REACTION OF SOME DICYANOPYRIDINES WITH METHYLMAGNESIUM IODIDE. OBSERVATION OF THE NUCLEAR OVERHAUSER EFFECT IN THE PRESENCE OF NMR SHIFT REAGENT

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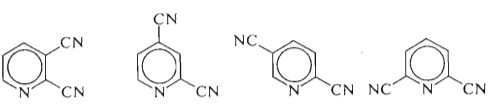
The reaction of methylmagnesium iodide with dicyanopyridines (in which one cyano group is always in the 2 position) was studied. The reaction yields only products which result from an attack on the nitrile groups. The reactivity of the studied compounds is discussed in terms of nucleophilic superdelocalizability and localization energy within the framework of simple HMO theory. In the case of 2,3-dicyanopyridine, cyclic enamine is formed in the reaction. The structure of the enamine was determined by nuclear Overhauser effect (NOE) experiments and confirmed by chemical shifts induced by NMR shift reagent. NOE was observed in the presence of $Eu(FOD)_3$ reagent. A new simultaneous application of the two recently developed techniques for structure and stereochemistry determination is outlined.

Within a general study of the reactivity of cyanoderivatives of pyridine we have undertaken an investigation of the reaction of methylmagnesium iodide with all four possible dicyanopyridines which have a cyano group in the 2 position (*I*–*IV*).

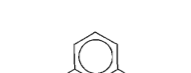


I *II* *III* *IV*

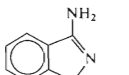
Of these reactions only that of 2,6-dicyanopyridine (*IV*) was previously described[1]. The hydrolysis of the reaction mixture was reported to yield only 11% of 2,6-diacetylpyridine (*V*). Our modification of the reaction conditions has increased the yield to 63·5%; thus compound *V* can be considered as the dominant product of the reaction.

Only the bicyclic enamine *VI* was isolated from the reaction of 2,3-dicyanopyridine (*I*)

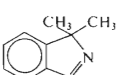
with methylmagnesium iodide (similar to the case of phthalodinitrile[2]), apparently because an immediate reaction of the 3-cyano group of the primary product (the 2-imino derivative) took place. The alternative structure *VII* for the final product was ruled out by NMR experiments to be described later.



V

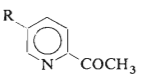


VI



VII

VIII, R = $COCH_3$
IX, R = CN
X, R = CO_2H
XI, R = H



XII, R = $COCH_3$
XIII, R = CN
XIV, R = CO_2H
XV, R = H

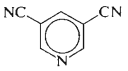
When a large excess of methylmagnesium iodide was used in the reactions of 2,4- and 2,5-dicyanopyridines (*II* and *III*), only the corresponding diacetylpyridines *VIII* and *XII* were obtained. When smaller amounts of organometallic reagent were used, ketonitriles *IX* and *XIII* could also be isolated by chromatography in addition to compounds *VIII* and *XII*. The structure of the ketonitriles was proven by hydrolysis followed by decarboxylation according to the scheme

$$IX \xrightarrow{H_2O} X \xrightarrow{-CO_2} XI \quad \text{or} \quad XIII \xrightarrow{H_2O} XIV \xrightarrow{-CO_2} XV.$$

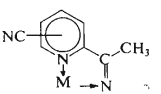
It can be concluded from the above experiments that the place of attack of methylmagnesium iodide is the functional group (CN) in all cyano-2-cyanopyridines (*I*–*IV*). Thus, pyridines substituted at the alpha position by a nitrile group differ markedly from 3,5-dicyanopyridine (*XVI*) and its alkyl derivatives[3,4] which are attacked exclusively at the unsubstituted alpha and gama positions of the heterocyclic ring.* In this connection it appeared interesting to compare this experimentally found reactivity with that predicted according to the reactivity indices calculated by the HMO method. We have already shown[5,6] that the superdelocalizability S_n and the atomic localization energies L_n are the appropriate theoretical quantities for the type of pyridine derivatives studied. It was found, however, that a satisfactory interpretation

* Preliminary experiments with 3,4-dicyanopyridine indicate that the reactivity of this compound represents an intermediate type between that of dicyano derivatives *I*–*IV* and that of *XVI*. This problem will receive attention elsewhere.

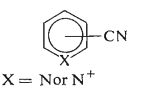
of the reactivity of compounds *I*–*IV* toward methylmagnesium iodide could be achieved only if independent scales are considered for the L_n and S_n quantities on the atomic centers of the pyridine ring and the nitrile group (Table I). We suggest that the cause for this restriction is that in the primary reaction intermediate the electronegativity of the hetero nitrogen atom is being increased in the sense shown in structure *XVII*. If this electronegativity increase is simulated by an increase in empirical coulombic integral h_X of the HMO method, it brings about (Table II) an increase in the reactivity of the carbon centers of nitrile groups in the alpha and gamma positions but not for those centers in the beta position of structure *XVIII*. Consequent-



XVI



XVII



XVIII

ly, the subsequent attack on the second nitrile group by the Grignard reagent is apparently much faster than the reaction of the intermediates generated in the primary attack on the beta and gamma nitrile groups which for steric reasons cannot directly affect the electronegativity of heterocyclic nitrogen. In accord with this assumption is our observation that in the reaction of 2,6-dicyanopyridine (*IV*) no ketonitrile could be obtained even if extremely small amounts of methylmagnesium iodide were used.

NMR PART

NMR spectroscopy was employed to distinguish between the two (*VI* and *VII*) possible structures of the bicyclic enamine. Although the chemical shifts and coupling constants obtained from proton NMR spectra measured under ordinary (Table III) conditions are not in any disagreement with the proposed structures, they do not allow differentiation between the structures. Therefore, nuclear Overhauser effect (NOE) experiments were performed and the following results were obtained: *1*) Irradiation of the line of $-CH_3$ protons had no effect on the other lines in the spectrum. *2*) Irradiation of the line of $-NH_2$ protons resulted in a total of 17 ± 4% NOE enhancement of the lines of the gamma proton.

Since the maximum possible distance between the $-NH_2$ proton and the gamma proton of the pyridine ring is 3·7 Å in structure *VI* and the minimum distance between the same protons is 6·4 Å in structure *VII*, and since NOE cannot be observed between protons more than 3·7 Å apart[7], it follows directly from the results of experiment 2 that the compound has structure *VI*. Moreover, if the compound had

TABLE I

HMO Reactivity Indices for Nucleophilic Attack on Cyano-2-cyanopyridines

Compound	Position of carbon atom[a]			
	2-CN	CN[b]	6	4
	Atomic localization energy[c]			
I	2·201	2·210	2·257	2·226
II	2·197	2·197	2·355	—
III	2·198	2·207	2·214	2·435
IV	2·205	2·205	—	2·374
XVI[d]	—	2·196	2·121	2·090
	Superdelocalizability[e]			
I	1·197	1·176	1·092	1·109
II	1·188	1·187	0·988	—
III	1·197	1·177	1·099	1·128
IV	1·189	1·189	—	0·991
XVI[d]	—	1·167	1·223	1·241

[a] Carbon atoms of nitrile groups and non-substituted carbons of heterocyclic ring; [b] second nitrile group; [c] values for nitrile groups were lowered by $0{\cdot}5\beta$; [d] values taken from ref.[5,6]; [e] values for nitrile groups were increased by $0{\cdot}2\beta^{-1}$.

TABLE II

Nucleophilic Superdelocalizability, S_n, in Dependence on Coulombic Integral at Pyridine Nitrogen Atom in Compounds *I*—*IV* and *XVIII*

Compound	Position[a]	S_N[b]	S_{N^+}[c]	ΔS
XVIII	2-CN	0·988	1·050	0·052
XVIII	3-CN	0·967	0·967	0·000
XVIII	4-CN	0·987	1·049	0·062
I	3-CN	0·976	0·978	0·002
II	4-CN	0·987	1·061	0·074
III	5-CN	0·977	0·977	0·000
IV	6-CN	0·989	1·063	0·074

[a] Position of nitrile group on pyridine ring; [b] nucleophilic superdelocalizability on carbon atom of nitrile group in ground state ($h_N = 0{\cdot}5$); [c] nucleophilic superdelocalizability on carbon atom of nitrile group at $h_N = 2{\cdot}0$.

structure *VII*, the $-CH_3$ group would be only 3·4 Å from the gamma proton, a large NOE[7] would be observed – in contrast to the findings of experiment 1.

Although the above results gave definite evidence in support of structure *VI*, additional evidence was sought in experiments with the NMR shift reagent $Eu(FOD)_3$. As is apparent from Table III, the largest lanthanide induced chemical shifts were experienced by the gamma proton and the smallest by the alpha proton. Such behaviour cannot be explained by the structure *VII*, and thus it is also in accord with the structure *VI*; *i.e.*, in agreement with the NOE results.

NOE experiments on the solution containing $Eu(FOD)_3$ were also performed. When beta proton multiplet was saturated to 50–80% (to achieve complete saturation four audiofrequency generators would be needed) an increase of 18 ± 2% was observed in the integral intensity of alpha proton multiplet (compared with 13 ± 4% without the shift reagent), but nil NOE enhancement was observed on the gamma proton lines (a NOE experiment on these lines could not be carried out in solutions without the reagent because of the proximity of the signals belonging to the two protons, Table III). It is worth mentioning in this respect that signals of gamma protons are broadened by the reagent to such an extent that only a broad doublet is seen in the spectrum. In summary, the results of the simultaneous use of shift reagent and NOE indicate that the site of complexation with $Eu(FOD)_3$ is the $-NH_2$ group. The lanthanide is far enough from the alpha proton that it does not affect its relaxation, but it is so close to gamma proton that it suppresses NOE and broadens its lines.

An important general conclusion from our experimental results is that NMR shift reagents can be used to facilitate (or to make possible in the first place) NOE ex-

TABLE III

Proton NMR Chemical Shifts and Coupling Constants in Enamine *VI*

Conditions	Chemical shifts[a] of protons					Coupling constants[b]		
	CH_3	NH_2	H_β	H_γ	H_α	$J_{\alpha-\beta}$	$J_{\alpha-\gamma}$	$J_{\beta-\gamma}$
B[c]	1·509	5·454	7·262	7·752	8·607	4·98	1·42	7·70
C[c]	1·805	—[d]	7·512	8·256	8·792	4·97	1·51	7·70
LIS[e]	0·291	—	0·250	0·504	0·185	—	—	—

[a] Chemical shifts are in p.p.m. units, relative to TMS line, positive shifts being to low field, the shifts are precise to ±0·05 p.p.m.; [b] coupling constants are in Hz units, for the analysis of the ABC spectrum see Experimental part. The coupling constants and shifts were assigned to alpha, beta and gamma protons of pyridine ring according to ref.[15]; [c] see Experimental part; [d] not measurable; [e] lanthanide induced shift determined as the difference between the values in the first and second row of the table.

TABLE IV
Reaction of Cyano-2-cyanopyridines with Methylmagnesium Iodide

Compound (procedure)	Product (m.p., °C)	Yield %	Formula (m.w.)	Calculated/Found % C	% H	% N
I (B)	*VI* (173—180)	38·4	$C_9H_{11}N_3$ (161·2)	67·06 67·29	6·88 6·98	26·07 25·79
II (A 1)	*VIII* (71—71·5)	37·1	$C_9H_9NO_2$ (163·2)	66·25 66·35	5·56 5·69	8·58 8·56
	IX (101—102)	26·3	$C_8H_6N_2O$ (146·2)	65·74 65·85	4·14 4·29	19·17 18·98
III (A 1)	*XII* (77—79)[a]	41·4	$C_9H_9NO_2$ (163·2)	66·25 66·52	5·56 5·74	8·58 8·82
	XIII (102—106)	45·6	$C_8H_6N_2O$ (146·2)	65·74 66·02	4·14 4·48	19·17 19·25
IV (A 2)	*V* (78—79)[b]	63·5	— —	— —	— —	— —

[a] Lit.[16] m.p. 81°C; [b] lit.[1] m.p. 79°C.

periments by increasing the shifts difference. Naturally, there are limitations to the applicability of this new combination of techniques. For example, the "observed" nucleus must be remote enough from the lanthanide atom so that electron-proton dipole-dipole relaxation will not be effective (the effect of relaxation is proportional[8] to r^{-6}, where r is the distance of the proton in question to Eu atom). One of the involved nuclei must, however, be close enough so that an observable shift is induced (the induced shift depends[9] on r^{-3}). It is our believe that the application of NOE in the presence of a shift reagent may become a new and valuable technique for structure determination, especially of complex organic compounds. (Apparently the same conclusion was reached by Tori and coworkers[10] in a paper published when this paper was being submitted.)

EXPERIMENTAL

Dicyanopyridines I—IV. The compounds were prepared from the corresponding amides by dehydration employing phosphorus oxychloride. The products were purified by vacuum sublimation and by crystalisation from ethanolic solutions. 2,3-dicyanopyridine (*I*) m.p. 77—78°C (lit.[11] m.p. 80—82°C), 2,4-dicyanopyridine (*II*) m.p. 87—89°C (lit.[12] m.p. 88—89°C), 2,5-dicyanopyridine (*III*) m.p. 111—111·5°C (lit.[11] m.p. 111—112°C), and 2,6-dicyanopyridine (*IV*) m.p. 123—124°C (lit.[1] m.p. 126°C).

Reaction of dicyanopyridines I—IV *with methylmagnesium iodide.* General procedure: A solution of Grignard reagent was prepared from 0·4 g of magnesium and 1 ml of methyl iodide in 20 ml of ether. Dicyanopyridine (0·5 g) dissolved in ether (20 ml) was then added dropwise to the solution of the Grignard reagent while stirring at room temperature. After stirring for 8 hours at room temperature the reaction mixture was decomposed by 30 g of ice and 1 ml of concentrated sulphuric acid. The product was isolated by the following procedures: *A*) The etheric layer was separated and the aqueous layer shaken with 3×50 ml of ether. The joint ether extracts were dried over $MgSO_4$, and the solvent was distilled off. The products were isolated either by chromatography (procedure *A* 1) or by sublimation (procedure *A* 2). The chromatography was carried out on Reanal alumina of III—IV activity (according to Brockmann). *B*) After separation of the etheric layer the aqueous layer was made alkaline by NaOH solution and repeatedly extracted by ether. The extract was dried over $MgSO_4$ and after the removal of the solvent the residue was chromatographed. The results are summarized in Table IV.

Degradation of ketonitriles IX *and* XIII *to monoacetylpyridines* XI *and* XV. A mixture of ketonitrile (0·1 g), concentrated hydrochloric acid (3 ml) and water (1·5 ml) was boiled for 3 hours. The liquid was removed by vacuum distillation, and the solid residue was dried under vacuum at 110—120°C (20 Torr) for 2 hours. The dry solid was then mixed with CaO (1 g) in a mortar and the mixture dry distilled. The resulting liquid was chromatographically compared with reference compound 2-,3- and 4-acetylpyridines. The chromatography was carried out on a Chrom II chromatograph at 160°C using Tridox as the stationary phase and nitrogen as the carrier gas. The products from ketonitrile *IX* and ketonitrile *XIII* have the same elution times as 4-acetylpyridine (*XI*) and 2-acetylpyridine (*XV*), respectively.

Calculations were carried out on National Elliot 803b and Tesla 200 computers using programs (authors: V. Kvasnička, Institute of Physical Chemistry, Czechoslovak Academy of Sciences and V. Skála) for the standard HMO method. The following parameters were employed: $h_{N(pyridine)} = 0{\cdot}5$, $h_{N(nitrile)} = 0{\cdot}5$ and $k_{C\equiv N(nitrile)} = 1{\cdot}4$.

NMR *spectroscopy.* All the proton NMR spectra were measured on a modified Tesla BS 477 spectrometer operating at 60 MHz. An internal lock was employed for stabilization of the frequency/field ratio. Irradiating frequencies were obtained by a standard side-band modulation technique using Tesla BM 524 and BM 269 A audio generators. The irradiating fields (H_{1eff}) were in the range 1·3—2·6 Hz.

Three solutions of the enamine were prepared: *A*) a 0·25M solution of the enamine in $CDCl_3$ was employed for NOE experiments using a lock on the line of methyl protons, *B*) a 0·30M solution of the enamine in $CDCl_3$ with a trace of hexamethyldisilane (HMDS) was used for all the other experiments with the HMDS line serving as the locking signal, *C*) the same solution as *B*) except that $Eu(FOD)_3$[tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-octane-4,6-dionato)europium(III)] was added to the enamine in molar ratio 1 : 12·5. This solution served both for measurements of the induced shifts and NOE enhancement in the presence of the shift reagent.
The dissolved oxygen was removed from the solutions by bubbling gaseous dry nitrogen through the solutions.

Analysis of the ABC spectra of pyridine protons was performed on a Tesla 200 computer using the direct method of Castellano and Waugh[13]; interprotonic distances were calculated on the same computer according to the method described by Thompson[14] using the usual values for bond lengths and angles.

The ABC proton chemical shifts were assigned to individual ring protons by analogy to the examples in the standard NMR text[15].

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