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NUCLEAR MAGNETIC RESONANCE SPECTRA OF INTERMEDIATES FORMED BY THE ACTION OF NUCLEOPHILES ON PYRIDINE AND PYRIDINIUM IONS

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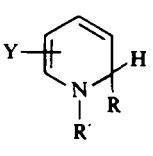
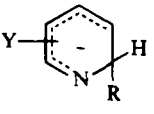
Abstract—1,2-Addition of butyl lithium to pyridine has been observed using NMR spectroscopy. Addition of cyanide ion to various pyridinium ions in DMSO solution has been shown to occur mainly in the 4-position. Only in the case of 3-ethoxycarbonyl-5-bromopyridium iodide has positive evidence been obtained for the formation of addition in the 6-position, although even in this case addition in the 4-position also occurs.

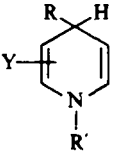
NUCLEOPHILIC substitution of hydrogen in pyridines may proceed via an addition–elimination mechanism in which a σ-complex is formed initially. For example, Ziegler *et al.*[1,2] observed that a precipitate was formed when equimolecular solutions of pyridine and alkyl or aryl lithium compounds were heated together at 70–100°. The precipitate contained lithium hydride and the corresponding 2-substituted alkyl or aryl-pyridines were formed. They therefore suggested that the intermediates may have structures of the type I, where R = alkyl or aryl and R′ = alkali metal. The observation that the addition of water to a solution of the intermediate yields the corresponding 1,2-dihydropyridine[3] supports this structure. Since then the reaction has been used as a general method for preparing 2-alkyl and 2-arylpyridines.[4] Substitution only occurs at the 2-position. Whilst there is not yet final agreement concerning the details of the Tchitchibabin reaction,[5] the general view is that the reaction proceeds by a nucleophilic attach at the 2-position, to yield in the case of sodamide + pyridine either the covalent structure I(Y = H, R = NH_2, R′ = Na) or the corresponding ionic structure II(Y = H, R = NH_2, X^+ = Na^+).[6]



I



II



III

Intermediates which have the general structure I, but for which R′ is an alkyl group rather than an alkali metal, may be formed by the action of nucleophiles on Y-substituted pyridinium ions. However, in many such systems there is considerable evidence for the dominance of the corresponding 1:4 complex (III) *vide infra*. In the case of 3-substituted or unsymmetrical 3,5-substituted pyridines there are of course three possible adducts, namely 1:2, 1:4 and 1:6. Particular interest has centred around

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this type of adduct because of the involvement of the pyridinium moiety of nicotinamide adenine dinucleotide as a hydride acceptor in enzymatic oxidation processes.[7] For this reason most studies have been made on pyridinium ions substituted by electronegative groups, particularly —$CONH_2$, in the 3-position. Grignard compounds, hydroxide ion and borohydride ion all react to yield, finally, 2-substituted products. However, other nucleophiles including cyanide ion and hydride ion (from dithionite) yield 1,4-dihydropyridines. Kosower[8] has suggested that with these latter nucleophiles the position of addition is determined by initially-formed charge-transfer complexes. The fact that one complex, originally postulated as a charge-transfer complex by Kosower,[8] is a σ-complex,[9] does not invalidate the general argument. Recent reviews of various aspects of nucleophilic addition to pyridines and pyridinium ions have been given.[6,10]

It is the purpose of this paper to adduce evidence from NMR spectroscopy for the existence of complexes of general type I and III, in various interactions.

RESULTS AND DISCUSSION

Butyl lithium plus pyridine. Butyl lithium itself shows no NMR absorption below 8 τ. However, the addition of one drop of pyridine to a 15% solution of butyl lithium in hexane gives rise to a yellow coloration and the appearance of five absorption bands, all of equal intensity, extra to the absorption of pyridine namely 3·2 τ (d, J = 6 c/s), 4·0 τ (double d, J = 6 c/s; J = 6 c/s), 5·1 τ (double d, J = 6 c/s, J = 5 c/s) and a multiplet centered around 6·5 τ. With time this set of absorptions increases in intensity at the expense of the pyridine absorption. Attempts to isolate the intermediate were unsuccessful. If the solution is finally heated to 80–90° for 90 min, 2-butylpyridine is formed.

The large upfield shift of the absorption of the complex relative to pyridine suggest that the "aromatic" ring current has been disrupted. Since nucleophilic attack at the 3-position is electronically unfavourable, and the product formed from attack in the 4-position would give rise to a maximum of three absorptions, it suggests that the adduct has the structure I (R = Bu, R′ = Li, Y = H). The alternative ionic structure II is unlikely since the complex is soluble in hexane. This conclusion is also in harmony with the well-known tendency of lithium to bond covalently.

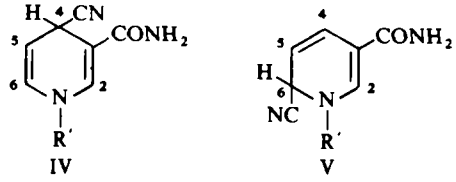
Cyanide ion plus unsubstituted methylpyridinium ion. This mixture in dimethylsulphoxide (DMSO) produces a yellow coloration (λ_{max} = 307 nm). The NMR spectrum shows the disappearance of the pyridinium ion absorptions and the immediate appearance of a new set of absorptions consisting of a doublet at 3·8 τ, J = 6·5 c/s and an unresolved multiplet at 5·5 τ. The relative intensities of these two absorptions appear to be in the ratio 2:3 when the absorption due to the Me group has been subtracted from the latter. This is confirmed by measuring the spectrum of the product formed by the attack of cyanide on methyl(d_3)-pyridinium. Here there is no Me absorption to overlap the absorptions corresponding to H_3, H_4 and H_5. In this case the integral ratio corresponding to (H_2H_6):$(H_3H_4H_5)$ can be measured directly as 2:3. Similar spectra were obtained from solutions in dimethylformamide, but no reaction was detected in aqueous solution. It was not found possible to isolate the product from DMSO. Addition of water decomposed the complex, probably by a reversal of the equilibrium. Of the two possible isomers, I or III, III (Y = H, R = CN, R′ = Me) is the more likely since I should give rise to five separate absorptions

from the ring protons. Although some of these may by chance be superimposed on each other, this is unlikely in the light of observations by Saunders and Gold[11] who observed five distinct resonances for the 1:2 dihydropyridine I (Y = R = H, R′ = Ph). Further evidence in favour of the 1:4 adduct is the similarity of the chemical shifts in its spectrum with those of the protons in the 2- and in the 3-position in III (Y = R = H, R′ = Ph), namely 6·27 τ and 4·53 τ in carbon tetrachloride solution.[12]

A similar result is obtained when cyanide ion is added to a solution of N-(*p*-dinitrobenzyl)-pyridinium methiodide in DMSO.

Cyanide ion plus nicotinamide methiodide. When an excess of cyanide ion is added to a solution of nicotinamide methiodide (N-methyl-3-amidopyridinium iodide) in DMSO, the solution becomes orange-yellow (λ_{max} = 337 nm) the absorptions in the NMR spectrum corresponding to the cation disappear completely and a new set of absorptions appear at 2·50 τ, 5·43 τ, 5·20 τ, 3·70 τ (Table 1). The solution is stable over a period of two weeks. A similar spectrum is obtained when D_2O is used as solvent. In this case also there is no change with time. The solid product, which has been described previously,[13] was isolated from aqueous solution. The NMR spectrum in DMSO (Fig. 1a and Table 1) is very similar to the spectrum of the product generated *in situ*.

Although the NMR spectrum is in agreement with the structure IV (R′ = Me), the spectrum is not inconsistent with structure V (R′ = Me). The ambiguity was resolved by the partial deuteration of nicotinamide methiodide in the 2- and 6-



positions. Solid products were isolated from the action of cyanide ion on these deuterated methiodides. The spectra of solutions of these products in DMSO are shown in Fig. 1b, 1c. By comparison with the spectrum shown in Fig. 1a, it is seen that the singlet at 2·73 τ due to 2-H, decreases as expected. The fact that the other absorption which decreases is the doublet at 3·73 τ suggests very strongly that the product is the 1,4-isomer (IV, R′ = Me) since, if it had been the 1,6-isomer (V, R′ = Me), the doublet at high field would have disappeared.

Cyanide ion plus N-*benzyl*-3-*carboxamidopyridinium chloride.* By the action of cyanide ion on a solution of N-benzyl-3-amidopyridinium chloride in DMSO, an NMR spectrum is obtained which is very similar to that described for IV, R′ = Me (Table 1). A solid product was isolated from the reaction in aqueous solution, which when redissolved in DMSO gave an NMR spectrum (Table 1) almost identical with that for the product generated *in situ*. These results suggest that the product IV, R′ = CH_2Ph is formed corresponding to the N-Me compound described in the previous section.

Cyanide ion plus N-*ethyl*-4-*ethoxycarbonylpyridinium iodide.* In this case the addition of cyanide ion to a solution of the pyridinium salt in DMSO causes a broadening and eventual disappearance of the pyridinium absorptions. However, no other absorptions are observed. The situation is very complicated. This may be due, at least

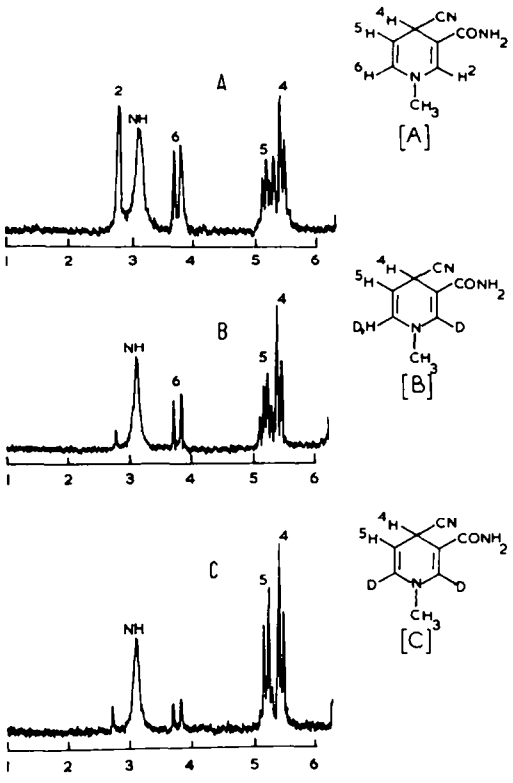


FIG. 1 NMR spectra of the adduct IV (R = Me) in DMSO solution derived from (A) undeuterated nicotinamide (B) and (C) nicotinamide partially deuterated as indicated.

TABLE 1. NMR CHEMICAL SHIFT DATA (AS τ-VALUES) AND COUPLING CONSTANTS J (c/s) OF THE RING-PROTON ABSORPTIONS OF COMPOUNDS OF THE GENERAL TYPE IV IN DMSO

R^1	H_2	H_4	H_5	H_6	$J_{2,6}$	$J_{4,5}$	$J_{5,6}$
CH_3[a]	2·73	5·43	5·20	3·73	1	5	7·5
CH_3[b]	2·50	5·43	5·20	3·70	1	5	7
$CH_2C_6H_5$[a]	2·50	5·35	5·20	3·73	1	5	7·5
$CH_2C_6H_5$[b]	2·50	5·37	5·20	3·63	1	5	7

[a] Solution of isolated compound.
[b] Compound generated *in situ*.

in part, to the formation of free radicals and the consequences of paramagnetic broadening.

Cyanide ion plus N-*methyl*-3-*cyanopyridinium iodide.* The addition of cyanide ion to a solution of 3-cyanopyridinium methiodide in DMSO causes a yellow coloration (λ_{max} = 337 nm), the collapse of the cation absorptions at 0·18 τ, 0·66 τ, 0·88 τ and 1·61 τ and the immediate appearance of a new set of absorptions at higher fields due to the adduct (Table 2). From aqueous solutions a solid may be isolated. The NMR of a

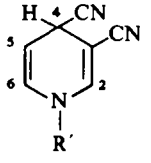
TABLE 2. NMR CHEMICAL SHIFT DATA (AS τ-VALUES) AND COUPLING CONSTANTS J (c/s) OF THE RING-PROTON ABSORPTIONS OF COMPOUNDS OF THE GENERAL TYPE VI.

R^1	solvent	H_2	H_4	H_5	H_6	$J_{2,6}$	$J_{4,5}$	$J_{5,6}$
CH_3[a]	DMSO	2·78	5·28	5·20	3·76	1	5	6
CH_3[b]	DMSO	2·70	5·3	5·20	3·72	1	5	6
CH_3[a]	$CDCl_3$	3·30	5·58	5·20	4·03	1	5	7
$CH_2C_6H_5$[b]	DMSO	2·35	5·1	5·00	3·57	1	5	6
$CH_2C_6H_5$[a]	$CDCl_3$	3·18	5·52	5·17	3·92	1	5	7

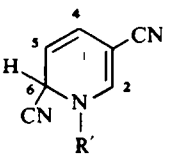
[a] Solution of isolated compound.
[b] Compound generated *in situ*.

solution of this solid redissolved in DMSO is very similar to the compound generated *in situ*. It is slightly different from that observed for solutions in $CDCl_3$ (Table 2). However, the UV spectra of these solutions are identical. Also dilution of the DMSO solution with $CDCl_3$ gives intermediate spectra which tend to the spectrum of solution in pure $CDCl_3$ as the $CDCl_3$ concentration is increased. These small differences in the NMR spectrum are therefore probably the result of specific solvent effects of the very polar DMSO.

The spectrum of the product could be assigned to either structure VI or VII (R′ = Me). The problem is identical with that already discussed in the case of structures



VI



VII

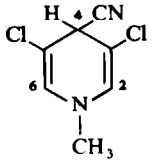
IV and V (R′ = Me), and it was resolved in a similar way by the synthesis of the 2,6-dideutero compound. Comparison of the NMR of this compound with that of the undeuterated compound in $CDCl_3$ solution shows that once again it is the doublet at lower fields which disappears making unambiguous the assignment of structure VI to the product.

Similar results were observed for the product formed by the action of cyanide ion on N-benzyl-3-cyanopyridinium bromide. (Table 2). There is good agreement between the NMR spectrum of this adduct, and the spectrum which has been reported for the product of the reaction between N-(2,6-dichlorobenzyl)-3-cyanopyridinium bromide and cyanide ion.[11] For the N-methyl and N-benzyl compounds reported in this section, no evidence for the prior formation of the 1,6-dihydro isomer has been observed. Such a scheme has been suggested by Lyle[14] for the reaction of 3-substituted pyridinium ions with cyanide ion in ethanolic solution.

The UV spectra of solutions of the pyridinium ion, both in DMSO and in water, to which cyanide ion has been added show only the appearance and increase in intensity of the bands due to the final products, namely the 1,4-dihydropyridines. In ethanolic solution, the results are somewhat different. Whereas the nicotinamide quaternary salts give only the appearance of single, time-invariable, absorptions, the 3-cyano-

pyridinium ions in the presence of cyanide ion show initially absorptions at ~250 nm and ~312 nm, the formed of which gradually disappears whilst the latter shifts to ~332 nm. These spectral changes may be due to the prior formation of 1,6-dihydropyridine which then isomerizes to the 1,4-dihydropyridine as suggested by Lyle.[14] However, the assignment of a structure to this transient species based only on its UV spectrum must be made with some reservation.

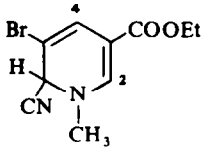
N-*Methyl*-3,5-*dichloropyridinium iodide plus cyanide ion.* The addition of cyanide ion to a solution of N-methyl-3,5-dichloropyridinium iodide in DMSO causes the disappearance of the absorptions of the cation at 0·52 τ (rel. intensity 2) and 0·86 τ (rel. intensity 1) and the immediate appearance of two new absorptions at 3·27 τ (rel. intensity 2) and 4·91 τ (rel. intensity 1). These may be assigned to the 2- and 6-protons and to the 4-protons respectively in VIII.



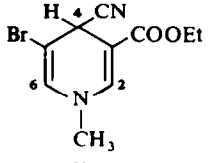
VIII

If attack had taken place at the 2-position, then three resonances of equal intensity would have been expected. Thus for symmetrically substituted pyridinium ions, the position of attack may be determined unambiguously.

N-*Methyl*-3-*ethoxycarbonyl*-5-*bromopyridinium iodide plus cyanide.* Following Lyle,[14] we have measured the NMR spectrum of a solution in $CDCl_3$ of the product obtained by the action of cyanide ion on N-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide in aqueous solution shows two sets of resonances. With time this spectrum changes until only one of the two sets of resonances remain; namely 2·84 τ (d, J = 1·5 c/s), 3·58 τ (d, J = 1·5 c/s), 2·7 τ (s), 5·76 τ q, J = 7 c/s), 6·87 τ (s) and 8·7 τ (t, J = 7 c/s). The relative intensities of these resonances are 1:1:1:2:3:3 respectively. These observations are similar to those made by Lyle[14] although he reported the isolation of the 1,6-dihydro isomer from aqueous solution, but only mixtures were obtained in the present instance, both by extraction with ether and with carbon tetrachloride. Lyle ascribed the changing NMR spectrum to the formation of IX and its isomerization to X.



IX



X

When the solid (which in $CDCl_3$ shows a spectrum corresponding to a mixture of the two isomers) is dissolved in DMSO, and the spectrum recorded immediately, only the absorptions which have been assigned to the 1,4-dihydro isomer (X) are observed. It would appear that the rate of isomerization in DMSO is very fast. Indeed, if cyanide ion is added to N-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide in

DMSO solution, only absorptions corresponding to X are observed. Isomerism also takes place in the solid phase over a period of a few days.

General conclusions. In the present work the only evidence from NMR spectroscopy of any isomerism between the possible 1,6-dihydro and 1,4-dihydro-isomers is in the case of the product of the action of cyanide on N-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide. Nicotinamide quaternary salts give only the 1,4-dihydro compound. All except N-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide give, by addition of cyanide, only one isomer in water and all give only one isomer in DMSO. Even if the extra absorptions observed in the UV spectrum of *ethanolic* solutions of N-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide plus cyanide observed by Lyle[14] are ascribed to the 1,6-isomer, then at least the production of this isomer is dependent on the solvent species and on the particular substituted pyridinium ion. Although the fact that species may not be detected by UV spectroscopy does not preclude their formation, it does place considerable restrictions on their lifetimes and/or their concentrations in the system. It would appear that two stable intermediates are only present when two sufficiently electronegative substituents are present in the ring to stabilize the intermediates, possibly in conjunction with added stabilization by solvation. Such a compound is N-methyl-3,5-dicyanopyridinium, which with cyanide forms the 2-adduct. On heating, this rearranges to form the 4-adduct.[15]

EXPERIMENTAL

All NMR spectra were measured on samples in 0·180″ tubes using a Perkin–Elmer R.10 spectrometer operating at 60·004 mc/s. UV and visible spectra were recorded using a Unicam SP 800 spectrophotometer.

Deuterated compounds. N-Methyl-3-carboxamidopyridinium iodide (2,6-dideuteronicotinamide methiodide) was prepared by the method of Dubb *et al.*[16] However, it was found that the large concentrations of Na_2CO_3 used in the published preparation inhibited the attack of cyanide ion, consequently much smaller concentrations were used, the solns being heated at 100° for 4–6 hr. The amount of exchange was checked by NMR. N-Methyl-2,6-Dideutero-3-cyanopyridinium iodide was prepared similarly.

Cyanide adducts. These were isolated from aqueous soln by extraction with ether, $CHCl_3$ or CCl_4. In the case of N-methyl-3-carboxamidopyridinium iodide (nicotinamide methiodide), the product could also be isolated by direct filtration. Because of the possibility of isomerization they were not recrystallized. Their NMR spectra indicated that they were pure.

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