REACTIONS OF THE CONDENSATES OF PICOLYLLITHIUM AND ACROLEIN AND METHACROLEIN

by

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REACTIONS OF THE CONDENSATES OF PICOLYLLITHIUM AND ACROLEIN AND METHACROLEIN

The purpose of this investigation was to study the addition and substitution reactions of the condensate of 2-picoline with certain unsaturated aldehydes. Such derivatives should show structural similarities with some of the naturally occurring alkaloids, notably those of the lupin group. As such, these compounds might be of some pharmacological interest and could be submitted for study with regard to physiological activity.

The initial condensation products of 2-picoline with α, β-unsaturated aldehydes are unsaturated alcohols with an allylic structure. The first studies of such unsaturated alcohols were begun by Braude and Timmons (8). Their investigations were started in an effort to find a suitable reagent for alkenylations. Grignard reagents have been used successfully for alkylations, arylations, and for alkynylations but had not proved satisfactory for alkenylations. isoButene had shown some reactivity as a Grignard reagent in alkenylations but the yields and the reactions were unsatisfactory. As a consequence of the slight reactivity shown by isobutene it was chosen as the first substance to examine with regard to its alkenylating properties when used if coupled with lithium.

Using the same procedure as was used in preparing styryllithium Braude and Timmons (8) succeeded in preparing isobutenyllithium. They treated isobutenyl bromide with lithium in an etheral solution. The lithium alkenyl, when treated with CO_2, formed the lithium salt of the unsaturated acid.

$$Me_2C{=}CHLi + CO_2 \text{ -------- } \underset{\text{I}}{Me_2C{=}CHCOOLi}$$

Isolated in addition were di(isobutenyl) ketone, formed by the condensation of the alkenyllithium with the lithium salt of the acid, and 1,1,4,4-tetramethyl-1,3-butadiene, the product of the condensation of isobutenyllithium with unreacted isobutenyl bromide.

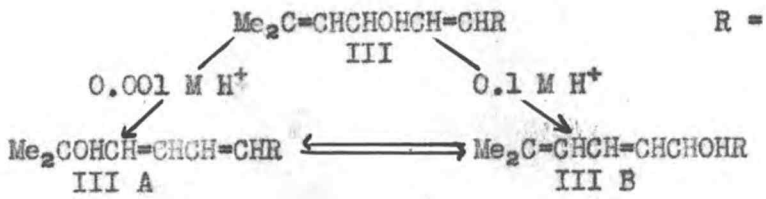
Benzaldehyde was successfully condensed with the isobutenyllithium to form the expected unsaturated alcohol.

$$Me_2C{=}CHLi + C_6H_5CHO \text{ -------- } \underset{\text{II}}{C_6H_5CHOHCH{=}CMe_2}$$

This unsaturated alcohol, when treated with dilute hydrochloric acid, underwent an oxotropic rearrangement in which an isomeric allylic alcohol was formed (8, 9).

$$\underset{\text{II}}{C_6H_5CHOHCH{=}CMe_2} \xrightarrow{HCl} \underset{\text{II A}}{C_6H_5CH{=}CHCOHMe_2}$$

isoButenyllithium was used in further studies of Braude and Timmons (9) to form condensation products with acrolein and with crotonaldehyde. Here, too, the expected carbinols were isolated, and again, in the presence of dilute hydrochloric acid, the oxotropic rearrangement was observed. In the presence of 0.001 M acid the hydroxyl group shifted completely and irreversibly to the more highly substituted side. When 0.1 M acid was employed an equilibrium mixture of equimolar quantities of two isomers was obtained.



Braude and Coles (5) have prepared cyclohexenyllithium and condensed it with acrolein and crotonaldehyde, forming the carbinols in yields of 45% and 60% respectively. They observed that the oxotropic rearrangement took place with these carbinols also. They have also investigated propenyllithium and its condensation products (6).

Braude and Forbes (7) have studied the reactions and oxotropic rearrangements of cyclopentenyllithium coupled with various unsaturated aldehydes.

The use of picoline as a condensing agent with aldehydes has been known for many years. In 1890 Matzdorf (20) heated 2-picoline with propionaldehyde, obtaining the condensation product α-picolyl-ethylalkine.

$$C_5H_4NCH_3 + CH_3CH_2CHO \text{ -------- } \underset{\text{IV}}{C_5H_4NCH_2CHOHCH_2CH_3}$$

A modification of Matzdorf's procedure enabled Loeffler and Stietzel (18) to condense 4-picoline with formaldehyde, forming γ-picolylalkine.

Spaeth and co-workers (26) heated equimolar quantities of cinnamaldehyde with 2-methyl-, 4-methyl-, and 2,5-dimethylpyridine, obtaining in small yields mixtures of the condensation products, butenols, with the dehydration products, butadienes.

$$C_6H_5CH{=}CHCHO + R\text{-}Me \longrightarrow C_6H_5CH{=}CHCHOHCH_2R \quad (V) + C_6H_5CH{=}CHCH{=}CHR \quad (VI)$$

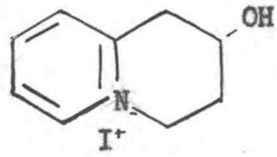
R = 2-pyridyl, 4-pyridyl, or 5-methyl-2-pyridyl

More recently Arens and co-workers (1) have condensed 2-methyl- and 2,4-dimethylpyridyllithium with β-ionone, and 2-methylpyridyllithium with crotonaldehyde. Upon hydrolysis the expected allyl alcohols were formed in moderate yields.

$$C_5H_4NCH_2Li + CH_3CH{=}CHCHO \longrightarrow C_5H_4NCH_2CHOHCH{=}CHCH_3 \quad (VII)$$

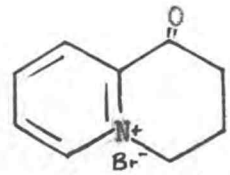
Quinolizinium salts, unsaturated compounds corresponding to quinolizidine, a saturated member of the lupin alkaloids, have recently been investigated extensively. Boekelheide and Gall (2) condensed picolyllithium with β-ethoxypropionaldehyde as the first step in their preparation of quinolizinium derivaties. The intermediate product was cyclized by treating it with hydroiodic acid, followed by neutralization with alkali to give the cyclic ammonium iodide.

$$C_5H_4NCH_2Li + EtOCH_2CH_2CHO \longrightarrow C_5H_4NCH_2CHOHCH_2CH_2OEt \quad (VIII)$$

VIII $\xrightarrow[2.\ \text{Alkali}]{1.\ \text{HI}}$ 

IX

Glover and Jones (12) condensed 2-cyanopyridine with 3-ethoxy-propylmagnesium bromide to form 2- γ-ethoxy-butyrylpyridine. This was treated with boiling aqueous HBr and the intermediate bromoketone was cyclized in boiling chloroform to yield 1,2,3,4-tetrahydro-1-oxo-quinolizinium bromide.

$C_5H_4NCOCH_2CH_2OEt$ —(1. HBr, 2. $CHCl_3$)→  X

Glover and Jones (13), by proper choice of the aliphatic precursor, have prepared compounds substituted in the 2-,3-, or 4-position.

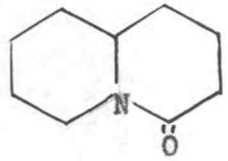
Nesmeyanov and Rubinskaya (22) have prepared quinolizinium compounds substituted in the 2- position by condensing 2-picolyl-lithium with acetoacetaldyhyde dimethylacetal, then treating the resulting precipitate with concentrated HBr.

Substitution in the 1- position of quinolizinium compounds was effected by condensing 2-acetylpyridine with 3-ethoxy-propyl-magnesium bromide (14). The condensation product was then cyclized by refluxing in aqueous HBr.

Richards and Stevens (24) started with β-oxo-aldehydes or ketones and converted them to monoacetals and/or enol ethers. These were then treated with picolyllithium. The resulting condensates were cyclized by refluxing with alcoholic picric acid, forming the corresponding quinolizinium picrates.

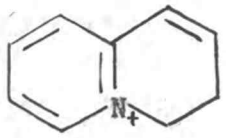
Doering and Weil (11), using a different method for cyclization of quinolizinium derivatives, succeeded in cyclizing 4-(2-piperidyl)-

butanoic acid by heating it in a molecular still under reduced pressure. They recovered α-nor lupinone contaminated with the starting material.

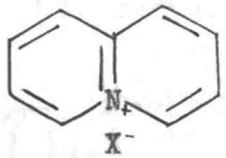
$C_5H_9NCH_2CH_2CH_2COOH$ ——— 

XI

Cyclic alcohols such as IX and cyclic ketones such as X can be dehydrated by heating with boiling acetic anhydride containing a drop of sulfuric acid (2,12). In this manner it is possible to prepare partially unsaturated rings and completely aromatic systems.

IX + $(CH_3CO)_2O$ + H^+ ——— 

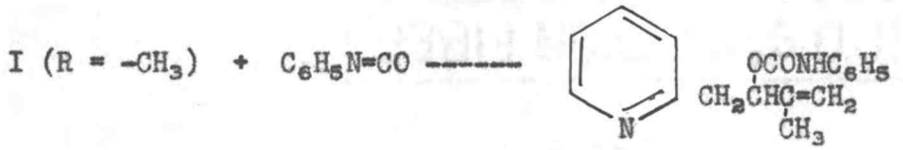
X^-

X + $(CH_3CO)_2O$ + H^+ $\triangleq$——— 

X^-

Flow Sheet
of Compounds Prepared

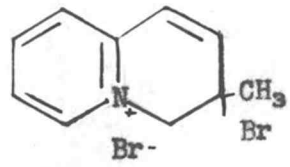
I



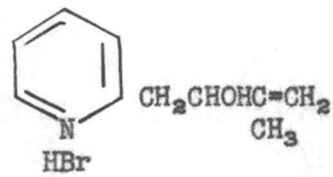
II

III A (R = $-CH_3$, R' = C_6H_5)
III B (R = R' = $-CH_3$)
III C (R = $-H$, R' = $-C_6H_5$)

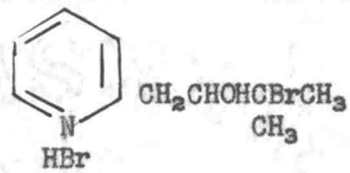
IV

IV + $(CH_3CO)_2O$ ——————— 

V

I (R = $-CH_3$) + HBr ——————— 

VI

VI + HBr ——————— 

VII

VI + Br_2 ———————

VIII

IX

X

Discussion

The condensation of some unsaturated aldehydes with lithium alkenyls has been reported by Braude and co-workers in a series of papers (5, p.2014-2019; 6, p. 2078-2084; 7, p. 1755-1761; 8, p. 2000-2006; 9, p. 2007-2011). Until recently little work had been done with picolyllithium in connection with condensations with unsaturated aldehydes. Arens and co-workers (1, p. 287-294) have condensed 2-picoline with crotonaldehyde and sorbaldehyde. Others (2, p. 1832-1836; 12, p. 1750-1754; 13, p. 3021-3028; 14, p. 1686-1691) have used picolyllithium in condensations with saturated aldehydes as an intermediate step for the synthesis of quinolizinium salts.

Recent work in this laboratory has been done to investigate the reactions of acrolein with picolyllithium. The present investigation was an extension of these studies.

The compound 1-(2-pyridyl)-3-methyl-3-butene-2-ol (I, R = $-CH_3$) was synthesized by following a procedure similar to that of Walter's (27, p. 757-759). Phenyllithium was prepared by letting metallic lithium react with bromobenzene in an etheral solution. 2-Picoline was added to this solution, resulting in a preferential transfer of the lithium to the 2-picoline and forming the typical blood-red picolyllithium. After cooling the mixture, freshly distilled methacrolein dissolved in ether was slowly added, forming the lithium salt. The salt was hydrolyzed by adding water to the solution followed by concentrated hydrochloric acid. After separating the ether and water layers the water-soluble condensation product was neutralized with sodium carbonate solution. The free base separated

as a thick red oil which was extracted with chloroform, dried, and distilled under reduced pressure.

Wischman (28), in a similar reaction, suggested that hydrolysis using only water gave better yields. This was not substantiated in the present investigation. When water alone was used to hydrolyze the lithium salt the product remained in the ether layer, which was dried and distilled as before to give the same product.

The product was obtained as a light yellow oil in yields up to 37%. The oil crystallized upon cooling overnight to form yellow to white crystals. The alcohol was recrystallized from petroleum ether or from a mixture of petroleum ether and diethyl ether as white needles. It was soluble in water as well as in many polar and non-polar organic solvents.

The phenylurethane derivative was prepared to characterize the alcohol, a compound not previously reported in the literature.

Braude et al (7, p. 1755-1761; 8, p. 2000-2006; 9, p. 2007-2011) have investigated the oxotropic rearrangements of certain carbinols made by similar methods, i.e. the condensation of unsaturated aldehydes with various lithium alkenyls. They have reported that these allylic alcohols undergo isomeric rearrangements in the presence of dilute acid. Because the condensates of 2-picoline and acrolein and methacrolein are also allylic alcohols, and because the hydrolysis of these condensates was carried out in an acid solution, it was necessary to establish whether such a rearrangement had occurred. The initial condensation products were therefore subjected to ozonolysis.

The condensate of 2-picoline and methacrolein (I, R = $-CH_3$) was dissolved in ethylene chloride, reported to be a favorable solvent for ozonolysis (16, p. 437-439), cooled to 0°C, and then ozone was passed into the solution until the unsaturated alcohol had been completely converted to the corresponding ozonide. The solution of ethylene chloride was added dropwise to a mixture of acetic acid and zinc dust to hydrolyze the ozonide. After the solvent had been removed by distillation a portion of the hydrolyzed solution was treated with methone (dimethyldihydroresocinol) to test for the presence of formaldehyde. The recovery of 1,3-cyclohexandedione-2,2-methylene-bis (5,5-dimethyl) confirmed the presence of formaldehyde, which was evidence that the terminal double bond of the alcohol was still present. This indication that no rearrangement had occurred agreed with the findings of Wischman (28) in connection with the condensate of acrolein and 2-picoline (I, R = -H).

The compound 2-hydroxy-3-bromo-3-methyl-1,2,3,4-tetrahydroquinolizinium bromide (IV) was formed by dissolving (I) in carbon tetrachloride. The quinolizinium compound dropped out of the solution as it was formed, adhering to the sides and bottom of the flask as a sticky material. When recrystallized from small amounts of isopropyl alcohol it was obtained as white crystals. The compound was water-soluble and showed the presence of an ionic bromide, as evidenced by the precipitation of silver bromide when treated with a silver nitrate solution.

Attempts were made to form esters of (IV) but without success. When (IV) was treated with acetic anhydride a crystalline compound was obtained. Analysis showed this to be 3-methyl-3-bromo-3,4-dihydroquinolizinium bromide (V). Boekelheide and Gall (2, p. 1832-1836) have reported the use of acetic anhydride containing a drop of sulfuric acid as a dehydrating agent. The formation of (V) indicates that the sulfuric acid is not always necessary to effect dehydration.

In another attempt to esterify (IV) it was treated with acid chlorides. In spite of an apparent reaction no pure compounds were isolated, due, perhaps, to the presence of unreacted (IV) which could not be separated from the reaction products.

Unlike the cyclic bromide salt the original condensate (I) reacted very readily with acid chlorides, forming hydrochloride salts of the esters produced by the reaction. Thus 1-(2-pyridyl hydrochloride)-3-methyl-3-butene-2-ol benzoate (IIIA) and 1-(2-pyridyl hydrochloride)-3-methyl-3-butene-2-ol acetate (IIIB) were formed by treating (I, R= $-CH_3$) with benzoyl chloride and acetyl chloride respectively. The reaction was exothermic and proceeded rapidly with the formation of the crude salt. The salts were recrystallized from a mixture of alcohol and ether, or from benzene. The acetate ester (III B) was further purified by sublimation at reduced pressures. These compounds were soluble in many polar solvents as well as in water. Water solutions of the ester salts gave an acid test to pH paper. The neutralization equivalent for each of the salts was determined by titration with sodium hydroxide, using phenolphthlein as an indicator.

In an attempt to form a cyclic ester salt (III A) was dissolved in isopropyl alcohol and treated with bromine. A white crystalline substance was obtained but analyses of the material proved contradictory and the true composition of the isolated product was not established.

In recent work in this laboratory the only product obtained when anhydrous hydrogen bromide was added to (I, R = -H) was 1-(2-pyridyl hydrobromide)-3-butene-2-ol (IX). The expected addition of hydrogen bromide to the double bond was not observed. Since the double bond was still present after the formation of the hydrobromide salt, it seemed likely that this unsaturated site might still be utilized in an addition reaction. Therefore (IX) was again prepared by bubbling anhydrous hydrogen bromide through a benzene solution of (I, R = -H). The product separated as a salt from the benzene solvent and was recrystallized from acetone. This salt was dissolved in chloroform and bromine added to it. A viscous liquid formed at the bottom of the reaction flask which was separated and dissolved in acetone. Ether reduced the solubility of the product, which separated as a white powder from the solution. Analysis showed this to be the addition product (X) in which bromine had added across the double bond.

In a similar reaction (I, R = $-CH_3$) was dissolved in benzene and hydrogen bromine gas passed through the cooled solution until the quaternary ammonium salt (VI) had formed and precipitated from the solution. This salt was dissolved in isopropyl alcohol and bromine added to the solution. The product separated as white crystals after ether was added to reduce the solubility of the substance. The

analysis of the compound corresponded to 1-(2-pyridyl hydrobromide)-3-methyl-3,4-dibromo-2-butanol (VIII).

The compound 1-(2-pyridyl hydrobromide)-3-methyl-3-bromo-2-butanol (VII) was prepared while trying to make more of the hydrobromide salt (VI). Anhydrous hydrogen bromide was added rapidly to a solution of (I) dissolved in benzene. Some heat was noticed as the addition of the gas proceeded. A tan liquid separated from the solution which was removed and dissolved in acetone. The acetone was removed under reduced pressure and the liquid cooled overnight. Partial solidification of the liquid had occurred. The whole material was thoroughly washed with ether and then dissolved in a small amount of acetone. Crystals were formed when the solution was cooled. Analysis of the compound indicated that hydrogen bromide had added to the double bond as well as forming the hydrobromide salt.

Several attempts were made to isolate the free amine ester. A Schotten-Bauman type reaction (21, p. 319-324) was carried out by treating (I, R = $-CH_3$) with benzoyl chloride in a 10% sodium hydroxide solution. Heat was evolved and a water-insoluble liquid formed which was washed with water and taken up in ether. The liquid was distilled under reduced pressure, but the only product identified was benzoic acid. If the amine ester had been formed it apparently had been decomposed during the distillation.

It has been reported that the benzoate hydrochloride and the free amine benzoate of pyridine methanol have been prepared (23, p.24-28 E). Because of the similar structures of these compounds with (I) and (III) a similar treatment was used in an attempt to isolate

the free amine benzoate of (I). The ester salt (III A) was dissolved in water and treated with a solution of sodium bicarbonate. A water-insoluble liquid, assumed to be the desired product, was separated, dried, and distilled under reduced pressure. Several liquid fractions were obtained, while part of the distillate solidified in the condenser and receiving flasks. Analysis of one of the liquid fractions gave results which were close to the predicted values, but it appeared to be contaminated with some other product or products. The solid material obtained was recrystallized from water and proved to be benzoic acid. It appears that whatever product or products had been formed from the initial reaction were at least partially decomposed during the distillation.

In another attempt to obtain the free amine ester the hydrochloride salt of the benzoate ester (III A) was dissolved in ethanol and treated with alcoholic sodium hydroxide. Sodium chloride was separated from the mixture and upon reducing the volume of the solvent a flocculent substance appeared. This was dissolved in carbon tetrachloride and treated with bromine. An oily semi-solid separated from the solution, and this was dissolved in butanol. Ether was added to cloud the butanol mixture and after several days of cooling, a crystalline substance was obtained whose carbon and hydrogen analysis indicated the possibility that bromine had added to the double bond of the free amine benzoate. This work, however, could not be repeated.

Houben and Fischer (17, p. 240-247) have described the use of trichloromethyl ketones for the esterification of primary, secondary,

and tertiary alcohols, and of phenols. Since this method of esterification does not involve the formation of a salt, it was attemped, using trichloroacetophenone for the esterifying agent. The trichloroacetophenone was prepared from directions given by Cohen et al (10, p. 3952-3953).

An etheral solution of (I, R = $-CH_3$), containing a small amount of sodium methoxide for a catalyst, was treated with trichloroacetophenone. An exothermic reaction took place immediately, turning the solution a cloudy brown. After sitting overnight the solution was distilled under reduced pressure. The first fraction obtained was a pleasant-smelling volatile liquid whose analysis corresponded to that of methyl benzoate. Several other fractions were obtained which solidified upon cooling. These proved to be the original alcohol (I) which apparently had not reacted with the Ketone. Further investigations with trichloromethyl ketones would likely prove of value and enable one to prepare esters of alcohols such as (I). A change of the reaction conditions would be needed to prepare the ester of (I) from trichloroacetophenone.

What was assumed to be the crude amine benzoate was prepared by treating a water solution of the ester salt (III A) with sodium carbonate and isolating the water-insoluble liquid which was formed. A portion of this material was dissolved in carbon tetrachloride and bromine was added to the mixture. A yellowish-red material formed in the flask. The solvent was removed and the precipitate washed with ether. Small portions of acetone were added to a portion of the amorphous material. The red color disappeared and the mass became white.

After recrystallizing from a mixture of acetone and ether, the sample was analyzed, but the results were not in agreement with the predicted values.

In an attempt to find a better solvent ethanol was used to dissolve the amorphous solid, rather than acetone. When stirred with limited amounts of ethanol the solid first dissolved, and then solidified as yellow crystals with a melting point some 50° higher than the white crystals obtained from the acetone solvent. Analysis of the two products differed from the expected values and also from each other. The true composition of these substances was not determined, but the curious behavior of the initial precipitate in these two different solvents should be investigated further.

Experimental

1-(2-pyridyl)-3-methyl-3-butene-2-ol

Into a one liter, 3-necked flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser protected with a calcium chloride tube was placed 6.9g (1 g. atom) of lithium chips in 400 cc of dry ether. A stream of dry nitrogen was passed through the system to maintain an anhydrous atmosphere. The solution was stirred as 10-15 cc of a mixture of 79g (0.5 mole) of dry bromobenzene in 100 cc of dry ether was added from the dropping funnel. If the reaction failed to start very soon the flask was warmed. The rest of the mixture was added to maintain a gentle reflux and stirred till all of the lithium had disappeared (2-3 hours). Forty-six grams (0.5 mole) of 2-picoline was next added and stirred one hour, during which time dark red picolyllithium was formed. The flask was cooled in an ice-salt mixture to 0°C and 34g (0.485 mole) of freshly distilled methacrolein (methacryaldehyde) in 50 cc of dry ether was added over a 20 minute period, during which time the red color disappeared. The nitrogen train was disconnected and the solution stirred an additional 15 minutes.

Hydrolysis of the lithium salt was effected by slowly adding first 100 cc of water and then 100 cc of concentrated hydrochloric acid. The water layer was separated and poured into a water solution of sodium carbonate to neutralize the excess acid. The product separated as a dark red oil which was taken up in 300 cc of chloroform. The lithium carbonate was filtered off and extracted four times with

200 cc portions of chlorofrom. The combined chloroform solution was dried over anhydrous magnesium sulfate and distilled under reduced pressure. The product was collected at 148 to 150°C at 12 mm pressure.

The yield of the oil was 27.2 grams. (Based upon the methacrolein used this was 37% of the theoretical value.) When cooled the light yellow oil solidified. This was recrystallized from a mixture of petroleum ether and ethyl ether to give white needles with a melting point of 55 to 56°C.

Anal. Calcd. for $C_{10}H_{13}ON$: C = 73.6, H = 8.03. Found: C = 73.0, H = 8.00.

1-(2-pyridyl)-3-methyl-3-butene-2-ol-phenyl urethane

One gram (0.00615 mole) of 1-(2-pyridyl)-3-methyl-3-butene-2-ol was stirred with one cc of phenyl isocyanate. The solution was allowed to stand for several minutes, during which time the product solidified. This was recrystallized from carbon tetrachloride as white crystals with a melting point of 137 to 138°C. Yield of the phenyl urethane derivative was 1.3 grams (65% of the theoretical).

Anal. Calcd. for $C_{17}H_{18}O_2N_2$: C = 72.45, H = 6.37. Found: C = 72.25, H = 6.64.

1,3-cyclohexanedione-2,2-methylene-bis(5,5-dimethyl) Ozonolysis of 1-(2-pyridyl)-3-methyl-3-butene-2-ol

One gram (0.00615 mole) of 1-(2-pyridyl)-3-methyl-3-butene-2-ol was dissolved in 40 cc of ethylene chloride and cooled to 0°C. Ozone was passed in at 50 cc per minute until a portion of the test solution showed no decolorization of bromine water (ca. 3 hours),

indicating complete conversion of the double bond to the corresponding ozonide. The solution of ethylene chloride was then added drop wise to 50 cc of 10% acetic acid and 1/2 gram of zinc dust in a 3-necked flask equipped with a mechanical stirrer and a Claisen head. The flask was heated on a steam bath and the ethylene chloride was removed by distillation.

The dimedone (methone) derivative was prepared by adding 3 cc of the hydrolyzed solution to 8 cc of a 50% ethanol-water solution and 0.8 g of dimethyldihydroresorcinol (methone). The mixture was heated on a steam bath with reflux for 10 minutes. Water was added to cloud the solution, which was then cooled. On cooling the solution, yellow crystals separated which were recrystallized from 50% ethanol to give white needles which melted at 192°C. Literature reports 191-191.5°C.

To verify the composition an authentic sample of the dimedone derivative was prepared from formaldehyde and methone. No depression of the melting point was found when this was mixed with the sample prepared as described above.

1-(2-pyridyl hydrochloride)-3-methyl-3-butene-2-ol-benzoate

One gram (0.00615 mole) of 1-(2-pyridyl)-3-methyl-3-butene-2-ol was dissolved in 30 cc of anhydrous ether. To this was added with stirring 0.9g (0.0062 mole) of benzoyl chloride. The solution was allowed to stand with occasional stirring for several hours, during which time a white precipitate settled out of the solution. This was filtered and recrystallized from benzene, or a benzene-chloroform mixture. The white crystals melt at 146-147°C.

The yield was 1.7g (85% of the theoretical).

Anal. Calcd. for $C_{17}H_{18}O_2NCl$: C = 67.25, H = 5.92, neut. equiv. = 303.5. Found: C = 67.16, H = 5.96, neut. equiv. = 299.

1-(2-pyridyl hydrochloride)-3-methyl-3-butene-2-ol-acetate

One gram (0.00615 mole) of 1-(2-pyridyl)-3-methyl-3-butene-2-ol was treated with an excess of acetyl chloride. Heat was evolved and after several minutes of constant stirring the resulting viscous liquid solidified to an off-white material which was washed with ether and filtered. A quantitative yield of the crude salt (1.48 grams) was obtained. This was recrystallized from benzene as white platelets with a melting point of 135-136°C. The crude salt may also be purified by sublimation under reduced pressure.

Anal. Calcd. for $C_{12}H_{16}O_2NCl$: C = 59.75, H = 6.63, neut. equiv. = 242. Found: C = 59.67, H = 6.61, neut. equiv. = 253.

1-(2-pyridyl hydrobromide)-3-methyl-3-butene-2-ol

Five grams (0.0308 mole) of 1-(2-pyridyl)-3-methyl-3-butene-2-ol were dissolved in 100 cc of benzene in a 3-necked flask equipped with a mechanical stirrer and a delivery tube. The flask was cooled in an ice-salt bath and anhydrous hydrogen bromide was slowly bubbled into the solution. Within 30 minutes the crude salt was precipitating from the cloudy solution. The gas was passed through the solution an additional 10 minutes. The crystals were filtered and recrystallized from acetone or a mixture of acetone and ether. Yield of the white crystals was 5.2 grams (71% of the theoretical). An additional 5 to 10% may be recovered by passing hydrogen bromide gas through the benzene filtrate as before. Melting point of the salt was 80°C.

Anal. Calcd. for $C_{10}H_{14}ONBr$: C = 46.18, H = 5.74, neut. equiv. = 244. Found: C = 49.16, H = 5.84, neut. equiv. = 252.

1-(2-pyridyl hydrobromide)-3-methyl-3-bromo-2-butanol

Into a 3-necked flask equipped with a mechanical stirrer and a delivery tube was placed 5 grams (0.0308 mole) of 1-(2-pyridyl)-3-methyl-3-butene-2-ol dissolved in 100 cc of benzene. Anhydrous hydrogen bromide was added rapidly over a 45 minute period. The flask was cooled somewhat to prevent loss of the solvent, since heat was evolved during the addition. A light tan liquid separated from the solution. The bulk of the solvent was removed by decantation and the rest by evaporation at reduced pressure. The tan liquid was cooled overnight, washed thoroughly with ether, and then the resulting highly viscous liquid was dissolved in a small amount of acetone. Upon standing, white crystals separated which were filtered and weighed. The yield was 4.2 grams (42% of the theoretical) of a salt melting at 110°C. The salt may be recrystallized from acetone or an acetone-ether mixture.

Anal. Calcd. for $C_{10}H_{15}ONBr_2$: C = 37.00, H = 4.63, Br = 49.2. Found: C = 37.14, H = 4.61, Br = 49.07.

1-(2-pyridyl hydrobromide)-3-methyl-3,4-dibromo-2-butanol

One gram (0.0045 mole) of 1-(2-pyridyl hydrobromide)-3-methyl-3-butene-2-ol was dissolved in 8 cc of isopropyl alcohol. Two thirds of one gram (0.0042 mole) of bromine was slowly added with constant stirring. Ether was added to the red colored solution until a cloudiness just did presist, and then the solution was cooled overnight. Four tenths of one gram (25% of the theoretical) of brownish crystals

were obtained which melted at 127.5°C. If excess ether was added to the initial solution a reddish liquid came out of the solution. The ether was decanted and the liquid dissolved in acetone, followed by the addition of carbon tetrachloride to reduce the solubility of the product. Impure crystals separated upon cooling overnight. Recrystallized from an acetone-carbon tetrachloride mixture the crystals appeared white but did not have a sharp melting point, the m.p. ranging from 120-130°C.

Anal. Calcd. for $C_{10}H_{14}ONBr_3$: C = 29.74, H = 3.47. Found: C = 29.57, H = 3.60.

2-hydroxy-3-methyl-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide

Five grams (0.0308 mole) of 1-(2-pyridyl)-3-methyl-3-butene-2-ol was dissolved in 27 cc of carbon tetrachloride in a 3-necked flask equipped with a mechanical stirrer and a dropping funnel. Four and nine tenths grams (0.0306 mole) of bromine dissolved in 50 cc of carbon tetrachloride were slowly added from the dropping funnel with stirring. A yellow-orange amorphous substance formed on the sides and bottom of the flask, with some heat being produced during the addition. When all of the bromine had been added the solution was stirred a few minutes longer and the solvent decanted. The gummy substance was recrystallized with some difficulty from isopropyl alcohol to give 7.4 grams of white crystals (75% of the theoretical). The crystals melted at 199°C.

Anal. Calcd. for $C_{10}H_{13}ONBr_2$: C = 37.15, H = 4.02. Found: C = 36.96, H = 4.02.

3-methyl-3-bromo-3,4-dihydroquinolizinium bromide

One gram (0.003 mole) of 2-hydroxy-3-methyl-3-bromo-1,2,3,4-tetrahydroquinolizinium bromide was placed in a 50 cc flask equipped with a reflux condenser, 5-7 cc of acetic anhydride added and the mixture refluxed for 10 minutes. On cooling the solution, which had turned a deep purple color, a pale pink precipitate was isolated which was filtered and washed with small portions of acetone. The yield was 0.87 grams (95% of the theoretical). Melting point of the crystals was 228°C. It was not found necessary to recrystallize the product.

Anal. Calcd. for $C_{10}H_{11}NBr_2$: C = 39.19, H = 3.70. Found: C = 39.49, H = 3.71.

1-(2-pyridyl)-3-butene-2-ol

Into a one liter 3-necked flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser provided with a calcium chloride tube was placed 6.9 grams (1 g. atom) of lithium chips in 400 cc of dry ether. Dry nitrogen was passed through the flask to insure anhydrous conditions. A small portion of a mixture of 79 grams (0.5 mole) of dry bromobenzene in 100 cc of dry ether was added from the dropping funnel. The reaction started soon after the initial addition, and the rest of the mixture was added to maintain a gentle reflux, then stirred until all of the lithium had disappeared. Forty-six grams (0.5 mole) of 2-picoline was then added and stirred one hour, forming picolyllithium. The flask was cooled in an ice-salt bath to 0°C and 28 grams (0.5 mole) of acrolein in 50 cc of dry ether was added over 20 minutes. The red color of the

picolyllithium was replaced with a milky-white color and after disconnecting the nitrogen train the solution was stirred an additional 15 minutes.

The lithium salt was hydrolyzed by the addition of first 100 cc of water and then 100 cc of concentrated hydrochloric acid. The water layer was separated and poured into a sodium carbonate solution to neutralize the excess acid. The product, which separated as an oil, was taken up in 300 cc of chloroform, then the lithium carbonate was filtered off and extracted with four portions of 200 cc each of chloroform. The combined chloroform solution was dried over anhydrous $MgSO_4$ and distilled under reduced pressure. The product was distilled at 150 to 153°C at 37 mm and 140°C at 10 to 12 mm. The light yellow oil solidified upon cooling, and when recrystallized from petroleum ether formed white needles with a melting point of 43.5 to 44.5°C. Yields ranged from 20 to 26 grams (27 to 35% of the theoretical value).

Anal. Calcd. for $C_9H_{11}ON$: C = 72.47, H = 7.37. Found: C = 72.34, H = 7.28.

1-(2-pyridyl hydrochloride)-3-butene-2-ol benzoate

One gram (0.0067 mole) of 1-(2-pyridyl)-3-butene-2-ol was dissolved in 30 cc of anhydrous ether. One gram (0.007 mole) of benzoyl chloride was added with stirring. The solution was allowed to stand with occasional stirring for several hours, during which time a white precipitate formed. The solid was filtered and recrystallized from a mixture of chloroform and ether. The white

crystals melted at 143°C. The yield was 1.45 grams (75% of the theoretical).

Anal. Calcd. for $C_{16}H_{16}O_2NCl$: C = 66.3, H = 5.54, neut. equiv. = 289.6. Found: C = 66.55, H = 5.73, neut. equiv. = 286.

1-(2-pyridyl hydrobromide)-3-butene-2-ol

Four grams (0.027 mole) of 1-(2-pyridyl)-3-butene-2-ol were dissolved in 100 cc of benzene in a flask equipped with a mechanical stirrer and a delivery tube. The flask was cooled in an ice bath as anhydrous hydrogen bromide was bubbled through the solution. Within 30 to 40 minutes a white solid had precipitated from the solution. This was filtered and washed with small portions of acetone. White needles were obtained upon recrystallization from acetone which melted at 97°C. The yield of the crude salt was 4.6 grams (75% of the theoretical). The melting point agreed with that of the compound prepared in the same manner and previously reported.

Anal. Calcd. for $C_9H_{12}ONBr$: neut. equiv. = 230. Found: neut. equiv. = 226 and 232.

1-(2-pyridyl hydrobromide)-3,4-dibromo-butane-2-ol

One gram (0.00435 mole) of 1-(2-pyridyl hydrobromide)-3-butene-2-ol was dissolved in 75 cc of chloroform and two thirds gram (0.0042 mole) of bromine dissolved in 5 cc of chloroform was slowly added with stirring. The solution turned yellow upon the addition of the bromine and a reddish viscous liquid dropped out of the solution. The liquid was separated from the solvent and dissolved in acetone. Ether was added to reduce the solubility of the product

in acetone, which brought down an amorphous white powder with a melting point of 108 to 109°C. The yield was 0.7 grams (41% of the theoretical).

Anal. Calcd. for $C_9H_{12}ONBr_3$: C = 27.73, H = 3.08. Found: C = 27.75. H = 3.14.

Summary

1. The condensation products of picolyllithium and acrolein and methacrolein have been prepared. These are free bases which contain an alcohol with an allylic type of structure.

2. The hydrochloride salts of the esters of these alcohols have been prepared.

3. Bromination of the free bases has resulted in the formation of quinolizinium salts, ring compounds in which nitrogen acts as a bridgehead atom for two rings.

4. Hydrogen bromide has been added to the free bases to form hydrobromide salts.

5. Bromine has been added to the hydrobromide salts of the bases.

6. The addition of hydrogen bromide to the hydrobromide salt of the condensate of methacrolein and picolyllithium has been observed.

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