Preparation Of 4,6-dimethylquinolizinium Salts As Potential Intermediatesin The Synthesis Of Cycl(3,3,3)azines.

PREPARATION OF 4,6-DIMETHYLQUINOLIZINIUM SALTS AS POTENTIAL INTERMEDIATES IN THE SYNTHESIS OF CYCL[3,3,3]AZINES

by

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ABSTRACT

The preparation of 4,6-dimethyl-2-phenyl- and 2,4,6-trimethylquinolizinium bromides 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. The mechanism of this ring-closure is discussed. Further, various functional derivatives of these and other quinolizinium salts have been obtained, and the ultraviolet spectra of a number of quinolizinium salts are discussed in terms of electron-release by substituents to the cationic ring system.

These 4,6-dimethylquinolizinium salts were desired as potential intermediates in the synthesis of the theoretically interesting cycl [3,3,3] azines. However, the compounds obtained were not converted to the corresponding cycl [3,3,3] azines under a variety of conditions.

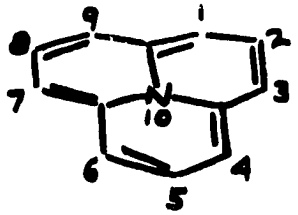
While the activity of a methyl group in the 2- or 4-position of the quinolizinium ring system has been shown to

parallel that of e.g., the 2-methyl group of 2-picoline methiodide, especially in reaction with aldehydes, the relative inertness in both the 4- and the 6-positions has been attributed to steric hindrance to the formation of a reactive anhydro base.

In addition, a number of unsuccessful approaches to the preparation of various quinolizinium salts are outlined.

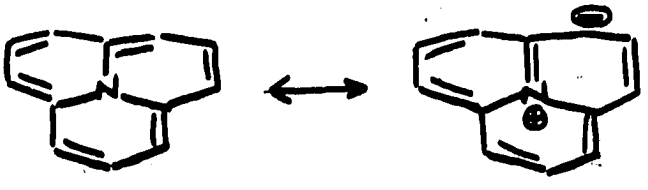
INTRODUCTION

Cycl[3,3,3]azine (I) is a member of a novel class of condensed heterocycles, consisting of a central nitrogen atom bonded to a completely conjugated hydrocarbon macrocycle. Theoretical interest in the cyclazines, as a class, arises from the possibility of considerable interaction of the free pair of electrons on nitrogen with the peripheral π-electron system. Such interaction would be expected to result in signifigant resonance stabilization and to give rise to certain physical and chemical properties, such as non-basicity and ease of electrophilic substitution.



I

Recent molecular-orbital studies have predicted the resonance energy of I to be somewhat greater than that of anthracene, and, in addition, that (valence bond) structures such as Ia would make important contributions to the ground state of the molecule. (1,3)



I Ia

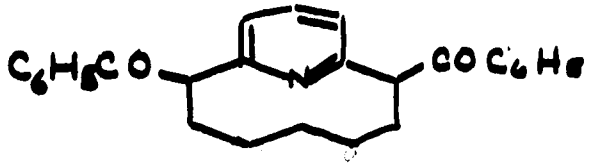
Similar calculations, using the same parameters, lead to a value for the resonance energy of the known cycl[3,2,2]azine (II) which is somewhat less than that of I and slightly less than the resonance

energy of naphthalene.Since these calculations do not take into account the strain energy resulting from the fusion of two five-membered rings in II,it would seem that the actual resonance energy of II is considerably less than that of I.

In accord with the predictions of theory,cycl[3,2,2]azine has been synthesized (1) along with a number of substituted derivatives (2),and has been found to be quite stable under ordinary conditions. The non-basicity of II and the ease with which it undergoes electrophilic substitution provide evidence for important contributions from canonical forms such as IIa and IIb.

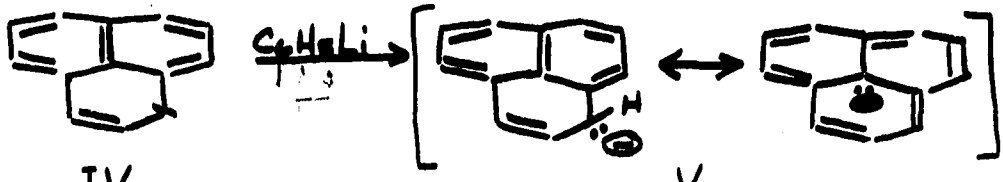
II IIa IIb

In order to test the theoretical predictions,the synthesis of cycl[3,3,3]azine (I) and its simple derivatives is of prime impottance.Only one attempt to prepare I appears in the literature (4), and this failed at an early stage.More recently in these laboratories,Beach has explored synthetic routes to the pyridocyclodecane III,closely related to I.(5)



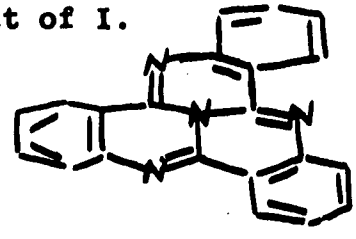
III

It may be noted that cycl[3,3,3]azine is isoelectronic with the reactive carbanion,V,resulting from treatment of perinaphthalene (IV) with strong base.(6)

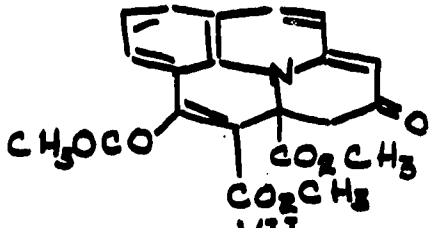


IV V

Condensed triaza derivatives of I,known as tricycloquinazolines (VI) are well known (7).In addition,one of the minor products of the reaction between dimethyl acetylenedicarboxylate and quinaldine has been formulated as VII (8),which contains a ring,system quite similar to that of I.

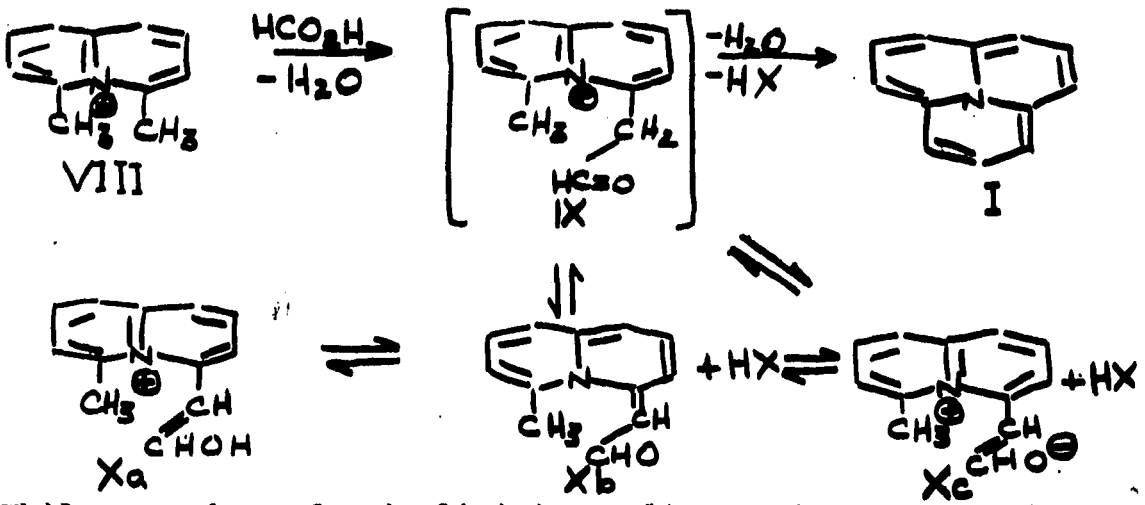


VI



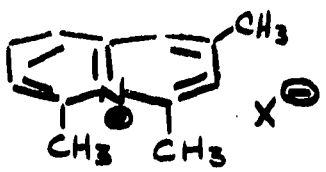
VII

While a number of synthetic approaches to cycl[3,3,3]azine can be visualized,it seems that a particularly attractive sequence would be the reaction of the 4,6-dimethylquinolizinium cation (VIII) with a suitable formic acid derivative (represented here as formic acid).It should be recognized that while the initial condensation (VIII→IX) will almost certainly be base-catalyzed,the intermediate IX may undergo rather facile loss of HX to give Xb and/or Xc,so that in the final step (IX→I),it may be neccessary to resort to acid catalysis.

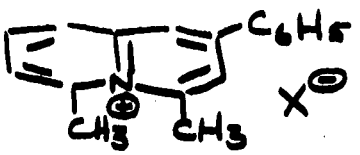


While a number of quinolizinium salts are known, none of these contains methyl groups at the 4- and 6- positions, as required for the ring closure to I outlined above. Thus the object of the work reported here was to prepare quinolizinium salts such as VIII, bearing suitable substituents, and to utilize these salts in the preparation of tricyclic compounds related to cycl[3,3,3]azine.

We have been successful in preparing 2,4,6-trimethylquinolizinium (XI) and 4,6-dimethyl-2-phenylquinolizinium (XII) salts, but all attempts to prepare the corresponding cycl[3,3,3]azines from these salts have failed.



XI



XII

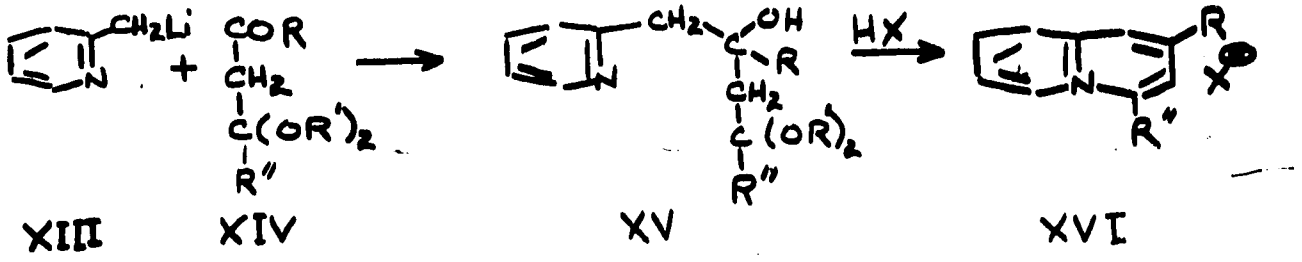
Nomenclature: The cyclazine nomenclature used here has been proposed by Boekelheide (1), with the numbering of the ring positions

as shown on pages 3 and 4.The quinolizinium cation and quinolizine nomenclature and numbering are those adopted by Chemical Abstracts.

RESULTS AND DISCUSSION

QUINOLIZINIUM SALTS

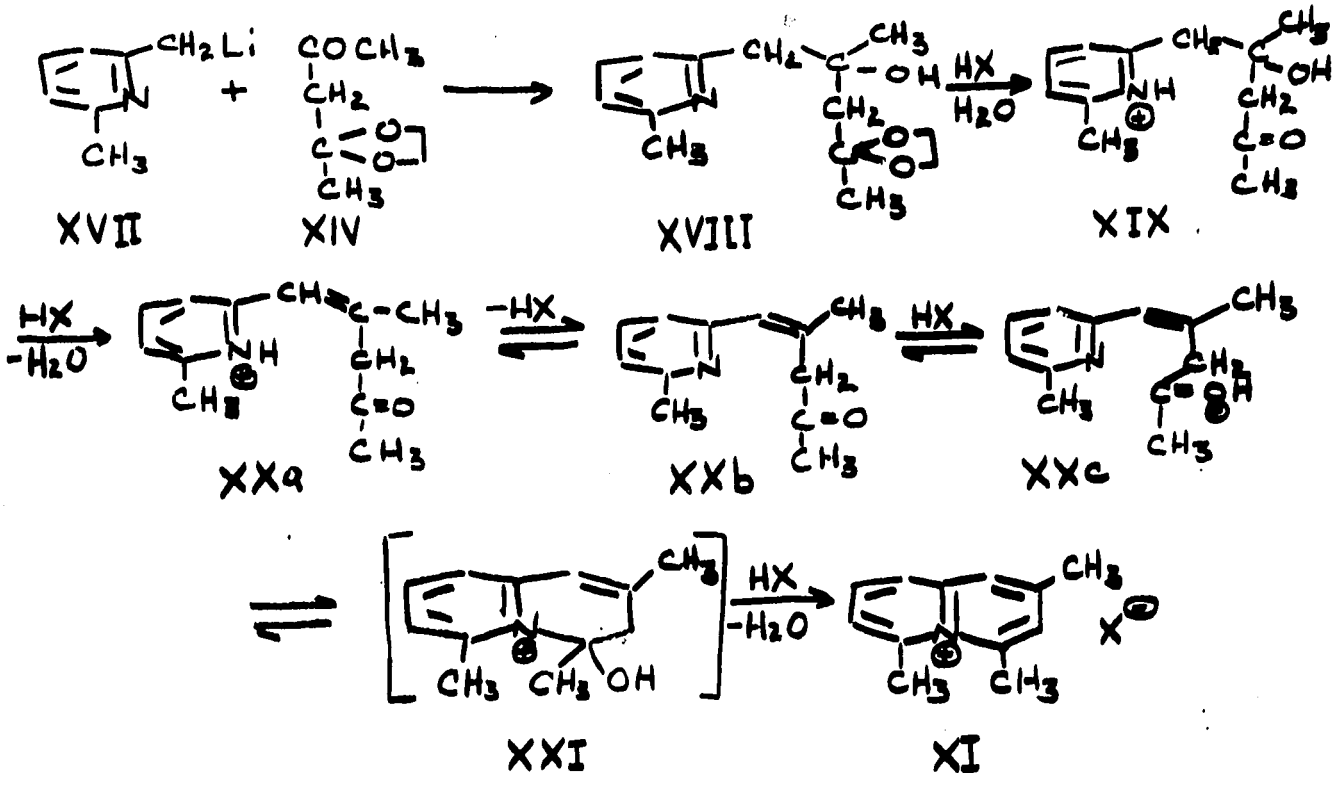
Quinolizinium salts have been known to exist in certain complex alkaloids for some time. However, synthetic routes to relatively simple quinolizinium cations have been developed only recently. One of the most general of these approaches, discovered by Woodward (9) and further elaborated by Richards and Stevens (10), consists of the reaction of picolyllithium (XIII) with the mono-ketal or enol ether of a β-dicarbonyl compound (XIV), followed by cyclodehydration of the intermediate adduct (XV) to the corresponding quinolizinium compound with acid (XV→XVI).



Richards and Stevens (10) have used this method to advantage in the preparation of 2,4-dimethyl-(XVI; R=R'=CH_3) and 2-methyl-4-phenyl-(XVI; R=C_6H_5, R'=CH_3) 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

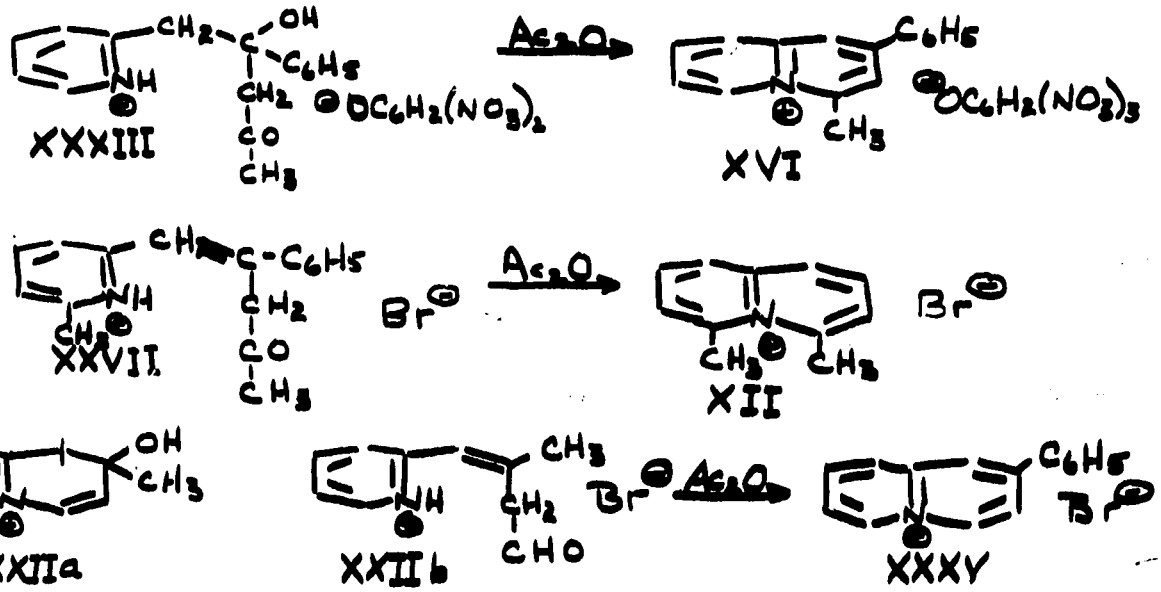
preparation of cycl [3,3,3]azines. It should be noted that this sequence cannot be applied to give 2-unsubstituted quinoliziniumsalts, since the requisite β-dialkoxyaldehydes (XIV:R=H) are not available.

Considerable difficulty was anticipated in the cyclodehydration of the corresponding lutidine adducts (e.g. XVIII) on the basis of the following mechanism,proposed for the formation of quinolizinium compouds from the addition compounds of picolyl- or lutidyl-lithium (XIII or XVII) with suitably protected β-diketones (e.g.XVI):



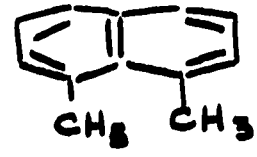
In accord with this postulated mechanism,Richards and Stevens (10) have isolated the picrate of the pyridyl ketone XXXIII (analogous to XIX as an intermediate in the formation of 2-phenyl-4-methylquinolizinium picrate (XVI). In addition,we have isolated

the hydrobromide of the unsaturated ketone XXVII (analagous to XXa)as an intermediate in the preparation of 4,6-dimethyl-2-phenyl-quinolizinium bromide (XII,vide infra),although XXa,itself,could not be isolated in pure form. Further,we have obtained spectral evidence for the formation of XIX on mild acid treatment of the adduct XVIII(Appendix,Figure 4). Nesmayanov (38) has isolated an intermediate,formulated as the hydroxydihydroquinolizinium salt XXIIa,in the preparation of 2-methylquinolizinium bromide (XXXV). Lacking further information,since this work is available to us only in abstract form,and in view of our experience with the ketone XXVII,it would seem that this could be formulated as the isomeric aldehyde derivative XXIIb,which is similar to the proposed intermediate XXa.



Consideration of the preceding mechanism shows that 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 (XX→XXI)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 resulting from non-bonded interaction between the 4- and 6- methyl groups of the intermediate XXI is further increased by dehydration to the planar quinolizinium cation XI. In this connection,examination of a molecular model of XI 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 of4- and 6- methyl groups is presumably of the order of 8 kcal./mole,the value obtained by Packard (11)for for the strain energy of the nearly isosteric 1,8-dimethylnaphthalene (XXIII).

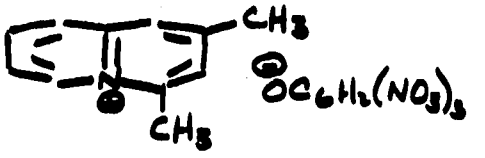


XXIII

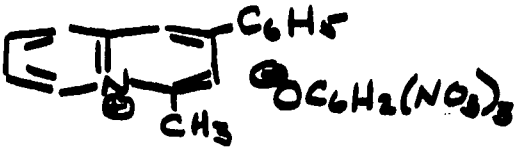
Further consideration of the proposed mechanism reveals that successful cyclodehydration depends on the rather complex acid-base equilibria (XXa⇌XXb⇌XXc).Thus,while excess mineral acid is neccessary for the dehydration steps (XIX→XXa and XXI→XI),the presence of a large excess of strong acid would suppress the dissociation of the salt XXa to the free base XXb,thus preventing attack of the pyridine nitrogen on the carbonyl group (XXc→XXI). It would appear that this is but another case of "optimum pH"such as that observed

in the well-known reactions of ketones with substituted hydrazines.

Previous work has shown that the formation of known quinolizinium salts is subject to a number of subtle factors. Thus, Richards and Stevens (10) have prepared a variety of quinolizinium salts, including 2,4-dimethylquinolizinium picrate (XXIX) 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 preparation of 2-phenyl-4-methylquinolizinium picrate (XVI). In this latter case the hydroxyketone picrate XXXIII resulted; this was subsequently cyclized XVI with acetic anhydride-sulfuric acid.

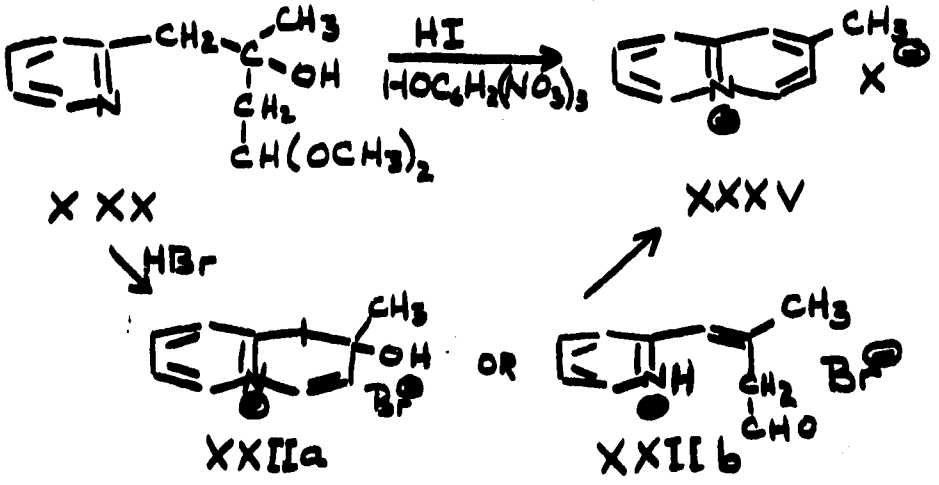


XXIX



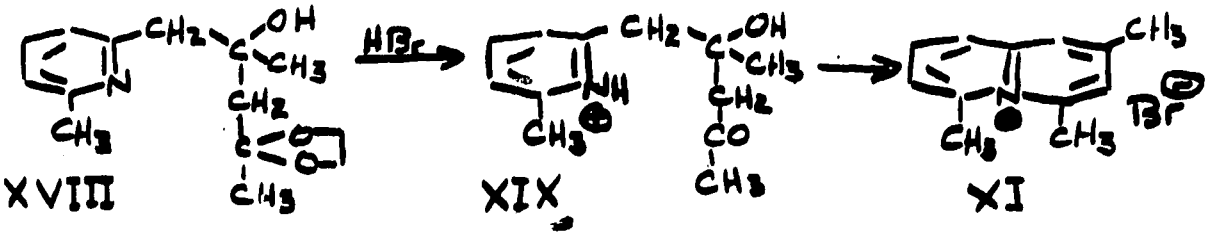
XVI

Similarly, these authors found that the action of hydriodic acid on the pyridyl acetal XXX gives 2-methylquinolizinium iodide directly (XXXV), while Nesmayanov (38) obtained the intermediate XXIIa or XXIIb by reacting XXX with excess concentrated hydrobromic acid; this was finally cyclized to XXXV with acetic anhydride-sulfuric acid.



As expected, the monoethylene ketal of acetylacetone (XIV) reacted smoothly with 2,6-lutidyllithium (XVII) to give 4,4-ethylenedioxy-2-methyl-1-(6'-methyl-2'-pyridyl)-2-pentanone (XVIII) as a somewhat impure pale yellow oil in 50-55% yeild. The structure of XVIII 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 carbonyl reagents. Thus, the ketone hydrobromide (XIX), prepared in situ by treatment of a dilute alcoholic solution of the ketal (XVIII) with hydrobromic acid, shows ultraviolet absorbtion characteristic of simple pyridines in acid solution, λ_{max} 273mμ (log ϵ 4.24; Appendix, Figure 4).

Numerous attempts to cyclize the hydroxy ketal XVIII with alcoholic picric acid, concentrated hydrobromic or hydriodic acids, or sulfuric or polyphosphoric acid, or phosphorous oxychloride were without success, tarry materials being formed under vigorous conditions. Finally, after considerable experimentation, it was found that treatment of the intermediate XVIII with slightly more than one equivalent of hydrobromic acid, followed by evaporation to dryness and cyclodehydration of the resulting crude ketone hydrobromide (XIX) with refluxing acetic anhydride for 18 hours resulted in a 50% yeild of the desired 2,4,6-trimethylquinolizinium bromide (XI). The use of traces of sulfuric acid as a catalyst in the final cyclodehydration led to extensive charring.

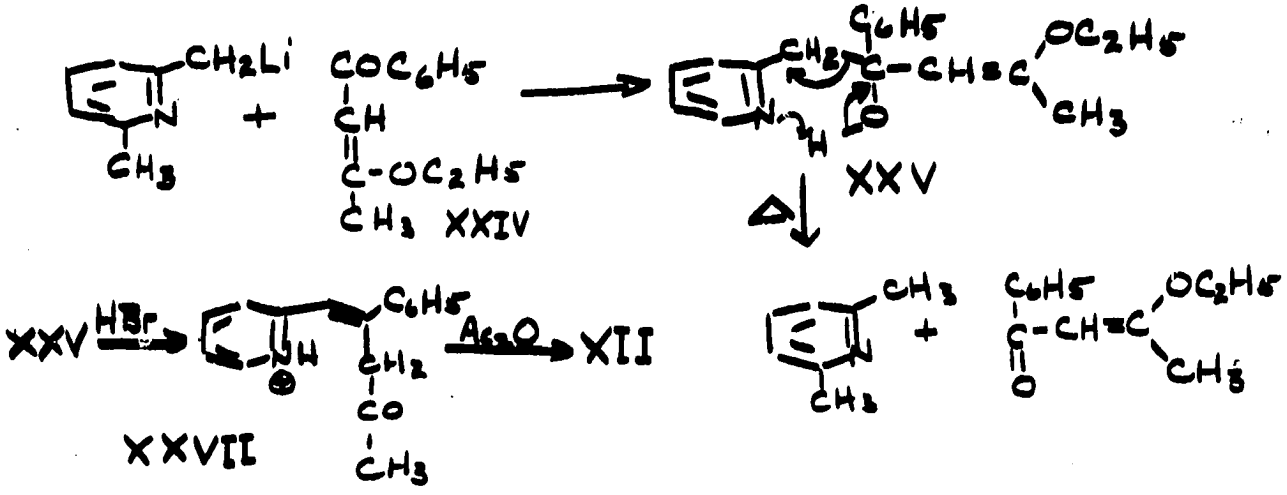


XVIII XIX XI

In an attempt to apply this same reaction sequence to the preparation of 4,6-dimethyl-2-phenylquinolizinium bromide (XII), lutidyllithium (XVII) was reacted with the enol ether of benzoylacetone (XXIV). While the color change and heating 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 (XII) in very low yeild. Thus, it appears that the intermediate enol ether (XXV) is unstable towards heat and reverts to lutidine (XXVI) and the benzoylacetone derivative (XXIV) 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 XXV 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.

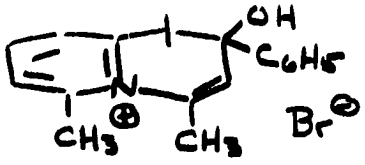
Low-temperature evaporation of most of the excess lutidine and subsequent acidification and cyclodehydration of the residue from this operation with acetic anhydride then gave 4,6-dimethyl-2-phenylquinolizinium bromide (XII) in 60% yeild,based on the enol ether(XXIV).



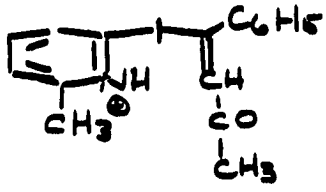
In this case,the hydrobromide of the unsaturated ketone (XXVII) could be separated after the final acidification and evaporation by brief treatment of the resulting viscous mass with warm acetic anhydride. After purification,XXVII was converted to the quinolizinium salt (XII) in 75% yeild by treatment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

The ketone hydrobromide (XXVII) gave satisfactory analytical results and formed a highly fluorescent phenylhydrazone. The fact that it shows normal ketonic carbonyl absorbtion at 1712 $cm.^{-1}$ in the infrared,along with phenylhydrazone formation,seems to be sufficient to exclude the alternative hydroxydihydroquinolizinium formulation (XXVIIa). Similarly, the double-bond isomer (XXVIIb) is excluded on the basis of the ultraviolet spectrum of XXVII

(Appendix,Figure 6) which shows λ_{max} 270 mμ (log ε 4.14),301 mμ(4.19). In comparison,benzalacetone (compare XXVIIb) has its long-wavelength maximum at 279 mμ (log ε 4.3),while the more extended conjugated system of 2-styrylpyridine shows maximum absorbtion at 310 mμ (log ε 4.4).(49,50).The latter is obviously more similar to the observed spectrum of XXVII).



XXVIIa



XXVII b

It is of interest that while 14-18 hours in refluxing acetic anhydride was neccessary to obtain a 60% overall yeild of 4,6-dimethyl-2-phenylquinolizinium bromide (XII),a similar reaction sequence starting with 2-picoline gave a 65% yeild of the known (10) 4-methyl-2-phenylquinolizinium bromide (XVI) in only 4 hours under the same conditions. The decrease in rate of ring-closure,going from the picoline to the lutidine adducts,reflects the increase in non-bonded repulsion between the potential 4- and 6- methyl groups in the latter series.

The structures of 2,4,6-trimethyl- (XI) and 4,6-dimethyl-2-phenyl- (XII) -quinolizinium bromides prepared in this investigation were assigned on the bases of analytical results of both the bromides and picrates,analogy of the method of formation with that of Woodward (9),Richards (10), and Nesmayanov (38),and the similarity of the spectra of the new compounds (XI and XII) with

the spectra of the known 2-methyl-(XXXV) and 2-phenyl-4-methyl(XVI)-quinolizinium bromides.

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

Thus, it appears that 2-alkyl- and 2,4- dialkyl- and 2,6- dialkylquinolizinium salts can be prepared under quite mild conditions from the corresponding pyridyl ketone precursor, while the presence of potential 2-phenyl or 4,6-dialkyl groups in the monocyclic ketonic precursor neccessitates the use of more drastic conditions for effective cyclodehydration.

The use of hydrobromic acid-acetic anhydride in this preparation of quinolizinium bromides has proved quite useful. Thus, this method gives fair to good yields of all the 2-, 2,4- and 2,4,6- substituted quinolizinium salts studied here.

Boekelheide has published the ultraviolet absorbtion spectra of unsubstituted quinolizinium salts and 4-methylquinolizinium picrate (12,13). Further he has shown that the wavelength of maximum absorbtion is not affected by the anion, since quinolizinium bromide, iodide and perchlorate have identical ultraviolet spectra, while the corresponding picrate shows the same maxima (±1 mu.) with increased extinction coefficient. Therefore, data from these compounds can be validly compared with the spectra of the quinolizinium salts prepared in the present work. These data are compiled in Table I.

TABLE I

ULTRAVIOLET AND VISIBLE ABSORBTION MAXIMA OF QUINOLIZINIUM SALTS

(Solvent-95% Ethanol)

Quinolizininium iodide (12)

λ_{max}	log ϵ
226 mμ	4.25
272	3.42
283	3.47
310	4.03
317	3.98
324	4.23

2-Methylquinolizinium bromide (XXXV;Fig.1)

λ_{max}	log ϵ
227 mμ	4.32
275	3.47
287	3.52
301	3.73
314	4.32
321	4.05
326	4.32

4-Methylquinolizinium picrate (13)

λ_{max}	log ϵ
230 mμ	4.49
290	3.77
317	4.22
330	4.40
333	4.18

2,4-Dimethylquinolizinium bromide (XXIX;Fig.2)

λ_{max}	log ϵ
231 mμ	4.37
236	4.38
291	3.59
317	4.08
326	4.05
332	4.28

2,6-Dimethylquinolizinium bromide (XXXI;Fig.3)

λ_{max}	log ϵ
229 mμ	4.35
234	4.34
274	3.50
290	3.55
319	4.08
327	4.06
334	4.28

2,4,6-Trimethylquinolizinium bromide (XI; Fig. 4)

λ_{max}	log ϵ
221 mμ	4.43
243	4.41
299	3.63
335	4.12
348	4.30

2-Phenyl-4-methylquinolizinium bromide (XVI; Fig.5)

λ_{max}	log ϵ
221 mμ	4.39
271	4.32
304	3.96
314	3.96
351	4.35

2-Phenyl-4,6-dimethylquinolizinium bromide (XII; Fig. 6)

λ_{max}	log ϵ
231 mμ	4.38
276	4.34
304	3.93
368	4.43

TABLE I (Contd)

STYRYLQUINOLIZINIUM SALTS

2-Styrylquinolizinium bromide (XL; Fig.1)

λ_{max}	log ϵ
279 mμ	3.86
297	3.83
301	4.03
323	4.23
344	4.21

2-Phenyl-4-p-dimethylamino-styrylquinolizinium bromide (XXXVII;Fig. 7)

λ_{max}	log ϵ
264 mμ	4.21
297	4.33
347	4.47
469	4.34

2-p-Dimethylaminostyryl-4,6-dimethylquinolizinium bromide (XXXVIII; Fig. 7)

λ_{max}	log ϵ
247 mμ	4.23
278	4.19
340	3.96
483	4.63

It can be seen that the spectra of the quinolizinium cation and its methylated homologs can be conveniently considered to be made up of three groups of absorbtion peaks;high intensity absorbtion in the 220-245 mμ region,lower intensity absorbtion in the in the interval between 270-310 mμ, and two or three peaks in the region 305-350 mμ.The effect of increasing methylation of the quinolizinium nucleus is to decrease the fine structure associated with the various absorbtion peaks and to cause increasing bathochromic shifts of the maxima. The shift of absorbtion to longer wavelength is presumably due to the inductive and hyperconjugative contribution of electrons by the methyl groups to the electron-deficient ring system.

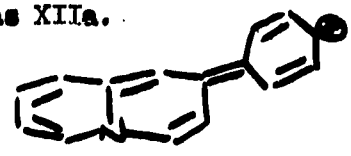
Considering,for simplicity,only the longest wavelength maxima of these compounds (305-350 mμ),it can be seen that the introduction of a single

methyl group at the 2-position(XXXV) causes a bathochromic shift of only 2 mμ,while a 4-methyl substituent leads to a larger shift of +9 mμ,relative to the unsubstituted quinolizinium cation. This is similar to the effect of 2- and 4- methyl groups on the spectra of quinoline.Thus a 2-methyl group attached to the quinoline nucleus results in a bathochromic shift of 7 mμ,relative to quinoline itself,while a 4-methyl substituent has no effect on the position of long wavelength absorbtion (47).This has been attributed to hyperconjugation of the methyl group with the heterocycle.It is interesting to note that in both the quinoline series and in the quinolizinium salts, a methyl group located ortho- to the ring nitrogen gives rise to a greater bathochromic shift than does a methyl group para- to the nitrogen. This may be due mainly to the smaller distance between the nitrogen and ortho-methyl group and to symmetry considerations (47).

The long wavelength maxima of 2,4-dimethyl- (XXIX) and 2,6-dimethyl-(XXXI) quinolizinium bromides occur at nearly the same position as that of the 4-methyl cation,bathochromic shifts of 8 and 10 mμ relative to the parent quinolizinium cation being observed. The lack of further displacement towards longer wavelength,on substitution of a second methyl group,may be due to the small bathochromic effect of the 2-methyl substituent and to the fact that electron donation by one methyl group increases the electron density of the ring system,thus minimizing the electron donating effect of the second methyl group. In harmony with this latter explanation,2,6-dimethylquinolizinium bromide (XXXI),with one methyl group on each ring, absorbs at slightly longer wavelength than does 2,4-dimethylquinolizinium bromide (XXIX),where this opposing effect of both methyl groups is confined to one ring.

While the spectrum of 2,4,6-trimethylquinolizinium bromide (XI) resembles the spectra of the other methylated quinolizinium salts in its general shape, much of the fine structure associated with the simpler compounds disappears in a general broadening of the absorbtion peaks, especially at longer wavelengths. The long wavelength maximum occurs at 348 mμ, a shift of +24 mμ relative to the quinolizinium cation, as a result of the relatively great bathochromic effect of the two methyl groups in ortho- positions with respect to nitrogen. The occurence of absorbtion at such long wavelengths indicates that steric repulsion between the bulky 4- and 6- substituents does not result in puckering of the ring system, since such a deviation from coplanarity would be expected to decrease conjugation of the (formal) 3,4- and 6,7- double bonds with the rest of the π-electron system, resulting in a shift of absorbtion to shorter wavelength.

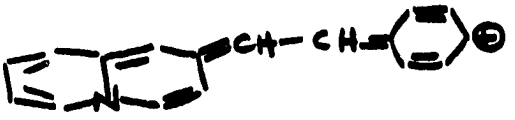
Comparison of the spectra of 2-phenyl-4-methyl-(XVI) and 2-phenyl-4,6-dimethyl-(XII) quinolizinium bromides with the related 2,4-dimethyl-(XXIX) and 2,4,6-trimethyl-(XI) quinolizinium bromides reveal that replacement of a 2-methyl substituent by a 2-phenyl group gives rise to a bathochromic shift of 19-20 mμ presumably as a result of resonance between the phenyl and quinolizinium ring systems, resulting in stabilization of the excited state by forms such as XIIa.



XIIa

Replacement of the methyl group in 2-methyl quinolizinium bromide (XXXV) by a styryl group leads to a bathochromic shift of 18 mμ, with respect to XXXV, due to stabilization of the excited state by forms such

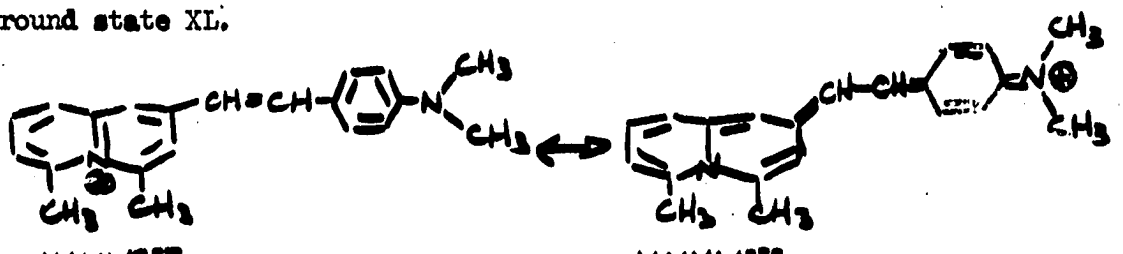
as XLa.



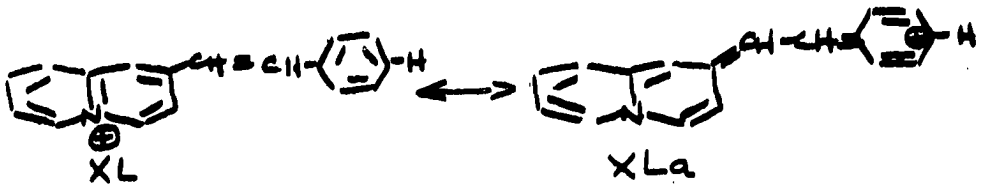
XLa

In contrast to the rather modest spectral shifts caused by the introduction of phenyl or styryl groups in conjugation with the quinolizinium system,the introduction of p-dimrthylaminostyryl groups causes shifts of more than 100 mμ,giving rise to absorbtion in the visible range,thus accounting for the deep red color of these compounds (XXXVII and XXXVIII).

Thus replacement of the 2-methyl group of 2,4,6-trimethylquinolizinium bromide (XI) by the p-dimethylaminostyryl group (XXXVIII)leads to a shift of 135 mμ,while replacement of the 4-methyl group of 2-phenyl-4-methyl-quinolizinium bromide (XVI) by the dimethylaminostryl group (XXXVII) gives rise to a bathochromic shift of 118 mμ in the long wavelength band.The large magnitude of the shift produced by this structural modification, compared to the effect of phenyl and styryl groups,is due to the contribution of canonical forms such as XXXVIIIa to the excited states of the molecules.The energy difference between an excited state such as XXXVIIIa,where the positive charge resides on the exocyclic nitrogen,and the corresponding ground state XXXVIII is much less than the difference between an excited state such as XLa,with positively charged carbon,and the ground state XL.



XXXVIII XXXVIII a



XL XLa

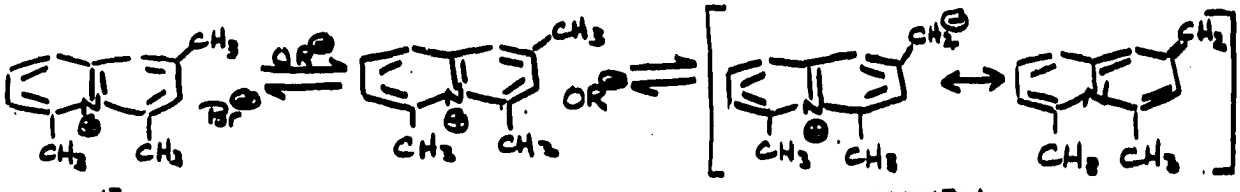
In addition,it is interesting that the spectra of all the styrylquinolizinium compounds studied (XXXVII,XXXVIII and XL) contain another maximum at nearly the same wavelength as that of the methyl compounds from which they are formally derived (XVI,XI and XXV,respectively), indicating a second excited state corresponding to that of the isolated quinolizinium nucleus.

While the preceding discussion deals mainly with shifts in the longest wavelength maxima of quinolizinium salts on substitution,similar shifts occur in the other absorbtion bands,although the trend of these shifts is not as clear-cut in some cases.

The infrared spectra of 2,4,6-trimethyl- (XI) and 4,6-dimethyl-2-phenyl-(XII) quinolizinium bromides have been examined,along with the spectra of the known 2-methyl-(XXXV) and 2-methyl-4-phenyl-(XVI) quinolizinium bromides.While the long wavelength absorbtion (above 6.5 μ) seems quite characteristic of the individual compounds,at shorter wavelengths all of these compounds show strong absorbtion at 1630-1652 $cm.^{-1}$,generally as a doublet,although the 2-methyl compound (XXXV) shows only a single band at 1652 $cm.^{-1}$.This absorbtion,near 6.2 μ,is attributed to C=C and C=N streching vibrations (48).The methylated salts (XI and XXXV) show C-H streching vibrations at 2980 $cm.^{-1}$,while the phenyl derivatives . . . and XVI) have a broad band in this region at ca.2990-3090 $cm.^{-1}$.Further,all the quinolizinium compounds examined have strong absorbtion bands in what is

generally considered the OH/NH region at 3420-3450 $cm.^{-1}$. While the origin of the latter band is uncertain,2,6-lutidine methiodide shows similar absorbtion at 3440 $cm.^{-1}$.It has been noted (48) that pyridine,itself,absorbs weakly at 3420 $cm.^{-1}$ in this same general region.

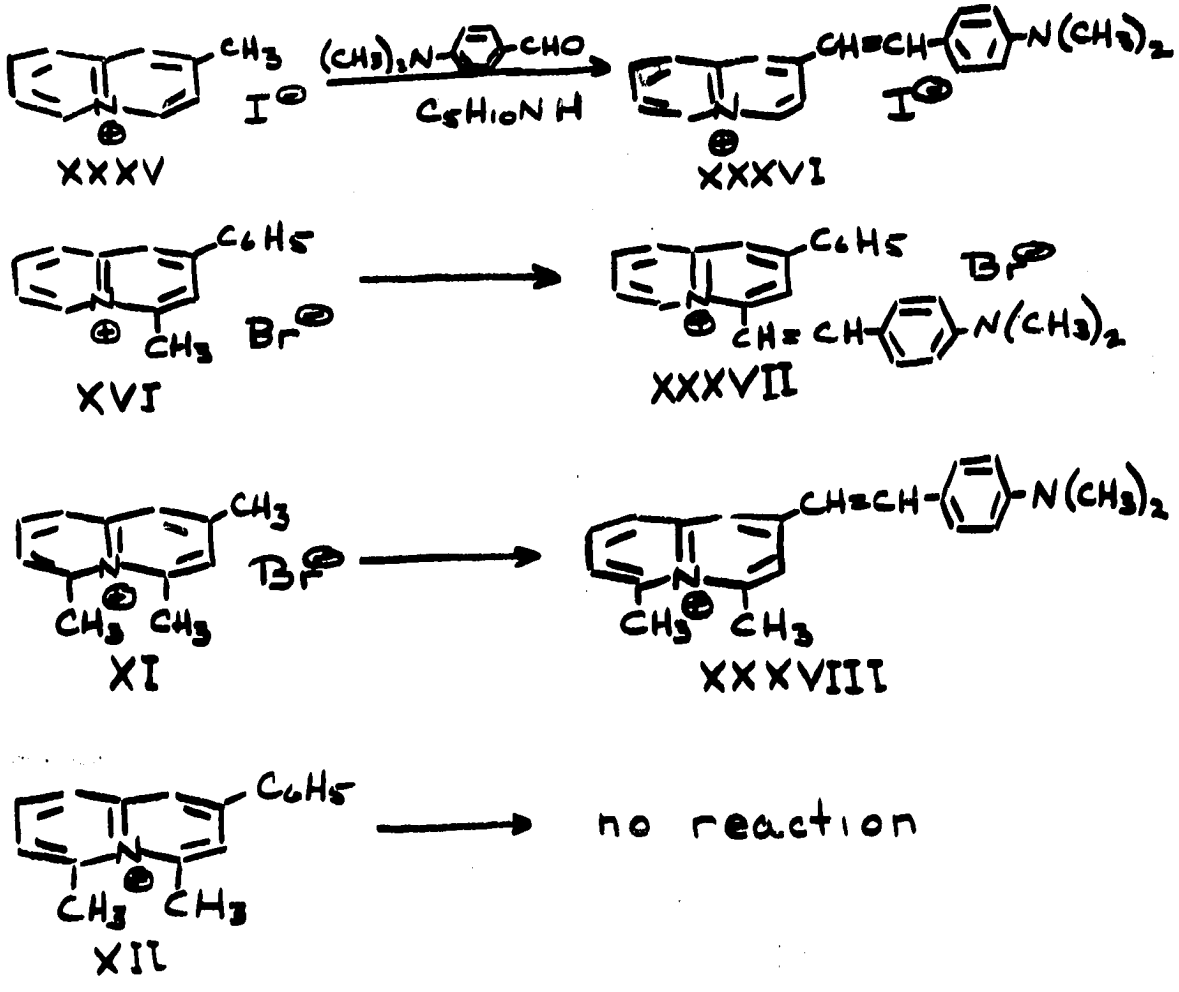
All the quinoizinium compounds studied were stable to acid conditions as implied by the method of formation.The salts give neutral aqueous solutions,and show no reaction with carbonate or bicarbonate solution. However,treatment of the methylquinolizinium salts with stronger bases,e.g. sodium hydroxide or ethoxide,resulted in the formation of dark,water-insoluble oils,which could not be characterized.Under strongly alkaline conditions,formation of the highly reactive,unstable anhydro-base presumably occurs (e.g. XI→XXXIV).This is completely analogous to the behavior of 2- and 4-methyl- pyridine and quinoline quaternary salts.Subsequent rapid decomposition of the anhydro-base XXXIV then results in intractable products.



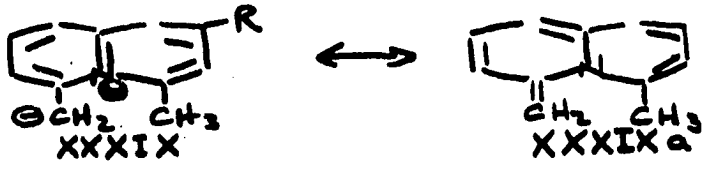
XI XXXIV

Richards and Stevens (10) have shown that 2-methylquinolizinium iodide (XXXV) condenses with p-dimethylaminobenzaldehyde in the presence of piperidine to form the 2-p-dimethylaminostyryl derivative (XXXVI).We have found that under the same conditions 4-methyl-2-phenylquinolizinium bromide (XVI) and 2,4,6-trimethylquinolizinium bromide (XI) also form condensation products,while 4,6-dimethyl-2-phenylquinolizinium bromide (XII) is recovered unchanged.The preparation of XXXVII from XVI represents the first demonstration of the activity of a 4- (or 6-) methyl group in the quinol-

izinium series.The structure of the product (XXXVIII) obtained from the trimethylquinolizinium ion (XI) is assumed to be as shown because of the failure of the 4,6-dimethylquinolizinium salt (XII) to react under these conditions.

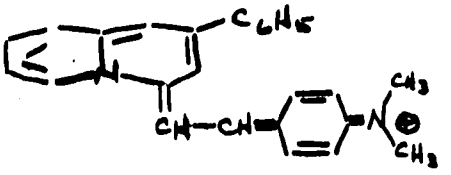


The failure to condense with aldehydes at the 4- or 6- methyl groups, when such groups are present in both positions,is attributed to steric hinderence to the formation of the reactive anhydro-base (XXXIX) by the neighboring methyl group.Thus,in order for XXXIX to be formed,by reaction with the base,piperidine,stabilization of this intermediate by forms

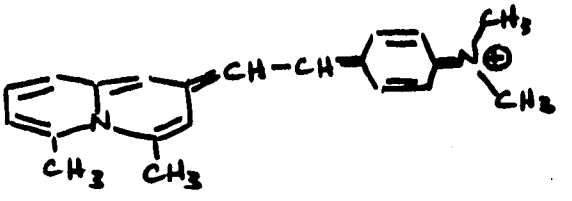


such as XXXIXa must be possible(14).This results in an increase in the H-C-H angle,a shortening of the C-4 to CH_2 bond and a tendency for the methylene group to become coplanar with the ring system.These effects, in turn,decrease the distance between the 6-methyl group and the reactive center,resulting in an increase in steric strain.Thus,formation of a reactive intermediate at the position in question should be much more difficult than similar reaction at the unhindered 2-position of XI.It should be noted that with the stronger base,hydroxide,decomposition of presumably occurs via the anhydrobase XXXIX ($R=C_6H_5$).

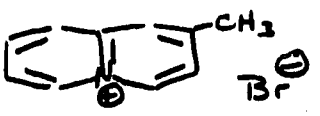
The p-dimethylaminostyrylquinolizinium salts XXXVII and XXXVIII are deep red substances which are reversibly decolorized by acid and fail to form quaternary salts with methyl iodide,consistent with important contributions of the resonance forms XXXVIIa and XXXVIIIa to the state of the molecule (10,15).



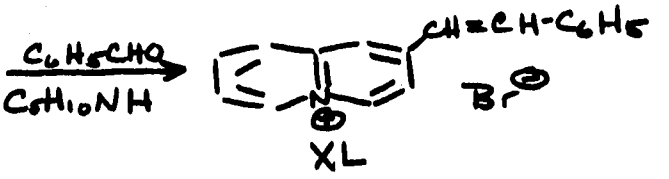
XXXVIIa



XXXVIIIa



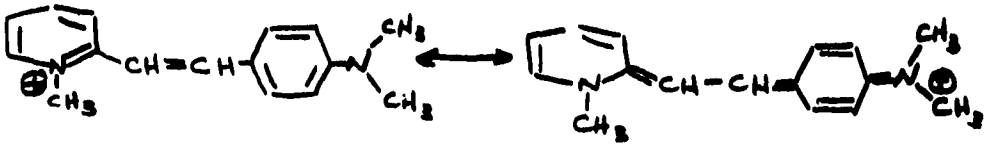
XXXV



XL

While 2-methylquinolizinium bromide (XXXV) reacts readily with benzaldehyde in the presence of piperidine to give the highly fluorescent 2-styrylquinolizinium bromide (XL),condensation of 2,4,6-trimethylquinolizinium bromide (XI) 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 XI does not react with p-nitro- or p-methoxy-benzaldehyde.Phillips (14,15) has shown that the condensation of 2-picoline methiodide with aromatic aldehydes is an equilibrium reaction,maximum yields being obtained with p-dimethylaminobenzaldehyde where important resonance stabilization of the product by forms such as XLI can occur.This author has also shown (14) that this type of condensation is extremely sensitive to small steric and inductive effects.



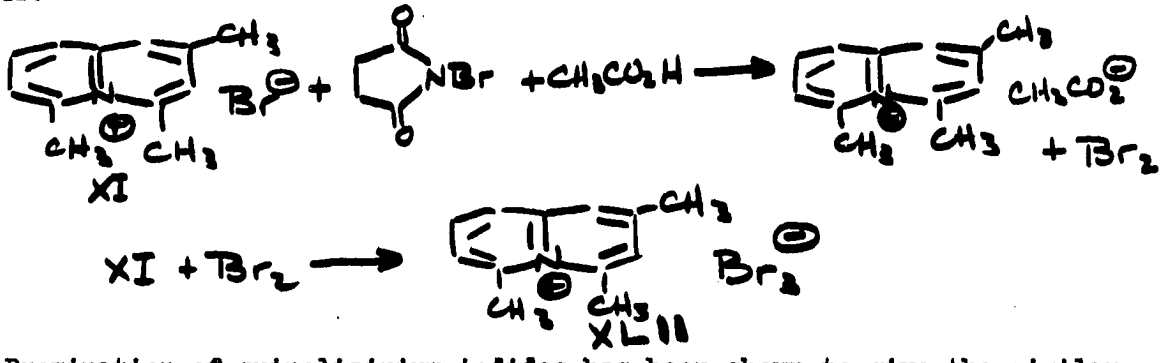
XLI

Thus,failure of XI to react with aldehydes other than p-dimethylamino-benzaldehyde is attributed to the inductive effect of the 4- and 6- methyl groups on the activity of the 2-methyl group and the lack of sufficient stabilization in the product to shift the equilibrium towards the styryl derivative.

The 2,4,6-trimethylquinolizinium salt (XI) also proved to be unreactive towards formaldehyde,in the presence of piperidine or triethylamine.

Treatment of 2,4,6-trimethylquinolizinium bromide (XI) with phenyl-lithium,followed by addition of benzaldehyde or gaseous formaldehyde resulted in the formation of intractable tars.In the former case,benzhydryl alcohol could be obtained.Apparently,formation and rapid decomposition of the anhydro-base takes place under these conditions.Similar observations have been made in the reaction of other quinolizinium salts with n-butyl-lithium (10).

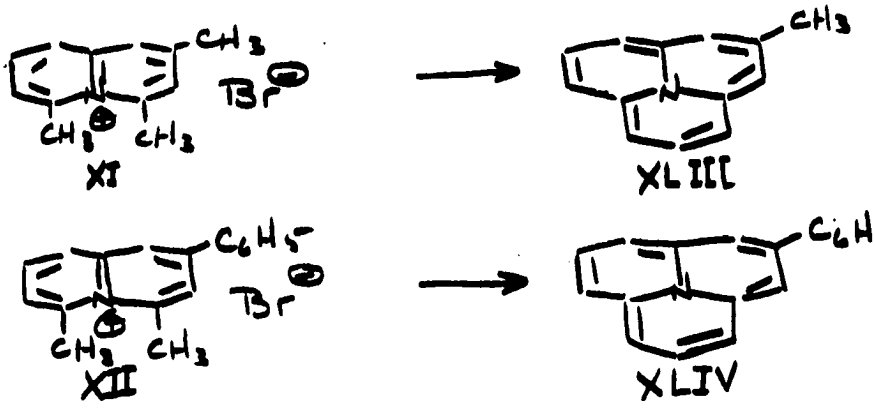
Bromination of 2,4,6-trimethylquinolizinium bromide (XI),in acetic acid gave the corresponding tribromide (XLII).The structure of XLII was verified by analysis,the fact that it liberates iodine from the starch-iodide reagent and by the formation of 2,4,6-trimethylquinolizinium picrate (XI),on treatment of an aqueous solution of XLII with sodium picrate.The tribromide (XLII)also resulted from the reaction of XI with N-bromosuccinimide in acetic acid and from the reaction of XI with bromine in acetic acid containing sodium acetate in excess.These latter conditions have been used for the preparation of ω-tribromo- quinaldine and -picoline (16).The reaction of XI with N-bromosuccinimide may take place in the following manner.



Bromination of quinolizinium iodides has been shown to give the similar dibromoiodides (10).

The tribromide XLII is quite stable to light and heat,but heating its solutions in water,alcohols or acetic acid results in the evolution of bromine and the recovery of the original salt (XI),as the picrate.No ring- or side-chain- bromination could be detected.

Numerous attempts to convert 2,4,6-trimethylquinolizinium bromide (XI) and 4,6-dimethyl-2-phenylquinolizinium bromide (XII) to the corresponding 2-methyl- or 2-phenyl-cycl[3,3,3]azines or derivatives,under a variety of conditions met with no success.



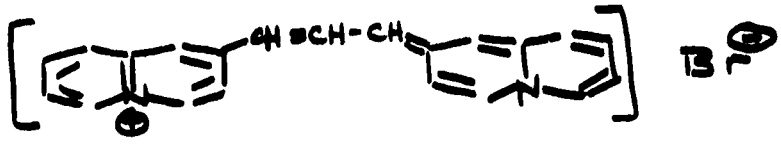
Heating 2,4,6-trimethylquinolizinium bromide (XI) with formic acid , formic acid-hydrobromic acid,or formic acid-sodium formate resulted in recovery of XI as the picrate.Treatment with sodium acetate in acetic anhydride was also without effect.Attempted side-chain formylation with dimethylformamide-phosphorous oxychloride gave some recovered XI,along with intractable material.

In the formation of cyanine dyes from e.g. quinaldine methiodide (XLV),the use of ethyl orthoformate in pyridine has been found to be most effective in a variety of cases (17,18).In the present cases,

the low solubility of both XI and XII in pyridine may not permit reaction. Thus,heating either the trimethyl-(XI) or dimethylphenyl-(XII)-quinolizinium bromides with excess ethyl orthoformate,in pyridine suspension, resulted in nearly quantitative recovery of the quinolizinium salts.It was also found that treatment of a hot pyridine suspension of 2-methylquinolizinium bromide (XXXV) with ethyl orthoformate gave only traces of a red substance;starting material was recovered in substantial amounts.

Here again,low solubility may prevent formation of appreciable

quantities of the cyanine-type salt XLVI.

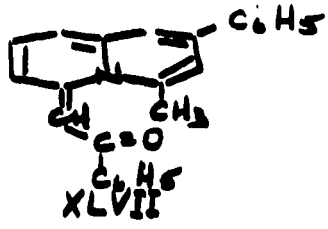


XLVI

Using somewhat different conditions,2,4,6-trimethylquinolizinium bromide (XI) was heated with excess ethyl orthoformate in the presence of excess pyridine or triethylamine in alcoholic solution.In this instance the starting quinolizinium salt XI was recovered.No reaction was observed when the quinolizinium salt XI was treated with ethyl orthoformate in refluxing acetic anhydride (19),or in alcohol in the presence of anhydrous zinc chloride.

Similarly,4,6-dimethyl-2-phenylquinolizinium bromide (XII) does not react with ethyl orthoformate under the conditions outlined above.

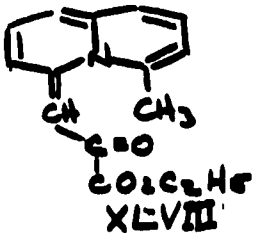
Baker and McEvoy have shown that certain compounds,such as quinaldine methiodide,can be converted to C-benzoyl derivatives under Schotten-Baumann conditions (20).Treatment of 4,6-dimethyl-2-phenylquinolizinium bromide(XII)with aqueous alkali in the presence of a chloroform solution of benzoyl chloride gave only intractable tarry products.No evidence for the formation of the benzoyl derivative (XLVII) was obtained.Apparently decomposition of the anhydro-base derived from XII takes place in preference to benzoylation.



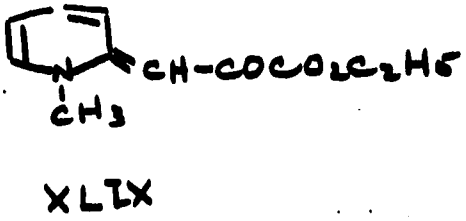
XLVII

Similarly,decomposition occured when XII was treated with sodium ethoxide and ethyl oxalate in ethanol,in an attempt to prepare the ethoxalyl derivative (XLVIII).A similar reaction has been used by Besso

(21) to prepare the pyridylpyruvic ester derivative (XLIX) from 2-picoline methiodide.



XLVIII



XLIX

Attempts to selectively remove one of the methyl groups of 2,4,6-trimethylquinolizinium bromide (XI)by oxidation with potassium permanganate failed.Thus,when these reactants were mixed,in the proportions specified by the equation

$$6\left[C_{11}H_{11}N(CH_3)_2\right]^{\oplus}Br^{\ominus} + 14\ KMnO_4 + 14\ H^{\oplus} \rightarrow 6\left[C_{11}H_{11}N(CO_2)\right] + 3\ Br_2 + 14\ MnO_2 + 14\ K^{\oplus} + 16\ H_2O,$$

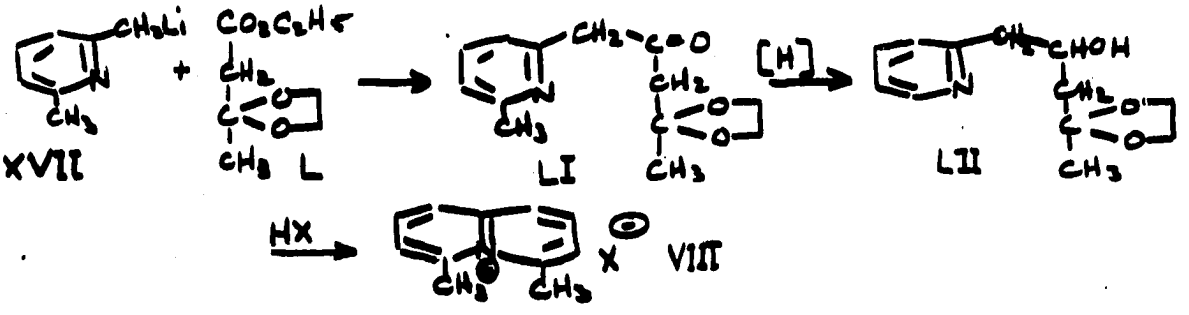
rapid formation of manganese dioxide was observed.However,when all the permanganate had been consumed,only XI could be obtained as the picrate, in 60 % recovery.

Intractable products were formed by the oxidation,with permanganate, of 2-p-dimethylaminostyrylquinolizinium bromide (XXXVIII).Presumably oxidation of this material produces unstable quinone derivatives from the dimethylaminophenyl residue,leading to deep-seated decomposition.

OTHER APPROACHES TO QUINOLIZINIUM SALTS

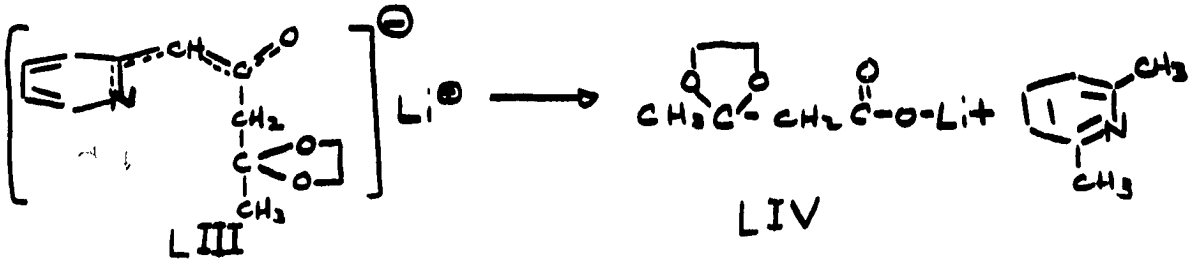
The direct synthesis of 4,6-dimethylquinolizinium salts by the method used for the preparation of various 2-substituted quinolizinium compounds is not feasible, since this would require the use of a ketal of acetoacetaldehyde in the reaction with lutidyllithium. Because of the greater reactivity of aldehydes, compared to ketones, it is not possible to prepare ketals from ketoaldehydes; instead, ketoacetals are produced.

A seemingly attractive alternative would be the reaction of lutidyllithium with a ketal of ethyl acetoacetate, to give the monoketal of a β-diketone (LI) which could be reduced to the correct state of oxidation for cyclodehydration to the 4,6-dimethylquinolizinium cation (VIII).



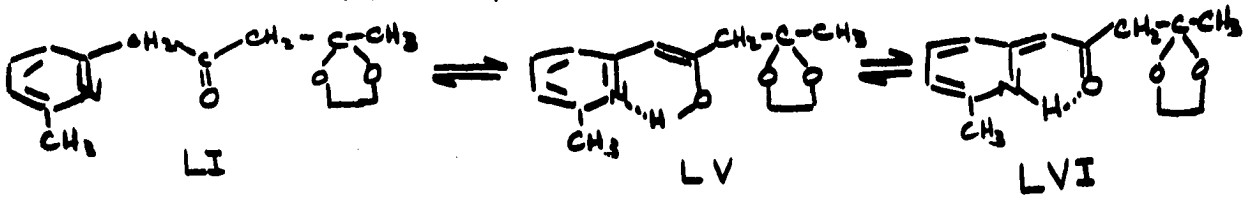
The addition of two moles of lutidyllithium to the ethylene ketal of ethyl acetoacetate (L) proceeded to give the lithium enolate (LIII) of LI. Treatment of this reaction mixture with two moles of acetic acid, prior to the addition of water was found to be neccessary, since the lithium salt LIII is quite soluble in water and seems to undergo rather rapid hydrolysis in the strongly basic aqueous solution resulting from quenching the reaction with water alone. Normal workup of the reaction, by addition of water to the reaction mixture, resulted in the almost immediate separation of considerable quantities of lithium carbonate, presumably arising from decarboxylation of the salt LIV. This is completely analogous to the

well-known basic cleavage of β-diketones, although the method by which LIV is decarboxylated is rather obscure.

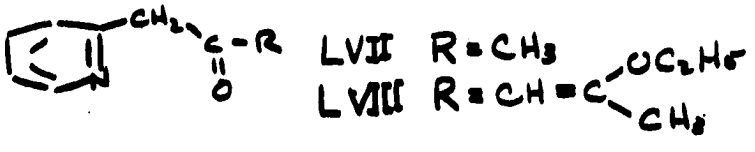


LIII LIV

After modifying the reaction so that partial acidification was effected before the addition of water, the yield of the ketone LI was increased to 45% , as compared with about 5% under the usual conditions. Compound LI was partially purified by distillation and characterized as the picrate of the free β-diketone. In the infrared, LI is devoid of absorbtion in the O-H region, but shows normal ketonic carbonyl absorbtion at 1715 $cm.^{-1}$, and further absorbtion peaks at 1650, 1548, 1578 and 1652 $cm.^{-1}$, in contrast to the usual pyridine doublet at 1600 and 1580 $cm.^{-1}$. This suggests contributions from the chelated enol form(s) LV and/or LVI.



LI LV LVI

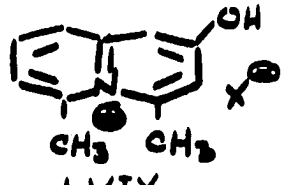


LVII R = CH_3
LVIII R = $CH=C(OC_2H_5)CH_3$

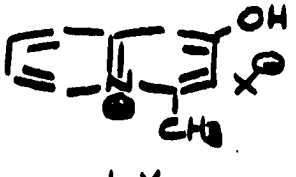
Previous work has shown that the basic reducing agents lithium aluminum hydride and aluminum amalgam are without effect on 2-pyridylacetone and on 1-(2'-pyridyl)-4-ethoxy-3-penten-2-one (LVIII), presumably due to the ease of formation of enolate salts, similar to LIII (10). We have also found that the use of sodium borohydride in the attempted reduction of the carbonyl

group of LIII gives only intractable mixtures,containing small amounts of starting material,identified as the picrate.Catalytic hydrogenation of LIII over palladium in acetic acid or platinum in ethanol was ineffective, possibly because of poisoning of the catalyst by LIII.The absorbtion of one mole of hydrogen took place in acetic acid,using platinum catalyst, but the resulting product was apparently a mixture of the alcohol and ring-reduced products,since it showed infrared absorbtion at 3510 (O-H) and 3330 (N-H) $cm.^{-1}$

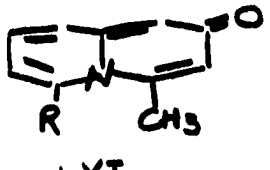
Various attempts to cyclize LIII with hydrochloric or hydrobromic acid and acetic anhydride resulted only in extensive decomposition,although in several instances,traces of unchanged starting material were recovered as the corresponding ketone salts and converted to the picrate.None of the anticipated ring-closed product,2-hydroxy-4,6-dimethylquinolizinium bromide (or chloride) LVIX.This was not unexpected,since Richards and Stevens (10) have prepared 2-hydroxy-4-methylquinolizinium picrate (LX), and found it to be quite unstable.It may be noted that these 2-hydroxy compounds are salts of the corresponding 2-quinolizones (LXI),which are presumably no more stable than 6-methyl-4-quinolizone (LXII),which has been shown to be decomposed by acid (4).



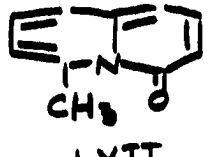
LVIX



LX



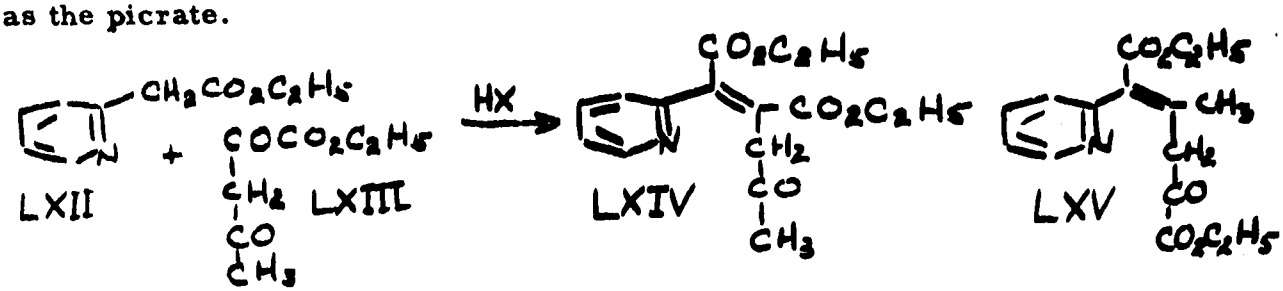
LXI



LXII

In a variation of the previously described synthesis of quinolizinium compounds,starting with organolithium reagents,ethyl 2-pyridylacetate (LXIII) has been condensed with ethyl acetopyruvate(LXIV) in the presence

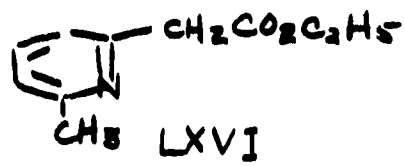
of one molar equivalent of acid. To give the salt of 1, 2-dicarbethoxy-1-(2'-pyridyl)-1-penten-4-one (LXIV) or the isomeric 1, 4-dicarbethoxy-3-methyl-4-(2'-pyridyl)-3-buten-1-one (LXV), isolated and characterized as the picrate.



Structure LXIV is preferred because of the known high activity of carbonyl groups situated α-to esters.

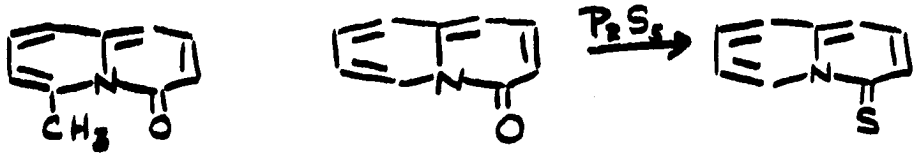
This type of condensation did not occur when ethyl (6-methyl-2-pyridyl)-acetate (LXVI) was used as the ester component, even when the reaction was run in acetic acid or anhydride instead of ethanol. The use of sodium ethoxide as the condensing agent was ineffective in both cases, presumably because of formation of the stable sodio derivative of aceto-pyruvic ester.

Since the desired product could not be obtained from LXVI, the product from pyridineacetic ester (LXIV) was not examined further. However, cyclization of this compound would provide an attractive route to acid derivatives of the quinolizinium cation.



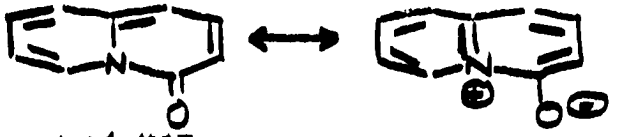
An attractive route to 4, 6-dimethylquinolizinium salts might be afforded by the use of 6-methyl-4-quinolizone (LXVII) which contains the desired bicyclic system. It might be expected that LXVII would

undergo the typical reaction of N-substituted pyridones, such as alkylation and halogenation at the 4-position with the formation of 4-alkyl- or 4-haloquinolizinium salts. However, in a projected synthesis of cycl [3, 3, 3]-azine (I) Boekelheide and Gall (4) have found that LXVII does not undergo thionation, while 4-quinolizone (LXVIII) is readily converted to 4-thio-quinolizone (LXIX).



LXVII LXVIII LXIX

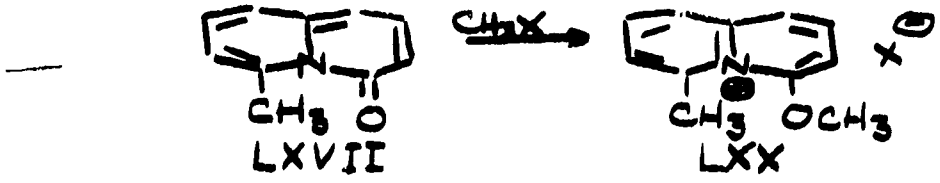
These authors also found that LXVIII is inactive towards lithium aluminum hydride or Grignard reagents. This lack of reactivity has been ascribed to resonance stabilization of the amide linkage by a rather large contribution from the canonical form LXVIIIa (4, 22). This is substantiated by the fact that LXVIII undergoes O-protonation on reaction with acids (22).



LXVIII LXVIIIa

In substantial agreement with this previous work, we have found that LXVII does not react with methyllithium in refluxing ethyl-or n-butyl ether solutions. In both cases only starting material was recovered, as the somewhat unstable picrate. No reaction occurred when LXVII was refluxed with methyl iodide or fused with methyl p-toluenesulfonate, in attempts to form the methoxyquinolizinium salt LXX. Unchanged

LXVII was recovered by sublimation.

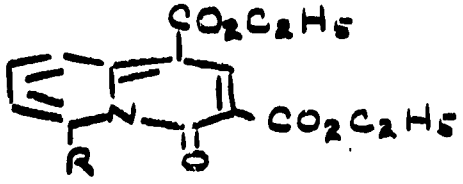


LXVII LXX

Treatment of LXVII with benzoyl chloride or p-toluenesulfonyl chloride in pyridine caused extensive decomposition, while, with acetyl chloride, the unstable "hydrochloride," 6-methyl-4-hydroxy-quinolizinium chloride LXXI was formed. This material could also be obtained by the addition of anhydrous hydrogen chloride to an ethereal solution of LXVII. This hydrochloride could not be purified extensively, but examination of its infrared spectrum shows the disappearance of the peak at 1693 $cm.^{-1}$ which is associated with the amide-type carbonyl bond in LXVII. The instability

LXXI

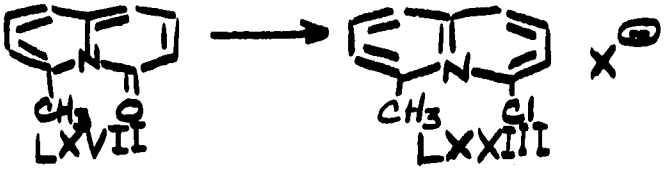
of LXVII towards acid has been encountered before. Thus Boekelheide has found that the diester LXXIIa is converted to 4-quinolizone by aqueous acid, while the 6-methyl analog LXXIIb undergoes ring-opening under these conditions.



LXXII a; R = CH_3
b; R = H

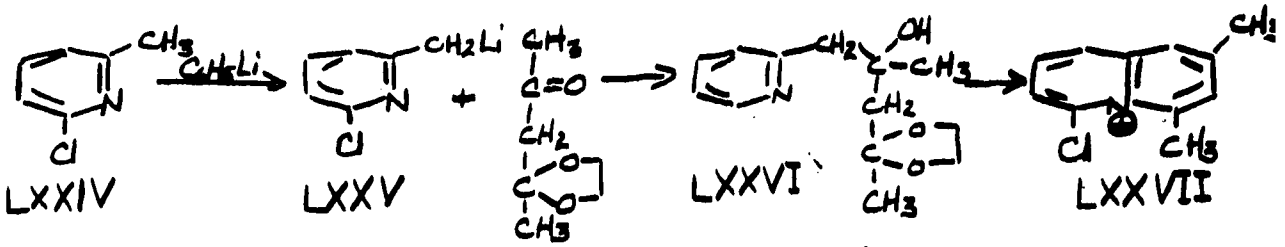
We have found that samples of the methylquinolizone LXVII are stable indefinitely at ice-chest temperature, but decompose slowly, with partial liquefication, at room temperature.

While treatment of N-alkylated pyridones with phosphorous oxychloride usually leads to dealkylation and formation of 2-chloropyridines, Wiley has found that the use of toluene as a diluent in this reaction permits the retention of the N-alkyl group (23). When 6-methyl-4-quinolizone (LXVII) was treated with phosphorous oxychloride in toluene or benzene, at room temperature or reflux, then added to alcohol or alcoholic sodium ethoxide or diethyl sodiomalonate only intractable tars resulted. Similarly, treatment of the quinolizone with phosphorous trichloride led to intractable products. The action of excess thionyl chloride on LXVII gave a green, sulfur-containing product, which also contained non-ionic chlorine. This material resisted all attempts at purification. Thus it appears that conventional methods are not effective for the conversion of 6-methyl-4-quinolizone (LXVII) to the related 4-chloroquinolizinium cation (LXXIII).

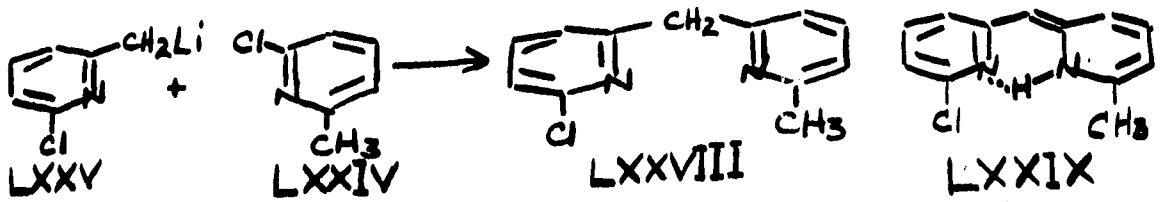


A different approach to the preparation of 2-substituted derivatives of LXXIII suggested itself. Lateral metallation of 6-chloro-2-picoline (LXXIV) with phenyllithium should give the chloropicolyllithium (LXXV) which, on treatment with e. g. the ketal of acetylacetone (XIV) would give an adduct LXXVI which might be cycldehydrated to the desired

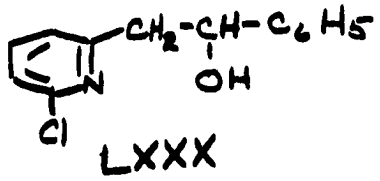
chloroquinolizinium salt (LXXVII).



Work in this direction was abandoned when it was found that while metallation of LXXIV took place as expected, the organolithium derivative LXXV reacted rapidly with another molecule of itself to give 6-chloro-6'-methyl-2, 2'-dipyridyl-methane (LXXVIII) as the only pure product.



When metallation of LXXIV was carried out at -78° and the resulting mixture treated with benzaldehyde after thirty minutes, nearly 85% of unchanged LXXIV was recovered on distillation of the basic fraction. In addition, benzhydryl alcohol was obtained as one of the neutral components of the mixture, showing that extensive metallation of LXXV had not occurred. Metallation at 0°, followed by the addition of benzaldehyde after ten minutes or thirty minutes resulted in the isolation of the chlorodipyridylmethane (LXXIX) as the only pure product. None of the desired 6-chloro-2-(α-hydroxyphenethyl)-pyridine (LXXX) could be obtained.



LXXX

The dipyridylmethane (LXXVIII) was identified by analytical data and the fact that its ultraviolet spectrum quite closely resembles that of the starting material (LXXIV), as shown in Table 2.

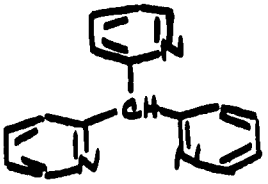
TABLE 2

Ultraviolet Absorption Spectra (in 95% Ethanol)

2-Chloro-6-methylpyridine (LXXIV)		6-Chloro-6'-methyl-2,2'-dipyridylmethane (LXXVIII)	
λ_{max}	log ε	λ_{max}	log ε
268.5 mμ	3.59	266.5 mμ	3.86
ca. 218 mμ	3.44	222 mμ	3.70

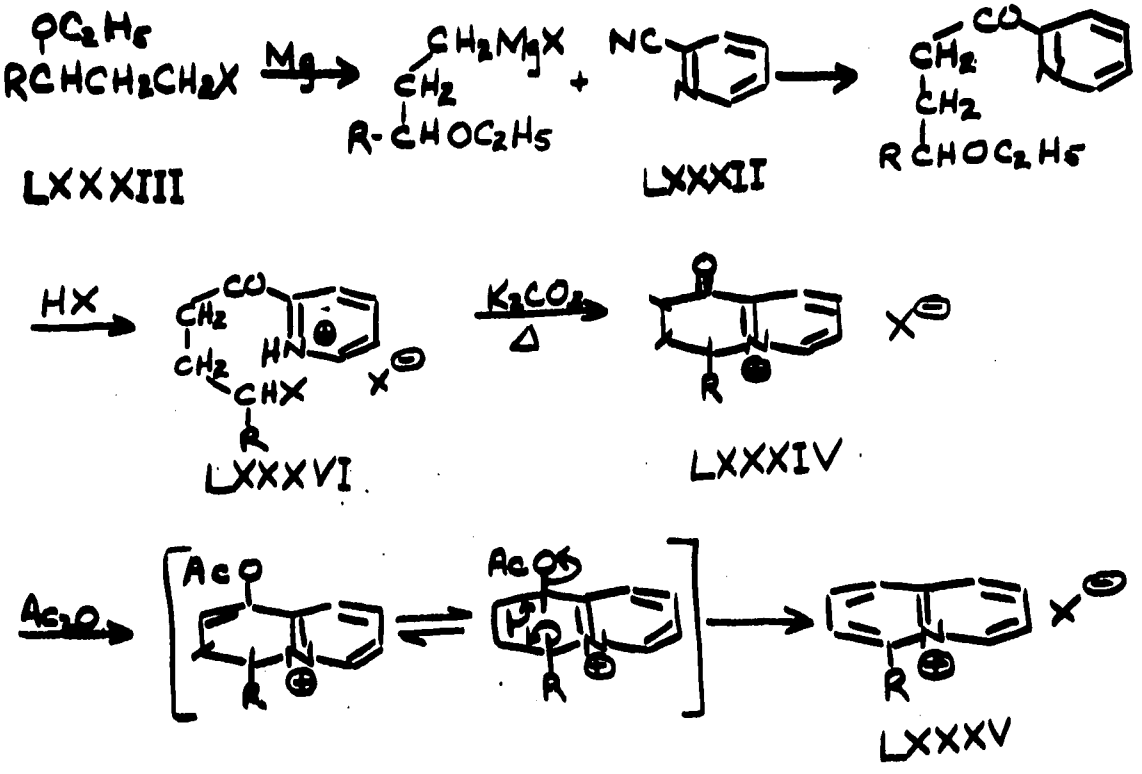
The slight shifts in the spectrum of LXXVIII relative to the spectrum of LXXIV are due to replacement of one of the chlorine atoms by the central methylene group of LXXVIII. The dipyridylmethane (LXXVIII) does not show absorption in the N-H region of the infrared spectrum, thus indicating the absence of appreciable amounts of the chelated tautomeric form LXXIX. This is confirmed by the similarity of the ultraviolet spectra of LXXIV and LXXVIII.

In this connection, it is of interest that the reaction of 2-picolyllithium with 2-bromopyridine has been reported to give 2,2',2''-tripyridylmethane (LXXXI) (24).



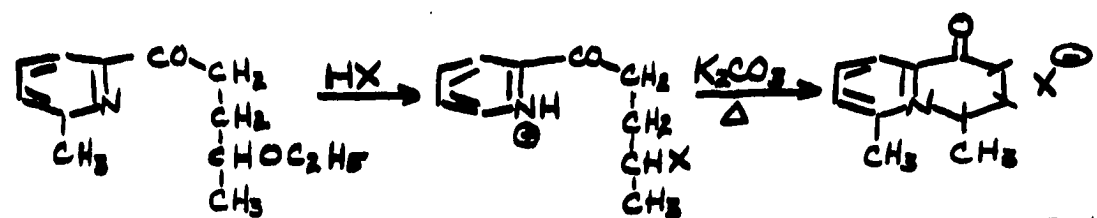
LXXXI

A novel synthesis of various substituted quinolizinium salts has been devised by Glover and Jones (25). This consists of reaction of picolinonitrile (LXXXII) with the Grignard reagent prepared from a γ-alkoxyalkyl halide (LXXXIII). Followed by ether cleavage and intramolecular alkylation to give the 1-keto-1, 2, 3, 4-tetrahydroquinolizinium salt (LXXXIV). Subsequent treatment with acetic anhydride results in aromatization to the quinolizinium salt (LXXXV). These authors propose the aromatization mechanism shown below.



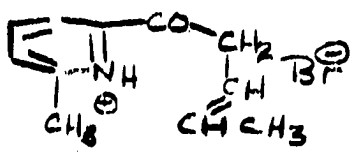
Considerably lower yields of the quinolizinium salt (LXXXV; R = CH_3) were obtained, undoubtedly due, at least in part, to competing dehydrohalogenation, which should be more important for the secondary halide (LXXXVI; R = CH_3) than for the primary halide (LXXXVI; R = H). A substituent, other than hydrogen, in the 6-position of the pyridine ring in LXXXVI would result in further increase in the extent of dehydrohalogenation, due to a steric blocking of the pyridine nitrogen.

In an attempt to adapt this synthesis to the preparation of 4, 6-dimethylquinolizinium salts (VIII), 3-ethoxy-1-bromobutane (LXXXIII; R = CH_3, X = Br) was converted to the Grignard reagent and added to 6-methyl-2-cyanopyridine. The resulting unstable liquid ketone (LXXXVII) was characterized as the 2, 4-dinitrophenylhydrazone. Attempts to cleave the ether group of LXXXVII with concentrated hydrobromic or hydriodic acids proceeded with the formation of the volatile ethyl halides and dark intractable products. Treatment of the resulting crude mixture with dinitrophenylhydrazine gave a very low yield of the 2, 4-dinitrophenylhydrazone of the desired ketotetrahydroquinolizinium compound (LXXXVIII) as the bromide. Unfortunately, attempts to remove the dinitrophenylhydrazone moiety from this derivative with

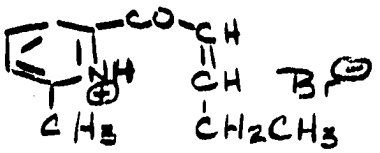


LXXXVII LXXXVIII

aqueous acid, or by exchange with formaldehyde were completely unsuccessful, as was an attempt to apply the acetic anhydride aromatization reaction to the derivative. Structure LXXXVIII is preferred for the product in question, rather than the monocyclic formulations LXXXIX or XC, since the dinitrophenylhydrazone is not acidic in methanol solution.

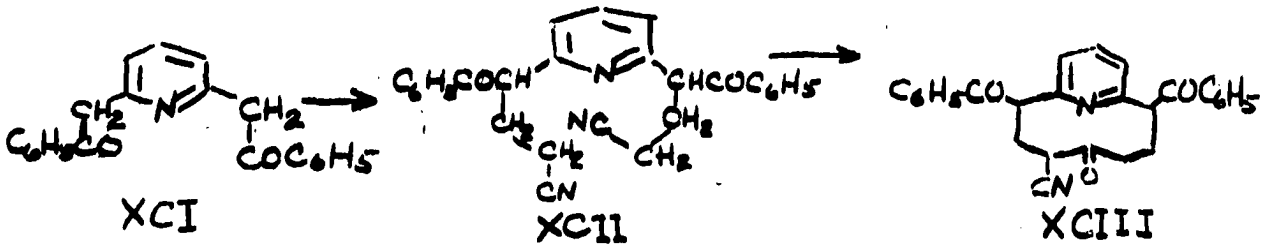


LXXXIX



XC

In an attempt to prepare a macrocyclic compound related to cycl[3, 3, 3]azine, we attempted the bis-cyanoethylation of 2, 6-diphenacylpyridine (XCI), under conditions previously used in the cyanoethylation of 2-phenacylpyridine (26). The expected product (XCII) might be cyclized, under the conditions of the Thorpe reaction, to give the pyridocyclodecanone (XCIII) which might be converted, in several steps, to cycl[3, 3, 3]azine.

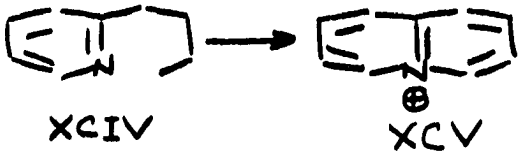


XCI XCII XCIII

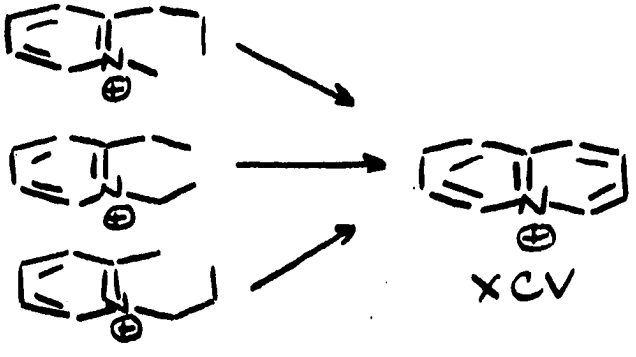
However, reaction of the diketone (XCI) with potassium hydroxide in ethanol, using an excess of acrylonitrile, resulted in hydrolysis of the benzoyl groups, benzoic acid and 2, 6-lutidine (as the picrate) being recovered. Similar results were obtained when potassium t-butoxide in t-butylalcohol was substituted for KOH. Analogous debenzoylation

of XCI has been encountered by Beach (5) in an attempted alkylation with pentamethylene dibromide. In our case, apparently no reaction of the anion derived from XCI occurs with acrylonitrile, but subsequent addition of water promotes base catalyzed debenzoylation.

It is apparent that most of the approaches to quinolizinium compounds mentioned previously can be formally separated into two steps: synthesis of a pyridine derivative, bearing a side chain suitable for cyclization and ring closure of this intermediate to the corresponding quinolizinium salt (XCIV → XCV).



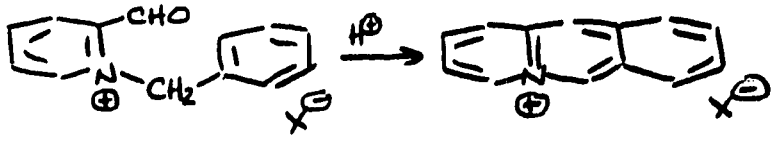
An attractive alternative to this approach would be the preparation and cyclization of suitable N-substituted pyridinium salts, as in the following schemes.



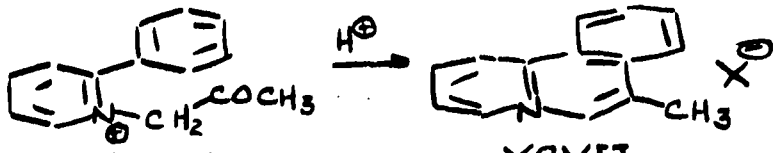
The Dieckmann ester condensation has been used, with considerable success, in similar ring closures in the completely saturated quinolizidine series (27), but apparently this approach has not been extended to aromatic compounds of the type which would be

desirable in this work.

Bradsher and co-workers have prepared a number of benzo[b]- and benzo[a]-quinolizinium salts (XCVI and XCVII, respectively) by cyclodehydration of 1-benzyl-2-formylpyridinium halides (XCVIII) and 1-acetonyl-2-phenylpryidinium halides (XCIX) respectively (28). However, this method is not applicable to the preparation of simple

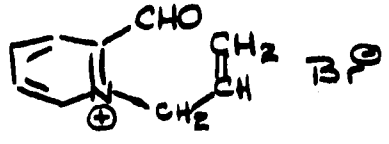


XCVIII XCVI



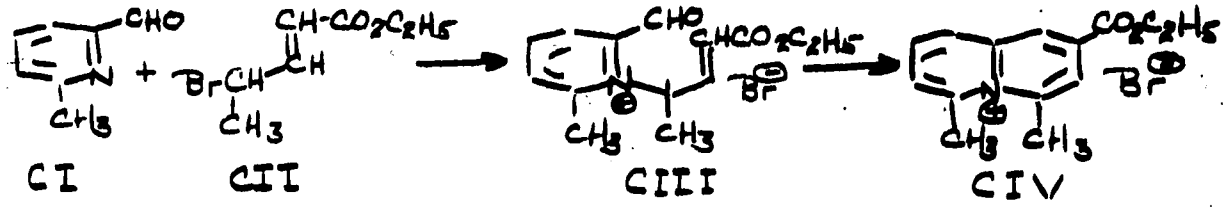
XCIX XCVII

quinolizinium cations, since Richards and Stevens (10) have shown that 1-allyl-2-formylpyridinium bromide (C) decomposes under cyclodehydrating conditions.



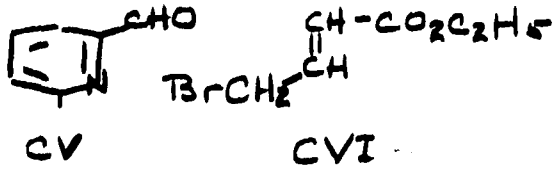
C

In the present work, it was anticipated that 6-methylpyridine-2-carboxaldehyde (CI) could be quaternized with ethyl 4-bromo-2-pentenoate (CII) to give the pyridinium salt (CIII), which might be cyclyzed to 2-carbethoxy-4, 6-dimethylquinolizinium bromide (CIV).



CI CII CIII CIV

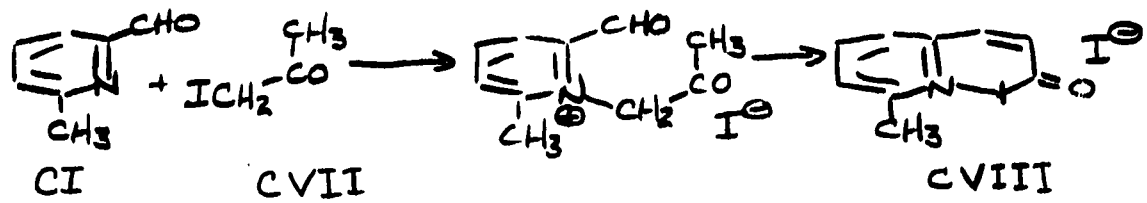
However, model experiments, using 2-picolinaldehyde (CV) and ethyl ω-bromocrotonate (CVI) failed to show any evidence of quaternization, even under forcing conditions. No bromide ion could be detected in the reaction mixtures in any instance. Similarly, replacement of CV with the 6-methylaldehyde (CI) gave no quaternary salt under any conditions. The failure of these aldehydes to undergo quaternization is due to a number of factors, including the thermal instability of pyridine aldehydes, and the resonance and steric effects of the pyridine substituents, especially the formyl group. The carbethoxy group of the ester presumably contributes a steric effect, since picolinaldehyde reacts normally with alkyl bromide (10).



CV CVI

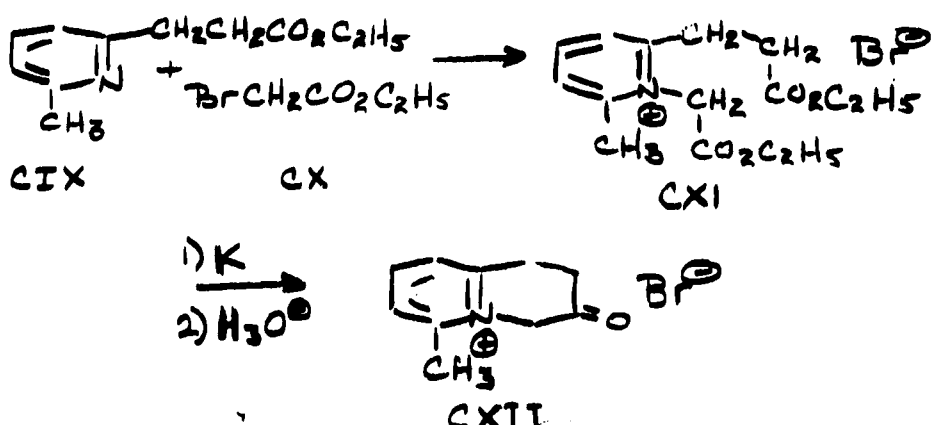
Bradsher has noted similar failures in the attempted quaternization of CI with benzyl bromide (29). In addition we have noted that 6-methyl-2-pyridine carboxaldehyde (CI) fails to react with iodoacetone, as does the corresponding aldoxime. The reaction of CI with iodoacetone (CVII) was used in an attempt to prepare 6-methyl-3-keto-3, 4-dihydroquinolizinium iodide (CVIII), in the hope that this latter compound might undergo alkylation at the 4-position, to give a salt

which might be converted to 4, 6-dimethylquinolizinium iodide. However, as noted, quaternization fails to occur.



CI CVII CVIII

In a somewhat similar approach, the quaternization of ethyl 3-(6'-methyl-2'-pyridyl)-propionate (CIX) with ethyl bromoacetate (CX) was effected by heating the reactants at 110° for three hours. This resulted in the production of ca. 75% of the theoretical amount of bromide as shown by titration of the crude resulting mixture. The salt (CXI) was obtained crystalline on one occasion, but proved to be very hygroscopic. Treatment of crude CXI with sodium ethoxide or potassium metal in toluene (27) led to intractable materials. Thus, ring closure of the salt CXI does not occur. It is suggested that strong bases may attack the substituents in the 2- and 6-positions of the pyridine ring, with the formation of the highly unstable anhydro base, and subsequent rapid decomposition, rather than formation of the desired anion at the carbon atom α-to the ester group.



CIX CX CXI CXII

Ring-closure and acid hydrolysis, with decarboxylation, of the intermediate β-keto ester would have afforded 6-methyl-3-keto-1, 2, 3, 4-tetrahydroquinolizinium bromide (CXII), which might have been alkylated at C-4 to give a useful intermediate. As expected, the ester (CIX) did not form a quaternary salt with ethyl α-bromopropionate. In this case, the picrate of the pyridyl ester (CIX) was recovered.

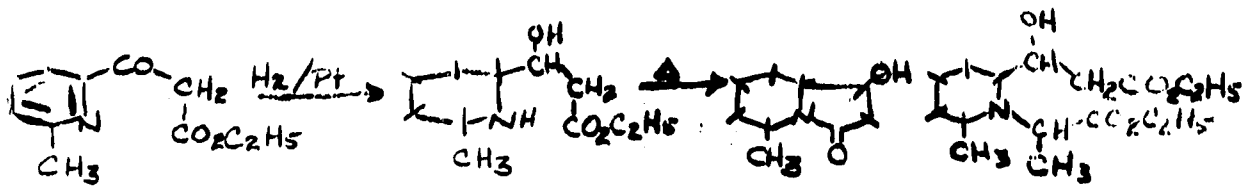
PREPARATION AND CYCLIZATION OF PIPERIDINE DERIVATIVES

For some time during the course of this investigation, it seemed that no practical synthesis of 4, 6-dimethylquinolizinium salts would be developed. For this reason, we attempted to prepare the saturated analogs of the desired compounds, 4, 6-dimethylquinolizidines. It was felt that the greater flexibility of the saturated compounds would compensate somewhat for the strain resulting from the introduction of rather bulky 4- and 6-substituents, thus rendering these compounds more easily accessible. Originally, we desired to convert the quinolizidines obtained to the corresponding quinolizinium salts by dehydrogenation. However, the preparation of suitable quinolizinium salts by other methods led to the abandoning of this approach.

It should be stated that the existence of a number of optically active centers in the saturated compounds obtained can give rise to mixtures of several stereoisomeric products. For this reason, suitable solid derivatives could not be obtained in most cases. Thus the structural assignments made in this section depend largely on spectral data and must be regarded as being somewhat uncertain.

Ethyl 6-methylpicolinoylacetate (CXIII) was prepared by the condensation of ethyl 6-methylpicolinate with ethyl acetate, using a slight modification of the method of Gilman and Broadbent (30). Reduction of this ester (CXIII) over platinum in acetic acid gave the piperidyl β-hydroxypropionate (CXIV); no hydrogenalysis of the hydroxyl group was observed. This ester was isolated as the acetate and converted to the picrate for analysis. Attempted distillation of the free base (CXIV)

gave anomalous results. On one occasion, the piperidine derivative distilled unchanged. However, attempts to repeat this experiment led to a different material with a boiling point about 30° higher than that of CXIV. This material was assigned the octahydropyrrocolone structure (CXV) on the basis of its infrared spectrum. Thus, in the infrared, the piperidine derivative (CXIV) shows absorption at 3520, 3450 (O-H) and 3160 cm.$^{-1}$ (N-H), while the γ-lactam (CXV) has only a single, somewhat broadened O-H band at 3400 cm.$^{-1}$; the N-H band of CXIV has completely disappeared. In addition, CXIV shows normal ester carbonyl absorption at 1732 cm.$^{-1}$, while the lactam (CXV) displays amide carbonyl absorption at lower frequency (1685 cm.$^{-1}$). This lactam, 1-hydroxy-4-methyl-3-ketoöctahydropyrrocoline (CXV), was also isolated when the piperidine derivative (CXIV) was heated with ethyl α-bromopropionate in an attempt to prepare the tertiary amine (CXVI) for cyclization to a quinolizidine.

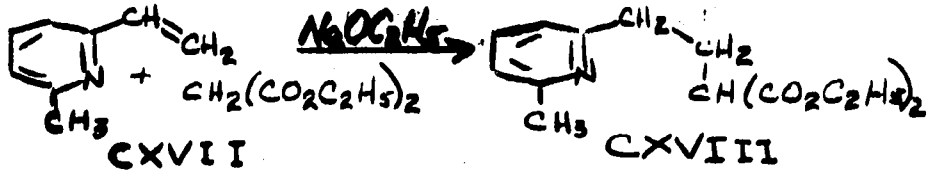


CXIII CXIV CXV CXVI

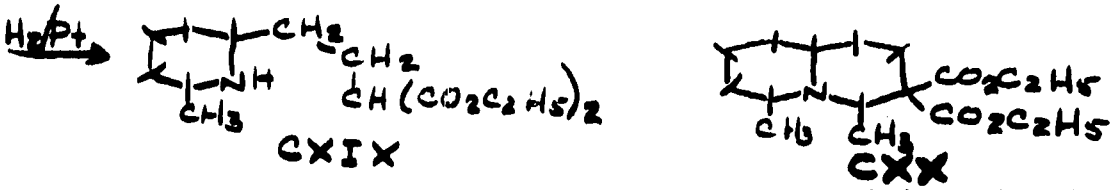
This tendency for CXIV to undergo intramolecular acylation, rather than alkylation is attributed to steric hindrance to the approach of the bulky bromopropionate to the nitrogen atom by the 2- and 6-substituents in the piperidine ring, since ethyl 3-(2'-piperidyl)-propionate is alkylated by this reagent (31).

Ring closure of 3-(2'-piperidyl)-propionic esters is a well-known method for the preparation of 3-ketoöctahydropyrrocolines (32). In another

projected synthesis of 4, 6-dimethylquinolizidine, Michael addition of diethylmalonate to 6-methyl-2-vinylpyridine (CXVII) gave the pyridylethyl malonate (CXVIII) which was reduced over platinum in acetic acid, to give the desired piperidine derivative (CXIX). This material did not react with acetaldehyde, under either acid or basic conditions, to form CXX.



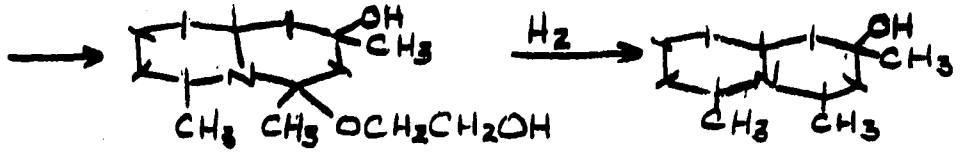
CXVII CXVIII



CXIX CXX

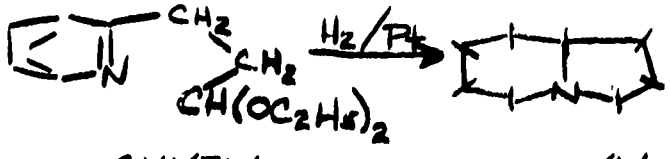
Rather unexpectedly, catalytic hydrogenation of 4, 4-ethylenedioxy-2-methyl-1-(6'-methyl-2'-pyridyl)-2-pentanol (XVIII) in acetic acid gave a basic liquid which did not give a positive test for secondary amine with the Ni^{+2}-carbon disulfide reagent (33), and thus cannot be the expected piperidine derivative CXXI. Instead, it appears that reductive cyclization has taken place, presumably via hydrogenalysis of the intermediate carbinolamine ether, to give 2-hydroxy-2, 4, 6-trimethylquinolizidine.

XVIII CXXI



CXIX CXXIII

A similar reaction, reductive cyclization of the acetal of pyridylpropionaldehyde (CXXIV) to pyrrocoline (CXXV) has been known for some time (34).



CXXIV CXXV

All attempts to further characterize the quinolizidine (CXXIII) have failed, presumably due to the presence of a number of stereoisomeric forms. Thus, while picric acid and methyl iodide react vigorously with the base, only oily derivatives are obtained. Similarly, no solid was obtained on attempted benzoylation.

While the infrared spectrum could be interpreted either on the basis of the piperidine (CXXI) or quinolizidine (CXXIII) structure, the latter is preferred on the basis of the negative test for secondary amine functions.

EXPERIMENTAL DETAILS

Melting points less than 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.

Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer, while ultraviolet and visible spectra were obtained by use of a Warren Spectracord and a Beckmann DK-2A instrument.

Elemental microanalyses were carried out by Dr. V. B. Fish, to whom the author expresses his appreciation.

4, 4-Ethylenedioxy-2-methyl-1-(6'-methyl-2'-pyridyl)-2-pentanol (XVIII): To a solution of 2, 6-lutidyllithium, prepared from 3.47 g. (0.5 mole) of lithium wire, 40 g.(0.25 mole) of bromobenzene and .27 g. (0.25 mole) of 2, 6-lutidine in ca. 150 ml. of ether, was added 18 g. (0.125 mole) of 4, 4-ethylenedioxy-2-pentanone (35) at such a rate that the ether boiled slowly. The reaction mixture became reddish-orange during this addition. The resulting mixture was stirred and refluxed for 90 minutes following this addition, 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 from the red solution was followed by distillation at reduced pressure. A forerun containing lutidine and bromobenzene

was taken off first, followed by 16.6 g. (52.9%) the desired product (XVIII), b. p. 135-142°/0.4 mm., n_D^{23} 1.5109.

An oily picrate was formed when XVIII was added to saturated alcoholic picric acid. This could not be crystallized.

2,4,6-Trimethylquinolizinium bromide (XI): Concentrated hydrobromic acid was added slowly to a mixture of 12.5 g. (0.05 mole) of XVIII and 35 ml. of water to pH 2. Excess acid was avoided. 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 XI 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 3 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.: Calc. for $C_{12}H_{14}N$ Br: 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.

The picrate was prepared from an aqueous solution of the bromide and sodium picrate. After recrystallization from 95% ethanol it had m. p. 138-138.5°.

Anal.: Calc. for $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 14.00.

Found: C, 53.85; H, 4.07; N, 13.75.

2-p-Dimethylaminostyryl-4, 6-dimethylquinolizinium bromide (XXXVIII): A solution of 0.5 g. (2 mmole) of the trimethylquinolizinium bromide (XI) and 0.45 g. (3 mmole) 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 XXXVIII, m. p. above 300° with decomposition from 280°. Recrystallization from absolute alcohol furnished the analytical sample as small deep red needles.

Anal.: Calc. 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.

Reaction of 2, 4, 6-trimethylquinolizinium bromide with benzaldehyde and triethylamine: A solution of 0.5 g. (2 mmole) of the trimethylquinolizinium salt (XI), 0.25 g. of benzaldehyde and 1 ml. (ca. 10 mmole) of triethylamine in 10 ml. of absolute ethanol was refluxed for twelve hours. The ethanol and excess triethylamine were removed in vacuo, the residue taken up in a minimum volume of hot absolute ethanol and cooled. Filtration then gave 0.30 g. (83.5%) of triethylamine hydrobromide, identical with an authentic sample (m. p. and mixed m. p. 247-8°). Addition of ethyl acetate to the filtrate removed further traces of ionic material. Evaporation of the alcohol-ethyl acetate solution left an orange-red gum

which, on trituration with dry ether gave ca. 50 mg. of orange powder. This latter substance melted at 110-122° d., but decomposed on attempted purification.

In a second experiment, it was shown that no triethylamine hydrobromide is formed when benzaldehyde is omitted from the original reaction mixture.

Reaction of 2, 4, 6-trimethylquinolizinium bromide (XI) with sodium hydroxide: A solution of 0.25 g. (1 mmole) of the trimethylquinolizinium bromide (XI) in 5 ml. of ethanol was treated with 0.15 ml. of 50% sodium hydroxide solution. The solution became very dark immediately. After five minutes, the mixture was acidified with saturated picric acid solution, then evaporated. The resulting brown tar was extracted several times with hot ethanol, and the combined ethanol solutions allowed to evaporate slowly at room temperature. The crystalline picrate mixture obtained in this manner was washed with water to remove sodium picrate, leaving 0.09 g. of solid, m. p. 164-173°. Repeated recrystallization from ethanol (charcoal) gave a trace of purified picrate, m. p. 174-175°, but the amount of this material obtained was insufficient for analysis.

2, 4, 6-Trimethylquinolizinium tribromide (XLII): A. A solution of 0.5 g. (2 mmole) of trimethylquinolizinium bromide in 8 ml. glacial acetic acid was treated with a solution of 0.35 g. (2.2 mmole) of bromine in 5 ml. of acetic acid at room temperature. The mixture was filtered after a few minutes, the solid was washed several times with small

volumes of acetic acid and air dried to give 0.80 g. (97%) of the tribromide (XLII), m. p. 125-128°. Four recrystallizations from methanol gave the analytical sample as long orange needles, m. p. 129-130°.

Anal.: Calc. for $C_{12}H_{14}N\,Br_3$: C, 34.98; H, 3.42; N, 3.40; Br, 58.20.

Found: C, 35.00; H, 3.50; N, 3.37; Br, 57.90.

Methanol solutions of the tribromide gave a positive test for oxidizing ability with KI-starch paper. Bromine was released (odor) on heating these solutions, as was H Br (pH paper), but the compound lost no bromine when dried at 65°.

Treatment of 0.1 g. of the tribromide, in aqueous methanol with saturated sodium picrate solution gave 0.1 g. of 2, 4, 6-trimethylquinolizinium picrate (XI), m. p. 137-138°. A mixture melting point determination with authentic material showed no depression.

B. A solution of 0.5 g. (2 mmole) of XI in 20 ml. of acetic acid was magnetically stirred while 0.36 g. (2 mM) of N-bromosuccinimide was added slowly. After addition was complete, 100 ml. of ethyl acetate was added to the mixture. The tribromide XLII precipitated slowly. The orange needles were collected and washed with ethyl acetate to give 0.40 g. (48%) of the tribromide, m. p. and mixed m. p. with authentic material 128.5-129.5°.

Permanganate oxidation of 2, 4, 6-trimethylquinolizinium bromide (XI): To a solution of 0.5 g. (2 mmole) of XI in 35 ml. of water and 0.15 ml. conc. H_2SO_4, 0.75 g. (4.75 mmole) of potassium permanganate was added, in small portions. The solution deposited manganese dioxide almost immediately, and the permanganate color was discharged quite

rapidly. After all the permanganate had been added, the mixture was stirred for one hour, then filtered. The MnO_2 was washed several times with warm water, then once with methanol. The combined aqueous solutions were evaporated to dryness under diminished pressure and the resulting solids extracted with hot absolute alcohol. Addition of alcoholic picric acid to these alcoholic extracts gave 0.5 g. (62% recovery) of trimethylquinolizinium picrate, m. p., alone or mixed with an authentic sample, 137-138°.

3-Ethoxy-1-phenyl-2-buten-1-one (Enol ether of benzoylacetone) (XXIV): The following represents some improvement over the method of Claisen (36), in that the use of ferric chloride results in the presence of considerable quantities of ferric benzoylacetonate, making distillation of the product troublesome.

A solution of 24.3 g. (0.15 mole) of benzoylacetone (37), 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''-Vigreaux column at such a rate that only ethyl formate distilled. The head temperature ranged up to 60° at the highest. After 36 hours, 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 $MgSO_4$ after a little pyridine had been added. Evaporation, followed by distillation gave the desired enol ether (XXIV) in 70% yield. Refractionation through a Vigreaux column gave 16.3 g. (60%) of the enol ether as a yellow oil, b. p. 97-101°/0.4mm. Its infrared spectrum was identical with that of a sample prepared by the method of Claisen (36).

4, 6-Dimethyl-2-phenylquinolizinium bromide (XII): 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 (XXIV) 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 hours. Then, it was cooled once again and poured into a mixture of 20 ml. of concentrated HCl and ca. 100 g. of ice. The resulting mixture was separated, the ether layer washed several times with dilute HCl, and the combined aqueous acid solutions basified with sodium bicarbonate. The resulting oil was extracted into ether, dried over $MgSO_4$ 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 HBr 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 coupound (XII) 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.: Calc. for $C_{12}H_{16}NBr$: C, 64.97; H, 5.13; N, 4.46; Br, 25.43.

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° d.

Anal.: Calc. 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 XII, 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. 128-38°/0.3mm., which, on treatment with dilute HBr 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 above, gave 0.72 g. (4.8%) of the desired quinolizinium bromide (XII).

4-Phenyl-5-(6'-methyl-2'-pyridyl)-4-buten-2-one hydrobromide (XXVII): 2,6-Lutidyllithium was added to the enol ether of benzoylacetone (XXIV), using the same quantities and techniques 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 HBr. The analytical sample has m. p. 177.5-178.5°. Slightly high carbon content suggests contamination by the free base or quinolizinium compound.

Anal.: Calc. 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. 143-4°.

Anal.: Calc. 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 this salt (XXVII) with hot acetic anhydride overnight gave 3.5 g. (74%) of 4, 6-dimethylquinolizinium bromide (XII).

4-Methyl-2-phenylquinolizinium bromide (XVI): 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 (XXIV) exactly as described in the preparation of 4, 6-dimethylquinolizinium bromide (XII) by procedure A above. The product (XVI) began to precipitate from the acetic anhydride solution soon after boiling commenced. The solution was refluxed for 4 hours, then cooled and filtered to give 9.85 g. (65.5%) of the quinolizinium salt (XVI), as brown crystals, m. p. 295° with previous decomposition. Two recrystallizations from 95% ethanol furnished white microcrystalline XVI of unchanged melting point.

The bromide was converted to the known picrate, m. p. 230° d., after crystallization from ethanol (lit. m. p. 226° d. (10)).

2-Phenyl-4-p-dimethylaminostyrylquinolizinium bromide (XXXVII): A solution of 0.3 g. (1 mmole) of 4-methyl-2-phenylquinolizinium bromide (XVI) and 0.3 g. (2 mmole) 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° d. This material, dried at 56°, contains one molecule of methanol of crystallization.

Anal.: Calc. 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.

4,4-Dimethoxy-2-methyl-2-(6'-methyl-2'-pyridyl)-2-butanol (XXX): 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, 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 XXX was obtained as a light yellow oil, b. p. 127-135°/0.4 mm.

2,6-Dimethylquinolizinium bromide and picrate (XXXI): A. A solution of 2.4 g. (0.01 mole) of the above hydroxy-acetal (XXX) 7 g. of picric acid and 25 ml. of absolute alcohol was refluxed for 2 hours, then cooled. Filtration then gave 3.22 g. (73.8%) of the crude quinolizinium picrate as green, somewhat sticky crystals. Several recrystallizations from 95% ethanol (charcoal) gave yellow needles, m. p. 137-138°.

Anal.: Calc. 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. (0.03 mole) of the hydroxy acetal (XXX) in ca. 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 hours 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° d. 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-ethylacetate to give yellowish needles, m. p. 215-7°.

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.

4,4-Ethylenedioxy-2-methyl-1-(2'-pyridyl)-2-pentanol: This material was prepared, in 54% yield, from 0.1 mole of 2-picolyllithium and 7.2 g. (0.05 mole) of the monoethylene ketal of acetylacetone, under the same conditions used in the synthesis of its 6'-methyl analog (XVIII). The yellow oil had b. p. 121-125°/0.4 mm.

2.4-Dimethylquinolizinium bromide and picrate (XXIX): A. Treatment of the above ketal (1 g.) with excess alcoholic picric acid (5 g.) at reflux for one hour gave, after cooling, 1.97 g. (51%) of the quinolizinium picrate, m. p. 150-154°. After treatment with charcoal and several crystallizations from 95% ethanol, the yellow plates had m. p. 154.5-155.5°

(lit. m. p. 152-3° (10)).

B. The quinolizinium bromide was prepared as previously described in the preparation of 2, 6-dimethylquinolizinium bromide, method B, except that the crude product was recrystallized directly from ethanol, to m. p. 244-246°. The crude yield was 58%.

The bromide was converted to the picrate with aqueous sodium picrate. The picrate obtained in this manner had m. p. 155-155.5°, alone and mixed with a sample prepared by method A, above.

2-Methylquinolizinium bromide and picrate (XXV): A. 4, 4-dimethoxy-2-methyl-1-(2'-pyridyl)-2-butanol was prepared by the method of Richards and Stevens (10) and converted to the quinolizinium picrate by alcoholic picric acid.

The greenish picrate had m. p. 165-167° after recrystallization from ethanol.

B. 4, 4-Dimethoxy-2-methyl-1-(2'-pyridyl)-2-butanol (4.5 g., 0.02 mole) was added to ca. 35 ml. of water, then the mixture was acidified to pH 2 with concentrated hydrobromic acid. The resulting solution was extracted with ether, the aqueous layer evaporated to dryness and the gummy solid residue was refluxed in 50 ml. of acetic anhydride. On cooling, 2.1 g. (47.5%) of crude 2-methylquinolizinium bromide separated as dark crystals m. p. 178-185°. This was crystallized twice from chloroform, then finally from ethanol-ethylacetate to give a white microcrystalline salt of m. p. 195-197° (lit. 185-186° (38)).

This bromide was converted to the quinolizinium picrate with aqueous sodium picrate. The picrate, after several crystallizations from alcohol,

was obtained as yellow needles, m. p. 167.5-168.5°, alone or mixed with the picrate obtained via method A, above (lit. m. p. 161° (10)).

2-Styrylquinolizinium bromide (XL): Two drops of piperidine were added to a refluxing solution of 0.45 g. (2 mmole) of 2-methylquinolizinium bromide and 0.3 g. (3 mmole) of benzaldehyde in 5 ml. of absolute ethanol. Heating was continued for 4 hours, then the orange mixture was chilled and filtered to give 0.31 g. (49.7%) of the styrylquinolizinium salt, m. p. 258-261° d. as brown needles. After two recrystallizations from methanol, the salt was obtained as light yellow needles, m. p. 261-262° d. Analytical values were not completely satisfactory.

Anal.: Calc. 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 fluorescent in ultraviolet light.

4,4-Ethylenedioxy-1-(6'-methyl-2'-pyridyl)-2-pentanone (LI): A solution of 0.5 mole of 2,6-lutidyllithium in 250 ml. of ether was prepared in the usual manner and cooled to 0°. This reagent was slowly pumped into a solution of 43.5 g. (0.25 mole) of ethyl 3,3-ethylenedioxybutyrate (L) in 300 ml. of ether, held at 0°, resulting in immediate discharge of the organometallic's color and precipitation of a white solid from the yellow solution. After allowing this solution to come to room temperature, while stirring was continued, a solution of 30 g. (0.5 mole) in 100 ml. of ether was added slowly, producing a reddish-yellow gel. Water (150 ml.) was then added, the resulting mixture separated,

and the aqueous phase (pH 8-9) extracted with several small portions of ether, until the ether extract was nearly colorless. The combined organic layers were cried over $MgSO_4$ and the solvent removed in vacuo. Distillation of the reddish residue gave 34.6 g. (58.8%) of the ketone (LI) as a yellow oil, b. p. 134-143°/0.3-0.4 mm. The product decomposed slowly at room temperature, developing an orange color on standing overnight, but appeared to be stable at ice-chest temperature.

Treatment of LI with excess ethanolic picric acid gave the picrate of 1-(6'-methyl-2'-pyridyl)-2,4-pentanedione as dark yellow plates, m. p. 158° d. after several recrystallizations from ethanol.

Anal.: Calc. for $C_{11}H_{13}NO_2 \cdot C_6H_3N_3O_7$: C, 48.57; H, 3.84; N, 13.33.

Found: C, 48.80; H, 4.08; N, 13.19, 13.18.

Attempted cyclodehydration of LI: Five grams of the ketone LII was added to 30 ml. of water, the resulting mixture was acidified to pH 2 with concentrated hydrochloric acid, and evaporated to dryness in vacuo, after ether extraction. The red residue was taken up in 50 ml. of acetic anhydride and heated for four hours at gentle reflux. No salt separated on cooling. Evaporation of the acetic anhydride in vacuo left a black, tarry mass which was taken up in a small volume of absolute ethanol. Cooling the alcoholic solution gave 0.92 g. of black, gummy solid. Several more recrystallizations from ethanol gave a white powder in a yield of 0.37 g. (6.5%), m. p. 248-250 d. A small sample of this solid was treated with aqueous sodium picrate to give the picrate of 1-(6'-methyl-2'-pyridyl)-2,4-pentanedione, m. p. 155-157° d., not depressed on admixture with

authentic material, prepared directly from the monoketal (LI).

Attempted preparation of 1-(6'-methyl-2'-pyridyl)-4, 4-ethylenedioxy-2-pentanol (LII): A. A solution of 5 g. of the ethylenedioxypentanone (LI) in 50 ml. of glacial acetic acid was shaken in a Parr apparatus in the presence of 0.5 g. of platinum dioxide under an initial hydrogen pressure of 35 psi. After 2.5 hours, the reaction was stopped, when a pressure drop of 1.7 psi. (1.1 mole H_2/mole LI) was noted. The catalyst was filtered off and the solvent evaporated at 50° in vacuo. Distillation of the residue gave 3.7 g. of a yellow oil, b. p. 123-129°/ 0.25 mm. This material showed bands in the infrared at 3510 (O-H), 3330 (N-H), 1740 (C = O), 1650, 1597, 1580 (pyridine) cm^{-1}. Thus it appears to be a complex mixture.

B. A solution of 4.7 g. (0.02 mole) of LI in 20 ml. of absolute methanol was treated with 0.2 g. (0.021 equiv.) of sodium borohydride at room temperature for four hours. The yellow color faded slightly. At this point, 3 ml. of concentrated hydrobromic acid was added and the solution evaporated to dryness. Refluxing the residue with 30 ml. of acetic anhydride gave only a dark, non-crystalline semisolid which could not be purified.

1, 2-Dicarbethoxy-1-(2'-pyridyl)-1-penten-4-one picrate (LXIV): Dry hydrogen chloride was bubbled into a cooled solution 5 g. (0.03 mole) of ethyl 2-pyridylacetate (LXIII (39)) in dry ether until the mixture was strongly acidic. The precipitated hydrochloride was filtered, washed well with ether, and dissolved in 20 ml. of absolute ethanol.

To this solution, 6.3 g. (0.04 mole) of ethyl acetopyruvate (LXIV (40)) was added, and the resulting mixture was refluxed overnight. Evaporation left a viscous yellow gum which was dissolved in fresh ethanol and treated with excess picric acid at reflux. After cooling, filtration gave 9.63 g. (60%) of the desired picrate (LXIV), m. p. 152-156°. Three crystallizations from absolute ethanol gave the analytical sample, m. p. 156.5-157.5° d.

Anal.: Calc. for $C_{16}H_{19}NO_5 \cdot C_6H_3N_3O_7$: C, 49.44; H, 4.15; N, 10.48.

Found: C, 49.34; H, 4.08; N, 10.63, 10.54.

6-Methyl-4-quinolizone hydrochloride (LXXI): A. A solution of 6-methyl-4-quinolizone (LXVII) (4) in ether was treated with dry hydrogen chloride until strongly acid. The cold mixture was filtered and the resulting brown solid washed well with ether. The material obtained in this manner had m. p. 149-151° d. Attempts to recrystallize this material failed, presumably because of the acid-instability of the ring-system. It lacks the amide carbonyl bond which appears at 1693 cm^{-1} in the infrared spectrum of the parent quinolizone.

B. A solution of 0.3 g. (2 mmole) of the quinolizone (LXVII) in 5 ml. of acetylchloride was allowed to stand at room temperature overnight. The excess acid chloride was removed in vacuo and the resulting brown solid suspended in ether and filtered. This material had m. p. 147-150° d., alone or on admixture with a sample of LXXI, prepared as in A, above.

Reaction of 6-methyl-4-quinolizone (LXVII) with thionyl chloride: Five ml. of thionyl chloride was added to 0.6 g. (4 mmole) of 6-methyl-4-quinolizone (LXVII). Some warming was noted, and acid fumes were given off. After standing for two hours, the mixture was warmed slightly while thionyl chloride was removed in vacuo. The resulting dark oil was suspended in ether, giving a greenish solid, which was filtered and washed with ether. This material (0.5 g.) had m. p. 136-144° d. and gave a negative test for chloride ion. Sodium fusion showed the presence of chlorine and sulfur, while treatment with aqueous base or attempted crystallization from alcohols led to decomposition.

Reaction of 6-methyl-2-chloropyridine with phenyllithium and benzaldehyde: A solution of 0.05 mole of phenyllithium in 30 ml. of ether was prepared in the usual manner. To this, a solution of 6.25 g. (0.05 mole) of 6-methyl-2-chloropyridine (LXXIV) (41, 42) in 15 ml. of ether. The addition was made as rapidly as possible, holding the reaction temperature at 0° in an ice bath. After stirring for ten minutes, 6.65 g. (0.065 mole) of benzaldehyde in 15 ml. of ether was added to the red organometallic solution. The cooling bath was removed and the solution allowed to warm to room temperature while stirring was continued for one hour. At this time 10 ml. of water was added, basic material was extracted from the ether layer with dilute hydrochloric acid and the acid solution basified with solid sodium carbonate. After removing the basic material by extraction with ether, the organic solution was dried over $MgSO_4$ and evaporated, leaving a residue which was heated at 100°/1 mm. for 30 minutes to remove benzaldehyde and starting material. The

resulting orange glass (4.62 g.) was extracted continuously with 60-70° petroleum ether for 2 hours to give 1.1 g. of yellow crystals and oil. After mechanical separation, the crystals were recrystallized several times to give very pale yellow needles of 6-chloro-6'-methyl-2,2'-dipyridylmethane (LXXVIII), m. p. 181-182°. The yield of purified material was only 0.30 g. (5.8%), although considerable loss of fairly pure material was experienced during purification.

Anal.: Calc. for $C_{12}H_{11}N_2Cl$: C, 65.90; H, 5.07; N, 12.81; Cl, 16.44.

Found: C, 66.00; H, 5.13; N, 12.56; Cl, 16.4.

4-Ethoxy-1-(6'-methyl-2'-pyridyl)-1-pentanone (LXXXVII): A solution of 10.85 g. (0.06 mole) of 3-ethoxy-1-bromobutane (25) in 15 ml. of ether was added to 1.40 g. (0.0575 mole) of clean magnesium shavings in 25 ml. of ether, after reaction was initiated by a crystal of iodine. The resulting mixture was stirred and heated for 1.5 hours after the initial reaction subsided, while most of the magnesium dissolved. To this Grignard solution was added a solution of 5.90 g. (0.05 mole) of 6-methyl-2-cyanopyridine. The reaction mixture, originally at 0°, was allowed to come to room temperature, with stirring overnight. The reaction was quenched with water, the mixture acidified with dilute hydrochloric acid, separated, and the ether layer extracted with two more small portions of dilute acid. After standing for an hour, to hydrolyze the intermediate imine, the acid solution was basified with solid sodium carbonate and extracted several times with ether. After drying over magnesium sulfate, the ether was evaporated and the residue distilled

to give 6.45 g. (58.3%) of the ketone LXXXVII, b. p. 148-155°/12 mm. as an unstable yellow oil.

The 2, 4-dinitrophenyl hydrazone was prepared by a standard procedure and recrystallized four times from ethanol to give orange needles of m. p. 123-124°.

Anal.: Calc. for $C_{19}H_{23}N_5O_5$: C, 56.85; H, 5.77; N, 17.45.

Found: C, 57.07; H, 5.86; N, 17.25.

2, 4-Dinitrophenylhydrazone of 1-keto-6-methyl-1, 2, 3, 4-tetrahydroquinolizinium bromide (LXXXVIII): A solution of 3.3 g. (0.015 mole) of the ketonic ether (LXXXVII) in 10 ml. of 48% hydrobromic acid was refluxed for four hours and the excess acid evaporated in vacuo. The dark tarry residue was taken up in water, neutralized with sodium bicarbonate and extracted into chloroform. The resulting chloroform solution was refluxed overnight after drying. Evaporation of the solvent left a black gum which was taken up in 95% ethanol, and treated with 4 g. (0.02 mole) of dinitrophenylhydrazine for two hours at reflux, in the presence of 12 ml. of hydrobromic acid. After cooling, the gummy red precipitate was crystallized three times from ethanol-ethyl acetate to give 0.58 g. (8.9%) of the desired derivative (LXXXVIII), m. p. 218° d.

Anal.: Calc. for $C_{17}H_{18}N_5O_4Br$: C, 46.80; H, 4.16; Br, 18.32.

Found: C, 46.90; H, 4.31; Br, 18.48.

Methanol or aqueous acetone solutions of LXXXVIII were non-acidic, but gave an immediate precipitate on treatment with silver nitrate solution.

Attempted cyanoethylation of 2, 6-diphenacylpyridine (XCI): A solution of 0.5 g. (0.022 mole) of sodium metal in 10 ml. of absolute alcohol was prepared. To this was added 3.15 g. (0.01 mole) of 2, 6-diphenacylpyridine (XCI) (5) in 5 ml. of absolute ethanol. The resulting orange solution was then stirred for 15 minutes before the slow addition of a solution of 1.1 g. (0.021 mole) of acrylonitrile in 5 ml. of alcohol. The temperature was increased slowly, by means of a water bath, to 60°, and stirring at this temperature was continued for two hours. The mixture was cooled, 2 ml. of glacial acetic acid was added, followed by 50 ml. of water. Evaporation of alcohol in vacuo, followed by addition of water to a volume of ca. 50 ml. left 1.65 g. of benzoic acid, m. p. 120-121°, undepressed on admixture with authentic material. After removal of the benzoic acid, an alcoholic solution of 3 g. of picric acid was added to the filtrate to give 2.47 g. of lutidine picrate, m. p. and mixed m. p. 166-168°. No other picrate could be isolated.

Similar results were obtained using KOH in ethanol or potassium t-butoxide in the corresponding alcohol.

Ethyl 3-(6'-methyl-2'-pyridyl)-propionate (CIX): A cooled solution of 12.1 g. (0.1 mole) of 6-methyl-2-pyridinecarboxaldehyde and 11.4 g. (0.11 mole) of malonic acid was prepared in 25 ml. of pyridine and stirred for 90 minutes in the presence of a drop of piperidine while warming to room temperature. Stirring was continued while the red mixture was heated on the steam bath for four hours, cooled and poured into 50 ml. of ice-water. The pH of the solution was adjusted to 4 by the addition of several small portions of 3N hydrochloric acid. The resulting suspension

was refrigerated overnight, then filtered to give 6.85 g. (42%) of 3-(6'-methyl-2'-pyridyl)-acrylic acid, m. p. 98-100°.

This crude unsaturated acid was hydrogenated in 75 ml. of 95% ethanol and 5 ml. of concentrated hydrochloric acid in the presence of 1.0 g. of 5% palladium-on-charcoal catalyst at an initial pressure of 25 psi. After six hours, no further drop in pressure was noted. A total of 3.1 psi.(102%) of hydrogen was absorbed. After removing the catalyst, the solution was evaporated to dryness, leaving the pyridyl propionic acid as a viscous yellow residue. This material was taken up in 10 ml. of absolute ethanol, 35 ml. of benzene was added, along with three drops of concentrated sulfuric acid, and the resulting homogeneous solution was refluxed under a Dean-Stark trap until no more lower (aqueous) layer collected. Most of the solvent was removed in vacuo, and the residue was taken up in water; the solution was carefully basified with solid sodium carbonate and extracted four times with ether. After drying over $MgSO_4$, the ether was evaporated and the residue distilled to give 5.82 g. (71.6%) of the methylpyridylpropionic ester (CIX) b. p. 137-140°/0.7 mm.

The picrate, prepared in 95% ethanol and recrystallized from the same solvent had m. p. 145-146°.

The preparation of the pyridylacrylic acid mentioned above is similar to that used by Ried and Keller (46) in the synthesis of 2-pyridylacrylic acid.

Quaternization of ethyl-3-(6'-methyl-2'-pyridyl)-propionate (CIX) with α-bromo esters: A. A mixture of 2.9 g. (0.015 mole) of the ester (CIX) and 3.5 g. (0.021 mole) of ethyl α-bromoacetate (CX) was heated at 110° under nitrogen for three days. Excess bromoacetate was removed in vacuo and the resulting red gummy quaternary salt (CXI) used directly in attempted cyclization reactions with sodium ethoxide and potassium metal.

In another run, using the same quantities of reagents as above, the quaternary salt was taken up in water, extracted with ether to remove the excess starting material, and titrated with 0.00943N silver nitrate. At the potentiometric end-point, 1.15 ml. of the standard solution had been consumed, corresponding to 72.3% quaternization.

Washing the crude quaternary salt obtained above with several portions of acetone left a small amount of white crystals, but this material proved to be too hygroscopic for purification.

B. Heating 0.4 g. (2.07 mmole) of the pyridylpropionic ester (CIX) with 0.45 g. (2.5 mmole) of ethyl α-bromopropionate, as above, followed by extraction with water, left a nearly colorless solid which did not contain nitrogen (polyacrylate-?). Treatment of the aqueous solution with alcoholic picric acid gave 0.61 g. (72.6%) of the picrate of the starting material (CIX), m. p. and mixed m. p. 144-146°.

Ethyl 6-methylpicolinoylacetate (CXIII): A suspension of dry sodium ethoxide, from 4.35 g. (0.15 mole) of sodium metal, in 150 ml. of dry benzene, was prepared. To this was added a mixture of 16.5 g. (0.10 mole) of ethyl 6-methylpicolinate (43) and 17.6 g. (0.20 mole) of ethyl

acetate, with vigorous stirring. The addition of the ester mixture was completed in 45 minutes; only negligible heating occurred. The resulting orange suspension was refluxed gently for one hour, then allowed to cool and stir overnight. The reaction mixture was poured into 100 ml. of ice-water containing 9 ml. of acetic acid, the two-phase mixture was separated and the aqueous layer extracted several times with ether. After drying, the volatile solvents were removed in vacuo and the residue distilled to give 14.29 g. (68.8%) of the desired β-keto ester (CXIII), b. p. 117-123°/0.4 mm.

The picrate was prepared and recrystallized from 95% ethanol, m. p. 129-129.5° d.

Anal.: Calc. for $C_{17}H_{16}N_4O_{10}$: C, 46.79; H, 3.70; N, 12.84.

Found: C, 46.92; H, 3.82; N, 12.90.

Freshly distilled keto ester (CXIII) was dark orange. The color faded rapidly at room temperature to light yellow, and freezing the sample in the ice-chest gave colorless needles after several days.

Ethyl 3-hydroxy-3-(6'-methyl-2'-piperidyl)-propionate hydroacetate (CXIV): A solution of 10.36 g. (0.05 mole) of ethyl 6-methylpicolinoylacetate (CXIII) in 100 ml. of glacial acetic acid containing 0.75 g. of platinum dioxide was hydrogenated overnight at an initial pressure of 48.5 psi. A pressure drop of 14.2 psi. was noted, corresponding to 98% of the theoretical. After filtering the catalyst, the colorless solution was evaporated to a viscous yellow liquid. Trituration with dry ether, followed by filtration gave 11.90 g. (86.5%) of the desired acetate salt of CXIV as a white powder, m. p. 128.5-130°.

The picrate was prepared in aqueous alcohol and recrystallized several times from 25% ethanol and had m. p. 141.5-142.5°.

Anal.: Calc. for $C_{17}H_{24}N_4O_9$: C, 45.94; H, 5.44; N, 12.61.

Found: C, 46.20; H, 5.38; N, 12.68.

The free base (CXIV) was obtained by treatment of 5.5 g. of the acetate salt with excess saturated potassium carbonate solution, extracted into ether and distilled, after drying the organic extracts over $MgSO_4$. The yield of free base, obtained as a colorless liquid of b. p. 114-122°/0.5 mm., was 3.12 g. (72.6%). This material showed infrared absorption at 3250, 3450 (O-H), 3160 (N-H) and 1732 (ester C = 0) cm^{-1}. The picrate, m. p. 141-142.5°, prepared from the free base was identical with that from the acetate salt, as shown by mixed melting point determination.

1-Hydroxy-3-ketooctahydropyrrocoline (CXV): Treatment of 5.5 g. (0.02 mole) of the piperidylpropionic ester (CXIV) acetate was treated with saturated potassium carbonate solution, as above. Distillation of the resulting basic product gave 2.13 g (63%) of a somewhat basic colorless liquid b. p. 154-157°/0.5 mm. Only traces of the free base (CXIV), b. p. ca. 120°/0.5 mm. was obtained in this experiment. The lactam (CXV) showed the following easily assigned bands in the infrared: 3400 (broad, O-H) and 1685 (amide C = 0) cm^{-1}. It also failed to give a picrate.

Diethyl 6-methyl-2-pyridylethylmalonate (CXVIII): The following procedure was patterned after that used by Boekelheide, in the pyridylethylation of malonic ester (44).

Sodium (2.3 g., 0.1 mole) was dissolved in 25 ml. of absolute ethanol; 37.5 g. (0.235 mole) of diethyl malonate was then added to give a slightly turbid solution. A solution of 11.9 g. (0.1 mole) of 6-methyl-2-vinylpyridine (45) in 20 ml. of absolute ethanol was slowly added to the refluxing sodiomalonate solution, the resulting mixture was stirred at reflux for eight hours, then cooled and acidified with dilute hydrochloric acid. Extraction with several large portions of ether removed unreacted malonic ester. The acidic aqueous layer was neutralized carefully with solid sodium bicarbonate and the resulting oil was extracted into ether. After drying over $MgSO_4$, the ether was removed in vacuo, and subsequent distillation gave a forerun of unreacted 6-methyl-2-vinlypyridine, followed by 10.90 g. (39.1%) of the desired pyridylethyl malonic ester (CXVIII) as a pale yellow liquid of b. p. 155-158°/0.7 mm.

The picrate, prepared in 95% ethanol and recrystallized from the same solvent, had m. p. 92.5-93.5°.

Anal.: Calc. for $C_{21}H_{24}N_4O_{11}$: C, 49.61; H, 4.76; N, 11.02.

Found: C, 49.80; H, 5.00; N, 10.92.

Diethyl 2-(6'-methyl-2'-piperidyl)-ethylmalonate (CXIX): A solution of 8.35 g. (0.03 mole) of diethyl 2-(6'-methyl-2'-pyridyl)-ethylmalonate (CXVIII) in 75 ml. of glacial acetic acid containing 0.75 g. of platinum dioxide catalyst was hydrogenated overnight at an initial pressure of 51 psi. The final pressure was 44.0 psi., so that 107% of the theoretical amount of hydrogen was absorbed. The catalyst was removed and the solution evaporated to a small volume. The free base was liberated by treatment of the residue with an excess of cold saturated potassium carbonate solution and

extracted into ether. After drying over $MgSO_4$, dry hydrogen chloride was passed into the ether solution until it became strongly acidic. The precipitated piperidylethylmalonic ester (CXIX) hydrochloride was filtered and washed with dry ether. The yield of hydrochloride, m. p. 129-131°, was 8.36 g. (87%).

The picrate was prepared for characterization in the usual way. After recrystallization from a small volume of 95% ethanol, it had m. p. 109-110°.

Anal.: Calc. for $C_{21}H_{30}N_4O_{11}$: C, 49.02; H, 5.88; N, 10.89.

Found: C, 48.89; H, 6.03; N, 10.60.

2-Hydroxy-2, 4, 6-trimethylquinolizidine (CXXIII): A solution of 10.0 g. (0.04 mole) of 4, 4-ethylenedioxy-2-methyl-1-(6'-methyl-2'-pyridyl)-2-pentanol (XVIII) in 100 ml. of glacial acetic acid containing 0.8 g. of platinum dioxide was hydrogenated overnight at an initial pressure of 48.5 psi. The total pressure drop was 9.5 psi., corresponding to 109% of the theoretical uptake of hydrogen. The catalyst was filtered, the solution evaporated to ca. 25 ml. and basified with saturated potassium carbonate solution. The resulting pale yellow oil was extracted into ether, dried over $MgSO_4$ and distilled to give 6.85 g. (87.3%) of the quinolizidine derivative (CXXIII) b. p. 109-111.5° at 0.2 mm. This is slightly lower than that of the starting material (XVIII, b. p. 117-124/0.15-0.25 mm.). The product was a colorless oil which seems to be stable at room temperature, in contrast to the starting material, which is pale yellow and becomes more highly colored on long standing. The product does not give a precipitate with the $NiCl_2$-carbon disulfide reagent, showing the absence of a secondary amine function. No solid derivatives could be obtained.

In its infrared spectrum (CCl_4), the product (CXXIII) had absorption peaks at 3490, 3310 and 3170 $cm.^{-1}$, attributed to free O-H and hydrogen-bonded O---H and N---H groups. It showed no significant absorption in the C = 0 region.

APPENDIX

SPECTRA OF QUINOLIZINIUM COMPOUNDS

FIGURE 1

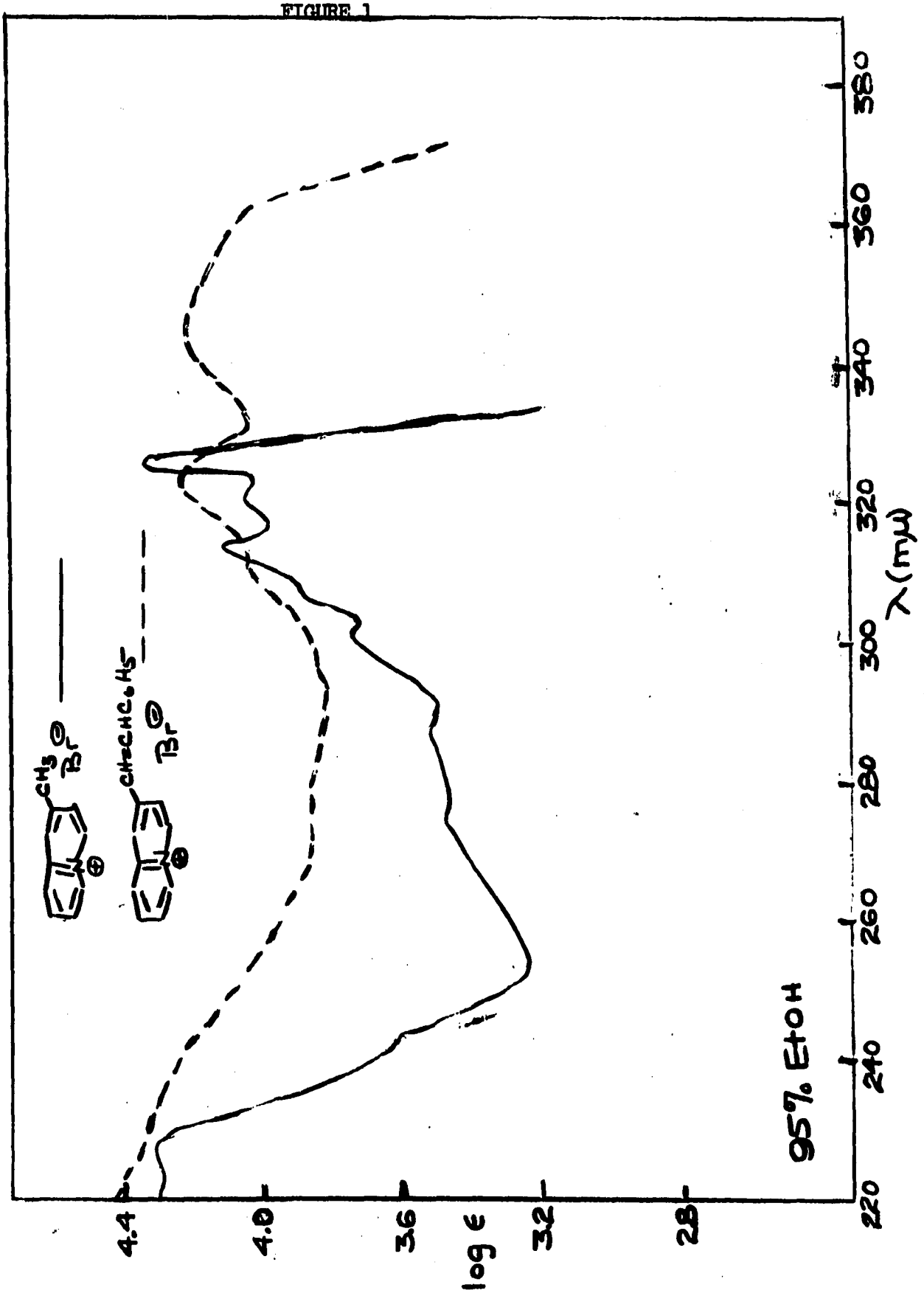


FIGURE 2

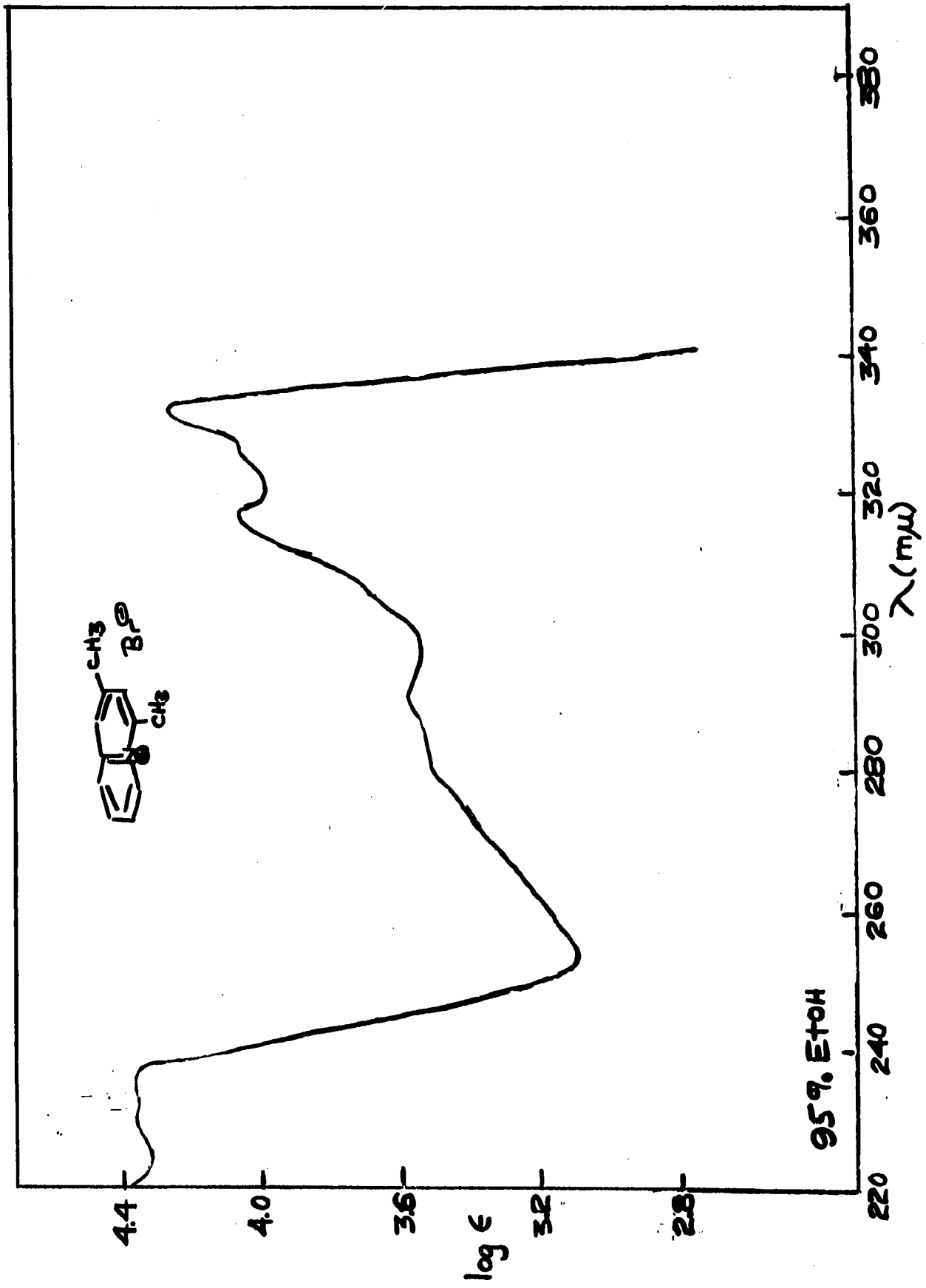


FIGURE 3

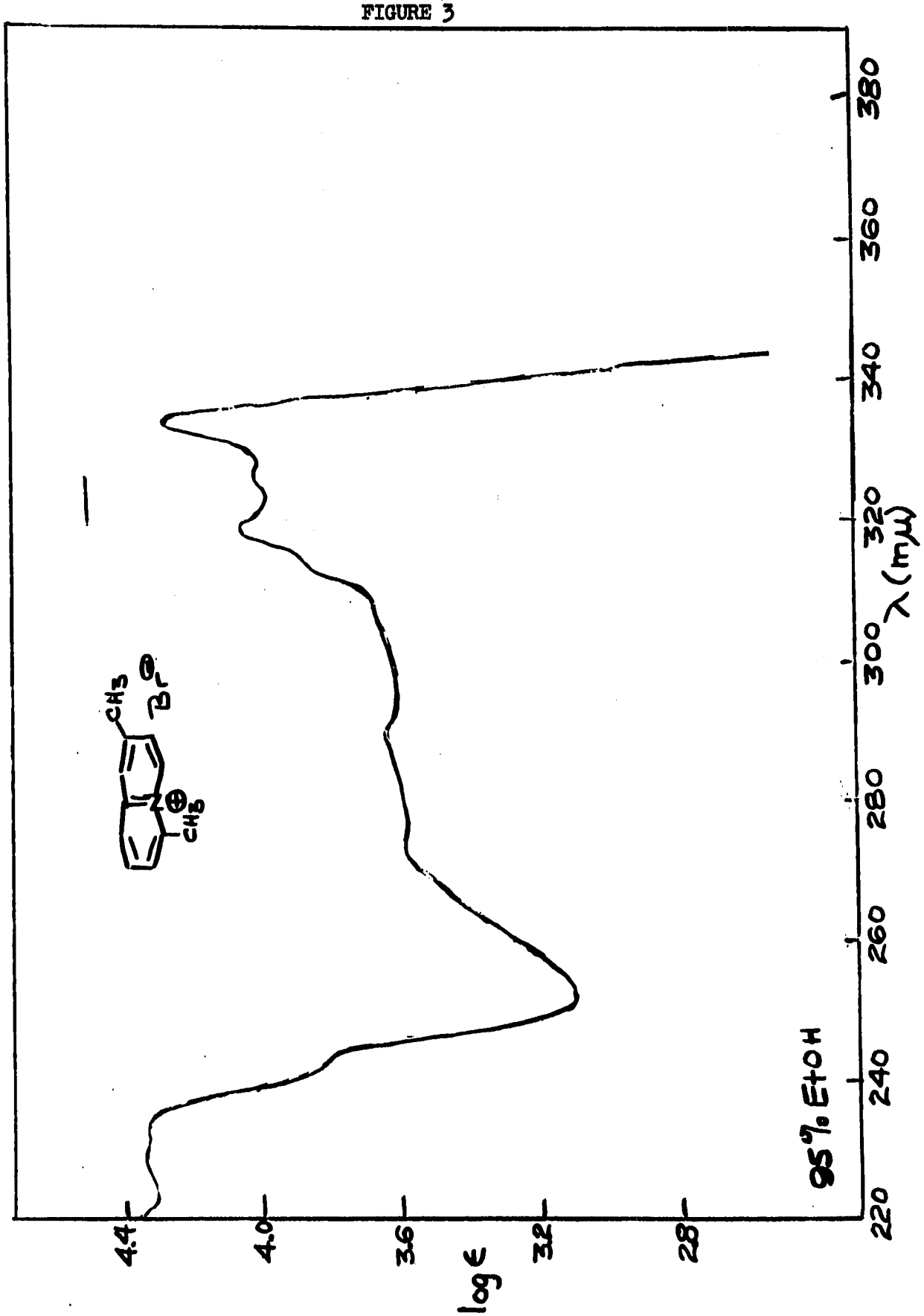


FIGURE 4

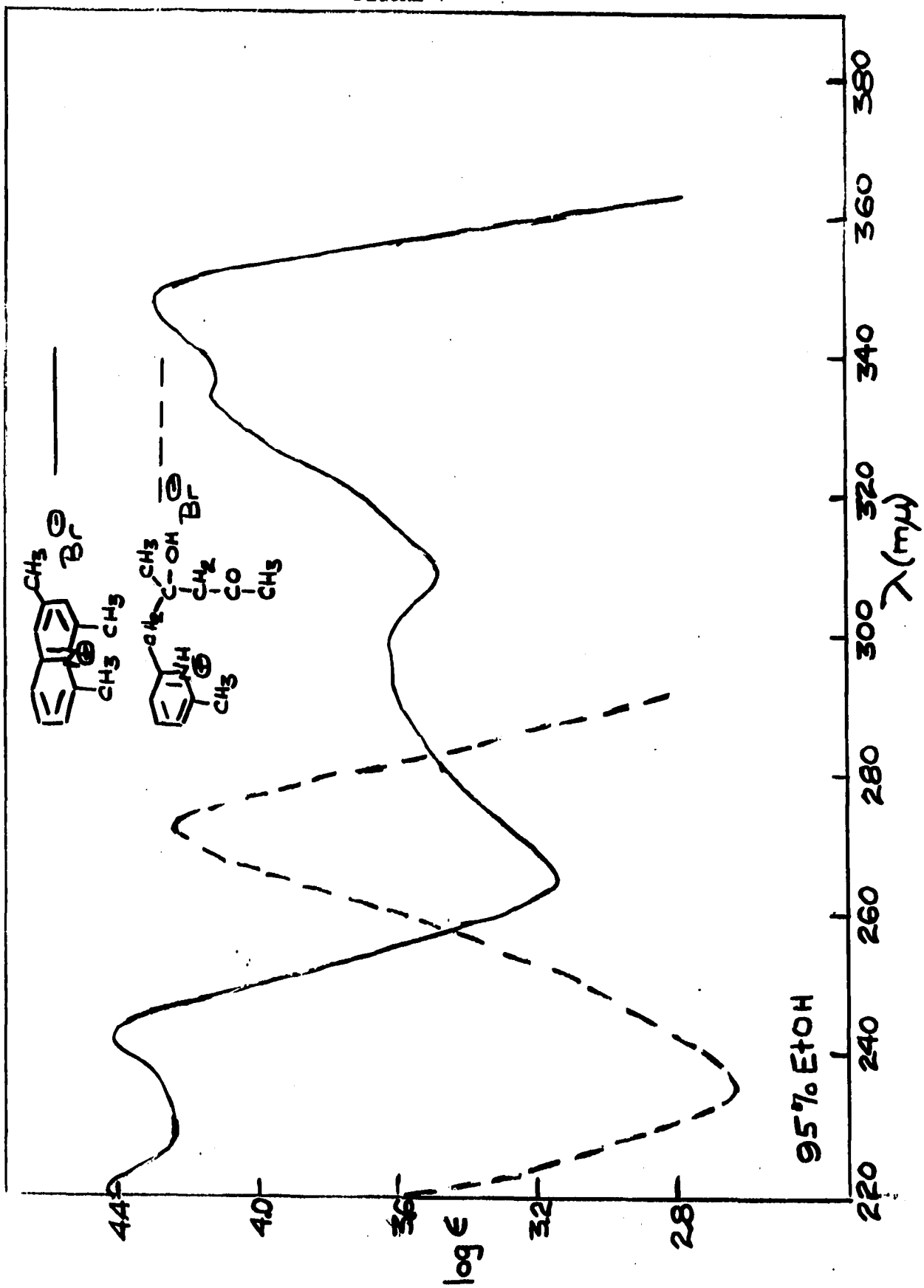


FIGURE 5

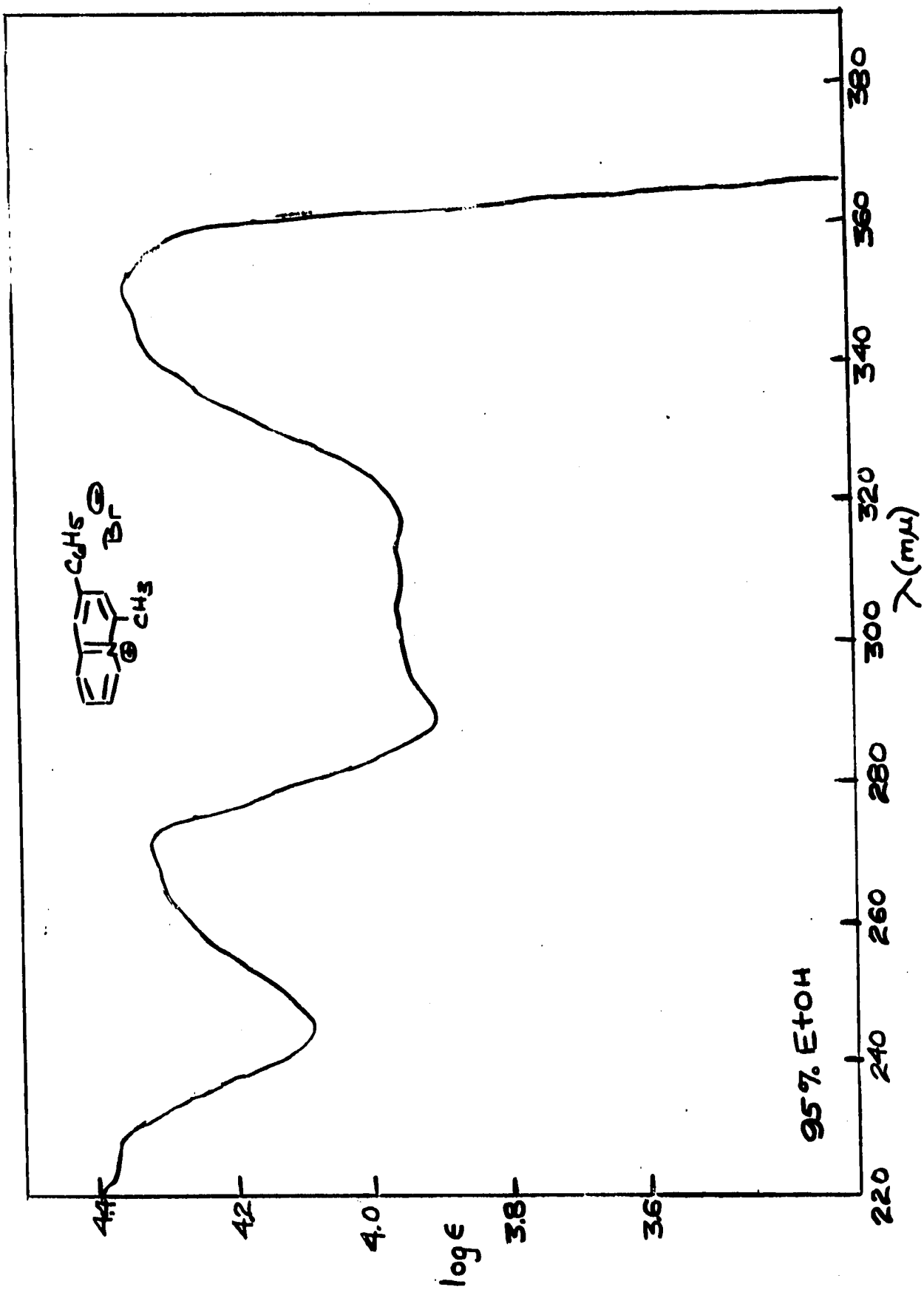


FIGURE 6

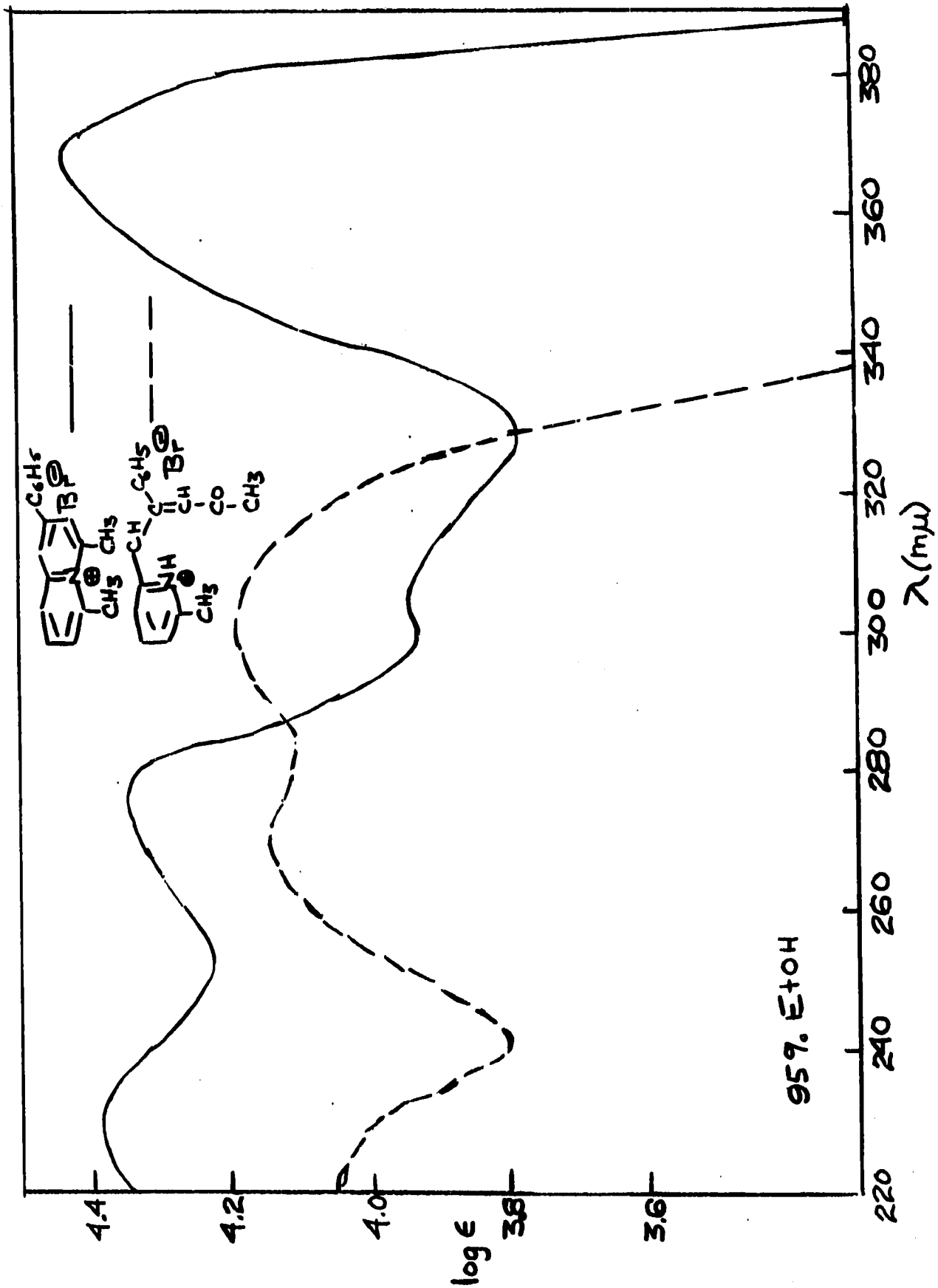


FIGURE 7

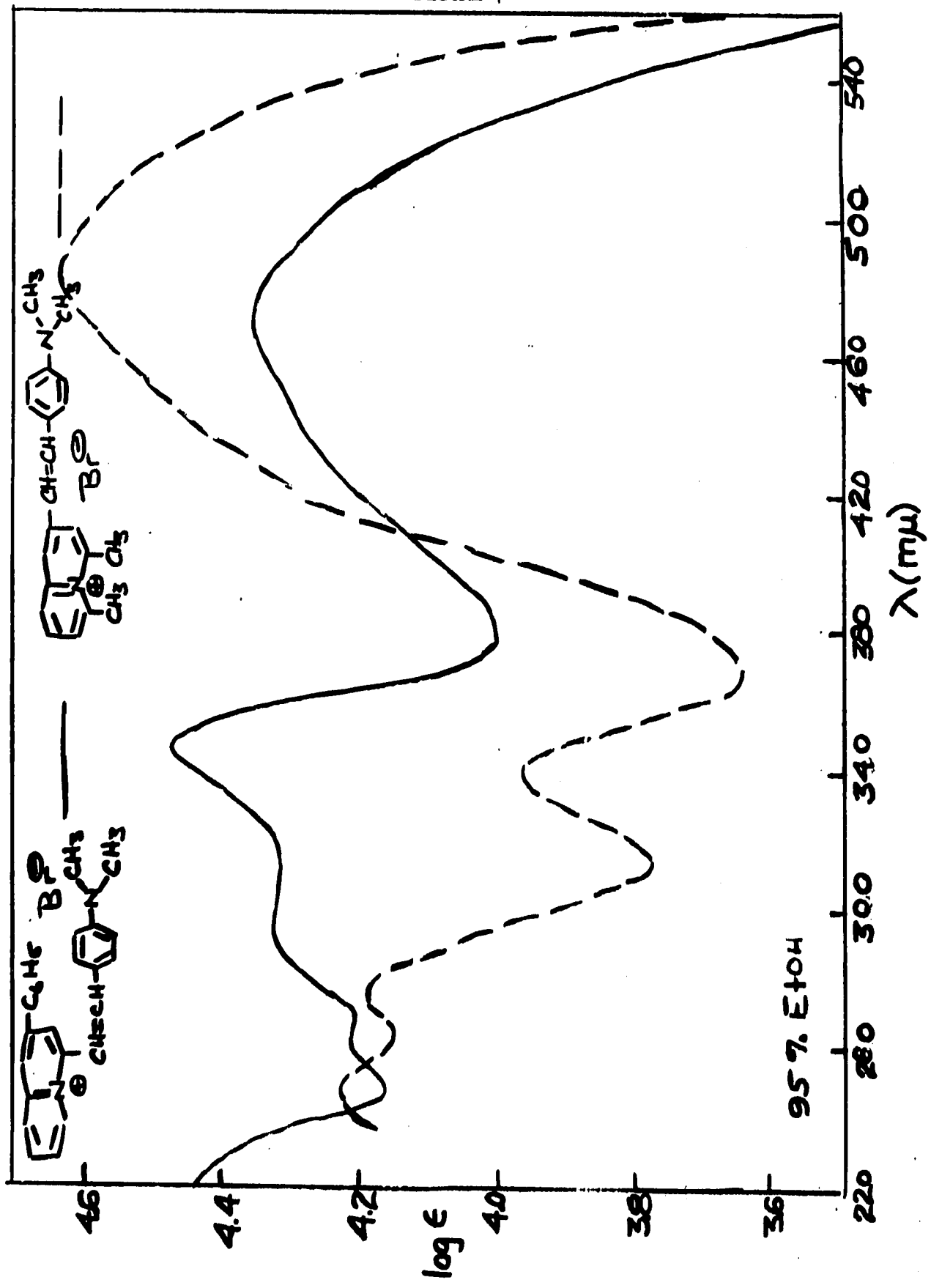


FIGURE 8

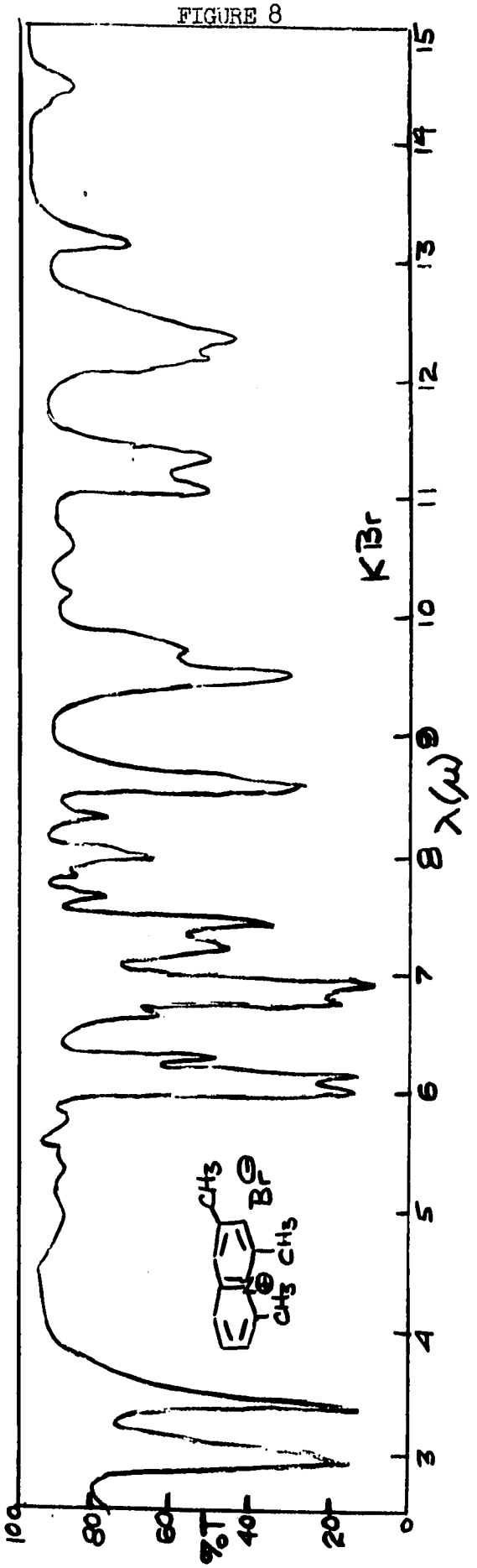


FIGURE 9

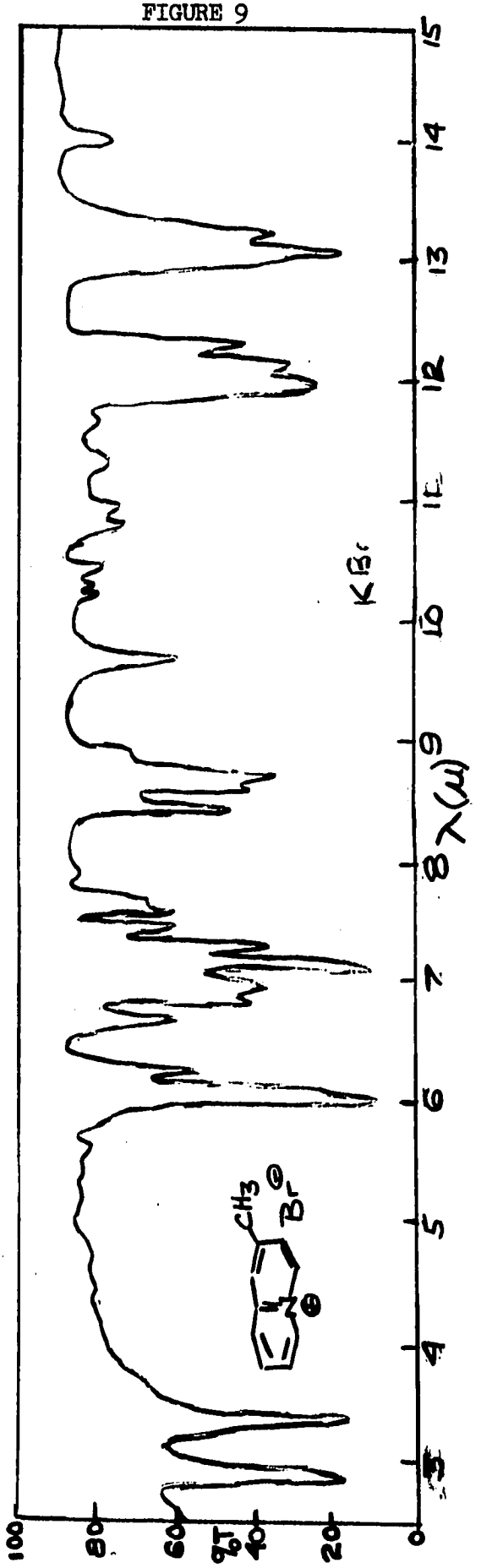


FIGURE 10

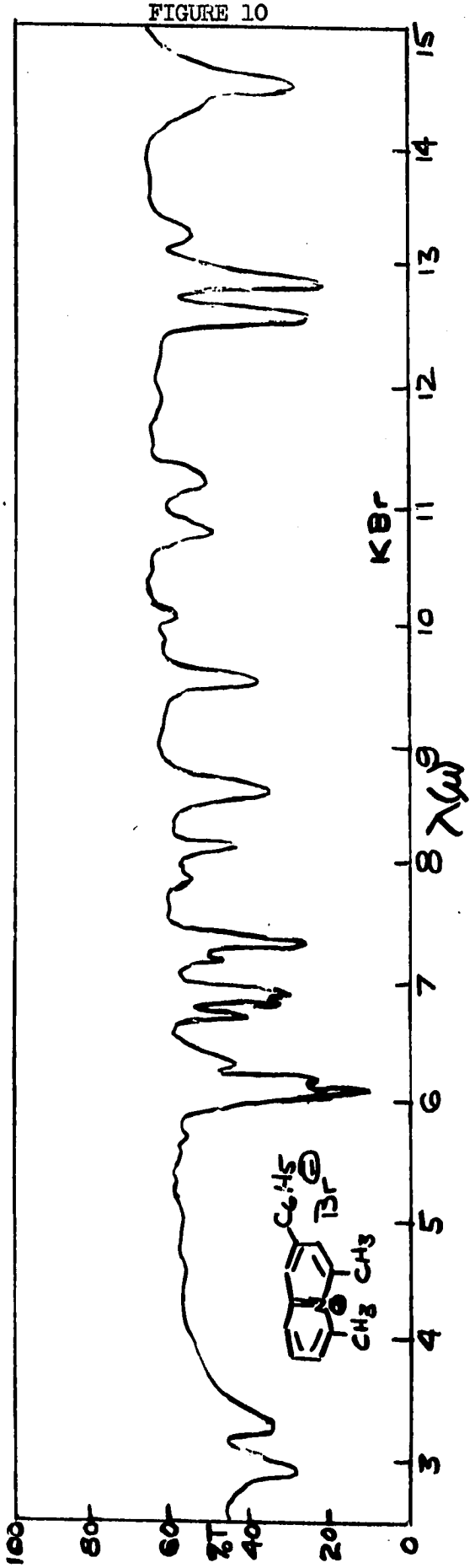
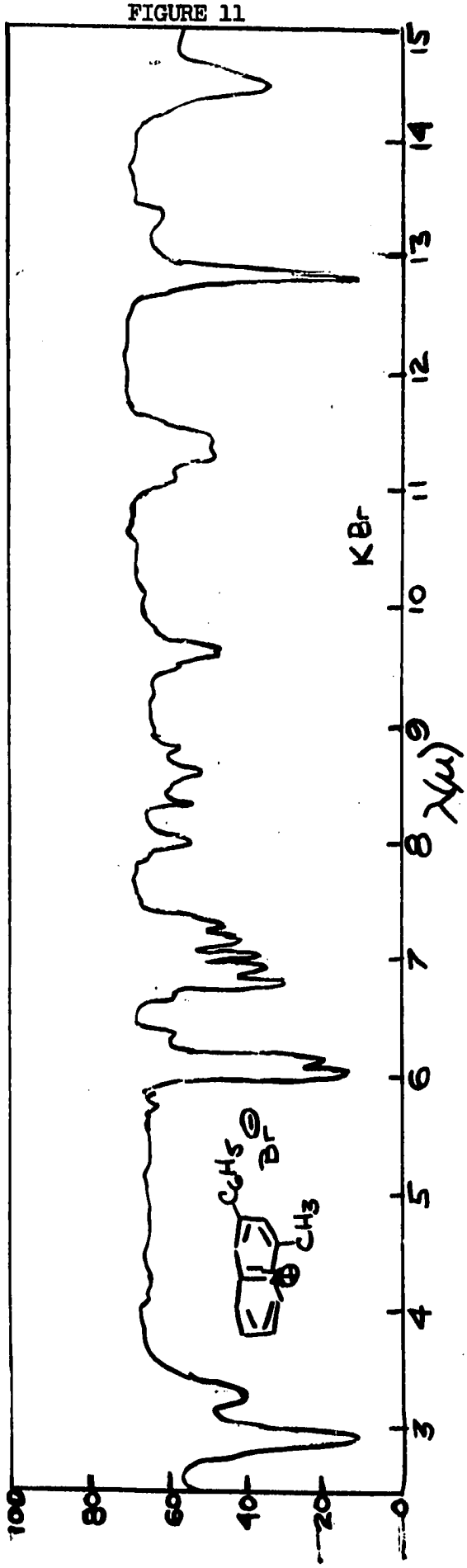


FIGURE 11



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