



Conformational Studies By Dynamic NMR. Part 51¹ Gear Effect In Substituted Pyridones.

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Abstract: Two conformational isomers have been NMR detected at -30° in 2-substituted pyridones having an isopropyl group bonded to the Nitrogen atom. Their existence is due to the restricted rotation of the N-isopropyl group influenced by the "gear effect" of the flanking 2-alkyl groups (Me, Et, Pr¹). The interconversion barrier for this process (~ 15 kcal/mol) was measured by total line shape analysis and is independent of the size of the flanking alkyl groups. Molecular Mechanics calculations and NOE difference experiments at -70° allow the unambiguous identification of the structures corresponding to the gear conformers.

INTRODUCTION

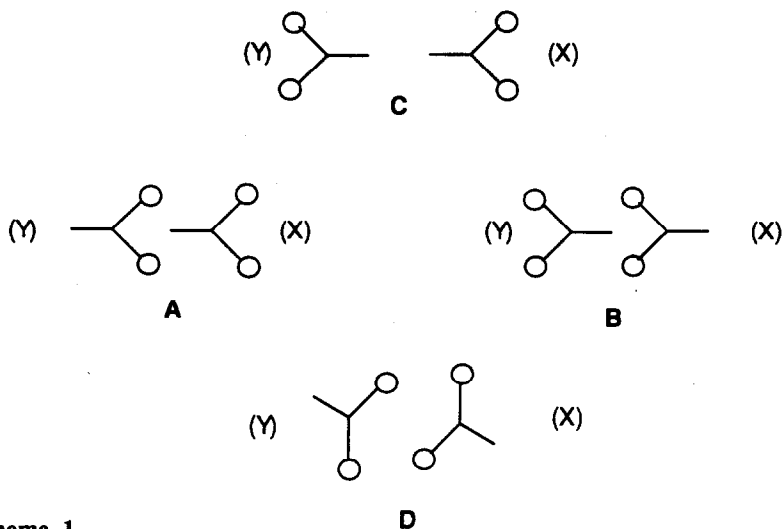
Two geminal or vicinal isopropyl groups bonded to a planar framework give rise to four energy minima each of which might in principle be populated.² Low temperature Dynamic NMR spectroscopy allows the detection of these conformers but usually only two are observed and the barrier to the interconversion process can be measured.

Examples of such investigations for the case of geminal isopropyl groups are reported in ref. 3-8 and for vicinal isopropyl groups in ref. 9-13. The presence of more than two vicinal isopropyl groups entails a variety of additional conformers.¹⁴⁻¹⁶

In the great majority of these situations the more stable conformers were found to be those where the two isopropyl groups adopt a geared conformation with each isopropyl methine hydrogen tucked into the notch between the methyl groups of the neighbouring isopropyl group.¹⁶ Such a "gear meshed" situation is illustrated in Scheme 1 (conformers A,B) where the same representation reported in the previous literature^{2,4-8,13} has been adopted.

In at least one case, however, conformer C was also detected.¹⁰ It was also observed^{2a} that "each isopropyl group tends to turn its bulky side toward the smaller of its neighbours" so that if the flanking group X is much smaller than Y (for instance when X is a lone pair or a hydrogen atom) structure A usually corresponds to that of the major conformer.^{4,6-8} The latter structure has been actually determined by X-ray diffraction in N-diisopropyl sulfinyl hydrazine,⁶ where Y is the SO moiety and X the lone pair of the sp² nitrogen.

Assignment of the conformers is usually carried out with the help of Molecular Mechanics calculations and by taking into account the low temperature proton chemical shifts.

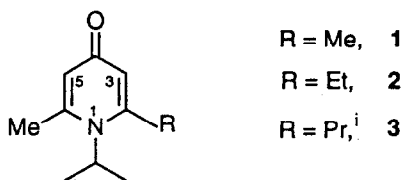


In the great majority of cases so far investigated the flanking groups were moieties (such as C=O, C=S, N=O, N=NR, S=O) which produce large downfield shifts for the signals of the nearby methine hydrogen in one of the conformers. On the contrary, the NOE effect, which would also be helpful for this purpose, has been rarely employed^{4,8} owing to the difficulties in carrying on the experiment at very low temperatures.

RESULTS AND DISCUSSION

Stereodynamics.

We have observed that line broadening effects are visible on varying the temperature of the NMR spectra of 2-alkyl derivatives of 1-isopropyl-6-methyl-4-pyridones, 1-3

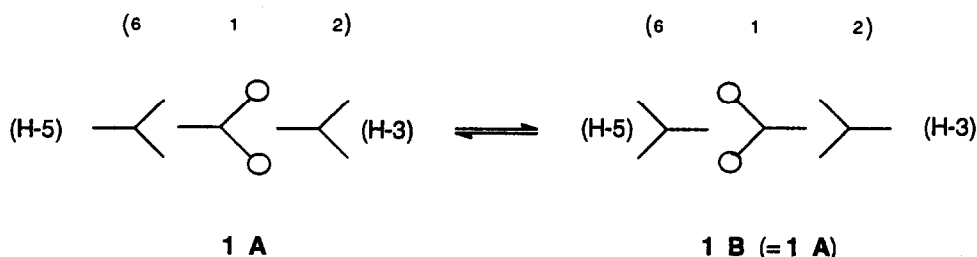


A typical example is offered by derivative 3 whose H^1 spectrum displays quite broad lines at room temperature for the 6-methyl group and for the two methine hydrogens of the isopropyl groups in positions 1 and 2. On lowering the temperature to -30°C these signals split into pairs, with relative integrated intensities of about 4:1. The signal of one of the sp^2 methine hydrogens is also split, although with a much smaller chemical shift separation. Clearly the apparent coincidence of all the remaining signals is accidental. The C^{13} low temperature spectrum of 3 also displays a separation for the majority of the lines, including those due to the three quaternary carbons. On raising the temperature well above 25°C (in toluene as solvent) all these broad H^1 and C^{13} signals sharpen, eventually yielding lines with the same width. This behaviour fits the expectation for an

equilibrium between two unequally populated conformers of the type described in Scheme 1, where Y is now the methyl group in position 6 and X the hydrogen atom in position 3. A very similar temperature dependence is observed for the spectrum of **2** (R=Et), where the conformer ratio at -30°C in CD_2Cl_2 is about 2:1.

When the N-isopropyl group of **2** is replaced by a phenyl group (yielding 1-phenyl-2-ethyl-6-methyl-4-pyridone **4**) the line broadening effect is no longer observed. This confirms that the conformers involved must be structures of the type described in Scheme 1, for the gear effect is brought about by the interplay between two sp^3 carbon atoms (i.e. atoms rotating about a threefold axis) and is thus hampered by the introduction of the phenyl moiety which behaves as a twofold rotor.

In the case of the symmetric derivative **1** (R=Me) the substituent in position 6 (i.e. the group labelled Y in Scheme 1) is equal to that in position 2. Thus, as shown in Scheme 2, the spectrum of structure **1A**, which is expected to be the preferred conformation, must be equal to that of **1B**. As a consequence compound **1** should display at low temperature a pair of equally intense signals for the methyl groups in positions 2,6 and for the methine hydrogens in positions 3,5, but a single signal for the hydrogen of the N-isopropyl group.



Scheme 2

The same will occur in the low temperature C^{13} spectrum where, in addition, the C-2, C-6 quaternary carbons should also display two equally intense lines. These expectations were fulfilled as the H^1 spectrum of **1** (at -50°C) is that of a single structure with only one CH septet and only one CH_3 doublet for the N-isopropyl moiety. At the same time two lines of equal intensity are observed for the 2- and 6-methyl groups. The absence of the predicted separation for the shifts of H-3 and H-5 can be attributed to accidental coincidence since the corresponding C-3 and C-5 C^{13} signals at -50°C yield a pair of lines, as do the methyl and the quaternary carbons in positions 2,6. On the other hand the C^{13} lines of the isopropyl moiety remain unsplit, as obviously does the signal of the C=O carbon.

Computer simulation of the line shape of the H^1 spectra of **1-3** allowed us to determine the rate constants and hence the ΔG^{\ddagger} values for the interconversion process. In particular the signals of the methyl groups in positions 2,6 were monitored, as they display a conveniently large chemical shift difference.

A typical example is reported in Figure 1 for derivative **3**. In the latter case simulations were also repeated by monitoring the CH signals of the 2-isopropyl group, which were reduced to a pair of singlets by decoupling at the frequency of the appropriate methyl signals. Within the estimated uncertainty (± 0.15 kcal/mol) the same ΔG^{\ddagger} value is obtained from the two analyses.

A small solvent effect was also detected since in a less polar solvent (toluene d-8) the ΔG^{\ddagger} of **2** turns out to be 14.6 kcal/mol, i.e. 0.5 kcal/mol smaller than in CD_2Cl_2 .

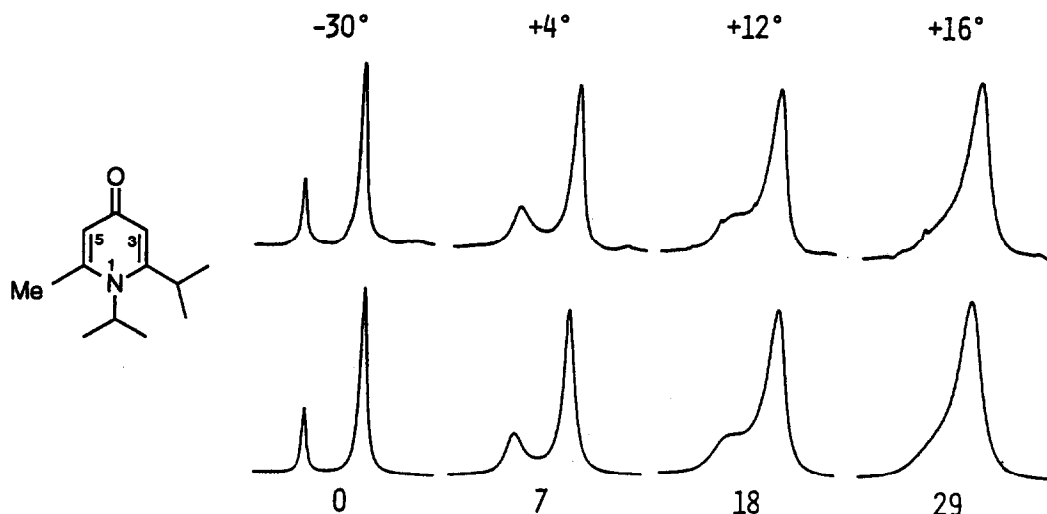


Figure 1. Temperature dependence of the 6-methyl signals of **3** in CD_2Cl_2 (top trace). Underneath is reported the computed line shape obtained with the rate constants (k in sec^{-1}) indicated. The conformer ratio is also temperature dependent (4:1 at -30°C but 2.5:1 at $+10^\circ\text{C}$).

The interconversion barriers for **1-3** in the same solvent were found (Table 1) to be equal within the experimental errors, a feature encountered in other analogous cases.^{8,12} Such an invariance of the barrier with the size of the R group suggests that the lower ground state strain in **1** with respect to **2** and **3** ($\text{R}=\text{Me}, \text{Et}, \text{Pr}^i$ respectively) is almost exactly counterbalanced by a higher transition state strain⁸ in **3** with respect to **2** as well as to **1**.

Table 1. Proton Chemical Shifts (δ in ppm at 200 MHz) for the 6- CH_3 Groups of **1-3** in CD_2Cl_2 at -30° . The Relative Intensity of the Two Signals is in Parenthesis. The Free Energy of Activation (in kcal/mol) and the Temperature Range of the Measurements are Also Reported.

Compound	δ (6- CH_3)	ΔG^*	T range ($^\circ\text{C}$)
1	2.492 (50 %); 2.405 (50 %)	15.0	$6^\circ\text{-}20^\circ$
2	2.489 (67 %); 2.382 (33 %)	15.1 ₅	$9^\circ\text{-}18^\circ$
3	2.480 (20 %); 2.358 (80 %)	15.1	$4^\circ\text{-}16^\circ$

Conformational analysis.

In order to obtain a reliable assignment of the two gear conformers of **2** and **3**, Molecular Mechanics calculations¹⁷ and NOE experiments were performed.

In the case of **3** these calculations indicate that a structure of type A (Scheme 1, where Y = Me-6 and X = H-3) is the most stable one. However structure B, which usually corresponds to the second detectable conformer is 3.9 kcal/mol less stable, which suggests that its population would be much too low to be NMR detectable. Structure D was computed to have an even higher energy difference (9.4 kcal/mol) and should be also discarded. On the other hand a structure of type C was found to be only 0.1 kcal/mol less stable than A, thus making it a likely candidate for the minor conformer of **3**. On the other hand such a small energy difference does not justify the conclusion that **3A** is the preferred conformer, without additional evidence. The computed structures **3A** and **3C** are reported in Figure 2 (top): internal motions with very low barriers such as N-inversion, ring reversal, and C-C libration (which are NMR invisible) provide the dynamic plane of symmetry which renders homotopic the pair of methyl groups within each isopropyl substituent.

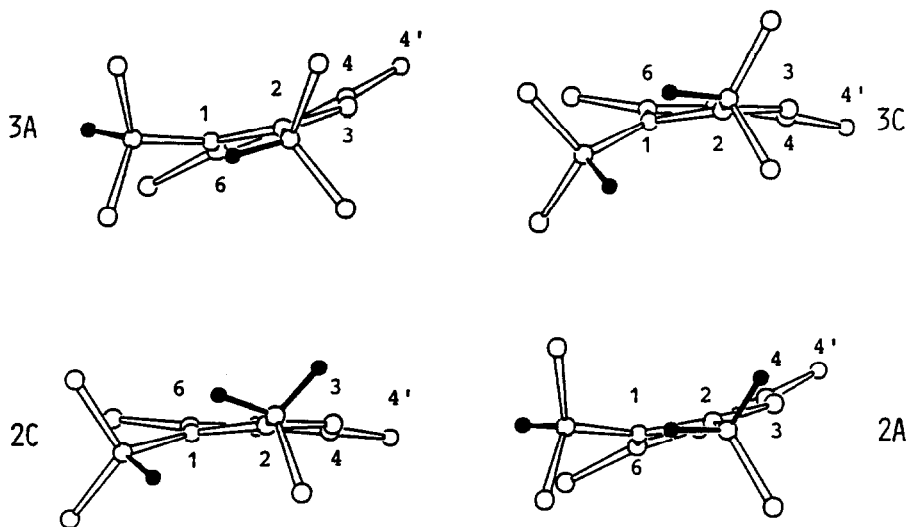


Figure 2 Structures of the observed gear conformers of **3** and **2** as obtained from MM calculations. The structures on the left (**3A**, **2C**) have the lower energies. For simplicity only the methine bonds of the isopropyl groups and the methylene bonds of the ethyl group are reported (in black). The atom in position 1 is Nitrogen, that indicated as 4' is Oxygen, all the others being Carbons.

Experimental evidence for assigning structures **3A**, **3C** was obtained by means of differential NOE experiments at -70°C . On the basis of the measured ΔG^{\ddagger} values the half life time of each conformer at this temperature is about 20 minutes, thus making negligible the saturation transfer effect between the conformers.¹⁸

Simultaneous irradiation of the NCH signals of both conformers of **3** yields an enhancement (1.7%) for the 6-methyl signal, but no effect on the methine signal of the 2-isopropyl group in the major conformer. On the contrary in the minor conformer there is an enhancement (5%) for the latter signal but no effect for the signal of the 6-methyl group (Table 2).

These results agree well with the structures **3A** and **3C** proposed, respectively, for the major and the minor conformers, for in **3A** the computed average interproton distance between NCH and the 6-methyl group

is much smaller (2.7 Å) than that between NCH and 2-CH hydrogens (3.7 Å). The opposite occurs in 3C where these distances are 4.5 and 2.1 Å, respectively (Table 2).

Finally structure 3B and structure 3D (as observed in many other similar cases) can be excluded for the minor conformer as we would not have detected the enhancement of the 2-CH signal, since the NCH/2-CH distance in 3B is equal to that of 3A and in 3D it is even longer, being 5.1 Å.

Table 2. Computed Energies (in Kcal/mol) and Averaged Interproton Distances (in Å) for the Conformers of 2 and 3. The Experimental Proportions of the Conformers and the Observed NOE Effects (in CD₂Cl₂) are also Reported.

Conformer	Energy ^a	Proportion ^b	Distance from NCH		NOE effect ^c
3A	0.0	80%	6-CH ₃	2.7	1.7%
			2-CH	3.7	-
3B	3.9	0%	6-CH ₃	4.5	
			2-CH	3.7	
3C	0.1	20%	6-CH ₃	4.5	-
			2-CH	2.1	5.0%
2A	0.3	33%	6-CH ₃	2.7	2.0%
			2- <u>CH</u> ₂ CH ₃	4.3	-
			2-CH ₂ <u>CH</u> ₃	5.5	-
2B	1.1	0%	6-CH ₃	4.5	
			2- <u>CH</u> ₂ CH ₃	2.3	
			2-CH ₂ <u>CH</u> ₃	4.5	
2C	0.0	67%	6-CH ₃	4.4	-
			2- <u>CH</u> ₂ CH ₃	2.8	3.4%
			2-CH ₂ <u>CH</u> ₃	3.1	1.1%

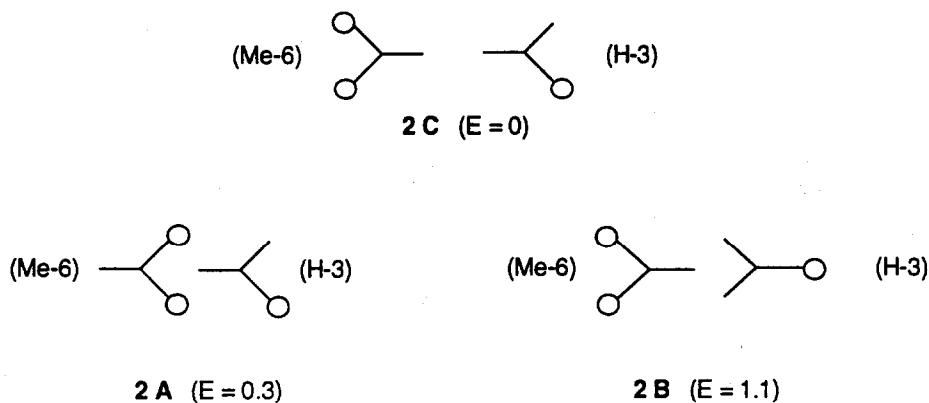
a) The energies for the more stable conformers (3A and 3C) were taken as 0.0 Kcal/mol.

b) Determined at -30°C.

c) Enhancement observed on irradiating the NCH signals of both conformers at -70°C.

The MM calculations for 2 indicate that there are three conformers (2A, 2C, 2B of Scheme 3, where the relative energies, E, in kcal/mol are shown) with similar energy levels. Their structures parallel the corresponding structures 3A, 3C, 3B of Scheme 1 somewhat.

Low temperature NOE measurements were once again used to decide which of these structures corresponds to the major and to the minor conformer. In Figure 3 (bottom) the proton signals (in CD_2Cl_2 at -70°C) for the CH_2 group in position 2 and for the CH_3 group in position 6 are displayed. The NOE difference spectrum obtained by irradiating the NCH signals of both conformers is shown on the top. The 6-methyl singlet of the minor conformer shows a noticeable (2%) enhancement whereas that of the major one does not. On the other hand the quartet of the CH_2 group of the minor conformer is unaffected, while that of the major conformer is enhanced by 3.4%. Structure **2A** has thus to be assigned to the minor conformer since it is the only conformation having a short NCH/6- CH_3 and a large NCH/2- CH_2 interproton distance (Table 2). Structures **2B** and **2C** could equally well explain the NOE observed for the major conformer, in that both have short NCH/6- CH_2 and large NCH/6- CH_3 interproton distances. A choice between these two could be made, however, by monitoring the NOE effect on the methyl group of the ethyl moiety in position 2. The NCH/ CH_3 distance is computed to be much smaller in **2C** (3.1 Å) than in **2B** (4.5 Å). The NOE observed on irradiation of the NCH signals shows that the triplet of this methyl group experiences a not negligible (1%) enhancement in the major conformer whereas no effect is detected in the minor one (Table 2), so conformer **2B** can be discarded. This leaves structures **2C** and **2A**, respectively, as the major and minor visible conformers (see Figure 2).



Scheme 3

Thus both the MM calculations and the NOE experiments suggest that the relative stability of conformers **A** and **C** has been reversed in **2** with respect to **3**, **3A** being more stable than **3C** whereas **2C** is more stable than **2A**. An independent support of this conclusion is offered by the low temperature chemical shifts of the 6-methyl groups reported in Table 1. Whereas in **3** the upfield signal (2.36 ppm) is more intense than its downfield companion (2.48 ppm), the opposite occurs in derivative **2** where the signal at 2.38 ppm has half the intensity of that at 2.49 ppm. Corresponding inversion was also observed consistently for the C^{13} signals of NCH, C-3, C-5, C-2, and C-6.

It is noteworthy that, despite the smallness of the energy differences involved, structures with the lowest computed energies actually correspond, in both **2** and **3**, to conformers found to be the most stable by means of

NOE experiments. As a consequence MM calculations can be relied upon when they indicate the structure of the preferred conformer of 1.

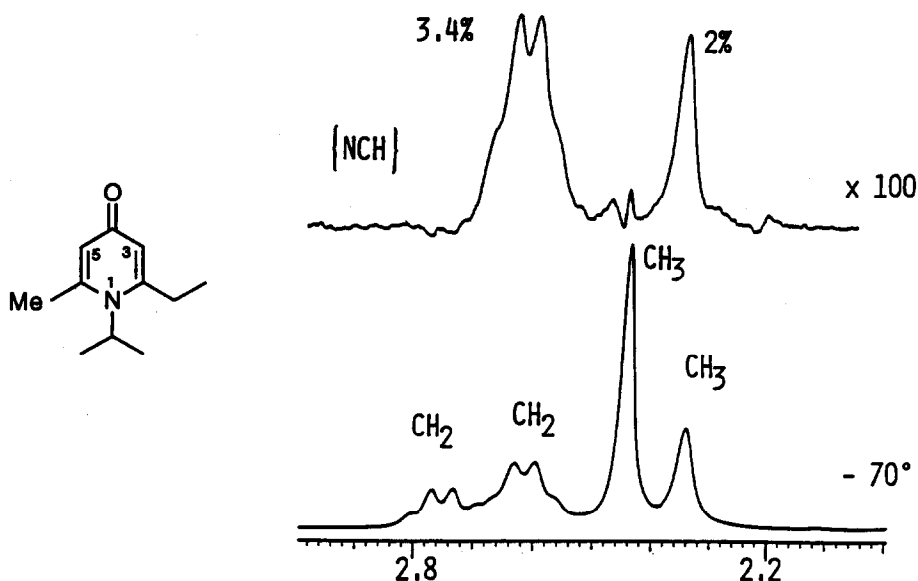


Figure 3. Proton NMR signals (lower trace) for the 2-CH₂ and for the 6-CH₃ groups of derivative 2 at -70°C, showing two unequally populated conformers. The top trace (vertically amplified 100 times) displays the NOE difference spectrum obtained at the same temperature by irradiating the NCH signals of both conformers. Enhancement is observed for the CH₃ singlet (2%) of the minor and for the CH₂ quartet (3.4%) of the major conformer.

CONCLUSIONS

The alkyl pyridones of the present investigation offer a quite convincing example of how the combined use of Molecular Mechanics calculations, Dynamic NMR spectroscopy and low temperature NOE experiments allows one to obtain reliable stereodynamic analysis of geared conformers.

EXPERIMENTAL

NMR Measurements.

Dynamic NMR spectra were obtained with a standard variable temperature device. The values of the temperature were measured by means of the methanol shift. The low temperature NOE experiments were carried out in nitrogen saturated CD₂Cl₂ solutions at 200 MHz. The signals were presaturated for 10 s before acquiring the spectrum with the decoupler turned off. The irradiation was carried out by setting the decoupler at the frequencies of the various lines of the multiplet to be saturated and cycling it over these lines (about 60 cycles). A program that accumulates the difference between two FID's (the one corresponding to the preirradiated spectrum and the one where the irradiation is kept away from any signal) was employed. A control spectrum, with half the number of the scans, was subsequently obtained in the same conditions and the NOE values determined by comparing the line intensities of the two spectra.

^1H NMR spectra were recorded on a Varian, Gemini 200 MHz spectrometer in CDCl_3 solutions. Chemical shifts are given in ppm from SiMe_4 . Coupling constants are given in Hz. Mass spectra were determined by the electron impact method on a VG 7070 instrument. GC-MS analyses were performed with an HP work station formed by an HP 5890 gaschromatograph equipped with a methyl silicone capillary column and by an HP 5970 mass detector. IR spectra were recorded on a Perkin Elmer 1600 FTIR apparatus. Melting points are uncorrected.

2,6-Dimethyl-1-isopropyl-pyridin-4-one (1), 2-ethyl-1-isopropyl-6-methyl pyridin-4-one (2)¹⁹, 1,2-diisopropyl-6-methyl-pyridin-4-one (3), were prepared by reaction of α' dianions of the appropriate β -isopropyl amino- α,β -unsaturated ketones with esters according to our previously reported procedure.¹⁹ Physical data of unknown compounds are reported below.

2,6-dimethyl-1-isopropyl-pyridin-4-one (1). Oil. ^1H NMR δ 1.55 (d, $J=7.5$, 6H, $(\text{CH}_3)_2\text{CH}$); 2.43 (bs, 6H, 2 CH_3); 4.75 (ept, J 7.5, 1H, $(\text{CH}_3)_2\text{CH}$); 6.25 (s, 2H, H-3, H-5). IR ν_{max} (CCl_4) 1632 cm^{-1} (C=O). MS $m/z(\%)$: 165 (M^+ , 68), 137 (46), 122 (30), 94 (100), 80 (23), 67 (25), 53 (50), 43 (74). (Found M^+ 165.11522, $\text{C}_{10}\text{H}_{15}\text{NO}$ requires: 165.11536).

1,2-isopropyl-6-methyl-pyridin-4-one (3) Mp. 65-67° ^1H NMR δ 0.87 (d, $J=7$, 6H, $(\text{CH}_3)_2\text{CH}$); 1.2 (d, $J=6$, 6H, $(\text{CH}_3)_2\text{CH}$); 2.05 (bs, 3H, CH_3); 2.88 (bm, 1H, $(\text{CH}_3)_2\text{CH}$); 4.41 (bm, $(\text{CH}_3)_2\text{CH}$); 5.75 (s, 1H, H-3 or H-5); 5.92 (s, 1H, H-3 or H-5). IR ν_{max} (CCl_4) 1635 cm^{-1} (C=O). MS $m/z(\%)$ 193 (M^+ , 47), 165 (13), 150 (100), 136 (26), 108 (74), 41 (31). (Found M^+ 193.14692, $\text{C}_{12}\text{H}_{19}\text{NO}$ requires: 193.14666).

ACKNOWLEDGMENT

The authors thank MURST and CNR, Rome for financial support.

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(Received in UK 25 October 1993; accepted 2 December 1993)