Spring 1960

PARTIALLY REDUCED PYRIDINE COMPOUNDS

DAVID ALAN NELSON

Recommended Citation

NELSON, DAVID ALAN, "PARTIALLY REDUCED PYRIDINE COMPOUNDS" (1960). *Doctoral Dissertations*. 765.
https://scholars.unh.edu/dissertation/765

NELSON, David Alan. PARTIALLY REDUCED
PYRIDINE COMPOUNDS.

University of New Hampshire, Ph. D., 1960
Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan

PARTIALLY REDUCED PYRIDINE COMPOUNDS

BY

DAVID ALAN NELSON

S. B., Massachusetts Institute of Technology, 1953

M. S., University of Rhode Island, 1955

A THESIS

Submitted to the University of New Hampshire

In Partial Fulfillment of

The Requirements for the Degree of

Doctor of Philosophy

Graduate School

Department of Chemistry

June, 1960

This thesis has been examined and approved.

Paul R. Jones

March 25, 1960

Date

ACKNOWLEDGEMENT

The author wishes to express his appreciation to Dr. Robert E. Lyle for his direction of this research and for his optimistic encouragement with the problem. He would also like to thank Dr. Paul R. Jones for his cooperation in the determination of infrared and ultraviolet absorption spectra.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

INTRODUCTION

INTRODUCTION

It has been known for many years that various reducing agents can cause partial reduction of the pyridine ring. The reducing agents which have been used include metal amalgams, sodium and alcohol, sodium dithionite ($Na_2S_2O_4$), sodium and potassium borohydride and lithium aluminum hydride. Partial reduction of the pyridine ring can also be effected by irradiation with X- and γ-rays, electrolytic, catalytic and enzymatic methods. Certain cyclization reactions, such as that of Hantzsch, lead directly to partially reduced pyridine compounds. Much of the earlier literature has been summarized in several reviews (1-4).

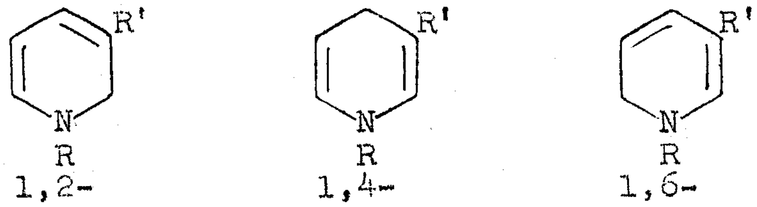
Partially reduced pyridine compounds are usually designated as dihydro- or tetrahydropyridines with appropriate numerical prefixes to indicate the positions of reduction. Thus, a 3-substituted pyridine compound could be reduced to three different dihydropyridines or four different tetrahydropyridines, assuming no unsaturation on the nitrogen atom. These structures are indicated in Figure 1.

Current research in the field of partially reduced pyridine compounds has been dominated by studies of dihydropyridines inspired by the discovery in 1935 (5) that an important enzyme system, that of Coenzyme I, or DPN-DPNH, involves a reversible reduction of a nicotinamide quaternary salt to a dihydronicotinamide structure. Using primarily 3-substituted pyridine quaternary salts as models for this enzyme system, many investigations have been made into the nature and mechanism of this reduction. Although a period of over twenty years of research has elapsed several aspects of the reductions of pyridine quaternary salts to dihydro- and tetrahydropyridines remain confused. In 1936 it was proposed (6) that the reduced nicotinamide portion of DPNH was a 1,2-dihydropyridine derivative, and it was not until 1954 that the structure was shown conclusively to be a 1,4-dihydroderivative (7). Until quite recently several workers maintained that sodium dithionite reduced pyridine quaternary salts to form 1,2-dihydroderivatives (8); however, it is now firmly established that this method produces solely 1,4-dihydropyridines. Since this error had been made by a primary investigator in the field, much of the literature prior to 1954 must be viewed with caution and reinterpreted on the basis of recent work.

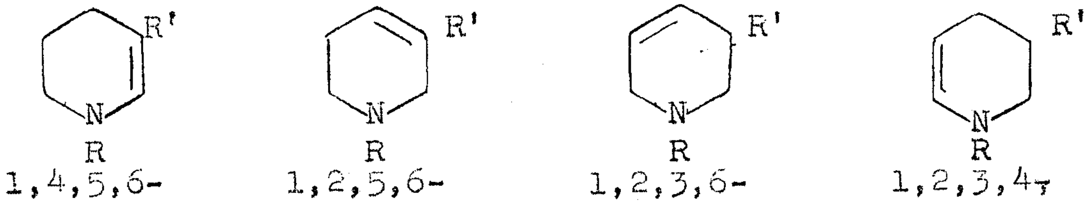
In 1958, when the present research was started, enzymatically reduced DPN was known to be a derivative of 1,4-dihydronicotinamide (7). Much earlier the product of the reduction of DPN by sodium dithionite had been found identical with the enzymatically reduced product (9). Deuterium transfer studies had been used to show that the 1-benzyldihydronicotinamide (10) and 1-methyl dihydronicotinamide (11) produced by reduction of the corresponding quaternary salts by sodium dithionite were 1,4-dihydropyridines. This fact was confirmed by nuclearmagnetic resonance studies (12, 13). It has been assumed in this research on the basis of these studies, that sodium dithionite reduces 3-substituted pyridine quaternary salts to 1,4-dihydropyridines.

Studies on the structures of dihydropyridines produced by other reducing agents, primarily sodium borohydride, indicate that mixtures of products are formed. Sodium borohydride has been shown to reduce 3-substituted pyridine quaternary salts to 1,2,5,6-tetrahydropyridines (14) as well as dihydropyridines. The same 1,4-dihydropyridine formed by dithionite reduction can be produced using sodium borohydride, as well as an isomeric dihydropyridine which has been formulated by Karrer as the 1,2-isomer (15). Recent work by Druey and Schenker (16) has shown conclusively that in the case of 1-methyl-3-cyanopyridinium bromide the dihydropyridine produced by sodium borohydride reduction is the 1,6-isomer. This finding casts doubt on the earlier reports of formation of 1,2-dihydropyridines by sodium borohydride reduction.

The present investigation was undertaken in order to study the reactions of dihydropyridine systems and to attempt to elucidate the mechanism of sodium dithionite and sodium borohydride reductions of 3-substituted pyridine quaternary salts and dihydropyridine compounds and the analysis of the reduction products by ultraviolet spectra. Because of the stability of 3-benzoylpyridine derivatives much emphasis was placed on this compound and its derivatives. The reactions of 3-benzoyldihydropyridines with various reagents were investigated, and the structures of the reaction products were determined. Finally, an attempt was made to correlate the infrared spectra of a number of quaternary salts and dihydropyridines.



Dihydropyridines



Tetrahydropyridines

Fig. 1. Typical Structures of Partially Reduced Pyridines.

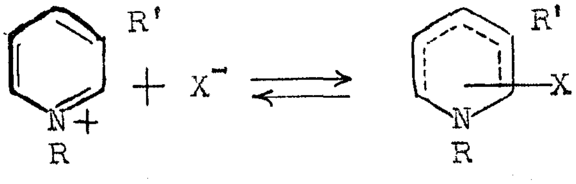


Fig. 2. General Equilibrium of Nucleophilic Addition to the Pyridinium Ring.

DISCUSSION

DISCUSSION

Preparation of quaternary salts. The 3-substituted pyridine quaternary salts used in this investivation were prepared by standard methods such as those described by Karrer (17). Several new salts of 3-benzoylpyridine, nicotinamide and methyl nicotinate were prepared and characterized. These are listed in Table I. In most cases it was found that isopropyl alcohol served as an excellent recrystallization solvent and is to be recommended as the solvent of choice in recrystallizing quaternary salts. The preparation of salts from benzyl halides and β-phenylethyl bromide was most successful if an excess of the halide was avoided, since the excess halide was difficult to remove and tended to cause the salts to be hygroscopic. An improved method was developed for the preparation of quaternary salts of β-(3-indolyl)-ethyl bromide. Reported quaternisations of isoquinolines and pyridines with β-(3-indolyl)-ethyl bromide suggested reaction times ranging from one day to several weeks at room temperature (18-20). The yields of salts were from 30 to 60%. It was found that heating equimolar amounts of the halide and pyridine derivative on a steam bath resulted in a yield of 80 to 90% of quaternary salt in 10 minutes. This method was used to prepare 1-β-(3-indolyl)ethyl-3-benzoylpyridinium bromide (XIII) and the corresponding salt of methyl nicotinate (X).

Preparation of dihydropyridines. The fact that nucleophiles will add to pyridinium quaternary salts to produce dihydropyridines has been demonstrated by many investigations. Nucleophiles which have been added include dimethylaniline (21) and hydroxylamine (22), anions of acetophenone (23), cyclohexanone (23), acetone (24) and dihydroxyacetone (25), and hydroxide (26), ethoxide (27), bisulfite (28), cyanide (29) and dithionite (30) ions. Some of these results have r cently been summarized by Kosower (31). Only in the case of the cyanide addition product has the position of addition definitely been shown to be 4- (32). The nature of the dithionite addition product has not been established, although the dihydropyridine resulting from its decomposition has been proved to be 1,4-, as mentioned previously. The structures of other addition products have been assigned, usually on the basis of spectral evidence, as 1,2-, 1,4- or 1,6-dihydropyridine derivatives.

The general situation involving the addition of any nucleophile to the pyridinium ring can be viewed as an equilibrium as shown in Figure 2. The stability of the adduct will depend both upon the nucleophilicity of the anion and the electrophilicity of the pyridinium ring. A more elaborate discussion of the addition mechanism has been presented by Kosower (33-37), who postulates the existence of "charge-transfer complexes" in solution.

In this investigation several new dihydropyridines were prepared. These new dihydropyridines are listed in Table II., together with three prepared previously by other investigators but also used in this investigation. The preparation of dihydropyridines by reduction of pyridinium salts with sodium dithionite was accomplished using methods already described in the literature (10, 38, 39). The relative success of these methods depended upon the nature of the quaternary salt used. Large groups on the nitrogen atom such as benzyl or β-phenylethyl and strongly electron-attracting groups on the 3-position such as benzoyl and acetyl seem to promote the formation of stable, solid dihydropyridine derivatives, whereas 3-amides and esters with low molecular weight groups on the nitrogen atom usually formed oils when reduced with sodium dithionite.

In three cases products were isolated whose qualitative elemental analyses indicated the presence of sulfur. It has been suggested that sodium dithionite reduction occurs by a preliminary attack of the $(SO_2H)^-$ ion on the pyridinium ring, and addition products formed from pyridinium quaternary salts and sodium dithionite have been isolated (40, 41). The significance of these addition products will be discussed in the section dealing with the mechanism of dithionite reductions.

It was found that under the same conditions of reduction 1-benzyl-3-benzoylpyridinium chloride (XVII) formed a dithionite addition product whereas 1-(β-phenylethyl)-3-benzoylpyridinium bromide (XXXII) was reduced to a dihydropyridine derivative. The increased electrophilicity of the pyridinium ring in XVII due to the benzyl group must increase the stability of the dithionite addition product to such an extent that it is not hydrolized to the dihydropyridine under the same conditions as XXXII, or the difference in solubility of the dithionite addition compounds of XVII and XXXII causes the precipitation of XVII before it can decompose. The dithionite addition compound of the quaternary salt XXXII could be isolated by treatment with a large excess of sodium dithionite. In this case the addition compound (XXXVII) precipitated at once from the reaction mixture, preventing further reaction.

The other dithionite addition compound was formed from 1-methyl-3-benzoyl-4-phenylpyridinium bromide (XLIII). In this case the phenyl group on the 4-position must be responsible for the increased stability and decreased solubility of the dithionite addition compound, for other studies have shown that under the same conditions 1-methyl-3-benzoyl-pyridinium bromide forms the dihydropyridine derivative (42). The dihydropyridine (XII) was isolated also from this reaction in small yield.

The formation and stability of the cyanide addition compounds were found to be closely related to the dithionite complexes. Karrer has presented evidence to show that 1-methyl-4-cyano-1,4-dihydronicotinamide (XXV) is partially dissociated in solution, for the ultraviolet spectrum of a solution of XXV shows bands due both to the addition compound and the quaternary salt (43). Kaplan has also investigated the formation of cyanide addition compounds for a large number of 3- and 4-substituted pyridine quaternary salts (29). The results of both of these investigators show that in order to isolate the cyanodihydropyridines a large excess of cyanide ion must be added to a solution of the quaternary salt.

In this study three new cyanide adducts were prepared using methods described in the literature (43). Two of these, 1-β-(3-indolyl)-ethyl-3-benzoyl-4-cyano-1,4-dihydropyridine (XXXIV) and 1-benzyl-3-benzoyl-4-cyano-1,4-dihydropyridine (XXXV), prepared from the corresponding 3-benzoylpyridine quaternary salts, formed very stable addition compounds. The ultraviolet spectra of XXXIV and XXXV in 95% ethanol showed no evidence of absorption due to the quaternary salt. In contrast, XXV is about 3% dissociated in methanol and 82% in water (29). Again the increased stability of the adduct can be attributed to the increased electrophilicity of the pyridinium ring due to the 3-benzoyl group. The other cyanide addition product was prepared from 3-benzoyl-4-phenylpyridine methobromide (XLIII). This addition compound, in contrast to XXXIV and XXXV, was quite unstable. A very large excess of cyanide was necessary to cause it to precipitate from the reaction. Recrystallization attempts resulted in much decomposition, and the compound seemed to decompose to a large extent in most polar solvents. The ultraviolet spectrum showed only a small maximum around 365 $m\mu$ indicative of a 1,4-dihydropyridine system and a large absorption around 250 $m\mu$. Evidence has been presented to show that cyanide addition compounds are derivatives of 1,4-dihydropyridines; that is, the attack of cyanide ion occurs at the 4-position of the pyridinium ring (32).

The results with 3-benzoyl-4-phenylpyridine support this conclusion. The 4-phenyl group must provide enough steric hindrance to prevent the formation of a stable addition compound even though the steric requirement of the nitrile group is low. If the addition had taken place at the 2- or 6-position, a stable addition product would be expected due to the stabilizing effect of the 3-benzoyl group indicated by XXXIV and XXXV. Therefore the structure is indicated as 1-methyl-3-benzoyl-4-phenyl-4-cyano-1,4-dihydropyridine (XL). The ultraviolet spectrum, as indicated above, is also consistent with this structure. The infrared spectrum showed a very weak band at 2180 cm.$^{-1}$ indicative of a nitrile group as well as other bands consistent with the dihydropyridine structure (see Table VII). Because of the instability of XL consistent elemental analyses could not be obtained, but the analytical values on the crude material suggested the presence of the elements of water in addition to the nitrile function. The nitrile bands in the infrared spectra of XXXIV and XXXV were very weak, at 2240 cm.$^{-1}$ and 2220 cm.$^{-1}$ respectively. 1-Methyl-3-carbamoyl-4-cyano-1,4-dihydropyridine (XXV) showed a slightly stronger band at 2220 cm.$^{-1}$. Anderson and Berkelhammer (27) have recently reported a stable crystalline cyanide-addition product from 1-benzyl-3-acetylpyridinium bromide which also appears to be essentially entirely covalent, analogous to the 3-benzoyl products prepared in this research.

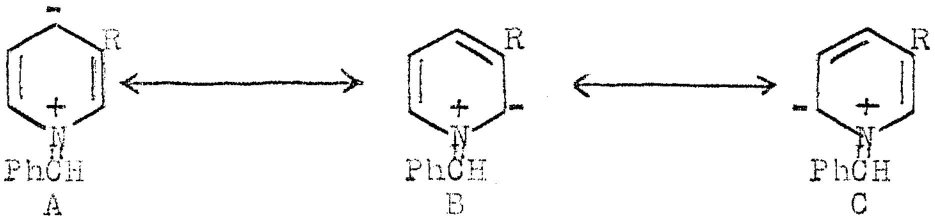
The reaction of hydroxide ion with 3-benzoylpyridinium salts was also investigated. Studies made previous to

1954 with this nucleophile had been interpreted to indicate addition at the 2-position of the ring; however, these interpretations were based largely on spectral data and oxidation of pyridinium salts in base to 2- or 6-pyridones. At that time reduced DPN was still considered to be a derivative of 1,2-dihydropyridine, and analogies which were made with the spectral changes of this compound were necessarily misleading. The latest data on this reaction have been presented by Anderson and Berkelhammer (27). These workers found that the addition of hydroxide to ethanolic solutions of several 3-substituted 1-benzylpyridinium salts resulted in the appearance of a band in the ultraviolet spectra from 314-325 mμ. Since these bands were at wavelengths 38-45 mμ shorter than those of the corresponding 1,4-dihydropyridine compounds, these workers concluded that addition had not occurred at the 4-position. Of the remaining positions for additions the 6- was favored over the 2- since it was expected that a 1,2-dihydro system would absorb at much longer wavelengths. In the case of 1-benzyl-3-acetylpyridinium bromide an unstable solid was formed which was found to absorb at 362 mμ in ethanol and 351 mμ in dioxane. This was assigned the formula of a dimolecular ether connected either at the 2- or 4-position on the basis of analytical data.

In view of the stability of other nucleophilic adducts of 3-benzoylpyridinium salts it was hoped that a pure addition product with hydroxide ion could be obtained; however, the product formed from 1-benzyl-3-benzoylpyridinium chloride and hydroxide was an amorphous yellow solid which decomposed on attempted recrystallization. This product showed an ultraviolet spectrum very similar to that obtained by Anderson and Berkelhammer on the addition of base to 1-benzyl-3-acetylpyridinium bromide. Results obtained by adding sodium hydroxide or sodium methoxide to solutions of 1-benzyl-3-benzoylpyridinium chloride and 1-(β-phenylethyl)-3-carbomethoxypyridinium bromide are shown in Table IV and agree with the results of Anderson and Berkelhammer. The solid obtained by the addition of sodium hydroxide to an aqueous solution of 1-benzyl-3-benzoylpyridinium bromide did not show absorption around 360 mμ, as reported by Anderson and Berkelhammer, but only the same absorption as that of an alcoholic solution of the salt to which base had been added. The absorption spectrum of a concentrated solution of the crude product showed a shoulder at 475 mμ. The infrared spectrum of the crude product had a strong absorption band at 1575 cm.$^{-1}$ as well as other bands indicative of a dihydropyridine system. The absorption band at 1650 cm.$^{-1}$ in conjunction with the dihydropyridine bands at 1675 cm.$^{-1}$ and 1580 cm.$^{-1}$ might indicate the presence of pyridones in the crude product. The ultraviolet spectra of the quaternary salts in basic solution could be interpreted as indicating the formation of a mixture of 2- and 6-pyridones since 1-methyl-3-carbamoyl-2- and 6-pyridones have been shown to absorb at 330 mμ and 260 mμ, respectively, by Pullman and Colowick (44). The unexplained band observed by Anderson and Berkelhammer at 278 mμ in the formation of their "dimolecular ether" could be likewise assigned to a 1-benzyl-

3-acetyl-6-pyridone.

There also exists the possibility that some of the products formed in these reactions might be pyridinium betaines of the type described by Kröhnke (LXI) (45). The ultraviolet spectra of these compounds have not been described, but it would not be unreasonable to expect the spectra to be similar to those of dihydropyridine derivatives when the resonance forms contributing to the resonance hybrid are considered (LXIA-C). The pyridinium betaines are described as yellow, unstable solids, similar to those obtained in these reactions.



LXI

The interpretation of the reaction of pyridinium salts with base is further complicated by the results obtained with 3-benzoylpyridinium salts in concentrated carbonate solution. When sodium carbonate was added to an aqueous solution of 1-(β-phenylethyl)-3-benzoylpyridinium bromide (XIV) a yellow solid precipitated. The same result was reported by Anderson and Berkelhammer for 1-benzyl-3-acetylpyridinium chloride, and these workers assumed this was the same product as was formed with hydroxide (27). The yellow precipitate from the solution of XIV and carbonate showed an absorption maximum in the ultraviolet spectrum at 382 mμ which corresponds to the absorption maximum of a 1,4-dihydropyridine. The absorption maximum of the yellow addition compound at 382 mμ disappeared on addition of acid, and a new absorption maximum appeared at 308 mμ. This behavior in ultraviolet absorption is typical of 1,4-dihydropyridines and stands in contrast to the changes in absorption spectra on addition of acid to the products formed with hydroxide or methoxide, in which case the quaternary salt was regenerated by the acid. An aqueous methanol solution of the carbonate product on reaction with sodium dithionite produced 1-(β-phenylethyl)-3-benzoyl-1,4-dihydropyridine (XXXII). Several 10^{-4}M quaternary salt solutions in 1M sodium carbonate, on standing for two days, gave absorption bands around 360 mμ in addition to the quaternary salt bands near 265 mμ. These results are given in Table IV. This absorption seems to represent a species different from either that produced with hydroxide or methoxide which have absorption maxima at 382 mμ. The "dimolecular ether" of Anderson and Berkelhammer absorbed at 362 mμ in ethanol, but this maximum was unstable. This maximum of the carbonate addition product, however, developed after long standing.

The data obtained in this investigation indicate that the products formed from 3-benzoylpyridinium salts and basic reagents depend both on the nature and concentration of the reagent. Mixtures of products are definitely formed and seem to include both 1,2- and 1,4-dihydropyridines as well as pyridones. Pyridinium betaines and "charge transfer complexes" may also be responsible for some of the ultraviolet absorption maxima observed. In view of the work of

Druey and Schenker (16) who showed that 1-methyl-3-cyano-1,6-dihydropyridine absorbed at slightly higher wavelengths than the corresponding 1,4-dihydropyridine (349 mμ vs. 340 mμ), the assignment of structure as 1,6-dihydropyridines to the species absorbing at 315-325 mμ made by Anderson and Berkelhammer is doubted.

Correlations of infrared spectra of quaternary salts. The infrared spectra of quaternary pyridinium salts have received very little attention in the literature (46, 47), and no mention of them was made in the second edition of Bellamy's book (48). Recently, Katritzky and coworkers correlated the infrared spectra of several 2-, 3-, and 4-substituted pyridines (49-51) but did not study the corresponding salts. As part of this investigation it was of interest to determine characteristic changes in infrared spectra which accompany the quaternization of the pyridine nitrogen.

The infrared spectra of 21 3-substituted pyridine quaternary salts were determined and compared with the infrared spectra of the parent pyridines. Several changes were noted in the spectra which were common to all salts prepared and these may be used to identify 3-substituted pyridine quaternary salts or to ascertain that quaternization of a 3-substituted pyridine has occurred.

In addition, the infrared spectra of seven 3-substituted pyridines were determined in the solid state as mulls in halocarbon and nujol and compared with the data given by Katritzky, Hands and Jones (50) for 3-substituted pyridines (see Table V). These workers determined spectra in chloroform solution and did not report bands below 1000 cm.$^{-1}$. By determining the spectra of mulls in nujol, four additional bands were found in the region of 1000 cm.$^{-1}$ - 650 cm.$^{-1}$ which were characteristic of 3-substituted pyridines and which changed on quaternization. These were at 968-953 cm.$^{-1}$, 830-825 cm.$^{-1}$, 775-735 cm.$^{-1}$ and 705-692 cm.$^{-1}$. Of these four, only the band at 705-692 cm.$^{-1}$ changed on quaternization. Although Katritzky did not report these bands, other workers have observed absorption in these regions at 1018-1012 cm.$^{-1}$, 820-770 cm.$^{-1}$, 715-712 cm.$^{-1}$ and 730-690 cm.$^{-1}$ (52, 53). Katritzky has made assignments based on analogies with <u>meta</u>-disubstituted benzenes. Bellamy also mentions that 3-substituted pyridines should be analogous to <u>meta</u>-disubstituted benzenes in the region of C-H out of plane deformations, 900-700 cm.$^{-1}$. The present work agrees well with the results of Katritzky and coworkers, although all of the 3-substituents of the pyridines examined in this work are electron-withdrawing, whereas Katritzky reported data for electron-donating substituents as well. This fact together with the difference in phase may account for the differences in limits for some of the bands.

Table VI lists the characteristic bands for the quaternary salts. Several generalizations can be made from the data in Table VI. Sixteen characteristic bands are listed for the quaternary salts, and this is the same number found for the 3-substituted pyridines. Since the formation of a quaternary salt consists largely in changing the charge distribution in the pyridine ring rather than affecting any formal bonds, it can be considered to a first approximation that certain bands characteristic of the 3-substituted pyridine ring will be shifted in position and intensity to some extent by quaternization of the nitrogen, but that the only new bands which might appear would be due to the 1-substituent. A new C-N bond is formed, but such vibrations usually give rise to bands which are weak and difficult to correlate. Bellamy gives bands at 1410 cm.$^{-1}$ (w.) and 1220-1020 cm.$^{-1}$ (m.-w.) as characteristic absorption of C-N stretching in aliphatic amines (54). Although the situation in a quaternary salt is not strictly analogous, a band was observed in some of the compounds in this region, usually as a weak band or a shoulder. The correlation is complicated in some cases by the presence of amide substituents which have also been reported to show absorption in this region (55). Bands are also found in the 1220-1020 cm.$^{-1}$ region, but these occur in the parent pyridine as well. A C-N bond correlation, then, is not obvious; however the band around 1410 cm.$^{-1}$ is listed where present (b.). The changes occurring on quaternization were determined by directly comparing the spectra of the pyridine and one of its quaternary salts. Six such comparisons were made, one for each of the pyridines listed in Table V except 3-acetyl.

If each of the sixteen bands is compared in position and intensity, several characteristic changes can be observed. In each case the band first mentioned is that of the 3-substituted pyridine and following this the corresponding quaternary salt band is listed.

(1) The aromatic C-H stretching vibration around 3050 cm.$^{-1}$ does not appear to change in any characteristic manner, except that in a series of salts with the same 3-substituent the group on the nitrogen atom affects the position of the band in some manner. Likewise, if the same alkylating group is attached to different 3-substituted pyridines differences in the position of absorption are observed, and no correlation is obvious.

(2) The band at 1603-1592 cm.$^{-1}$ in the pyridine is shifted to 1662-1625 cm.$^{-1}$ on quaternisation, and the intensity of the band is diminished from strong to medium. This appears to be one of the most characteristic changes occurring in the formation of a quaternary salt. This shift is large and probably is associated with an increased C-N double bond character due to the change in charge distribution around the nitrogen atom. Katritzky (56) reported a similar situation in which the 1602 cm.$^{-1}$ band in a 4-substituted pyridine shifted to 1640 cm.$^{-1}$ on formation of the boron trichloride adduct, and the formation of amine oxides causes similar shifts, although smaller in value (57, 58).

(3) The band at 1585-1567 cm.$^{-1}$ (m.-s.) maintains a fairly constant position, 1595 cm.$^{-1}$ (w.-m.) but decreases somewhat in intensity on salt formation.

(4) The weak band at 1490-1477 cm.$^{-1}$ is shifted to 1518-1495 cm.$^{-1}$ and increases to medium intensity.

(5) The band at 1428-1414 cm.$^{-1}$ is a strong and

characteristic one for 3-substituted pyridines. This band is replaced by a band at 1465-1440 cm.$^{-1}$ (m.) in the spectrum of the quaternary salt. The bands (2), (3), (4) and (5) have all been assigned to C-C and C-N vibrations by Katritzky.

(6) The band at 1340-1325 cm.$^{-1}$ (m.) in the pyridines is relatively unchanged by quaternization. It remains at 1355-1237 cm.$^{-1}$ (m.).

(7) (8) (9) The three bands 1245-1237 cm.$^{-1}$ (m.-w.), 1204-1188 cm.$^{-1}$ (m.) and 1130-1115 cm.$^{-1}$ (m.-s.) shift to 1220-1188 cm.$^{-1}$ (m.-s.), 1165-1125 cm.$^{-1}$ (m.) and 1125-1090 cm.$^{-1}$ (m.-w.) on conversion of the pyridine to the salt. In the quaternary salt these bands usually form an easily recoginzed triplet with consistent relative intensities; the first being strongest, the second intermediate, and the third weakest.

(10) (11) (12) (13) The bands in this region are displaced more than 100 cm.$^{-1}$ and one significant intensity change seems to indicate the approximation of a band-to-band correspondence may be invalid in this region. Assignments are difficult in this region and it is more valuable for purposes of correlation to note the overall changes which occur. In the 3-substituted pyridines the bands at 1100-1035 cm.$^{-1}$, 1039-1035 cm.$^{-1}$ and 969-953 cm.$^{-1}$ vary in intensity from weak to medium; however, the band at 1029-1021 cm.$^{-1}$ is strong and easily recoginzed in a 3-substituted pyridine. In the quaternary salt characteristic bands appear at 975-950 cm.$^{-1}$, 942-915 cm.$^{-1}$, 918-870 cm.$^{-1}$

and 855-828 cm.$^{-1}$. These four bands are of weak intensity and are equally spaced and in some compounds show up as an easily recognized group. This quartet is sometimes difficult to identify when a phenyl substituent is present in the molecule.

(14) The band at 832-807 cm.$^{-1}$ (m.) shifts to 793-775 cm.$^{-1}$ (m.-w.) in the salt.

(15) (16) It was mentioned above that 3-substituted pyridines showed two strong bands in the region below 800 cm.$^{-1}$, one at 775-753 cm.$^{-1}$ and one at 705-692 cm.$^{-1}$. In the quaternary salt these two bands remain as strong bands. The former band moves to slightly higher frequency numbers, and the latter moves to a range 690-660 cm.$^{-1}$. In the absence of phenyl groups, two additional bands appear in this region near 730 cm.$^{-1}$ (w.) and another weak band at 690-655 cm.$^{-1}$. The presence of other aromatic groups usually masks these weak bands, and sometimes the strong band around 750 cm.$^{-1}$ is not resolved. These two additional bands are indicated in Table VI when they occur (c, d).

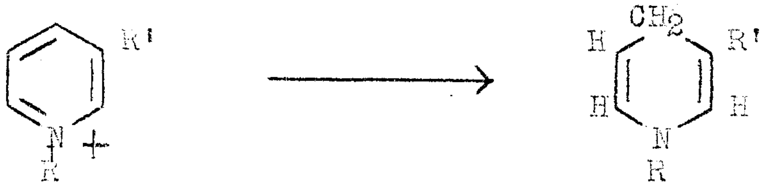
In summarizing these results three easily recognized differences exist between the spectra of the pyridines and the corresponding quaternary salts. First, a band appears at 1632-1625 cm.$^{-1}$ (m.) in the spectrum of the quaternary salt, and second and third, strong bands at 1428-1414 cm.$^{-1}$ and 1030-1021 cm.$^{-1}$ disappear from the spectrum of the 3-substituted pyridine on quaternization.

<u>Correlations of infrared spectra of dihydropyridines.</u> Prior to 1958 no infrared spectra of dihydropyridines produced from the reduction of 3-substituted pyridine quaternary salts could be found in the literature. Since this time two publications have included such spectra. Karrer and Traber (15) published the infrared spectra of several isomeric pairs of 1,4- and supposedly 1,2-dihydropyridines but made no correlations. More recently Schenker and Druey (16) reproduced spectra of 1-methyl-3-cyano-1,4-dihydropyridine and 1-methyl-3-cyano-1,6-dihydropyridine. These workers assigned bands to C=C and/or C=N stretching vibrations but made no differentiation between them.

The infrared spectra were determined of all dihydropyridine compounds prepared in this investigation which could be obtained as solids. As discussed above, the structures of some of these dihydropyridines are uncertain, particularly those of the dithionite addition compounds; however, the dihydropyridines formed by reduction with sodium dithionite or by addition of cyanide have been shown to be 1,4-derivatives. In the case of those compounds of known structure direct comparisons of the spectra could be made with the spectra of the corresponding quaternary salt and any characteristic changes could be noted.

The infrared spectral data are presented in Table VII, which gives the bands which appear to be common to all dihydropyridines prepared. Direct comparison was made of the spectra of the dihydropyridine and the corresponding quaternary salt. In this manner it was hoped to establish characteristic changes in spectra which accompany the formation of a 1,4-dihydropyridine as well as presenting a general correlation of a 1,4-dihydropyridine nucleus. By comparing the spectral data of compounds of known structure with those of compounds of uncertain structure a method of assigning to the structure a 1,2-, 1,4-, or 1,6-dihydropyridine nucleus might be possible.

An analysis of the data given in Table VII indicates several bands which can be correlated with a 1,4-dihydropyridine structure. Several changes would be anticipated on the basis of the structural changes involved, primarily those of the aromatic pyridinium ring and the formation of two C-C double bonds (LXII).



LXII

Absorption bands would also be expected for vibration of the cis-hydrogen on the double bond and for the new methylene group which is formed. In many cases the substituent groups interfered with interpretation; however, satisfactory correlations consistent with those predicted could be made in several cases. The individual bands listed in Table VII will be considered in order.

(1) The region around 3000 cm.$^{-1}$ is complicated by the presence of aromatic groups. Bands due to the aromatic hydrogens on the pyridinium ring should disappear; however, the vibrations of the cis-hydrogens on the double

bond also absorb in this region. The latter should be stronger than aromatic, C-H stretching vibrations. The disappearance of band (1) from several quaternary salts was observed; however, in many cases this region of the spectrum was poorly resolved and the expected changes could not be observed.

(2) In most spectra of 3-substituted-1,4-dihydropyridines a medium band appears at 2830-2800 cm.$^{-1}$. This band is not present in 3,4-substituted dihydropyridines or in the dithionite addition products. This band may be due to the methylene group which is formed at the 4-position on reduction.

(3-7) In the region of C-C, C-O, C-N double bond stretching frequencies from 1700 to 1500 cm.$^{-1}$, the most significant absorption bands occur, and it is apparent that the nature of the 3-substituent affects the pattern of absorption bands in this region. The dihydropyridines are therefore grouped according to the 3-substituent for the discussion of this region: (a) 3-CONH$_2$ and -CONHNH$_2$, (b) 3-COOEt, (c) 3-CN, (d) 3-COPh and (e) miscellaneous compounds (XXXVI, XXXVII, XXXIX, XLI, XLII).

(a) The 1,4-dihydropyridines with amide or hydrazide substituents show characteristic absorption bands at (2) 1685-1680 cm.$^{-1}$ (s.), (3) 1655-1645 cm.$^{-1}$ (sh.-w.), (4) 1645-1630 cm.$^{-1}$ (s.) and (5) 1580-1565 cm.$^{-1}$ (s.). Bands (4) and (5) for 1-methyl-4-cyano-1,4-dihydronicotinamide are displaced to 1665 cm.$^{-1}$ (s.) and 1605 cm.$^{-1}$ (s.) (b, c). Only one example was obtained of a 3-cyano- and a 3-carbethoxy-1,4-dihydropyridine. Bands (2-5) are in comparable positions, except that 1-benzyl-3-cyano-1,4-dihydropyridine (XXIX) shows no (4) band.

(d) The 3-benzoyl-1,4-dihydropyridines show the four bands at (2) 1672-1665 cm.$^{-1}$ (m.-s.), (3) 1655-1650 cm.$^{-1}$ (w.-sh.), (4) 1625-1610 cm.$^{-1}$ (m.-s.) and (5) 1560-1535 cm.$^{-1}$ (s.). Band (5) is usually the strongest band in the spectrum.

(e) The dithionite addition products XXXVI, XXXVII and XXXIX show a spectrum similar to 3-benzoyl-1,4-dihydropyridine compounds. The spectra of 2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine (XLI) and 3-benzoyl-4-phenyl-1,4-dihydropyridine (XLII) are consistent with those of other 3-carbethoxy- and 3-benzoyl-1,4-dihydropyridines respectively, and also show an additional strong band at 1518 cm.$^{-1}$. This may be assigned to an N-H bending vibration.

In order to interpret the 1700-1500 cm.$^{-1}$ region of the spectrum consider first the spectrum of 1-β-(3-indolyl)-ethyl-3-carbomethoxy-1,4-dihydropyridine (XXVIII). In the corresponding quaternary salt (X) the ester C-O double bond stretching absorption is at 1733 cm.$^{-1}$. In the spectrum of XXVIII there are two bands, one at 1677 cm.$^{-1}$ and one at 1663 cm.$^{-1}$ in this region. The band at 1677 cm.$^{-1}$ appears to be one which is present in the spectra of all 1,4-dihydropyridines in the range of 1685-1655 cm.$^{-1}$. For this reason the 1663 cm.$^{-1}$ band is assigned to the C-O double bond stretching absorption of XXVII. An analogous band is present in the spectrum of XLI at 1660 cm.$^{-1}$. In the case of esters the carbonyl stretching band is shifted to lower frequency by about 60 cm.$^{-1}$ when the quaternary salt is reduced to a dihydropyridine. Evidence to be presented in the discussion of reactions of dihydropyridines indicates that the band at 1685-1665 cm.$^{-1}$ should be assigned to a stretching vibration of the 5,6-double bond and nitrogen system of the dihydropyridine. The conclusion is made, therefore, that the structure of a 1,4-dihydropyridine with an electron-withdrawing 3-substituent should be represented as a resonance hybrid of the canonical forms shown in Figure 3. Since such compounds seem to retain the 5,6-double bond character but lose most of their carbonyl character, form C must make a large contribution to the resonance hybrid.

The ester carbonyl of XXVIII then, has sufficient single bond character to cause a shift of 60 cm.$^{-1}$ from the parent quaternary salt. In the spectra of 1,4-dihydropyridines with a 3-amide or 3-hydrazide substituent there is a strong band at 1645-1630 cm.$^{-1}$. This is assigned to the amide carbonyl which has sufficient single bond character to cause a shift of 40-50 cm.$^{-1}$. The corresponding amide carbonyl bands in the quaternary salts are found from 1690 to 1677 cm.$^{-1}$ and range in intensity from medium to strong. In the 1,4-dihydropyridines with an amide or hydrazide substituent there is an absorption band in the narrow region 1685-1680 cm.$^{-1}$ which is consistently strong; however, this absorption is assigned as a stretching vibration of the 5,6-double bond and nitrogen system. The spectra of the 3-

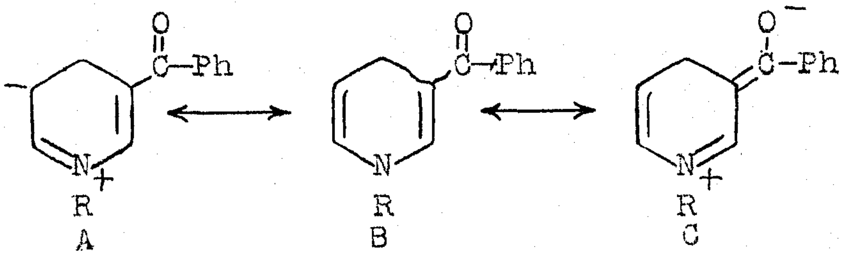


Fig. 3. Resonance Forms of 3-Benzoyl-1,4-dihydropyridine.

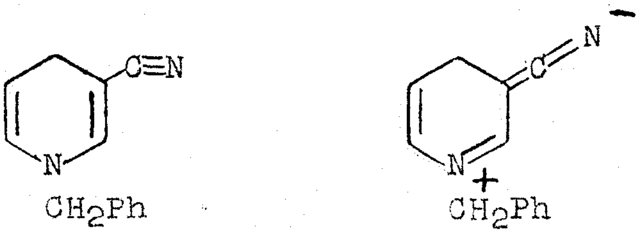


Fig. 4. Resonance Forms of 1-Benzyl-3-cyano-1,4-dihydropyridine.

benzoyl-1,4-dihydropyridines can be interpreted in a similar manner. The carbonyl stretching frequency in quaternary salts of 3-benzoylpyridine is found at 1675-1665 cm.$^{-1}$ (s.). In the corresponding dihydropyridines, there remains a band at 1672-1665 cm.$^{-1}$ but the intensity is diminished considerably. This fact was noted by Fuson and Miller (59) in preparing 3-aroyl-4-phenyl-1,4-dihydropyridine; however, no explanation was presented. There also appears in the spectra of 3-benzoyl-1,4-dihydropyridines a band at 1625-1610 cm.$^{-1}$ (m.-s.). This is assigned to the displaced C-O stretching vibration of the carbonyl and the 1672-1665 cm.$^{-1}$ band to a stretching vibration of the 5,6-double bond and nitrogen system. This interpretation is supported by the findings of Cromwell and coworkers (60) who investigated the infrared spectra of a number of β-amino-α,β-unsaturated ketones. These workers found the carbonyl stretching frequency from 60 to 80 cm.$^{-1}$ lower than that of the saturated ketone in the range 1636 to 1590 cm.$^{-1}$ (s.). These workers also reported another very strong band at 1592-1536 cm.$^{-1}$ in the spectra of these compounds and assigned it to a C-C double bond stretching vibration. Since the 2,3-double bond has considerable single bond character similar to the carbonyl, such assignment is reasonable and would correspond to the strong band found at 1605-1535 cm.$^{-1}$ in the spectra of 1,4-dihydropyridine compounds. No (4) band would be expected in the spectrum of 1-benzyl-3-cyano-1,4-dihydropyridine since the nitrile group would assume the character of a species which absorbs in the same region as the nitrile group (61) (see Figure 4.). A shift does occur from 2260 cm.$^{-1}$ (w.) in the quaternary salt to 2200 cm.$^{-1}$ (s.) in the dihydropyridine and this is consistent with the new resonating system formed by reduction.

The remaining portion of the spectrum usually showed several strong bands which were common to all dihydropyridines. The bands listed in Table VII are all those of the dihydropyridines which do not occur at the same position in the corresponding quaternary salt or are bands of increased intensity occurring at approximately the same positions as bands in the quaternary salt.

(6, 7, 8) Almost all dihydropyridines showed two strong bands at 1455-1407 cm.$^{-1}$ (6) and 1388-1360 cm.$^{-1}$ (8). In several cases a third band of lower intensity was found between these two, at 1410-1395 cm.$^{-1}$ (7).

(9, 10, 11) Three strong bands were exhibited by all dihydropyridines at 1355-1300 cm.$^{-1}$, 1305-1255 cm.$^{-1}$, and 1240-1190 cm.$^{-1}$. In several cases bands were present at comparable locations and intensities in the parent quaternary salts. Bands (9) and (11) coincide in position with (6) and (7) of the quaternary salts; however the dihydropyridine bands were usually much stronger.

(12, 13, 14) Three medium to strong bands were observed in most compounds at 1200-1170 cm.$^{-1}$, 1168-1090 cm.$^{-1}$ and 1090-1045 cm.$^{-1}$. These occur in the same range as bands (8) and (9) of the quaternary salts, but since (12-14) are stronger than (8) and (9) of the quaternary salts they are considered as being characteristic of the 1,4-dihydropyridine system.

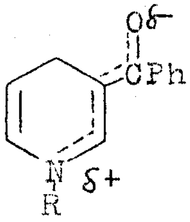
(15) This band at 1030-993 cm.$^{-1}$, although weak, is present in all except one case.

(16, 17) Several compounds exhibited one or two new weak bands in the regions 998-898 cm.$^{-1}$ and 880-810 cm.$^{-1}$; however these are difficult to assign with certainty and cover a wide range. For this reason their usefullness in correlation is small, but their presence could be used for confirmatory evidence of a 1,4-dihydropyridine structure.

(18) In a few cases a strong band was observed in the range 750 to 700 cm.$^{-1}$ and may be due to the cis-double bond system which should give rise to a strong band in this region. In most cases this region was obscured by aromatic bands.

Most other assignments are not obvious. Band (8) may also be due to the unsaturation which should show a band in this region. Tertiary amines show two medium bands in the region 1125-1025 cm.$^{-1}$ and 1225-1125 cm.$^{-1}$. Part or all of bands (11) through (14) are in this range and may be assigned in part to C-N stretching vibrations.

To summarize, the most prominent band appearing in the spectrum of a 1,4-dihydropyridine with an electron withdrawing 3-substituent is found from 1600 to 1500 cm.$^{-1}$ and is usually the strongest band in the spectrum. Two bands, characteristic of a pyridinium salt, disappear from the spectrum of the corresponding dihydropyridine, (2) at 1665-1625 cm.$^{-1}$ and (16) at 690-665 cm.$^{-1}$. The other bands of known 1,4-dihydropyridines indicate a structure in which the 5,6-bond has most of the double bond character expected of a vinyl amine while the 2,3-bond and carbonyl group at the 3-position have considerable single bond character (LXIV).



LXIV

Ultraviolet and visible spectra of reduction mixtures of quaternary salts. In an attempt to elucidate the mechanism of the reduction of 3-substituted quaternary salts by sodium borohydride or sodium dithionite reactions were carried out directly in the absorption cell of a recording ultraviolet spectrophotometer. In this manner it was possible to record the spectra of unstable intermediates which could not be charactorized by other means. By repetitively scanning the spectrum as the reduction progressed, the changes in absorption could be recorded.

A method used to isolate unstable dihydropyridine compounds was to run the reduction in a separatory funnel containing a solution of the quaternary salt in aqueous base, usually sodium carbonate, and a layer of chloroform. The sodium dithionite or borohydride was added and the mixture was shaken for a short time. The dihydropyridine was extracted into the chloroform as it was formed. A drop or two of this chloroform extract was added to the absorption cell containing solvent and the spectrum was recorded as rapidly as possible. The details of these methods are given in the Experimental section.

Table VIII gives the results for a series of nicotinamide quaternary salts. Column I indicates the absorption maxima of the products isolated from reduction with sodium dithionite, and Column II shows the maxima resulting when the salts were reduced in the cell using sodium dithionite. The maxima were first observed at the higher value and shifted to the lower value as the reduction proceeded. The concentration of quaternary salt in the cell was about 10^{-1}M. Column III lists the maxima of the products isolated from reaction with sodium borohydride, and Column IV records the maxima produced when the salts were reduced in the cell using sodium borohydride. The concentration of the salt in this case was about 10^{-4}M.

Figure 5 shows a series of spectra representing the products isolated from the sodium borohydride reduction of VI and several transformations of these reduction products. The original spectrum is that with the maxima labelled AB indicating the values listed in Column III. Spectrum A'B' results from adding excess sodium borohydride to the product AB in the absorption cell. Spectrum CD is that of the original chloroform extract after it had been standing for two days. The corresponding maxima for the other compounds are listed in Column V. Spectrum E results from adding 3 drops of 6N hydrochloric acid to the absorption cell containing the original product. The corresponding values for the other compounds are listed in Column VI. After the acid

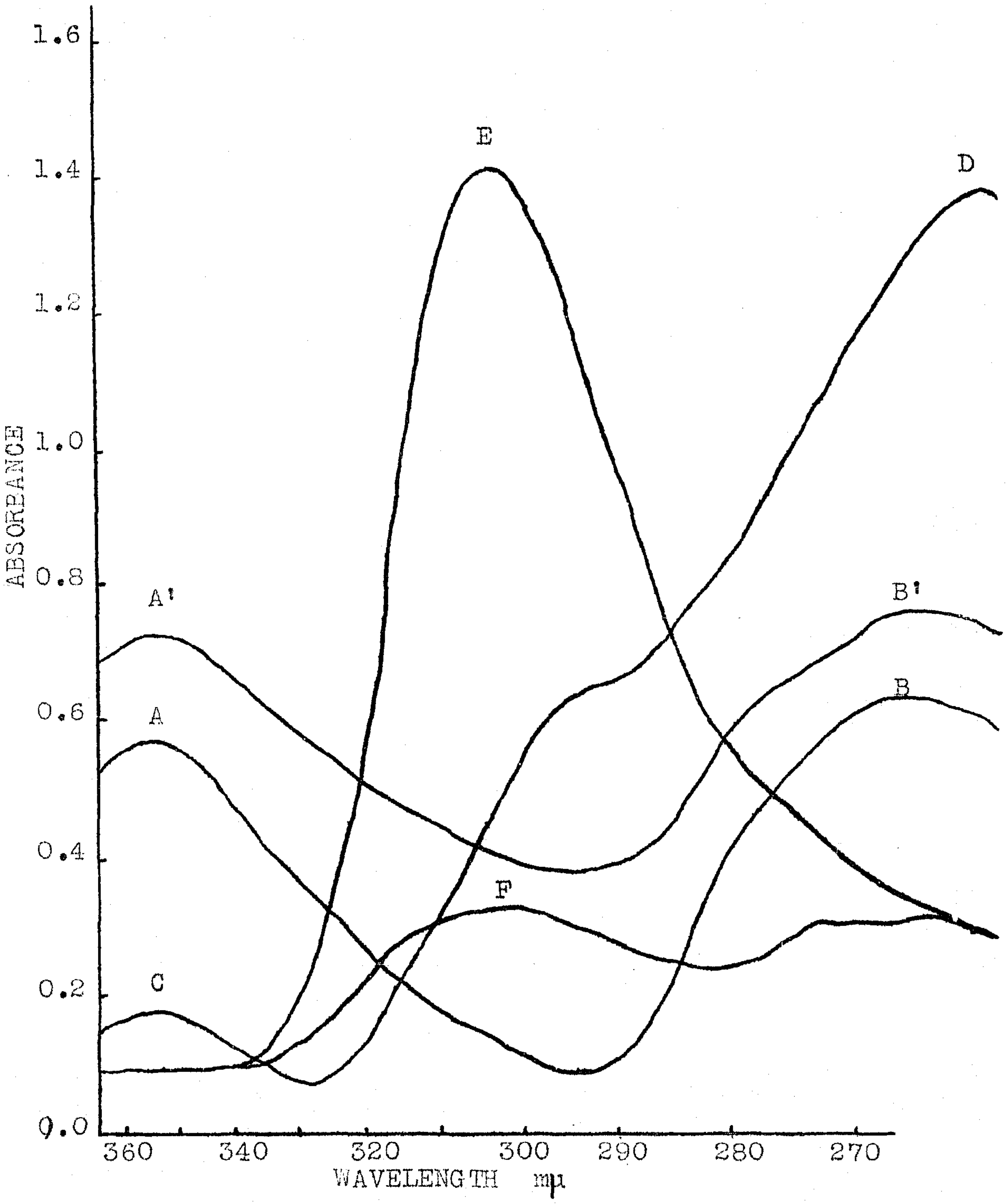


Fig. 5. Ultraviolet Absorption Spectra of the Products of Reduction of 1-Methyl-3-carbamoylpyridinium Iodide (VI) with Sodium Borohydride.

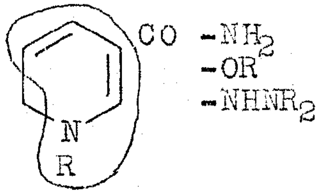
solutions had been allowed to stand for 4 hours, their spectra were redetermined, and result is curve F. All of the compounds in the series gave a similar set of curves. The ratios of absorbances of the different maxima are indicated in Table VIII, the letters corresponding to the maxima in Figure 5.

Tables X and XI list the maxima observed when 10^{-4}M solutions of several 3-substituted quaternary salts were reduced in the absorption cell. The solvents and reducing agents are indicated in the heading of the tables. Four amides listed in Table VIII were also reduced under these conditions (I, II, III, XXII).

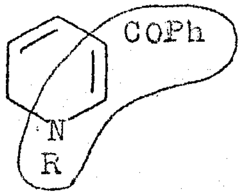
The results of these reductions seem to fall into two separate groups, one comprising those from 3-benzoylpyridinium salts and the other made up of results from 3-carbamoyl- and 3-carbomethoxypyridinium salts. Reductions with sodium borohydride will be considered first. When solutions of 3-benzoylpyridinium salts in methanol are treated with limited amounts of sodium borohydride, three bands appear in the spectra: at 300-310 mμ, ϵ 3000-7000; at 370-375 mμ, ϵ 4400-10,200; and at 470-475 mμ, ϵ 5000-6500. In aqueous solution the high wavelength band is found at slightly longer wavelengths, at 485-490 mμ. The other group of compounds, amides, esters and hydrazides, also show three bands, at 255-268 mμ, ϵ 4000-9000; 358-364 mμ, ϵ 3600-6600; and 410sh-425 mμ, ϵ 3200-4400 (425-440 mμ in aqueous solution). When an excess of sodium borohydride was added the long wavelength band in all cases was destroyed. The other two bands appeared to be relatively stable to excess sodium borohydride; however, there were some variations in the relative intensities and rates of disappearance of the bands in different solvents. With 3-benzoyl compounds the bands were more intense and developed rapidly, and the long wavelength band decreased more rapidly in methanol than in aqueous solutions. With the amides and esters, the reverse situation was true, for the long wavelength band was much more stable in methanol than in water. In the case of 1-methyl-3-carbomethoxypyridinium bromide (IX) the band at 425 mµ did not decrease at all on standing with excess sodium borohydride for one-half hour. In aqueous solution the band was completely destroyed after one minute had elapsed. Other amides and esters showed results similar to this. In the case of 1-(β-phenylethyl)-3-(1,1-dimethylhydrazido)-pyridinium bromide (XLIV) the long wavelength band was visible only as a shoulder in methanol and not at all in aqueous solution. This compound also exhibited an anomalous band at 305 mµ which may have been due to decomposition of the 1,4-dihydropyridine. The short wavelength band was at 255 mµ, a wavelength lower than that shown by any amides and esters for this band. The salt, 1-methyl-4-benzoylpyridinium bromide (XLV), showed no maximum after the addition of sodium borohydride, even though the spectrum was scanned as rapidly as possible. On addition of sodium borohydride to a solution of 1-methyl-3-benzoyl-4-phenylpyridinium bromide (XLIII) an additional strong band at 240 mµ appeared. In this case the intensity of the 310 mµ band decreased as the intensity of the 240 mμ band increased. The band at 360 mμ remained at a constant intensity during these changes.

Of the three bands produced in the ultraviolet spectrum when pyridinium salts are reduced with sodium borohydride two have previously been reported in the literature, namely the band around 360 mμ and the band around 260 mμ. The long wavelength band has not been observed previously, no doubt due to its instability. Regarding the band around 260 mμ, Stein and Stiassny (62) reported that the reduction of 1-propyl-3-carbamoylpyridinium iodide (V) on reduction with sodium borohydride gave a product whose ultraviolet spectrum showed absorption at 260 mμ and 360 mμ, similar to the results obtained in this investigation. It was found that part of the absorption at 360 mμ was due to the 1,4-dihydropyridine, since the product could be separated into two components. One showed only a single maximum at 360 mμ and was the same as the product from sodium dithionite reduction of V. The fact that the same 1,4-dihydropyridine produced by dithionite reduction can also be formed by sodium borohydride has been substantiated by a number of other investigations (15). The other product from the sodium borohydride reduction of V isolated by Stein and Stiassny showed absorption at 260 mμ and 360 mμ. This product could also be produced by X-irradiation or electrolytic reduction of V. The recent work of Druey and Schenker (16) has shown that 1-methyl-3-cyano-1,6-dihydropyridine absorbs at 240 mμ and 349 mμ. The corresponding

1,4-dihydropyridine exhibits a single maximum at 340 mμ. The long wavelength bands of these two are so close together they probably would not be resolved into two bands in a mixture of the compounds. The band at 240 mμ reported by Druey and Schenker confirms the assignment of a 1,6-dihydropyridine made by Stein and Stiassny for their product. In the present research the bands at 260 mμ and 360 mμ are therefore due to a mixture of 1,4- and 1,6-dihydroderivatives. In the case of 3-benzoyl derivatives the band around 300 mμ would correspond to the 260 mμ band in esters and amides. This would indicate that the 3-substituent is involved in the short wavelength chromophore of the 1,6-dihydroderivative. The band around 360 mμ in the 1,6-dihydropyridine must be due to the unsaturated system as a whole. The secondary chromophore in the case of amides and esters may result from the unshared pair on the nitrogen atom and the two double bonds in the ring. This system LXXV would be expected to approach the absorption of the pyridinium ring (65) which is observed. Since 3-carbamoyl-1,4,5,6-tetrahydropyridines absorb near 300 mμ this chromophore cannot contribute to the spectrum to any great extent. In the case of the greater electron attracting 3-benzoyl group the predominance may be given to the β-amino-α,β-unsaturated ketone chromophore (LXXVI) which absorbs near 300 mμ.

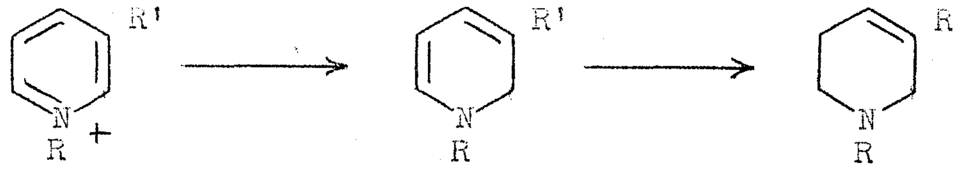


LXXV



LXXVI

It is known also that sodium borohydride will form 1,2,5,6-tetrahydropyridines (LXXVIII) from 3-substituted pyridinium salts (14). Since both the 1,4- and 1,6-isomers appear to be stable to excess sodium borohydride, it is reasonable to assume that the reduction to the tetrahydro-isomer takes place through the 1,2-dihydroderivative (LXXVII) excluding some more complex and less obvious mechanism. The long wavelength band occurring around 420-480 mμ could then be assigned to the 1,2-dihydroderivative, and the rapid destruction of this band indicates the further reduction to the tetrahydropyridine. This facile reduction to the tetrahydropyridine would preclude the isolation of the 1,2-dihydroderivative. Most compounds previously described as 1,2-dihydropyridines obtained by sodium borohydride reduction of 3-substituted pyridinium salts have been shown to be 1,4- or 1,6-derivatives.



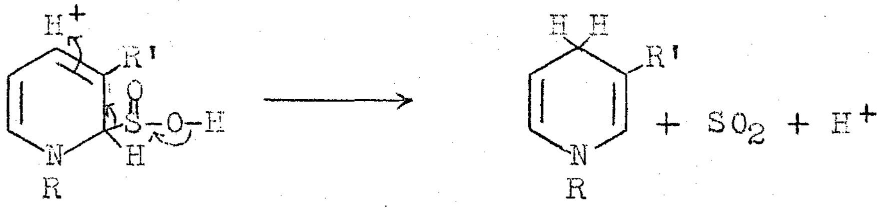
LXXVII LXXVIII

It is difficult to find an analogy for the chromophore of a 3-carbonyl-1,2-dihydropyridine. The wavelengths of the maxima are quite long, being shifted bathochromically from 65 to 90 mμ from the absorption maximum of the corresponding 1,4-dihydroderivative in methanol solution. The long wavelength band of 6-diethylamino-3,5-hexadiene-2-one occurs at 378 mμ (54). Cyclohexadiene absorbs at 256 mμ while 2,4-hexadiene absorbs at 227 mμ (65). If a similar bathochromic shift occurred when the aminodiene mentioned above was constrained in a 6-membered ring to simulate a 3-acetyl-1,2-dihydropyridine, the absorption maximum would be only around 410 mμ. It must be concluded that either the 3-carbonyl-1,2-dihydropyridine system is anomalous in its absorption or that there is some other factor which causes absorption at such long wavelengths. The possibility that some sort of a boron complex is formed cannot be neglected. It appears that boron-containing organic substances can be isolated from reductions with sodium borohydride and some sort of a boron adduct may be involved at some stage of the reduction. The mechanism for sodium borohydride reduction, however, has not been elucidated and may simply involve attack of hydride ion.

Treatment of 1-methyl-4-benzoylpyridinium bromide (XLV) with sodium borohydride forms 1-methyl-4-(1-hydroxy-1-phenylmethyl)-1,2,5,6-tetrahydropyridine; however no absorption maxima were observed in the ultraviolet spectrum recorded while the reduction was proceeding. Attack probably occurs at the <u>ortho</u>-positions giving a dihydroderivative which cannot be stabilized by conjugation with the 4-benzoyl group and so is immediately reduced to the tetrahydro alcohol. The carbonyl must also be reduced as fast or faster than the ring since there is no evidence for the formation of an α,β-unsaturated ketone system. The strong absorption exhibited by XLIV at 240 mμ is no doubt due to the styrene system of the tetrahydroderivative.

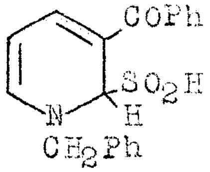
The mechanism of sodium dithionite reduction of

3-substituted pyridine quaternary salts has received some attention in the literature. In 1955 Swallow (40) noted that reduction of DPN with sodium dithionite in alkaline solution gave a bright yellow substance which was not DPNH, and which he assumed to be an addition product of a fragment of the dithionite ion and the pyridine ring of DPN. The adduct absorbed at 355 $m\mu$ whereas DPNH absorbs at 340 $m\mu$. After the proof of structure of dithionite reduced products as 1,4-dihydropyridine derivatives most investigators assumed that the reaction occurred by nucleophilic attack of the $(HSO_2)^-$ ion at the 4-position followed by decomposition to form the dihydropyridine (36). The existence of the dithionite adduct has been generally accepted, however the position of addition is still in question. Recently Wallenfels and Schüly (41) published a communication reporting the isolation of a stable, crystalline dithionite adduct and postulating a mechanism involving the addition of the $(HSO_2)^-$ ion at the 2-position of the ring followed by decomposition and addition of hydrogen ion at the 4-position (LXXIX). This conclusion was based on spectral evidence, which, however, was not published at the time and has not been published to date.



LXXIX

As has been discussed in the section on preparation of dihydropyridines, two dithionite addition products were obtained in the present research, XXXVI from XVII, and XXXVII from XV. A third addition product, XXXIX obtained from XLIII, was of questionable purity. Compound XXXVI gave a correct analysis for the structures previously proposed for these adducts. No analyses have been reported for the dithionite addition products obtained by other investigators.



XXXVI

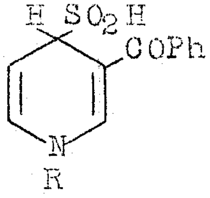
In observing the spectral changes taking place when solutions of 3-substituted pyridinium salts were reduced with sodium dithionite it was determined that the concentration of quaternary salt must be much higher in the case of amides and esters for reduction to take place than when sodium borohydride is used. At salt concentrations of 10^{-4}M no evidence of reduction was observed. A large excess of dithionite was added and subsequently destroyed by shaking the cell contents with air. The original intensity of the quaternary salt band around 265 mu was practically unchanged. It was necessary to use salt concentrations of the order of 10^{-1}M to obtain reductions with esters and amides. Salts substituted with 3-benzoyl groups were reduced by dithionite at a concentration of 10^{-4}M. These facts are interpreted reasonably on the basis of the equilibrium involving attack of a nucleophilic species on the electrophilic pyridinium salt previously discussed. The addition of the strongly nucleophilic borohydride (or hydride) ion must be practically irreversible when compared with most other anions. In the case of dithionite either a large concentration of quaternary salt or a strongly electrophilic salt such as 3-benzoylpyridinium ion must be used to shift the equilibrium in favor of the adduct.

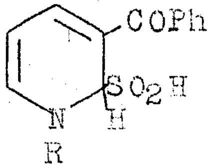
Reference to Table VII shows that 3-carbamoylpyridinium salts when reduced with sodium dithionite in aqueous base in the absorption cell show initial absorption at 370-374 mμ. This shifts to 355-360 mμ as the reduction proceeds. The latter value represents the absorption shown by the product isolated from dithionite reductions and is due to the 1,4-dihydropyridine which is formed. When 3-benzoyl quaternary salts were reduced in aqueous solution only one band was noticed, at 386-390 mμ. (See Table XI.) When the solvent for the 3-benzoylpyridinium ion was 10^{-5}M sodium carbonate solution a band was noticed around 415 mμ on the first scan in two cases. This rapidly shifted to the 386-390 mμ value as the reduction proceeded. If the solvent was 1M sodium carbonate solution in all cases the 3-benzoyl salts showed only a maximum at 405-410 mμ which was stable to excess dithionite. Swallow (40) had already noted that the product he assumed to be the dithionite adduct of DPN was stable only in alkaline solution, and it was reasonable to conclude in the present case that this long wavelength band was due to the dithionite addition product. In order to substantiate this conclusion a sample of isolated dithionite addition product from XV (XXXVII) was dissolved in a solution of 1M sodium carbonate and its ultraviolet spectrum was determined. The value of the maximum observed was 410 mμ, identical with that observed when dithionite was added to a solution of XV in 1M sodium carbonate in the absorption cell.

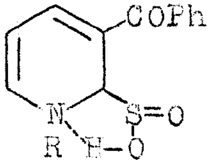
The question of whether the 370-374 mμ band initially observed in the reduction of amides and esters is also due to the dithionite addition product is not as easy to answer. It was not possible to isolate addition products of the amides. The values reported by Swallow are of this order; 355 mμ for the addition product and 340 mμ for the dihydro derivative of DPN. Two facts make the present case uncertain, however. The extinction values for the 3-benzoyl dithionite adducts were about one-half of those of the corresponding dihydropyridines. In the case of the amides the extinction of the original band at 370-374 mμ was as high or higher than the final band at 355 mμ. When 10^{-4}M solutions of 3-carbamoyl salts were treated with dithionite in 1M carbonate solution, end absorption and in some cases a shoulder was noted in the region around 370-380 mμ, however this band disappeared quite rapidly. The reductions in which the shift was noted from 370-374 mμ to 355-360 mμ were carried out in less basic solutions in which the addition product would be expected to be less stable; however, the concentration of the salt was higher. The dithionite must add to the ring at some stage of the reaction. The adduct could, however, be decomposed almost as rapidly as it was formed and show no individual absorption.

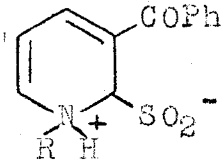
The fact that the 370-374 mμ band appears to be more intense and persists longer than the corresponding 410 mμ band observed with 3-benzoyl salts under the same conditions is evidence against this band being due to the dithionite addition compound of the 3-carbamoyl salts, since these are known to be less stable.

It would appear that the spectral evidence to which Wallenfels and Schüly were alluding in support of their mechanism is this hypsochromic shift noted when the 3-benzoyl quaternary salts are reduced with dithionite. If the structure of the dithionite addition product were LXXX the absorption maximum could reasonably be lower than that of the corresponding dihydropyridine. Assuming the cyanide addition products are 1,4-dihydropyridine derivatives, for which there is evidence, the substitution of a $-C\equiv N$ group for hydrogen at the 4-position causes a hypsochromic shift of 20 to 25 mμ. A phenyl group at the 4-position causes a hypsochromic shift of 14 mμ, and assuming some of the products of 3-benzoyl salts in carbonate solution result from addition of hydroxide ion to the 4-position of the pyridinium ring then a hydroxyl group causes a hypsochromic shift of 30 mμ. The presence of a nucleophilic substituent on the 4-position of a 1,4-dihydropyridine system thus appears to cause a hypsochromic shift of from 14 to 30 mμ in the ultraviolet spectrum when compared to the corresponding unsubstituted 1,4-dihydropyridine.


LXXX


LXXXI


LXXXIII

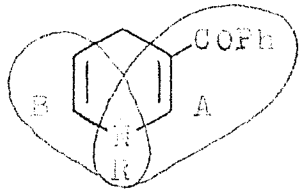

LXXXIV

Since HSO_2 is such a substituent, the absorption maximum of structure LXXX would be expected to be at shorter wavelengths than 385 mμ, however, the absorption maximum of XXXVII is found at a wavelength 25 mμ longer. On the other hand, if the 470 mμ band obtained in reductions with sodium borohydride represent the 1,2-dihydro system, then the wavelength of the absorption maximum at 415 mμ seems too short for structure LXXXI. Since a nucleophilic substituent at the 4-position lowers the wavelength of absorption of a 1,4-dihydropyridine system the presence of one at the 2-position could reasonably be expected to lower the wavelength of absorption of a 1,2-dihydropyridine system. Other factors such as hydrogen bonding between the nitrogen atom and the OH of the sulfinic acid group would also be expected to lower the wavelength of absorption by involving the free pair of electrons on the nitrogen atom (LXXXIII). The structure of the dithionite addition product may even approach LXXIV. The evidence of this research is interpreted to indicate addition of dithionite at the 2-position of the ring and to support the mechanism of dithionite reduction proposed by Wallenfels and Schöly.

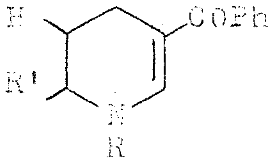
<u>Spectra of isolated dihydropyridine compounds and</u>

their acid reaction products. The ultraviolet absorption spectra of all dihydropyridines which were isolated were determined in both neutral and acid media. In agreement with numerous other researches (5, 17, 38) it was found that addition of acid to a dihydropyridine system resulted in a hypsochromic shift of 50-65 mμ in the maximum of absorption with a corresponding two to three fold hyperchromic shift in intensity of absorption. The experimental values are given in Table III. It was also noticed that another absorption occurred at shorter wavelength, around 240 mμ, sometimes occurring as a maximum and sometimes as a shoulder or inflection. Little has been mentioned by other workers in this field about either the presence, intensity or cause of this absorption. Table III also indicates this absorption, where present, and its apparent intensity in both neutral and acid solution. Usually the absorption curve is rising in this region toward a maximum in the far ultraviolet, and it was not possible to obtain reliable extinction values. Some of the data in Table XII also apply to this discussion.

The electronic arrangement of a 3-benzoyl-1,4-dihydropyridine system (LXXXV) requires the presence of two separate conjugated systems, one the β-amino-α,β-unsaturated ketone system LXXXVA and the other the vinylamine system LXXXVB. Due to the relative positions of the ring unsaturation system B cannot directly conjugate with system A. The systems can interact through the nitrogen atom and this fact is demonstrated by the bathochromic shift of the maximum of absorption of LXXXV relative to systems such as LXXXVI. However, the hypochromic shift observed in going from LXXXVI to LXXXV indicates that the 5,6-double bond does not directly extend the length of the conjugated system, for if this were the case the intensity of absorption should increase as well as the wavelength. The effect is analogous to that of γ,δ-unsaturation on the absorption by α,β-unsaturated cyclic ketones. The absorption maximum of 1-acetyl-cyclohexene occurs at 232 mμ, ϵ 12,500, and that of 1-acetyl-1,4-cyclohexadiene at 245 mμ, ϵ 4000 (67).



LXXXV

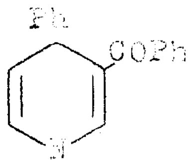


LXXXVI

The LXXXVA chromophore itself is a complex one, being composed of a β-amino-α,β-unsaturated carbonyl system and a benzoyl system, the aromatic ring of which cannot conjugate directly with the nitrogen. In situations such as this, a separate band would be expected in the ultraviolet spectrum for each separate chromophore. Thus for 3-benzoyl-1,4-dihydropyridines, three separate bands would theoretically be present. Leonard has demonstrated that cyclic vinyl amines show absorption in the range 230-240 mμ with an extinction of 5000-7000 (68). The benzoyl chromophore in acetophenone absorbs at 240 mμ, ϵ 13,000 (69), and the β-amino-α,β-unsaturated carbonyl chromophore in the range 290-310 mμ, ϵ 30,000 (70). The ultraviolet spectra of dihydropyridines and their reaction products can be interpreted in most cases by an analysis in terms of these three chromophoric systems.

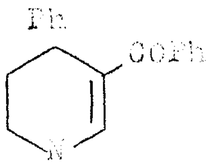
The fact that most 3-benzoyl-1,4-dihydropyridines show absorption maxima around 240 mμ in both neutral and acid media would indicate that this absorption is due to the benzoyl chromophore. Since the intensity of this absorption is much stronger than that of the vinyl amine chromophore the former would be expected to mask any contribution due to the latter system. Inconsistencies were found with 3-carbamoyl and 3-carbomethoxy-1,4-dihydropyridines, however in many cases a point of inflection was noticed around 240 mμ which disappeared on treatment with acid. The vinyl amine chromophore would be destroyed on treatment with acid and it is reasonable to assume that it is responsible for absorption in this region.

The ultraviolet spectra of the series of compounds XLII, LII, LV, and LVI indicate the effect of reducing the ability of the unshared electrons on the nitrogen atom to enter into conjugation. Acetylation of XLII to form LV causes a marked hypsochromic shift in the long wavelength absorption maximum, however the intensity decreases only slightly. A very strong band is now observed at 244 mμ which may be due to an increased contribution from the benzoyl chromophore. Acetylation of LII causes a smaller hypsochromic shift in the long wavelength absorption and no appreciable change in the intensity of the band. A point of inflection at 227 mμ in the spectrum of LII becomes a maximum at 235 mμ in the spectrum of LVI with significant intensity, although not as great as the corresponding 244 mμ band in LV. Again, the fact that compounds such as LII and LVI show maximum absorption around 240 mμ indicates it must be due in some manner to a second chromophore associated with the benzoyl group. As Table XII indicates almost every compound prepared in the 3-benzoyl-4-phenyl-1,4-dihydropyridine series shows absorption maxima in this region in both neutral and acid solutions.



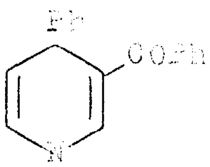
H 360 mμ

XLII



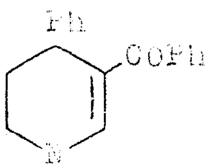
H 305 mμ

LII



CH_3CO 322 mμ

LV



CH_3CO 298 mμ

LVI

Reactions of dihydropyridines. Because of the instability of dihydropyridine compounds reactions of these systems have been little studied, except where they are involved as a reaction intermediate. A few facts are known concerning reactions of these systems, however. They are easily reoxidized to the corresponding pyridine, either by air or oxidizing reagents. This, for example, is the basis for the Hantzsch pyridine synthesis and the mechanism of action of DPN. Both 1,4- and 1,6-dihydropyridines undergo a reaction with acid which results in the destruction of the dihydropyridine system. This reaction is associated with a hypsochromic shift of about 50 mμ in the long wavelength absorption maximum in the ultraviolet spectrum and was first noticed on studies of DPN. Recently Anderson and Berkelhammer (38) have shown, in the case of 1-benzyl-3-

3-acetyl-1,4-dihydropyridine, that this reaction involves the addition of a molecule of water to the 5,6-double bond of the dihyoropyridine (see Figure 6.).

The reductive cyclization of β -indolylethyl-isoquinolinium salts by lithium aluminum hydride and sodium borohydride has been reported (18, 19). The authors suggest that the cyclisation occurs by way of a dihydro intermediate, however no definite evidence for the mechanism has been presented. The failure of pyridinium salts to cyclise under similar conditions has been reported (71). The possibility existed that a β -indolylethyl-dihydropyridine might cyclise on treatment with dilute acid, either by a direct attack of the indole part of the molecule on the protonated dihydropyridine (LXV), or by a dehydration of a 6-hydroxy-1,4,5,6-tetrahydropyridine of the type reported by Anderson and Berkelhammer (58) (see Figure 7.).

The 1-β-(3-indolyl)-ethyl-3-substituted pyridinium salts were prepared by reaction of β -(3-indolyl)-ethyl bromide (72) with the appropriate pyridine. Reduction of 1-β-(3-indolyl)-ethyl-3-benzoylpyridinium bromide (XIII) with sodium dithionite formed a solid, stable dihydropyridine, and although the analysis indicated an extra atom of oxygen the infrared and ultraviolet spectra were consistent with the structure XXXIII. The 3-benzoyl dihydropyridine was treated with aqueous hydrochloric acid under varying conditions. The same product was obtained whether it was isolated from the acid reaction mixture or from a basified reaction mixture. This fact indicated that the product was

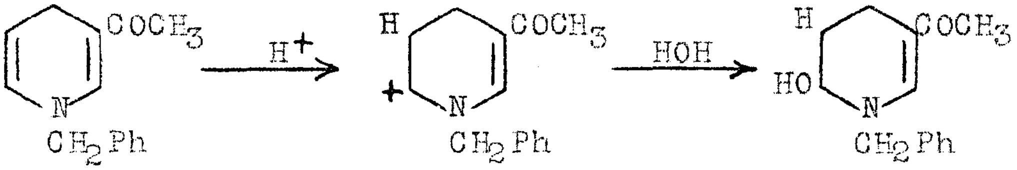


Fig. 6. Acid Reaction of 1-Benzyl-3-acetyl-1,4-dihydropyridine.

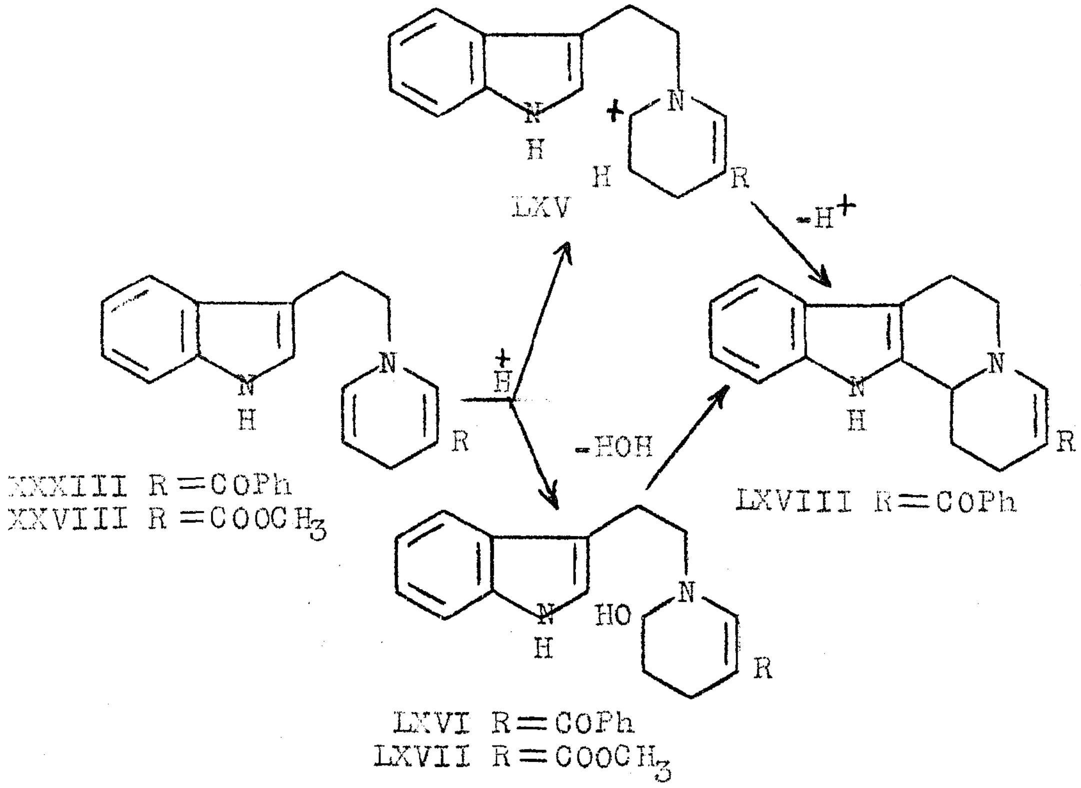


Fig. 7. Acid Reactions of 1-β-indolylethyl-1,4-dihydropyridines.

non-basic. The analysis of the unrecrystallized aqueous acid product indicated addition of a molecule of water, and the conclusion first drawn was that the product might be LXVI. When the reaction was run in glacial acetic acid, however, a product was obtained whose analysis indicated the desired product LXVIII. When the crude product from the aqueous acid reactions was recrystallized it proved to be identical with the product from the glacial acetic acid. The possibility that the aqueous acid product might have undergone dehydration to LXVIII on recrystallization was dismissed on the basis of the identity of the infrared spectra of the unrecrystallized aqueous acid product and the product from glacial acetic acid. The molecule of water indicated in the analysis might have been present as water of crystallization, but this was not indicated by the infrared spectrum. The analysis of the crude product may have been coincidental, and it appears in any case that LXVI was not formed.

The pure acid product, then, was non-basic, and formed in both aqueous and non-aqueous media. The ultraviolet spectrum of LXVIII showed a maximum at 308 mμ which supports the structure LXVIII. The infrared spectrum was also consistent with a β-amino-α,β-unsaturated ketone, showing strong bands at 1615 (m.), 1550 (s.), 1555 (s.), 1220 (s.), 1186 (s.), 1137 (s.) and 1065 (s.) cm.$^{-1}$. The crude precipitated product from glacial acetic acid did show a strong band at 1695 cm.$^{-1}$, and other differences between the crude spectrum and the spectrum of the recrystallized material suggest that the former may have been a hydroacetate salt. The N-H stretching band shifted from 3310 cm.$^{-1}$ in the crude product to 3200 cm.$^{-1}$ in the recrystallized product. The crude material also showed bands at 2600 cm.$^{-1}$, characteristic of amine salts, which disappeared on recrystallization. The salt must be unstable and formed only due to the large excess of acetic acid present and the insolubility in acetic acid, since salt formation was not observed in the reactions with aqueous hydrochloric acid.

The product formed when 1-β-(3-indolyl)-ethyl-3-carbomethoxypyridinium bromide (X) was reduced with sodium dithionite showed bands characteristic of a dihydropyridine system. The ester band shifted from 1735 cm.$^{-1}$ in the salt to 1665 cm.$^{-1}$ in the reduced product. There were other strong bands at 1677 cm.$^{-1}$ and 1602 cm.$^{-1}$. These facts, together with the ultraviolet absorption maximum at 355 mμ, indicated that the desired dihydropyridine had formed, although a sample could not be purified for analysis. Treatment of the reduction product with glacial acetic acid followed by neutralisation with potassium carbonate or reaction with ethanolic hydrogen chloride followed by neutralization gave the same product. The analyses indicated an emperical formula which would result from the addition of water to the dihydro system, and the ultraviolet spectrum was also consistent with the structure LXVII. No evidence was found which would indicate the desired cyclization had occurred.

One other attempt was made to cyclize an indolylethyl dihydropyridine, this time using 1-β-(3-indolyl)-ethyl-3-benzoyl-4-cyano-1,4-dihydropyridine (XXXIV). Treatment with glacial acetic acid caused decomposition of the compound, and dilute hydrochloric acid caused no reaction with the compound.

The unusual stability of 3-benzoyl-4-phenyl-1,4-dihydropyridine (XLII) suggested this compound for an investigation of the reactions of dihydropyridine systems. Similar products are obtained from the Hantzsch synthesis; however, the number of substituents on the ring in these compounds as well as their symmetrical structure made them unsuitable for the purposes of this study.

The first reaction investigated was that of XLII with hydrogen chloride. When hydrogen chloride gas was passed into a solution of XLII in methanol, benzene, ether or chloroform, a crude yellow product was formed the analysis of which suggested that a hydrogen chloride molecule had added. By analogy with the results of Anderson and Berkelhammer, this compound was assigned the structure XLVII. Further evidence in favor of this structure was the loss of absorption in the ultraviolet spectrum at 360 mμ and a greatly diminished absorption in the infrared spectrum at 1670 cm.$^{-1}$. A pure sample representing this structure could not be obtained due to subsequent reactions which occurred very readily. If XLVII was treated with water in any manner, such as dissolving in 95% ethanol or adding water to a methanolic solution, a second compound immediately precipitated. This product showed a very high melting point, 290-

295°, and melted without decomposition. These observations suggested that the compound might be a dimer. Anderson and Berkelhammer isolated a second product from the reaction of 1-benzyl-3-acetyl-1,4-dihydropyridine with aqueous hydrochloric acid which they assigned the dimeric structure XLVIII. In the present case the analytical data for the high melting compound did not indicate addition of water but were consistent with the emperical formula of XLII. The ultraviolet spectrum showed two maxima, one at 360 mμ, ϵ 15,000 and at 308 μ, ϵ 24,000. This indicated that the dimer contained both the 1,4-dihydro system of XLII and the 1,4,5,6-tetrahydro system of XLVII. The infrared spectrum also showed bands attributable to both of these systems. The absorption at 1670 cm.$^{-1}$ was about one-half of that for XLII and both the presence of two bands in the N-H stretching region, at 3340 and 3220 cm.$^{-1}$ and the presence of additional bands in the region from 1700-1500 cm.$^{-1}$ indicated the presence of two different β-amino-α,β-unsaturated carbonyl systems. The sum of all this evidence indicates the structure of the dimer to be XLIX. Although a molecular weight determination could not be made due to the insolubility of the compound, the extinction values of the ultraviolet absorption maxima are in agreement with this structure. XLII has an extinction of 10,800 at 360 mμ and 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine has an extinction of 24,000 at 305 mμ. If XLII was treated with hydrogen chloride in 95% ethanol or aqueous methanol, or if 6N hydrochloric acid was added to an alcoholic solution of XLII, the dimer precipitated directly from the reaction mixture.

Several other reactions were carried out on the crude acid product, XLVII. It was found that recrystallization from dry acetone transformed the product in some manner to produce a yellow, crystalline material LI which melted over a narrow range near 170°. This product was also readily converted to the dimer IX by treatment with water and in many cases LI was contaminated with XLIX. The recrystallized product was found to be different from the crude XLVII on a comparison of the infrared spectra. In addition to showing all the bands in the spectrum of XLVII the spectrum of LI showed bands at 2460, 2340, 2080, and 1950 cm.$^{-1}$ and a stronger band at 1675 cm.$^{-1}$. The bands from 2460 cm.$^{-1}$ to 1950 cm.$^{-1}$ have been attributed by Witkop (75) to the ammonium and immonium bonds of the hydrochloride salt of pyridine. The latter two absorption bands indicate the presence of a $-C=C-\overset{+}{N}H=C-$ system which would also be expected to show the absorption between 2460-1950 cm.$^{-1}$ of the pyridinium acid salts. Oxidation to the pyridinium system seemed unlikely, but since Witkop had also demonstrated that the isolated $-\overset{+}{N}H=C-$ grouping absorbed at lower frequencies in the infrared, 1980 cm.$^{-1}$, some system different than this was indicated. The extinction of the band at 308 $m\mu$ in the ultraviolet absorption spectrum was only about one-half of that expected for a β-amino-α,β-unsaturated ketone and a dimeric structure possessing only one such chromophore was indicated. The compound contained chlorine, and the analytical data most closely corresponded to the structure LI. Since the crude acid product (XLVII) also showed an extinction of only one-half that expected from a β-amino-α,β-unsaturated ketone, there is a possibility that this, too, possessed a dimeric structure. The bands at 2080 and 1950 cm.$^{-1}$, however, were definitely absent from the infrared spectrum of XLVII. The near identity of the spectra of XLVII and LI in all other respects indicated a close similarity in structure, and thus structure XLVII must be considered uncertain.

If the pure acid product LI or the crude product XLVII were treated with water, the dimer XLIX was formed. If the acid products were dissolved in methanol and water was added, XLIX precipitated. A second compound (L) was also isolated which was colorless, whereas XLIX was yellow, relatively soluble in ethanol, from which it could be recrystallized, and showed absorption at 306 mμ in the ultraviolet spectrum. If a sodium bicarbonate solution was added to an alcoholic solution of LI, L was formed exclusively. If LI was dissolved in methanol and solid potassium hydroxide was added, a solid was precipitated which was L. This product isolated from basic media was isomeric with the dimer XLIX. The ultraviolet absorption indicated only a β-amino-α,β-unsaturated ketone chromophore, however there was a band in the infrared spectrum at 1575 cm.$^{-1}$. This band has been assigned to the 5,6-double bond in several 1,4-dihydropyridine systems, as has been discussed previously, but the lack of an absorption maximum at 360 mμ in the ultraviolet spectrum of L indicated the absence of this chromophore.

The only reasonable explanation of the 1675 cm.$^{-1}$ absorption band is to attribute it to a benzoyl carbonyl which has regained its double bond character by removal from a β-amino-α,β-unsaturated ketone system. The most plausible structure for L is simply the base of the purified acid product LI. The absorption in the infrared spectrum of LI at 1675 cm.$^{-1}$ could be explained on the same basis, since this compound also showed only a single maximum, 308 mμ, in the ultraviolet spectrum above 300 mμ.

It was possible to acetylate dihydro and tetrahydropyridine compounds possessing an N-H group by means of acetic anhydride in pyridine at elevated temperatures. The characteristic changes noted in the infrared spectra of these products were all consistent with N-acetylation, loss of N-H absorption, a new band attributable to the amide carbonyl around 1700 cm.$^{-1}$, and a shifting of the strong bands around 1570 cm.$^{-1}$ to higher frequency. This latter observation indicates that the acetyl group on the nitrogen atom disrupted the β-amino-α,β-unsaturated carbonyl system by partially localizing the unshared electrons on the nitrogen and supports the assignment of structure to these products as N-acetyl compounds. The possibility of oxygen acetylation can be eliminated since the grouping -C=CR-O-CO-R (74) shows strong absorption in the infrared region at 1776-1800 cm.$^{-1}$. Such absorption was not observed in the spectra of the acetylated products. Compounds XLII, LII, and XLIX were acetylated to produce LV, LVI, and LVII respectively. The crude acid product XLVII when acetylated gave a crude product whose infrared spectrum closely resembled that of LVII. The ultraviolet spectrum of the acetylated dimer LVII closely represented the summation of the spectra of LVI and LV, although the 322 mμ band of the latter was not resolved into a separate maximum.

Treatment of the acetylated products LVI and LVII with acid in the ultraviolet absorption cell had little or no affect on their spectra. The spectrum of LV, however, changed in a manner characteristic of a 1,4-dihydropyridine. This observation further confirms the structure of these products. The fact that LVII is not affected rapidly by acid, in spite of its 1,4-dihydropyridine structure, may be due to the substituent at the 5-position of the dihydropyridine ring which prevents the attack of the proton at this position. The stability of LVII in acid is paralled by that of the parent dimer XLIV, whose dihydropyridine system is also stable in acid solution.

The reaction of XLII with phenylmagnesium bromide was attempted using essentially the same conditions used to prepare XLII from 3-benzoylpyridine. No reaction occurred, a fact which emphasized the unreactivity of the carbonyl group. When XLII was treated with a large excess of phenyllithium a blue color developed in the reaction mixture and persisted until air was admitted during the hydrolysis. A polymeric red product was isolated, and its infrared spectrum was similar in many respects to that of 3-benzoyl-4-phenylpyridine. A strong band at 1670 cm.$^{-1}$ and the lack of strong bands in the 1600-1500 cm.$^{-1}$ region indicated a loss of the original 1,4-dihydropyridine chromophore. The ultraviolet absorption maximum 249 mμ also indicated a change in the original structure. The results of this reaction might be interpreted in the following manner. The initial reaction is undoubtably the loss of the N-H proton. This would result in the formation of an anion and the stabilization of the β-amino-α,β-unsaturated ketone system in the enol-form. The blue color observed in the reaction could be due to this highly-conjugated ion. The proton at the 4-position would also be acidic and might be replaced giving an intermediate which could easily be oxidized to 3-benzoyl-4-phenyl-pyridine during the hydrolysis. Various polymerization reactions might also be expected, which could give rise to the amorphous product observed. In any case the reaction does not occur by simple addition to the carbonyl group, demonstrating again the non-reactivity of this function.

When a sample of XLII was heated with excess methyl iodide a product was obtained whose infrared spectrum showed no N-H band, no band at 1670 cm.$^{-1}$ and a strong band at 1595 cm.$^{-1}$. There was no absorption at 1670 and 1610 cm.$^{-1}$ in the product and it was apparent that the original 1,4-dihydropyridine system had been altered in some manner. The ultraviolet spectrum, however, continued to show a strong band at 360 mμ, in addition to weak absorption at 290 mμ and a maximum at 247 mμ at a much lower intensity than the 258 mμ band of XLII. The most reasonable structure which can be proposed to explain these data is LVIX, although the elemental analyses did not support this structure.

When a collection of residues from several preparations of XLII was dissolved in ethanol a portion was found to be insoluble even on prolonged boiling. The infrared spectrum of this compound differed from that of XLII in having bands at 2920 and 2900 cm.$^{-1}$, only a very weak band at 1675 cm.$^{-1}$, and bands at 1555 and 1036 cm.$^{-1}$ (s.). The remainder of the spectrum was very similar to that of XLII. The ultraviolet absorption maximum was at 302 mμ with an inflection at 250 mμ. The spectral data indicate addition of some group to the 5,6-double bond of XLII, and the analytical data were consistent with the addition of a molecule of ethyl alcohol to give LX. The infrared bands at 2920, 2900 and 1555 cm.$^{-1}$ are attributable to the methyl and methylene groups, and the strong band at 1068 cm.$^{-1}$ to the C-O stretching of the ether linkage. Compound LX could be oxidized to 3-benzoyl-4-phenylpyridine by means of chloranil. This reaction demonstrated that the addition of ethanol must be reversible. When LII was treated with chloranil under the same conditions no oxidation occurred, indicating that tetrahydropyridines in general are not oxidized by this reagent.

In order to determine the nature of the unsaturated system of a 3-benzoyl-1,4-dihydropyridine structure, 3-benzoyl-4-phenyl-1,4-dihydropyridine (XLII) was reduced catalytically using platinum oxide catalyst in neutral, methanolic solution at atmospheric pressure. It was found that 1 mole of hydrogen was absorbed readily, and on standing a product (LII) crystallized from the methanol solution. LII showed an absorption maximum in the ultraviolet spectrum at 305 mμ which indicated the presence of a β-amino α,β-unsaturated ketone chromophors. The infrared spectrum of the reduction product (LII) showed loss of absorption at 3080, 1670, 1370 and 788 cm.$^{-1}$, all bands which could be attributable to a cis-double bond, and new bands at 2930 and 1465 cm.$^{-1}$ which could be assigned to methylene groups. The analytical data were consistent with the assigned structure of 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (LII).

In order to test the generality of this reduction another dihydropyridine, 1-β-phenylethyl-3-benzoyl-1,4-dihydropyridine (XXXII) was hydrogenated under similar conditions. Two products were obtained from the reduction mixture. One showed absorption in the ultraviolet at 322 mμ, the same value noted for the acid reaction product of XLII, and hydrogenation of the 5,6-double bond was again indicated. The analytical data supported this assignment of structure as 1-β-phenylethyl-3-benzoyl-1,4,5,6-tetrahydropyridine (LIII). The infrared spectrum of the product showed no absorption at 1670 cm.$^{-1}$. The second product showed only benzenoid absorption in the ultraviolet spectrum and bands in the infrared spectrum at 3180 and 1090 cm.$^{-1}$, indicative of an alcohol. Complete reduction of the ring was indicated and the product was assigned the structure of 3-(1-β-phenyl)-ethylpiperidylphenyl carbinol (LIV). This assignment was confirmed by elemental analyses.

These reactions emphasize the inertness of the β-amino-α,β-unsaturated ketone system as found in 3-benzoyl-1,4-dihydropyridine systems. The loss of absorption in the infrared spectrum at 1670 cm.$^{-1}$ on hydrogenation of the 5,6-double bond confirms the assignment of this band to the -C=C-N- system. The coincidence of ordinary benzoyl carbonyl absorption near 1670 cm.$^{-1}$ originally suggested reduction of the carbonyl group to an alcohol; however, both the lack of additional absorption above 3000 cm.$^{-1}$ in the infrared spectrum, and the ultraviolet absorption at 305 mμ in the reduction products required an alternative explanation. When the analysis of the infrared spectra of dihydropyridine compounds revealed the original carbonyl stretching frequency had been shifted to much lower frequency, the fact that the double bond and not the carbonyl group had been reduced became apparent.

The infrared spectra of the reduction products showed very little change in the region 1650-1500 cm.$^{-1}$. The strong bands found in this region are thus characteristic of the β-amino-α,β-unsaturated ketone system rather than of the dihydropyridine system as a whole. The N-H stretching frequency of XLII is found at 3280 cm.$^{-1}$, and that of the reduction product LII at 3295 cm.$^{-1}$. The near constancy of this band seems to indicate that the 5,6-double bond is only slightly associated with the free electron pair on the nitrogen atom.

Further catalytic reduction of LII was attempted, but no hydrogen was absorbed and the starting material was recovered unchanged. Similarly, when hydrogenation of XLII was attempted in acid solution no reduction occurred, for the ultraviolet absorption spectrum of the reaction mixture did not change during the reaction. Druey and Schenker reported that they were unable to reduce 1-methyl-3-cyano-4-(1-cyano-1-phenyl)-methyl-1,4,5,6-tetrahydropyridine catalytically (75) and Chaykin, Meinhart and Krebs (76) observed that DPNH appeared to absorb only 1 mole of hydrogen on catalytic reduction. These facts all indicate that the 2,3-double bond of a 1,4,5,6-tetrahydropyridine with an electron-withdrawing 3-substituent is stable to catalytic hydrogenation, and in the case of 3-benzoyl substituents the carbonyl group is also not reduced. The formation of LIV from the catalytic hydrogenation of XXXII thus appears to be anomalous, and can be most easily explained by assuming the presence of some 1-β-phenylethyl-3-benzoylpyridine quaternary salt in the crude sample of XXXII which was used for the reduction.

Catalytic reduction of XXV was also attempted and the reaction was followed by periodically observing the ultraviolet spectrum of the reaction mixture. When the reduction was run for 24 hours the observed changes were an increase in intensity of the band at 268 mμ due to the quaternary salt and a shifting of the dihydropyridine band from 340 to 355 mμ. Since the latter value represents the maximum exhibited by 1-methyl-3-carbamoyl-1,4-dihydropyridine itself, it would appear in this case that both reversal of cyanide addition and replacement of cyanide by hydrogen had occurred. A very small yield of a high melting product was obtained from this reaction which showed a maximum in the ultraviolet at 258 mμ and was probably a small amount of quaternary salt. If the 355 mμ band observed in the reduction mixture does represent the 1,4-dihydropyridine then its non-reduction is interesting in view of the reported results of Chaykin, Meinhart and Krebs.

In order to prevent the reversal of the cyanide addition product the reduction of VI in the presence of excess cyanide ion was attempted. The reduction proceeded slowly, but after one week there was no evidence of a 340 mμ band in the ultraviolet spectrum of the reduction mixture. A slight maximum was observed at 296 mμ which is in the expected region for a 1,4,5,6-tetrahydropyridine. The absorbance, however, was rising continually at wavelengths shorter than this maximum, and it was apparent that a mixture of products had been formed.

In a similar manner XI was hydrogenated in the presence of excess cyanide ion. The reduction took place so slowly in this case that the 340 mμ band of the cyanide addition product was not destroyed until 25 days had elapsed. There was a corresponding increase in absorption at 260 mμ, the small amount of product isolated showed an absorption maximum at this value and had the characteristic spectrum of a pyridinium salt.

It would appear, therefore, that the presence of the cyanide group in the 4-position of a 1,4-dihydropyridine system alters the nature of the reduction. This fact is no doubt associated with the reversibility of the cyanide addition reaction and a poisoning of the catalyst by cyanide ion.

Several di- and tetrahydropyridines were reduced with lithium aluminum hydride. In no case could a pure compound be isolated, however, the infrared spectra of all the reduction products were decidedly similar. The compounds which were reduced are listed in Table XV together with the prominent infrared bands appearing in the spectra of the reduction products. The most important features of these spectra are the bands at 1650-1670 cm.$^{-1}$ and the lack of strong bands in the region 1600-1500 cm.$^{-1}$. The spectral evidence indicates that the β-amino-α,β-unsaturated ketone system has been destroyed in some manner. This could occur either by reduction of the 2,3-double bond of the ring or by reduction of the carbonyl group at the 3-position. If the double bond is reduced, then stability of the benzoyl group in the presence of lithium aluminum hydride would not be expected; however, the infrared bands around 1670 cm.$^{-1}$ persist. Since this band was assigned to the 5,6-double bond in the dihydropyridines it would appear reasonable to assume that this bond, where present, has been unaffected by the reducing agent. It is known that pyridines can be reduced to dihydropyridines by lithium aluminum hydride. The fact that compounds such as XLVII and LVI which do not show a 1675 cm.$^{-1}$ band develop a band in this region on reduction with lithium aluminum hydride indicates that the 2,3-double bond must have become part of a vinyl amine system. All of these observations support reduction of the carbonyl group as the primary reaction with lithium aluminum hydride.

The analogy has been drawn between β-amino-α,β-

unsaturated ketones and amides (60), but whether or not the carbonyl group is reduced to an alcohol or a methylene group is difficult to determine. The reduction products from XLII did not show any absorption above 3100 cm.$^{-1}$. This would indicate that the N-H function has been affected in some manner, and the simple reduction of the carbonyl group probably does not represent the entire reaction. The infrared spectra of the reduction products from three acetyl derivatives, however, all showed strong, broad bands around 3300 cm.$^{-1}$. The ultraviolet absorption spectra of various reduction products usually showed strong absorption around 244 mμ, which could be attributed to a vinyl amine system, but there were indications of more complex reactions occurring. Several products from XLII showed absorption around 300-310 mμ, which could represent a tetrahydropyridine structure. When lithium aluminum hydride was added to a solution of XLII in ether in the ultraviolet absorption cell there was an initial maximum observed at 425 mμ which was destroyed very rapidly. The ultraviolet spectral data are summarized in Table XIV. This table also indicates the infrared bands observed above 3100 cm.$^{-1}$ and the positions of the band around 1670 cm.$^{-1}$.

Reduction of 3-benzoyl-4-phenylpyridine with either lithium aluminum hydride or sodium borohydride resulted in reduction of the benzoyl group to form 3-(4-phenylpyridyl)-phenyl carbinol. This reaction demonstrated that the 3-benzoyl group reacts normally when not attached to a dihydropyridine system.

Treatment of 3-benzoyl-4-phenylpyridine with phenylmagnesium bromide produced the expected 3-(4-phenylpyridyl)-diphenyl carbinol (LXXIII) and also a yellow product which showed bands in the infrared spectrum characteristic of a 1,4-dihydropyridine system. A band at 3400 cm.$^{-1}$ (s.b.) was assignable to the O-H stretching frequency of the carbinol; however, a second band at 3290 cm.$^{-1}$ (s.) and bands at 1670, 1650, 1558 and 1518 cm.$^{-1}$ (s.) definitely indicated that the addition of the phenyl Grignard reagent to the pyridine ring had occurred. This reaction, then, is analogous to the reaction of 3-benzoylpyridine with phenyl Grignard reagent to form XLII and 3-pyridyl-diphenyl carbinol. Compound LXIV, however, unlike XLII, was not stable and attempts to purify it led to decomposition.

When an ethereal solution of phenylmagnesium bromide was added to a suspension of XVII in ether a crude red oil precipitated at once and could not be further purified. The ultraviolet spectrum of this oil showed maxima at 465, 362 and 246 mμ. These results indicate that addition at the 2- and 4-positions had occurred, with the possibility of some attack at the 6-position as well. The appearance of a 465 mμ maximum supports the assignment of the long-wavelength band found in the sodium borohydride reductions to a 1,2-dihydropyridine system.

In order to determine whether some of the products produced by the reaction of base on 3-benzoylpyridine quaternary salts were pyridones a sample of XIV was oxidized with potassium ferricyanide in aqueous base. This reagent has been shown to produce 2- and 6-pyridones from 3-substituted pyridinium salts. The product obtained showed maxima in the ultraviolet spectrum at 290 mμ and 252 mμ and was thus shown to be the 6-isomer (LXXI) by analogy to the data of Pullman and Colowick (44).

The observations of the altered character of the carbonyl group in 3-benzoyl-1,4-dihydro and 1,2,5,6-tetrahydropyridine systems made in this research are consistent with observations of other investigators. Such systems are thus another example of carbonyl-nitrogen interactions which arise either from direct conjugation of the nitrogen atom with the carbonyl group or from an intramolecular interaction of the type observed by Leonard with certain aminoacyloins (77).

The examples of addition to the 5,6-double bond of a 3-benzoyl-1,4-dihydropyridine system obtained in the present research support the conclusion that this reaction is of a general nature rather than a specific one involving only an acid catalyzed addition of water. The dimeric products formed from 3-benzoyl-4-phenyl-1,4-dihydropyridine show that electrophiles other than a proton will add to the 5-position, and nucleophiles such as chloride and ethoxide can add at the 6-position under appropriate conditions. The cyclization of 1-β-(3-indolyl)-ethyl-3-benzoyl-1,4-dihydropyridine to the hexahydroindoloquinolizine LXVIII is another example of this addition, and these examples suggest that this reaction may have useful synthetic applications.

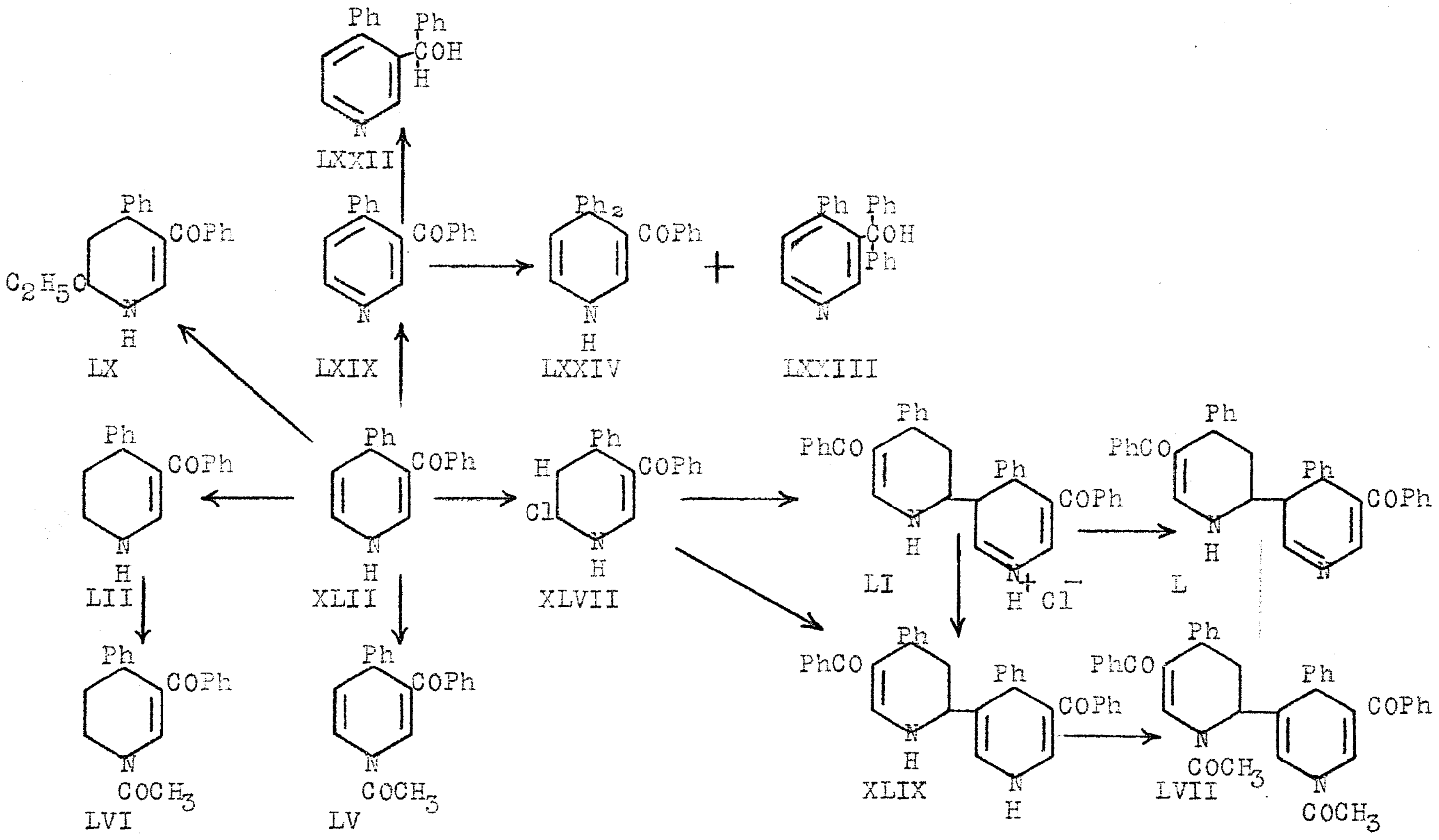


Fig.8. Transformation Products of 3-Benzoyl-4-phenyl-1,4-dihydropyridine.

EXPERIMENTAL

GENERAL

Melting points are uncorrected.

Infrared spectra were determined on a Perkin-Elmer Model 21 Infrared Spectrophotometer equipped with sodium chloride optics. Ultraviolet and visible spectra were determined on a Perkin-Elmer Model 4000 Recording Spectrophotometer equipped with a repetitive scanning accessory.

Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tennessee and Schwartzkopf Microanalytical Laboratory, Woodside, New York.

EXPERIMENTAL

Methods of preparation of quaternary salts. (See Table I). (a) Equimolar amounts of the pyridine and the halide were heated together with no solvent. The reaction mixture solidified as the salt was formed.

(b) A solution of equimolar amounts of the pyridine and the halide in isopropyl alcohol was heated under reflux. After heating for the indicated time (see Table I) the solvent was removed by distillation under reduced pressure. If the salt did not crystallize the resulting oil was triturated first with several portions of petroleum ether and then with anhydrous ether until crystallization occurred. The salts were usually recrystallized from isopropyl alcohol.

(c) This method was similar to method (b) except that a two to three-fold excess of the halide was used. In the case of methobromides a solution of methyl bromide in isopropyl alcohol was made by bubbling in the gas until the increase in weight indicated the desired amount had been dissolved in the alcohol.

1-Phenacyl-3-benzoylpyridinium bromide (XVI). To a 20.0 g. (0.11 mole) sample of 3-benzoylpyridine in 50 ml. of ether was added a solution of 22.0 g. (0.11 mole) phenacyl bromide in 150 ml. of ether. After standing overnight the ether was removed by distillation and the gummy residual oil was dissolved in hot isopropyl alcohol. On cooling the solution the product reprecipitated as an oil. Trituration of the oil with ether and then 60-90° ligroin did not cause the salt to solidify.

The ether and ligroin washings were allowed to evaporate, giving a small quantity of crystalline XVI, m.p. 195-196°.

Preparation of dihydropyridines by reduction with sodium dithionite. Two methods were used to prepare dihydropyridines for isolation. These methods have been described in the literature and differ primarily in the fact that one uses sodium carbonate as a base whereas the other uses sodium bicarbonate.

(a) In the method of Mauzerall and Westheimer(10) a solution of 0.04 mole of quaternary salt in 50 ml. of water was added to a solution of 13.8 g. (0.13 mole) of anhydrous sodium carbonate and 25.7 g. (0.13 mole) of 86.7% sodium dithionite in 50 ml. of water. The dihydropyridine precipitated as a solid or an oil. This method was particularly successful when used to prepare dihydro derivatives of 3-hydrazide pyridinium salts.

(b) In the method of Anderson and Berkelhammer(38), 26.0 g. (0.13 mole) of 86.7% sodium dithionite was added in small portions during a period of 5 min. to a solution of 0.04 mole of the quaternary salt and 18.4 g. (0.18 mole) of sodium bicarbonate in 75 ml. of water. The reaction was stirred with a magnetic stirrer. Solidification of the dihydropyridine occurred usually in a few minutes, or else the product did not crystallize.

(c) Preparation of dihydropyridines by reaction with sodium cyanide. The method used was essentially the same as that described by Karrer(43) for the preparation of 1-methyl-4-cyano-1,4-dihydropyridine.

1-Benzyl-3-benzoyl-4-cyano-1,4-dihydropyridine(XXXV).. Addition of a solution of 3.25 g. (0.05 mole) of potassium cyanide in water to an aqueous solution of 1.55 g. (0.005 mole) of the benzyl chloride salt of 3-benzoylpyridine caused the immediate precipitation of a yellow solid. Recrystallization from ethanol gave pure XXXV, m.p. 113-115°.

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 79.96; H, 5.37. Found: C, 79.60; H, 5.35.

1-β-(3-Indolyl)ethyl-3-benzoyl-4-cyano-1,4-dihydropyridine (XXXIV). A solution of 2.0 g. (0.005 mole) of the pyridinium bromide in 50 ml. of water was added to a solution of 3.25 g. (0.05 mole) of potassium cyanide in water. A yellow precipitate formed immediately, was removed by filtration, and was washed several times with water. On washing the product color changed from yellow to brown. Recrystallization from ethanol gave brown crystals of XXXIV, m.p. 163-168°.

Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.17; H, 5.42. Found: C, 78.46; H, 5.48.

Dithionite addition product of 1-(β-phenylethyl)-3-benzoylpyridinium bromide (XV). A 1.0 g. sample of XV was dissolved in 10 ml. of water and 2.6 g. of sodium dithionite was added with stirring. A yellow oil precipitated at once. The aqueous layer was decanted and the oil was triturated under ether, causing it to solidify. The dithionite addition product XXXVII showed no sharp melting point, but gradually decomposed on heating.

Preparation of 1-β-phenylethyl-3-benzoyl-1,4-dihydropyridine (XXXII) from an isolated intermediate. A 1.0 g. sample of XV was dissolved in 10 ml. of water and 1.4 g. of sodium carbonate was added to the solution with stirring. An orange oil precipitated. The aqueous layer was decanted and the oil was dissolved in 25 ml. of methanol. Water was added until the solution was just cloudy, and then 2.6 g. of sodium dithionite was added. All of the dithionite did not dissolve. The methanol was removed by distillation under reduced pressure without heating. A crude orange solid, m.p. 75-85°, precipitated. The infrared spectrum of this product was identical with that of XXXII prepared by method (b).

Reaction of 1-methyl-3-benzoyl-4-phenylpyridinium bromide (XLIII) with sodium dithionite. (a) A 2.5 g. sample of XLIII was dissolved in 150 ml. of a 2:1 ethanol-water mixture. Sodium bicarbonate, 4.0 g., was added followed by 6.9 g. of sodium dithionite. The ethanol was removed by distillation under reduced pressure with stirring. As the ethanol was removed an orange precipitate formed in the flask. When most of the ethanol was gone a gummy orange solid had formed. This yielded a light yellow residue when triturated with methanol, and this residue did not melt below 220° but only darkened on heating. A sodium fusion analysis was positive for nitrogen and sulfur. The ultraviolet spectrum in ethanol showed maxima at 360 and 310 mμ in neutral solution, and 304 mμ in acid solution. The remaining aqueous solution was extracted with benzene and the benzene extract was concentrated by evaporation under reduced pressure yielding a red oil. The ultraviolet spectrum of the oil in ethanol showed a maximum at 370 mμ in neutral solution. In acid the maximum shifted to 308 mμ.

(b) A 1.0 g. sample of XLIII was dissolved in hot water and the solution cooled to room temperature. Sodium bicarbonate, 2.0 g. was added followed by 3.5 g. of sodium dithionite with stirring. A red tar precipitated in a few minutes. This was taken up in benzene, the benzene solution was dried, and the benzene was evaporated under reduced pressure. The red product was triturated with petroleum ether, but it would not solidify. Some material had dissolved in the petroleum ether and on standing a yellow solid, (XXXVIII) m.p. 70–80°, precipitated and was removed by filtration. A sodium fusion analysis was positive for nitrogen and negative for sulfur. The ultraviolet spectrum in ethanol showed maxima at 360 and 245 mμ in neutral solution, and in acid solution the 360 maximum shifted to 308 mμ.

<u>Anal</u>. Calcd. for $C_{19}H_{17}NO$: C, 83.0; H, 6.22. Calcd. for $C_{19}H_{17}NO\cdot H_2O$: C, 74.4; H, 5.59. Found: C, 75.29; H, 5.73.

(c) A 3.5 g. sample of XLIII was dissolved in 100 ml. of previously boiled water and filtered into a 500 ml. threenecked flask into which nitrogen was passed. Sodium bicarbonate, 4.6 g., was added and then 7.0 g. of sodium dithionite. The reaction was stirred with a magnetic stirrer. A red tar soon precipitated. The reaction was allowed to stand for 4 hrs., but the product did not solidify. The reaction was acidified with 25 ml. of 6N hydrochloric acid. The red tar dissolved with the formation of a yellow solution. Some ethanol was added to help dissolve the tar. The solution was filtered to remove a small amount of undissolved material and then the solution was basified with sodium bicarbonate. The ethanol was removed by distillation under reduced pressure and a red oil resulted again. This was taken up in chloroform. One-half of the chloroform solution was treated with hydrogen chloride gas and a yellow solution resulted again. The chloroform was removed by distillation under reduced pressure and the resulting yellow foam was crystallized by trituration with anhydrous ether. Recrystallization from isopropyl alcohol-ether gave LXX, m.p. 146-148°. A Beilstein test for halogen was negative, sodium fusion for sulfur was positive.

Anal. Calcd. for $C_{18}H_{18}NO_4S$: C, 64.0; H, 5.10. Found: C, 64.58; H, 5.21.

The ultraviolet absorption spectrum in ethanol showed maxima at 238 and 320 mμ. No other product could be obtained from the unacidified chloroform solution except some starting material.

Reaction of 1-methyl-3-benzoyl-4-phenylpyridinium bromide (XLIII) with sodium hydroxide. A 1.0 g. sample of

XLIII was dissolved in 50 ml. of ethanol and 1.0 g. of flake sodium hydroxide was added. The solution turned yellow at once. After standing 15 min. the reaction was poured into water, and an orange tar separated. This tar was extracted with hot petroleum ether, and the saturated petroleum ether solution was allowed to evaporate, yielding an orange solid, m.p. ac. 70°. The ultraviolet absorption spectrum in ethanol showed an inflection at 300 mµ and a maximum at 244 mµ.

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.14; H, 5.88. Found: C, 67.53; H, 5.72.

1-Methyl-3-benzoyl-4-cyano-4-phenyl-1,4-dihydropyridine (XL). A 1.0 g. sample of XLIII was dissolved in 50 ml. of water and about 0.5 g. of sodium cyanide in 10 ml. of water was added. A small amount of yellow solid precipitated. About 3 g. more of solid sodium cyanide was added to the solution. This caused the precipitation of additional yellow solid, but on isolation by filtration and washing with water the product turned brown. The ultraviolet absorption spectrum in ethanol showed a maximum at 360 mµ and a shoulder at 300 mµ. Treatment with acid decreased the maximum at 360 mµ and produced a maximum at 300 mµ.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 76.0; H, 5.07. Found: C, 75.25; H, 5.10.

The crude XL melted at 75–80° and could not be recrystallized without extensive decomposition.

used were 1) aqueous potassium carbonate solution and 2) methanol.

(b) A solution of 1.0 g. of a substituted pyridine quaternary salt and 0.1 g. of potassium carbonate in 10 ml. of water was placed in a 25 ml. separatory funnel and 5 ml. of chloroform was added. After addition of 0.1 g. of sodium borohydride, the mixture was shaken for 15 sec. The dihydropyridine which formed was extracted into the chloroform layer, which was separated and used for spectral studies.

Reductions with sodium dithionite. (c) This method was similar to (a). The solvents used were 1) water and 2) aqueous sodium carbonate solution.

(d) This method was similar to (b) except that the reductions were run either 1) in water alone or 2) in aqueous sodium carbonate solution. The concentration of salt was about 10^{-1} M.

Reduction of 1-β-(3-indolyl)ethyl-3-benzoylpyridinium bromide (XIII) with sodium dithionite. A solution of 1.0 g. of XIII in 25 ml. of water was added to a solution of 1.4 g. of sodium carbonate and 2.6 g. of sodium dithionite in 25 ml. of water. After a few minutes glistening yellow plates precipitated. On further standing a yellow powder also began to precipitate. The product was collected by filtration, plates and powder combined and on recrystallization from ethanol gave 1-β-(3-indolyl)ethyl-3-benzoyl-1,4-dihydropyridine (XXXIII), m.p. 160-163°. On standing a green precipitate formed in the mother liquor from the reduction mixture. This solid turned yellow when collected and dried on the filter paper and was shown to be identical to XXXIII by comparison of the infrared and ultraviolet spectra.

Anal: Calcd. for $C_{22}H_{20}N_2O$: C, 80.5; H, 6.16. Calcd. for $C_{22}H_{20}N_2O \cdot H_2O$: C, 76.72; H, 5.87. Found: C, 76.88; H, 5.62.

Reactions of XXXIII with acid. (a) With acetic acid. A 1.0 g. sample of the XXXIII was dissolved in 50 ml. of glacial acetic acid. After standing for a few minutes a white solid precipitated. Recrystallization from chloroform-ethanol gave a pure sample of LXVIII, m.p. 250-255°.

Anal: Calcd. for $C_{22}H_{20}N_2O$: C, 80.5; H, 6.16. Found: C, 80.22; H, 5.82.

(b) With acetic acid in chloroform solution. A 2.0 g. sample of XXXIII was dissolved in 50 ml. of chloroform and 10 ml. of glacial acetic acid was added. The reaction was allowed to stand at room temperature for 24 hrs. and then was neutralized with 12.0 g. of solid potassium carbonate. The potassium acetate was removed by filtration and the filtrate was concentrated. A light yellow solid separated which melted at 250-255°. A mixture melting point with LXVIII showed no depression and the infrared spectra were identical

(c) With hydrochloric acid at elevated temperature.. A 1.0 g. sample of XXXIII was dissolved in 50 ml. of ethanol, 10 ml. of 6N hydrochloric acid was added, and the mixture was heated on the steam bath for 2 hrs. The ethanol was removed by distillation under reduced pressure, and 25 ml. of water was added, giving a crude sample of LXVIII, m.p. 245-250°.

(d) With hydrochloric acid at room temperature. A 2.0 g. sample of XXXIII was dissolved in 50 ml. of ethanol and 10 ml. of 6N hydrochloric acid was added. The mixture was allowed to stand for 0.5 hr. and then some of the ethanol was removed by distillation under reduced pressure. Some water was added giving a solid, m.p. 250-260°. The remainder of the ethanol was then removed, and the reaction was basified with sodium carbonate solution. The solid which precipitated was the same as that from the acid reaction mixture before basification as shown by an identical infrared spectrum. Both products showed ultraviolet absorption spectra identical with that of LXVIII, and were assumed to be crude LXVIII.

Reaction of 1-β-(3-indolyl)ethyl-3-carbomethoxy-1,4-dihydropyridine (XXVIII) with acid. A 1.0 g. sample of XXVIII was dissolved in ethanol and 5 drops of 6N hydrochloric acid were added. The reaction was followed spectrophotometrically. When the band at 355 mμ., characteristic of the dihydro system, was destroyed, the mixture was basified with potassium carbonate solution. The solid which precipitated was recrystallized from ethanol-ether, giving XLVII, m.p. 169-170°. The same product was obtained if the dihydropyridine was dissolved in glacial acetic acid and the reaction worked up in the same manner.

Anal: Calcd. for $C_{17}H_{20}N_2O_3$: C, 61.9; H, 7.07.

Found: C, 72.55; H, 7.10.

Reaction of 1-β-(3-indolyl)ethyl-3-benzoyl-4-cyano-1,4-dihydropyridine (XXXIV) with acid. A 1.0 g. sample of XXXIV was dissolved in 25 ml. of glacial acetic acid with slight warming. The mixture was allowed to stand for 16 hrs. On neutralizing the solution with aqueous bicarbonate only a red tar was isolated, and no pure product could be obtained..

A second 1.0 g. sample was suspended in 1N hydrochloric acid and stirred for 12 hrs. Most of the cyanide addition product remained in suspension. The undissolved material was removed and was shown from its infrared spectrum to be identical with the starting material. The filtrate was neutralized with solid bicarbonate and a small amount of a solid precipitated and could not be purified.

3-Benzoyl-4-phenyl-1,4-dihydropyridine (XLII). This compound was prepared by the method of Fuson and Miller(59) with the following modification in work-up. After the Grignard complex was hydrolyzed, most of the product precipitated and floated on top of the water layer. The solid was removed by filtration, and concentration of the ether filtrate yielded a small additional amount of XLII together with the 3-pyridyldiphenyl carbinol. Recrystallization from ethanol gave pure XLII, m.p. 148-152° (lit. 142-148°).

3-Benzoyl-4-phenyl-6-chloro-1,4,5,6-tetrahydropyridine (XLVII). A 1.0 g. sample of XLII was dissolved in 100 ml.

of benzene and hydrogen chloride gas was bubbled into the solution. The crude XLVII precipitated at once and was removed by filtration. The product was dried in a vacuum desiccator over potassium hydroxide. If methanol was used as a solvent for the reaction, compound XLVII was also obtained after the solvent was removed by distillation under reduced pressure.

Anal: Calcd. for $C_{18}H_{16}ClNO$: Cl, 11.90. Found: Cl, 14.56.

3-Benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-4,5-dihydropyridine hydrochloride (LI). A sample of crude XLVII was recrystallized from dry acetone giving pure LI, m.p. 168-172°.

Anal: Calcd. for $C_{36}H_{31}ClN_2O_2$: Cl, 6.36. Found: Cl, 6.36.

3-Benzoyl-4-phenyl-5[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-4,5-dihydropyridine (L). A 1.0 g. sample of LI was dissolved in 50 ml. of methanol and 1.0 g. of solid potassium hydroxide was added. The reaction was allowed to stand for 24 hrs. with occasional shaking and then was poured into water. The precipitated product was recrystallized from ethanol, giving pure L, m.p. 220-225°.

Anal: Calcd. for $C_{36}H_{30}N_2O_2$: C, 82.70; H, 5.80; N, 5.37. Found: C, 82.51; H, 5.57; N, 5.38.

The dimer L was also obtained when the crude XLVII was added to 50% aqueous ethanol. The dimer XLIX precipitated at once and was removed by filtration. The filtrate was allowed to stand and some of the ethanol had evaporated causing precipitation of a product which proved to be identical with L on comparison of the infrared spectra. If XLVII was added to 10% sodium carbonate solution L was formed exclusively.

3-Benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-1,4-dihydropyridine (XLIX). A 5.0 g. sample of XLII was dissolved in 50 ml. of ethanol, and 10 ml. of 6N hydrochloric acid was added. The reaction was heated on the steam bath for a few minutes and then was poured into 200 ml. of water. The precipitated solid was recrystallized from dimethyl formamide giving pure XLIX, m.p. 290-295°.

Anal: Calcd. for $C_{36}H_{30}N_2O_2$: C, 82.70; H, 5.80; N, 5.37. Found: C, 82.30; H, 5.59; N, 5.63.

The dimer XLIX was also prepared by adding water to a methanolic solution of XLVII.

1-Acetyl-3-benzoyl-4-phenyl-1,4-dihydropyridine (LV). A 1.0 g. sample of XLII was dissolved in 25 ml. of pyridine, and 5.0 ml. of acetic anhydride was added. The reaction was heated for 4 hrs. on the steam bath and then was poured into 200 ml. of water. A solid separated which was removed by filtration and was recrystallized from ethanol-chloroform, giving pure LV, m.p. 182-183°.

Anal: Calcd. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65. Found: C, 79.37; H, 5.79.

1-Acetyl-3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (LVI). A 1.0 g. sample of LII was dissolved in 50 ml. of pyridine, and 5.0 ml. of acetic anhydride was added. The reaction was heated for 6 hrs. on the steam bath and then poured into water. The precipitated solid was recrystallized from ethanol, giving pure LVI, m.p. 159-161°.

Anal: Calcd. for $C_{20}H_{19}NO_2$: C, 79.20; H, 6.27; N, 4.59. Found: C, 79.28; H, 6.32; N, 4.59.

1-Acetyl-3-benzoyl-4-phenyl-5-[6-(1-acetyl-3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-1,4-dihydropyridine (LVII). When treated by the same procedure used to prepare LV, XLIX gave LVII, m.p. 255-257°, when recrystallized from ethanol-chloroform.

Anal: Calcd. for $C_{40}H_{34}N_2O_4$: C, 79.18; H, 5.66; N, 462. Found: C, 79.71; H, 5.96; N, 6.35.

Reaction of 1-β-(3-indolyl)ethyl-3-benzoyl-1,4-dihydropyridine with acetic anhydride. A 2.0 g. sample of the dihydropyridine was dissolved in 20 ml. of pyridine, and 4.0 ml. of acetic anhydride was added. The mixture was allowed to stand for 16 hrs. and then was poured into water. The Brown precipitate which separated proved to be starting material, m.p. 161-163°, after recrystallization from ethanol.

Reaction of XLII with phenylmagnesium bromide. A solution of 5.2 g. (0.02 mole) of XLII in tetrahydrofuran was added to a solution of 0.04 mole of phenylmagnesium bromide in ether. After the addition the reaction was stirred for

0.5 hr. and then was hydrolyzed with saturated ammonium chloride solution. The organic layer was separated and extracted with water three times to remove most of the tetrahydrofuran. As the extraction proceeded unreacted starting material, m.p. 150–151°, precipitated from the ether layer. No other material was isolated.

Reaction of XLII with phenyllithium. A solution of 5.2 g. (0.02 mole) of XLII in 100 ml. of tetrahydrofuran was added rapidly to a solution of phenyllithium, prepared from 4.75 ml. (7.1 g., 0.045 mole) of bromobenzene and 0.62 g. (0.09 mole) of lithium, in 200 ml. of ether. An initial blue color developed which changed to orange as the reaction proceeded. The reaction was heated under reflux for 1 hr. and then was hydrolyzed with water. The ethereal layer was extracted three times with water, dried over magnesium sulfate, and concentrated by evaporation. Addition of 60–90° ligroin caused precipitation of a yellow oil from which was isolated some starting material, m.p. 149–151°. No other product could be obtained.

The reaction was run again using a four-fold excess of phenyllithium, and the reaction was heated under reflux for 5 hrs. In this case the blue color persisted during the reaction. As soon as air was admitted to the flask the reaction mixture turned red. The only product isolated was a red tar partly soluble in 60–90° ligroin.

3-Benzoyl-4-phenyl-6-ethoxy-1,4,5,6-tetrahydropyridine

(LX). When a collection of residues from several preparations of XLII was dissolved in ethanol a portion was found to be insoluble even on prolonged boiling. This product was recrystallized from dimethyl formamide and gave pure LX, m.p. 154–156°.

Anal. Calcd. for $C_{20}H_{22}NO_2$: C, 77.89; H, 7.15. Found: C, 77.91; H, 7.15.

Oxidation of LX with chloranil. A 0.5 g. sample of LX was suspended in 50 ml. of benzene and 0.5 g. of chloranil was added. The mixture was heated for 24 hrs., and after washing with 5–50 ml. portions of 10% sodium hydroxide solution, the benzene was removed by distillation under reduced pressure. The resulting oil solidified on trituration and was recrystallized from ethanol-water, giving pure 3-benzoyl-4-phenyl pyridine (LXIX), m.p. 87–88°. The infrared spectrum of this product was identical with that of a sample of LXIX prepared by oxidation of XLII with chloranil.

Reaction of 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (LII) with chloranil. A 1.0 g. sample of LII was heated under reflux with 1.0 g. of chloranil in 100 ml. of benzene for 8 hrs. The reaction mixture turned blue. Subsequently, the reaction mixture was extracted with 5–30 ml. and 2–100 ml. portions of 10% sodium hydroxide solution. The benzene solution remained blue. Concentration of the benzene solution under reduced pressure caused precipitation of 1.0 g. of the starting material, m.p. 179–181°.

Reaction of XLIX with chloranil. A 1.0 g. sample of

XLIX was treated with chloranil under the same conditions as LII except that dimethyl formamide was used as a solvent. Extensive decomposition occurred during the reaction and only a gummy black residue remained when the solvent was removed by distillation under reduced pressure.

Reaction of XLII with methyl iodide. A 3.6 g. (0.014 mole) sample of XLII was dissolved in 50 ml. of methanol and 1.0 ml. (2.28 g., 0.016 mole) of methyl iodide was added. There was no change in the ultraviolet spectrum on mixing. An additional 5.0 ml. of methyl iodide was added and the mixture was heated under reflux for 36 hrs, after which the excess methyl iodide was removed by distillation on the steam bath. Recrystallization of the precipitated solid gave a light yellow product, m.p. 260–270°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 83.0; H, 6.23. Found: C, 80.45; H, 6.01.

Catalytic hydrogenation of XLII. A 5.0 g. sample of XLII was dissolved in 100 ml. of ethanol, and 0.1 g. of platinum oxide was added. The compound was hydrogenated at 3 atm. for 2 hrs. Samples were withdrawn at 15 min. intervals, and their ultraviolet absorption spectra were recorded. When the reaction was complete the original band at 364 mμ was no longer present and a band had appeared at 305 mμ. On standing the ethanol solution gave crystals of pure 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (LII), m.p. 180–181°. The same product was obtained when methanol or tetrahydrofuran was used as a solvent.

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.2; H, 6.52; N, 5.33. Found: C, 82.02; H, 6.74; N, 5.40.

Catalytic hydrogenation of XXXII. A 1.0 g. sample of XXXII was dissolved in 50 ml. of ethanol and 0.1 g. of platinum oxide was added. The mixture was shaken with hydrogen at 3 atm. for 16 hrs. The oil resulting when the catalyst and solvent were removed was crystallized from 60–90° ligroin and yielded colorless needles of 1-β-phenylethyl-3-benzoyl-1,4,5,6-tetrahydropyridine (LIII), m.p. 105–106°.

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.6; H, 7.28; N, 4.82. Found: C, 83.09; H, 7.53; N, 4.94.

Concentration of the filtrate yielded more LIII and colorless clusters of 3-(1-β-phenylethylpiperidyl)phenyl carbinol (LIV), m.p. 120–122°.

Catalytic hydrogenation of LII. A 1.0 g. sample of LII was dissolved in methanol and the solution was acidified by bubbling in hydrogen chloride gas. The solution was hydrogenated at 3 atm. for 4 hrs. using platinum oxide catalyst. No uptake of hydrogen was observed. The catalyst was removed and most of the solvent was removed by distillation under reduced pressure. One-half of the remaining solution was poured into water and the other half was basified with sodium bicarbonate. A crystalline product, m.p. 180–181°, separated in both cases. The identity of both products was established as LII by mixture melting point determinations with an authentic sample

<u>Catalytic hydrogenation of XLII in acid solution</u>. A 5.0 g. sample of XLII was dissolved in methanol and hydrogen chloride gas was bubbled in for 5 min. Hydrogenation at 3 atm. was attempted using platinum oxide catalyst. No uptake of hydrogen was observed and there was no change in the ultraviolet spectrum taken at intervals during the hydrogenation (Maxima at 304 and 238 mμ). The catalyst was removed and the methanol was removed by distillation under reduced pressure. The resulting product was identical with XLVII prepared by other methods.

<u>Catalytic hydrogenation of XXV.</u> A sample of XXV was hydrogenated using platinum oxide catalyst and hydrogen at 3 atm. in dimethyl formamide solution. The reduction proceeded slowly. Samples were taken at intervals of about one-half hr. and the ultraviolet absorption spectra recorded. When the reaction seemed to be complete the solvent was removed by distillation under reduced pressure and the residual oil was dissolved in methanol. Concentration of the methanol solution by evaporation yielded a small amount of brown needles, m.p. 230–235°(d.). At the start, the ultraviolet spectrum showed maxima at 340 mμ, (A=1.36) and 266 mμ, (A=0.34). At the end of the reduction the spectra showed maxima at 355 mμ, (A=0.8) and 266 mμ, (A=1.32). The product was not

characterized.

Catalytic hydrogenation of XI in the presence of cyanide ion. A 5.0 g. sample of XI and 2.0 g. of potassium cyanide were dissolved in a mixture of 230 ml. of ethanol and 20 ml. of water and hydrogenated at 3 atm. using platinum oxide catalyst. The reaction was followed by observing the changes in the ultraviolet spectrum. The reduction proceeded very slowly and was not complete until after 25 days. At the start the ultraviolet spectrum showed a maximum at 340 mμ, (A=1.65) and at the finish maxima at 260 mμ, (A=0.96), 241 mμ, (A=0.98) and 235 mμ, (A=1.05). A product was isolated by first adding silver nitrate to precipitate the excess cyanide ion, then adding sodium chloride to remove the excess silver ions. Concentration of the remaining solution by evaporation under reduced pressure afforded a small amount of crystalline product, m.p. 206-207°. This material was not characterized.

Reaction of XLII with lithium aluminum hydride. A 5.0 g. sample of XLII was dissolved in 100 ml. of freshly distilled tetrahydrofuran and excess lithium aluminum hydride, about 1 g., was added in portions. After the initial reaction had subsided, the mixture was heated under reflux for 8 hrs. The excess lithium aluminum hydride was decomposed with methanol. The residue was dissolved in water and extracted with ether, and the ether extract was dried over magnesium sulfate. Removal of the ether by distillation under reduced pressure left an oil which was triturated with petroleum ether. When the petroleum ether washings were poured into water, a solid separated which had a long m.p. range, 90-110°. This material could be recrystallized from petroleum ether, but its purity was not improved.

Reduction of XXXIII with lithium aluminum hydride. A 0.4 g. sample of XXXIII was suspended in 75 ml. of ether and 0.5 g. of lithium aluminum hydride was added. The mixture was stirred for 8 hrs. The excess lithium aluminum hydride was decomposed with methanol, and the ether solution was washed with water. The ether layer was dried over magnesium sulfate and concentrated by evaporation. Addition of petroleum ether caused the precipitation of an orange tar which solidified to some extent on trituration but showed no sharp melting point. The product could not be purified further.

Other reductions with lithium aluminum hydride. Several other compounds were reduced with lithium aluminum hydride under essentially the same conditions used with XXXIII. A 1.0 g. sample of the compound was suspended in 50 ml. of anhydrous ether and 0.5 g. of lithium aluminum hydride was added. The mixture was stirred for 8 hrs. and filtered, and the excess hydride was decomposed with water. The ether layer was separated, dried over magnesium sulfate, and concentrated by evaporation. Addition of petroleum ether caused the precipitation of an oil which could sometimes be crystallized by trituration. In no case was a pure product obtained which could be analyzed. Infrared spectra were determined as films or chloroform solutions. The prominent bands are given in Table XV.

Reaction of XLII with sodium borohydride. A 2.0 g. sample of XLII was dissolved in 50 ml. of methanol and cooled to 0° in an ice bath. Sodium borohydride, 2.0 g., was added with stirring. The mixture was allowad to stand for 1 hr., 10 ml. of water was added, and the mixture was heated to boiling. On cooling in an ice bath the solution deposited yellow crystals which did not melt below 230°. A flame test indicated the presence of sodium. The crystals were removed by filtration, the filtrate was heated to boiling and water was added until the hot filtrate just became cloudy. On cooling the filtrate yielded a product, m.p. 150°, which was shown to be pure XLII by a comparison of its infrared spectra with that of an authentic sample. The infrared spectrum of the high melting product was also identical with that of the starting material.

Reaction of XXXIII with sodium borohydride. A 2.0 g. sample of XXXIII was dissolved in 300 ml. of methanol, and 2.0 g. of sodium borohydride was added. After the bubbling had subsided an additional 4.0 g. of borohydride was added followed by 20 ml. of water. The methanol was removed by distillation on the steam bath and the resulting yellow oil was crystallized from benzene, affording a product, m. p. 158–161°. The infrared spectrum of this product was identical with that of the starting material.

Other reductions with sodium borohydride. Several other compounds were reduced with sodium borohydride under similar conditions. A 0.5–1.0 g. sample of the compound was dissolved in methanol and 1–2 g. of sodium borohydride was added. When the reaction was complete, it was poured into water and the product was collected by filtration. The results of these reductions are given in Table 15.

Preparation of 3-benzoyl-4-phenylpyridine (LXIX). A solution of 11.7 g. (0.0449 mole) XLII and 11.0 g. (0.0449 mole) of chloranil in 800 ml. of benzene was heated under reflux for 8 hrs. About 600 ml. of solvent was removed by distillation under reduced pressure, and the remaining benzene solution was extracted with 5–300 ml. portions of 10% sodium hydroxide solution. The benzene solution was separated, and the remaining benzene was removed by distillation under reduced pressure on the steam bath. The resulting oil was triturated until it solidified, yielding 64% of LXIX, m.p. 87–88°. The literature reports this method produces an 83% yield of LXIX, m.p. 89.5–90° (59).

The methobromide of LXIX was prepared by dissolving 7.5 g. of LXIX in 50 ml. of methanol, cooling the solution to 0° and dissolving 5.0 g. of methyl bromide in the solution. The reaction was allowed to stand for 24 hrs. at room temperature, tightly stoppered. The reaction was then recooled to 0°, the stopper removed and the methanol evaporated, yielding and concentrated by evaporation, giving a product, m.p. 147.5–148°. This was shown to be identical with LXXII by a mixture melting point determination and comparison of infrared spectra.

Reaction of LXIX with phenylmagnesium bromide. A 5.0 g. sample of LXIX was dissolved in ether and added to an ethereal solution of 0.4 mole of phenylmagnesium bromide. The reaction was stirred for 20 min. and then was hydrolyzed with saturated ammonium chloride solution. A yellow precipitate formed, and this was removed by filtration. An attempt was made to recrystallize the yellow precipitate from a water–dimethyl formamide mixture and an oil resulted. This oil was taken up in benzene, and the solution was concentrated by evaporation. No pure product was obtained, however. The product was assigned the structure of 3–benzoyl–4,4–diphenyl–1,4–dihydropyridine (LXXIV) on analysis of the infrared spectrum. The ethereal filtrate was dried over magnesium sulfate and the solution was concentrated by evaporation. After several washings with petroleum ether the resulting oil was dissolved in ether and a white solid precipitated. This afforded pure 3–(4–phenylpyridyl)diphenyl carbinol (LXXIII), m.p. 131–132° after recrystallization from ether.

Anal. Calcd. for $C_{24}H_{19}NO$: C, 85.43; H, 5.68. Found: C, 85.36; H, 5.72.

Oxidation of 3–benzoylpyridine methobromide with ferricyanide. A 2.0 g. (0.0073 mole) sample of 3–benzoylpyridine methobromide was dissolved in 10 ml. of water. At 0.5 hr. intervals 1.0 ml. portions of a solution of 1.68 g.

pure methobromide (XLIII), m.p. 233–235°.

Anal. Calcd. for $C_{19}H_{16}BrNO$: Br, 22.56. Found: Br, 22.49.

The methiodide of XLIX, m.p. 215–217°, was prepared on a small scale by triturating some of the crude oily pyridine with methyl iodide.

Reduction of LXIX. (a) With lithium aluminum hydride. A 1.0 g. sample of LXIX was dissolved in 50 ml. of ether and excess lithium aluminum hydride was added. After the reaction ceased, about 10 min., a white precipitate had formed in the flask. The unreacted lithium aluminum hydride was decomposed with methanol and the reaction mixture was poured into water. The mixture was placed in a separatory funnel, 50 ml. of ether was added, and the mixture was washed with water several times. The ether layer was separated and dried over potassium carbonate, and the solution was concentrated by evaporation, affording pure crystals of 3-(4-phenylpyridyl)phenyl carbinol (LXXII), m.p. 148–149°.

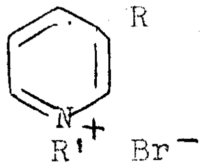
Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79. Found: C, 82.63; H, 5.99.

(b) With sodium borohydride. A 1.0 g. sample of LXIX was dissolved in 50 ml. of methanol at 0° and 1.0 g. of sodium borohydride was added. No bubbling was observed. The reaction was allowed to come to room temperature and stand for a day. Water was added and the mixture was extracted with ether. The ether extract was dried over potassium carbonate of sodium hydroxide in 3 ml. of water and 1.5 ml. portions of a solution of 4.8 g. of potassium ferricyanide in 8 ml. of hot water were added. The first addition of base caused the precipitation of yellow oil. Ten ml. of methanol was added to the reaction before the first portion of ferricyanide was added. The oil solidified, and since the reaction was not homogeneous it was stirred with mechanical stirrer. When all the reactants had been added a brown solid remained in the flask. This was removed by filtration and recrystallized from methanol, yielding 1-methyl-3-benzoyl-6-pyridone (LXXI), m.p. 178-179°.

Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20. Found: C, 73.12; H, 5.39.

TABLE I

3-SUBSTITUTED PYRIDINE QUATERNARY SALTS



Compound No.	R	R'	M.P.
I	CH_2 $CHCH_2$-	-$CONH_2$	150-151°
II	$(CH_3)_2CHCH_2CH_2$-	-$CONH_2$	228-230° (d.)
III	CH_3-	-$CONH_2$	217-220°
IX	CH_3-	-COOEt	151-155°
X	Indolylethyl-[a]	-COOEt	197-200°
XII	$(CH_3)_2CHCH_2CH_2$-	-COPh	110-111°
XIII	Indolylethyl-[a]	-COPh	196-198°
XIV	CH_3-	-COPh	153-155°
XV	$PhCH_2CH_2$-	-COPh	145-146°
XVI	$PhCOCH_2$-	-COPh	195-196°
XVII	$PhCH_2$-[b]	-COPh	177-179°
XXII	$\frac{1}{2}(CH_2)_5$-[c]	-$CONH_2$	205-206°
XXIIA	$Br(CH_2)_5$-	-COPh	d
XLIII	CH_3-	-COPh,4-Ph-	233-235°
XLIV	$PhCH_2CH_2$-	-$CONHN(CH_3)_2$	228-230°
XLV	CH_3-	-COPh[e]	162-165°

[a] β-(3-indolyl)-ethyl-. [b] Chloride salt. [c] Double salt of pentamethylene dibromide. [d] Could not be recrystallized. [e] 4-isomer.

TABLE I (cont.)

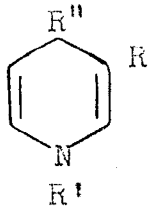
Compound No.	Preparation[f,g] Method	Temp.	Time (hr.)	Recryst. Solvent	% Halogen Calcd.	Found
I	(b)	82°	3	h	32.88	32.66
II	(c)	82°	8	i	29.25	28.91
III	(c)	25°	12	j	36.82	40.20
IX	(c)	25°	12	j	32.55	34.30
X	(a)	100°	10 min.	i	22.12	21.94
XII	(b)	82°	6	j	23.91	23.98
XIII	(b)	25°	10 da. 50%	j	19.62	19.28
XIV	(c)	25°	12	j	28.73	28.40
XV	(b)	82°	6	j	21.71	21.62
XVI	g				21.82	22.08
XVII	(b)	82°	6	j	11.24	11.48
XXII	(c)	82°	8	i	33.71	33.81
XXIIA	(c)	82°	8	d	19.35	18.26[k]
XLIII	(c)	25°	12	j	22.56	22.49
XLIV	m	25°	8 10%	j	22.82	
XLV	(c)	25°	12	j	28.73	28.40

---

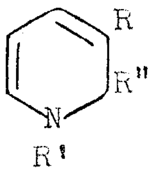
[f] Yields were consistently 80-90% except where noted. [g] See Experimental. [h] Isopropyl alcohol-methanol. [i] Ethanol. [j] Isopropyl alcohol. [k] Analysis of crude salt. [m] From corresponding ester salt and dimethylhydrazine.

TABLE II

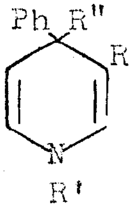
PROPERTIES OF DIHYDROPYRIDINES



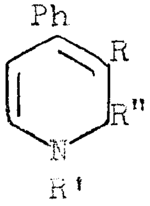
TYPE I



TYPE II



TYPE III



TYPE IV

Compound No.	Type	R	R'	R"	M.P.
XXV	I	$-CONH_2$	CH_3-	$-CN$	125° (d.)
XXVII	I	$-CONHNH_2$	$PhCH_2CH_2-$	H-	126-128°
XXVIII	I	$-COOCH_3$	Indole[a]	H-	105-110°
XXX	I	-COPh	CH_3-	H-	67-69°
XXXI	I	-COPh	i-Amyl-	H-	b
XXXII	I	-COPh	$PhCH_2CH_2-$	H-	90-95°
XXXIII	I	-COPh	Indole[a]	H-	160-163°
XXXIV	I	-COPh	Indole[a]	$-CN$	163-168° (d.)
XXXV	I	-COPh	$PhCH_2-$	$-CN$	113-115°
XXXVI	II	-COPh	$PhCH_2-$	$-SO_2H$	(d.)
XXXVII	II	-COPh	$PhCH_2CH_2-$	$-SO_2H$	(d.)
XXXVIII	III	-COPh	CH_3-	H-	70-80°
XXXIX	IV	-COPh	CH_3-	$-SO_2H$	b
XL	III	-COPh	CH_3-	$-CN$	75-80°
XLII	I	-COPh	H-	Ph-	148-152°

[a] β-(3-indolyl)-ethyl-. [b] Obtained as an oil.

TABLE II (cont.)

Compound No.	Prep. Method[c]	Yield %	R.S.[d]	Analysis %			
				Calcd.		Found	
				C	H	C	H
XXV	(c)	80	e	58.89	5.55	58.96	5.61[f]
XXVII	(a)	72	e	69.11	7.50	69.17	7.28
XXVIII	(a)	50	g	h			
XXX	(b)		i	78.49	6.54	78.39	6.58[j]
XXXI	(b)	75	g	h			
XXXII	(b)	90	k	83.01	6.62	83.08	6.81
XXXIII	(a)[c]	90	e	76.72	5.87	76.88	5.62[m]
XXXIV	(c)	90	e	78.17	5.42	78.46	5.48
XXXV	(c)	75	e	79.96	5.37	79.60	5.35
XXXVI	(b)	90	g	67.34	5.03	66.2	5.13
XXXVII	-[c]	90	g	h,n			
XXXVIII	(b)	20	k	h			
XXXIX	(b)	10	g	h			
XL	(c)	50	g	76.04	5.07	75.25	5.10[m]
XLII	-[c]	45	e	82.73	5.79	82.94	6.07[p]

[c] See Experimental. [d] Recrystallizing solvent. [e] 95% ethanol. [f] Ref. (43). [g] Could not be recrystallized. [h] Could not be purified for analysis. [i] 50% ethanol. [j] Ref. (42). [k] 60-90° ligroin. [m] Analysis indicates 1 extra atom of O. [n] Sodium fusion analysis for S positive. [p] Ref. (59).

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF DIHYDROPYRIDINES

Compound No.	Maxima (mμ) and Extinction			
	Neutral Solution[a]		Acid Solution[b]	
XXV	340		272	
XXVII	353	7600	294	17500
	234[c]	8700		
XXVIII	355		293	
XXX	385		322	
XXXI	383		320	
XXXII	385	7200	322	14000
	245	8200	236	10000
XXXIII	384	5900	318	25500
			240[c]	9500
XXXIV	364	9400	310	26000
XXXV	360	9600	303	11600
	230[c]	9400	230[c]	9400
XXXVI	370[c]			
XXXVII	380[c]		322	
	328			
XXXVIII[d]	360	4000	308	20000
	290[c]	7500		
	244	17300		
XXXIX	360			
	310			
XL[d]	360	4000	296	11000
	290[c]	6800		
	240[c]	13800		
XLII	360	10800	305	23000
	234	11400	236	19000

---

[a] 10^{-4} M in methanol. [b] 3 drops of 6N hydrochloric acid added to the absorption cell. [c] Inflection. [d] Decomposed in solution. Extinction values are estimated.

TABLE IV

ULTRAVIOLET ABSORPTION MAXIMA EXHIBITED BY 3-SUBSTITUTED PYRIDINE QUATERNARY SALTS WITH VARIOUS BASIC REAGENTS

Compound No.	Reagent	max (mμ) in Methanol	ε or A Ratio[a]	
XI	Sodium methoxide[b]	258 315	0.72	c
XV	Sodium carbonate[d]	382		e
XVII	Sodium methoxide[b]	287 332	9000 14200	
XVII	Sodium hydroxide[b]	287 332	9000 14200	g
XVII	Sodium methoxide[b,f]	273 335	0.82	h
XIII	Sodium carbonate[i]	266	8200	
XIV	i	268 355	12600 3300	
XV	i	270 355	10700 4300	
XVI	i	268 355sh	12400 2800	
XVII	i	288 358	10400 9400	

---

[a] Ratio of absorbance of shorter max over longer max.
[b] Solid reagent added directly to absorption cell. [c] Maxima replaced by one at 264 mu after standing overnight. [d] Solid product obtained by adding solid sodium carbonate to an aqueous solution of the salt. [e] Maximum changed to 308 mu on addition of 6N hydrochloric acid. [f] Ethanol solvent. [g] Shoulder observed at 475 mu which decreased rapidly. [h] Maxima replaced by one at 264 mu on addition of 6N hydrochloric acid.
[i] Maxima were observed after these salts had been standing for 2 days in 1M aqueous sodium carbonate.

TABLE V

INFRARED ABSORPTION BANDS OF 3-SUBSTITUTED PYRIDINES

3-Substituent	Number and Position of Band (in cm.$^{-1}$)															
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.
$-COOCH_3$[a]	3020	1596	1578	1483	1425	1330	1240	1195	1115	1090	1038	1025	960	825	740	700
$-COOPh$[a]	3040	1600	1575	1477	1417	1330	1237	1195	1118	1095	1037	1025	962	825	733	705
$-CONH_2$[b]	3050	1595	1576	1490	1425	1340	1237	1204	1125	1090	1035	1028	968	827	775[c]	700
$-CN$[d,e]	3060	1592	1567	1477	1422	1337	1240	1190	1128	1095	1038	1025	960	830	f	700
$-COOH$[b]	3080	1600	1585	1483	1420	1325	1240	1188	1125	1090	1035	1030	955	830	745	692
$-COCH_3$[a]	3060	1592	1580	1478	1425	1330	1245	1198	1120	1095	1035	1021	957	807	750	702
$-CONHNH_2$[b]	3020	1603	1578	1480	1428	1343	-	1195	1130	1100	1039	1030	953	832	765[c]	705
Intensity	m	s	m-s	w	m-s	m	w-m	m	w-m	sh-w	sh-m	s	w-m	m	s	s
g		1608- 1584	1582- 1567	1472- 1465	1428- 1414		1240- 1200		1130- 1114	1112- 1096	1039- 1035	1029- 1021				

[a] Smear. [b] Mull in Halocarbon oil from 4000-1300 cm.$^{-1}$, in Nujol from 1300-650 cm.$^{-1}$ [c] Weak, broad band. [d] Chloroform solution. [e] Spectrum courtesy of J. H. Supple. [f] Obscured by solvent. [g] Band positions reported in Ref. (30).

TABLE VI

INFRARED ABSORPTION BANDS OF 3-SUBSTITUTED PYRIDINE QUATERNARY SALTS[a]

Compound No.	3-Subst.	1-Subst.	Number and Position of Band (in cm.$^{-1}$)						
			1.	(a)	2.	3.	4.	5.	(b)
I	$CONH_2$	CH_2 $CHCH_2Br$	3080	1697	1625	1595	1515	1450	1425
II	$CONH_2$	i-Amyl Br	3040	1700	1630	1595	1518	1460	-
III	$CONH_2$	CH_3Br	3040	1687	1635	1595	1500	1445	1415
IV	$CONH_2$	$PhCH_2CH_2Br$	3030	1690	1625	1587	1507	1460	-
V	$CONH_2$	$CH_3CH_2CH_2I$	3060	1698	1640	1593	1510	1465	-
VI	$CONH_2$	CH_3I	3050	1690	1635	1593	1513	1455	1410
VII	$CONH_2$	$PhCH_2Cl$	3040	1700	1625	1590	1518	1440	1415
VIII	CN	$PhCH_2Br$[b]	3010	2260	1637	1580	1510	1450	1435
IX	$COOCH_3$	CH_3Br	3060	1725	1645	1590	1510	1455	1408
X	$COOCH_3$	Indole[c]	3050	1733	1625	1590	1505	1455	1428
XI	$COOCH_3$	$PhCH_2CH_2Br$	3070	1737	1640	1585	1500	1455	1445
XII	COPh	i-Amyl Br	3030	1670	1628	1580	1495	1452	-
XIII	COPh	Indole[c]	3080	1665	1630	1585	1500	1454	1405
XIV	COPh	CH_3Br	3050	1665	1637	1578	1510	1452	1420
XV	COPh	$PhCH_2CH_2Br$	3020	1673	1635	1580	1505	1450	1410
XVI	COPh	$PhCOCH_2Br$	3010	1675	1638	1587	1502	1455	-
XVII	COPh	$PhCH_2Cl$	3020	1676	1640	1590	1507	1452	-
XVIII	$CONHNH_2$	CH_3I	3040	1670	1635	1593	-	-	-
XIX	$CONHNH_2$	$PhCH_2Cl$	3080	1675	1662	1583	1510	1445	-
XX	$CONHNH_2$	$PhCH_2CH_2Br$	3040	1677	1640	1590	1505	1463	-
XXI	d	$PhCH_2Cl$	3060	1700	1635	1585	-	1442	-
			m	s	m-s	w-m	m	m-s	w-m

---

[a] Mull in Halocarbon oil from 4000-1300 cm.$^{-1}$, in Nujol from 1300-650 cm.$^{-1}$. [b] Courtesy of J. H. Supple. [c] β-(3-indolyl)-ethyl bromide. [d] N-(1-piperidyl)-carbamoyl hydrochloride.

TABLE VI (cont.)

Compound	Number and Position of Band (in cm.$^{-1}$)												
No.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	(c)	16.	(d)
I	1350	1195	1140	1108	950	915	878	838	775	762	720	660	685
II	1330	1210	1142	1110	955	920	895	843	775	750	725	675	653
III	1320	1212	1125	1106	952	928	897	832	775	-	725	670	-
IV	1340	1215	1140	1105	950	922	893	840	787	745	-	680	655
V	1330	1210	1137	1118	960	920	900	835	795	738	-	683	670
VI	1345	1220	1152	1120	970	940	913	845	800	753	735	678	665
VII	1355	1190	1140	1110	960	925	890	843	770	-	-	670	655
VIII	1345	1212	1147	1120	968	940	898	840	770	-	-	680	-
IX	1355	1213	1140	1108	975	922	883	828	792	753	720	665	690
X	1337	1200	1165	1122	975	933	900	850	765	745	735	665	685
XI	1325	1196	1163	1123	973	915	878	835	775	750	717	680	-
XII	1323	1203	1157	1090	950	917	885	850	790	780	720	678	685
XIII	1320	1205	1152	1110	952	932	905	835	790	757	-	675	660
XIV	1325	1215	1155	-	965	918	890	850	792	-	-	670	690
XV	1327	1212	1143	1115	975	940	895	837	790	752	-	677	690
XVI	1315	1212	1140	1105	965	940	918	855	795	-	-	685	665
XVII	1350	1212	1140	1125	972	938	900	835	788	770	720	678	688
XVIII	1335	1220	1150	1118	975	935	910	842	-	742	722	670	693
XIX	1350	1220	1153	1107	955	942	905	835	-	755	723	685	660
XX	1343	1220	1160	1105	960	940	920	852	785	765	-	678	693
XXI	1355	1207	1130	1118	960	930	898	852	783	737	-	690	670
	w-m	m-s	m	w-m	w-m	w-m	w-m	w-m	w-m	m-s	w-m	s	w-m

TABLE VII

INFRARED ABSORPTION SPECTRA OF DIHYDROPYRIDINES

Compound No.	Number and Position of Band (in cm.$^{-1}$) 1.	2.	3.	4.	5.	6.	7.	8.	9.
XXIII[a]	2810	1685	-	1645	1565	1430	-	1388	1348
XXIV[c]	2800	1683	1655	1640	1575	1428	-	1385	1350
XXV	-	1685	1665	-	1605	1430	-	-	1300[b]
XXVI[h]	2800	1682	1645	1630	1575	1415	-	-	1333[b]
XXVII	2820	1680	1655	1630	1580	1418	1405	1360	1303
XXVIII	2830	1677	1635	1663	1602	1410	1400	1383	1325
XXIX[i, j]	2840	1680	1642	-	1605	1407	-	-	1320
XXX[k]	2820	1670	1645	1610	1570	1408	-	1385	1330
XXXI	2820	1670	1640	1610	1562	1415	-	1385	1325
XXXII	2820	1672	1655	1613	1565	1415	1400	1387	1330
XXXIII	2830	1670	1650	1620[d]	1537	1420	1405	1395	1328
XXXIV	-	1672	1655	1607	1558	1425	-	1370	1325
XXXV	-	1678	1650	1613	1565	1433	1400	1370	1335
XXXVI	-	1665	-	1627	1560[d]	-	-	-	1325
XXXVII	-	1670	1655	1615	1555	1425	1410	-	1350
XXXVIII	-	1667	1645	-	1568	-	-	1370	1325[b]
XXXIX	-	1665[m]	1633[p]	1612	1562	1412	1400	1377	-
XL	-	1670	-	1625	1565	-	1406	-	1355
XLI[q]	2880	1695	1635	1660	-	-	1395	1370	1325
XLII	2855	1670	1650	1618	1570	-	1398	1370	1328
	m	m-s	sh-w	m-s	s	s	m-s	s	s

---

[a] 1-benzyl-3-carbamoyl-1,4-dihydropyridine. Ref. (10). [b] Band present in parent quaternary salt at same position but with diminished intensity. [c] 1-β-phenylethyl-3-carbamoyl-1,4-dihydropyridine. DAN, NIH-CY3789. [d] Shoulder. [e] Masked by $CHCl_3$ solvent. [g] Band present in parent quaternary salt at same position with approximately equal inten-

TABLE VII (cont.)

Compound	Number and Position of Band (in cm.$^{-1}$)								
No.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.
XXIII	1302	1240	1170	1090	1073	1027	920[b]	870	720	
XXIV	1300	1235	1192	1092	1075[d]	1030[d]	998	e	e	
XXV	1268	g	1185	1105	1070[b]	1028	920	863	738	
XXVI	1300	-	1175	1145	1080	1005	930	810	-	
XXVII	1267	-	-	1145	1093	1000	937	-	-	
XXVIII	1295	1225	1190	1143	1090	1035	990	815	-	
XXIX	1260	1190	1175	1120[b]	1075[b]	1032[b]	986	-	720	
XXX	1295[b]	1220[b]	1180[b]	1095	1078	1002	898	835	717	
XXXI	-	1215	1200[b]	1130	1115[d]	993	888	-	700	
XXXII	g	1235	1215[b]	1130	1075[b]	995	925	767	733	
XXXIII	1235	1213	1190[b]	1168	-	998	-	-	-	
XXXIV	1263	1208	-	1128	-	1030[b]	980	877	-	
XXXV	1262	1217	1190	1125	1080[b]	1025	995	875	723	
XXXVI	1245[m]	-	1195[n]	-	1075	998	-	845	750	
XXXVII	1266[m]	-	1195[n]	1120	1045	1013	-	-	-	
XXXVIII	1245	-	-	1128	1072[b]	1025	-	-	-	
XXXIX	-	-	1190[m]	1135	-	1025	-	-	-	
XL	-	-	-	1130	-	-	-	880	-	
XLI	1305	1215	-	1115	1060	1020	975	875	750	
XLII	1273 s	1238 s	1195[m] m-s	1145 m-s	1070 m-s	1030 w	980 w	- w	- s	

---

sity. [h]1-benzyl-3-hydrazido-1,4-dihydropyridine. DAN, NIH-CY3789. [i]1-benzyl-3-cyano-1,4-dihydropyridine. [j]Spectrum courtesy of J. H. Supple. [k]Spectrum courtesy of G. H. Warner. [m]Very weak band. [n]Very strong band due to dithionite. [p]Medium band. [q]2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine.

TABLE VIII

ULTRAVIOLET ABSORPTION SPECTRA OF NICOTINAMIDE QUATERNARY SALT REDUCTION PRODUCTS AND CORRESPONDING ACID REACTION PRODUCTS

Compound No.	Max mµ Reduction Method[a]						Absorbance Ratio[b]				
	I	II	III	IV	V	VI	A/B	C/D	E/A	F/A	C/A
I	355	374-360	357 272	410sh 360 272	357 265	304	.77	.18	3.5	.81	.29
II	352	370-355	358 266	425sh 360-355 266	355 266	302	1.1	.18	2.9	1.3	.29
III	355	375-355	355 268	427 355 268	355 265	303	.94	.20	2.8	1.0	.42
IV	355	370-355	358 260	420sh 364 260	350 264	304	1.1	.46	2.9	.83	.88
V	356	374-364	356 268	415sh 355 268	356 266	304	1.3	.14	2.8	1.1	.44
VI	355	370-355	355 267	425sh 370-358 266	355 258	304	.90	.12	2.5	.55	.29

[a] See Experimental. I, II, III, IV are methods d,c,b,a. V is III after 2 days, VI is I with acid. [b] See Figure 5. and discussion.

TABLE IX

ULTRAVIOLET ABSORPTION SPECTRA OF 3-SUBSTITUTED PYRIDINE QUATERNARY SALTS

Compound No.	10^{-4}M in Methanol			
	Maxima	Extinction	Minima	Extinction
I	265	4150	242	1800
	272sh	3600		
II	265	3850	245	1950
	272sh	3200		
III	266	3800	248	2050
	272sh	3300		
IX	265	4400	238	650
	271sh	3700		
X	270	8100	242	1550
	280sh	6000	287	4650
	288	4700	315	1080
	330	1140		
XIII	266	14250	240	7800
	288sh	7200	322	950
	340	1040		
XIV	264	9750	241	550
	340sh	150		
XV	264	10400	243	7250
	335sh	180		
XVI	250	17000	230	14000
	340sh	200		
XVII	263	10400	243	8100
	335sh	180		
XXII	266	7000	244	3800
	272sh	6200		
XXIIA	266		240	
XLIII	264	17300	235	10100
	295sh	11500		
XLIV	265	5950	242	3200
	272sh	4400		
XLV	268	8100	244	5000

.TABLE X

ULTRAVIOLET ABSORPTION SPECTRA OF REDUCTION MIXTURES OF 3-SUBSTITUTED PYRIDINE QUATERNARY SALTS

Compound No.	Maxima (mμ) and Extinction					
	Reduced with Sodium Borohydride		Reduced with Sodium Dithionite			
	10^{-4}M in Methanol		10^{-4}M in Water		10^{-4}M in 1M Carbonate	
I	264	6900[a]	b			
II	268	5000[a]	b			
III	263	4000	b			
IX	260	6000	c		264	8600
X	266	9000[d]	b		e	
XIII	310sh	4200[d]	f		e	
XIV	300	3200[a]	f		e	
XV	300	3000[a]	f		e	
XVI	308	3000[g]	f		e	
XVII	300	3000[a]	310	2400[h]	e	
XXII	266	10300[a]	b			
XLIII	310 240	7100[g] 19200				
XLIV	255	6250	b			

[a] Stable. [b] Results similar to IX. [c] No reduction observed under these conditions. [d] Indole maxima not shown. [e] Spectrum same as in water. [f] Results similar to XVII. [g] Decays slowly. [h] Minimum. [i] Decays rapidly. [j] Maxima show at very high conc. of salt and shift from longer to shorter value.

TABLE XI

VISIBLE ABSORPTION SPECTRA OF REDUCTION MIXTURES OF 3-SUBSTITUTED PYRIDINE QUATERNARY SALTS

Compound No.	Reduced with Sodium Borohydride Maxima (mμ) and Extinction			
	10^{-4}M in Methanol		10^{-4}M in Water	
I	364 410sh	4700[b] 3800[b]	364 440	5100[ae] 2800[c]
II	364 410sh	4500[b] 3800[a]	364 445	4850[ae] 4200[c]
III	370 415sh	4400[b] 4000[a]	364 425	4500[ae] 3200[c]
IX	425 362	4400[b] 4500[b]	440 355	2500[c] 3000[a]
X	362 425	3600[b] 3200[a]	355 425	2800[b] 1100[c]
XIII	370 475	7000[a] 5000[c]	370 490	2400[b] 1000[a]
XIV	475 366	6500[a] 5400[a]	490 366	2400[a] 2100[b]
XV	468 369	5900[a] 7600[a]	475 375	1800[a] 2400[b]
XVI	370 470	6800[a] 6500[a]	370 480	3300[b] 3000[a]
XVII	470 374	6500[a] 10200[a]	485 372	2650[a] 3800[b]
XXII	364 410sh	8400[b] 6700[a]	362 425	8200[ae] 4700[c]
XLIII	360 485	5300[a] 3400[a]	360 500	5800[b] 2500[a]
XLIV	358	6600[a]	355	4100[b]
XLV	d		d	

TABLE XI (cont.)

Compound No.	Reduced with Sodium Dithionite Maxima ($m\mu$) and Extinction					
	10^{-4}M in Water		10^{-4}M in 10^{-3} Carbonate		10^{-4}M in 1M Carbonate	
I		d		d	370sh $372\text{-}355^{fa}$	3600^b
II					$374\text{-}360^{fa}$	
III		d		d	g $375\text{-}355^{fa}$	
IX		d		d	375^f $375\text{-}355^{fa}$	
X		d		d	d	
XIII	390	12200^b	390	11800^b	410	6600^b
XIV	388	11000^b	420 388	2200^c 11500^b	410	7800^b
XV					410	6700^b
XVI	386	10500^b	388	7800^b	405	6600^b
XVII	388	13300^b	415 386	4550^c 13000^b	410	7700^b
XLIII	374	3400^a	374	4800^h	i	
XLIV		d		d	d	
XLV		d		d	440	3650^c

[a] Decays slowly. [b] Stable. [c] Decays rapidly. [d] No reduction observed under these conditions. [e] Shifts to 358 $m\mu$. [f] Maxima show at very high conc. of salt and shift from longer to shorter value. [g] End absorption only. [h] Maximum extinction masked by dithionite band. Excess dithionite had to be destroyed by shaking with air, and the 374 $m\mu$ maximum was also reduced in intensity. [i] Precipitate formed in the cell.

TABLE XII

ULTRAVIOLET ABSORPTION SPECTRA OF TRANSFORMATION PRODUCTS OF 3-BENZOYL-4-PHENYL-1,4-DIHYDROPYRIDINE(XLII)

Compound No.	Maxima (mμ) and Extinction Neutral Solution[a]		Acid Solution[b]	
XLII	360 234	10800 11400	305 236	23000 19000
XLVII[c]	360 308[e] 234[e]	3600 11400 10100	d	
XLIX	360 308	14800 24000	360 305	18400 24800
L	306 238	27200 20800	308 258 234	34000 18400 19600
LI	308 238	19900 14700	313 260 235	23600 13200 14400
LII	305[e] 227[e]	24000 10400	305 234	24000 10000
LIII	320 234	24300 8600	315 238	23600 9400
LV	322 244	8000 18600	309 234	19200 9000
LVI	298 235	24800 12800	297 234	30000 15200
LVII	300 242	17600 22000	d	
LX	302 230	15000 9000	308 233	16400 7600

---

[a] 5×10^{-5}M in methanol. [b] 3 drops of 6N hydrochloric acid added to the absorption cell. [c] Assumed M.W. of 298. [d] No change in acid. [e] Inflection.

TABLE XIII

INFRARED ABSORPTION BANDS OF TRANSFORMATION PRODUCTS OF 3-BENZOYL-4-PHENYL-1,4-DIHYDROPYRIDINE(XLII) 1700-1500 cm.$^{-1}$

Compound No.	Band Position in cm.$^{-1}$[a]						
XLII	1670m	1618m	1587s	1570s	1518s		
XLIX	1680m	1620m	1605m	1585s	1565s	1555s	1525s
L	1670s	1615m	1603m	1585s	1573s	1560s	1520s
LI	1675s	1635w	1620w	1602s	1590s	1572s	
LII	1613m	1585s	1557s	1515s			
LIII	1630s	1605m	1585s	1557s			
LV	1703s	1665s	1642s	1615s			
LVI	1687s	1627m	1603s				
LVII	1697w	1685s	1670s	1650s	1630w	1617s	
LX	1675w	1620m	1600m	1587s	1565s	1515s	

---

[a] Determined as mulls in Halocarbon oil.

TABLE XV

MAJOR INFRARED ABSORPTION BANDS OF LITHIUM ALUMINUM HYDRIDE REDUCTION PRODUCTS

Compound No.	Position of Band (in cm.$^{-1}$)																
XXXIII[a]	1665	1600	1580	1495	1455	1230	1205	1180	1155	1090	1025	970	920	840	720		695
XLII[a,c,d]	1670	1600	1583	1495	1455	1230	1200	1183	1137	1105	1025	975	925	850	760	720	695
XLIX[c,d]	1675	1600	1575	1497	1453	1230	1200			1105	1075		925	845	800		695
LI[a]	1677	1605	1590	1500	1455		1210	1155		1075	1025	970	915	837	763	730	695
LV[b]	1670	1600	1590	1500	1455		1220	1155	1125	1075	1025	960	915	840	750		695
LVI[b]	1680	1605	1585	1500	1455	1240	1215	1183	1137	1108	1055	980	915	850	755	730	695

---

[a] Mull in Halocarbon oil from 4000-1300 cm.$^{-1}$, in Nujol from 1300-650 cm.$^{-1}$ [b] Smear.
[c] Chloroform solution. [d] Composite curve.

TABLE XIV

ULTRAVIOLET AND INFRARED ABSORPTION MAXIMA OF LITHIUM ALUMINUM HYDRIDE REDUCTION PRODUCTS

Compound No.	Reduction Solvent	Ultraviolet max mμ			Infrared max cm.$^{-1}$	
XXXIII	Ether		244	225		1665
XLII	Ether	315				1670
XLII	Ether[a]	425				
XLII	THF		246			1670
XLVIII	Ether	290[b]	270[b]		3320	1670
XLIX	DMF	300				
LV	Ether				3300	1870
LVI	Ether	290[b]	245		3350	1680

[a] Observed on addition of lithium aluminum hydride directly to absorption cell. [b] Inflection.

TABLE XVI

REDUCTIONS WITH SODIUM BOROHYDRIDE

Compound No.	Temp.	Product	Yield, %
XXIII	0°	No Reaction.	
XXX	[c]	No Reaction.	
XXXIII	25°	No Reaction.	
XLII	0°, 66°	No Reaction.	
XLIX[a]	90°	No Reaction.	
LI	0°, 25°	No Reaction.[b]	
LV	66°	XLII	80
LVI	25°	LII	90
LVII	25°	XLII	50

[a] Solvent was DMF. [b] XLIX was formed on work-up. [c] Spectroscopic evidence only.

BIBLIOGRAPHY

(1) H. S. Mosher, *Heterocyclic Compounds*, edited by R. C. Elderfield, Vol. I, John Wiley and Sons, Inc., New York, 1950, p. 462.

(2) *Chemistry of Carbon Compounds*, edited by E. H. Rodd, Vol. IV A, Elvsevier, New York, 1957, p. 495.

(3) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers Inc., New York, 1956, pp. 781-806.

(4) J. J. Panouse, Bull. Soc. Chim., D53 (1953).

(5) O. Warburg, W. Christian, and A. Griese, Biochem. Z., *282*, 1197 (1935).

(6) P. Karrer *et*. *al*., Helv. Chim. Acta, 19, 1028 (1936).

(7) M. Pullman, A. San Pietro, and S. P. Colowick, J. Biol. Chem., *266*, 129 (1956).

(8) H. Kuhnis, W. Traber, and P. Karrer, Helv. Chim. Acta, *40*, 751 (1957).

(9) P. Karrer and O. Warburg, Biochem. Z., *285*, 297 (1930).

(10) D. Mauzerall and F. H. Westheimer, J. Am. Chem. Soc., *77*, 2261 (1955).

(11) G. W. Rafter and S. P. Colowick, J. Biol. Chem., *209*, 773 (1954).

(12) H. E. Dubb, M. Saunders, and J. H. Wang, J. Am. Chem. Soc., *80*, 1767 (1958).

(13) F. H. Westheimer and R. F. Hutton, Tetrahedron, *3*, 76 (1958).

(14) J. J. Panouse, Compt. rend., *233*, 260, 1200 (1951).

(15) W. Traber and P. Karrer. Helv. Chim. Acta *41*, 2066 (1958).

(16) K. Schenker and J. Druey, Helv. Chim. Acta, *42*, 1960 (1959).

(17) P. Karrer and F. J. Stare, Helv. Chim. Acta, *20*, 418 (1937).

(18) J. W. Huffman, J. Am. Chem. Soc., *80*, 5193 (1958).

(19) K. T. Potts and Sir R. Robinson, J. Chem. Soc., 2675 (1955).

(20) J. Thesing, H. Ramlock, and C. H. Willersinn, Ber., 89, 2896 (1956).

(21) W. E. McEwen, R. H. Terss, and I. W. Elliot, J. Am. Chem. Soc., 74, 3605 (1952).

(22) R. M. Burton and N. O. Kaplan, J. Biol. Chem., 211, 447 (1954).

(23) W. von Doering and W. E. McEwen, J. Am. Chem. Soc., 73, 2104 (1951).

(24) J. W. Huff, J. Biol. Chem., 167, 151 (1947).

(25) R. M. Burton and N. O. Kaplan, J. Biol Chem., 206, 283 (1954).

(26) N. O. Kaplan, S. P. Colowick, and C. C. Barnes, J. Biol Chem., 191, 461 (1951).

(27) A. G. Anderson, Jr., and G. Berkelhammer, J. Org. Chem., 23, 1109 (1958).

(28) O. Meyerhof, P. Ohlmeyer, and W. Mohle, Biochem. Z., 279, 113 (1938).

(29) M. R. Lamborg, R. M. Burton, and N. O. Kaplan, J. Am. Chem. Soc., 79, 6173 (1957).

(30) M. Y. Yarmolinsky and S. P. Colowick, Federation Proc., 13, 327 (1954).

(31) E. M. Kosower, J. Am. Chem. Soc., 28, 3497 (1956).

(32) A. San Pietro, J. Biol. Chem., 217, 579 (1955).

(33) R. S. Mulliken, J. Am. Chem. Soc., 74, 811 (1952).

(34) E. M. Kosower, J. Am. Chem. Soc., 77, 3883 (1955).

(35) E. M. Kosower, J. Am. Chem. Soc., 78, 3493 (1956).

(36) E. M. Kosower, J. Am. Chem. Soc., 78, 5838 (1956).

(37) E. M. Kosower, J. Am. Chem. Soc., 78, 5701 (1956).

(38) A. G. Anderson, Jr., and G. Berkelhammer, J. Am. Chem. Soc., 80, 992 (1958).

(39) L. J. Haynes and A. R. Todd, J. Chem. Soc., 303 (1950).

(40) A. J. Swallow, Biochem. J., 60, 443 (1955).

(41) K. Wallenfels and H. Schüly, Angew. Chem., 70, (1958).

(42) G. H. Warner, Ph. D. Thesis, Univ. of New Hampshire, (1959).

(43) M. Marti, M. Viscontini and P. Karrer, Helv. Chim. Acta, 39, 1451 (1956).

(44) M. E. Pullman and S. P. Colowick, J. Biol. Chem., 206, 121 (1954).

(45) F. Krohnke, Angew. Chem., 65, 605 (1953).

(46) R. M. Randal, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Co. Inc., New York (1949).

(47) H. M. Hershenson, *Infrared Absorption Spectra*, Academic Press, New York (1959).

(48) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd Ed., Wiley, New York (1958).

(49) A. R. Katritzky and A. R. Hands, J. Chem. Soc., 2202 (1958).

(50) A. R. Katritzky, A. R. Hands, and R. A. Jones, J. Chem. Soc., 3165 (1958).

(51) A. R. Katritzky and J. N. Gardner, J. Chem. Soc., 2198 (1958).

(52) G. L. Cook and F. M. Church, J. Phys. Chem., 61, 458 (1957).

(53) H. Shindo, Pharm. Bull. (Japan), 5, 472 (1957).

(54) L. J. Bellamy, *op. cit.*, p. 249.

(55) L. J. Bellamy, *op. cit.*, p. 220.

(56) A. R. Katritzky, J. Chem. Soc., 4162 (1958).

(57) A. R. Katritzky and J. N. Gardner, J. Chem. Soc., 2192 (1958).

(58) A. R. Katritzky and A. R. Hands, J. Chem. Soc., 2195 (1958).

(59) R. C. Fuson and F. A. Miller, J. Am. Chem. Soc., 79, 3478 (1957).

(60) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, J. Am. Chem. Soc., 71, 3337 (1949).

(61) M. S. Newman, T. Fukunaga, and T. Miwa, J. Am. Chem. Soc., 82, 873 (1960).

(62) G. Stein and G. Stiassny, Nature, 176, 734 (1955).

(63) A. E. Gillam and E. S. Stern, Electronic Absorption Spectroscopy, 2nd Ed., Edward Arnold, Ltd., London, 1957, p. 226.

(64) A. E. Gillam and E. S. Stern, op. cit., p. 96.

(65) A. E. Gillam and E. S. Stern, op. cit., p. 93.

(66) Y. Paiss and G. Stein, J. Chem. Soc., 2095 (1958).

(67) A. E. Gillam and E. S. Stern, op. cit., p. 256.

(68) N. J. Leonard and D. M. Locke, J. Am. Chem. Soc., 77, 437 (1955).

(69) A. E. Gillam and E. S. Stern, op. cit., p. 141.

(70) K. Bowden, E. A. Braude, E. R. H. Jones, and B. Weedon, J. Chem. Soc., 45 (1946).

(71) R. C. Elderfield, B. Fischer, and J. M. Lagowski, J. Org. Chem., 22, 1367 (1957).

(72) T. Hoskins and K. Shimodaira, Ann., 520, 19 (1935).

(73) B. Witkop, J. Am. Chem. Soc., 70, 5597 (1954).

(74) L. J. Bellamy, op. cit., p. 182.

(75) K. Schenker and J. Druey, Helv. Chim. Acta, 42, 2571 (1959).

(76) S. Chaykin, J. O. Meinhart, and E. G. Krebs, J. Biol. Chem., 220, 811 (1956).

(77) N. J. Leonard, R. C. Fox, and M. Oki, J. Am. Chem. Soc., 76, 5711 (1954).

BIOGRAPHICAL DATA

David Alan Nelson

Date of Birth - June 13, 1931

Place of Birth - Melrose, Massachusetts

Secondary education - Gamaliel Bradford Senior High School,
Wellesley, Massachusetts

Collegiate institutions attended:	Dates	Degree
Massachusetts Institute of Technology	1949-53	S. B.
University of Rhode Island	1953-55	M. S.