Preparation and N.m.r. Spectra of some Hydrazono-malonates and -crotonates

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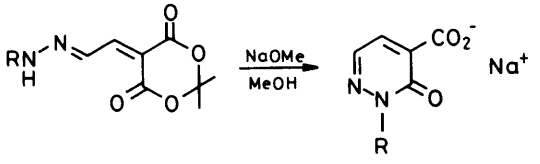
Treatment of the Meldrum's acid derivative (**4**) with dilute sodium methoxide solution gives the malonate half-esters (**5**) which may be alkylated to the diester (**6**), or decarboxylated to give the *E* and *Z* crotonates (**7a**) and (**7b**). The n.m.r. spectra (^{1}H, ^{13}C and variable-temperature ^{1}H) of these derivatives are discussed in detail.

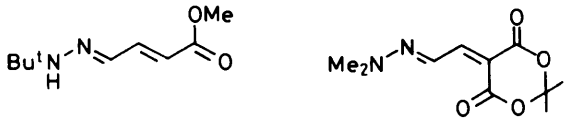
In a recent paper, we described the formation of 2,3-dihydro-3-oxopyridazine-4-carboxylates (**2**) by cyclisation of the hydrazones (**1**) in dilute sodium methoxide solution (Scheme 1).[1] In



(**1**) (**2**)

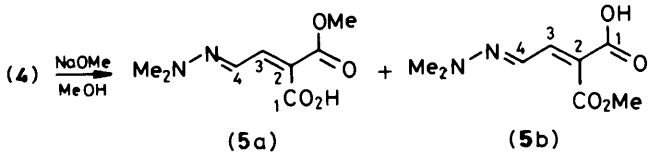
Scheme 1.

general, the reaction proceeds in good yield under mild conditions, and with an absence of side reactions. However, in one case (R = Bu^t), the yield of the heterocycle was low, and a minor product, (**3**), was isolated in 1% yield. Whereas the cyclisation is initiated by base abstraction of the hydrazone proton, the formation of (**3**) is most likely to occur by competitive nucleophilic attack of the methoxide ion at C-4 of the dioxanedione ring. We now report the optimisation of this latter process by the use of the *N,N*-disubstituted hydrazone (**4**) and give a detailed account of the ^{1}H and ^{13}C n.m.r. spectra of the products.



(**3**) (**4**)

The initial cleavage of the Meldrum's acid ring of (**4**) takes place under very mild conditions. Thus treatment of (**4**) with a two-fold excess of sodium methoxide in methanol for 2 h at room temperature is sufficient to give a quantitative yield of the half ester (**5**), obtained as a mixture of *E* and *Z* isomers [(**5a**) and (**5b**) respectively] in an 85:15 ratio (Scheme 2). The stereochemical assignment followed from the decarboxylation studies (see below), but was expected on the basis of nucleophilic attack from the less hindered side of the starting material (**4**). Alkylation of the mixture of half esters (**5**) using iodomethane-potassium carbonate in dimethylformamide gave an 89% yield of the dimethyl malonate (**6**).



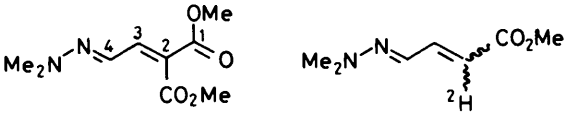
(**5a**) (**5b**)

Scheme 2.

Table 1. Assignment of ^{1}H n.m.r. signals (δ_H) for the conjugated systems of (**5**), (**6**), and (**7**)[a]

	2-H	3-H	4-H	J_{23}/Hz	J_{34}/Hz
(**7a**)	5.70	7.29	6.75	15.4	9.3
(**7b**)	5.61	6.73	8.02	11.4	9.5
(**6**)		7.59	7.33		9.8
(**5a**)		7.93	8.12		9.9
(**5b**)		8.20	7.41		10.3

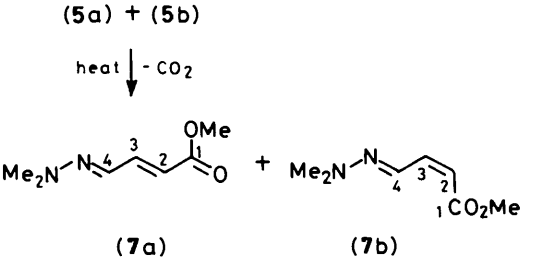
[a] Recorded at 80 or 200 MHz for solutions in C[^{2}H]Cl$_3$.



(**6**) (**8**)

Three sets of conditions were used for the attempted decarboxylation of the half esters (**5**), though none were totally satisfactory (Scheme 3). First, the original basic solution from (**4**) was heated under reflux for an extended period, as used in the model formation of (**3**),[1] and in related decompositions of aminomethylene Meldrum's acid derivatives,[2] but no hydrazones were present in the neutral/basic fraction on work-up.

Decarboxylation of the isolated half ester (**5**) under neutral conditions (toluene, reflux) required extended reaction times and gave a very low yield of impure product (**7**) together with much unspecified decomposition. However, a moderate yield of much better quality product was obtained by vacuum thermolysis of the neat material at 160—165 °C. Under these conditions, the *E* and *Z* isomers of the ester (**7**) were formed in an 80:20 ratio: the stereochemical assignment follows primarily from the magnitude of the vicinal coupling constants (*E* isomer; $^3J_{HH}$ 15.4 Hz: *Z* isomer: $^3J_{HH}$ 11.4 Hz). The correspondence of isomeric ratios of starting materials and products also confirms the assignment of the stereochemistry of the half-esters (**5**). On a preparative scale, the two isomers (**7**) are readily separated by chromatography on silica: the present method therefore complements an earlier synthesis of hydrazonocrotonates by Wittig methods[3] which gives the *E* isomer only.



(**7a**) (**7b**)

Scheme 3.

Table 2. Assignment of ^{13}C n.m.r. signals (δ_C for the conjugated systems of (**5**), (**6**), and (**7**)[a]

	C-1	C-2 ($^1J_{CH}$/Hz)	C-4 ($^1J_{CH}$/Hz)	C-3 ($^1J_{CH}$/Hz)	Other	$^nJ_{CH}$/Hz	
						$^2J_{2\text{-C},3\text{-H}} = 2.27$[b]	
(**7a**)	167.47	116.64 (161.44)	128.11 (159.85)	143.38 (156.56)		$^3J_{4\text{-C},2\text{-H}}$	7.88
						$^2J_{3\text{-C},4\text{-H}}$	9.56
						$\Sigma J_{1\text{-C,H}}$	17.5
(**7b**)	167.28	112.12 (164.23)	129.11 (168.20)	143.74 (154.37)		$^3J_{4\text{-C},2\text{-H}}$	11.77
						$^2J_{3\text{-C},4\text{-H}}$	8.99
						$\Sigma J_{1\text{-C,H}}$	18.5
(**6**)	165.92	116.89	126.09 (168.77)	147.18 (158.48)	165.73 (CO_2Me)	$^2J_{3\text{-C},4\text{-H}}$	7.11
						c	
(**5a**)	165.24	106.37	128.14	154.53	171.37 (CO_2H)		
(**5b**)	166.26	107.33.	126.95	154.24	170.48 (CO_2H)		

[a] Measured at 50 MHz for solutions in $C[^2H]Cl_3$. [b] Resolved after resolution enhancement. [c] Also complex overlapping signals for the two carbonyls at *ca.* δ166.

The *E* and *Z* isomers are surprisingly configurationally stable, in view of the push–pull nature of the conjugation (Figure) as reflected in restricted rotation about the N–N bond (see below). The thermodynamically less stable *Z*-isomer remains unchanged after many weeks at room temperature, though isomerisation becomes detectable when it is heated in toluene. Treatment of the *E*:*Z* mixture with base also causes no change in isomer ratio, though acid conditions promote *O*-protonation, which causes an increase in the proportion of the *E*-isomer to 93%.

Full assignment of the ^1H n.m.r. spectra was straightforward for the first order three-spin systems (**7a**) and (**7b**) both of which show a vicinal coupling $^3J_{HH}$ of *ca.* 9.4 Hz ($^3J_{34}$) with a larger coupling (15.4 and 11.4 Hz respectively) representing interaction across the *E* and *Z* double bond ($^3J_{23}$). In both (**7a**) and (**7b**) the 4-H doublet was broadened by long-range coupling to the *N*-methyl groups. This feature is general for such hydrazones; the coupling may be resolved in favourable cases [*e.g.* (**9**),[4,5] 2-H, $^5J_{HH}$ 0.68 Hz, after resolution enhancement], and was used to make the assignments of the spectra of (**5**) and (**6**) shown in Table 1.

The most notable feature which is apparent from these spectra is the pronounced deshielding effects of proximate ester—and in particular carboxylic acid—functions. For example, 3-H of the *E* ester (**7a**) is deshielded by 0.56 p.p.m. relative to that of the *Z*-ester (**7b**) while in the latter compound 4-H is deshielded by 1.27 p.p.m. relative to the corresponding proton in (**7a**) The enhanced effect of the carboxylic acid group is exemplified by a comparison of the chemical shift of 4-H in the diester (**6**) and the half-esters (**5a**) and (**5b**): the adjacent carboxylate [in (**5a**)] causes an added shift of >0.7 p.p.m. to high frequency.

These pronounced variations in chemical shift are not found in the ^{13}C n.m.r. spectra of these materials. Consequently, the assignments of the chemical shifts of (**7a**) given in Table 2 were made rigorously by specific decoupling of the corresponding ^1H resonance and the other assignments follow by analogy. Analysis of the principal minor couplings was made either by the use of the deuteriated compound [(**8**) applicable to (**7a**)], or by specific low-power ^1H-decoupling [(**7b**)], or, by inspection [(**6**)]. The carbonyl resonances were either too complex [(**7a**) and (**6**)] or of too low intensity [(**7b**)] for convenient analysis by these methods. The deuteriated compound (**8**) was prepared

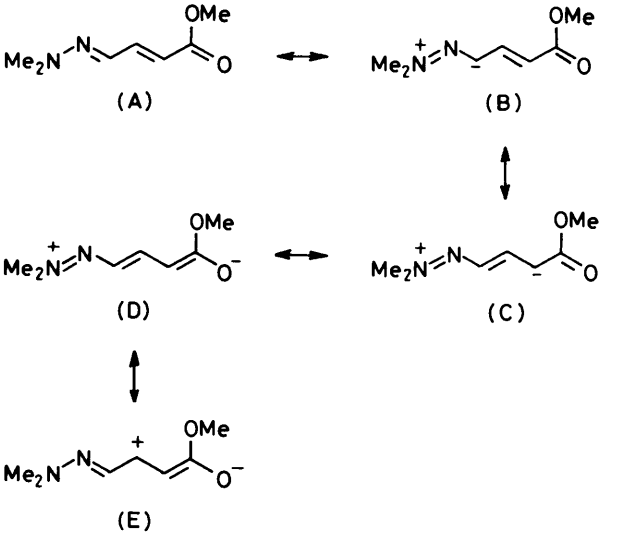


Figure.

with *ca.* 70% ^2H-incorporation by vacuum thermolysis of the half-ester (**5**) after exchange with $[^2H]$methanol.[6]

Apart from the general similarity in the magnitude of the parameters for compounds (**5**)—(**7**), some features from Table 2 are of particular interest. First, the C-2 and C-4 methine carbon resonances appear at relatively low frequency reflecting the electron-rich nature of these sites [Figure: structures (B) and (C), *cf.* structure (E)]. Increased electron-withdrawal in the malonates (**5**) and (**6**) causes the expected deshielding at C-3 [Figure: structure (E)], which is especially pronounced in the carboxylic acids (**5a**) and (**5b**). The presence of a *Z*-ester function causes an increase of *ca.* 9 Hz in $^1J_{CH}$ at C-4 [compounds (**7b**) and (**6**)], with insignificant changes at the other sites. The only minor coupling constant which involves 2-H, is sensitive to the configuration of the double bond[7] [(**7a**); *E*, $^3J_{C\text{-}4,2\text{-}H}$ 7.9 Hz: (**7b**); *Z*, $^3J_{4\text{-C},2\text{-H}}$ 11.8 Hz]; couplings to 3-H are small, and may be resolved only in special cases after line narrowing.

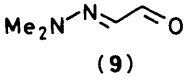
Restricted rotation about the N,N-bond is a sensitive probe

Table 3a. Variable temperature n.m.r. data for (**5a**), (**6**), (**7a**), and (**7b**)

Compd.	Coalescence temperature T_c/°C	Peak separation Δν/Hz	$\Delta G^{\ddagger}$/[f] kJ mol^{-1}
(**5a**)	−45	68.1	45.8
(**6**)	−63	63.8	42.1
(**7a**)	−104	*ca.* 61 [b]	33.7
(**7b**)	−96.5	*ca.* 57 [c,d]	35.3 [d]
(**4**)			58.0 [e]

[a] Data were recorded at 200 MHz for solutions in [$^2H_6$]acetone. [b] Measured as half-height linewidth at T_c.[10] [c] Measured at −104 °C, just 8 °C below T_c, but the lowest achievable temperature. [d] An increase in peak separation of 11 Hz causes a reduction in $\Delta G^{\ddagger}$ of *ca.* 0.3 kJ mol^{-1}. [e] Reference 1. [f] measurement of T_c to ± 2 °C gives rise to an error in $\Delta G^{\ddagger}$ of < ± 0.5 kJ mol^{-1}.

of electron delocalisation as implied by the Figure, and we have already reported data for the hydrazone (**9**; $\Delta G^{\ddagger}$ 51.2 kJ mol^{-1})[5] and for related compounds.[1,8] In the present examples, coalescence phenomena were observable for all the compounds of interest which allows an estimate of the free energy of activation (Table 3). It is clear that a second electron-withdrawing group [in (**5a**) and (**6**)] promotes a significant increase in $\Delta G^{\ddagger}$ for the rotation, but the barrier remains less than for the model compound (**9**). There are two reasons for this. First, extension of



(**9**)

the conjugation is known to make rotation in such systems more facile. Second, as reflected in the Hammett σ^- parameter, which encompasses inductive and conjugative effects, the ester group is less effective at withdrawing electrons than the aldehyde function. Significantly, the slight difference between $\Delta G^{\ddagger}$ for the diester (**6**) and the half-ester (**5a**) can also be explained on this basis, since $\sigma^-(CO_2H) > \sigma^-(CO_2Me)$. The delocalisation of the diester is much improved by maintaining the two ester groups in a rigid, planar configuration, as in the cyclic malonate (**4**)[1] (Table 3). Similar arguments account for the relative pK_a values of diethyl malonate and Meldrum's acid.[9]

The relative order of the restricted rotation of the two crotonates (**7a**) and (**7b**) is more surprising. It is normally expected that *trans* conjugation is the most efficient (as is generally found, for example, in u.v. spectra[11]) yet our results suggest that better delocalisation of the *Z* system (**7b**) contributes to the increased $\Delta G^{\ddagger}$. These results were measured at the extreme range of the solvent system, and other examples are needed to establish whether or not the effect is general.

Experimental

Unless stated otherwise, ^1H and ^{13}C n.m.r. spectra were recorded at 200 and 50 MHz respectively, for solutions in [^2H]chloroform.

Methyl 2-(1,1-*Dimethyl*-1,2-*diazabutadien*-4-*ylidene*)*malonate* (**5**).—A suspension of 5-(1,1-dimethyl-1,2-diazabutadien-4-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione[1] (**4**) (3.39 g, 15 mmol) in methanol (15 ml) was treated with a solution of sodium methoxide [from sodium (0.69 g, 30 mmol)] in methanol (15 ml), and the mixture was stirred at room temperature. After 2 h, the homogeneous solution which had formed was added to water (150 ml) and extracted with methylene dichloride (1 × 30 ml) to remove any remaining starting material. The aqueous layer was acidified (1M-HCl) and extracted with methylene dichloride (3 × 50 ml). The organic extracts were dried (Na_2SO_4) and concentrated, to give a brown oil which crystallised after some days at −20 °C. The yellow solid (2.87 g, 96%) so obtained, was identified as an 85:15 mixture of the *E* (**5a**) and *Z* (**5b**) isomers of the *methyl malonate*, m.p. 71—73 °C (from cyclohexane) (Found: C, 47.6; H, 6.0; N, 13.9. $C_8H_{12}N_2O_4$ requires C, 48.0; H, 6.0; N, 14.0%); δ_H (*E* isomer) 11.79 (1 H, br s), 8.12 (1 H, d, ^3J 9.9 Hz), 7.93 (1 H, d, ^3J 9.9 Hz), 3.79 (3 H, s), and 3.25 (6 H, s); δ_H (*Z* isomer) 8.20 (1 H, d, ^3J 10.3 Hz), 7.41 (1 H, d, ^3J 10.3 Hz), and 3.85 (3 H, s) (other signals coincident with those of *E* isomer); δ_C (*E* isomer) 171.38 (q), 165.24 (q), 154.53, 128.14, 106.37 (q), 52.51, and 43.23; δ_C (*Z* isomer) 170.48 (q), 166.26 (q), 154.24, 126.95, 107.33 (q), 52.35, and 43.23; *m/z* 200 (M^+, 71%), 156 (59), 138 (100), 124 (41), and 53 (85).

Dimethyl 2-(1,1-*Dimethyl*-1,2-*diazabutadien*-4-*ylidene*)*malonate* (**6**).—A mixture of the monomethyl ester (0.40 g, 2 mmol), iodomethane (0.57 g, 4 mmol), anhydrous potassium carbonate (0.55 g, 4 mmol), and dimethylformamide (5 ml) was stirred overnight at room temperature. The mixture was then poured into water (10 ml), and extracted with ether (3 × 20 ml). The organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a yellow oil which crystallised after bulb-to-bulb distillation at 145—147 °C (0.1 Torr). The *dimethyl malonate* (0.38 g, 89%) had m.p. 49—50 °C (from cyclohexane) (Found: C, 50.3; H, 6.65; N, 13.0. $C_9H_{14}N_2O_4$ requires C, 50.45; H, 6.55; N, 13.1%); δ_H (80 MHz) 7.59 (1 H, d, ^3J 9.8 Hz), 7.33 (1 H, br d, ^3J 9.8 Hz), 3.77 (3 H, s), 3.72 (3 H, s), and 3.11 (6 H, d, ^5J 0.54 Hz); δ_C 165.93 (q), 165.73 (q), 147.18, 126.10, 116.89 (q), 51.63, 51.51, and 42.43; *m/z* 214 (M^+, 89%), 183 (42), 170 (33), 155 (22), 138 (100), 59 (39), and 53 (56).

Decarboxylation of Methyl 2-(1,1-*Dimethyl*-1,2-*diazabutadien*-4-*ylidene*)*malonate* (**5**).—(a) *In toluene solution.* Reaction conditions were optimised by a preliminary thermolysis using [$^2H_8$]toluene as solvent in which the progress of the decarboxylation was monitored by ^1H n.m.r. spectroscopy. Thus, a solution of the monomethyl ester (0.40 g, 2 mmol) in toluene (20 ml) was heated under reflux for 70 h. Traces of starting material were removed by extraction with sodium hydroxide solution (1M; 1 × 10 ml). The aqueous layer was back-extracted with methylene dichloride (2 × 10 ml), and the combined toluene and methylene dichloride layers were dried (Na_2SO_4) and concentrated. Bulb-to-bulb distillation of the residual brown oil gave methyl 4-(dimethylhydrazono)crotonate (0.023 g, 7.4%), b.p. 83—85 °C (0.1 Torr), as an 86:14 mixture of *E* (**7a**) and *Z* (**7b**) isomers [see section (b) below for spectroscopic data].

(b) *Thermolysis* in vacuo. The monomethyl ester (1.00 g, 5 mmol) was heated (Kugelrohr) to 160—165 °C *in vacuo* (10^{-1} Torr) in a flask which was loosely packed with glass wool. The total distillate (0.58 g) was dissolved in methylene dichloride (10 ml), and extracted with aqueous sodium hydroxide (2M; 1 × 10 ml) to remove acidic impurities. The aqueous layer was back-extracted with methylene dichloride (1 × 10 ml), and the combined organic extracts were dried (Na_2SO_4), and concentrated to give a yellow oil (0.27 g, 35%) which was predominantly an 80:20 mixture of *E* (**7a**) and *Z* (**7b**) isomers of methyl 4-(dimethylhydrazono)crotonate respectively. These were separated by dry column flash chromatography[12] on silica using gradient elution [hexane—hexane:ether (1:1)]. The *Z* isomer, which was eluted first from the column, had m.p. *ca.* 22 °C (Found: M^+, 156.0897. $C_7H_{12}N_2O_2$ requires M^+, 156.0899), δ_H 8.02 (1 H, br, d, ^3J 9.5 Hz), 6.73 (1 H, dd, ^3J 9.5 and 11.4 Hz), 5.61 (1 H, d, ^3J 11.4 Hz), 3.71 (3 H, s), and 3.07 (6 H, s); δ_C 167.28 (q), 143.74, 129.11, 112.23, 50.63, and 42.18; *m/z* 156 (M^+, 100%), 125 (39), 112 (37), 97 (47), 80 (95), and 55 (16). The *E* isomer, which was the major component, had b.p. 83—85 °C

(0.1 Torr), and was solid at −20 °C (Found: M^+, 156.0901. $C_7H_{12}N_2O_2$ requires M^+, 156.0899); δ_H (80 MHz) 7.29 (1 H, dd, ^3J 9.3 and 15.4 Hz), 6.75 (1 H, br, d, ^3J 9.3 Hz), 5.70 (1 H, d, ^3J 15.4 Hz), 3.61 (3 H, s), and 2.92 (6 H, s) (the alkene chemical shifts are somewhat concentration dependent); δ_C 167.47 (q), 143.38, 128.11, 116.64, 50.89, and 41.97; *m/z* 156 (M^+, 67%), 125 (52), 112 (45), 97 (50), 80 (100), and 55 (24). A third, trace component (*ca.* 5%) which was obtained from the column, was apparently a complex mixture.

(c) *Thermolysis in vacuo of* [^{2}H]*-labelled derivative.* Dissolution of the monomethyl ester (0.4 g, 2 mmol) in [^{2}H]methanol caused deuterium exchange at the carboxylic acid group; the solution was then subjected to bulb-to-bulb distillation at 0.1 Torr to remove the solvent. Decarboxylation was then effected at 160—170 °C (0.1 Torr) to give a crude distillate (0.29 g) which was purified by base extraction as described in (b) above. The ^{1}H n.m.r. spectrum of the crude product showed *ca.* 70% deuterium incorporation at the 2-position, which proved to be sufficient for the ^{13}C n.m.r. assignments (see Discussion section).

Equilibration of E *and* Z *Isomers of Methyl* 4-(*Dimethylhydrazono*)*crotonate* (**7a**) *and* (**7b**).—(a) *Thermal equilibration.* A solution of the *Z*-isomer in [$^2H_8$]toluene was heated at 100 °C in the probe of an n.m.r. spectrometer. After 90 min, the extent of isomerisation was *ca.* 5%.

(b) *Equilibration with acid.* A sample containing an 80:20 *E*:*Z* mixture was dissolved in methylene dichloride and was shaken with dilute hydrochloric acid (1M) in a separating funnel for 15 min. The aqueous layer was extracted thrice with methylene dichloride, and the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated, to give a 93% recovery of product. The isomer distribution was 93:7 *E*:*Z*, which probably corresponds to the equilibrium mixture under these conditions.

(c) *Treatment with base.* A sample containing an 82:18 *E*:*Z* mixture was dissolved in [^{2}H]chloroform and was shaken with a solution of sodium [^{2}H]hydroxide. No deuterium incorporation was observed under these conditions (^{1}H n.m.r.), and, within experimental error, the isomer ratio remained unchanged.

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References

1 H. McNab and I. Stobie, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1845.
2 For example, J. P. Célérier, E. Deloisy, G. Lhommet, and P. Maitte, *J. Org. Chem.*, 1979, **44**, 3089.
3 T. Severin and H. Poehlmann, *Chem. Ber.*, 1978, **111**, 1564.
4 T. Severin and H. Poehlmann, *Chem. Ber.*, 1977, **110**, 491.
5 H. McNab, *J. Chem. Res.*, 1979, (*S*), 121; (*M*), 1451.
6 *cf.* H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1203.
7 *cf.* P. E. Hansen, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1981, **14**, 175.
8 M. E.-A. Murray, PhD Thesis, University of Edinburgh, 1985; H. McNab and M. E.-A. Murray, unpublished work.
9 H. McNab, *Chem. Soc. Rev.*, 1978, **7**, 345.
10 For example J. Sandström, 'Dynamic N.m.r. Spectroscopy,' Academic Press, London, 1982, p. 79.
11 For example, R. M. Silverstein, C. G. Bassler, and T. C. Morrill, 'Spectrometric Identification of Organic Compounds,' 3rd edn., Wiley, New York, 1974, p. 241.
12 L. M. Harwood, *Aldrichimica Acta*, 1985, **18**, 25.

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