for 24 hr. at room temperature the reaction mixture was cooled to −15° for 1 hr. Filtration gave 12.2 g. of yellow solid product. Attempted recrystallization from a variety of solvents always resulted in decomposition. An analytical sample was prepared by successive trituration and filtration first with cold 6 *M* acetic acid and then with two portions of ethanol, to give a yellow powder, m.p. 143–145°, infrared absorption: ν_{max}^{KBr} near 3550 (m) and 3400 (m) (water OH), 1730 (m–s) (keto C=O), 1658 (m–s) (water OH), 1529 (s) and 1340 (m–s) (C—NO_2); ultraviolet absorption: λ_{max}^{EtOH} 233 mμ, 314 mμ, 420 mμ.

Anal. Calcd. for $C_{16}H_{12}N_2O_3 \cdot {}^1/_2H_2O$: C, 66.43; H, 4.53; N, 9.68. Found: C, 66.80; H, 5.59; N, 10.43.

On standing for a few hours at room temperature, an alcoholic solution of IX and benzaldehyde gave III, identified by mixture melting point with an authentic sample.

Nitropyruvaldehyde Bis(*p*-bromophenyl)hydrazone (VIIIb).—A solution of 0.5 g. of IX, 0.6 g. of *p*-bromophenylhydrazine hydrochloride, and 4 drops of acetic acid in 30 ml. of ethanol was refluxed for 0.5 hr. Cooling and filtration gave a yellow solid which was recrystallized from ethanol, yellow crystals, m.p. 175.4–176.2°. This material was shown by comparison of melting point and infrared spectrum to be identical to authentic material prepared in a similar way from compound I, *p*-bromophenylhydrazine, and hydrochloric acid in ethanol.

Anal. Calcd. for $C_{15}H_{12}N_5O_2Br_2$: C, 39.58; H, 2.89; N, 15.39; Br, 35.11. Found: C, 39.81; H, 3.11; N, 15.03; Br, 34.87.

2,5-Dihydroxy-4-nitro-1,2,3-triphenyl-1,2-dihydropyridine (XIII).—A suspension of 2.0 g. of III in 200 ml. of ethanol containing 100 ml. of concentrated hydrochloric acid was heated to reflux. After 5 to 10 min. all of the material dissolved, and then almost immediately bright orange crystals precipitated from the mixture. After 1.5 hr. of refluxing, the mixture was cooled and filtered to give 1.46 g. of product. Successive recrystallization from ethanol–ethyl acetate gave orange crystals, m.p. 225–226° dec.; infrared absorption: $\nu_{max}^{CH_2Cl_2}$ near 3450 (m–s) (OH), 1640 (m–s) (C=C), 1500 (s) and 1360 (s) (C—NO_2).

Anal. Calcd. for $C_{29}H_{18}N_2O_4$: C, 71.49; H, 4.69; N, 7.25. Found: C, 71.70; H, 4.64; N, 8.25.

Treatment of the filtrate from the above reaction with 2,4-dinitrophenylhydrazine gave less than 0.1 g. of benzaldehyde 2,4-dinitrophenylhydrazone, identified by mixture melting point with an authentic specimen.

The **monobenzoyl derivative of XIII** was obtained by treating a chloroform solution of XIII with benzoyl chloride and 5% aqueous sodium hydroxide solution. After several hours of stirring at room temperature, the chloroform solution was separated, dried, and distilled, and the residue was recrystallized from ethanol–chloroform to give yellow crystals, m.p. 254–261° (uncor.), infrared absorption: $\nu_{max}^{CH_2Cl_2}$ near 3500 (m) (OH), near 1750 (s) (C=O).

Anal. Calcd. for $C_{30}H_{22}N_2O_4$: C, 73.46; H, 4.52. Found: C, 73.46; H, 4.43.

The Synthesis of Several 4,6-Dimethylquinolizinium Salts, Possible Precursors of Cycl[3.3.3]azine[1a]

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The preparation of 2,4,6-trimethyl- and 2-phenyl-4,6-dimethylquinolizinium salts has been accomplished by the reaction of 2,6-lutidyllithium with the appropriate protected β-diketone, followed by cyclodehydration of the intermediate pyridyl ketone with hydrobromic acid and acetic anhydride. Various functional derivatives of these and other quinolizinium salts have been obtained. The 4,6-dimethylquinolizinium salts were desired as intermediates in the synthesis of cycl[3.3.3]azine. Numerous reagents and conditions were employed in an attempt to bring the 4- or 6-methyl groups into reaction. These attempts were uniformally unsuccessful.

Preparation of Quinolizinium Salts.—While a number of quinolizinium salts are known, none of these contains methyl groups at the 4- and 6-positions, as may be considered desirable for ring closure to cycl[3.3.3]azine. Thus the object of the work reported here was to prepare quinolizinium salts such as (IX), and to explore the routes whereby these salts might be converted to cycl[3.3.3]azines.

Quinolizinium salts have been known to exist in certain complex alkaloids for some time. However, synthetic routes to relatively simple quinolizinium cations have been developed only recently. One of the most general of these approaches, discovered by Woodward and MacLamore[2] and further elaborated by Richards and Stevens,[3] consists of the reaction of picolyllithium (Ia) with the mono ketal or enol ether of a β-dicarbonyl compound (II), followed by cyclodehydration of the intermediate adduct (IIIb) to the corresponding quinolizinium compound (IX) with acid (sequence A).

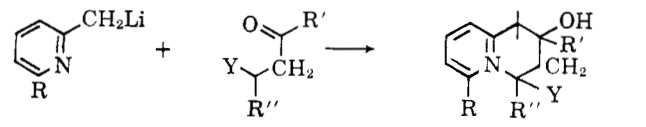
Richards and Stevens[3] have used this method to advantage in the preparation, among others, of 2,4-dimethyl- and 2-phenyl-4-methyl-(IXb)quinolizinium picrates. These two compounds were of considerable interest to us, since the substitution of 2,6-lutidine for picoline in the initial step should provide quinolizinium salts with methyl groups in the 4- and 6- positions as required for the preparation of cycl[3.3.3]azines. In accord with their postulated mechanism, Richards and Stevens have isolated the picrate of the pyridyl ketone (IVb) analogous to IVa as an intermediate in the formation of 2-phenyl-4-methylquinolizinium picrate (IXb). In addition, we have isolated the hydrobromide of the unsaturated ketone (Vb) analogous to Va as an intermediate in the preparation of 4,6-dimethyl-2-phenylquinolizinium bromide (IXc), although Va, itself, could not be isolated in pure form. Further, we have obtained spectral evidence for the formation of (IVa) on mild acid treatment of the adduct (IIIa). Nesmeyanov[4] has reported the isolation of an intermediate, formulated as the hydroxydihydroquinolizinium salt (X), in the preparation of 2-methylquinolizinium bromide (IXd). Lacking further information, since this work is available to us only in abstract form, and in view of our experience with the ketone (Vb), it would seem that this could be formulated as the iso-

(1) (a) Taken from the Ph.D. dissertation of H. V. Hansen. Present address, Metcalf Laboratory of Chemistry, Brown University, Providence, R. I; (b) Lehigh Student Chemistry Foundation Fellow, 1959–1961.

(2) R. B. Woodward and W. M. MacLamore, *J. Am. Chem. Soc.*, **71**, 379 (1949).

(3) A. Richards and T. S. Stevens, *J. Chem. Soc.*, 3067 (1958).

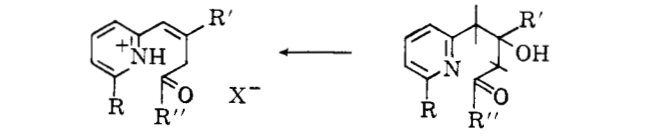
(4) A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR*, **116**, 93 (1957).



I
a. R = H
b. R = CH_3
c. R = Cl

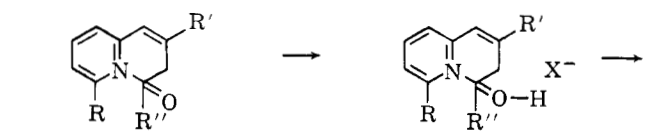
II
a. R′ = R″=CH_3 Y = OCH_2CH_2—O—
b. R′ = CH_3, R″ = H Y = $(OCH_3)_2$

III
a. R = R′ = R″ = CH_3 Y = —OCH_2CH_2O—
b. R = R″ = H,R′ = CH_3 Y = $(OCH_3)_2$
c. R = R′ = CH_3, R″ = H Y = $(OCH_3)_2$
d. R = Cl, R′ = R″ = CH_3 Y = —OCH_2CH_2O—
e. R = H,R′ = R″ = CH_3 Y—OCH_2CH_2



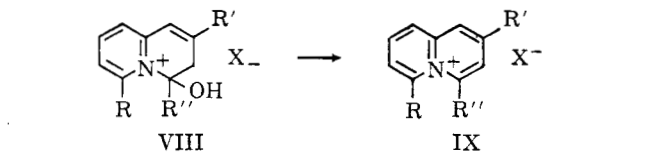
V
a. R = R′ = R″ = CH_3, X^- = Br^-
b. R = R″ = CH_3, R′ = C_6H_5, X^- = Br^-

IV
a. R = R′ = R″ = CH_3
b. R = H, R′ = C_6H_5, R″ = CH_3



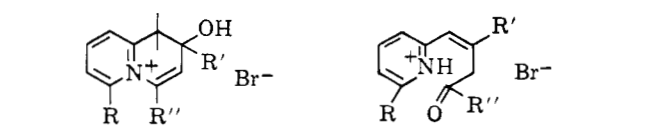
VI
a. R = R′ = R″ = CH_3

VII
a. R = R′ = R″ = CH_3, X^- = Br^-



VIII
a. R = R′ = R″ = CH_3, X = Br^-

IX
a. R = R′ = R″CH_3, X = Br^-
b. R = H, R′ = C_6H_5, R″ = CH_3, X = Br^- or picrate
c. R = R″ = CH_3·R′ = C_6H_5, X^- = Br^-
d. R = R″ = H,R′ = CH_3· X = Br^- or I^-
e. R = R′ = CH_3,R″ = H,X = picrate



X
a. R = R″ = H,R′ = CH_3
b. R = R″ = CH_3, R′ = C_6H_5

XI
a. R = R″ = H,R′ = CH_3
b. R = R′ = CH_3, R′ = C_6H_5

Sequence A

meric aldehyde derivative (XIa), which is similar to the proposed intermediate (Va).

Difficulty was anticipated at several points in the application of the reaction sequence to the preparation of 4,6-dimethylquinolizinium salts. The presence of a 6-methyl group on the pyridine ring in the adduct would be expected to hinder the formation of the bond between the pyridine nitrogen and carbonyl carbon (VII → VIII) since, as the carbonyl group approaches the ring, the 6-methyl group and the ω-methyl group of the side-chain are brought close together so that steric repulsion becomes important. The steric strain[5] resulting from nonbonded interaction between the 4- and 6-methyl groups of the intermediate (VIIIa) is further increased by dehydration to the planar quinolizinium cation (IX).

Further consideration of the proposed mechanism reveals that successful cyclodehydration depends on the rather complex acid base equilibria (V ⇄ VI ⇄ VII). Thus, while excess mineral acid is necessary for the dehydration steps (IV → V) and (VIII → IX), the presence of a large excess of strong acid would suppress the dissociation of the salt (V) to the free base (VI), thus preventing attack of the pyridine nitrogen on the carbonyl group (VII → VIII).[6]

As expected, the monoethylene ketal of acetylacetone (IIa) reacted smoothly with 2,6-lutidyllithium (Ib) to give 4,4 - ethylenedioxy - 2 - methyl - 1 - (6′ - methyl-2′-pyridyl)-2-pentanone (IIIa) as a somewhat impure pale-yellow oil in 50–55% yield. The structure of IIIa was assigned mainly on the basis of its method of formation, conversion to the corresponding quinolizinium salt, and spectral data, since solid derivatives could not be obtained with picric acid or the usual carbanyl reagents. Thus, the ketone hydrobro mide (IVa), prepared *in situ* by treatment of a dilute alcoholic solution of the ketal (IIIa) with hydrobromic acid, shows ultraviolet absorption characteristic of simple pyridines in acid solution (λ_{max} 273 mμ, log ε 4.24).

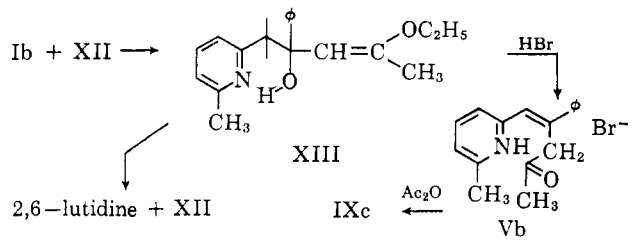
Numerous attempts to cyclize the hydroxy ketal IIIa with alcoholic picric acid, concentrated hydrobromic, or hydriodic acids, or sulfuric or polyphosphoric acid, or phosphorus oxychloride were without success, tarry materials being formed under vigorous conditions. Finally, treatment with slightly more than one equivalent of hydrobromic acid, followed by evaporation to dryness and cyclodehydration of the resulting crude ketone hydrobromide (IVa) with refluxing acetic anhydride for eighteen hours, resulted in a 50% yield of the desired 2,4,6-trimethylquinolizinium bromide (IXa). The use of traces of sulfuric acid as a catalyst in the final cyclodehydration led to extensive charring.

In an attempt to apply this same reaction sequence to the preparation of 4,6-dimethyl-2-phenylquinolizinium bromide (IXc), lutidyllithium (Ib) reacted with the enol ether of benzoylacetone [XII. C_6H_5—CO—CH=$C(CH_3)OC_2H_5$]. While color change and heating

(5) In this connection, examination of a molecular model of IX shows that the hydrogen atoms of the 4- and 6-methyl groups are actually interlocked in their least-strained conformation, severely restricting free rotation of the methyl groups. The strain energy produced by the interaction of 4- and 6-methyl groups is presumably of the order of 8 kcal./mole, the value obtained by Packer for the strain energy of the nearly isosteric 1,8-dimethylnaphthalene. J. Packer, J. Vaughn, and E. Wong, *J. Am. Chem. Soc.*, **80**, 905 (1958).

(6) Previous work has shown that the formation of known quinolizinium salts is also subject to a number of more subtle factors. Thus, Richards and Stevens[3] have prepared a variety of quinolizinium salts, including 2,4-dimethylquinolizinium picrate, by treatment of the appropriate picoline-β-dicarbonyl compound adduct with excess picric acid in boiling ethanol. However, as previously noted, these conditions were not sufficiently vigorous for the formation of 2-phenyl-4-methylquinolizinium picrate (IXb). In this latter case the hydroxy ketone picrate (IVb) resulted; this was subsequently cyclized with acetic anhydride–sulfuric acid. Similarly, these authors found that the action of hydriodic acid on the pyridyl acetal IIIb gives 2-methylquinolizinium iodide (IXd) directly, while Nesmeyanov[4] obtained the intermediate Xa or XIa by treating IIIb with excess concentrated hydrobromic acid; this was finally cyclized to IXd with acetic anhydride-sulfuric acid.

effect indicated that the organometallic was being consumed, attempted distillation of the crude basic product, followed by treatment with dilute aqueous acid, resulted in the recovery of substantial amounts of benzoylacetone. Subsequent cyclodehydration of the acid-soluble material gave the desired quinolizinium bromide (IXc) in very low yield. Thus, it appears that the intermediate enol ether (XIII) is unstable towards heat and reverts to lutidine and the benzoylacetone derivative (XII) with the regeneration of the conjugated carbonyl group of the latter. It is attractive to consider this disproportionation as the result of an intramolecular base-catalyzed reaction *via* the quasi-six-membered ring, as shown below, although intermolecular reaction, involving another molecule of XIII or lutidine cannot be excluded.



This difficulty was bypassed by direct treatment of the organometallic reaction mixture with excess dilute mineral acid, followed by treatment with potassium carbonate and ether extraction. Low-temperature evaporation of most of the excess lutidine and subsequent acidification and cyclodehydration of the residue from this operation with acetic anhydride then gave 4,6-dimethyl-2-phenylquinolizinium bromide (IXc) in 60% yield, based on the enol ether (XII).

In this case, the hydrobromide of the unsaturated ketone (Vb) could be separated after the final acidification and evaporation by brief treatment of the resulting viscous mass with warm acetic anhydride. After purification, Vb was converted to the quinolizinium salt (IXc) in 75% yield by treatment with refluxing acetic anhydride for 14–18 hours.

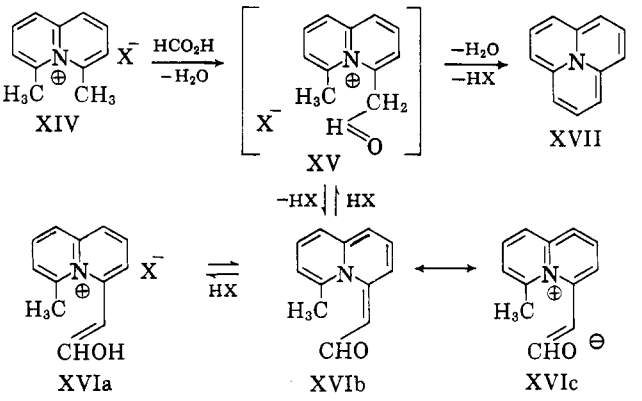
The ketone hydrobromide (Vb) gave satisfactory analytical results and formed a highly fluorescent phenylhydrazone. The fact that it shows normal ketonic carbonyl absorption at 1712 cm.$^{-1}$ in the infrared, along with phenylhydrazone formation, seems to be sufficient to exclude the alternative hydroxydihydroquinolizinium structure (Xb). Similarly, the double-bond isomer (XIb) is excluded on the basis of the ultraviolet spectrum of Vb which shows λ_{max} 270 mμ (log ϵ 4.14), 301 mμ (4.19).[7]

It is of interest that while fourteen to eighteen hours in refluxing acetic anhydride were necessary to obtain a 60% over-all yield of 4,6-dimethyl-2-phenylquinolizinium bromide (IXc), a similar reaction sequence starting with 2-picoline gave a 65% yield of the known[3] 4-methyl-2-phenylquinolizinium bromide (IXb) in only four hours under the same conditions. The decrease in rate of ring closure, going from the picoline to the lutidine adducts, reflects the increase in nonbonded repulsion between the potential 4- and 6-methyl groups in the latter series.

The structures of 2,4,6-trimethyl- and 4,6-dimethyl-2-phenylquinolizinium bromides (IXa and IXc, respectively) prepared in this study were assigned on the bases of analytical results of both the bromides and picrates, analogy of the method of formation with that of Woodward,[1] Richards,[3] and Nesmeyanov,[4] and the similarity of the spectra of the new compounds (IXa) and (IXc) with the spectra of the known 2-methyl- and 2-phenyl-4-methylquinolizinium bromides (IXd and IXb, respectively).

In an attempt to define further the steric requirements for cyclization of lutidine-β-dicarbonyl adducts, lutidyllithium reacted with acetoacetaldehyde dimethyl acetal to give a 40% yield of the pyridyl acetal IIIc. This material was cyclized under mild conditions, with excess picric acid in ethanol to 2,6-dimethylquinolizinium picrate (IXe), although the salt obtained from the reaction mixture appeared to be quite impure, so that the yield of pure IXe was rather low (15–20%).

Attempted Ring Closures to Cycl[3.3.3]azines.—While a number of synthetic approaches to cycl[3.3.3]-azines can be visualized, it seemed that a particularly attractive sequence would be the reaction of a 4,6-dimethylquinolizinium salt (XIV) with a suitable formic acid derivative (represented here as formic acid). It was recognized that while the initial condensation (XIV–XV) will almost certainly be base-catalyzed, the intermediate XV may undergo rather facile loss of HX to give XVIb and/or XVIc, so that in the final step (XV–XVII) acid catalysis might be required.



All the quinolizinium compounds studied were stable to acid conditions as implied by the method of formation. The salts gave neutral aqueous solutions and showed no reaction with carbonate or bicarbonate solution. However, treatment of the methylquinolizinium salts with the stronger bases, sodium hydroxide or ethoxide, resulted in the formation of dark, water-insoluble oils which could not be characterized.

Richards and Stevens[3] have shown that 2-methylquinolizinium iodide condenses with *p*-dimethylaminobenzaldehyde in the presence of piperidine to form the 2-*p*-dimethylaminostyryl derivative. We have found that under the same conditions 4-methyl-2-phenylquinolizinium bromide (IXb) also forms condensation products, while 4,6 - dimethyl - 2 - phenylquinolizinium bromide (IXc) is recovered unchanged. The product is assumed to bear the dimethylaminostyryl group at the 2-position since salt IXc failed to react.

(7) In comparison, benzalacetone (compare XIb) has its long-wavelength maximum at 279 mμ (log ϵ 4.3), while the more extended conjugated system of 2-styrylpyridine shows maximum absorption at 310 mμ (log ϵ 4.4). The latter is obviously more similar to the observed spectrum of Vb. N. H. Cromwell and W. B. Watson, *J. Org. Chem.*, **14**, 414 (1949), and J. L. Bills and C. R. Noller, *J. Am. Chem. Soc.*, **70**, 957 (1948).

The failure to condense with aldehydes at the 4- or 6-methyl groups, when such groups are present in both positions, is attributed to steric hindrance by the neighboring methyl group[8] to the formation of the reactive anhydrobase. It should be noted that with the stronger base, hydroxide, decomposition is the only detectable result.

While 2-methylquinolizinium bromide reacts readily with benzaldehyde in the presence of piperidine to give the highly fluorescent 2-styrylquinolizinium bromide, condensation of 2,4,6-trimethylquinolizinium bromide with benzaldehyde, using piperidine or triethylamine as catalysts, failed to occur. The use of excess triethylamine in this reaction gave a high yield of triethylamine hydrobromide and a small amount of an unstable solid, which could not be characterized.

We have also found that IXa does not react with *p*-nitro- or *p*-methoxybenzaldehyde nor with formaldehyde in the presence of either piperidine or triethylamine.

Treatment of 2,4,6-trimethylquinolizinium bromide with phenyllithium, followed by addition of benzaldehyde or gaseous formaldehyde resulted in the formation of intractable tars. In the former case, benzhydryl alcohol could be obtained. Similar observations have been made in the reaction of other quinolizinium salts with *n*-butyllithium.[3]

Heating, 2,4,6-trimethylquinolizinium bromide (IXa) with formic acid, formic acid–hydrobromic acid, or formic acid–sodium formate resulted in recovery of IXa as the picrate. Treatment with sodium acetate in acetic anhydride was also without effect. Attempted side-chain formylation with dimethyl-formamide-phosphorus oxychloride gave some recovered IXa along with intractable material. Hamer[9] and Brooker[10] have found that ethyl orthoformate is an effective reagent in the preparation of cyanine type dyes. Using somewhat different conditions, 2,4,6-trimethylquinolizinium bromide (IXa) and 4,6-dimethyl-2-phenylquinolizinium bromide (IXc) were heated with excess ethyl orthoformate in the presence of excess pyridine or triethylamine in alcoholic solution. In this instance the starting quinolizinium salts were recovered. No reaction was observed when the salts were treated with ethyl orthoformate in refluxing acetic anhydride[11] or in alcohol in the presence of anhydrous zinc chloride. Treatment of a hot pyridine suspension of 2-methylquinolizinium bromide (IXd) with ethyl orthoformate gave only traces of a red substance; starting material was recovered in substantial amounts. Low solubility may prevent formation of appreciable quantities of the cyanine-type salt.

Baker and McEvoy have shown that certain compounds, such as quinaldine methiodide, can be converted to C-benzoyl derivatives under Schotten–Baumann conditions.[12] Treatment of 4,6 - dimethyl - 2-phenylquinolizinium bromide (IXc) with aqueous alkali in the presence of a chloroform solution of benzoyl chloride gave only intractable tarry products. No evidence for the formation of the benzoyl derivative was obtained.

Similarly, decomposition occurred when IXc was treated with sodium ethoxide and ethyl oxalate in ethanol, in an attempt to prepare the ethoxyalyl derivative.

Attempts to remove selectively one of the methyl groups of 2,4,6-trimethylquinolizinium bromide (IXa) by oxidation with potassium permanganate failed. Intractable products were formed by the oxidation, with permanganate, of 2 - *p* - dimethylaminostyrylquinolizinium bromide.

Bromination of 2,4,6-trimethylquinolizinium bromide (IXa), in acetic acid gave the corresponding tribromide. The tribromide also resulted from the reaction of IXa with N-bromosuccinimide in acetic acid and from the reaction of IXa with bromine in acetic acid containing sodium acetate in excess.

Experimental[13]

Elemental microanalyses were carried out by Dr. V. B. Fish, to whom the authors express their appreciation.

4,4-Ethylenedioxy-2-methyl-1-(6′-methyl-2′-pyridyl)-2-pentanol (IIIa).—To a solution of 2,6-lutidyllithium, prepared from 3.47 g. (0.5 g.-atom) of lithium wire, 40 g. (0.25 mole) of bromobenzene, and 27 g. (0.25 mole) of 2,6-lutidine in about 150 ml. of ether, was added 18 g. (0.125 mole) of 4,4-ethylenedioxy-2-pentanone at such a rate that the ether boiled slowly. The reaction mixture, which became reddish orange during this addition, was stirred and refluxed for 90 min. more, then cooled in an ice bath while 25 ml. of water was added slowly. The two-phase mixture was separated, the aqueous layer was washed with several small portions of ether and the combined ethereal solutions were dried over magnesium sulfate.

Evaporation of ether, followed by distillation at reduced pressure, yielded a forerun containing lutidine and bromobenzene and then 16.6 g. (52.9%) of the desired product (IIIa), b.p. 135–142°/0.4 mm., $n^{23}D$ 1.5109.

An oily picrate, which could not be crystallized, was formed when IIIa was added to saturated alcoholic picric acid.

2,4,6-Trimethylquinolizinium Bromide (IXa).—Concentrated hydrobromic acid was added slowly to a mixture of 12.5 g. (0.05 mole) of IIIa and 35 ml. of water (to pH 2). The resulting mixture was extracted with ether to remove traces of biphenyl, then evaporated to dryness on the steam bath *in vacuo*. The red, gummy residue was dissolved in 100 ml. of acetic anhydride and heated at gentle reflux overnight. On cooling, the solution deposited 7.36 g. (59%) of IXa as tan crystals. A further 2.58 g. was obtained on partial evaporation of the acetic acid and anhydride mother liquor for a total yield of 9.84 g. (82%). This crude material was recrystallized three times from absolute ethanol to give 6.94 g. (55.5%) of slightly off-white microcrystals, m.p. 300° with previous decomposition from 270°. The analytical sample was obtained by recrystallizing this material several more times, until the mother liquor was no longer colored.

Anal. Calcd. for $C_{12}H_{14}NBr$: C, 57.16; H, 5.60; N, 5.56; Br, 31.69. Found: C, 57.04; H, 5.81; N, 5.36; Br, 31.79.

2-*p*-Dimethylaminostyryl-4,6-dimethylquinolizinium Bromide.—A solution of 0.5 g. (2 mmoles) of the trimethylquinolizinium bromide (IXa) and 0.45 g. (3 mmoles) of *p*-dimethylaminobenzaldehyde in 7 ml. of absolute ethanol was heated overnight in the presence of a drop of piperidine. The deep red solution was evaporated to dryness *in vacuo*, the residue taken up in methanol and warmed while ethyl acetate was added to precipitate the product. After cooling, the solution was filtered to give 0.48 g. (63%) of crude product, m.p. above 300° with decomposition from 280°. Recrystallization from absolute alcohol furnished the analytical sample as small deep red needles.

Anal. Calcd. for $C_{21}H_{23}N_2Br$: C, 65.80; H, 6.05; N, 7.31. Found: C, 65.89; H, 6.40; N, 7.05, 7.07.

(8) A. P. Phillips, *J. Org. Chem.*, **13**, 622 (1948); **12**, 333 (1947), has shown that this type of condensation is extremely sensitive to small steric and inductive effects.

(9) F. M. Hamer, *J. Chem. Soc.*, 1927, 2796.

(10) L. G. S. Brooker and F. C. White, *J. Am. Chem. Soc.*, **57**, 2480 (1935); **73**, 5332 (1951).

(11) W. Konig, *Ber.*, **55**, 3293 (1922); **57**, 685 (1924).

(12) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 118 (1955).

(13) Melting points below 250° were determined in a stirred oil bath, using Anschütz thermometers. Melting points higher than 250° were determined in a gas-heated copper block, All melting and boiling points are uncorrected.

3-Ethoxy-1-phenyl-2-buten-1-one (Enol Ether of Benzoylacetone).[14]—A solution of 24.3 g. (0.15 mole) of benzoylacetone, 24.3 g. (0.164 mole) of ethyl orthoformate, and 0.5 g. of *p*-toluenesulfonic acid in 150 ml. of dry benzene was heated under an 8 in.-Vigreux column at such a rate that only ethyl formate distilled. The head temperature ranged up to 60° at the highest. After 36 hr., 10.6 g. (95%) of distillate had been collected. The mixture was cooled and poured onto excess aqueous potassium carbonate and extracted. The benzene solution was dried over magnesium sulfate after a little pyridine had been added. Evaporation, followed by distillation through a Vigreux column gave 16.3 g. (60%) of the enol ether as a yellow oil, b.p. 97–101°/0.4 mm. Its infrared spectrum was identical with that of a sample prepared by the method of Claisen.[14]

4,6-Dimethyl-2-phenylquinolizinium Bromide (IXc). A.—An ether solution of 0.1 mole of 2,6-lutidyllithium was prepared in the usual way and cooled to 0°. A solution of 9.5 g. (0.05 mole) of the enol ether of benzoylacetone (XII) in 25 ml. of ether was added slowly, causing the color of the solution to go from deep red to dark green or yellow. After this addition, the mixture was allowed to come to room temperature during 4 hr. Then, it was cooled once again and poured into a mixture of 20 ml. of concentrated hydrochloric acid and about 100 g. of ice. The resulting mixture was separated, the ether layer washed several times with dilute hydrochloric acid, and the combined aqueous acid solutions made basic with sodium bicarbonate. The resulting oil was extracted into ether, dried over magnesium sulfate and evaporated, most of the excess lutidine being removed at 40° (water bath) and 0.5 mm. The viscous residue was then covered with about 50 ml. of water, and concentrated hydrobromic acid was added carefully to pH 2. This solution was then evaporated on the steam bath *in vacuo* to dryness. The residue was dissolved in 100 ml. of acetic anhydride and heated at reflux overnight. Cooling the solution gave 9.0 g. (60.5%) of the crude quinolizinium compound (IXc) as light tan needles, m.p. 297°, with previous decomposition. Several recrystallizations from 95% ethanol afforded slightly off-white crystals, but did not change the melting point.

Anal. Calcd. for $C_{12}H_{16}N$ Br: C, 64.97; H, 5.13; N, 4.46; Br, 25.4. Found: C, 65.13; H, 5.00; N, 4.51; Br, 25.67.

The picrate was prepared from the bromide and aqueous sodium picrate and recrystallized from ethanol–acetone, m.p. 212.5° dec.

Anal. Calcd. for $C_{23}H_{18}N_4O_7$: C, 59.74; H, 3.92; N, 12.12. Found: C, 60.10: H, 3.81; N, 11.36; 11.60.

Reworking the acetic acid–acetic anhydride mother liquors from the reaction gave only traces of IXc, along with some lutidine hydrobromide.

B.—In a similar reaction, in which water was used to quench the organometallic solution, attempted distillation of the resulting ether-soluble bases gave a yellow oil, b.p. 128–138°/0.3 mm., which, on treatment with dilute hydrobromic acid gave 6.3 g. (72% recovery) of benzoylacetone, m.p. 52–56°. Evaporation of the acid solution, followed by treatment with acetic anhydride, as described gave 0.72 g. (4.8%) of the desired quinolizinium bromide.

4-Phenyl-5-(6′methyl-2′-pyridyl)-4-buten-2-one Hydrobromide (Vb).—2,6-Lutidyllithium was added to the enol ether of benzoylacetone (XII), using the same quantities and technique as in procedure A above. However, when the acetic anhydride was warmed slightly (*not* refluxed) for a few minutes to dissolve the gummy hydrobromide, a white solid was produced. This material was filtered, washed with acetic anhydride and ethyl acetate to give 6.0 g. (36%) of the purified hydrobromide, which was recrystallized for analysis from methanol containing a little hydrobromic acid. The analytical sample has m.p. 117.5–178.5°. Slightly high carbon content suggests contamination by the free base or quinolizinium compound.

Anal. Calcd. for $C_{17}H_{18}NOBr$: C, 61.45; H, 5.46; N, 4.22. Found: C, 62.25; H, 5.65; N, 4.45.

The phenylhydrazone was prepared in aqueous alcohol and recrystallized from 95% ethanol, m.p. 143–144°.

Anal. Calcd. for $C_{23}H_{23}N_3$: C, 80.90; H, 6.79; N, 12.31. Found: C, 80.85; H, 6.63; N, 12.18.

This derivative shows strong yellow-white fluorescence under ultraviolet light.

Treatment of 5.0 g. of the salt (Vb) with hot acetic anhydride overnight gave 3.5 g. (74%) of 2-phenyl-4,6-dimethylquinolizinium bromide (IXc).

4-Methyl-2-phenylquinolizinium Bromide (IXb).—This material was prepared by the reaction of 0.1 mole of 2-picolyllithium with 9.5 g. (0.05 mole) of benzoylacetone enol ether (XII) exactly as described in the preparation of 2-phenyl-4,6-dimethylquinolizinium bromide (IXd) by procedure A, col. 1. The product began to precipitate from the acetic anhydride solution soon after boiling commenced. The solution was refluxed for 4 hr., then cooled and filtered to give 9.85 g. (65.5%) of the quinolizinium salt (IXb), as brown crystals, m.p. 295° with previous decomposition. Two recrystallizations from 95% ethanol furnished white microcrystals of unchanged melting point.

The bromide was converted to the known picrate, m.p. 230° dec., after crystallization from ethanol (lit.,[3] m.p. 226° dec.).

2-Phenyl-4-dimethylaminostyrylquinolizinium Bromide.—A solution of 0.3 g. (1 mmole) of 4-methyl-2-phenylquinolizinium bromide (IXb) and 0.3 g. (2 mmoles) of *p*-dimethylaminobenzaldehyde in 5 ml. of absolute ethanol, containing 3 drops of piperidine was refluxed gently overnight, then chilled and filtered to give 0.25 g. of the condensation product (58%). Two recrystallizations from methanol gave the analytical sample as fine red needles, m.p. 280° dec. This material, dried at 56°, contained one molecule of methanol of crystallization.

Anal. Calcd. for $C_{25}H_{23}N_2Br \cdot CH_3OH$: C, 67.38; H, 5.87; N, 6.05. Found: C, 67.89; H, 5.94; N, 6.15.

2,6-Dimethylquinolizinium Bromide and Picrate (IXe).—A solution of 0.1 mole of 2,6-lutidyllithium was prepared in the usual way. To this was added a solution of 6.6 g. (0.05 mole) of acetoacetaldehyde dimethyl acetal (IIb) at 0°. The resulting mixture was stirred for an additional hour, at room temperature, water was added, the layers separated, the aqueous layer extracted several times with ether, and the combined ethereal solutions dried ($MgSO_4$) and distilled. After removal of low boiling material, 5.1 g. (42.6%) of IIIc was obtained as a light yellow oil, b.p. 127–135°/0.4 mm.

A. A solution of 2.4 g. (0.01 mole) of the above hydroxyacetal (IIIc), 7 g. of picric acid, and 25 ml. of absolute alcohol was refluxed for 2 hr., and cooled. Filtration then gave 3.22 g. (73.8%) of the crude quinolizinium picrate (IXe) as green, somewhat sticky crystals. Several recrystallizations from 95% ethanol (charcoal) gave yellow needles, m.p. 137–138°.

Anal. Calcd. for $C_{17}H_{14}N_4O_7$: C, 52.85; H, 3.65; N, 14.50. Found: C, 52.83; H, 3.14; N, 14.29.

B. Concentrated hydrobromic acid was added to a mixture of 7.2 g. (0.02 mole) of the hydroxy acetal (IIIc) in about 50 ml. of water, to pH 2. The resulting solution was extracted with ether and evaporated to dryness *in vacuo*. The residue was heated for 12 hr. in 50 ml. of acetic anhydride, at the boiling point. On cooling, this solution gave 5.8 g. (80.5%) of 2,6-dimethylquinolizinium bromide as dark crystals m.p. 214° dec. The crude product was taken up in hot chloroform, the solution concentrated until the first crystals appeared, then cooled slowly and filtered. This procedure was repeated once more, then the product was crystallized once from ethanol–ethyl acetate to give yellowish needles, m.p. 215–217°.

This bromide was converted to the corresponding picrate with aqueous sodium picrate. This derivative had m.p. 136.5–138°, undepressed on admixture with a sample prepared by method A, above.

2-Styrylquinolizinium Bromide.—Two drops of piperidine were added to a refluxing solution of 0.45 g. (2 mmoles) of 2-methylquinolizinium bromide and 0.3 g. (3 mmoles) of benzaldehyde in 5 ml. of absolute ethanol. Heating was continued for 4 hr., then the orange mixture was chilled and filtered to give 0.31 g. (49.7%) of the styrylquinolizinium salt, m.p. 258–261° dec. as brown needles. After two recrystallizations from methanol, the salt was obtained as light yellow needles, m.p. 261–262° dec.

Anal. Calcd. for $C_{17}H_{14}NBr$: C, 65.40; H, 4.52; N, 4.49. Found: C, 65.09; H, 5.39; N, 4.20.

This compound shows strong yellow fluorescence in ultraviolet light.

(14) This procedure represents some improvement over the method of Claisen [L. Claisen, *Ber.*, **40**, 3909 (1907)] in that the use of ferric chloride results in the presence of considerable quantities of ferric benzoylacetonate, making distillation of the product troublesome.