

Synthesis and Stereochemistry of Spiropyrazolines

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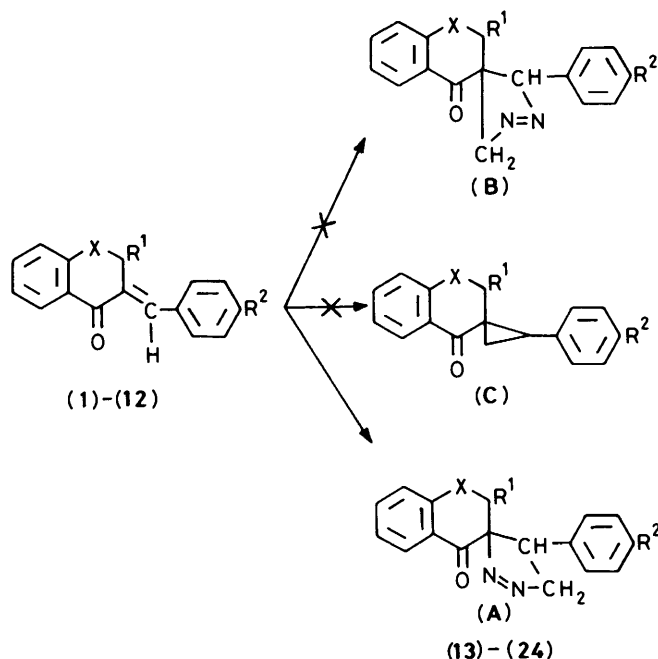
Spiropyrazolines have been synthesized by 1,3-dipolar cycloaddition of an 2-arylidene-1-tetralone, 3-arylidene-chromanones, -1-thiochromanones, and -flavanones with diazomethane. The relative configuration and stereochemistry of the products have been determined by means of one-dimensional difference N.O.E. measurements. It is shown that ring-closure reaction is regioselective, yielding stereohomogeneous spiropyrazolines in one step.

The preparation of pyrazolines by the reaction of diazomethane with chalcones and related compounds has been investigated by several research groups, but there are conflicting reports in the literature as far as the structures of compounds prepared in this way are concerned.¹⁻⁴ In our previous studies it was found that this reaction leads to the formation of 3-aryl-4-aryl-2-pyrazolines.⁵ Spiropyrazolines have also been synthesized by the reaction of diazomethane and exocyclic $\alpha\beta$ -unsaturated ketones.⁶⁻⁸ However, the reaction involving the synthesis of spiropyrazolines has hitherto been investigated only in a few cases and the relative configuration and stereochemistry of the compounds obtained were not elucidated. Direct formation of cyclopropane derivatives in the case of the reaction of diazomethane with compounds possessing the activated double bond has also been observed.⁹

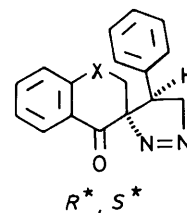
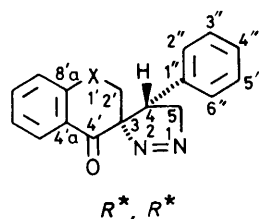
We report here the reaction of various exocyclic $\alpha\beta$ -unsaturated ketones (1)–(12) with diazomethane and the n.m.r. spectroscopic investigation of the stereochemistry of the compounds prepared [(13)–(24)]. $\alpha\beta$ -Unsaturated ketones (1)–(12), used as the starting materials, were *E*-isomers synthesized by the piperidine-catalysed condensation of the appropriate ketones and aldehydes.¹⁰

Compounds (1)–(12) were allowed to react with diazomethane in a mixture of anhydrous ether and acetone and homogeneous spiropyrazolines (13)–(24) were obtained in good yield.

Taking into consideration the electron distribution of the $\alpha\beta$ -unsaturated ketones and the positively charged β -carbon atom, it can be expected that the carbon atom of the diazomethane will link to the β -position and product (A) will be formed. Previous ¹³C n.m.r. studies¹¹ and quantum chemical calculations¹² showed, however, that depending on the substitution of the aryl group, considerable positive charge may appear on the α -carbon atom as well, and, therefore, structure (B) should also be taken into account. In analogy with experiments performed by Jurasek and Kovac,⁹ formation of type (C) cyclopropane derivatives is also possible but, because of the nitrogen content of the prepared substances, this possibility can be excluded in this case. Structure (B) could also be excluded since ³J(H,H) couplings were detected between the methine and methylene protons of the pyrazoline ring. The reaction afforded homogeneous product in high yield in each case, and no minor component could be detected by careful thin-layer chromatography. From this it can be concluded that the alteration of the X and Ar group, which influences the electron distribution of the conjugates part of the starting dipolarophile, is without much influence on the regioselectivity of the reaction. Com-



	(1)	(2)	(3)	(4)	(5)	(6)
	(13)	(14)	(15)	(16)	(17)	(18)
X	CH ₂	S	S	S	O	O
R ¹	H	H	H	H	H	H
R ²	H	H	Pr ⁱ	NO ₂	H	Pr ⁱ
	(7)	(8)	(9)	(10)	(11)	(12)
	(19)	(20)	(21)	(22)	(23)	(24)
X	O	O	O	O	O	O
R ¹	H	H	Ph	Ph	Ph	Ph
R ²	OMe	Br	H	Pr ⁱ	OMe	NO ₂



pounds (13)–(20) contain two, and substances (21)–(24) three, centres of chirality and, therefore, two or four diastereoisomeric

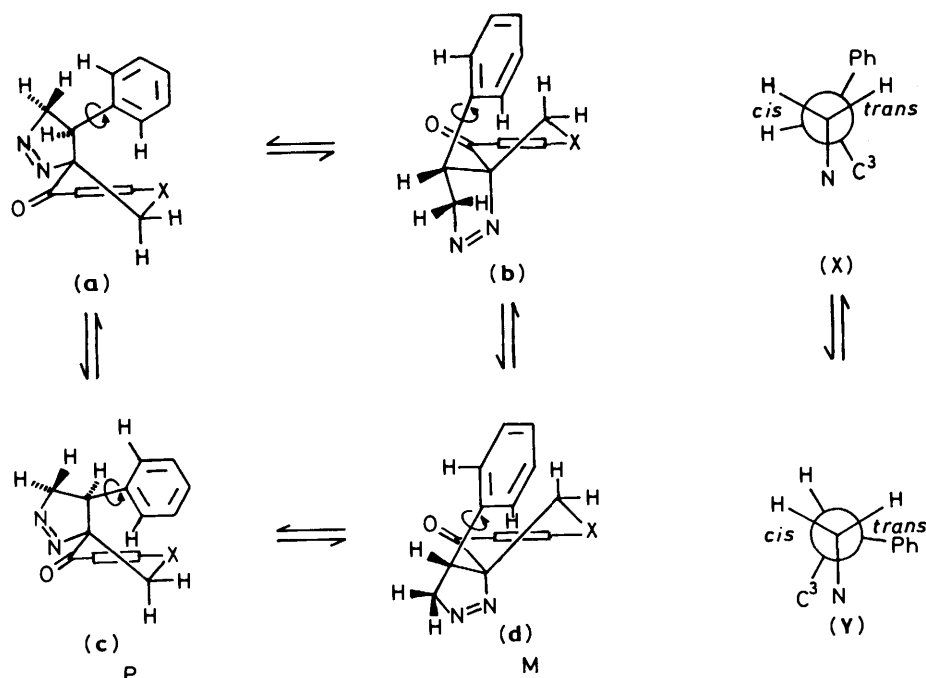


Table 1. ^1H Chemical shifts and selected coupling constants (Hz) for compounds (13), (14), (17), and (21) in CDCl_3

	(13) ^a	(14) ^a	(17) ^a	(21) ^a	(26) ^b
4-H	3.91	3.77	3.80	3.88	3.55
5- H_{cis}	5.00	4.85	4.94	4.98	4.20
5- H_{trans}	5.06	5.13	5.18	5.19	4.62
1'- H_{ax}	3.51				
1'- H_{eq}	2.84				
2'- H_{ax}	1.88	3.00	4.10		6.48
2'- H_{eq}	2.14	3.73	4.50	5.53	
5'-H	8.06	8.11	7.93	7.90	
6'-H	7.34	7.21	7.16	7.16	
7'-H	7.53	7.43	7.32	7.48	
8'-H	7.27	7.28	7.10		
2'',6''-H	6.95	6.98	6.91	6.91	
$^2J_{\text{H}_2-5}$	17.87	17.60	18.42	18.15	
J_{cis}	7.97	8.25	8.52	8.25	9.27
J_{trans}	4.67	2.20	3.02	0.55	6.85
$^2J_{\text{H}_2-2'}$	14.02	13.75	12.65		

^a Measured at 400 MHz. ^b Measured at 100 MHz.

pairs should be taken into consideration. Although the compounds investigated are racemates, owing to a better understanding of the stereochemistry, enantiomers possessing the *R* configuration at C-3 are illustrated in each case. To facilitate the presentation of the spectroscopic data, the numbering system depicted was adopted.

The determination of the structure is rendered more difficult by the fact that both the condensed and the pyrazoline rings are flexible and, therefore, the conformation equilibria (a) \rightleftharpoons (b) \rightleftharpoons (c) \rightleftharpoons (d) should be taken into account. In conformers (a) and (c) the helicity of the half-chair containing the carbonyl group is P while it is M in conformers (b) and (d). Dihedral angles between 4-H and 5- H_2 are significantly different in the (X) and (Y) envelope conformers of the pyrazoline ring, which is distinctly visible from a Newman projection of the C-5-C-4 bond. In conformer (Y) the dihedral angle (θ) between 4-H and 5- H_{trans} is nearly 90° which results in a 3J coupling constant of 0.

Table 2. Results of proton-proton one-dimensional N.O.E. difference experiments on compounds (13), (14), (17), and (21)

	Proton irradiated	Proton observed, N.O.E. (%) ^a
(13)	4-H	2'',6''-H (7%), 5- H_2 (4%)
	2'',6''-H	4-H (11%), 2'- H_{ax} (3%), 2'- H_{eq} (3%), 1'- H_{eq} (3%)
(14)	2'',6''-H	4-H (14%), 5- H_{trans} (5%), 2'- H_{ax} (2%), 2'- H_{eq} (6%)
	4-H	5- H_{trans} (6%), 2'- H_{ax} (5%), 2'- H_{eq} (5%)
(17)	2'',6''-H	4-H (15%), 5- H_{trans} (6%), 2'- H_{ax} (5%), 2'- H_{eq} (5%)
(21)	2'- H_{eq}	2'',6''-H (10%)

^a The N.O.E. enhancements % refer to 1 H.

This angle is *ca.* 150° in conformer (X). However, it is interesting that the 4-H, 5- H_{cis} dihedral angles are nearly the same in both (X) and (Y) (*ca.* 30°) and, therefore, they are insensitive to the alteration of the (X) \rightleftharpoons (Y) equilibrium. ^1H N.m.r. chemical shifts and characteristic coupling constants of compounds (13), (14), (17), and (21) measured at 400 MHz are summarized in Table 1. A common characteristic of the ^1H spectra is the substantial paramagnetic shift of 5-H which is, first of all, a consequence of the anisotropic effect of the *peri* carbonyl group.^{13,14} On the basis of the 3J coupling constants of 4-H and 5- H_2 it was possible to determine the dominant conformer for the pyrazoline ring and the (X) \rightleftharpoons (Y) equilibrium. On the basis of the measured $J(4\text{-H}, 5\text{-H}_{trans})$ of 0.55 Hz, the predominant conformation is (Y) for compound (21). This may be a consequence of the steric interaction between the phenyl groups at C-2' and C-4. In the case of compound (14) the larger fraction of conformer (X) is reflected in the $J(4\text{-H}, 5\text{-H}_{trans})$ values of 2.20 Hz. A further increase was found for compounds (17) (3.02 Hz) and (13) (4.67 Hz). The latter coupling constant suggests that the (X):(Y) ratio is *ca.* 1. Differentiation between the *R**,*R** and *R**,*S** structure was achieved by one-dimensional proton-proton difference N.O.E. measurements. The magnitudes of the N.O.E. depends to a large extent on the intramolecular proton-proton distances.^{15,16} Characteristic N.O.E. data of compounds (13), (14), (17), and (21) are summarized in Table 2. These corroborate the assignment as well. Irradiation of 4-H of compound (13) resulted in a considerable N.O.E. for signals at δ

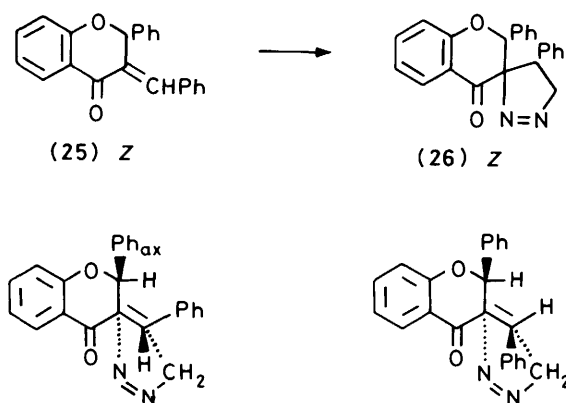
Table 3. ^{13}C Chemical shifts (p.p.m.) of compounds (13)—(24) and (26) (CDCl_3)

	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)	(26)
C-3	101.0	97.9	97.8	98.0	97.9	97.9	97.8	97.7	102.5	102.7	102.4	102.9	101.2
C-4	43.5	44.3	44.0	44.0	42.3	41.9	41.7	44.6	41.9	41.6	41.5	42.5	40.8
C-5	84.9	85.1	85.0	84.5	83.5	85.5	85.5	85.2	88.3	88.3	88.3	87.4	84.1
C-1'	29.6												
C-2'	26.6	30.8	30.9	30.6	69.4	69.6	69.4	69.2	81.9	82.2	81.9	81.8	80.9
C-4'	192.0	187.6	187.7	187.0	185.9	185.9	185.0	185.6	185.5	185.8	185.8	185.2	188.1
C-4a'	131.7	129.1	129.2	128.8	119.4	119.5	119.3	119.2	119.8	120.0	120.0	119.6	120.1
C-5'	126.9	130.5	130.5	130.7	127.9	127.9	127.9	128.6	128.5*	128.6*	128.6*	129.1	128.8
C-6'	127.4	125.1	125.0	125.4	121.8	121.8	121.8	121.3	121.2	121.4	121.4	122.0	122.0
C-7'	134.3	133.9	133.8	134.2	136.9	136.9	136.9	135.3	137.2	137.4	137.4	137.8	136.2
C-8'	128.8	127.6*	127.2	127.4	118.8	118.1	118.1	118.6	118.5	118.8	118.7	118.9	117.3
C-8a'	144.4	142.1	142.1	141.3	161.6	161.7	161.6	161.5	159.6	159.9	159.8	160.0	160.4
C-1''	138.6	138.0	135.2	145.6	136.8	134.0	128.6	135.9	137.6	135.4	128.4	145.5	133.8*
C-2'',6''	128.7	128.6	128.4	129.5	128.9	127.9	128.9	132.1	128.0	128.1	129.3	129.3	128.3 ^b
C-3'',5''	128.3	128.4	126.6	123.7	127.9	126.9	114.2	132.1	126.9	126.8	113.4	123.1	125.6
C-4''	128.3	127.2*	148.3	147.2	127.9	148.5	159.1	121.8	128.0	147.8	158.5	147.0	127.3 ^a
C-1'''									135.0	135.0	135.2	134.9	135.6 ^a
C-2''',6'''									128.0	128.1	128.1	128.6	128.5 ^b
C-3''',5'''									127.9	127.8	127.9	127.7	128.5 ^b
C-4'''									129.9*	127.8*	127.1*	127.5	127.1 ^a

* ^{a,b} Tentative assignment.

6.95 and 5.0—5.1, proving that the former signal is due to the 2'',6''-H *ortho* protons of the phenyl moiety and the latter to the 5-H₂ methylene protons. It is decisive in the differentiation of the diastereoisomeric structures that in the course of the above-mentioned experiment no N.O.E. was detected for the protons of the carbonyl-containing ring. The *R*,R** relative configuration of compound (13) is shown by the above experiment taking into account the (a) ⇌ (b) ⇌ (c) ⇌ (d) equilibria as well. A further direct corroboration of this was the fact that on saturating the 2'',6''-H signals, an intensity increase was observed for 1'-H_{eq} and 2'-H_{ax} signals found in the vicinity. Since an N.O.E. is not observed for the 1'-H_{ax} signal in the (a) ⇌ (b) ⇌ (c) ⇌ (d) equilibria, the protonation of conformers (a) and (c) of P helicity should be very low because in these cases 1'-H_{ax} is very near the *ortho* protons. In conformer (a) this proximity results in hindered rotation of the phenyl group. It is characteristic that, contrary to the usual trend, the chemical shift of axial 1'-H is higher by 0.67 p.p.m. than that of 1'-H_{eq}. Besides the anisotropic effect of the condensed aromatic ring, deshielding caused by the syn-axial -N=N- group may also play a part in this effect.

In compounds (14) and (17) irradiation of the *ortho* protons enhanced the intensity of only one of the 5-H₂ methylene protons (5-H_{trans}) which is on the same side of the pyrazoline ring. This corroborates the assignment deduced from the coupling pattern. These measurements proved the *R*,R** relative configuration of compounds (14) and (17) as well, and the preference of conformers (b) and (d) of M helicity. Because of the introduction of the C-2' phenyl group, four diastereoisomers should be differentiated in the case of (21). On the basis of *J*(4-H, 5-H_{trans}) 0.55 Hz, the pyrazoline ring should exist in the (Y) type conformation and, therefore, it is sufficient to consider only structures obtained by the introduction of the 2'-phenyl group into conformers (c) and (d). It is a characteristic of the ¹H n.m.r. spectrum that the chemical shifts of the 2'',6''-H *ortho* protons are unchanged while the signals of the *ortho* protons arising from the 2'-phenyl group are considerably shifted to higher field (δ 6.42) and are separated. This diamagnetic shift cannot originate from the sterically very unfavourable parallel 1,3-arrangement of the two phenyl groups since in this case a diamagnetic shift of the 2'',6''-H signals should also be observed. Therefore, the upfield shift of the 2'',6''-H *ortho* protons is due



only to the fact that the 2'-phenyl group is quasi-axial when the *ortho* protons in question are above the plane of the condensed phenyl ring. Irradiation of 2-H_{eq} enhanced the intensity of the 2'',6''-H signal which proved that C-3 and C-4 have the *R*,R** configuration in this case as well. The *R** or *S** configuration of C-2' is not possible with these experiments and hence it can only be concluded that 2'-H is equatorial.

If the formation of this spiro-pyrazoline ring is a one-step process, starting from *E*-(9) and *Z*-3-benzylidene-flavanone (25), different diastereoisomers are obtained. When the cycloaddition is a two-step process, the same product(s) should be expected in both cases. Starting from (25), compound (26) was obtained as a homogeneous product which, on the basis of the ¹H and ¹³C n.m.r. spectra, is an epimer of compound (21). This proves that 1,3-dipolar cycloaddition to 3-benzylidene-flavanone and related compounds of diazomethane is a one-step process.

Formerly it was observed that the phenyl group is quasi-axial in the (*E*)-3-benzylidene-flavanone.¹⁷ In the transition state leading to (21), diazomethane can link to the sterically non-hindered side affording the *R** configuration at C-2'.

¹³C Chemical shifts and assignments of compounds (13), (14), (17), (21), and (26) are summarized in Table 3. ¹³C Analysis of the starting arylidenes and the effect of the R² substituents were utilized for the assignment.¹⁸ ¹³C Chemical shifts of the condensed aromatic ring are insensitive to the alteration of R².

Table 4. Physical constants and analytical data of compounds (13)–(24) and (26)

Compound	M.p. (°C)	Yield (%)	Overall formula	Required (%)			Found (%)		
				C	H	N	C	H	N
(13)	70	78.5	C ₁₈ H ₁₆ N ₂ O	78.3	5.8	10.1	78.25	5.7	10.1
(14)	112	83.3	C ₁₇ H ₁₄ N ₂ OS	69.4	4.8	9.5	69.6	4.8	9.4
(15)	79	79.1	C ₂₀ H ₂₀ N ₂ OS	71.4	5.95	8.3	71.25	5.9	8.3
(16)	148	87.7	C ₁₇ H ₁₃ N ₃ O ₃ S	60.2	3.8	14.15	60.2	3.95	14.5
(17)	142	89.2	C ₁₇ H ₁₄ N ₂ O ₂	73.4	5.0	10.1	73.4	5.1	10.1
(18)	94	78.9	C ₂₀ H ₂₀ N ₂ O ₂	75.0	6.25	8.75	74.8	6.15	8.7
(19)	112	92.5	C ₁₈ H ₁₆ N ₂ O ₃	70.1	5.2	9.1	70.9	5.2	9.2
(20)	138	83.3	C ₁₇ H ₁₃ BrN ₂ O ₂	57.1	3.6	7.8	57.5	3.6	7.7
(21)	139	85.4	C ₂₃ H ₁₈ N ₂ O ₂	78.0	5.1	7.1	78.3	5.1	8.0
(22)	126	81.8	C ₂₆ H ₂₄ N ₂ O ₂	78.8	6.1	7.1	78.8	6.1	7.1
(23)	128	85.0	C ₂₄ H ₂₀ N ₂ O ₃	75.0	5.2	7.3	74.7	5.4	7.4
(24)	164	90.6	C ₂₃ H ₁₇ N ₃ O ₄	69.2	4.3	10.5	69.1	4.2	10.4
(26)	173	81.2	C ₂₃ H ₁₈ N ₂ O ₂	78.0	5.1	7.9	77.3	5.0	7.8

Introduction of the 2'-phenyl group in (21) resulted in a characteristic change in comparison with (17). The downfield shift of the C-2' and C-3 signals is unambiguously due to the α and β SCS (phenyl) effect. The influence of the γ -gauche phenyl group¹⁹ causes an unexpected 0.4 p.p.m. upfield shift on the C-4 signal. This may be the consequence of the fact that, contrary to (17) in compound (21) the (Y) conformation predominates. This may be the reason for the anomalously high (4.0 p.p.m.) δ SCS (phenyl) effect observed for the C-5 signal as well.

Experimental

M.p.s are uncorrected. T.l.c. was performed on Kieselgel 60 F₂₅₄ (Merck) layer using light petroleum ether-acetone [7:3 (v/v)] as eluant. N.m.r. spectra were recorded in CDCl₃ using Me₄Si as internal standard. ¹³C N.m.r. experiments were carried out at 25 MHz, using a JEOL FX-100 spectrometer. ¹H Measurements were performed on Bruker WH-400/DS or JEOL FX-100 instruments at 400 or 100 MHz, respectively. The solutions used for the 400 MHz N.O.E. difference experiments were degassed four times using the freeze-pump-thaw technique and then sealed under vacuum. For N.O.E. measurements a delay time of 8 s was used.

General Procedure for the Preparation of Spiropyrazolines.—A mixture of the appropriate $\alpha\beta$ -unsaturated ketone [(1)–(12), (25)] (0.5 g), diazomethane (*ca.* 2 molequiv.), anhydrous ether, and acetone was left to stand in refrigerator for one day, the solvent was evaporated under reduced pressure, and the residue crystallized from methanol to obtain compounds (13)–(24) and (26) (Table 4).

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References

- L. I. Smith and W. B. Pings, *J. Org. Chem.*, 1937, **2**, 23.
- S. G. Gathe, R. Kaushal, and S. S. Deshapande, *J. Indian Chem. Soc.*, 1950, **27**, 633.
- I. A. Aleksandrova, N. A. Dorofeeva, A. V. Chernova, and V. K. Khairullin, *Zh. Org. Khim.*, 1978, **14**, 1974.
- G. H. Sayed and H. Kjoson, *Indian J. Chem., Sect. B*, 1980, **19**, 980.
- A. L. Tökés, Á. Szöllösy, G. Tóth, and A. Lévai, *Acta Chim. Hung.*, 1983, **112**, 335.
- A. Mustafa and M. K. Hilmy, *J. Chem. Soc.*, 1951, 3254.
- A. K. Fateen and M. M. Ali, *Indian J. Chem., Sect. B*, 1972, **10**, 968.
- A. K. Fateen and A. M. Kaddah, *Rev. Roum. Chim.*, 1978, **23**, 791.
- J. Prousek, A. Jurásek, and J. Kovác, *Collect. Czech. Chem. Commun.*, 1980, **45**, 1704.
- (a) A. Lévai and E. H. Hetey, *Pharmazie*, 1978, **33**, 378; (b) A. Lévai and J. B. Schäg, *ibid.*, 1979, **34**, 749.
- Á. Szöllösy, G. Tóth, A. Lévai, and Z. Dinya, *Acta Chim. Hung.*, 1983, **112**, 343.
- E. Solcaniova, S. Toma, and S. Gronowitz, *Org. Magn. Reson.*, 1976, **8**, 439.
- H. M. McConnel and R. E. Robertson, *J. Chem. Phys.*, 1958, **29**, 1361.
- J. W. ApSimon, W. G. Craid, P. V. Demarco, D. V. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1967, **23**, 1967.
- J. H. Noggle and R. E. Schirmer, 'The Nuclear Overhauser Effect,' Academic Press, New York, 1971.
- J. K. M. Sanders and J. D. Merish, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1982, **15**, 353.
- D. D. Keane, K. G. Marathe, W. I. O'Sullivan, E. M. Philbin, R. M. Simons, and P. C. Teague, *J. Org. Chem.*, 1970, **35**, 2286.
- D. F. Ewing, *Org. Magn. Reson.*, 1979, **12**, 499.
- (a) F. Ungemach, D. Soerens, R. Weber, M. DiPierro, O. Campos, P. Mokry, J. M. Cook, and J. V. Silverton, *J. Am. Chem. Soc.*, 1980, **102**, 6976; (b) G. Tóth, Á. Szöllösy, A. Lévai, and H. Duddeck, *Org. Magn. Reson.*, 1982, **20**, 133.

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