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5-HALOGENOPYRIMIDINES*—V[1]

SOLVENT EFFECTS ON THE NMR SPECTRA OF PYRIMIDINES AND CONSIDERATION ON THE ASSOCIATION OF 4-HYDROXYPYRIMIDINES

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Abstract—NMR spectra of a number of 5-unsubstituted and 5-halogenopyrimidines were determined in solvents of varying acidity. The C-5-halogen atom causes downfield shift of the resonance peak for the methyl group attached to the C-6-position. Methoxy groups at the C-2- and C-4-positions are differentiated for 5-halogeno-2,4-dimethoxy-6-methylpyrimidine which can not be separated for 5-unsubstituted pyrimidines, and variation for their chemical shifts in acidic solvents are discussed. A certain amount of hydrogen bonding is suggested for 4-hydroxypyrimidines on the basis of the concentration effect for the NH resonance peak.

GRONOWITZ, *et al.*[2,3] investigated the NMR spectra of a number of substituted, in particular 2-substituted, pyrimidines and discussed the structures of several potentially tautomeric amino-, hydroxy-, and mercapto-pyrimidines. They also studied the substituent effects on the chemical shifts of the ring protons of substituted pyrimidines in different neutral solvents. There are also several reports[4–8] dealing with the NMR spectra of the naturally occurring pyrimidines and their corresponding nucleosides.

In the preceding papers preparations of 5-halogenopyrimidines by N-halogenosuccinimides were described. In the course of this study, the NMR spectra of many 5-unsubstituted and 5-halogenopyrimidines have been obtained in solvents of varying acidity. Interest was especially concerned with the chemical shifts of substituents attached to a pyrimidine ring as well as those of the ring protons and, in addition, their variations caused by the C-5-halogen atom. Typical examples are illustrated in this paper. The methyl and methylene protons of n-butylamine, morpholine, and piperidine attached to a pyrimidine ring are not considered in the present paper.

EXPERIMENTAL

All spectra were obtained at 60 Mc using a Nihon-Denshi type high-resolution NMR spectrometer at 25° with TMS as an internal standard.

* All compounds are named as hydroxy, mercapto, and aminopyrimidines whatever their keto forms may exist.

[1] Part IV. T. Nishiwaki, *Tetrahedron*, **22**, 2401 (1966).
[2] S. Gronowitz and R. Hoffmann, *Arkiv Kemi* **16**, 459 (1960).
[3] S. Gronowitz, B. Norrman, B. Gestblom, B. Mathiasson and R. Hoffmann, *Arkiv Kemi* **22**, 65 (1964).
[4] O. Jardetsky, *Biopolymers* **1**, 501 (1964).
[5] J. Kokko, L. Mandell and J. Goldstein, *J. Amer. Chem. Soc.* **84**, 1042 (1962).
[6] E. Becker, H. Miles and R. Bradley, *J. Amer. Chem. Soc.* **87**, 5575 (1965).
[7] A. Katritsky and A. Waring, *J. Chem. Soc.* 3046 (1963).
[8] G. Reddy, R. Hobgood, Jr and A. Goldstein, *J. Amer. Chem. Soc.* **84**, 336 (1962).

RESULTS AND DISCUSSION

The chemical shifts and coupling constants of the ring protons and substituents of a pyrimidine ring listed in Tables 1 and 2, show several interesting trends.

It has been observed[3] that the bromine atom of 5-bromopyrimidine causes a small but discernible upfield shift of the resonance peak for the C-2-proton and downfield

TABLE 1. CHEMICAL SHIFTS OF SUBSTITUENTS IN 5-UNSUBSTITUTED AND 5-HALOGENOPYRIMIDINES[a]

	Substituents				Chemical shifts				
Compound	2	4	5	6	5H	Me	OMe	OEt	SMe
1		Me	H	Me	6·07	2·21	--	—	—
2		Me	Cl	Me	—	2·34	--	—	--
3		Me	Br	Me	—	2·40	—	—	—
4		Me	H	Me	6·15	2·23	—	—	—
5		Me	Cl	Me	—	2·46	—	—	—
6		Me	Br	Me	—	2·42	—	—	—
7	n-BuNH	Me	H	Me	6·14	2·21	—	—	—
8	n-BuNH	Me	Cl	Me	—	2·36	—	—	—
9	OEt	Me	H	Me	6·53	2·31	—	1·36, 4·30[d]	—
10[b]	OEt	Me	Br	Me	—	2·52	—	1·40, 4·34[d]	—
11	OMe	OMe	H	Me	5·96	2·26	3·83	—	—
12	OMe	OMe	Cl	Me	—	2·41	3·98, 3·88	—	—
13	OMe	OMe	Br	Me	—	2·46	3·98, 3·88	—	—
14	SMe	Cl	H	Me	6·79	2·43	—	—	2·53
15	SMe	Cl	Br	Me	—	2·50	—	—	2·60
16[c,e]	NH_2	OEt	H	Me	5·93	2·23	—	1·34, 4·25[d]	—
17[c,e]	NH_2	OEt	Br	Me	—	2·42	—	1·38, 4·40[d]	—

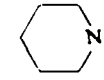
[a] Spectra were obtained in CCl_4 (10% w/v solution) unless otherwise indicated.
[b] Refers to the crude compd. See Part IV of this series.
[c] Spectra were obtained in $CDCl_3$.
[d] $J = 6$ c/s.
[e] NH_2 protons are observed at 5·38 ppm (Compd. 16) or 5·35 ppm (Compd. 17).

shift for the C-4- (or 6) proton. It is clear from Table 1 that this downfield shift caused by the C-5-bromine is further transmitted to a methyl group attached to the C-6-position of a pyrimidine nucleus. The C-5-chlorine also causes the downfield shift. But the shifts are of varying magnitude and no correlation can be obtained between the magnitude of the deshielding of the C-6-methyl and the kind of a halogen at the C-5. Inductive effect of a halogen atom is a likely cause of this downfield shift for the

C-6-proton or C-6-methyl, which, however, will not be the sole cause, since if it acted alone, the shift of the said proton or methyl would vary in the order: Cl, Br. Magnetic moment anisotropy is an important cause and, in addition, a steric factor should not be excluded.[9]

This distinct downward trend caused by the C-5-halogen also affects the chemical shifts of other substituents. Thus the chemical shifts of methylthio or ethoxy groups at

TABLE 2. CHEMICAL SHIFTS OF SUBSTITUENTS OF PYRIMIDINES IN NEUTRAL AND ACIDIC SOLVENTS[a]

Compound	Substituents 2	4	5	6	Solvent[b]	Chemical shifts 2H	4H	5H	Me	OMe	OEt	SMe
1		Me	H	Me	A	—	—	6·07	2·21	—	—	—
1					B	—	—	6·44	2·41	—	—	—
1					C	—	—	6·65	2·55		—	—
9	OEt	Me	H	Me	A	—	—	6·53	2·31	—	1·36, 4·30[d]	—
9					C	—	—	7·20	2·73	—	1·52, 4·80[d]	—
11	OMe	OMe	H	Me	A	—	—	5·96	2·26	3·83	—	—
11					B	—	—	6·33	2·38	4·00	—	—
11					C	—	—	6·61	2·58	4·33, 4·27	—	—
13	OMe	OMe	Br	Me	A	—	—	—	2·46	3·98, 3·89	—	—
13					B	—	—	—	2·55	4·03, 3·96	—	—
13					C	—	—	—	2·77	4·37, 4·33	—	—
18	SMe	H	H	Me	A	—	8·30[e]	6·78[e]	2·39	—	—	2·48
18					B	—	8·50[e]	7·00[e]	2·45	—	—	2·54
18					C	—	8·80[e]	7·10[e]	2·84	—	—	2·84
19	H	OH	H	Me	D	8·13[e]	—	6·33[e]	2·33	—	—	—
19					B	8·47[f]	—	6·50	2·40	—	—	—
19					C	9·40[f]	—	6·82	2·63	—	—	—
20	H	OH	Br	Me	E	8·13	—	—	2·36	—	—	—
20					B	8·36	—	—	2·50	—	—	—
20					C	9·40	—	—	2·78	—	—	—
21	Me	OH	H	Me	D	—	—	6·15	2·46, 2·29	—	—	—
21					B	—	—	6·37	2·50, 2·32	—	—	—
21					C	—	—	6·68	2·94, 2·60	—	—	—

[a] Chemical shifts are shown as ppm.
[b] A: CCl_4; B: HOAc; C: CF_3COOH; D: $CDCl_3$; E: Me_2SO.
[c] As to the $J_{4H,5H}$ see the text.
[d] J = 6·0 c/s.
[e] $J_{2H,4H}$ = 1·5 c/s.
[f] Splitting was not well discerned.

the C-2-position show a negligible downfield shift, but the limited number of examples does not warrant any comment.

It is of interest that the spectra of 5-chloro- or 5-bromo-2,4-dimethoxy-6-methylpyrimidine in carbon tetrachloride show two non-equivalent methoxy groups well separated by 0·1 ppm (Figs. 1, 2) whereas only a single peak is observed for 2,4-dimethoxy-6-methylpyrimidine. The chemical shifts for these non-equivalent methoxy groups were of the same magnitude irrespective of the kind of halogen atom. As it is supposed that the downfield shift by the C-5-halogen will be more pronounced for the C-4, the signal in the lower field (3·98 ppm) may be the C-4-methoxyl. However, in view of the position of the C-2-H and C-4-H in the spectrum of 5-bromopyrimidine[3] and the spectral observations of these compounds in acidic solvents described later assignment of the lower field signal to the C-2-methoxyl will be reasonable.

As the acidity of solvents is increased, the line width of the C-2-proton resonance

[9] C. Haigh, M. Palmer and B. Semple, *J. Chem. Soc.* 6004 (1965).

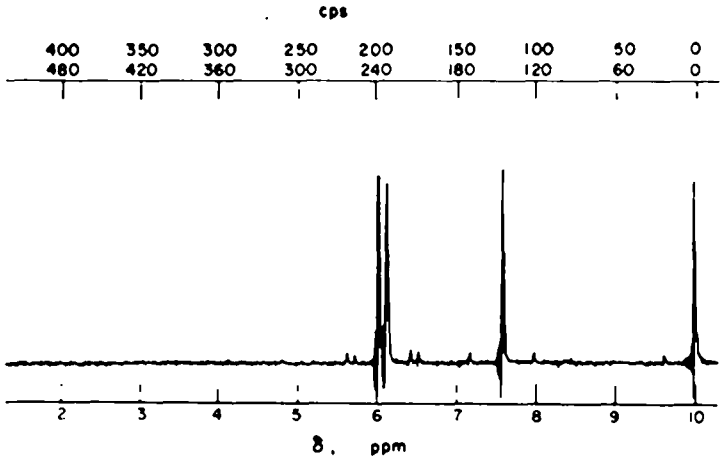


FIG. 1. The NMR spectrum of 5-chloro-2,4-dimethoxy-6-methylpyrimidine in carbon tetrachloride

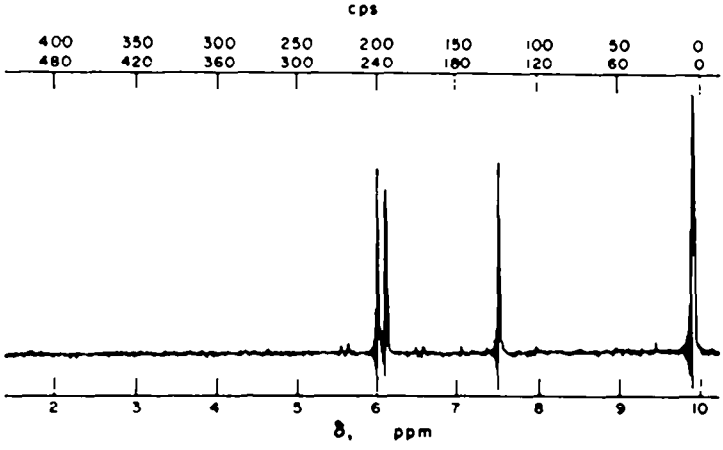


FIG. 2. The NMR spectrum of 5-bromo-2,4-dimethoxy-6-methylpyrimidine in carbon tetrachloride.

in 4-hydroxy-6-methylpyrimidine becomes narrower, which somewhat broadens in neutral solvents presumably by the nitrogen quadrupole broadening effect. A similar sharpening of the C-4-proton and less for the C-5-proton of 2-methylthio-6-methylpyrimidine were also observed. For this pyrimidine the hydrogen at the C-4 couples to the C-5 ($J_{4H,5H} = 4{\cdot}8$ c/s) with two doublets at 8·30 and 6·78 ppm in carbon tetrachloride, which agrees with the ortho coupling constant for pyrimidine previously reported.[8] Protonation of the ring nitrogen atom brings about a small increase in the coupling constant $J_{4H,5H}$ (5·7 c/s in acetic acid; 6·1 c/s in trifluoroacetic acid). This is a surprising but interesting observation because there is a report that the vicinal proton couplings in olefinic compounds $CH_2{=}CHX$ are reduced by electronegative substituents with the relationship: $J_{trans} = 19 - 3{\cdot}3\Delta E$ and $J_{cis} = 11{\cdot}7 - 4{\cdot}0\Delta E$, where ΔE is the difference in electronegativity between X and the hydrogen atom it replaces.[10] A similar tendency has been noted for $J_{5H,6Me}$ (*vide infra*).

[10] C. Banwell and N. Sheppard, *Discuss. Faraday Soc.* **34**, 115 (1962).

As it will be seen from Table 2 the resonance peak of the nuclear protons show pronounced downfield shift in solvents of increasing acidity. This tendency is more remarkable for the C-2-proton, which moves downward more than 1 ppm in trifluoroacetic acid. This downfield shift is still observed for the C-4-proton and to a lesser extent for the C-5-proton. These phenomena are in accord with some delocalization of charge through a protonated nitrogen atom, which will be smaller for C-5. Such shifts are expected in view of the observations for α- or β-hydrogens in pyridine[11] or in 4-substituted pyridine[12] and 4-hydrogen in 2-substituted thiazole,[13] which are deshielded on protonation of the ring nitrogen atom.

A similar trend is also seen for the C-6-methyl attached to a pyrimidine ring. The resonance peak of the C-6-methyl shows a small shift (−0·2 ppm) in acetic acid and a much larger shift (−0·3 to −0·5 ppm) in trifluoroacetic acid, in keeping with the observations for picoline, lutidine, or quinaldine.[14] Two non-equivalent methyl signals separated by 0·17 ppm were recognized for 2,6-dimethyl-4-hydroxypyrimidine in deuterochloroform, both of which shifted downward in acetic acid or trifluoroacetic acid. Separation of two bands becomes larger in trifluoroacetic acid (0·34 ppm), which may be due to the much larger effect of the protonated nitrogen atom on the C-2-methyl. A signal in the lower field is assigned to the C-2-methyl on the basis of its spectral position.

Coupling (J = 1·2 c/s) was noticed for the C-5-proton and C-6-methyl for 2,6-dimethyl-4-hydroxypyrimidine in trifluoroacetic acid. This value is markedly higher than the one ($J_{6Me,5H}$ = 0·5 c/s) determined from the C^{13}-H coupling for 6-methylpyrimidine[8] and may be associated with a similar increase of coupling constant $J_{4,5}$ for 2-methylthio-6-methylpyrimidine in acidic solvent.

A methoxy group is reported to show a negligible shift (+0·03 to −0·11 ppm) on changing from deuterochloroform to perdeuteroacetic acid and only a small (−0·08 to −0·37 ppm) further downfield in trifluoroacetic acid.[14] This downfield shift with increasing acidity of solvents is also observed for the C-2- or C-4-methoxyls. It is noteworthy that the methoxy signal of 2,4-dimethoxy-6-methylpyrimidine appears as a singlet in carbon tetrachloride (3·83 ppm) or in acetic acid (4·00 ppm) while two distinct bands (4·33 and 4·27 ppm) were seen for this pyrimidine in trifluoroacetic acid (Fig. 3). The signal in the lower field may be the C-2-methoxyl because this signal is likely to be affected more extensively by the protonated nitrogen atom. For 5-bromo-2,4-dimethoxy-6-methylpyrimidine two bands were seen for the methoxyls even in carbon tetrachloride (Table 1), both of which shifted downward in acetic acid or trifluoroacetic acid. But the distance between the two bands becomes narrower with increasing acidity of solvent (0·09 ppm in carbon tetrachloride; 0·07 ppm in acetic acid; 0·04 ppm in trifluoroacetic acid). Combined effects on the C-4-methoxyl of the C-5-bromine and the protonated nitogen atom are greater than in the case of the C-2-methoxyl and have brought the C-4-methoxyl further downward than they have the C-2-methoxyl, so that the chemical shift will now be very close.

2,4-Dimethoxy-6-methylpyrimidine, when scanned at the reduced sweep rate of 0·36 c/s/sec, showed its methyl group as a doublet ($J_{6H,6Me}$ = 1·2 c/s) in trifluoroacetic

[11] V. Gil and J. Murrell, *Trans. Faraday Soc.* **60**, 248 (1964).
[12] A. Katritzky and J. Lagowski, *J. Chem. Soc.* 43 (1961).
[13] G. Clarke and D. Williams, *J. Chem. Soc.* 4597 (1965).
[14] J. Ma and E. Warnhoff, *Canad. J. Chem.* **43**, 1849 (1965).

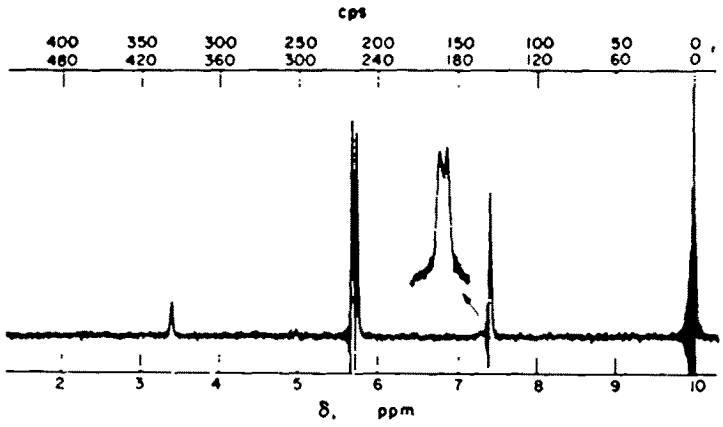


FIG. 3. The NMR spectrum of 2,4-dimethoxy-6-methylpyrimidine in trifluoroacetic acid.

acid, each of which exhibited an additional splitting ($J = 0{\cdot}3$ c/s) suggesting a likely coupling to the NH now formed by protonation. But in acetic acid this coupling ($J_{5H,6Me}$) decreased to 0·9 c/s and an additional splitting was not well discerned.

The downward trend of the chemical shift with increasing acidity of solvent is also noticed for N-methyl groups. The spectrum of 1,3,6-trimethyluracil shows resonance peaks at 2·25 (6-Me), 3·16, 3·33 (N-Me), and 5·65 (5-H) in dimethylsulfoxide, and undergoes larger shifts in passing to acidic solution (2·28, 3·29, 3·41 and 5·84 ppm in acetic acid; 2·50, 3·60, 3·65 and 6·22 ppm in trifluoroacetic acid). If it is assumed that the chemical shifts of N-methyls in this pyrimidine paralleled those of the pyrimidine moeity in caffein, the chemical shifts of which have been suggested,[15] then the signal appearing at higher field may be assigned to the N-methyl adjacent with two carbonyl groups.

From UV spectral considerations 4-hydroxypyrimidine has been suggested to exist as an equilibrium of two oxo forms.[16] In view of the successful application of NMR spectroscopy to structural problems[17] fine structures of monohydroxypyrimidines may be differentiated. During the present study the spectra of 2,6-dimethyl-4-hydroxypyrimidine and 2-ethylthio-6-hydroxypyrimidine were obtained over a range of concentrations in deuterochloroform at 25°. The spectrum of 4-hydroxy-6-methylpyrimidine was determined only over a limited range of concentrations, since this pyrimidine was less soluble in deuterochloroform at 25°. The chemical shifts and coupling constants for these pyrimidines are listed in Table 3. It will be seen from this Table that the hydrogens attached to carbon atoms are concentration-independent. However, pronounced concentration-dependence has been noted for the NH signal which can be seen as a broad peak in the lowest field of the spectrum. In deuterium oxide this broad peak disappeared for 2,6-dimethyl-4-hydroxypyrimidine and 4-hydroxy-6-methylpyrimidine probably due to rapid exchange, thus confirming the last assignment. Variations of the chemical shifts of the NH for these two pyrimidines are shown in Figs. 4 and 5. Over the range of 3 to 20% solution the chemical shift changes

[15] T. Alexander and M. Maienthal, *J. Pharm. Sci.* **53**, 962 (1964).
[16] D. Brown, *The Pyrimidines* p. 483. Intersceince, New York (1962).
[17] A. Katritzky and R. Reavill, *J. Chem. Soc.* 753 (1963).

TABLE 3. EFFECT OF CONCENTRATION ON THE NMR SPECTRA OF 4-HYDROXYPYRIMIDINES IN $CDCl_3$ AT 25°

Compound	Concentration (%)	Chemical shifts 2H	5H	Me	SEt
19[a]	1	8·12[b]	6·31[b]	2·35	—
19	3	8·13[b]	6·33[b]	2·33	—
19	5	8·13[b]	6·33[b]	2·33	—
21	3	—	6·15	2·30, 2·47	—
21	5	—	6·15	2·29, 2·46	—
21	7	—	6·15	2·29, 2·46	—
21	10	—	6·15	2·29, 2·46	—
21	15	—	6·14	2·29, 2·45	—
21	20	—	6·15	2·30, 2·48	—
22[c]	3	4H 7·88[d]	6·23[d]	—	1·39, 3·22[e]
22	5	4H 7·88[d]	6·23[d]	—	1·36, 3·20[e]
22	10	4H 7·90[d]	6·27[d]	—	1·41, 3·22[e]
22	15	4H 7·90[d]	6·26[d]	—	1·41, 3·22[e]
22	20	4H 7·88[d]	6·24[d]	—	1·38, 3·20[e]

[a] NH signal; 12·23 ppm at 3%; 12·48 ppm at 5%. The NH peak was not observed at the concentration of 1%.

[b] $J_{2H,5H} = 1·5$ c/s.

[c] Compound 22 is 4-hydroxy-2-ethylthiopyrimidine.

[d] $J_{5H,6H} = 5·4$ c/s.

[e] $J = 6·3$ c/s.

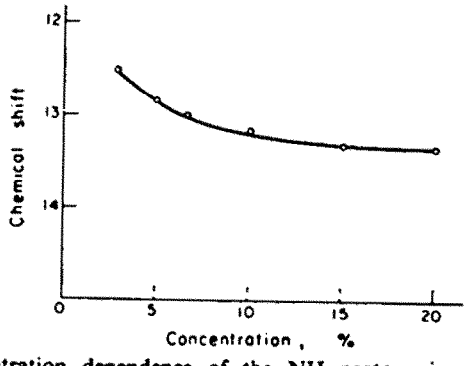


FIG. 4. Concentration dependence of the NH proton signal for 2,6-dimethyl-4-hydroxypyrimidine.

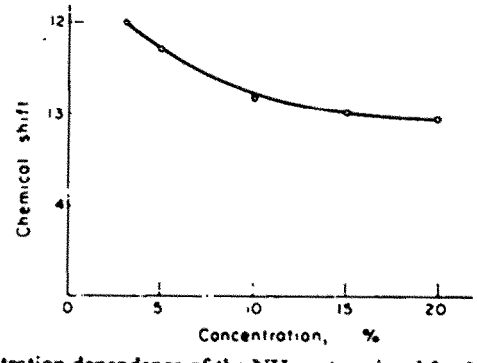


FIG. 5. Concentration dependence of the NH proton signal for 2-ethylthio-4-hydroxypyrimidine.

by 1 ppm. A shift to lower field with increase of concentration from 3 to 5% was also observed for 4-hydroxy-6-methylpyrimidine.

Although it is unadvisable to discuss the fine structures of these pyrimidines from insufficient data now available, the very appearance of a discernible NH signal suggests the presence in organic solvents of the oxo forms for these pyrimidines. It is of interest to note that recently Nakanishi *et al.*[18] have disclosed from NMR spectral observations that the main species present in aqueous solution of 4-hydroxypyrimidine is the 3,4-dihydro-4-oxo form. In addition, such pronounced downfield shift of the NH signal with the increase of concentration suggests a certain amount of solute–solute hydrogen bonding through either or both of NH—N and NH—O, which is usually reduced on dilution with concomitant shifts to higher field.[19]

[18] Y. Inoue, N. Furutachi and K. Nakanishi, *J. Org. Chem.* **31**, 175 (1966).

[19] J. Emsley, J. Feeney and U. Sutchiffe, *High Resolution Nuclear Magnetic Resonance Spectroscopy* p. 537. Pergamon Press, Oxford (1965).