white crystalline product, m.p. 190°. The reported[18] melting point of the dimedone derivative of formaldehyde is 189°.

1-(α-Pyridyl)-2-butanol (II). In a hydrogenation flask, 0.5 g. of 1-(α-pyridyl)-3-buten-2-ol was placed along with 75 ml. of absolute ethyl alcohol and 0.5 g. of platinum oxide. After hydrogenation for 3 hr. at 35 lbs. per sq. in., the catalyst was removed by filtration and the ethyl alcohol evaporated under reduced pressure. A light yellow oil was obtained which distilled at 125–130°, 18 mm. pressure. The reported value for this compound is 127–129°.[17]

One gram of the purified alcohol was heated on a steam bath with 2 g. of phenyl isocyanate for 10 to 15 min. The product obtained was then triturated with 10 ml. of carbon tetrachloride and filtered. The residue was recrystallized from acetone and water yielding a fine white powder, m.p. 235°.

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.1; H, 6.66. Found: C, 71.1; H, 6.58.

1-(α-Pyridyl)-3-butene-2-one (VII). Five grams of 1-(α-pyridyl)-3-butene-2-ol was dissolved in a flask containing an excess of acetone. Seven grams of aluminum isopropoxide was added and the mixture refluxed overnight. The aluminum isopropoxide was removed by filtration and the acetone was evaporated leaving a dark yellow oil. After purification by distillation, a light yellow oil was isolated with a sharp odor resembling that of acrolein, b.p. 190–200° atmospheric pressure.

Anal. Calcd. for C_9H_9NO: C, 73.4; H, 6.12. Found: C, 73.1; H, 6.21.

Using the procedure of Shriner and Fuson,[18] a 2,4-dinitrophenylhydrazone was prepared, m.p. 87–89°.

1-(α-Pyridyl)-3-butene-2-ol hydrogen bromide (V). Ten grams of 1-(α-pyridyl)-3-butene-2-ol was dissolved in 200 ml. of anhydrous benzene and the mixture cooled to 0°. Hydrogen bromide gas (tank) was then passed through the mixture for 2 hr. A white gummy product precipitated out of solution which was removed by filtration or decantation of the benzene. The resulting gum was recrystallized from acetone several times yielding 4.5 g. (29%) of large white needles, m.p. 97°.

Anal. Calcd. for $C_9H_{12}NOBr$: C, 46.8; H, 5.22; N, 6.10. Found: C, 46.9; H, 5.22; N, 6.35.

Ozonolysis of the salt yielded an aldehyde which formed a dimedone derivative with a melting point corresponding to that of the dimedone derivative of formaldehyde.

2-Hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide (III): Two grams of 1-(α-pyridyl)-3-butene-2-ol was dissolved in 50 ml. of carbon tetrachloride and 2.2 g. of bromine in 20 ml. of carbon tetrachloride added dropwise. A slight warming was noticed as the solution turned a cloudy yellow color and a residue formed on the sides of the flask. After all the bromine was added, the carbon tetrachloride was removed by decantation. The residue was recrystallized from methanol yielding 3 g. (70%) of a white crystalline compound, m.p. 178–179°.

Anal. Calcd. for $C_9H_{11}NOBr_2$: C, 34.9; H, 3.56. Found: C, 34.7; H, 3.66.

3-Bromo-3,4-dihydroquinolizinium bromide (IV) was prepared using the method of Boekelheide and Gall[7] to prepare 3,4-dihydroquinolizinium iodide. From 1 g. of 2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide, 4 ml. of acetic anhydride and 1 drop of concd. sulfuric acid, there was obtained a dark purple precipitate. This yielded a crystalline purple product from ethyl acetate and alcohol, m.p. 169–171°.

Anal. Calcd. for $C_9H_9NBr_2$: C, 37.1; H, 3.09. Found: C, 37.2; H, 3.25.

2-Hydroxy-3-bromo-octahydroquinolizine (VI). A mixture of 500 mg. of 2-hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide, 20 ml. of ethanol, and 50 mg. of Adams catalyst was subjected to hydrogenation at room temperature and atmospheric pressure. Three and a half moles of hydrogen were absorbed in 3 hr. The solution was filtered to remove the catalyst and the ethanol evaporated to a volume of about 5 to 10 cc. After cooling, a white crystalline compound precipitated, which after recrystallization yielded a white powder, m.p. gradual decomposition above 208°.

Anal. Calcd. for $C_9H_{17}NOBr_2$: C, 34.3; H, 5.40. Found: C, 34.4; H, 5.38.

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