Partially Reduced Pyridines. I. The Properties of 3-Benzoyl-4-phenyl-1,4-dihydropyridine[1]

ROBERT E. LYLE AND DAVID A. NELSON[2]

Department of Chemistry, University of New Hampshire, Durham, New Hampshire

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The product of the reaction of phenylmagnesium bromide with 3-benzoylpyridine has been shown to have the structure 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) as suggested by Fuson and Miller.[3] A study of the physical and chemical properties of 3-benzoyl-4-phenyl-1,4-dihydropyridine has supported many of the postulated reactions and mechanisms of reactions of 1,4-dihydropyridines and reduced diphosphopyridine nucleotide (DPNH). Compound I has thus been shown to be a useful model for the coenzyme DPNH.

The discovery that the coenzymatic reaction of diphosphopyridine nucleotide involves the conversion of a pyridinium ring to a 1,4-dihydropyridine has led to an active interest in the mechanisms of reduction of pyridines and their salts, which includes, of course, the attack of nucleophiles on the pyridine derivatives.[4]

It is evident that these dihydropyridines contain enamine systems which should provide reactive sites at the 3- or 5-positions for the introduction of electrophilic substituents and at the 2-, 4-, or 6-positions for nucleophilic groups. During the course of such an investigation in this laboratory, Fuson and Miller[3] reported the synthesis of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) by the nucleophilic attack of the phenyl group of phenylmagnesium bromide on 3-benzoylpyridine. This 1,4-dihydropyridine system offered several structural features not available with the 1,4-dihydropyridine system which results from dithionite reduction of pyridinium salts or the Hansch synthesis. The nitrogen of I is secondary rather than tertiary, and there is a substituent on the 4-position of I but no substituent on the 5-position. I has a high molecular weight and an electron-withdrawing, unsaturated substituent which should increase the stability and crystallinity of the partially reduced pyridine rings. Thus compound I was attractive for studying the properties of 1,4-dihydropyridines.

The first problem was to ascertain unequivocally that the product of the Grignard reaction was indeed a 4-substituted 1,4-dihydropyridine.[5] The n.m.r. spectrum of the pyridine (IV) resulting from the chloranil oxidation of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) was consistent only with the structure, 3-benzoyl-4-phenylpyridine (IV). A consideration of the n.m.r. spectrum of 3-benzoylpyridine (Fig. 1) shows that the bands due to the 4-hydrogen are the two triplets found at 1.95 and 1.84 τ. An examination of the n.m.r. spectrum of 3-benzoyl-4-phenylpyridine shows no bands between 2.05 and 1.27 τ. Thus it is evident that there is no 4-hydrogen in the latter compound proving the position of the phenyl substituent. That the nitrogen of I was secondary was evident from the infrared spectrum and the acylation of I to 1-acetyl-3-benzoyl-4-

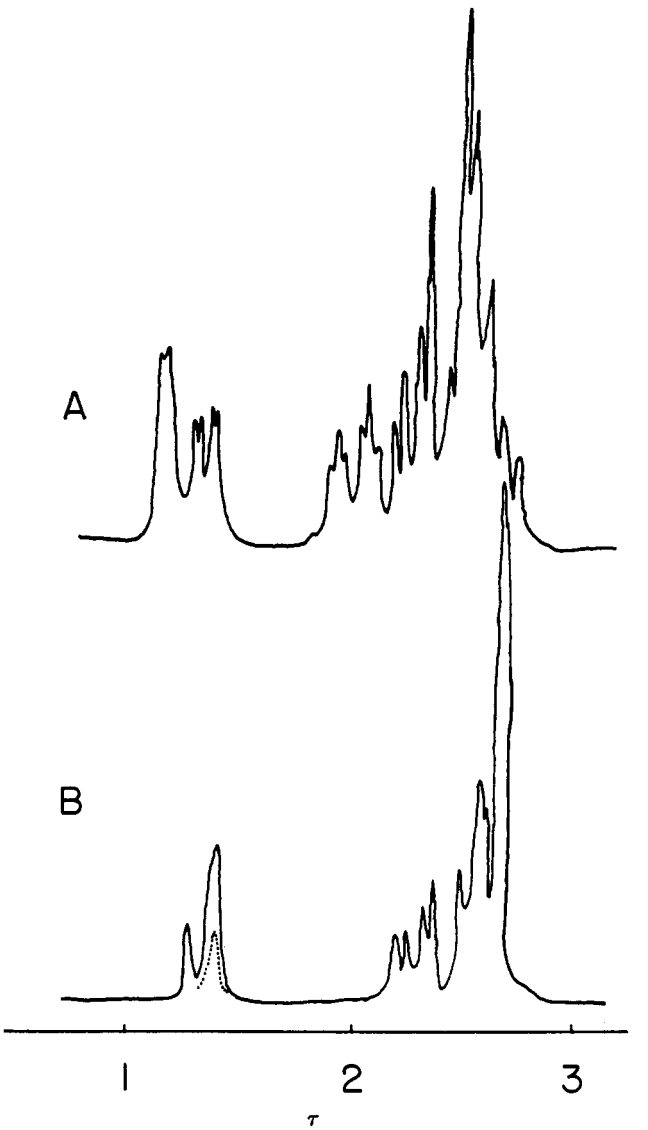

Fig. 1.—Nuclear magnetic resonance spectra of 3-benzoylpyridine (curve A) and 3-benzoyl-4-phenylpyridine (IV) (curve B).

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(2) The material for this paper was taken from the thesis of David A. Nelson presented to the graduate faculty of the University of New Hampshire in partial fulfillment of the requirements for the Ph.D. degree. Present address: Department of Chemistry, University of Wyoming, Laramie, Wyo.

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

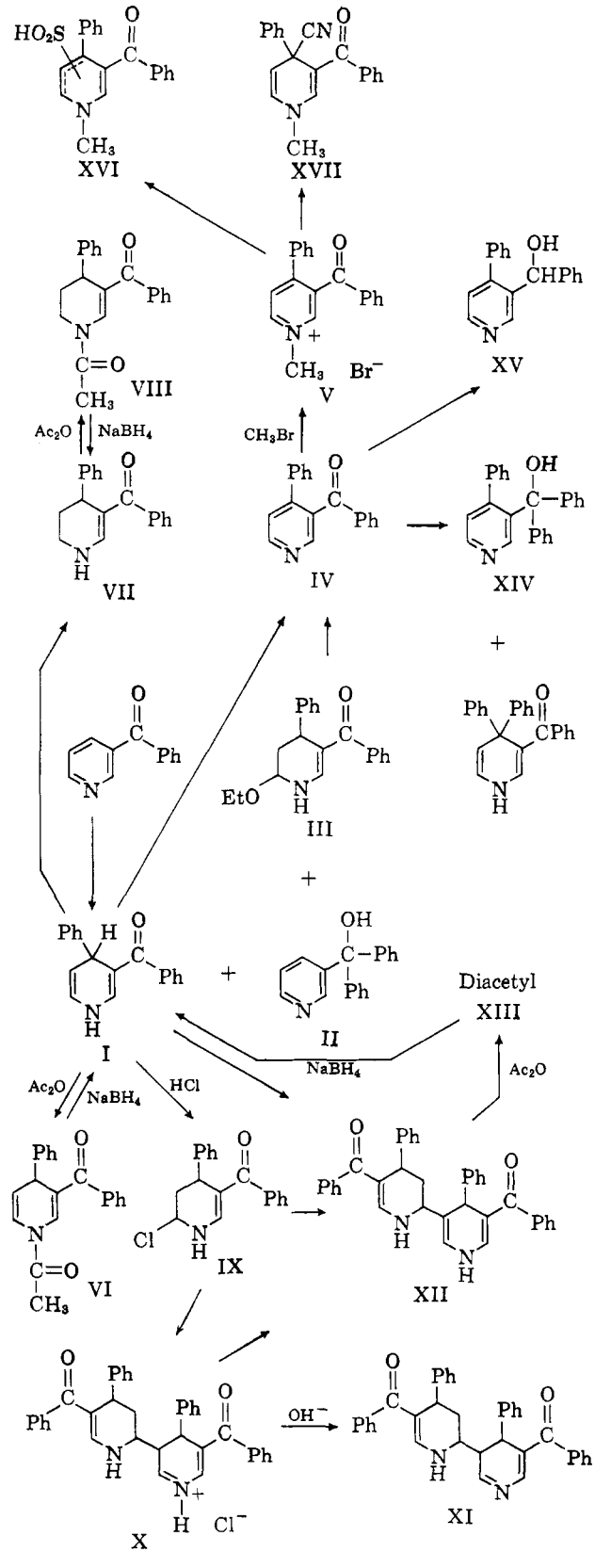
(4)(a) Series by F. H. Westheimer, see B. E. Norcross, P. E. Klinedinst, and F. H. Westheimer, *ibid.* **84**, 797 (1962), for leading references; (b) series by P. Karrer, *Helv. Chim. Acta*, **41**, 2066 (1958), for leading references; (c) series by K. Schenker and J. Druey, *ibid.*, **42**, 1960 (1959), for leading references; (d) A. G. Anderson, Jr., and G. Berkelhammer, *J. Org. Chem.*, **23**, 1109 (1958); *J. Am. Chem. Soc.*, **80**, 992 (1958); (e) series by E. M. Kosower, see E. M. Kosower, D. Hoffmann, and K. Wallenfels, *ibid.*, **84**, 2755 (1962); (f) K. Wallenfels and D. Hoffmann, *Tetrahedron Letters*, No. **4**, 154 (1962); (g) E. A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.*, 3257 (1960); (h) D. C. Dittmer and J. M. Kolyer, *J. Org. Chem.*, **27**, 56 (1962); (i) N. Sugiyama, G. Inouye, and K. Ito, *Bull. Chem. Soc. Japan*, **35**, 927 (1962).

(5) The reactions of pyridines with organolithium and Grignard reagents are not consistent in giving either 1,2- or 1,4-dihydropyridines. Compare R. A. Abramovitch, G. C. Seng, and A. D. Notation, *Can. J. Chem.*, **38**, 761 (1960) and R. A. Abramovitch and C. S. Giam, *ibid.*, **40**, 213 (1962), with R. Lukeš and J. Kuthan, *Collection Czech. Chem. Commun.*, **26**, 1422, 1845 (1961), and H. Gilman and H. A. McNinch, *J. Org. Chem.*, **27**, 1889 (1962).

phenyl-1,4-dihydropyridine (VI). A comparison of the ultraviolet absorption spectrum of I in methanol [λ_{max} 360 mμ (ϵ 1.08 × 10^4); λ_{max} 234 mμ (ϵ 1.14 × 10^4)] and acidic methanol [λ_{max} 305 mμ (ϵ 2.30 × 10^4); λ_{max} 236 mμ (ϵ 1.90 × 10^4)] with the behavior of other 3-benzoyl-1,4-dihydropyridines[6] further confirmed the 1,4-dihydro system of I. The catalytic hydrogenation of I in alcohol absorbed only one mole of hydrogen, and the product (VII) was resistent to further hydrogenation in neutral or acidic medium. The failure of VII to show absorption near 1675 cm.$^{-1}$ in the infrared spectrum was of some concern since Fuson and Miller[3] had assigned a band in this region in the spectrum of I to the carbon to oxygen double bond stretching frequency. A consideration of the infrared spectra of partially reduced 1-methyl-3-cyanopyridine[4c] and various β-amino-α,β-unsaturated ketones,[7] however, suggested that the carbon–oxygen stretching frequency of the carbonyl of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) should be at lower frequency than 1675 cm.$^{-1}$. Thus an absorption band which appears at 1618 cm.$^{-1}$ in the spectrum of I can be assigned to the carbonyl stretching vibration. A similar band appears at 1613 cm.$^{-1}$ in the spectrum of VII confirming the presence of the 2,3-double bond in VII. Thus the disappearance of the absorption band at 1675 cm.$^{-1}$ on hydrogenation of I leads to the assignment of this absorption to a stretching vibration of the 5,6-double bond of I and the assignment of the structure 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine to VII. The ultraviolet absorption spectrum of VII supports this assignment, for the spectrum of VII in methanol [λ_{max} 305 mμ (ϵ 2.40 × 10^4); λ_{max} 227 mμ (ϵ 1.04 × 10^4)] is similar to that observed on addition of acid to I, a reaction which supposedly attacks the 5,6-double bond of a 1,4-dihydropyridine.[4d] That VII retained the secondary nitrogen was confirmed by the infrared spectrum and acylation of VII to the 1-acetyl derivative VIII.

These spectral observations were useful in assigning the structure to an insoluble material which was obtained from a combination of the residues of many preparations of I. This material showed a very weak band at 1675 cm.$^{-1}$ and a medium band at 1620 cm.$^{-1}$ in the infrared spectrum, and absorption maxima at 302 mμ (1.50 × 10^4) and 230 mμ (9.0 × 10^3) in the ultraviolet spectrum. These properties suggest a 3-benzoyl-1,4,5,6-tetrahydropyridine system and, in combination with the elemental analyses, allow the assignment of structure as 3-benzoyl-6-ethoxy-4-phenyl-1,4,5,6-tetrahydropyridine (III) to the material formed by addition of the elements of ethanol to I during the recrystallization of I from ethanol. The structure was confirmed by the decomposition and dehydrogenation of III to 3-benzoyl-4-phenylpyridine (IV) on reaction with chloranil.

The nature of the reaction of acid with a 1,4-dihydropyridine has been shown to occur by an attack of a proton on the 5-position of the partially reduced ring. The resulting salt may then undergo attack by a nucleophile such as water, halide ion, etc., to give a 1,4,5,6-tetrahydropyridine. Few products have been isolated and characterized from such reactions, however.[4d] The reaction of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) with acid was investigated in an attempt further to elucidate this reaction. Possible structures for the products of these reactions and a possible mechanism for their formation can be derived by assuming a proton attack on the 5-position of I and a subsequent reaction of the resulting electrophile



(6) David A. Nelson, Ph.D. thesis, University of New Hampshire, June, 1960.

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

on a 5-position of a second molecule of I (see flow sheet).

The reaction of I with anhydrous hydrogen chloride in methanol, benzene, ether, or chloroform led to an unstable solid which on the basis of the ultraviolet absorption spectrum [λ_{max} 360 mμ (ϵ 3.6 $\times$ 10^3); λ_{max} 308 mμ (ϵ 1.14 $\times$ 10^4); λ_{inf} 234 mμ (ϵ 1.01 $\times$ 10^4)] in methanol and the infrared spectrum was assumed to be 3-benzoyl-6-chloro-4-phenyl-1,4,5,6-tetrahydropyridine (IX). The reaction of IX with water, even treatment with 95% ethanol, gave a high melting material XII. The melting point and poor solubility of XII suggested a dimeric structure. Unlike dimers proposed by Anderson and Berkelhammer[4d] XII, on the basis of analyses, did not contain additional oxygen. The ultraviolet absorption spectrum of XII showed maxima at 360 mμ (ϵ 1.50 $\times$ 10^4) and 308 mμ (ϵ 2.40 $\times$ 10^4) suggesting that XII contained both a 1,4-dihydropyridine system such as I and a 1,4,5,6-tetrahydropyridine system such as VII. The infrared spectrum of XII also showed bands characteristic of both systems. XII was converted to an acetyl derivative (XIII), the analyses of which required a diacetyl derivative if XII were dimeric. These data all suggest the structure of XII to be 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-1,4-dihydropyridine.

The recrystallization of the unstable compound IX from dry acetone led to a new material X which could be converted to the dimer XII on reaction with water. The infrared spectrum of X, however, clearly showed it to be an ammonium salt, for there was extensive absorption in the 2500-cm.$^{-1}$ region. More definitive, however, were two bands at 2080 and 1950 cm.$^{-1}$ which have been assigned by Witkop[8] to the H—$\overset{+}{N}$= C of proton salts of pyridine or other H—$\overset{+}{N}$=C systems. Since aromatization of IX was unlikely under these conditions and since X gave an ultraviolet absorption spectrum characteristic of a 3-benzoyl-1,4,5,6-tetrahydropyridine system with reduced intensity, the compound was assigned a dimeric structure (X) with only one 1,4,5,6-tetrahydropyridine system but containing a C=$\overset{+}{N}$—H group.

The neutralization of a solution of X in nonaqueous solution gave a dimer (XI) isomeric with XII. This new dimer showed maximal ultraviolet absorption only at 306 mμ (ϵ 2.72 $\times$ 10^4) and 238 mμ (ϵ 2.08 $\times$ 10^4) indicative of a 3-benzoyl-1,4,5,6-tetrahydropyridine system. The infrared absorption spectrum showed a band at 1675 cm.$^{-1}$, but the absence of an absorption maximum at 360 mμ eliminated the possibility of a 1,4-dihydropyridine system. Thus it would appear that XI contains one benzoyl group not conjugated with the free pair of electrons on the nitrogen. These conditions are met by assigning the structure 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-4,5-dihydropyridine to XI. A similar series of reactions was suggested by Schenker and Druey[4c] to explain the changes in the ultraviolet absorption spectrum of 1-methyl-3-cyano-1,4-dihydropyridine on addition of acid; however, they were unable to isolate or characterize any product from the reaction.[9]

The spectral properties of I described above as well as the failure of the carbonyl of I to undergo reaction with sodium borohydride, phenylmagnesium bromide, phenyllithium, and lithium aluminum hydride all suggest that the resonance form Ib contributes heavily to the structure of I. Similarly the properties of VII also suggest a high electron density on the carbonyl oxygen and nearly single bond character of the carbonyl C—O bond. The N-acetyl group of VI and VIII, the acetyl derivatives of I and VII, would be expected to interfere with the conjugation of the nitrogen free pair of electrons and the carbonyl group by forming a crossed conjugated system. Thus the sodium borohydride reduction of these compounds was investigated. A very remarkable reaction occurred. In each case the acetyl group was reductively removed to form the deacetyl or parent compound. For comparison the diacetyl (XIII) derivative of XII was treated with sodium borohydride, and 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) was formed in 50% yield. These reactions appear to be the first examples of reductions of amides by sodium borohydride, and further confirm the unusual conjugation which exists between the nitrogen free pair of electrons and the carbonyl group, for instead of the acetyl group increasing the electrophilicity of the carbonyl carbon and allowing reduction of the ketone, the β-amino-α,β-unsaturated carbonyl system increased the electrophilicity of the amide carbonyl and thus allowed reduction to occur there. The nature of the amide grouping might be compared with that found with bridgehead lactams. Other properties which show these systems to be comparable are under investigation.

To eliminate the possibility that the 4-phenyl substituent was inducing an unusual reactivity on the 3-benzoyl function due to steric effects, the carbonyl properties of 3-benzoyl-4-phenylpyridine (IV) were investigated. Lithium aluminum hydride or sodium borohydride caused the reduction of the carbonyl group to produce 4-phenyl-3-pyridylphenylcarbinol (XV) with no apparent difficulty. The reaction of IV with phenylmagnesium bromide gave some material which appeared to result from an attack of the Grignard reagent on the pyridine nucleus; however, the only product characterized [4-phenyl-3-pyridyldiphenylcarbinol (XIV)] was formed by addition to the carbonyl. Thus the unusual properties of the carbonyl of I were caused by its conjugation with the dihydropyridine system and not some steric effect of the 4-phenyl substituent.

Attempts to cause the conversion of the quaternary salt of 3-benzoyl-4-phenylpyridine (V) to a dihydropyridine system by nucleophilic attack were largely unsuccessful. The reaction of V with sodium dithionite produced oils which could not be crystallized or purified, but the impure materials gave infrared and ultraviolet spectra characteristic of the 1,4-dihydropyridine system of I. From one reaction a crude solid was isolated. This material contained sulfur and appeared to be a derivative of the sulfinic acid XVI. An unstable solid was isolated from the reaction of V with an excess of sodium cyanide. The cyanide addition compound appeared to be a 1,4-

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

(9) The advantage of using a 1-unsubstituted 1,4-dihydropyridine, such as I, for the investigation of this reaction with acid is evident since isolable products were obtained by loss of a proton rather than requiring the addition of a nucleophile.

dihydropyridine, but its instability prevented the complete characterization. The elemental analyses of both of the latter compounds indicated an atom of oxygen in excess of the expected formulas XVI and XVII, respectively.

Experimental

3-Benzoyl-4-phenyl-1,4-dihydropyridine (I).—The title compound was prepared following the procedure of Fuson and Miller[3] with only slight modification. The hydrolysis of the Grignard reaction caused the precipitation of the product which was removed by filtration. Only a small amount of I mixed with most of the 3-pyridyldiphenylcarbinol (II) was obtained from the ether solution. Recrystallization of the dihydropyridine I from ethanol gave I, m.p. 148–152°, in yields comparable to those reported previously.

Anal. Calcd. for $C_{18}H_{14}NO$: C, 82.73; H, 5.79. Found: C, 82.94; H, 6.07.

A collection of the residues from a number of isolations of I and II was treated with ethanol, and a portion of the material was found to be insoluble. The material was recrystallized from dimethylformamide to give a small yield of 3-benzoyl-4-phenyl-6-ethoxy-1,4,5,6-tetrahydropyridine (III), 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.

The oxidation of 0.5 g. of III with 0.5 g. of chloranil in 50 ml. of benzene following the procedure of Fuson and Miller[3] gave a quantitative yield of 3-benzoyl-4-phenylpyridine (IV), m.p. 87–88°. The infrared spectrum of this material was identical with that of an authentic sample of IV prepared from I.

3-Benzoyl-4-phenylpyridine (IV).—The preparation of IV from I followed the method of Fuson and Miller[3] to give IV (64%), m.p. 87–88° (lit., m.p. 89.5–90.0°). The methobromide (V) of IV was prepared by allowing a solution of 7.5 g. of IV and 5.0 g. of methyl bromide in 50 ml. of methanol to stand for 24 hr. at room temperature. Removal of the solvent by distillation under reduced pressure gave a quantitative yield of V, m.p. 233–235°.

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

1-Acetyl-3-benzoyl-4-phenyl-1,4-dihydropyridine (VI).—A solution of 1.0 g. of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) in 25 ml. of anhydrous pyridine was treated with 5.0 ml. of acetic anhydride. The mixture was heated on a steam bath for 4 hr. and poured into 200 ml. of water. The solid which separated was removed by filtration and recrystallized from ethanol–chloroform to give a quantitative yield of VI, m.p. 182–183°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65. Found: C, 79.37; H, 5.79.

3-Benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VII).—A 5.0-g. sample of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) was hydrogenated over 0.1 g. of platinum oxide in 100 ml. of ethanol. The catalyst was removed by filtration, and the filtrate deposited a quantitative yield of 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VII), m.p. 180–181°.

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.

1-Acetyl-3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VIII).—Following the procedure for the preparation of VI, 3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VII) was converted in quantitative yield to the 1-acetyl derivative (VIII), 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.

The Reactions of 3-Benzoyl-4-phenyl-1,4-dihydropyridine (I) **with Hydrogen Chloride.**—The reaction of 1.0 g. of I with hydrogen chloride in benzene led to the precipitation of an impure material which could not be purified without transformation. This impure material was assigned the structure 3-benzoyl-6-chloro-4-phenyl-1,4,5,6-tetrahydropyridine (IX) although correct analytical data were not obtained. The recrystallization of IX from acetone caused the quantitative conversion to 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-4,5-dihydropyridine hydrochloride (X), m.p. 168–172°.

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

The reaction of IX or X with base in alcoholic solution and dilution of the resulting mixture with water led to the quantitative precipitation of 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-4,5-dihydropyridine (XI). Recrystallization of the solid from ethanol gave XI, 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.

A mixture of 5.0 g. of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) with 10 ml. of 6 *N* hydrochloric acid in 50 ml. of ethanol was heated on a steam bath for several minutes and poured into 200 ml. of water to give a quantitative yield of 3-benzoyl-4-phenyl-5-[6-(3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-1,4-dihydropyridine (XII). Recrystallization of the solid from dimethyl formamide gave purified XII, 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.

XII was also formed in quantitative yield on diluting a methanolic solution of 3-benzoyl-6-chloro-4-phenyl-1,4,5,6-tetrahydropyridine (IX) with water.

The diacetyl derivative (XIII) of XII was prepared by the procedure used for the syntheses of VI and VIII. Recrystallization of the solid from ethanol–chloroform gave purified XIII, m.p. 255–257°.

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

The Reduction of the N-Acetyl Derivatives VI, VIII, and XIII.—A 0.5- to 1.0-g. sample of the acetyl derivative was dissolved in methanol, and 1–2 g. of sodium borohydride was added. When the reaction was complete, the solution was poured into water, and the solid which precipitated was collected by filtration. In each case the yield is indicated after the product. Each product was identified by melting point, mixture melting point, and infrared spectrum. 1-Acetyl-3-benzoyl-4-phenyl-1,4-dihydropyridine (VI) and 1-acetyl-3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridine (VIII) gave the parent pyridines I (80%) and VII (90%), respectively. 1-Acetyl-3-benzoyl-4-phenyl-5-[6-(1-acetyl-3-benzoyl-4-phenyl-1,4,5,6-tetrahydropyridyl)]-1,4-dihydropyridine (XIII), however, was converted to 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) (50%).

The Reactions of 3-Benzoyl-4-phenylpyridine (IV) **and Its Methobromide** (V). (a) **The Reaction of IV with Phenylmagnesium Bromide.**—Following the procedure for the preparation of 3-benzoyl-4-phenyl-1,4-dihydropyridine (I) from 3-benzoylpyridine,[3] 5.0 g. of 3-benzoyl-4-phenylpyridine (IV) was treated with an ethereal solution of 0.4 mole of phenylmagnesium bromide. The reaction mixture was hydrolyzed with ammonium chloride. A yellow precipitate formed during the hydrolysis; however, this material could not be purified. The infrared spectrum of this impure solid showed many bands charaacteristic of a 1,4-dihydropyridine.[5] The ethereal solution was concentrated and the residue was extracted with petroleum ether. The material which was insoluble was dissolved in ether, and a white solid precipitated from the ether solution. Recrystallization of the solid from ether gave a small yield of 3-(4-phenylpyridyl)diphenylcarbinol (XIV), m.p. 131–132°.

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

(b) **The Reaction of IV with Lithium Aluminum Hydride.**—The reaction of 1.0 g. of 3-benzoyl-4-phenylpyridine (IV) with an excess of lithium aluminum hydride in 50 ml. of anhydrous ether gave, after the usual work-up, a quantitative yield of 3-(4-phenylpyridyl)phenylcarbinol (XV), 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.

(c) **The Reaction of IV with Sodium Borohydride.**—The reduction of 1.0 g. of IV with 1.0 g. of sodium borohydride in 50 ml. of methanol gave a quantitative yield of XV, m.p. 147.5–148.0°. The infrared spectrum of this product was identical with that of the reduction product from lithium aluminum hydride.

(d) **The Reaction of the Methobromide V with Sodium Dithionite.**—A solution of 3.5 g. of 3-benzoyl-4-phenylpyridine methobromide (V) in 100 ml. of boiled water was treated with 4.6 g. of sodium bicarbonate and 7.0 g. of sodium dithionite under nitrogen. The red oil which precipitated during the reaction did not crystallize. Acidification of the reaction mixture and addition of a little ethanol caused the dissolution of the oil. The solution was neutralized with sodium bicarbonate, and the oil which separated was taken up in chloroform. The chloroform solution was divided into two parts. The solvent was removed from one portion and extraction of the residue with various organic solvents gave a small amount of the methobromide V as residue. The second portion of chloroform was saturated with hydrogen chlo-

ride, the solvent was removed by distillation under reduced pressure, and the residue was crystallized by trituration with petroleum ether. Recrystallization of the solid from isopropyl alcohol–ether gave a small yield of solid, m.p. 146–148°. The solid gave a negative Beilstein test for halogen and positive sodium fusion tests for nitrogen and sulfur. The compound appeared to be a 3-benzoyl-1-methyl-4-phenyldihydropyridinesulfinic acid (XVI), plus oxygen or water.

Anal. Calcd. for $C_{18}H_{16}NO_4S$: C, 64.00; H, 5.10. Found: C, 64.58; H, 5.21.

(e) **The Reaction of the Methobromide V with Sodium Cyanide.**—A 1.0-g. sample of V was dissolved in 50 ml. of water and 0.5 g. of sodium cyanide was added. A small amount of yellow precipitate formed. The addition of an additional 3.0 g. of sodium cyanide caused further precipitation. The solid was removed by filtration and washed with water. During this process the solid turned brown. Recrystallization of the solid was accompanied by a darkening in color. Thus analyses were determined on crude material, m.p. 75–80°. The analytical data suggest that this compound is a 3-benzoyl-1-methyl-4-phenylcyano-1,4-dihydropyridine (XVII), plus oxygen or water.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 76.00; H, 5.07. Found: C, 75.25; H, 5.10.

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The Synthesis of L-Valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline[1]

JANAKIRAMAN RAMACHANDRAN AND CHOH HAO LI

Hormone Research Laboratory, University of California, Berkeley, California

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The peptide sequence, L-valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline, which occurs in adrenocorticotropins, has been synthesized by the reaction of carbobenzoxy-L-valyl-N$^{\epsilon}$-tosyl-L-lysine azide with L-valyl-L-tyrosyl-L-proline benzyl ester, followed by hydrogenation and treatment with sodium in liquid ammonia. The protected pentapeptide was obtained in crystalline form. A side reaction was observed when carbobenzoxy-L-valine *p*-nitrophenyl ester was coupled with L-tyrosine methyl ester hydrochloride in the presence of *excess* triethylamine. The by-product was identified as O-(carbobenzoxy-L-valyl-)-L-tyrosine methyl ester. The disubstituted by-product, N,O-di(carbobenzoxy-L-valyl)-L-tyrosine methyl ester, was also isolated from this reaction.

The pentapeptide L-valyl-L-lysyl-L-valyl-L-tyrosyl-L-proline (VI) occurs at position 20–24 in the amino acid sequence[2–4] of adrenocorticotropins (ACTH) isolated from pituitary glands of various species. It is generally assumed[2,5] that the adrenocorticotropic activity resides in the sequence consisting of the first twenty-four or twenty-eight amino acid residues. Indeed, we have recently reported the synthesis[6] of a nonadecapeptide corresponding to the first nineteen amino acid residues of adrenocorticotropins and have shown that it possesses approximately 50% of the potency of the natural product. Subsequently, other investigators[7–9] have described briefly the synthesis of ACTH analogues consisting of 19, 20, 23, and 24 amino acid residues. In the course of the synthesis of the tetracosapeptide, we have obtained peptide VI and crystalline L-valyl-N$^{\epsilon}$-tosyl-L-lysyl-L-valyl-L-tyrosyl-L-proline (V).

The scheme for the synthesis of VI is given in Fig. 1. The benzyl group was employed for the protection of the C-terminus in order to avoid saponification at the end of the synthesis. The protected dipeptide (I) carbobenzoxy-L-valyl-L-tyrosine methyl ester[10,11] was obtained in good yield by coupling carbobenzoxy-L-valine and tyrosine methyl ester *via* the dicyclohexylcarbodiimide (DCCI) procedure.[12] Carbobenzoxy-L-valyl-L-tyrosyl-L-proline benzyl ester (II)[14] was prepared in 75% yield by the reaction of carbobenzoxy-L-valyl-L-tyrosine azide with L-proline benzyl ester. The use of dicyclohexylcarbodiimide with carbobenzoxy-L-valyl-L-tyrosine was avoided because of the reported racemization with this combination in an analogous synthesis.[13] A sample of the protected tripeptide was hydrogenated exhaustively in the presence of palladium. The free tripeptide L-valyl-L-tyrosyl-L-proline was isolated and crystallized from methanol–water.

Carbobenzoxy-L-valyl-N$^{\epsilon}$-tosyl-L-lysine methyl ester[16] was prepared by the reaction of carbobenzoxy-L-

(1) Taken from a portion of the Ph.D. thesis of J. Ramachandran at the University of California, 1962.

(2) K. S. Howard, R. G. Shepherd, E. A. Eigner, D. S. Davies, and P. H. Bell, *J. Am. Chem. Soc.*, **77**, 3419 (1955); R. G. Shepherd, S. D. Wilson, K. S. Howard, P. H. Bell, D. S. Davies, S. B. Davis, E. A. Eigner, and N. E. Shakespeare, *ibid.*, **78**, 5067 (1956).

(3) C. H. Li, I. Geschwind, R. D. Cole, I. D. Raacke, J. I. Harris, and J. S. Dixon, *Nature*, **176**, 687 (1955).

(4) C. H. Li, J. S. Dixon, and D. Chung, *J. Am. Chem. Soc.*, **80**, 2587 (1958); *Biochem. Biophys. Acta*, **46**, 324 (1961).

(5) C. H. Li, *Advan. Protein Chem.*, **11**, 101 (1956).

(6) C. H. Li, J. Meienhofer, E. Schnabel, D. Chung, T. Lo, and J. Ramachandran, *J. Am. Chem. Soc.*, **82**, 5760 (1960); **83**, 4449 (1961).

(7) R. Schwyzer, W. Rittel, H. Kappeler, and B. Iselin, *Angew. Chem.*, **23**, 915 (1960); H. Kappeler and R. Schwyzer, *Helv. Chim. Acta*, **44**, 1136 (1961).

(8) K. Hofmann, H. Yajima, N. Yanaihara, T. Y. Liu, and S. Lande, *J. Am. Chem. Soc.*, **83**, 487 (1961).

(9) K. Hofmann, T. Y. Liu, H. Yajima, N. Yanaihara, C. Yanaihara, and J. L. Humes, *ibid.*, **84**, 1054 (1962).

(10) W. Rittel, B. Iselin, H. Kappeler, B. Riniker, and R. Schwyzer, *Helv. Chim. Acta*, **40**, 614 (1957).

(11) H. Schwarz, F. M. Bumpus, and I. H. Page, *J. Am. Chem. Soc.*, **79**, 5697 (1957).

(12) J. C. Sheehan and G. P. Hess, *ibid.*, **77**, 1067 (1955).

(13) B. Riniker and R. Schwyzer, *Helv. Chim. Acta*, **44**, 658, 674, 677, 685 (1961).

(14) Pannemann,[15] *et al.*, reported the synthesis of II by the use of ethoxyethane; carbobenzoxy-L-valyl-L-tyrosine reacted with L-proline benzyl ester hydrochloride by refluxing with ethoxyethene in moist ethyl acetate for 2.5 hr. The protected tripeptide was obtained in 61% yield.

(15) H. J. Pannemann, A. F. Marx, and J. F. Arens, *Rec. trav. chim.*, **78**, 487 (1959).

(16) R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **41**, 1582 (1958).