[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

A Study of the Primary Acid Reaction on Model Compounds of Reduced Diphosphopyridine Nucleotide[1,2]

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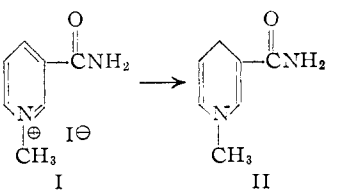
3-Acetyl-, 3-carbomethoxy- and 3-N-ethyl-N-phenylcarbamoyl-1-benzyl-1,4-dihydropyridine have been prepared as model compounds of reduced diphosphopyridine nucleotide. The behavior of these compounds and also of 1-propyl- and 1-benzyl-1,4-dihydronicotinamide in dilute acid has been investigated. From the observed changes in absorption spectra, kinetic studies and the characterization of pure crystalline products from the 3-acetyl derivative, the nature of the primary reaction in acid is postulated and structures for the products are assigned.

I. Introduction

The participation of diphosphopyridine nucleotide (DPN)[3] and triphosphopyridine nucleotide (TPN) in oxidation–reduction reactions in living cells is well established. Examples are the processes of yeast-catalyzed fermentation, glycolysis in muscle, and the oxidation of non-phosphorylated intermediates in the tricarboxylic acid cycle. The latter is the source of a considerable amount of the energy of muscular action. Accordingly, there has been an ever increasing interest in the specific functions of these substances including efforts to interpret the chemical changes involved in terms of molecular structural formulas.

The present investigation was directed primarily toward a more complete understanding of the so-called primary acid reaction of DPNH through a study of this process on model compounds. The instability of DPNH and TPNH in acid has been known for some time,[4–6] and is characterized by the disappearance of fluorescence, the loss of absorption at 340 mμ, and the appearance of a new band at 290–300 mμ. The latter is unstable and, in a secondary reaction, diminishes in intensity at a rate dependent upon the acid concentration. It has also been discovered[7] that the enzyme glyceraldehyde 3-phosphate dehydrogenase in the presence of inorganic phosphate catalyzes a chemical change of DPNH which is characterized by a spectral alteration almost identical to that which accompanies the primary reaction in acid.[8] While the acid and enzymatically produced products are not identical (the former is not reconvertible to DPNH by the enzyme system) they must be very similar in structure. Thus knowledge of the nature of the acid reaction and products is of importance in this connection as well as from the standpoint of the chemistry of hydropyridine compounds.

That the nicotinamide portion of the molecule was the site of the oxidation–reduction in pyridine nucleotides was shown[9] over twenty years ago and this work also initiated the use of model substances for the study of the reactions concerned. Thus the finding[10,11] that 1-methyl-3-carbamoylpyridinium iodide (I) was reduced with dithionite to an acid-labile, easily oxidized dihydro compound having an absorption maximum at 360 mμ contributed to the assignment of the position of linkage of the nicotinamide portion in DPN to the rest of the molecule. The structure of the product from dithionite reduction of I (or DPN) was in doubt until recently, but convincing evidence now has been accumulated that the 1,4-dihydroformulation (II) is correct.[12–19] This work also served to reinforce the validity of 1-alkyl derivatives of nicotinamide as model compounds for the study of the reactions of the nucleotides.



There have been few speculations in the literature concerning the transformations involved in the reactions of the dihydro compounds with acid or the products formed. Karrer[20,21] suggested that the product(s) arose from the addition of the positive and negative components of the acid across

(1) From the Ph.D. Thesis of Gerald Berkelhammer.

(2) Supported in part by a research grant (No. RG-3844) from the National Institutes of Health, Public Health Service.

(3) The following abbreviations will be used: DPN (also called Coenzyme I), DPNH (reduced DPN), TPN (triphosphopyridine nucleotide or Coenzyme II), TPNH (reduced TPN) and DPNH-X (product formed from DPNH in presence of glyceraldehyde 3-phosphate dehydrogenase).

(4) O. Warburg and W. Christian, *Biochem. Z.*, **274**, 112 (1934).

(5) H. von Euler, F. Schlenk, H. Heiwinkel and B. Hogberg, *Z. physiol. Chem.*, **256**, 208 (1938).

(6) E. Haas, *Biochem. Z.*, **288**, 123 (1936).

(7) G. W. Rafter, S. Chaykin and E. G. Krebs, *J. Biol. Chem.*, **208**, 799 (1953).

(8) The possible role of the product of this process (DPNH-X) in the conversion of energy of metabolites into energy useful in life processes as well as the enzymatic reconversion of DPNH-X to DPNH has been discussed elsewhere: S. Chaykin, Doctoral Thesis, University of Washington, 1954; J. O. Meinhart, S. Chaykin and E. G. Krebs, *J. Biol. Chem.*, **220**, 821 (1956).

(9) O. Warburg, W. Christian and A. Griese, *Biochem. Z.*, **282**, 157 (1935).

(10) P. Karrer and O. Warburg, *ibid.*, **285**, 297 (1936).

(11) P. Karrer, G. Schwarzenbach, F. Benz and U. Solmssen, *Helv. Chim. Acta*, **19**, 811 (1936).

(12) P. Karrer, B. Ringier, J. Buchi, H. Fritzsche and U. Solmssen, *ibid.*, **20**, 55 (1937).

(13) O. Mumm and J. Diederichsen, *Ann.*, **538**, 195 (1939).

(14) D. Craig, L. Schaafgen and W. P. Tyler, THIS JOURNAL, **70**, 1624 (1948).

(15) D. Craig, A. K. Kuder and J. Efroymson, *ibid.*, **72**, 5236 (1950).

(16) M. E. Pullman, A. San Pietro and S. P. Colowick, *J. Biol. Chem.*, **206**, 129 (1954).

(17) G. W. Rafter and S. P. Colowick, *ibid.*, **209**, 773 (1954).

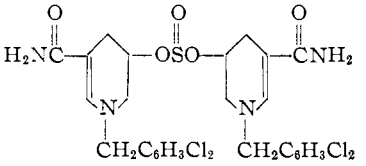
(18) D. Mauzerall and F. H. Westheimer, THIS JOURNAL, **77**, 2261 (1955).

(19) F. A. Loewus, B. Vennesland and D. L. Harris, *ibid.*, **77**, 3391 (1955).

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

(21) P. Karrer, F. W. Kahnt, R. Epstein, W. Jaffe and T. Ishil, *ibid.*, **21**, 223 (1938).

one of the double bonds in the ring. Very recently there has been a further communication on this subject[22] which described the isolation of a crystalline solid from the action of sulfurous acid on a dichlorobenzyldihydronicotinamide. The structure of the compound was shown as III or the analogous one with the sulfite linkages at the 6-positions on the rings. The isolation of this product is in keeping with the known stabilization of the absorption maximum at *ca.* 290 mμ (resulting from the primary acid reaction) by bisulfite[6,23] and cysteine[23]



III

and with the results of Chaykin, *et al.*,[24] on the hydrogenation of DPNH-X and the primary acid reaction product from DPN. The behavior of the type noted with sulfurous acid is not general, however, as it has been found[8,23] that the reaction of DPNH with P^{32}-labeled phosphoric acid gave a product which exhibited no radioactivity. To our knowledge no pure products incorporating the negative portion of the acid have been isolated with acids (*e.g.*, hydrochloric, sulfuric, etc.) that afford only weakly nucleophilic anions

II. Preparation of Model Compounds

Karrer and co-workers[12,20,21,25] have described the preparation of and action of acid on several 1-alkyldihydronicotinamides, but the use of groups other than carboxamido in the 3-position has not been reported. With the view toward the use of different groups to provide one measure of the limits of the acid reaction and, also, to perhaps aid in the attainment of crystalline products amenable to characterization, several new model compounds were prepared. The benzyl group was chosen as the alkyl substituent after examination of the properties of the compounds made by Karrer; and the acetyl, carbomethoxy and N-ethyl-N-phenylcarbamoyl groups were selected as variations for the 3-position.

The 3-acetylpyridine needed was obtained commercially or, for the most part, prepared in 52% over-all yield from nicotinic acid by a Claisen condensation between ethyl nicotinate and ethyl acetate with subsequent hydrolysis of the intermediate ethyl nicotinylacetate. Methyl nicotinate was obtained in 64% yield from nicotinic acid. N-Ethylnicotinanilide was prepared readily from nicotinic acid and N-ethylaniline in 71% yield. The benzylochlorides of these substituted pyridines were prepared in the usual manner and, with the exception of the derivative from 3-acetylpyridine which was crystalline and easily purified, were hygroscopic oils.

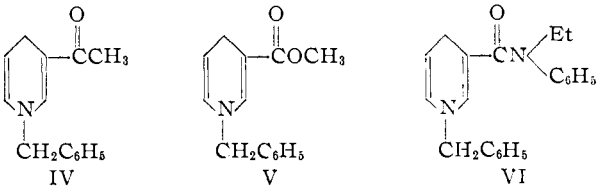
(22) K. Wallenfels and H. Schülz, *Biochem. Z.*, **329**, 75 (1957). This paper was published after our work had been completed.

(23) G. W. Rafter, Doctoral Thesis, University of Washington, 1953.

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

(25) P. Karrer, G. Schwarzenbach and G. Utzinger, *Helv. Chim. Acta*, **20**, 72 (1937).

Reduction of the quaternary pyridinium salts by sodium dithionite in mildly alkaline solution gave yellow solids which were formulated as 1-benzyl-3-acetyl-1,4-dihydropyridine (IV), methyl 1-benzyl-1,4-dihydronicotinate (V) and N-ethyl-1-benzyl-1,4-dihydronicotinanilide (VI). Each reduced alcoholic silver nitrate in the cold and displayed an absorption maximum between 350 and 375 mμ.



IV V VI

III. Changes in Ultraviolet Absorption Spectra

The three dihydro compounds (IV, V and VI) along with the previously known 1-propyl- (VII) and 1-benzyldihydronicotinamides (VIII) were subjected to the action of dilute hydrochloric acid and the changes in ultraviolet absorption observed. From the data given in Table I, it seems probable that each of the compounds was converted by acid to initial products which are probably similar since they possess maxima in the same region. Also, the ratio of the intensity of the acid product absorption to that of the parent dihydropyridine was of the same order of magnitude for each pair. A final similarity was found in the circumstance that the absorption peaks produced were all unstable in acid solution.[26] It appears, therefore, that groups other than carboxamide which have a carbonyl attached to the ring can suffice in the primary acid reaction.

TABLE I

ACID-INDUCED CHANGES IN THE ULTRAVIOLET SPECTRA OF MODEL COMPOUNDS OF DPNH IN 50% ETHANOL

Dihydro compound	λ_{max}, mμ Neutral soln.	Acidic soln.[a]	λ_{max} (neut.) − λ_{max} (acid), mμ	$\frac{\epsilon_{max} \text{ acid soln.}}{\epsilon_{max} \text{ neut. soln.}}$
IV	374	307	67	2.76
V	355	289	66	2.10[b]
VI	363	306	57	2.45
VII	357	294	63	2.62
VIII	354	290	64	2.82

[a] Approximately 0.01 ml. of 6 or 12 *N* HCl added to solution of dihydro compound in a 1-cm. Cary cell. Spectrum traced when acid product band fully developed. [b] Minimum value. Possibly should be greater owing to rapid secondary acid reaction undergone by this compound.

IV. Kinetic Studies

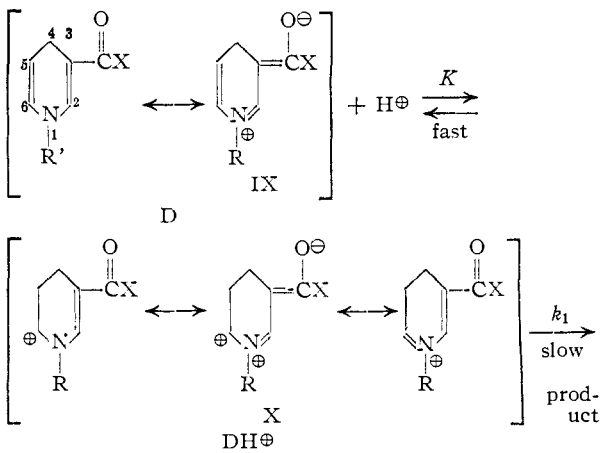
The relative simplicity of the structures of the model compounds limited the possible courses for the reaction with acid which would be consistent with the spectral data and it was thought that quantitative rate studies would aid in discerning the correct one. The rates of the primary acid reactions of the five compounds were measured spectrophotometrically at two different acid concentrations. For four of the five, comparable rate

(26) The rates of the secondary acid reaction varied. The peak from the acetyl compound decreased slowly and that from the carbomethoxy compound very rapidly, with the others intermediate between these two.

constants were calculated from both the diminishing absorption of the dihydro compound and the increasing absorption of the acid product. The exception, methyl 1-benzyldihydronicotinate (V), was found to undergo a secondary acid reaction at a rate sufficiently rapid to prevent measurement at 290 mμ. The reaction was successfully followed at 355 mμ.

Pseudo first-order rate constants were calculated from plots of log $(D_\infty - D)$ or log $(D - D_\infty)$ *versus* time and are listed in Table II. An average of twelve points were used in each plot and all of the points were on the straight line, within the limits of error and precision of the method. With the more slowly reacting 1-benzyl-3-acetyl (IV) and 1-benzyl-3-carbomethoxy (V) compounds the region from 10 to 90% of reaction was covered. The 1-benzyl-3-carbamoyl compound VI reacted somewhat faster and was observed over the region of 30 to 90%. For the rapidly reacting 1-propyl-3-carbamoyl (VII) and 1-benzyl-3-(N-ethyl-N-phenyl)-carbamoyl (VIII) derivatives the region of 50 to 90% of reaction was measured. The solvent (49% alcohol) was chosen to achieve the necessary solubility for all five compounds. One group of runs in water is tabulated for VI and shows a more rapid rate in this solvent. The data show a doubling in rate with a corresponding increase in acid concentration except for the carbomethoxy derivative.

The kinetic results are consistent with a mechanism involving an initial rapid protonation equilibrium followed by a slow step



The observed rate would be given by

$$-d(D)/dt = k_1(DH^+)$$

Since $(DH^+) = K(D)(H^+)$, a pseudo first-order rate expression is obtained

$$-d(D)/dt = k_1K(H^+)(D)$$

The site of protonation is purposely shown as position 5. One reason for this is that the ultraviolet spectra indicated that the β-amino-α,β-unsaturated carbonyl chromophore remained intact.[27]

(27) Known compounds possessing this chromophore show quite similar absorption. Examples are ethyl 1,4,5,6-tetrahydronicotinate which shows (approx.) λ_{max} 295 mμ, ε 13,500 (ref. 22); ethyl β-diethylaminocrotonate with λ_{max} 287 mμ, ε 30,500; and 1-(1-piperidyl)-1-hexen-3-one with λ_{max} 308 mμ, ε 28,000 [K. Bowden, E. A. Braude, E. R. H. Jones and B. Weedon, *J. Chem. Soc.*, 45 (1946)].

TABLE II

RATES OF PRIMARY ACID REACTIONS IN 48.9% ETHANOL (25°)

Dihydro compound	Wave length followed, mμ	k(sec.$^{-1}$) in ethanolic HCl[a] 7.7×10^{-3} N	3.85×10^{-3} N	Relative rates[b]
IV	375	3.4×10^{-4}	1.63×10^{-4}	1
	309	3.3×10^{-4}	1.69×10^{-4}	
V	355	4.0×10^{-3}	2.35×10^{-3}	14
VI	355	1.18×10^{-2}	0.59×10^{-2}	36
	290	1.10×10^{-2}	0.60×10^{-2}	
	295[c]	1.01×10^{-2}[c]		
	358[c]	1.00×10^{-2}[c]		
VII	355	3.9×10^{-2}	2.1×10^{-2}	130
	290	4.1×10^{-2}	2.2×10^{-2}	
VIII	365	5.1×10^{-2}	2.8×10^{-2}	164
	306	5.6×10^{-2}	2.7×10^{-2}	

[a] Each k-value represents the mean calculated from the results of two runs, with the exceptions that all values for IV are based on single runs, as are the values for VII in 3.85×10^{-3} N acid. [b] Based on runs in 3.85×10^{-3} N acid. [c] Run in 6.1×10^{-4} N aqueous hydrochloric acid.

If this very plausible supposition is accepted there remain only two likely positions: 5 and 6. Of these the former seems the more favorable in light of the work of Adams and Mahan[28] and Leonard and Gash[29] who found that tertiary vinyl amines are protonated in the β-position. Further evidence on this point based on the structure of a pure product isolated from the reaction will be discussed in a following section.

The order of relative rates depicted in Table II is explicable on the basis of the partial mechanism given. Any factor which operates in such a fashion as to increase the thermodynamic stability of D relative to DH^+ (or decrease the stability of DH^+ relative to D) would give a smaller value for K in the rate expression and hence a slower rate. The contribution of the canonical structure IX to the stabilization of D should be in the order X = $CH_3 > OCH_3 > NH_2 > N(Et)(C_6H_5)$.[30] Since X, the resonance form in the conjugate acid analogous to IX, cannot assume much importance owing to the proximity of the two positive charges, this will also be the order in which loss of resonance stabilization in going to DH^+ will be felt. The order of rates, then, should be just the reverse and this was found to be experimentally the case. The faster rate found for 1-propyldihydronicotinamide (VII) compared with the 1-benzyldihydronicotinamide (VI) might be due to the effect of the probable difference in the basicities of the respective ring nitrogens (pK_B of propylamine = 3.41; pK_B of benzylamine = 4.70) on the stability, in each case, of the conjugate acid relative to the free base.

V. Reaction Products

Extensive efforts to isolate crystalline products absorbing in the region near 300 mμ were successful only in the case of the 1-benzyl-3-acetyl-1,4-dihydropyridine (IV). The primary acid reaction of IV in dilute aqueous acid yielded two pure, solid products. One possessed an empirical formula in-

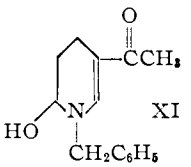
(28) R. Adams and J. E. Mahan, THIS JOURNAL, 64, 2588 (1942).

(29) N. J. Leonard and V. W. Gash, *ibid.*, 76, 278 (1954).

(30) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 127.

dicative of the addition of one molecule of water per molecule of dihydro compound. The second contained the elements of the dihydro compound and those of water in the ratio 2:1. A 74% total yield of crude acid products was realized after allowing a 0.04 *M* solution of the dihydro compound in 0.25 *N* hydrochloric acid to stand for 75 minutes. Of this, half was one product and half the other. More dilute solutions gave increasingly greater proportions of the first substance and it was the sole product obtained (92.5%) from a 0.002 *M* solution of the dihydro compound in 0.04 *N* acid.

The first product was assigned the structure of 1 - benzyl - 2 - hydroxy - 5 - acetyl - 1,2,3,4 - tetrahydropyridine (XI) on the basis of the following properties, together with the spectral and kinetic data presented in the preceding discussion. XI was obtained as a stable, colorless, crystalline solid melting at 119.5–120.5°. Its infrared spectrum showed a relatively intense band in the OH region and the shortest wave length band in the carbonyl region was at 6.16 μ. The latter is in the re-



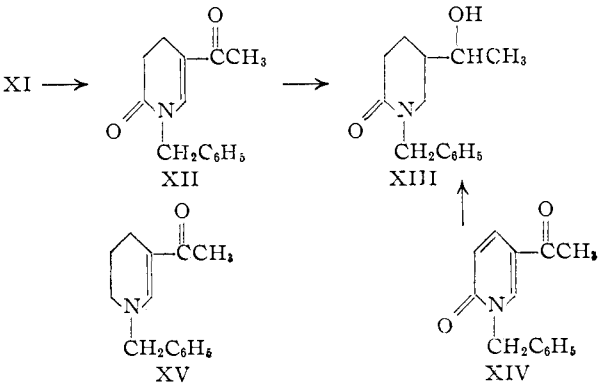
XI

gion of absorption of the carbonyl group in other β-amino-α,β-unsaturated ketones (vinylogous amides).[31] Also, a strong band observed at 6.39 μ is characteristic of the bathochromically shifted double bond absorption of a vinylogous amide.[31] These data, the ultraviolet absorption (λ_{max} 305 mμ, ϵ 29,600) and the interpretation of the kinetic results (above) on the basis of solvent attack at the 6-position in the rate-determining step are all in accord with the structure proposed.

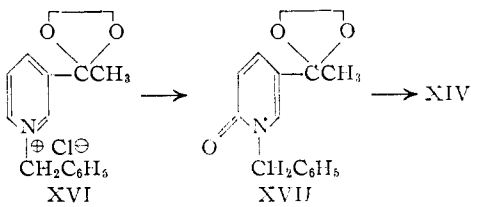
Further evidence for the correctness of XI was provided by the observation that the product gave slow, positive tests with both phenylhydrazine and 2,4-dinitrophenylhydrazine in acidic solution. Since Cromwell, *et al.*,[31] have found that vinylogous amides do not give phenylhydrazones, it seems plausible that the reaction in the present case is due to acid-catalyzed ring opening at the 6-position to give the tautomeric amino aldehyde. This constitutes a further indication that protonation occurs at position 5 rather than 6, since the product from the latter possibility corresponding to XI would be less likely to give this reaction.

Direct chemical proof for the presence of the oxygen function at the 6-position was provided by the oxidation of XI with chromic anhydride–pyridine complex (or, in lower yield, by the Oppenauer method) followed by quantitative (2 moles) hydrogenation of the product XII to give a compound (XIII) identical in every respect with one resulting from the uptake of 3 moles of hydrogen by 1-benzyl-5-acetyl-2-pyridone (XIV).

The evidence (in addition to elementary analysis) for XIII as the structure of the common reduction product is as follows: The infrared spectrum exhibited a band at 3.05 μ (hydroxyl) and at 6.15 μ (amide carbonyl) and the ultraviolet spectrum showed only end absorption. The compound was non-basic (insoluble in 10% sulfuric acid). It gave a negative 2,4-dinitrophenylhydrazine test but a positive iodoform test. If the oxidation product XII were isomeric (carbonyl β to the ring nitrogen) then, in order obtain the same reduction product as from XIV, hydrogenolysis of the ring carbonyl would have to occur to yield XV. But the latter definitely can be ruled out on the basis of elementary analysis, the absence of absorption in the ultraviolet region and the presence of the hydroxyl band in the infrared.



For the synthesis of the pyridone XIV, 3-acetylpyridine was converted to the ethylene ketal derivative and the product then quaternized by reaction with benzyl chloride to give XVI. Oxidation of the latter with potassium ferricyanide in basic solution produced 1-benzyl-5-acetyl-2-pyridone ethylene ketal (XVII) which was transformed readily into XIV. Since ferricyanide oxidation of pyridin-



ium salts leads to 2-pyridones in some cases and 6-pyridones in others, it was necessary to prove the structure of XIV. This was accomplished by sodium hypoiodite oxidation to 1-benzyl-5-carboxy-2-pyridone (XVIII) which was identical to the sample of XVIII prepared by the ferricyanide oxidation of 1-benzyl-3-carboxypyridinium chloride (XIX), a reaction known to give the carbonyl in the position shown.[32]

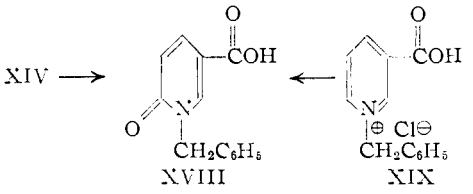
The ultraviolet absorption spectrum curve of XVIII was essentially identical (λ_{max} in ethanol at 260 mμ, ϵ 15,700, and 299–308 mμ, ϵ 4800) to that of a sample of the corresponding 1-methyl compound[32] and markedly different from that of a sample of 1-methyl-3-carbamoyl-2-pyridone[32] (λ_{max} in ethanol at 234 mμ, ϵ 5000, and 326 mμ, ϵ 8300; λ_{min} at *ca.* 265 mμ).

The total of the evidence and reasoning presented bearing on the primary acid reaction and the

(31) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, THIS JOURNAL, **71**, 3337 (1949).

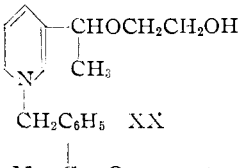
(32) W. Holman and C. Wiegand, *Biochem. J.*, **43**, 423 (1948); H. Bradlow and C. VanderWerf, *J. Org. Chem.*, **16**, 73 (1951); J. Huff, *J. Biol. Chem.*, **171**, 639 (1947).

structure of XI strongly suggest that the product obtained by Wallenfels and Schüly[22] is the 6- rather than the 5-isomer (III).



XVIII XIX

The conversion of XVII to a reduced derivative was also attempted by treatment with lithium aluminum hydride. Reaction with an excess of the reagent gave a basic, yellow oil in 50% yield. The analysis, infrared spectrum (strong band at 3.02 μ and no characteristic band for the ethylenedioxy group at 11.5 μ), and the property of reducing alcoholic silver nitrate readily at room temperature suggested the dihydropyridine structure XX.



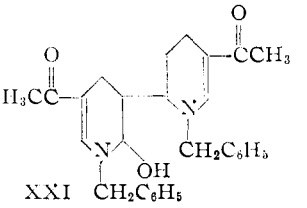
XX

Since the $=N-\underset{|}{C}-O-$ system is known to undergo cleavage by lithium aluminum hydride at the C—O bond[33] and the $=N-\underset{|}{C}=\underset{|}{C}-\underset{|}{C}-O-$ system in XVII is a vinylog of this, the postulated cleavage of the ether is reasonable. The formation of an insoluble complex (a precipitate was observed) by XX may account for the retention of the second ether linkage.

The second product from the reaction of acid on IV was also a stable, colorless, crystalline solid having a sharp melting point (177.5°). Its ultraviolet spectrum displayed a maximum at 307 mμ which had a molar extinction coefficient of 54,200 based on a molecular weight of 445 (see below). Purification of the crude material was effected by repeated recrystallization from ethanol or by hydrogenation of the associated impurities over a platinum catalyst. The elementary analysis suggested an empirical formula of $C_{28}H_{32}N_2O_3$ and a number of experiments to determine the molecular weight were made. Cryoscopic determinations in benzene, dioxane or ethylene carbonate were unsuccessful for various reasons. The Rast method gave values of 385 and 389 with camphor and 336 and 350 with cyclohexanol. A determination by the isothermal distillation method[34] gave an approximate value of 355. These results are not too satisfactory, but all are nearer the calculated value for a dimeric than for a monomeric compound.

The substance was very weakly basic. It precipitated directly from solution when prepared in hydrochloric acid of concentrations up to 0.2 *N* but was titratable, in acetonitrile, with perchloric acid diluted with glacial acetic acid. Potentiometric measurement of the titration showed two deflections. This was indicative of a diacidic base and, further, molecular weight values calculated from a series of three such determinations gave a mean value of 445 with an average deviation of 24.

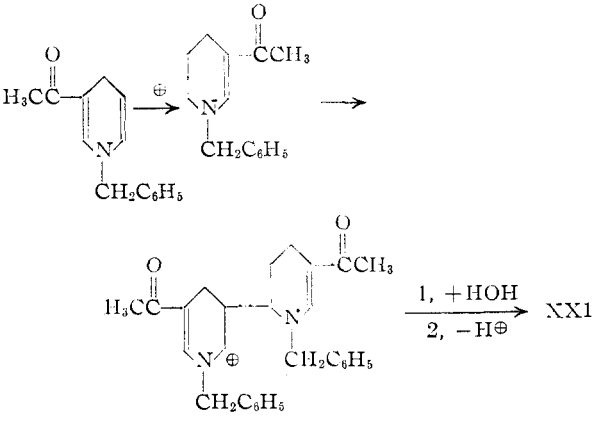
The structure which is thought to best fit the available data is XXI. It is consistent with the ultraviolet absorption (above) and the finding of



XXI

bands in the infrared spectrum at 3.07 μ (OH region) and at 6.23 and 6.40 μ (carbonyl and double bond in vinylogous amide). It affords an explanation for the very slow positive 2,4-dinitrophenylhydrazine test (opening of the ring having the hydroxyl) and essentially neutral character observed.

The linkage of the two rings as shown could arise through a mechanism (shown) which is reasonable and which has the favorable aspect of involving a species formulated (above) as an intermediate in the formation of the other product of the reaction (XI).



XXI

Products from the reaction of the other dihydropyridine compounds with acid were obtained only as resinous solids of indefinite melting point and were not suitable for further study.

The authors are grateful for many helpful discussions with Professor Edwin G. Krebs and Dr. Josephine O. Meinhart.

Experimental[35,36]

Ethyl Nicotinate.—Nicotinic acid was esterified according to the method of Gilman and Broadbent[37] with the exceptions that a double quantity of sulfuric acid was employed, the time of refluxing was 4 hours, and ammonium hydroxide was used instead of potassium carbonate to liberate the product from its sulfate salt. A yield of 68% of ester, b.p. 97.5–98° at 9 mm. (reported[37] 107–108° at 16 mm.), was obtained.

(33) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 807 ff.

(34) Performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(35) Melting points are corrected unless otherwise stated. Boiling points are uncorrected. Elementary analyses were performed by B. J. Nist and C. H. Ludwig.

(36) Ultraviolet spectra were determined with a Cary model 11S recording spectrophotometer and a Beckman model DU spectrophotometer.

(37) H. Gilman and H. S. Broadbent, THIS JOURNAL, **70**, 2755 (1948).

3-Acetylpyridine.—A sodium ethoxide catalyzed Claisen condensation between ethyl nicotinate and ethyl acetate, as described by Kolloff and Hunter,[38] produced 3-acetylpyridine in 76% over-all yield upon hydrolysis of the intermediate β-keto ester. The product boiled at 93.5–94° at 9 mm. (reported[38] 93° at 7 mm.).

1-Benzyl-3-acetylpyridinium Chloride.—A solution of 3-acetylpyridine (30.6 g., 0.25 mole) and benzyl chloride (32 g., 0.27 mole) in 60 ml. of anhydrous methanol was heated under reflux for two hours. The methanol was removed under vacuum and the residual salt washed thoroughly with ether. The tan-pink salt (56 g., 90%) was sufficiently pure (m.p. 183–185°) for all further reactions. Recrystallization could be effected (90% recovery) from methanol–ethyl acetate to give fine tan needles, m.p. 185.5–186°.

Anal. Calcd. for $C_{14}H_{14}NOCl$: C, 67.88; H, 6.09. Found: C, 68.07; H, 6.27.

1-Benzyl-3-acetyl-1,4-dihydropyridine (IV).—A stirred solution of 3-acetylpyridine benzylochloride (24.8 g., 0.1 mole) and sodium bicarbonate (46 g.) in 600 ml. of water was treated with sodium dithionite (69.6 g., 0.4 mole) in small portions over a period of a few minutes. The solution evolved carbon dioxide with frothing and assumed a deep orange color which heightened to yellow as the solid yellow product precipitated. Stirring was continued for 9 hr. The separated product was washed on the filter with several portions of cold water and dried over phosphorus pentoxide under vacuum for 12 hr. The yield of crude material (m.p. 58–65°) was 18.5 g. (87%). Purification was accomplished (65–70% recovery) by recrystallization from several liters of water with the addition of sufficient ethanol to effect solution (prolonged contact with boiling water caused decompostion) and then from 30–60° petroleum ether. The product was obtained as yellow plates which melted at 61–67° and in an ethanol solution exhibited λ_{max} at 371 mμ (ε 10,400) and λ_{min} at 289 mμ (ε 200).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.82; H, 7.09. Found: C, 78.59; H, 7.10.

Methyl Nicotinate.—Nicotinic acid (94 g., 0.76 mole) was esterified according to the method of Levine and Sneed[39] in 64% yield. The product distilled at 97–98.5° at 12.5 mm. (reported[39] 108–109° at 21 mm.) and melted at 39.5–41.5° (reported[40] 38°).

Methyl 1-Benzyl-1,4-dihydronicotinate (V).—A solution of methyl nicotinate (27.4 g., 0.2 mole) and benzyl chloride (41.6 g., 0.33 mole) in anhydrous methanol was heated under reflux for 24 hr. and the solvent then removed. The heavy sirup which remained was shaken several times with ether and then placed in a vacuum desiccator over calcium chloride and kept under constant aspiration for several days. The partially crystallized material was scratched until solid and washed on a fritted disk funnel with several portions of ether. It was then replaced in the desiccator and kept under aspiration for several days. The yield of colorless, extremely hygroscopic salt was 46 g. (87%), m.p. 132–133° (uncor.) with decomposition.

The dithionite reduction of the salt was carried out as described for the preparation of VI (below). A typical run utilized 7.8 g. (0.03 mole) of the pyridinium salt with 12.0 g. sodium carbonate monohydrate and yielded 3.24 g. (47%) of crude V, which precipitated as a lemon-yellow solid, m.p. 85–90° (uncor.), following the usual color changes and was separated after stirring for 30 min. It was found important to measure the sodium carbonate exactly as larger proportions resulted in markedly slower reaction and small proportions cause rapid formation of an oil which could not be crystallized. Recrystallization of the product on a small scale (<100 mg.) was successful from ethanol, but this procedure often gave decomposition with larger amounts. Quantities of 100 mg. or greater were purified (21% recovery) by adding water to a boiling methanol solution until the cloud point was almost reached and then cooling. The pure material was thus obtained as lemon-yellow crystals, m.p. 90–91° dec., with the melting point bath preheated to 70° and then raised rapidly to 85°. Slow heating from room temperature resulted in shrinking and darkening with ultimate melting and decomposition at *ca.* 150°. The compound was best stored in a freezer. An ethanol solution showed an absorption maximum at 352 mμ (ε 7,250) and a minimum at 290 mμ (ε 650).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.31; H, 6.59. Found: C, 72.89; H, 6.08.

N-Ethylnicotinanilide.—A mixture of nicotinic acid (24.6 g., 0.2 mole), N-ethylaniline (25.0 g., 0.21 mole) and phosphorus pentachloride (25.0 g., 0.24 mole) was heated at a bath temperature of 140–150°. The mixture liquefied, hydrogen chloride was evolved and, after 4 hr., the cooled mixture was diluted with 400 ml. of water. The solution was made alkaline with aqueous sodium hydroxide and extracted with four 150-ml. portions of ether. The solvent was removed (air stream) from the dried (magnesium sulfate) solution and the residual oil distilled. After a small forerun, the product was collected (34.6 g., 71%) as the fraction boiling at 137.5–143° at 0.2 mm. (reported[41] 186–190° at 3 mm.) as an oil which solidified on standing and tended to turn orange with time. Recrystallization from acetone gave a 63% recovery of material melting at 64.5–66° (reported[41] 63°).

N-Ethyl-1-benzyl-1,4-dihydronicotinanilide (VI).—A solution of N-ethylnicotinanilide (9.0 g., 0.04 mole) in 25 ml. of benzyl chloride was heated at a bath temperature of 130° for 20 min., during which time it became light brown in color. The quaternary salt formed was precipitated as a light yellow oil by the addition of a large excess of ether. Several ether washings, followed by trituration of the oil with ether gave 13.2 g. (94%) of a light tan, hygroscopic solid, m.p. 129–130° (uncor.).

A cloudy solution of crude (oily) salt (7.0 g., 0.02 mole) and 8.0 g. of sodium carbonate monohydrate in 150 ml. of water was cleared by extraction with 80 ml. of ether. It was then stirred in a round-bottom flask while 10.4 g. (0.06 mole) of sodium dithionite was added. The solution became deep orange in color and about 5 min. after the addition was complete a yellow oil separated. This solidified to form a fine, lemon-yellow solid as the reaction proceeded but, when collected, became sticky and tended to discolor. The yield of crude product was *ca.* 70%. Purification of a small sample was effected by chromatography of an ethereal solution on Florisil. The solid obtained on removal of the solvent melted at 82–85.5°. It was stable when stored in a refrigerator at atmospheric pressure (under vacuum over calcium chloride it became oily and discolored). An ethanol solution showed an absorption maximum at 360 mμ (ε 6490) and a minimum at 308 mμ (ε 700).

Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.97. Found: C, 78.92; H, 6.90.

1-Benzyl-3-carbamoylpyridinium Chloride.—The general procedure and relative quantities of reactants were those of Karrer and Stare.[20] The quaternary salt was separated from the cooled solution by filtration rather than distillation (of the benzyl chloride) since severe bumping was experienced with the latter procedure. A yield of 149.6 g. (74%) of product melting at 235–236° dec. (reported[20] 236°) was realized, including a second crop from the filtrate, from 100 g. of nicotinamide.

1-Benzyl-1,4-dihydronicotinamide (VIII).—The general procedure was that described above for the preparation of IV. A typical preparation involved 49.8 g. (0.2 mole) of nicotinamide benzylochloride, 130.2 g. of sodium dithionite, 92 g. of sodium bicarbonate and 1200 ml. of water. The product separated as a yellow oil which solidified as the reaction proceeded. Stirring was continued for 2 hr. and the collected solid recrystallized by dissolving in 170 ml. of hot ethanol, filtering the hot solution, adding 800 ml. of boiling water to the filtrate, and scratching the sides of the flask while cooling it in ice. The product usually oiled out and then solidified as a mixture of fine yellow needles and bulky orange crystals. Recrystallization gave 30.5 g. (71.2%) of yellow needles, m.p. 110–114° (reported[20] sintering at 115° and complete melting at 123°).[20] An ethanol solution gave λ_{max} at 353 mμ (log ε 3.87) and λ_{min} at 290 mμ (ε 900). The reported[18] absorption maximum is 355 mμ (log ε 3.86). The product was stored in a freezer.

1-Propyl-3-carbamoylpyridinium Bromide.—Nicotinamide (100 g., 0.32 mole) was heated under reflux with 111 ml. (150 g., 1.22 moles) of *n*-propyl bromide in 400 ml. of

(38) H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **63**, 492 (1941).
(39) R. Levine and J. K. Sneed, *ibid.*, **73**, 5614 (1951).
(40) Y. Hukusima, *J. Chem. Soc. Japan*, **61**, 121 (1940).
(41) A. S. Sadykov and V. I. Maksimov, *J. Gen. Chem.* (*USSR*), **16**, 1719 (1946) [*C. A.*, **41**, 5865 (1947)].

propanol for 6 hr. The yellowish salt (184 g.) which was separated after cooling was recrystallized twice from 1200 ml. of propanol and yielded 156.8 g. (78.5%) of colorless crystals, m.p. 167.5–172° (reported[42] 174°).

1-**Propyl-1,4-dihydronicotinamide** (VII).—The procedure given for the preparation of IV was followed and the yellow dihydro compound was obtained as an oil from reaction of 112 g. (0.47 mole) of nicotinamide propobromide, 360 g. of sodium dithionite and 430 g. of anhydrous sodium carbonate for 75 min. Rubbing the oil (seeding was helpful) caused solidification and the product was then recrystallized (with some loss) from 2 l. of boiling, air-free water. The fine yellow needles (42.3 g., 54.2%) formed melted at 88–91° dec. Melting points which have been reported for this compound are 86°,[43] 91–92°,[18] 93°[44] and 96°.[20] The ultraviolet spectrum of an ethanol solution showed a maximum at 355 mμ (ε 7150) and a broad minimum centered at 282 mμ (ε 600). The compound slowly darkened and became sticky on standing in air at room temperature and was kept in a freezer.

Procedure for Kinetic Measurements.—The solvent was prepared by mixing 1771 g. of 95% ethanol with 1629 g. of water. The average of two density measurements gave a value corresponding to 48.9% ethanol by weight for the solution. The solvent was shown to be unchanged over the period of the determinations by the obtaining of the same rate constant for the reaction of 1-benzyldihydronicotinamide on the first and last days.

The rates of the primary acid reactions were obtained by following the change in intensity of absorption (of the dihydro product and/or the product from the primary acid reaction) on a Beckman model DU spectrophotometer fitted with standard Beckman thermospacers through which water from a constant temperature (25.00 ± 0.05°) bath was circulated. Concentrations of the solutions were so chosen that, when an increasing absorption was followed, the final optical density reading (D_∞) was in a region, *i.e.*, 1.0 or less, where a precise value could be obtained. Solutions two or three times as concentrated were used in following bands of diminishing intensity.

The procedure for a run was as follows: Exactly 3.0 ml. of the solution of purified dihydro compound was added from a microburet to a Beckman cell equipped with a tight-fitting ground glass stopper. The stoppered cell was allowed to come to thermal equilibrium in the cell compartment for 10 min., then removed and 0.40 ml. of either 0.588 or 0.293 *N* hydrochloric acid was added rapidly from a Gilmont ultramicroburet. This gave a solution 7.7×10^{-3} or 3.83×10^{-3} *N* in hydrochloric acid. After the covered well was inverted and shaken, it was quickly replaced in the cell compartment and a timer, reading to 0.01 minute, started at a convenient optical density reading. Readings were taken by setting the Beckman scale at a series of optical densities and recording the time that the needle crossed the zero mark. The dark current was zeroed at the beginning of each run and for the D_∞ readings.

Primary Acid Reaction of 1-Benzyl-3-acetyl-1,4-dihydropyridine (IV).—Freshly recrystallized IV (5.0 g., 0.023 mole) was stirred with 600 ml. of 0.25 *N* hydrochloric acid for 75 min. During this time the materially gradually went into solution. Traces of insoluble material were removed (filtration) and the solution brought to neutrality with solid sodium bicarbonate. A precipitate of crude XXI formed as a cream colored solid, m.p. 158–163°, during the neutralization and this was collected (1.94 g., 37%) and purified by repeated recrystallization from ethanol to give colorless clusters of needles which melted at 177.5° when the preheated (160°) bath was heated rapidly to 170° and at 169–170° when the bath was heated slowly. An ethanol solution displayed an absorption maximum at 307 mμ (ε 54,200).

Anal. Calcd. for $C_{28}H_{32}N_2O_3$: C, 75.64; H, 7.25; N, 6.30. Found: C, 75.64; H, 7.04; N, 5.88.

Addition of 4 ml. of a 10% aqueous solution of chloroplatinic acid to a solution of 0.2 g. of XXI in 2 ml. of ethanol and 0.5 ml. of 8 *N* hydrochloric acid precipitated a spongy solid (presumably the chloroplatinate derivative). Attempted recrystallization from ethanol gave an oil which solidified on rubbing and then melted at 181–189° dec.

The filtrate (from the separation of crude XXI) was extracted with four 100-ml. portions of chloroform. The combined extracts were washed with 25 ml. of water, dried over magnesium sulfate, and the solvent removed under vacuum. The light tan solid (2.01 g.) melted at 118–119.5° after crystallization from benzene and amounted to 1.34 g. (24.3%) of XI. A sample recrystallized twice from ethanol formed colorless, stout prisms, m.p. 119.5–120.5°. The compound crystallized from benzene as needles. Drying over phosphorus pentoxide *in vacuo* for 5 hr. produced yellowing, but no decomposition occurred in 1 hr. An ethanol solution showed an absorption maximum at 305 mμ (ε 29,600).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.68; H, 7.41; N, 6.06. Found: C, 72.41; H, 7.36; N, 5.80.

When the reaction was carried out with weaker acid and a more dilute solution of the dihydro compound, the proportion of XI in the total product increased. Thus 9.0 g. (0.042 mole) of IV in 4 l. of 0.04 *N* hydrochloric acid for 30 min. formed 5.04 g. (52%) of XI and 3.12 g. (33%) of XXI; and 0.21 g. (0.001 mole) of IV in 0.0077 *N* hydrochloric acid for 75 min. yielded 0.21 g. (92.5%) of XI and no XXI.

The use of less pure dihydro compound and more concentrated acid often led to the formation of dark-colored XXI. This was best purified by dissolving it in the minimum amount of ethanol and shaking the solution with Adams catalyst under hydrogen at atmospheric pressure. The uptake of hydrogen was controlled such that no more than one-third of one molar equivalent for one double bond was absorbed. Removal of the catalyst and concentration of the filtrate gave quite pure XXI, m.p. 168–170°.

1-**Benzyl-5-acetyl-3,4-dihydro-2-pyridone** (XII).—A chromic anhydride–pyridine complex reagent was prepared from 1.8 g. (0.018 mole) of chromic anhydride and 18 ml. of pyridine according to the procedure of Poos, *et al.*[45] To this yellow slurry was added 1.4 g. of 1-benzyl-2-hydroxy-5-acetyl-1,2,3,4-tetrahydropyridine (XI) dissolved in 18 ml. of pyridine. The mixture turned dark and a brown oil separated on the sides of the flask. The stoppered flask and contents were allowed to stand for 14 hr., after which the reaction mixture was diluted with 100 ml. of water and then extracted with six 50-ml. portions of ether. Filtration to remove the brown solid that separated during the process aided the extraction. Removal of the solvent from the dried (sodium sulfate) extracts *in vacuo* left an oil which solidified with the aid of scratching. The crude brown solid (0.83 g.) crystallized from hexane as a yellow solid (0.41 g.). Recrystallization gave 0.35 g. (25%) of pale yellow needles which softened at 71° and melted at 74–76°. An ethanol solution showed an absorption maximum at 294 mμ (ε 16,600).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.31; H, 6.59. Found: C, 73.32; H, 6.60.

From an Oppenauer oxidation of XI with aluminum isopropoxide and quinone according to the method of Djerassi[46] was obtained a red solid which, even though not purified further, gave the same infrared absorption spectrum (chloroform solvent) as the product (XII) obtained above.

3-**Acetylpyridine Ethylene Ketal.**—A biphasic reaction mixture consisting of freshly distilled 3-acetylpyridine (30.3 g., 0.25 mole), ethylene glycol (100 ml.), dry toluene (150 ml.), concentrated sulfuric acid (6 drops), and *p*-toluenesulfonic acid monohydrate (0.25 g.) was heated under reflux for 9 hr. A modified Dean–Stark phase separator[47] was then substituted for the condenser and the water and glycol removed until there was no further layering of the condensate (50 hr.). After neutralization of the catalyst with solid sodium carbonate, the toluene was removed (vacuum) and the residue fractionated with a spinning band column at a reflux ratio of 100:1. A forerun of toluene and 3-acetylpyridine was followed by 23 ml. (25.2 g., 61%) of product, b.p. 135–138° at 33 mm., $n^{25}D$ 1.5089. The infrared spectrum (neat) displayed a strong band at 9.62 μ and

(42) W. Ciusa, P. M. Strocchi and G. Adano, *Gazz. chim. ital.*, **80**, 608 (1950).

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

(44) P. R. Brook, F. Blumer, H. J. V. Krishna, S. Schnell and P. Karrer, *Helv. Chim. Acta*, **39**, 667 (1956).

(45) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(46) C. Djerassi, *ibid.*, **71**, 1009 (1949).

(47) H. J. Dauben, B. Loken and H. J. Ringold, *ibid.*, **76**, 1359 (1954).

medium intensity bands at 10.55 and 11.45 μ. These are apparently characteristic of the ethylenedioxy group.[48]

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71. Found: C, 65.28; H, 6.48.

1-Benzyl-5-acetyl-2-pyridone Ethylene Ketal (XVII).—3-Acetylpyridine ethylene ketal (11.5 g., 0.07 mole) was heated under reflux with benzyl chloride (15 g., 0.12 mole) in 40 ml. of anhydrous methanol for 2.5 hr. The reaction mixture was then allowed to stand overnight, the solvent removed under vacuum, and the glassy residue dissolved in 150 ml. of water. The aqueous solution was extracted twice with ether to remove excess benzyl chloride and was presumed to contain the desired quaternary salt XVI.

To the stirred, ice-cooled solution of the benzylochloride were added, simultaneously and from separate dropping funnels over a period of 30 min., solutions of potassium ferricyanide (63 g., 0.19 mole, in 150 ml. of water) and potassium hydroxide (34 g., 0.61 mole, in 100 ml. of water). Stirring was continued for an additional 5 hr. at room temperature. The reaction mixture was extracted with four 200-ml. portions of ether and two 100-ml. portions of chloroform. Removal of the solvents (vacuum) from the combined, dried (sodium sulfate) extracts left an oil which upon distillation afforded, following a small (1.8 g.) forerun of 3-acetylpyridine ethylene ketal, the product (11.1 g., 70% net yield) as a viscous yellow oil (b.p. 176–178° at 0.3 mm.) which on standing solidified to a waxy solid, m.p. 62–67°. Two recrystallizations from ether gave colorless crystals, m.p. 68.5–69.5°. The infrared spectrum (chloroform) exhibited a band at 6.0 μ (carbonyl) and ketal bands at 9.62, 10.53 and 11.46 μ.[48] The ultraviolet spectrum had maxima (ethanol) at 233 mμ (ε 7580) and 308–309 mμ (ε 4610).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 71.05; H, 6.22.

1-Benzyl-5-acetyl-2-pyridone (XIV).—To a solution of the crude 1-benzyl-5-acetyl-2-pyridone ethylene ketal (2.4 g., 0.01 mole) prepared above in 75 ml. of 50% ethanol was added 1 ml. of concentrated sulfuric acid. After 30 min., the mixture was extracted with three 50-ml. portions of chloroform. The extracts were washed once with water, dried over sodium sulfate, and the solvent removed under vacuum. The residual oil (1.72 g.) solidified to a tan powder when rubbed and an ethanol solution of this was treated with Norite and filtered. The solvent was removed (air stream), the residue taken up in benzene, reprecipitated by the addition of hexane and then recrystallized twice from ether. The colorless crystals (0.96 g., 51%) melted at 77–78°. The ultraviolet spectrum (ethanol) showed a maximum at 278 mμ (ε 17,200). The infrared spectrum displayed a shoulder at 5.92 μ and a strong band at 6.04 μ.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.95; H, 5.76. Found: C, 73.75; H, 5.50.

1-Benzyl-5-carboxy-2-pyridone (XVIII). A. From 1-Benzyl-3-carboxypyridinium Chloride (XIX).—A solution of nicotinic acid (10 g., 0.081 mole) and benzyl chloride (20 g., 0.157 mole) in 200 ml. of methanol was heated under reflux for 20 hr. and then concentrated to one-fourth the original volume. The precipitate of unreacted nicotinic acid was separated, the filtrate concentrated under vacuum, and one-third (5 g.) of the viscous yellow residue mixed with a few ml. of water. The undissolved nicotinic acid (1 g.) was separated and the filtrate, which was presumed to contain a maximum of 4 g. of the desired salt XIX, diluted to a volume of 75 ml. with water.

The solution was stirred during the simultaneous addition over a 15-min. period of an aqueous solution (60 ml.) of potassium ferricyanide (20 g., 0.061 mole) and an aqueous solution (65 ml.) of potassium hydroxide (17 g., 0.30 mole). The reaction mixture was allowed to stand for an additional 3 hr. and then acidified with concentrated hydrochloric acid, whereupon a blue-green precipitate (2.35 g.) separated. Recrystallization from ethanol (Norite) gave colorless crystals (1.52 g., 41% net over-all yield), m.p. 205–206°. An ethanol solution showed absorption maxima at 260 mμ (ε 15,700) and 299–308 mμ (ε 4799).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84. Found: C, 68.03; H, 4.58.

B. From 1-Benzyl-5-acetyl-2-pyridone (XIV).—The oxidation of XIV (70 mg., 0.31 mmole) with sodium hypoiodite was carried out as described by Shriner and Fuson.[49] The product was isolated by separating the precipitated iodoform, acidifying the filtrate with hydrochloric acid, adding a crystal of sodium thiosulfate to remove the iodine color, and extracting the acidic solution with three 20-ml. portions of chloroform. The extracts were washed with 10 ml. of water and dried over magnesium sulfate. Removal of the solvent left 64 mg. of a brown solid. A quantitative measurement of the ultraviolet spectrum at 260 and 299 mμ showed that, by comparison with the absorption of a pure sample (above), the crude product contained 80–85% of XVIII. Recrystallization from ethanol (Norite) afforded a few mg. of colorless crystals, m.p. 204–205°, whose infrared spectrum (Nujol mull) was identical to that of the material obtained in A.

1-Benzyl-5-(1-hydroxyethyl)-3,4,5,6-tetrahydro-2-pyridone (XIII). A. From 1-Benzyl-5-acetyl-2-pyridone (XIV).—When 0.54 g. (2.4 mmoles) of XIV was treated with hydrogen over Adams catalyst at atmospheric pressure and room temperature, the uptake of hydrogen was 176 ml. (102% of the theoretical for 3 molar equivalents). Removal of the catalyst and evaporation of the solvent left a colorless oil (0.55 g.) that changed on standing overnight into a sticky solid. Three recrystallizations from benzene–hexane gave waxy needles which had a wide melting range (30–60°). The infrared spectrum displayed absorption at 3.05 μ and a strong band at 6.15 μ. The ultraviolet spectrum showed only end absorption. The compound gave a positive iodoform test and a negative test with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{14}H_{18}NO_2$: C, 72.05; H, 8.21. Found: C, 71.61; H, 8.12.

B. From 1-Benzyl-5-acetyl-3,4-dihydro-2-pyridone (XII).—Reduction of 0.23 g. (1.0 mmole) of XII with hydrogen ceased (4 hr.) after the uptake of 46 ml. (96% of the theoretical for 2 molar equivalents). The residue (0.23 g.) remaining after removal of the catalyst and solvent was a colorless oil which on standing crystallized to a sticky solid. Recrystallization from benzene–hexane as described in A gave waxy needles identical (melting range, mixed melting point and infrared spectrum) with the product obtained in A.

Lithium Aluminum Hydride Reduction of 1-Benzyl-5-acetyl-2-pyridone Ethylene Ketal.—1-Benzyl-5-acetyl-2-pyridone ethylene ketal (4 g., 0.015 mole) in 90 ml. of dry ether was added over a period of 30 min., with stirring, to a suspension of 2.4 g. (0.064 mole) of lithium aluminum hydride in 60 ml. of dry ether. A purple precipitate was immediately evident. The mixture was heated under reflux for 5 hr., the product complex and excess hydride hydrolyzed with water and the precipitated salts removed by filtration. The solvent was removed (air stream) from the dried (magnesium sulfate) filtrate and the residue distilled. The crude product (2.1 g., 51%) was obtained as a viscous orange oil, b.p. 140–172° at 0.4 mm. Redistillation gave 1.2 g. (29%) of viscous yellow oil, b.p. 164–165° at 0.05 mm. or 172° at 0.5 mm., which was basic to litmus and, in ethanol solution, showed an absorption maximum at 245 mμ. The product reduced 50% alcoholic silver nitrate readily at room temperature. It dissolved readily in 10% sulfuric acid and was recovered unchanged from the solution on neutralization.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 71.05; H, 6.22.

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(48) A sample of the ethylene ketal of methyl ethyl ketone, kindly supplied by Dr. G. Merrill Andrus, showed bands of the same relative intensities at 9.6, 10.57 and 11.55 μ.

(49) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 138.