# Identification of *N*-Methylpyrazole Analog Isomers by $^{13}C$ NMR



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Using several *N*-methyl pyrazole analogs the utility of $^{13}C$ nmr in determining isomeric structures was examined. The chemical shift assignments of the pyrazole carbons and thus the isomeric structures were determined using a combination of proton coupled and proton decoupled $^{13}C$ nmr spectra.

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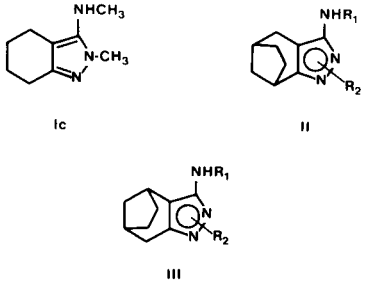
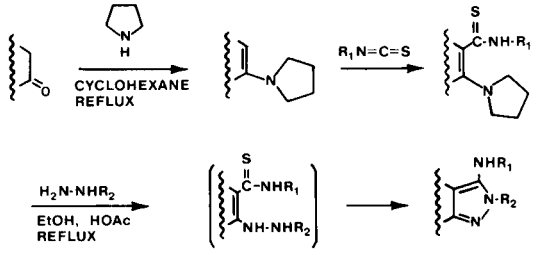
The search for an active anti-inflammatory agent which is both non-acidic and non-steroidal lead to the synthesis of several bicyclic analogs (II, III) of tetrydamine (Ic), a known anti-inflammatory agent with moderate activity (1). Along with the activity (2), these bicyclic fused pyrazoles presented an interesting problem in structure proof.

FIGURE 1




The bicyclic compounds were synthesized by a method similar to that described for tetrydamine (1) as shown in Scheme I.

SCHEME I.




According to Jacquier and Maury (3), $R_2$ in such systems should be in the 2-position. For tetrydamine, if acetic acid is not used, the intermediate (shown in brackets) can be isolated and its structure determined. Subsequent cyclization in refluxing ethanol-acetic acid gives the 2-substituted species.

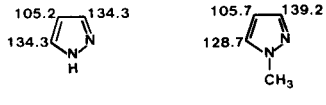
The technique of intermediate isolation is useful, but time consuming and not necessarily always accurate since rearrangements cannot be completely ruled out under the given reaction conditions. The ideal structure proof would be on the final product. Our problem then was to unambiguously determine, by spectral means, the structure of the single isomer of the bicyclic tetrydamine analogs using only the *N*-unsubstituted compounds (Ia, IIa, IIIa) as a reference.

The 60 MHz proton nmr spectra of the bicyclic compounds were determined and although the spectra were in complete agreement with the general structure, no way for identification of a single geometric isomer was evident. Proton nmr might have been helpful if both isomers were available, but this was not the case.

Mass spectral data proved relatively useless. In all cases, the first fragmentation is the loss of the methyl group attached to the pyrazole ring nitrogen, thus eliminating the existence of any isomeric forms in later fragmentations. Correct molecular ions were found for each compound.

According to Levy and Nelson (4), pyrazole has a symmetrical nature in the $^{13}C$ nmr due to its rapid tautomerism. However, when one of the nitrogens is methylated and the tautomerism disrupted, the two carbons adjacent to the nitrogens show significant shifts. The carbon adjacent to the methylated nitrogen is shifted upfield by 5.6

FIGURE 2




ppm and the carbon adjacent to the non-methylated nitrogen is shifted downfield by 4.9 ppm. The carbon not adjacent to either nitrogen is shifted only 0.5 ppm downfield by the methylation. Since the bicyclic compounds of interest are substituted pyrazoles, this finding should be able to be applied without major difficulty.

The analogy between *N*-methylpyrazole and such fully substituted pyrazoles is certainly not perfect, but variations due to substituent effects could be minimized if

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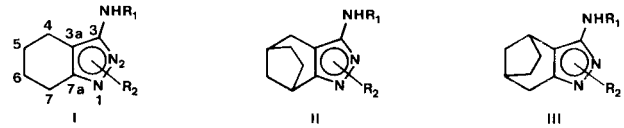
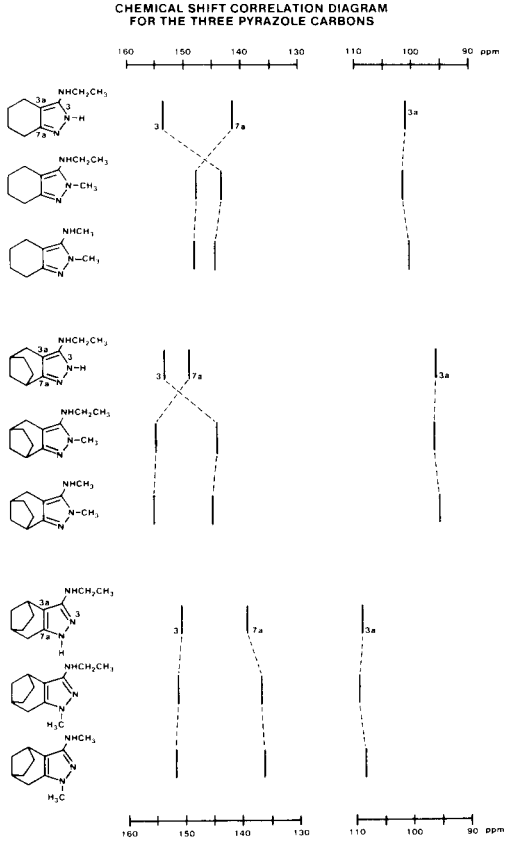
**Table I (a)**




| Compound | $R_1$ | $R_2$ | m.p., °C | Recrystallization Solvent | Molecular Formula | Analysis,%, Calcd./Found C | H | N | Carbon Chemical Shift,ppm C-7a | C-3a | C-3 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ia | $CH_2CH_3$ | H | 171-172 | Isopropanol | $C_9H_{15}N_3 \cdot C_2H_2O_4$ | 51.74<br>51.81 | 6.73<br>6.86 | | 141.4 | 101.0 | 153.5 |
| Ib | $CH_2CH_3$ | 2-$CH_3$ | (b) | | $C_{10}H_{16}N_3$ | | (c) | | 147.4 | 101.8 | 143.3 |
| Ic | $CH_3$ | 2-$CH_3$ | 86-88 | Hexane | $C_9H_{15}N_3$ | | (d) | | 147.7 | 100.7 | 144.5 |
| IIa | $CH_2CH_3$ | H | 129-130 | Acetonitrile | $C_{11}H_{17}N_3$ | 69.07<br>68.93 | 8.96<br>9.01 | | 149.0 | 96.0 | 153.3 |
| IIb | $CH_2CH_3$ | 2-$CH_3$ | 99-100 | Acetonitrile | $C_{12}H_{19}N_3$ | 70.20<br>70.28 | 9.33<br>9.42 | 20.47<br>20.27 | 155.0 | 96.2 | 144.1 |
| IIc | $CH_3$ | 2-$CH_3$ | 106-107 | Acetonitrile | $C_{11}H_{17}N_3$ | 69.07<br>68.67 | 8.96<br>8.93 | 21.97<br>21.90 | 155.3 | 95.4 | 145.2 |
| IIIa | $CH_2CH_3$ | H | 123-124 | Ethyl Acetate | $C_{11}H_{17}N_3$ | 69.07<br>69.14 | 8.96<br>9.07 | 21.97<br>21.80 | 139.0 | 108.9 | 150.5 |
| IIIb | $CH_2CH_3$ | 1-$CH_3$ | 121-122 | Hexane | $C_{12}H_{19}N_3$ | 70.20<br>70.07 | 9.33<br>9.43 | 20.47<br>20.61 | 137.2 | 109.7 | 151.1 |
| IIIc | $CH_3$ | 1-$CH_3$ | 115-117 | Hexane | $C_{11}H_{17}N_3$ | 69.07<br>69.34 | 8.96<br>9.14 | 21.97<br>22.02 | 136.8 | 108.3 | 151.7 |

(a) X-ray crystallographic studies (5) on a related compound, 3-ethylamino-4,7-methano-2-methyl-4,5,6,7-Tetrahydro (-) indazole, have verified the 2-methyl substitution predicted by $^{13}C$ nmr data. (b) b.p. 95°C/0.1 mm Hg. (c) Reference 1, example 6. (d) Reference 1, example 5.




similar substituents in nearly identical substituent patterns were chosen. Three classes of compounds were chosen (Table I) which illustrate substitution parameters similar enough that any major chemical shift differences should be due to the methyl substitution on the pyrazole nitrogen.

## Class I Compounds.

The initial goal was to establish a method for unambiguous identification of the three pyrazole carbons. In 3-ethylamino-4,5,6,7-tetrahydroindazole (Ia) the resonances at 153.5, 141.4, and 101.0 ppm represent the three pyrazole carbons. The resonance at 101.0 ppm can be assigned by chemical shift to carbon 3a, the carbon adjacent to neither pyrazole nitrogen. Carbons 3 and 7a are close enough in chemical shift that accurate assignment is difficult, but a completely coupled $^{13}C$ spectrum yields the necessary information. The proximity of carbon 7a to a proton bearing carbon (C-7) permits observation of long-range $^{13}C$-$^{1}H$ coupling. Carbon 3, however, is adjacent only to one quaternary carbon and two nitrogens, thus no long-range coupling should be observable.

As expected, for compound Ia, in the completely coupled $^{13}C$ nmr spectrum the resonance at 153.5 ppm remains a sharp singlet while the resonance at 141.4 ppm collapses into a broad singlet because of long-range coupling. Carbon 3 is thus assigned at 153.5 ppm and carbon 7a at 141.4 ppm.

Compound Ib, 3-ethylamino-2-methyl-4,5,6,7-tetrahydroindazole, differs from Ia only by the methyl substitution on the pyrazole nitrogen. A completely coupled spectrum gives the assignments found in Table I, carbon 3 at 143.3 ppm and carbon 7a at 147.4 ppm. Substitution of a methyl group on one of the pyrazole nitrogens causes carbon 3 to shift 10.2 ppm upfield and carbon 7a 6.0 ppm downfield relative to Ia. By reference to *N*-methyl pyrazole, the methyl group must be on the nitrogen adjacent to carbon 3. Methyl substitution must therefore be in the 2-position.

An interesting limitation of this assignment technique for carbon 3 is that it does not work well in all instances, but is apparently dependent upon the group attached to carbon 3. In general, if $R_1$ is ethyl, carbon 3 remains a sharp singlet when complete coupling is permitted, but under identical conditions, collapses to a broad singlet if $R_1$ is methyl. Although the failure of this assignment technique to work in all cases is inconvenient, this phenomenon reinforces the assignment of carbon 3 since the change in spectral behavior is caused by a subtle alteration only in the substituent at carbon 3. The assignment of the resonances and hence the position of substitution in 2-methyl-3-methylamino-4,5,6,7-tetrahydroindazole (Ic) can be accomplished by comparison to Ib. The use of Ib as a model for the assignments in Ic shows small chemical shift differences which can be explained by the change of $R_1$ from ethyl to methyl.

Class II Compounds (6).

The carbon assignments for this group of bicyclic analogs are accomplished in the same manner as for class I using 5,7-ethano-3-ethylamino-4,5,6,7-tetrahydroindazole (IIa) as the basis for chemical shift assignment of the three pyrazole carbons. From Table I and the correlation diagram, it is evident that 5,7-ethano-3-ethylamino-2-methyl-4,5,6,7-tetrahydroindazole (IIb) exhibits a shielded 3 carbon and a deshielded 7a carbon relative to IIa. The direction of the shift of carbons 3 and 7a is identical to that displayed in Ib and therefore the assignment of a 2-methyl group is consistent. The structural assignment of 5,7-ethano-2-methyl-3-methylamino-4,5,6,7-tetrahydroindazole (IIc) can be made by reference to IIb and again the 2-methyl substitution pattern is consistent.

Class III Compounds (6).

The aromatic region in the proton decoupled $^{13}C$ nmr spectrum of 4,6-ethano-3-ethylamino-4,5,6,7-tetrahydroindazole (IIIa) looks very similar to that of Ia and not too unlike IIa. The completely coupled $^{13}C$ spectrum of IIIa shows carbon 3 at 150.5 ppm and carbon 7a at 139.0 ppm. The coupled $^{13}C$ spectrum of IIIb permits assignment of carbon 3 to the resonance at 151.1 ppm and carbon 7a to the peak at 137.2 ppm. This unexpected result means that carbon 3 shifts 0.6 ppm downfield and carbon 7a 1.8 ppm upfield, indicating by the opposite shift directions and different shift magnitudes that for IIIb the methyl substitution is in the 1-position, giving 4,6-ethano-3-ethylamino-1-methyl-4,5,6,7-tetrahydroindazole (IIIb). The assignment of 4,6-ethano-3-methylamino-1-methyl-4,5,6,7-tetrahydroindazole (IIIc) is based on direct comparison to IIIb.

Unlike classes I and II, compounds IIIb and IIIc show relatively small chemical shifts with respect to IIIa, but the shifts are in the predicted direction for 1-substitution. Additionally, the difference in the entire shift pattern for carbons 3 and 7a (see correlation diagram) also suggests a substitution pattern which is different from the 2-substitution evident in compounds of classes I and II. It is interesting to note that the *N*-methylation chemical shifts for carbons 3 ($\sim$9 ppm) and 7a ($\sim$6 ppm) of compounds in classes I and II are larger than the shifts produced by *N*-methylation of pyrazole ($\sim$5 ppm). Class III compounds exhibit a corresponding damping effect on the *N*-methylation chemical shifts of carbons 3 ($\sim$1 ppm) and 7a ($\sim$2 ppm) in relation of those of *N*-methylpyrazole. The enhancement (cases I and II) and damping (case III) are greater for carbon 3 than for 7a. The chemical shift enhancement upfield for carbon 3 and downfield for carbon 7a, as well as the damping effects for the shifts in the opposite directions are due, at least in part, to the basic substitution pattern on the unmethylated pyrazole nucleus. Furthermore, in all cases the carbon adjacent to the nitrogen bearing the methyl group shows the greater chemical shift difference in comparison to the unsubstituted parent compound.

The reason for the difference in the course of the reactions leading to 2-substitution in cases I and II and 1-substitution in case III is not clear at present. These differences, however, offer an excellent illustration of the utility of $^{13}C$ nmr in structure determination for these bicyclic fused pyrazoles when only one isomer is available.

## EXPERIMENTAL

All $^{13}C$ nmr spectra were determined as deuteriochloroform solutions at 20 MHz with a Varian CFT-20 Fourier Transform nmr spectrometer using 8K data points and a 4KHz spectral width. All chemical shifts are given relative to internal tetramethylsilane.

## REFERENCES AND NOTES

(1) G. Massaroli, U. S. Patent 3,520,901 (1970).

(2) V. Bauer, M. Agnew and R. Effland, U. S. Patent 3,928,378 (1975).

(3) R. Jacquier and G. Maury, *Bull. Soc. Chim. France*, 1, 316 (1967).

(4) G. Levy and G. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N.Y., 1972, p. 97.

(5) Personal Communication from Dr. E. F. Paulus (Hoechst AG, Frankfurt, West Germany).

(6) Nomenclature was chosen for consistency in the ring numbering system and is not necessarily correct by recognized standards.