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# Some applications of $^{13}$C NMR spectroscopy in heterocyclic structure assignments*

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**Abstract.** The usefulness of $^{13}$C NMR spectral data in solving otherwise intractable structural problems in heterocyclic chemistry is illustrated with ring systems such as imidazoles, pyrazoles, thiazoles, pyrimidines, benzodioxoles, benzodioxanes, benzoxazines, benzothiazines, quinoxalines, imidazopyrazoles, imidazothiazoles, pyridobenzoxazines, thiazolobenzimidazoles, thiazinobenzimidazoles, pyrimidobenzimidazoles, naphthodioxanes and perimidines. For example, using both chemical shifts and coupling constants, especially the one across three bonds, it has been possible to assign unique structures to the addition products of acetylenedicarboxylic esters to a variety of dinucleophiles such as thioureas, guanidines, 2-aminophenol, 2-aminothiophenol, 1,8-dihydroxy and 1,8-diaminonaphthalenes and 8-hydroxy-1,2,3,4-tetrahydroquinoline. These parameters also allow easy differentiation of isomeric imidazoles arising from N-alkylation of nitroimidazoles or nitration of imidazoles and of isomeric pyrazoles obtained from the reaction of hydrazines with ethoxymethylene derivatives of 1,3-dicarbonyl compounds.

**Keywords.** $^{13}$C chemical shifts; C–H coupling constants.

## 1. Introduction

NMR spectroscopy has developed into a versatile and powerful tool for structural assignments in organic chemistry. Until about a decade ago, NMR information was confined mostly to the protons at the periphery of organic molecules and did not extend widely to carbon atoms which form the basic core. This was due to the fact that $^{12}$C, although present in great abundance has no nuclear spin and hence does not give a NMR signal. On the other hand $^{13}$C has a spin of 1/2 and does generate a signal. However, due to its extremely low natural abundance aggravated by an unfavourable gyromagnetic ratio, the nucleus is bedevilled by very poor sensitivity. Hence routine measurements of $^{13}$C NMR spectra in natural abundance were not feasible earlier. The disability has disappeared with the advent of pulsed excitation combined with Fourier transform techniques which are now featured in commercial FT NMR spectrometers. The ready availability of $^{13}$C NMR spectra has offered the organic chemists a weapon *par excellence* for diverse investigations including structural assignments in all their intimate details (Nagarajan 1980; Wehrli and Wirthlin 1976). In recent years we have used the technique efficiently in elucidating structures of a variety of heterocycles arising from reactions such as addition of acetylene dicarboxylic esters to dinucleophiles and condensation of hydrazines with ethoxymethylene derivatives of 1,3-dicarbonyl compounds as well as of products of alkylation and acylation of azoles. We wish to review briefly our contributions in this area. In all these cases, $^{13}$C NMR spectroscopy turned out to be the most reliable if not unique tool for structure determinations.

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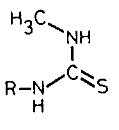
## 2. Products of addition of acetylene dicarboxylic esters to dinucleophiles

### 2.1 *Products from thiocarbamoyl derivatives*

The reaction proceeds with great facility and often gives rise to unique products whose structures have been the subject of controversy, with thiazolinones (type 3) (Hendrikson *et al* 1964; Nagase 1973) and thiazinones (type 5) (Lown and Ma 1967) being the major contenders. With unsymmetrical thioureas, either of the two nitrogen atoms can participate in the formation of the lactam. Finally in the case of thiazolinones, the carboalkoxymethylidene unit can be part of a fumarate (Z configuration) or a maleate (E configuration) skeleton. We were able to marshall the help of $^{13}$C NMR spectra especially $^3J_{CH}$ coupling for establishing the thiazolinone structures uniquely (Vögeli *et al* 1978). For example the $^{13}$C NMR spectrum of the product from N-(4-bromophenyl)-N$^1$-methyl-thiourea (1) and dimethyl acetylene dicarboxylate (2) (DMAD) showed the signal due to the lactam carbon atom at 164·4 ppm which was involved in two $^3J_{CH}$ interactions—one with a *cis*-placed proton to the extent of 5·3 Hz and another with the adjacent N-methyl protons to the tune of 2·6 Hz. This allowed us to deduce the structure of the product uniquely as 3, ruling out 5. Alkaline hydrolysis of 3 followed by acidification afforded a separable mixture of the thiazolinone carboxylic acid 4 and the thiazinone carboxylic acid 6 which were readily distinguished by their $^{13}$C NMR spectra (Nagarajan *et al* 1983). The relevant data are: 4 $\delta$C(4) 165·0 ppm; $^3J_{C(4)H(\alpha)}$ 6, $^3J_{C(4)H(CH_3)}$ 2·8 Hz; for 6: $\delta$C(4) 162·5 ppm; $^2J_{C(4)H(5)}$ 2·5 and $^3J_{C(4)H(CH_3)}$ 1·5 Hz. Structural assignments of 4 and 6 were substantiated by x-ray crystallographic studies.



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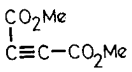

$\overset{CO_2Me}{C}\equiv C-CO_2Me$

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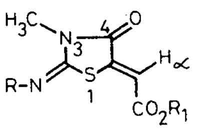
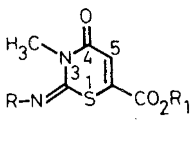


3 R$_1$ = Me

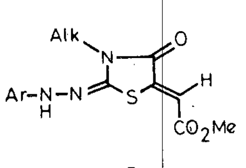
4 R$_1$ = H



5 R$_1$ = Me

6 R$_1$ = H

( 1–6 R = 4-bromophenyl )



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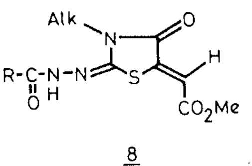

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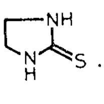

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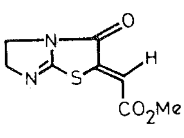

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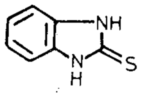
Carboxymethylidenethiazolinone structures were similarly rigorously assigned to the products from various substituted monoalkyl, monoaryl, dialkyl, alkyl aryl, diaryl, aryl arylalkyl and diarylalkyl-thioureas as well as to those from cyclic thioureas, piperidine-1-thiocarboxamide and thiobenzamide (Vögeli *et al* 1978). With aryl alkyl (*e.g.* N-methyl-N′-phenyl) and aryl arylalkyl (*e.g.* N-benzyl-N′-phenyl) thioureas, regioselective, often regiospecific reaction occurred to afford products in which the more basic alkyl or aralkyl substituted N atom was involved in the lactam bond. Steric effects, affecting regiospecificity/selectivity were also manifested as follows: N(2-diphenylyl)-N′-phenylthiourea and N-phenyl-N′-(t-butyl) thiourea gave 2-(2-diphenylyl) and 2-(t-butyl)imino-3-phenylthiazolinones as the major isolable products. Both were hydrolysed by concentrated HCl to the same 5-carboxymethylidene-3-phenylthiazoline-2,4-dione as the one obtained from acid hydrolysis of the DMAD adduct of N,N′-diphenyl thiourea. N-Ethyl-N′-methylthiourea afforded both possible products with the 2-ethylimino (3 R = Et) predominating over the 2-methylimino derivative in the ratio of 3:2, while N-(t-butyl)-N′-methylthiourea gave rise to only 3 (R = t-Bu) (Nagarajan 1978). In all these cases, the signal due to C(4) showed appropriate multiplicity, the last one for example, having only one $^{3}J_{CH}$ coupling with a *cis*-placed vinyl proton. 1-Aryl and 1-acyl 4-alkylthiosemicarbazides afforded 7 and 8 respectively, structure assignments arising from $^{13}$C NMR data (Nagarajan 1978).

The reaction of imidazolidinethione (9) produced the imidazothiazoline 10 uniquely. On the other hand benzimidazoline-2-thione (11) was reported to afford a mixture of two products in varying proportions, depending upon methanol or acetic acid being the solvent (Mckillop *et al* 1978). The product that could be obtained pure readily was considered to be 12 and the other one suspected to be 13. We were successful in isolating pure 13 and in using $^{13}$C together with $^{1}$H NMR data for definitive total structure assignments (Nagarajan *et al* 1979): 12 $\delta$C(4) 157·4; $^{3}J_{CH}$ 6 Hz; 13 $\delta$C(5) 159·1; $^{2}J_{CH} \leqslant 1$ Hz. 12 and 13 could be equilibrated in methanol under acid catalysis with 13 preponderating in the mixture, while methanolic sodium methoxide transformed 12 completely into 13 (Wade 1979). The reaction course of DMAD with 11 is different from the one with 9 perhaps because of the strain involved in fusing a second 5-membered ring to benzimidazole, which renders 13 stabler in relation to 12. A similar behavioural dichotomy was observed with acyclic guanidines and 2-aminobenzazoles (*vide infra*).

Ethyl phenyl propiolate and 11 on the other hand gave thiazinone 14 as the only isolable product. NMR spectral data were used to revise an earlier incorrect structure assignment (Nair *et al* 1979a).



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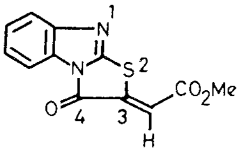

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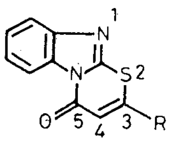
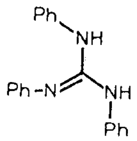


13 R = $CO_2Me$

14 R = Ph



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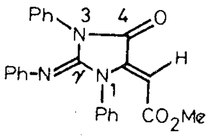

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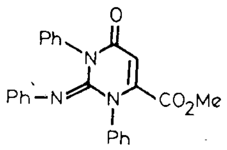

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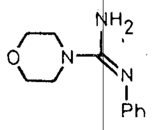
## 2.2 *Products from guanidines*

N,N′,N″-triphenylguanidine (15) and DMAD have been reported to yield a pyrimidinone 17 (Lown and Ma 1967). $^{13}$C NMR spectral data revealed beyond doubt that the product was correctly formulated as 16. δC(4) 162·7 ppm; $^{3}J_{CH}$ 5·9 Hz. An interesting observation in the $^{1}$H NMR spectrum of 16 was the heavy shielding of the methoxyl protons by N-phenyl group: δ(O)$CH_3$ 3·15 ppm. Structure 16 has been confirmed by x-ray studies (Acheson and Wallis 1981). Similar observations with the product of guanidine 18 led us to assign structure 19 to the product (Nagarajan 1978; Nagarajan *et al* 1985a).

Pyrrolidine-1-carboxamidine 20 and DMAD led to the formation of imidazolidinone 21 isolated as its salt with 20. Incidentally 21 happened to be identical with a preparation obtained from treatment of the product from thiourea and DMAD with pyrrolidine followed by cyclisation with acetic anhydride and thus structure 22 assigned to the last compound (Winterfeldt and Nelke 1967) needs to be revised (Nagarajan *et al* 1985a).



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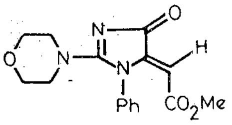

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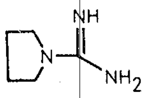

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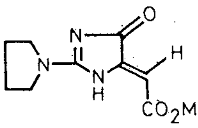

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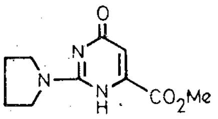

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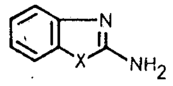
## 2.3 *Products from 2-aminobenzimidazole 23 and 2-aminobenzothiazole 24 and* DMAD

Unlike acyclic guanidines, the product from 23 was a pyrimidobenzimidazole 25 as evident from the multiplicity of the signals due to the ester C=O carbon atom (δ161·1 ppm; dxq; $^{3}J_{CH(2)}$ 4·3, $^{3}J_{CH(OCH_3)}$ 3·9 Hz); lactam carbon atom (δ165·3 ppm; s). The product 26 from 2-aminobenzothiazole (24) exhibited similar features in the $^{13}$C NMR spectrum. These data would have fitted both structures 25 (26) and 27. However in their $^{1}$H NMR spectra, a signal due to a highly deshielded aromatic proton (H*) was not observed, thus ruling out 27 in favour of 25 (26) (Vögeli *et al* 1978). These structures had derived support earlier from x-ray studies.

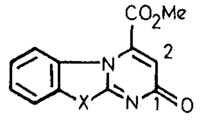
## 2.4 *Products from catechol, 2-aminophenol, 8-hydroxy-1,2,3,4-tetrahydroquinoline, o-phenylenediamine and 2-aminothiophenol*

Addition of catechol to DMAD in the presence of a little sodium methoxide afforded in high yield a 1 : 1 adduct. This was formulated as the benzodioxole derivative 28 and not the dioxane 30. Structure 28 followed from a study of $^{1}$H and $^{13}$C NMR spectra. Diagnostic $^{13}$C data were signals at about δ43 (t, $^{1}J_{CH}$ 130 Hz) and 98 ppm (t, $^{2}J_{CH}$ 6 Hz) in addition to the observation of two sets of signals for the ester $CH_3$ and C=O carbon atoms. Alkaline hydrolysis of 28 and acidification gave a mixture of acids 29 and 31 which afforded the methyl ester 32. The lactone carbon atom in 32 gave a NMR signal at



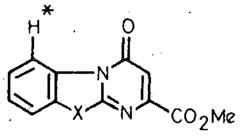
23 X = NH

24 X = S

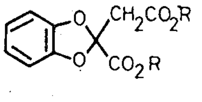


25 X = NH

26 X = S

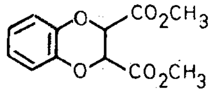


27 X = NH, S



28 R = $CH_3$

29 R = H



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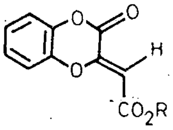
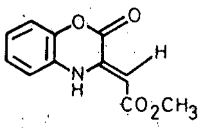


31 R = H

32 R = $CH_3$

153·8 ppm as a doublet with $^3J_{CH}$ 3·7 Hz and the ester C=O carbon atom at 163·3 ppm split into a quartet (Vögeli *et al* 1978). In contrast to catechol, 2-aminophenol and 2-aminothiophenol upon reaction with DMAD yielded products with the loss of elements of methanol. A detailed analysis (Vögeli *et al* 1978) of their $^{13}$C NMR spectra confirmed structures 33 and 34 respectively assigned earlier from other considerations.

The reaction of 8-hydroxy-1,2,3,4-tetrahydroquinoline (35) with acetylenedicarboxylic esters can give rise to six possible products. Interestingly the singular homogeneous (TLC) product that was obtained using the diethyl ester turned out to be an equilibrating mixture of 36 and 37 (Vögeli *et al* 1978; Nair *et al* 1979b). The two geometrical isomers differ in the coupling constants of the ring C=O carbon atom with the vinyl proton (5·3 and 11·3 Hz respectively). This represents a unique example in our comprehensive studies wherein both E and Z isomers were encountered and identified by the greater magnitude of the *trans* $^3J_{CH}$ coupling constant compared to that of *cis* $^3J_{CH}$ (Vögeli and Philipsborn 1975).



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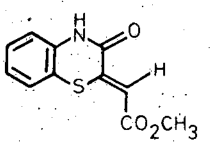

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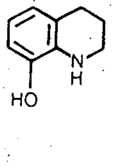

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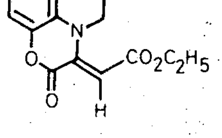

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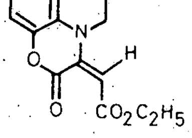

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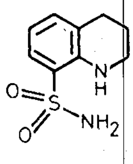
### 2.5 *Product from 1,2,3,4-tetrahydroquinoline-8-sulphonamide* (38)

Reaction of 38 with DMAD gave a single 1 : 1 adduct for which structures 39 and 40 were possible. 39 was the obvious choice on the basis of $^{13}C$ NMR data $\delta C$ ($\underline{CH_2}COMe$) 39·5 ppm; t, $^1J_{CH}$ 135 Hz; $\delta C(C\!<^{N}_{N}$ 77·8 ppm; t, $^2J_{CH}$ 5 Hz) (Nagarajan *et al* 1985b).



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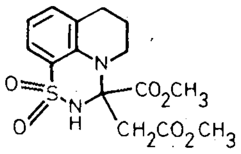

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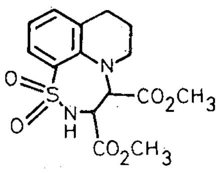

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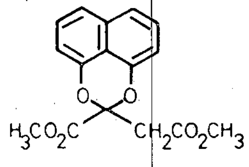

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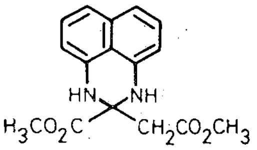

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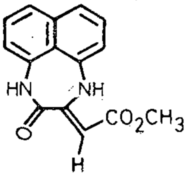

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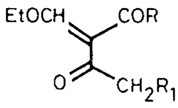
### 2.6 *Products from the reaction of* DMAD *with 1,8-dihydroxynaphthalene and 1,8-diaminonaphthalene*

The behaviour of 1,8-dihydroxynaphthalene towards DMAD paralleled that of catechol and afforded the 1 : 1 adduct 41 in 50 % yield; besides $^1H$ NMR data, $^{13}C$ data were used to derive the structure; mainly a triplet at 42·7 ($^1J_{CH}$ 133 Hz), triplet at 98·1 ($^2J_{CH}$ 5·9 Hz), quartets at 52 and 53·0 ($^1J_{CH}$ 148 Hz) and overlapping quartets at 167·5 and 166·9 ppm with small coupling constants (Nair *et al* 1979b).

Somewhat in contrast, 1,8-diaminonaphthalene produced a separable mixture of two compounds. One was the perimidine 42 ($\delta C$ ($\underline{C}H_2$) 43·6; t, $^1J_{CH}$ 137 Hz, $\delta C$ ($C\!<^{N}_{N}$) 69·4, t, $^2J_{CH}$ 6 Hz) which had been given an incorrect structure earlier (Iwanami 1962). The second product was identified as 43 (Nair *et al* 1979b).

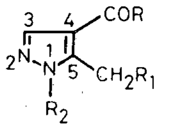
## 3. Pyrazoles from monosubstituted hydrazines and ethoxymethylene derivatives of 1,3-dicarbonyl compounds (Nagarajan 1982; Nagarajan 1983, Nagarajan *et al* 1985c).

Earlier studies had extended the known formation of pyrazoles from 1,3-diketones and monosubstituted hydrazines to ethoxymethylene acetylacetone 44. The resultant products were uniformly formulated as 1-substituted-4-acetyl-5-methylpyrazoles (46) which were used as substrates for Mannich reactions with phenylpiperazines and phenyltetrahydropyridines, giving rise to drugs with potent effects on cardiovascular and central nervous systems (Nagarajan and Arya 1982).



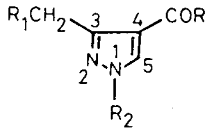
44 $R = CH_3$; $R_1 = H$

45 $R = CH_3$; $R_1 = OCH_3$



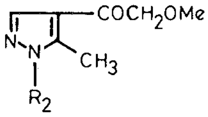
46 $R = CH_3$; $R_1 = H$

47 $R = CH_3$; $R_1 = OCH_3$



48 $R = CH_3$; $R_1 = H$

49 $R = CH_3$; $R_1 = OCH_3$



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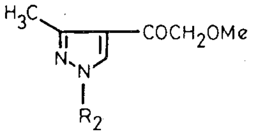

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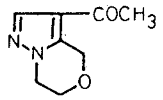

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The reaction of 44 with monosubstituted hydrazines can give rise to one or both of two products 46 and 48, if we make the reasonable assumption that the incipient formyl group (=CHOEt) in 44 will initiate the reaction with $R_2NHNH_2$. The nature and composition of products will then depend upon the relative nucleophilicites of the two hydrazine N atoms which in turn are determined by the nature of $R_2$. In the case of ethoxymethylene derivatives of unsymmetrical 1,3-diketones like 45, four possibilities 47, 49, 50 and 51 arise. The determining factors for the composition of the product mixture will be the relative nucleophilicites of the two N atoms in $R_2NHNH_2$ and the electrophilicites of the two C=O groups, COR and $COCH_2R_1$. In the case of 45, the CO group attached to $CH_2OMe$ can be justifiably expected to be stronger and more reactive compared to the one hooked to a $CH_3$ group.

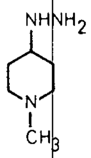
We have used $^{13}$C NMR spectroscopy advantageously in reinvestigating the earlier work and expanding its horizons. Thus, the reaction of 44 with 2-hydroxyethyl hydrazine afforded 48 ($R_2 = CH_2CH_2OH$) as the major and 46 ($R_2 = CH_2CH_2OH$) as the minor products, correcting the earlier literature where the sole products obtained in high yields using 2-hydroxyethyl and other alkyl hydrazines were considered to be 46 (Arya 1968; Arya *et al* 1971). Critical for the revised assignments were chemical shifts and splitting patterns of the proton-bearing carbon atom in the pyrazole rings: C-3 in 46 ($R_2 = CH_2CH_2OH$) $\delta$141·2 ppm, d, $^1J_{CH}$ 185 Hz. C-5 in 48 ($R_2 = CH_2CH_2OH$) $\delta$135·8 ppm; d × t; $^1J_{CH}$ 185, $^3J_{CH}$ 2·5 Hz. In fact for all the alkyl or aralkyl hydrazines studied 48 was the major and in a few cases the sole product and 46, the minor one. With aryl hydrazines, on the other hand, consistent with the greater nucleophilicity of the unencumbered N atom, 46 ($R_2$ = Ar) was the major product and in the case of 4-nitrophenyl hydrazine, the sole product. As with the pairs 46 ($R_2$ = alkyl) and 48 ($R_2$ = alkyl), C-3 in 46 ($R_2$ = Ph) appeared more downfield ($\delta$141·9 ppm) than C-5 in 48 ($R_2$ = Ph) ($\delta$130·8 ppm). Although a long-range $^3J_{CH}$ coupling was not possible in 48 ($R_2$ = aryl) compared to 48 ($R_2$ = methyl etc), the differences in the chemical shifts of the two series was sufficiently pronounced to be of diagnostic utility. The differences are obviously to be attributed to the fact that C(3) in 46 is attached to a biligant N atom while C(5) in 48 is tied to a triligant one. Again in the case of aryl hydrazines and 44, substitution at position 4 with electron-donating substituents increased the nucleophilicity of the N atom and consequently the relative proportion of 48 in the product mixture.

As a consequence of these studies, it became clear that unlike in the case of alkyl hydrazines, pyrazoles obtained earlier from aryl hydrazines and 44 were indeed 1-aryl-4-acetyl-5-methyl derivatives 46 and structures assigned to Mannach bases obtained from them then needed no revision (Arya 1966; Arya *et al* 1969).

2-Hydroxyethyl hydrazine and 45 afforded a mixture of the two pyrazoles 47 and 49 ($R_2 = CH_2CH_2OH$) the former being the minor product. 50 and 51, if formed, were in undetectable quantities. Crucial $^{13}C$ NMR data were as follows: 47: C-3, $\delta$141·2 ppm; d, $^1J_{CH}$186 Hz; 49 C-5, $\delta$135·8 ppm; d × t; $^1J_{CH}$ 189, $^3J_{CH}$ 2·4 Hz. Use of these data for structure assignments was convincingly vindicated when 47 underwent HBr mediated dimethylative ring closure to 52.

Solvent-induced proton shifts (Takeuchi *et al* 1978; Nagarajan *et al* 1982a) could be used to distinguish between 46 and 48 with limited validity; but $^{15}N$ NMR spectroscopy provided clear-cut answers: N(2) in 46 showed a large geminal coupling with H(3) to the extent of about 13 Hz which was not possible with 48 (Chen *et al* 1983).

Pyrazole formation from ethoxymethylene derivatives of other unsymmetrical 1,3-dicarbonyl compounds like benzoyl acetone, acetoacetonitrile and ethyl acetoacetate was also studied using $^{13}C$ NMR spectroscopy. Earlier patterns were maintained in these cases as well, except that in the reaction of the last compound with 1-methyl-4-piperidylhydrazine (53), a mixture of 54 ($\delta$C(3) 140·6, d) and 55 ($\delta$C(5) 131·0; d × d) was formed in the ratio of 5:2 revealing a role for steric factors.



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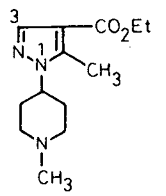

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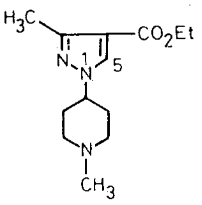

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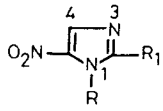
## 4. Alkyl and aryl derivatives of nitroimidazoles and nitropyrazoles

5-Nitroimidazole derivatives with potent antimicrobial properties (Nair and Nagarajan 1983; Nagarajan *et al* 1984) are obtained by nitrating 1-substituted imidazoles or by alkylation/arylation of 1-unsubstituted-4-nitroimidazoles. These are accompanied in these reactions by 4-nitro isomers which are spectacularly inactive *in vivo*. Among the spectroscopic techniques available to differentiate between the two series, solvent-induced differences in the chemical shifts of H(4) in 56 and H(5) in 58 are of some help (Takeuchi *et al* 1978; Nagarajan *et al* 1982a). More definitive discrimination is possible using $^{13}C$ NMR spectroscopy (Nagarajan *et al* 1982d). Thus, the sole proton-bearing C(4) in 56 and C(5) in 58 are readily picked up in the $^{13}C$ NMR spectra. The former is a doublet with a chemical shift of 131·7 ppm and $^1J_{CH}$ of 199 Hz. The latter is a doublet split further into a fine quartet; $\delta$122·3, $^1J_{CH}$ 200 Hz and $^3J_{CH(CH_3)}$ 3 Hz. Absolute differentiation linked to presence or absence of long-range coupling is not possible with 57 and 59, but chemical shift differences still persist: $\delta$C (4) in 57

132·4 ppm; δC (5) in 59, 121·5 ppm. In fact for a large number of isomeric pairs studied, the 5-nitroimidazoles had δC (4) in the narrow range of 130–133 ppm and their 4-nitro counterparts had δC (5) at 120–124 ppm. The difference is to be traced to C (4) in the former being attached to a biligant N atom and C (5) of the latter to a triligant one. $^{15}$N NMR spectroscopy is also of diagnostic value in such cases (Chen *et al* 1983).

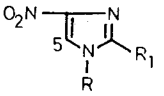
Two further points are worth noting. Both in the case of pyrazoles and imidazoles coupling of carbon atoms is not observed with protons three bonds removed, if these are located in a ring as part of an alkylene group (e.g. **10**). Secondly, N-unsubstituted imidazoles and pyrazoles are capable of tautomerism and both $^{13}$C (Nagarajan *et al* 1982a, 1985c) and $^{15}$N (Chen *et al* 1983) NMR spectra provide equilibrium data.

In an extension of this work, we have studied the $^{13}$C NMR spectra of all the three possible 1-methyl-*x*-nitropyrazoles 60–62 and two (63, 64) of the three possible 1-methyl dinitropyrazoles (63–65). Pertinent data are 60: C(4) δ108·1; d × d; C(5) δ133·2; d × q 61 : C(3) δ135·8; d × d; C(5) 129·5, d × q; 62 C(3) 137·8; d × d; C(4) 106·4, d × d (Nagarajan and Shenoy 1985) 63 C(5), δ132·0; d × q; 64 C(3), δ133·8, d (Nagarajan 1980).



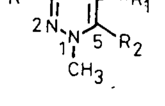
56 R = $R_1$= Me

57 R = $4\text{-}NO_2C_6H_4$ ; $R_1$= Me



58 R = $R_1$= Me

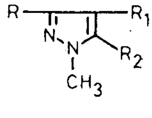
59 R = $4\text{-}NO_2C_6H_4$ ;$R_1$= Me



60 R = $NO_2$ ; $R_1$= $R_2$ = H

61 R = $R_2$= H ; $R_1$= $NO_2$

62 R = $R_1$ = H ;$R_2$= $NO_2$



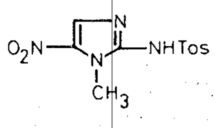
63 R = $R_1$ = $NO_2$ ; $R_2$= H

64 R = H , $R_1$= $R_2$= $NO_2$

65 R = $R_2$=$NO_2$ ; $R_1$ = H

## 5. Imidazopyrazoles from cyclo addition reaction of a nitroimidazole and diazomethane

The unique contribution of $^{13}$C NMR spectroscopy to solutions of structural problems not easily amenable to more conventional techniques is perhaps best illustrated in the complex mixture of products arising from the reaction of the toluene sulphonamido-nitroimidazole 66 with diazomethane. The formation of this bewildering array of products 67–73 (two more are not relevant for this discussion and are hence not shown) (Sudarsanam *et al* 1980; Nagarajan *et al* 1982b) with the exception of 67 has been traced to the participation of nitroimidazoline 68 in a cycloaddition reaction with the methylating agent. The isomeric N-methyl derivatives 67 and 68 were best distinguished by their $^{13}$C NMR spectra: 67 C(4) δ130·3, d, $^1J_{CH}$ 202 Hz; 68 C(4) δ122·7; d × q; $^1J_{CH}$ 211, $^3J_{CH}$ 1·8 Hz. The pair of imidazopyrazoles 70 and 72 were similarly identified: 70 : C(3) δ120·0; d; $^1J_{CH}$ 195 Hz; 71 C(3) δ113·4; d × q; $^1J_{CH}$ 198; $^3J_{CH}$ 3·5 Hz. Presence or absence of three bond C–H couplings could not be used as a criterion to characterize the methyl carbamoylimidazopyrazoles 71 and 73 which were artefacts in this reaction. However, chemical shifts came to our rescue: 71 $\delta$C(3) 119·1; 73 $\delta$C(3) 110 ppm, following the well-established pattern among the isomeric pyrazoles treated in §3. A similar profitable exercise was carried out on thiazolopyrazoles obtained by the treatment of 2-dichloroacetamido-5-nitrothiazole (Sudarsanam *et al* 1980; Nagarajan *et al* 1982b).



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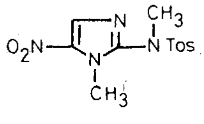

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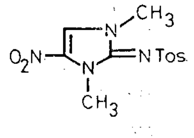

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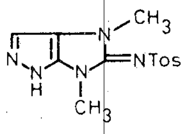

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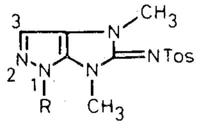
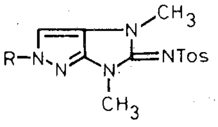


70 R = $CH_3$

71 R = $CONHCH_3$



72 R = $CH_3$

73 R = $CONHCH_3$

## References

Acheson R M and Wallis J D 1981 *J. Chem. Soc. Perkin I* 415

Arya V P 1966 in *CNS drugs* (New Delhi: Council of Scientific and Industrial Research) p.'33.

Arya V P 1968 S. African Patent 6800955 to CIBA Ltd.; July 9; *Chem. Abst.* 1969 **70** 57831

Arya V P, Grewal R S, David J and Kaul C L 1967 *Experientia* **23** 514

Arya V P, Grewal R S, Kaul C L, Ghate S P, Mehta D V and George T 1969 *J. Pharm. Sci.* **58** 432

Arya V P, Grewal R S, Kaul C L and Ghate S P 1971 *Experientia* **27** 1186

Chen B C, Philipsborn W von and Nagarajan K 1983 *Helv. Chim. Acta* **66** 1537

Hendrikson J B, Rees R and Templeton J F 1964 *J. Am. Chem. Soc.* **86** 107

Iwanami Y 1962 *Nippon Kagaku Zaashi* **83** 597; *Chem. Abst.* 1963 **59** 3920

Lown J W and Ma J C N 1967 *Can. J. Chem.* **45** 939, 953

Mckillop A, Bellinger G A A, Preston P N, Davidson A and King T J 1978 *Tetrahedron Lett.* 262

Nagarajan K 1978 Abstracts of Seminar on Recent Advances in Heterocyclic chemistry, National Chemical Laboratory, Pune, September 25, 26, p. 6

Nagarajan K 1980 *J. Sci. Ind. Res.* **39** 28

Nagarajan K 1982 Abstracts of symposium on application of NMR in chemistry and biology, Calcutta, January 8–10.

Nagarajan K 1983 Abstracts of the Nineth International Congress of Heterocyclic chemistry, Tokyo, August 21–26

Nagarajan K, Ranga Rao V and Shah R K 1971 *Indian J. Chem.* **9** 532

Nagarajan K, Nair M D and Desai J A 1979 *Tetrahedron Lett.* 53

Nagarajan K and Arya V P 1982 *J. Sci. Ind. Res.* **41** 232

Nagarajan K, Sudarsanam V, Parthasarathy P C, Arya V P and Shenoy S J 1982a *Indian J. Chem.* **B21** 1006

Nagarajan K, Sudarsanam V, Shenoy S J and Rama Rao K 1982b *Indian J. Chem.* **B21** 997

Nagarajan K, Nair M D, Shenoy S J and Kartha G 1983 *Proc. Indian Acad. Sci.* (*Chem. Sci.*) **92** 99

Nagarajan K, Arya V P, George T, Nair M D, Sudarsanam V, Ray D K and Shrivastava V B 1984 *Indian J. Chem.* **B23** 342

Nagarajan K, Arya V P and Shenoy S J 1985a to be published

Nagarajan K, Bhat G A and Ranga Rao K 1985b to be published

Nagarajan K, Arya V P and Shenoy S J 1985c *J. Chem. Soc. Perkin I* Communicated

Nagarajan K and Shenoy S J 1985 to be published

Nagase H 1973 *Chem. Pharm. Bull. Jpn* **21** 270
Nair M D, Nagarajan K and Desai J A 1979a *Indian J. Chem.* **B18** 479
Nair M D, Nagarajan K, Desai J A, Kulkarni Y S and Shah R K 1979b *Proc. Indian Acad. Sci.* **A88** Part I, 1
Nair M D and Nagarajan K 1983 *Progr. Drug Res.* **27** 163
Sudarsanam V, Nagarajan K, Rama Rao K and Shenoy S J 1980 *Tetrahedron Lett.* 4757
Takeuchi Y, Yeh H J C, Kirk K L and Cohen L A 1978 *J. Org. Chem.* **43** 3571 and references cited therein
Vögeli G and Philipsborn W von 1975 *Org. Magn. Res.* **7** 617
Vögeli G, Philipsborn W von, Nagarajan K and Nair M D 1978 *Helv. Chim. Acta* **61** 607
Wade J J 1979 *J. Org. Chem.* **44** 1816
Wehrli F W and Wirthlin T 1976 *Interpretation of carbon-13 NMR spectra*, (London: Heydon & Son)
Winterfeldt E and Nelke J M 1967 *Ber. deutsch. chem. Ges.* **100** 3671