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A STUDY OF SOME SIMPLE QUINOLIZINIUM DERIVATIVES[1,2]

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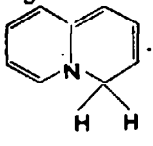
Abstract—The preparation of a series of 4,6-dimethylquinolizinium derivatives is described. Although these derivatives would appear to be logical precursors for the synthesis of cycl(3.3.3)-azine derivatives, attempts to effect such conversions were unsuccessful.

IN OUR original publication describing a synthesis of the quinolizinium ion II,[7] the ultimate goal of this work was a synthesis of a compound containing the parent structure III, a molecule now designated as cycl(3.3.3.)azine.[8,9] An obvious method for the elaboration of the quinolizinium ion II to give III would be through the preparation of the corresponding 4,6-dimethyl derivative IV which, on treatment with ethyl orthoformate or some other equivalent molecule, would be expected to give III. Since our first publication on the synthesis of II, we have prepared several such 4,6-dimethyl derivatives but have had no success in their conversion to derivatives of III. Because of the continuing interest in the synthesis of III as evidenced from numerous inquiries and to avoid fruitless duplication of effort by others, the present publication describing these simple quinolizinium derivatives and reporting their unsuccessful conversion to derivatives of III is made at this time.

[1] In our paper (ref. 7) originally describing the parent molecule II of this system, the name dehydroquinolizinium ion was given in deference to the Chemical Abstracts name quinolizine used to designate structure I,  . Clearly an oxidation or dehydrogenation is required to transform I to the corresponding ion II. However, Chemical Abstracts has ignored this relationship and in abstracting our papers has used the name quinolizinium to designate the ion II. Since quinolizine remains a hypothetical molecule and since succeeding authors who have entered this field have accepted the Chemical Abstracts nomenclature, we bow to the weight of current practice and in this, as well as future manuscripts, will employ the quinolizinium nomenclature for the ion II.

I

[2] We are indebted to the U.S. Army Research Office (Durham) for support in part of this research.

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[5] Abstracted in part from the Ph.D. dissertation of H. X. K., University of Rochester (1960).

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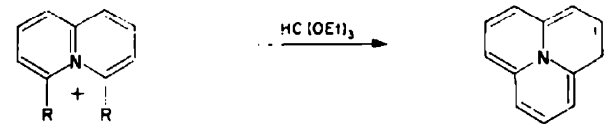
[7] V. Boekelheide and W. G. Gall, *J. Amer. Chem. Soc.*, **76**, 1832 (1954).

[8] R. J. Windgassen, Jr., W. W. Saunders, Jr. and V. Boekelheide, *J. Amer. Chem. Soc.*, **81**, 1459 (1959).

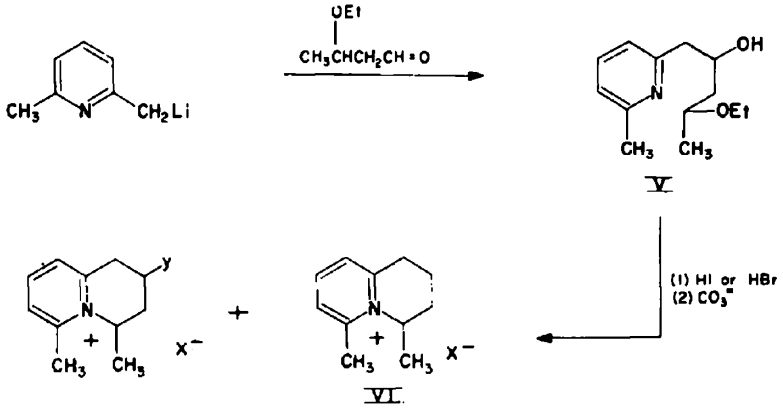
[9] In an earlier publication (V. Boekelheide and W. G. Gall, *J. Org. Chem.*, **19**, 499 (1954)) the name tricyclazine was used for III.



II, R = H
IV, R = CH_3

III.

Initially, the synthesis of the 4,6-dimethylquinolizinium ion IV was undertaken following the same general procedure outlined in our earlier publications.[7,10] As illustrated, the reaction between 2,6-lutidyllithium and β-ethoxybutyraldehyde gave the expected carbinol V in 52% yield. When the carbinol V was treated with hydriodic acid and then with base in the usual fashion for conversion to the corresponding cyclic quaternary salts, it was found that the product was a mixture which eventually was separated into its two components (VI and VII) by partition chromatography over powdered cellulose. That the formation of the tetrahydroquinolizinium ion VI was due to concomitant hydrogenolysis during the reaction with hydriodic acid could be shown by varying the period of time of this treatment. After two hours of heating V with hydriodic acid followed by the usual work-up, the ratio of VI to VII was 15:85; whereas after a period of ten hours heating with hydriodic acid, the ratio of VI to VII was 70:30.



V

VII, Y = −OH
VIII, Y = −OAc
IX, Y = −Br

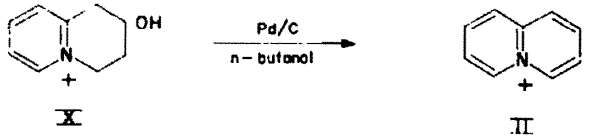
VI

Previously,[7,10] dehydration of 1,2,3,4-tetrahydro-2-hydroxy-quinolizinium derivatives had occurred very smoothly in high yield using acetic anhydride containing a trace of strong acid. However, in the case of the 4,6-dimethyl derivative VII, these conditions simply led to the corresponding acetate VIII. This difference in behavior is undoubtedly a reflection of the increased steric strain involved when the methyl groups at the 4-and 6-position are forced into a more nearly coplanar arrangement. Since the ease of dehydration might be related to the stereochemistry of the molecule, it was of interest to study the epimeric alcohol corresponding to VII. When the carbinol V was treated with hydrobromic acid under fairly strong conditions, the work-up with base led to the corresponding bromide IX. Subsequent reaction of IX

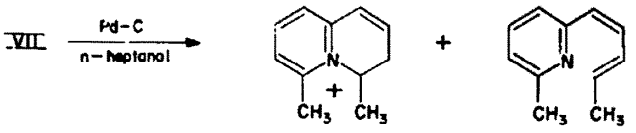
[10] V. Boekelheide and J. M. Ross, *J. Amer. Chem. Soc.*, **77**, 5691 (1955).

with mercuric acetate in aqueous acetic acid gave the desired epimeric alcohol. However, this behaved in a similar fashion to VII and did not undergo dehydration.

The possibility was then considered of effecting aromatization by simultaneous dehydration and dehydrogenation. In preliminary studies it was shown that 2-hydroxy-1,2,3,4-tetrahydroquinolizinium bromide (X) is converted to quinolizinium bromide in 39% yield by heating with a 10% palladium-on-charcoal catalyst in n-butanol. However, VII was unaffected by these conditions. At higher temperatures using boiling n-heptanol as solvent, VII as the quaternary bromide underwent dehydration to give XI in good yield. Under similar conditions the corresponding quaternary iodide of VII exhibited ring cleavage to form XII. Although there was an indication from the ultraviolet absorption spectra of the crude mixtures that the 4,6-dimethylquinolizinium ion (IV) had been formed in small amount in each case, no pure substance having the properties expected for IV could be isolated.



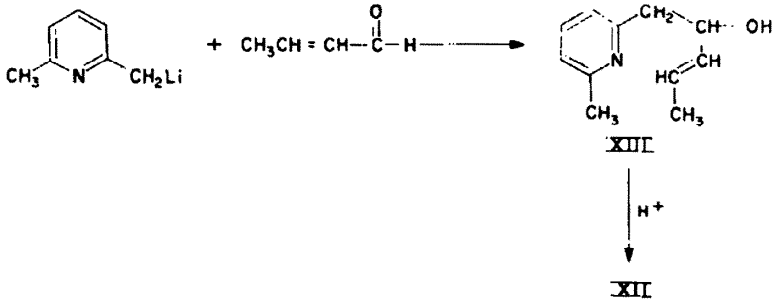
X IV



XI XII

The structure of XI has been assigned from spectral evidence. However, the structure of XII was established by an independent synthesis. Treatment of 2,6-lutidyllithium with crotonaldehyde gave the corresponding carbinol XIII which with acid led directly to XII. Although it seemed possible that the hydrobromide or hydroiodide salts of XII might spontaneoulsy cyclize to give XI, this was not observed.

In view of the lack of success in the dehydrogenation step, other methods of preparing 4,6-dimethylquinolizinium derivatives which would avoid dehydrogenation were investigated. The first of these was modeled on the procedure of Glover and



XIII

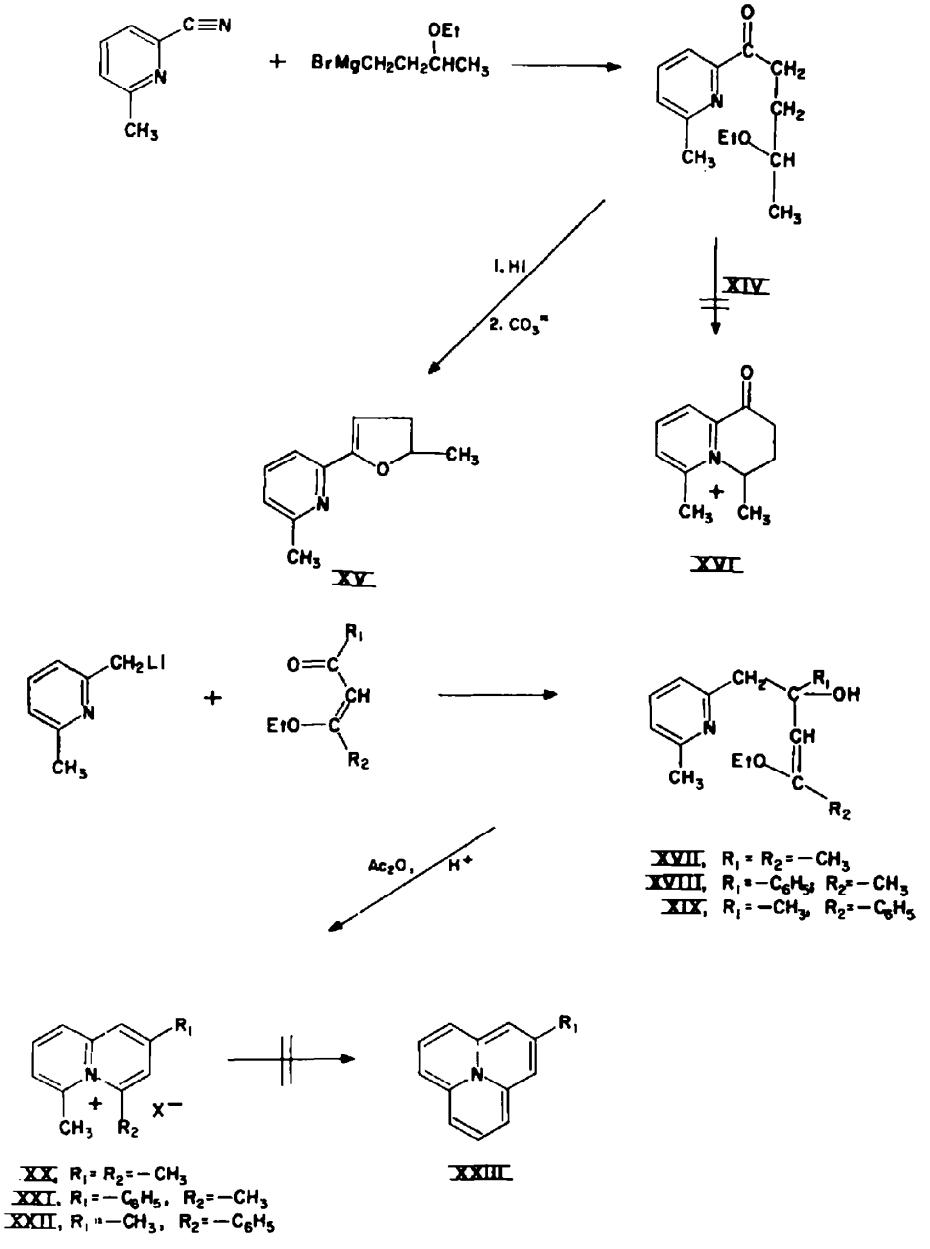
XII

Jones.[11] The reaction of 6-methyl-2-cyanopyridine with the Grignard reagent from 1-bromo-3-ethoxybutane proceeded smoothly in good yield to give the ketone XIV.

[11] E. E. Glover and G. Jones, *Chem. & Ind.* 1456 (1956).

Cleavage of the ether linkage followed by cyclization led to the dihydrofuran XV rather than the expected dihydroquinolizone XVI. Again, the steric interference of the two methyls is probably responsible for the change in the mode of cyclization.

A further variation for the synthesis of quinoliziniun derivatives has been devised by Richards and Stevens[12] and by Nesmeyanov and Rybinskaya.[13] This procedure is limited to the preparation of 2-substituted quinolizinium derivatives but avoids the



dehydrogenation step. When their procedure was investigated for the type of derivatives we desired, the syntheses proceeded in a straight-forward fashion to give the 2,4,6-trimethylquinolizinium ion (XX) and 2-phenyl-4,6-dimethylquinolizinium ion (XXI). Because of the controversy in the literature concerning the correct assignment of structure of the two possible enol ethers of benzoylacetone,[14,15] the isomeric enol ether was also carried through the same reaction sequence to give the alternate product, the 4-phenyl-2,6-dimethylquinolizinium ion (XXII).

With 4,6-dimethylquinolizinium derivatives at hand, an extensive study of their possible conversion to derivatives of cycl(3.3.3)azine was undertaken. Despite many attempts to effect a cyclic condensation of the 4,6-dimethyl groups with various carbonyl compounds-ethyl formate, ethyl orthoformate, methyl benzoate, and diethoxymethyl acetate—using various bases—triethylamine, pyrolidine, potassium *t*-butoxide, phenyllithium, sodium hydride, and sodamide—and even some acid catalysts—acetic anhydride and zinc chloride—in various solvents, nothing useful could be isolated having the properties to be expected for a cycl(3.3.3)azine derivative.

EXPERIMENTAL[16]

β-Ethoxybutyraldehyde. A suspension of 50 g 1,1,3-triethoxybutane[17] in 150 ml 5% H_2SO_4 aq was warmed at 45–50° for 45 min with stirring. The mixture became homogeneous after 0·5 hr. The cooled solution was then extracted 4 times with 50 ml portions ether. The combined ether extracts were dried ($NaHCO_3$), concentrated and the residual oil distilled. Redistillation of the main fraction gave 13·1 g (43%) of a colorless, lachsymetory oil, b.p. 46° at 22 mm, n_D^{20} 1·4068; d_{4^0} 0·895.[18] (Found: C, 61·67; H, 10·42. Calc. for $C_6H_{12}O_2$: C, 62·04; H, 10·41%).

*4-Ethoxy-*1-(2-(6-*methylpyridyl*))-2-*Pentanol* (V). To a prepared solution of 0·6 moles 2,6-lutidyllithium in 550 ml ether kept at 0°, 45·4 g (0·39 mole) β-ethoxybutyraldehyde was added dropwise with stirring. The lithium complex was decomposed by addition of 100 ml water and the solution was then extracted with 250 ml 3 N HCl. The aqueous solution was then added to excess 30% K_2CO_3 aq and the resulting mixture extracted with chloroform. After the chloroform extracts had been dried (K_2CO_3), it was concentrated and the residue distilled to give 62·8 g (72%) of a pale yellow oil, b.p. 102° at 1 mm; n_D^{20} 1·4975; d_{27} 0·959. (Found: C, 70·13; H, 9·52; N, 6·45; Calc. for $C_{12}H_{21}NO_2$: C, 69·92; H, 9·48; N, 6·27%).

Cyclization of V *to* 1,2,3,4-*tetrahydro*-4,6-*dimethylquinolizinium iodide* (VI) *and* 2-*hydroxy*-1,2,3,4-*tetrahydro*-4,6-*dimethylquinolizinium iodide* (VII). A solution of 5·2 g V in 50 ml 47% HI was heated on a steam bath for 2 hr. Concentration of the reaction mixture (red. press.) gave a yellow gum which was dissolved in 50 ml water, 50 ml chloroform was then added, and the aqueous solution made basic with excess $NaHCO_3$. The chloroform solution was washed with water, dried briefly (K_2CO_3), and then heated under reflux on a steam bath. After the mixture had been heated for 2 hr, an oil separated from the chloroform and the mixture was then concentrated. The residue was taken up in hot ethanol, ethyl acetate was added and from the cold solution 4·8 g of pale yellow crystals separated which melted over a range. These were then converted to the corresponding quaternary bromide by passage over an ion exchange column (*Dowex*-2, Br^-) to give 4·2 g of a yellow solid. Partition chromatography of the bromide over powdered cellulose (Whatman) using a solvent mixture of n-butanol, water and formic acid in the ratio of 11·1 : 1·35 : 2·0 with collection of 50 ml fractions led to separation of the 2 quaternary salts.

[13] A. Richards and T. S. Stevens, *J. Chem. Soc.* 3067 (1958).
[14] A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk. S.S.S.R.* **116**, 93 (1957).
[15] L. Claisen, *Ber. Dtsch. Chem. Ges.* **40**, 3903 (1907).
[16] C. Weygand, *Ber. Dtsch. Chem. Ges.* **58**, 1473 (1925).
[16] Analyses by A. Smith, T. Montzka, W. Manser and Micro-Tech Laboratories.
[17] G. Meier, *Ber. Dtsch. Chem. Ges.* **76**, 1016 (1943).
[18] F. Krausz, *Ann. Chim.* **12**, 811 (1949) has reported the preparation of this compound (b.p. 54° at 21 mm, n_D^{20} 1·4075) but without details regarding yield or analysis.

1,2,3,4-Tertahydro-4,6-dimethylquinolizinium bromide (VI) was obtained by combining fractions 18 to 30, concentrating, and then recrystallizing the residue from an ethanol–ether mixture to give 438 mg white crystals, m.p. 248°. These crystals showed the absence of −NH or −OH absorption in the IR and typical pyridine absorption (270–280 mμ) in the UV. (Found: C, 54·16; H, 6·50; Calc. for $C_{11}H_{16}NBr$: C, 54·55; H, 6·66%).

1,2,3,4-Tetrahydro-4,6-dimethylquinolizinium iodide (VI) was obtained by ion exchange (*Dowex*-2 I^-) with the corresponding bromide to give, after recrystallization from ethanol, white crystals, m.p. 200–204°. (Found: C, 45·72; H, 5·64; N, 4·88; Calc. for $C_{11}H_{16}NI$: C, 45·69; H, 5·59; N, 4·84%).

2-Hydroxy-1,2,3,4-tetrahydro-4,6-dimethylquinolizinium bromide (VII) was obtained by combining fractions 48 to 88, concentrating, and recrystallizing the residual solid from an ethanol–ether mixture. This gave 2·52 g cream-colored needles, m.p. 157–157·5°. (Found: C, 51·12; H, 6·34; N, 5·53; Calc. for $C_{11}H_{16}NOBr$: C, 51·17; H, 6·23; N, 5·43%).

2-Hydroxy-1,2,3,4-tetrahydro-4,6-dimethylquinolizinium iodide (VII) was obtained by ion exchange (*Dowex*-2, I^-) of the corresponding bromide and after recrystallization from an ethanol-ethyl acetate mixture formed cream-colored needles, m.p. 149–150 ω. dec. (Found: C, 43·58; H, 5·49; N, 4·55; Calc. for $C_{11}H_{16}NOI$: C, 43·29; H, 5·29; N, 4·59%).

When the above reaction was carried out in the same way but with the period of heating with HI extended to 10 hr, the ratio of VI to VII was changed to a ratio of 70 : 30. The presence of VI and VII is readily determined by paper chromatography using the n-butanol–water–formic acid mixture wherein VI has an R_f of 0·40 and VII an R_f of 0·22.

2-Bromo-1,2,3,4-tetrahydro-4,6-dimethylquinolizinium bromide (IX). A solution of 11·0 g V in 100 ml 60% HBr (prepared from water and gaseous HBr) was heated in a sealed tube at 110° for 2 hr. After removal from the tubes the contents were concentrated (red. press.) and the residue dissolved in 75 ml water suspended over a layer of chloroform (75 ml). A cold, saturated $NaHCO_3$ aq was then added until the aqueous layer was strongly basic. The chloroform layer was separated, washed with water, dried briefly (K_2CO_3) and then boiled under reflux for 45 min. Concentration of the chloroform solution gave an oil which was taken up in hot ethanol, treated with decolorizing charcoal, and then recrystallized from an ethanol–ethyl acetate mixture. This gave 2·2 g white needles, m.p. 184·5–185°. (Found: C, 41·42; H, 4·58; N, 4·61; Br; 49·60; Calc. for $C_{11}H_{16}NBr$: C, 41·41; H, 4·71; N, 4·36; Br, 49·78%).

Epimer of alcohol VII *from the reaction of mercuric acetate and* IX. A solution of 480 mg IX in 3·0 ml 5% acetic acid solution was added to a solution of 1·9 g mercuric acetate in 12·0 ml 5% acetic acid. The resulting solution was heated on the steam bath (under N_2 atm) for 1·5 hr. The mercuric ion was then precipitated by passing in H_2S and the solution filtered. Passage of the filtrate over an ion exchange column (*Dowex*-2, Br^-) followed by concentration gave a white solid. This, on recrystallization from an ethanol–ether mixture, gave white, featherly crystals, m.p. 188·2–188·5°. (Found: C, 50·90; H, 6·23; Calc. for $C_{11}H_{16}NOBr$: C, 51·17; H, 6·25%).

2-Acetoxy-1,2,3,4-tetrahydro-4,6-dimethylquinolizinium perchlorate (VIII). For the reaction with acetic anhyeride, a 350 mg sample of the 2-hydroxy-1,2,3,4-tetrahydro-4,6-dimethylquinolizinium bromide (VII, m.p. 157–157·5°) was first converted to the corresponding perchlorate by dissolving it in methanol and passing it over an ion exchange column (*Dowex*-2, ClO_4^-). Concentration of the methanol eluate followed by vacuum drying gave white crystals which were taken up in 2 ml acetic anhydride and treated with a drop of 60% perchloric acid. The solution was boiled under reflux for 5 min. cooled, and a small amount of ether added to induce crystallization. The fine, white needles were collected and recrystallized from ethanol to give 245 mg (70%) white needles, m.p. 161–162°. Absorption in the IR at 5·76 and 8·04 μ showed the presence of the acetoxy group. (Found: C, 49·01; H, 5·67; Calc. for $C_{13}H_{18}NO_6Cl$: C, 48·83; H, 5·67%).

Conversion of 2-hydroxy-1,2,3,4-tetrahydroquinolizinium bromide to quinolizinium bromide (II). A mixture of 400 mg 2-hydroxy-1,2,3,4-tetrahydroquinolizinium bromide[7] and 450 mg 10% Pd–C catalyst[10] in 30 ml n-butanol was boiled under reflux for 3 hr (under N_2 atm.). After removal of the catalyst, the solution was cooled and crystallization was initiated by addition of a small amount of ether. The crystals were collected and then recrystallized from an ethanol-ethyl acetate mixture to give 142 mg (39%) white crystals, m.p. 249–250°. The UV absorption spectrum of these crystals was identical with that reported previously for quinolizinium iodide (II).[7] Furthermore, conversion of the

[10] R. Mozingo, *Org. Syn., Coll.* Vol. 3, J. Wiley and Sons, New York, New York, 1955, p. 687.

bromide to the corresponding picrate gave yellow needles, m.p. 180–181° undepressed by admixture of an authentic sample of quinolizinium picrate.[7]

Treatment of 2-hydroxy-1,2,3,4-tetrahydro-4,6-dimethylquinolizinium bromide (VII) *with palladium catalyst.* A mixture of 265 mg VII, (m.p. 157–157·5°) and 270 mg 10% Pd–C catalyst[19] in 15 ml n-heptanol was heated at 175° (under N_2 atm) for 1 hr. After removal of the catalyst, the solution was concentrated to 3 ml and 15 ml ether added in small portions over a period of 4 hr. The crystals were collected and recrystallized from an ethanol–ether mixture to give 150 mg (61%) white crystals, m.p. 153–154°. These crystals are assumed to be 3,4-dihydro-4,6-dimethylquinolizinium bromide (XI) based on their composition and the close correspondence of their UV absorption spectrum (λ_{max} 316 mμ (log ε 3·99) and λ_{min} 268 mμ (log ε 2·89)) to that of 3,4-dihydroquinolizinium iodide.[7] (Found: C, 54·72; H, 5·64; N, 5·84; Calc. for $C_{11}H_{14}NBr$: C, 55·01; H, 5·88; N, 5·83%).

When the above experiment was repeated in the absence of the Pd–C catalyst, the same product was isolated in 65% yield.

Treatment of 2-hydroxy-1,2,3,4-tetrahydro-4,6-dimethylquinolizinium iodide (VII) *with palladium catalyst.* A mixture of 350 mg VII (m.p. 149–150°) and 400 mg 10% Pd–C catalyst[19] in 15 ml n-heptanol was boiled under reflux for 1 hr. After removal of the catalyst, the filtrate was concentrated to 5 ml and 10 ml ether was slowly added. When nothing separated, 10 ml saturated solution of picric acid in ether was added. This caused the separation of 110 mg yellow crystals, m.p. 153–165°, undepressed by admixture of an authentic sample of 1-(2-(6-methylpyridyl))-penta-1,3-diene picrate (see below).

1-(2-(6-(Methylpyridyl))-pent-3-en-2-ol (XIII). A solution of 35 g crotonaldehyde in 82 ml anhydrous ether was added dropwise with stirring to a cooled (0–10°) solution of 0·5 moles 2,6-lutidyllithium in 500 ml ether. Water was then added and the product was extracted using 250 ml 3 N HCl. The aqueous solution was then made basic with K_2CO_3 and the liberated organic base extracted with chloroform. After the chloroform solution had been dried, it was concentrated and distillation of the residual oil gave 49·1 g (55%) pale-yellow, viscous oil, b.p. 75–76° at 0·04 mm, n_D^{20} 1·5259, d_{27} 0·968. (Found: C, 74·46; H, 8·84; Calc. for $C_{11}H_{15}NO$: C, 74·54; H, 8·53%).

The *o-acetyl* derivative of XIII was prepared in 55% yield using isopropenyl acetate and conc H_2SO_4 and was obtained after distillation as a colorless oil, b.p. 76–77° at 0·7 mm, n_D^{21} 1·5574. (Found: C, 70·01; H, 7·52; Calc. for $C_{13}H_{17}NO_2$: C, 71·20; H, 7·82%).

1-(2-(6-Methylpyridyl))-penta-1,3-diene (XII). A solution of 4·5 g XIII in 5 ml 48% HBr was allowed to stand at room temp for 4 hr. The solution was then concentrated and the residual gum taken up in hot chloroform. When the chloroform solution was allowed to stand overnight in the cold, there separated 1·95 g (30%) of the hydrobromide of XII, m.p. 145–150°. This, on recrystallization from an ethanol–ethyl acetate mixture, gave white plates, m.p. 153–155°. In the UV, these showed absorption maxima at 329 mμ (log ε 4·25) and 269 mμ (log ε 4·06). (Found: C, 55·08; H, 5·96; N, 6·27; Calc. for $C_{11}H_{14}NBr$: C, 55·01; H, 5·88; N, 5·83%).

The free base corresponding to XII was prepared from the hydrobromide and, after distillation, was obtained as a pale yellow oil, b.p. 90–91° at 1 mm, n_D^{19} 1·6032. (Found: C, 82·69; H, 8·34; Calc. for $C_{11}H_{13}N$: C, 82·97; H, 8·23%).

The *picrate* of XII was prepared in ethanol and after recrystallization from the same solvent gave yellow needles, m.p. 156–158·5°. (Found: C, 52·83; H, 4·32; Calc. for $C_{17}H_{16}N_4O_7$: C, 52·58; H, 4·15%).

The *perchlorate* of XII was prepared in aqueous ethanol and gave featherly needles, m.p. 91–92°, corresponding to the monohydrate. (Found: C, 47·95; H, 5·94; Calc. for $C_{11}H_{14}NO_4Cl \cdot H_2O$: C, 47·57; H, 5·81%).

The *hydriodide* of XII was prepared in a similar manner to that described for the hydrobromide and gave lemon-yellow plates, m.p. 160·5–161°. (Found: C, 45·90; H, 4·87; Calc. for $C_{11}H_{14}NI$: C, 46·01; N, 4·91%).

3-Ethoxybutan-1-ol. A solution of 60·0 g β-ethoxybutryaldehyde (see the first experiment) in 150 ml ether was added dropwise with stirring to a solution of 19·4 g $LiAlH_4$ in 925 ml ether. After the addition was complete, the mixture was boiled under reflux for 2 hr and then decomposed by successive additions of 45 ml ethyl acetate and 105 ml saturated Na_2SO_4 aq. The precipitated hydroxides were removed by filtration, the filtrate was concentrated, and the residual oil was distilled to give 52·5 g (86%) colorless oil, b.p. 74–79° at 21 mm, n_D^{25} 1·4143. (Found: C, 60·75; H, 11·80; Calc. for $C_6H_{14}O_2$: C, 60·98; H, 11·94%).

1-Bromo-3-ethoxybutane. Phosphorous tribromide (18·7 g) was added in small portions to 24·78 g 3-ethoxybutan-1-ol. After the initial exothermic reaction was complete, the mixture was boiled under reflux for 1 hr. Then, all material distilling below 160° (atm. press) was collected in a receiver containing 30 ml water. The heavier organic layer was separated, dried, and distilled to give 24·8 g (65%) pale yellow oil, b.p. 56–60° at 14 mm. (Found: C, 39·61; H, 7·11; Br, 44·64; Calc. for $C_6H_{13}OBr$: C, 39·80; H, 7·23; Br, 44·14%).

4-Ethoxy-1-(2-(6-methylpyridyl))-pentan-1-one (XIV). A solution of 29·4 g 1-bromo-3-ethoxybutane in 20 ml ether was added dropwise to 4·33 g Mg in 80 ml ether. Addition was slow initially until the exothermic reaction began and then it was continued at a rate to maintain gentle boiling. To the Grignard reagent so prepared there was added dropwise with stirring a solution of 15·1 g 6-methyl-2-cyanopyridine in 180 ml ether. After addition was complete, the reaction mixture was boiled under reflux for 2 hr before being poured onto a mixture of 50 ml conc HCl and 100 g ice. The aqueous layer was separated, heated at 90% for 1 hr, and then made basic (NH_4OH). The organic layer was removed by extraction with ether, dried ($MgSO_4$), concentrated, and then distilled to give 17·96 g (50%) yellow oil, b.p. 95–98° at 3 mm, n_D^{24} 1·4930. (Found: C, 70·34; H, 8·98; N, 6·56; Calc. for $C_{13}H_{19}NO_2$: C, 70·55; H, 8·66; N, 6·33%).

2,3-Dihydro-2-methyl-5-(2-(6-methylpyridyl))-furan (XV). A solution of 1·63 g XIV in 20 ml 47% HI was boiled under reflux for 4 hr. The reaction mixture was then concentrated (red. press.) and the residue taken up in 40 ml hot water. After the solution was neutralized (K_2CO_3) the organic layer was extracted with 3 × 100 ml portions chloroform. The chloroform fraction was dried briefly, concentrated to ½ volume, and allowed to stand overnight in the cold. There separated 600 mg colorless needles which, after recrystallization from aqueous ethanol, melted at 124–125°. The solubility of these crystals in ether and benzene showed it to be non-ionic. Its composition and its absorption in the IR (strong band at 6·05 μ corresponding to the enol ether) are in accord with structure XV. (Found: C, 75·34; H, 7·82; N, 7·91; Calc. for $C_{11}H_{13}NO$: C, 75·40; H, 7·48; N, 7·99%).

4-Ethoxy-2-methyl-1-(2-(6-methylpyridyl))-3-penten-2-ol (XVII). A solution of 35·8 g 4-ethoxy-3-penten-2-one[12] in 20 ml ether was added dropwise with stirring to a solution of 0·3 mole 2,6-lutidyllithium in 300 ml ether held at 0°. After addition was complete, the mixture was allowed to warm to room temp and stirred for 5 hr. The reddish-brown mixture was poured onto ice, and the organic layer was separated, dried, and concentrated. Distillation of the residual oil gave 51·6 g (75%) pale yellow oil, b.p. 107–114° at 0·35 mm, n_D^{24} 1·5032. (Found: C, 71·73; H, 8·70; N, 5·81; Calc. for $C_{14}H_{21}NO_2$: C, 71·45; H, 9·00; N, 5·95%).

2,4,6-Trimethylquinolizinium bromide (XX). A solution of 51·5 g XVII in 250 ml acetic anhydride containing 7 drops conc. H_2SO_4 was heated under reflux for 40 min. Water (50 ml) was added to the cold reaction mixture and the solution concentrated (red. press.). The residue was taken up in 400 ml water and then passed over an ion exchange column (*Dowex*-2, Br^-). Concentration of the eluate gave 30 g crude crystals, m.p. 270–300 (dec). These were purified by treatment with charcoal and recrystallization from dimethylformamide to give 16·5 g (30%) greyish-white crystals, m.p. > 400°. (Found C, 56·94; H, 5·49; N, 5·58; Br, 31·65. Calc. for $C_{12}H_{14}NBr$: C, 57·18; H, 5·55; N, 5·56; Br, 31·71%).

The *picrate* of XX was prepared from the corresponding bromide using ethanolic picric acid and, after recrystallization from ethanol, gave yellow needles, m.p. 137–138°. (Found: C, 53·92; H, 4·04; N, 13·82; Calc. for $C_{18}H_{16}N_4O_7$: C, 54·00; H, 4·03; N, 14·00%).

The *perchlorate* of XX was prepared by passing the corresponding bromide over an ion exchange column (*Dowex*-2, ClO_4^-) and recrystallizing the product from absolute ethanol giving prisims, m.p. 156·5–157·0°. (Found: C, 53·32; H, 4·96; N, 5·28; Cl, 13·17; Calc. for $C_{12}H_{14}NO_4Cl$: C, 53·05; H, 5·20; N, 5·16; Cl, 13·04%).

The *tetraphenylborate* of XX was prepared by treating the corresponding bromide with a 2% aqueous solution of sodium tetraphenylborate. The resulting precipitate was recrystallized from acetone to give white crystals, m.p. 217–218·5°. (Found: C, 87·78; H, 6·93; Calc, for $C_{36}H_{34}NB$: C, 87·95; H, 6·99%).

4-Ethoxy-2-phenyl-1-(2-(6-methylpyridyl))-3-penten-2-ol (XVIII). A solution of 5·71 g 3-ethoxy-1-phenyl-2-buten-1-one[20] in 10 ml ether was added dropwise with stirring to a solution of 0·05 moles 2,6-lutidyllithium in 35 ml ether held at 0°. The work-up of the reaction mixture was the same as described for XVII. However, since the product decomposed on attempted distillation, it was purified by chromatography over alumina. The ether eluate gave 4·46 g (50%) yellow oil. (Found: C, 76·73; H, 7·77; N, 4·99; Calc. for $C_{19}H_{23}NO_2$: C, 76·73; H, 7·80; N, 4·71%).

4,6-Dimethyl-2-phenylquinolizinium bromide (XXI). A solution of 70·0 g XVIII in 400 ml acetic anhydride containing 1 ml conc H_2SO_4 was boiled for 35 min and then cooled. The work-up of the reaction mixture was the same as described for XX. The crude product melted in the range of 280–300° (dec). However, after recrystallization from dimethylformamide, there was obtained 12·8 g (20%) white crystals, m.p. > 350°. (Found: C, 65·07; H, 5·28; N, 4·53; Br, 25·27; Calc. for $C_{17}H_{14}NBr$: C, 65·00; H, 5·08; N, 4·45; Br, 25·47%).

The *picrate* of XXI was prepared from the corresponding bromide using ethanolic picric acid and, after recrystallization from ethanol, was obtained as yellow needles, m.p. 212–213°. (Found: C, 59·84; H, 3·84; N, 12·31; Calc. for $C_{23}H_{16}N_4O_7$: C, 59·74; 3·92; N, 12·12%).

The *tetraphenylborate* of XXI was prepared from the corresponding bromide using aqueous sodium tetraphenylborate. Crystallization of the precipitate from acetone gave prisms, m.p. 186–187°. (Found: C, 89·05; H, 6·54; Calc. for $C_{41}H_{36}NB$: C, 89·06; H, 6·52%).

4-Ethoxy-4-phenyl-2-methyl-1-(2-(6-methylpyridyl))-3-buten-2-ol (XIX). A solution of 4·85 g 1-ethoxy-1-phenyl-1-buten-3-one[21] in 15 ml ether was added dropwise with stirring to 0·03 mole 2,6-lutidyllithium in 50 ml ether held at 0°. After the addition was complete, the mixture was allowed to warm to room temp and stand overnight with stirring. It was then poured onto ice and the ether layer was separated, dried, and concentrated. The residue was then chromatographed over alumina using ether for elution. The main fraction consisted of 1·34 g yellow oil. (Found: C 76·73; H, 7·26; N, 4·67; Calc. for $C_{19}H_{23}NO_2$: C, 76·73; H, 7·80; N, 4·71%).

2,6-Dimethyl-4-phenylquinolizinium tetraphenylborate (XXII). A solution of 1·0 g XIX in 10 ml acetic anhydride containing 1 drop H_2SO_4 was boiled under reflux for 1 hr. Concentration of the solution gave a residue which was taken up in warm water and passsed over an ion exchange column (*Dowex*-2, Br^-). Concentration of the eluate gave an amorphous solid that could not be crystallized and so it was redissolved in water and treated with sodium tetraphenylborate. The resulting precipitate was recrystallized from aqueous acetone to yield 520 mg greyish-white crystals, m.p. 184–185°. A mixture of these crystals and 2-phenyl-4,6-dimethylquinolizinium tetraphenylborate (XXI) melted over a range from 158–175°. (Found: C, 89·83; H, 6·88; N, 2·68; Calc. for $C_{41}H_{36}NB$: C, 89·06; H, 6·52; N, 2·53%).

[20] This "A" ether was prepared as described by Claisen[14] in 68% yield. In contrast to Weygand (ref. 15) we found the properties of the "A" ether in good agreement with those reported by Claisen and distinctly different from the "B" ether of Ruhemann and Watson (ref. 21).

[21] S. Ruhemann and E. R. Watson, *J. Chem. Soc.*, 85, 1170 (1904).