Potential Coenzyme Inhibitors. IV.[1a] 3-Acetyl Substituted Pyridine and Dihydropyridine Derivatives

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A number of 3-acetyl substituted pyridinium derivatives have been prepared and the addition reactions with KCN have been followed by uv spectroscopy. Nmr studies show that the CN adducts have 4-cyano-1,4-dihydropyridine structures, and the influence of the 3-Ac group upon the ring-proton shielding is discussed. In these systems the 3-Ac group is found to be a more effective electron-withdrawing entity than a 3-carbamoyl group. From the absorption spectra, equilibrium constants for the CN addition reactions have been estimated and the values related to the electronic effects exerted by the 3-Ac and 4-Me substituents. The significance of these results to the design of potentially effective coenzyme inhibitors is given and results of tumour growth inhibitory tests upon two of the 3-acetylpyridinium compounds are also presented.

In part III[1a] equilibrium constants for the addition reactions between cyanide ions and 4-Me substituted quaternary nicotinamide salts were calculated and it was shown that the constants for CN addition to 4-methylnicotinamide salts were much lower (0.05–0.09%) than when the 4-Me groups were absent. A desirable condition of the present chemotherapeutic approach is that the rate of hydride addition to a 4-substituted NAD should be at least comparable with, or greater than, the rate of hydride transfer to the natural coenzyme NAD. The equilibrium constant for the reaction between CN^- and NAD was determined in the present work and found to be 258 mol^{-1} at 25° in aq solution (Walter and Kaplan[2] reported k = 243 mol^{-1} at 20° in aq MeOH solution and Wallenfels and Dieckmann[3] gave k = 250 mol^{-1}). The corresponding value for 4-methyl-NAD was calculated to be 0.20 mol^{-1} at 25° in aq solution.

Walter and Kaplan[2] gave a value of 0.95 mol^{-1} for 4-methyl-NAD in aq MeOH media, and found that the CN complex in aq solution had a maximum absorption at 340 mμ compared with 322 mμ in the MeOH solution. They commented that these wavelength differences were difficult to explain as the NAD–cyanide spectra as well as the spectra of the other coenzyme analogs are not as greatly altered by the change in the dielectric constant of the medium.[4] They considered that because of this "abnormal" spectral shift with CN^- it was possible that the reaction may not proceed in the usual way, but that addition to other positions besides the 4 position may have occurred. In the present work it has been found that whereas small changes in the dielectric constant of the medium have little effect upon the wavelength position of CN^- addition complexes of nicotinamide derivatives (shown in the preceding part of this series[1a] to be 4-cyano-1,4-dihydronicotinamide derivatives), larger changes give rise to appreciable differences in wavelength. Thus for CN^- concentrations of 0.5 M and 2.5 M, the absorption maxima for the cyanide complex of 4-methyl-NAD are situated at 323 and 332 mμ, respectively, compared with 323 and 329 mμ for 3-carbamoyl-1,4-dihydro-4-cyano-4-methyl-1-(tetraacetyl-β-D-glucopyranosyl)pyridine (I, R = tetraacetyl-β-D-glucopyranosyl), and 327 and 332 mμ for the propoxymethyl analog (I, R = propoxymethyl). With all the pyridinium salts studied in this work and previously[1a,5] as well as for NAD and 4-methyl-NAD similar such effects have been observed. Indeed, the wavelength position for the absorption of a 4-cyano-1,4-dihydropyridine derivative at the 300- to 360-mμ region should be affected by the dielectric constant of the medium, since the excitation of bonding electrons in dipolar functions conjugated with nitrogen heterocyclic ring systems is known to be markedly influenced by the nature of the medium.[6,7]

The equilibrium constant values for the coenzymes are in accordance with those obtained previously for the model compounds[1a] (see Table II for k_{CONH_2} values), the value for 4-methyl-NAD being about 0.08% of that for NAD. Some improvement in the anionic affinity of the 4-substituted NAD is clearly required, and might be effected by either of two possible ways: (1) introduction of ring substituents which activate the 4 position of the nicotinamide ring toward addition of anions, *e.g.*, Wallenfels[8] has shown that the equilibrium constant for cyanide addition to the nicotinamide derivative II is increased 3000-fold by incorporation of a 5-carbamoyl group; (2) substitution of existing groups in the 4-methylnicotinamide ring, *e.g.*, the use of electron-withdrawing substituents in the 3 or 4 positions should affect the anionic affinity of the 4 position. Suitable 3 substituents would be those such as –CHO, $-COCH_3$, $-CSNH_2$, which when incorporated into 3-substituted NADs, provide enzymically active coenzymes.[9] Now it is known that 3-acetylpyridine is converted into 3-acetyl-NAD in tissues *in vivo* or when incubated *in vitro* with NADase[10] and can act as a nicotinamide antagonist.[11] Moreover, Wallenfels[8] has shown that the CN^- equilibrium constant is increased about 140-fold when the 3-carbamoyl group in II is replaced by

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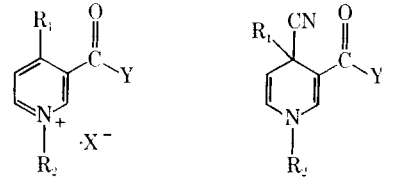
TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA AT 28°

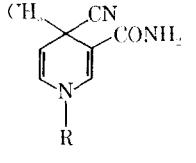


IV

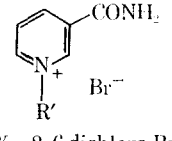
V

No.	Structure[a]	R_1	R_2[b]	X	Y	Chemical shifts, ppm 2-H	4-H	5-H	6-H	3-$COCH_3$	1-Me	NCH_2	Coupling constants, cps $J_{1',2'}$	$J_{2',3'}$	$J_{4,5}$	$J_{5,6}$	$J_{1',4}$	$J_{5,1'}$
1	IV	H	Bz	Br	NH_2	9.52	9.09	8.36	9.26			6.03	1.5	0.5	8.0	6.0	0.8	0.4
2	IV	H	Bz	Br	Me	9.66	9.25	8.45	9.35	2.90		6.12	1.2	0.4	7.2	6.0	0.9	
3	IV	H	Pm	Cl	NH_2	9.50	9.05	8.41	9.36			6.12		0.5	7.8	6.1		
4	IV	H	Pm	Cl	Me	9.67	9.21	8.48	9.46	2.91		6.22		0.5	7.1	6.1		
5	IV	H	Tg	Br	NH_2	9.71	9.05	8.45	9.47			6.49	1.6	0.5	8.5	6.0	0.9	0.5
6	IV	H	Tg	Br	Me	9.88	9.22	8.53	9.59	2.89		6.58		0.5	8.3	6.2		0.5
7	IV	Me	Bz	Br	NH_2	9.20		8.16	9.02		2.82	5.95	1.8	0.5		6.1		
8	IV	Me	Bz	Br	Me	9.35		8.15	8.98	2.79	2.85	5.97	1.6	0.4		6.5		
9	IV	Me	Pm	Cl	NH_2	9.19		8.54	9.28		2.84	6.17	1.3	0.4		6.1		
10	IV	Me	Pm	Cl	Me	9.34		8.53	9.27	2.80	2.90	6.20				6.0		
11	IV	Me	Tg	Br	NH_2	9.29		8.25	9.18		2.81	6.38	1.0	0.4		6.2		
12	IV	Me	Tg	Br	Me	9.47		8.27	9.21	2.79	2.88	6.40		0.4		6.8		
13	IV	Me	DBR	Cl	NH_2	9.30		8.22	9.21		2.87	6.54	1.0	0.6		6.2		
14	IV	H	RAP	NH	NH_2	9.58	9.09	8.48	9.43			6.30		0.5	7.8	6.0	1.1	
15	IV	Me	RAP		NH_2	9.31		8.22	9.18		2.81	6.28	1.0	0.5		6.2		
16	V	H	Bz		NH_2	7.13	4.50	4.81	6.17			4.45	1.7		4.5	7.7	1.5	
17	V	H	Bz		Me	7.63	4.56	5.02	6.26	2.99		4.59	1.1		4.6	8.1		
18	V	Me	Bz		Me	7.54		4.94	6.17	3.11	0.83	4.55	1.7	0.7		7.2		
19	V	Me	DBR		NH_2	7.19		4.86	6.35		0.87	5.02	1.7	0.5		7.5		
20	V	Me	DBR		Me	7.40		4.83	6.38	2.99	0.86	5.12	1.5	0.5		7.1		

[a] Solvent for **1**–**15** was D_2O, internal standard DSS; for **16**–**20** solvent was acetonitrile, internal standard TMS. [b] RAP = ribofuranose adenosine pyrophosphate, DBR = dibenzoylribofuranose. For NAD chemical shifts of adenine protons were 2-H, 8.54; 8-H, 8.69; C1′-H, 6.21; $J_{Pyr1',2'}$, 5.5; $J_{Ade1',2'}$, 5.6. For 4-Me-NAD 2-H, 8.75; 8-H, 8.90; C-1′-H, 6.25; $J_{Pyr1',2'}$, 6.3; $J_{Ade1',2'}$, 5.6. For **13**, $J_{Pyr1',2'}$, 6.2; $J_{Ade1',2'}$, 5.3. [c] Corresponding 3-carbamoyl derivative not available, see previous paper.[2a] The preparation of **1**, **3**, **5**, **7**, **9**, and **11** was described in a previous paper.[2c]

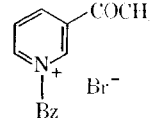


I



(R′ = 2,6-dichloro-Bz)

II



III

Table II
Cyanide Addition Reactions

Structure IV							
R	R_1		k_{COCH_3}	k_{CONH_2}	k_{COCH_3}/k_{CONH_2}	λ_{max}[a]	ϵ_{max}[a]
Bz	H	Br	4,062 ± 300	6.5 ± 0.3	625	263	3890
Bz	Me	Br	2.25 ± 0.20	0.005 ± 0.001	450	260	3251
Pm	H	Cl	57,120 ± 400	510 ± 51	112	267	4021
Pm	Me	Cl	35.3 ± 1.6	0.36 ± 0.04	98	262	3905
Tg	H	Br	412,000 ± 8,300	4,000 ± 50	103	265	5600
Tg	Me	Br	230 ± 10	2.0 ± 0.2	115	261	5460
DBR	Me	Cl	190 ± 20	1.9 ± 0.1	100	266	5500

[a] 3-Acetyl quaternary salt in EtOH.

3-acetyl (k for acetyl compound = 2,300 mol^{-1}) and has obtained equilibrium constants of 250 mol^{-1} for NAD, and 29,000 mol^{-1} for 3-acetyl-NAD.[3] Both Cilento[12] and Kaplan and coworkers,[13] have demonstrated that 3-acetyl-NAD is more efficient than NAD as a H^- acceptor by the use of transhydrogenation experiments. In addition, 3-acetyl-1-benzylpyridinium chloride has been reported as having some antitumor properties against the Yoshida sarcoma in rats,[14] although the 3-carbamoyl analog was inactive. It was decided therefore to prepare some model 3-Ac-substituted pyridinium salts, to study the CN^- addition reactions, and to test two of the compounds (3-acetyl-1-benzylpyridinium bromide III, R = H, and the 4-methyl analog III, R = Me) for possible antitumor properties against the Yoshida sarcoma.

Nmr Spectra.—The nmr spectra of NAD, 4-methyl-NAD, and various 3-Ac-substituted pyridinium salts (IV; Y = Me) are presented in Table I, together with a number of 3-carbamoyl analogs (IV; Y = NH_2) for purposes of comparison.

It has been shown previously[1a] that addition of CN^- to nicotinamide derivatives leads to 1,4-addition, the reaction products being 4-cyano-1,4-dihydropyridine derivatives. In the present work various CN adducts were prepared from the 3-acetylpyridine salts (IV; Y = Me). The assignments for some of these compounds (**17**, **18**, **20**) are presented in Table I together with those for some model 3-carbamoyl-4-cyano-1,4-dihydropyridine derivatives (**16**, **19**), and show that, as expected, the structures of the products correspond to 3-acetyl-4-cyano-1,4-dihydropyridine systems (see previous part in this series[1a]). It is noteworthy that for the two pairs, **16** and **17**, and **19** and **20**, the corresponding chemical shifts of the pyridine ring protons do not differ greatly except in the case of the 2 protons, the 3-acetyl derivatives giving much higher resonance values than the 3-carbamoyl analogues. The 2,3-double bond in 4-cyano-1,4-dihydropyridine systems is conjugated with the carbonyl of the 3 substituent, and any difference in the inductive properties of group Y of the 3 substituent should markedly affect the shielding of the 2 proton. The 4, 5, and 6 protons which are not conjugated to the CO of the 3 substituent are much less affected, as expected. It appears therefore, that the 3-Ac group is more effective as an electron-withdrawing entity in these systems than the 3-carbamoyl group, in accordance with the CN^- equilibrium constant data obtained by Wallenfels.[8] Further evidence is provided from the nmr spectra of the pairs of quaternary salts (**1**–**12**). All the protons in the acetyl series of compounds are resonating at higher field values than those for the corresponding 3-carbamoyl derivatives the relative shift differences being greatest for the 2 and 4 protons adjacent to the 3 substituent. Anisotropic shielding by the carbamoyl bonding electrons will also effect the pyridine ring proton shifts, although the effect is less important for the 5 and 6 protons than for the 2 and 4 protons, due to the attenuation with distance.

The proton assignments for the quaternary derivatives (IV; Y = Me) conform to the general pattern established by previous workers for 3-acetyl[15] and 3-carbamoyl[16] pyridine systems. The 3-carbamoyl pyridinium salts form a useful model series on which to base the assignments for the pyridine ring protons of 4-methyl-NAD. The nmr spectra of NAD have been extensively studied by other workers[17,18] and our assignments for NAD agree well with those of Kaplan and coworkers.[18] The pyridine ring of 4-methyl-NAD was analysed in terms of an ABX system to a first approximation and it is seen from Table I that both the chemical shifts and the coupling constants of 4-methyl-NAD closely resemble those for the model 4-methylnicotinamide nucleosides (**11**, **13**). The inductive effect of the 4-Me group in all these compounds upon the ring charge is clearly reflected in the lower field resonances compared to the corresponding analogues lacking the 4-Me group.

Cyanide Addition Reactions.—The results for the cyanide addition reactions are given in Table II.

In each case the 3-acetyl-4-methyl compounds have values of k which are between 0.05 and 0.06% of the values for the corresponding 3-acetyl derivatives lacking 4 substituents, analogous to the results obtained for the 3-carbamoyl series[1a] (see Table II). Any increase in the electrophilicity of the 4 position caused by a change in the nature of the 3 substituent, should affect the ratio of equilibrium constants to a greater extent in the benzyl compounds than in the other derivatives, consistent with the differing electronic effects of the 1 substituents. Propoxymethyl, tetraacetyl-β-D-glucopyranosyl, and

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dibenzoylribofuranosyl groups are electron-withdrawing entities, whereas the benzyl group, by virtue of its electron-repelling properties, tends to dampen the positive charge (on the 1-N) which affects the reactivity of the 4 position.[19] In agreement with this, the equilibrium constants for the derivatives with electron-withdrawing 1 substituents are increased by approximately the same ratio (98- to 115-fold) by the substitution of 3-acetyl for 3-carbamoyl, whilst there are larger changes in ratio for the benzyl compounds.

By Wallenfels' method[8] the approximate mathematical relationships between the values for the compounds with electron-withdrawing 1 substituents may be utilized to estimate approximate equilibrium constant values for other derivatives. On this basis the value for 3-acetyl-NAD should be between 258 × 98 and 258 × 115 or 25,300–29,700 mol^{-1}, which compares very favourably with the value of 29,000 mol^{-1} obtained by Wallenfels and Dieckmann.[3] This encourages one to put forward a tentative suggested value for the cyanide addition constant for 3-acetyl-4-methyl-NAD, which is at present under preparation,[20] of 20–33 mol^{-1}, which would be a substantial improvement compared with the constant for 4-methyl-NAD.

3-Acetyl-1-benzyl-4-methylpyridinium bromide (III; R = Me) caused 48% inhibition of the tumor weight of rats bearing the Yoshida sarcoma, at a dose of 25 mg/kg, whilst 3-acetyl-1-benzylpyridinium bromide (III; R = H) gave 14% inhibition at a dose of 30 mg/kg. The 4-Me appears therefore to contribute a favorable effect upon the carcinostatic properties of such pyridinium compounds.

Experimental Section

Absorption spectra were recorded on a Unicam SP 800A spectrophotometer linked to an SP 21 slave-recorder. The temperature was maintained at 25.0° by a Shandon K2 ultrathermostat. CN^- equilibrium constants were obtained by the method of Wallenfels.[3,8] Melting points were determined in open capillary tubes and are corrected. Compounds whose elemental analyses are indicated only by symbols showed values within 0.4% of the theoretical values. Evaporations were carried out under reduced pressure. 3-Acetyl-1-benzylpyridinium bromide was prepared by the method of Van Eys.[21]

3-Acetyl-1-benzyl-4-methylpyridinium Bromide.—A solution of 1 g (0.008 mol) of 3-acetyl-4-methylpyridine[22] and 3 g of benzyl bromide in 50 ml of EtOH was heated under reflux for 1 hr, cooled, and Et_2O (100 ml) added. The solid was filtered off, and recrystallization of this precipitate from EtOH gave 2 g (90%) of colorless needles, mp 144–145°. *Anal.* ($C_{15}H_{16}BrNO$) C, H, N.

3-Acetyl-1-propoxymethylpyridinium Chloride.—Freshly distilled chloromethyl-*n*-propyl ether[23] (7.5 ml) was added to a solution of 5 g (0.04 mol) of 3-acetylpyridine in 100 ml of AcMe. After 1 hr at room temperature, the solid was collected and recrystallization from AcMe–MeOH gave 8 g (88%) of pale brown needles, mp 20–22°. *Anal.* ($C_{11}H_{16}ClNO_2$) C, H, N. In a similar way, **3-acetyl-4-methyl-1-propoxymethylpyridinium chloride** was prepared from 1 g (0.008 mol) of 3-acetyl-4-methylpyridine,[22] and gave 1 g (55%) of cream needles, mp 31–32°. *Anal.* ($C_{12}H_{18}ClNO_2$) C, H, N.

3-Acetyl-1-(tetraacetyl-β-D-glucopyranosyl)pyridinium Bromide.—A solution of 7 g of acetobromo-β-D-glucose[24] in 50 ml of MeCN was added to a solution of 5 g (0.04 mol) of 3-acetylpyridine, and the mixture was heated under reflux for 30 min. After leaving the mixture for 4 days at room temperature, MeCN was evaporated off and 100 ml of EtOH was added. Upon cooling in ice, a cream precipitate appeared and was collected. Recrystallization from EtOH gave 5 g (22%) of cream needles, mp 158–159°. *Anal.* ($C_{21}H_{26}BrNO_{10}$) C, H, N. In a similar way, **3-acetyl-4-methyl-1-(tetraacetyl-β-D-glucopyranosyl)pyridinium bromide** was prepared from 5 g (0.04 mol) of 3-acetyl-4-methylpyridine,[22] and gave 5.5 g (27%) of colorless needles, mp 198–199°. *Anal.* ($C_{22}H_{28}BrNO_{10}$) C, H, N.

3-Acetyl-1-benzyl-4-cyano-1,4-dihydropyridine.—A solution of 3 g of KCN in 50 ml of H_2O at 0° was added to a solution of 1 g (0.003 mol) of 3-acetyl-1-benzylpyridinium bromide in 50 ml of H_2O at 0°. A bright yellow oil formed and subsequently solidified. Recrystallization from MeCN–Et_2O gave 0.5 g (62%) of yellow needles, mp 89–91°. *Anal.* ($C_{15}H_{14}N_2O$) C, H, N. Similarly, **3-acetyl-1-benzyl-4-cyano-1,4-dihydro-4-methylpyridine** was prepared from 1 g (0.003 mol) of 3-acetyl-1-benzyl-4-methylpyridinium bromide and gave 0.2 g (25%) of orange plates, mp 95–98°. *Anal.* ($C_{16}H_{16}N_2O$) C, H, N. Also, from 1 g (0.002 mol) of 3-acetyl-1-(3′,5′-di-*O*-benzoyl-D-ribofuranosyl)-4-methylpyridinium chloride[25] there was prepared the **3-acetyl-4-cyano-1,4-dihydropyridine derivative** as 0.5 g (55%) of rose-colored prisms, mp 80–82°. *Anal.* ($C_{26}H_{26}N_2O_7$) C, H, N. Also, **1-(3′,5′-di-*O*-benzoyl-D-ribofuranosyl-3-carbamoyl-4-cyano-4-methyl-1,4-dihydropyridine** was prepared from 5 g (0.01 mol) of 1-(3,5-di-*O*-benzoyl-D-ribofuranosyl)-3-carbamoyl-4-methylpyridinium chloride[26] and gave 2 g (49%) of cream needles, mp 72–74°. *Anal.* ($C_{27}H_{25}N_3O_7$) C, H, N.

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