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A 400 MHz ^{1}H NMR STUDY OF THE EIGHT BASIC HETEROYOHIMBINE ALKALOIDS

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Abstract—A 400 MHz ^{1}H NMR study of the eight basic heteroyohimbine alkaloids has permitted the chemical shifts of all the protons to be established and most of the main coupling constants to be determined. A conformational study of the heteroyohimbine structures is presented.

During the last years much progress has been made both in the ^{1}H NMR instrumentation and techniques. The utilization of a sufficiently powerful magnetic field can permit the recognition of each proton in the ^{1}H NMR spectra of even relatively complicated molecules. In the present communication we describe the results obtained by a 400 MHz ^{1}H NMR study of the basic stereoisomeric heteroyohimbine alkaloid structures. For some earlier, fragmentary ^{1}H NMR data concerning the heteroyohimbine alkaloids under investigation, see Refs. 1–8.

Stereochemical considerations

The basic heteroyohimbine alkaloids may be represented by the gross structure **1**. This means that 2^4 or 16 stereoisomers are possible. However, as the C–15 hydrogen in all heteroyohimbine alkaloids presently known is α,[9–11] the number of stereoisomers to be considered is reduced to eight. This permits the heteroyohimbine nucleus to occur in four configurations, which, by analogy with the yohimbine skeleton nomenclature, are called "normal" (3α, 15α, 20β), "pseudo" (3β, 15α, 20β), "allo" (3α, 15α, 20α), and "epiallo" (3β, 15α, 20α).

The stereochemical considerations of heteroyohimbine alkaloids are, however, complicated by the fact that several conformations are possible. Considering as the first approximation only the conformations where the *C* ring is in the half-chair form, the *D* ring in the chair form and the *E* ring in the "half-chair" form, three conformations (**a**, **b**, **c**), due to nitrogen inversion and *cis*-decalin type ring interconversion, are in theory possible for the "allo" and "epiallo" series. In the "normal" and "pseudo" series the *trans*-fusion of *D* and *E* rings causes conformational rigidity which does not permit *cis*-decalin type ring interconversion between *C* and *D* rings. Moreover, as the *trans* diaxial *C*/*D* ring juncture is not possible, the nitrogen inversion is ruled out in "pseudo" series.

Thus, taking into account the above mentioned restrictions, three theoretically possible conformations can be presented for "allo" and "epiallo" series, two for "normal" series and one for "pseudo" series (Scheme 1).

The classification of the heteroyohimbine alkaloid structures into eight stereochemical groups (A–H) follows the suggestion of Shamma and Richey.[2]

RESULTS AND DISCUSSION

Application of consecutive double resonance operations permitted all the protons in the eight basic heteroyohimbine alkaloids (tetrahydroalstonine **2**, akuammigine **3**, rauniticine **4**, 3-isorauniticine **5**, ajmalicine **6**, 19-epiajmalicine **7**, 3-iso-ajmalicine **8** and 3-iso-19-epi-ajmalicine **9**) to be discovered and the coupling constants presented in Table 1 to be determined.

The spectrum of akuammigine **3**, and in lesser amount that of rauniticine **4**, taken at room temperature, showed broadening of several signals. At 60°C the signals were much sharper and permitted most of the coupling constants to be determined (Table 1).

Of the 24 protons of tetrahydroalstonine **2** the identification of 13 (CH_3–(δ 1.38), CH_3O–(δ 3.74), H–19β (δ 4.48), H–11 (δ 7.10), H–10 (δ 7.05), H–9 (δ 7.24), H–12 (δ 7.42), H–17 (δ 7.55) and NH (δ 7.86)) is straightforward.

The irradiation of H–19β allows the identification of H–20α (δ 1.68), which irradiation permits the identification of both H–21's (δ 3.08 and δ 2.72) and H–15 (δ 2.76). The irradition of H–15 reveals both H–14's (δ 2.50 and δ 1.52) and furnishes supplementary evidence on the correctness of the H–20α assignment. The disappearance of the small long range coupling (0.5 Hz) between H–15 and H–17 gives a supplementary confirmation for the H–15 assignment. The irradiation of the H–14 signals fixes the δ 3.32 signal to H–3. The remaining 4 protons (C(5)–C(6) ethano bridge) form a separate system (except a small interaction between H–6's and H–3), which, by consecutive irradiation, can be easily resolved.

The assignment of the signals of the other heteroyohimbine alkaloids (Table 1) followed a procedure similar to that described for tetrahydroalstonine **2**.

The coupling constants found (Table 1) and the dihedral angles in different H–C–C–H systems, measured with the aid of Dreiding models, for different conformations under consideration, clearly support, in good agreement with the earlier stereochemical suggestions,[2,12,13] the preponderance of conformers **2a**, **5a**, **6a**, and **7a** in $CDCl_3$ solution for tetrahydroalstonine **2**,

*Assignments can be interchanged.

Table 1. ^{1}H NMR data of the eight basic heteroyohimbine alkaloids

Chemical shifts

	2	3	4	5	6	7	8	9
H-3	3.32 br d	3.78 br d[b]	3.48 br d	3.12 br d	3.42 br d	3.37 br d	4.56 br s	4.52 br s
H-5α	2.54 ddd	3.13 dd	2.65 m	3.1 m	2.68 td	2.68 td	3.3-3.4 m	3.3-3.4 m
H-5β	2.92 ddd	2.94 m	3.00 dd	2.62 td	3.10 dd	3.12 dd	3.3-3.4 m	3.3-3.4 m
H-6α	2.67 br d	3.05 m	2.67 br d	3.0 m	2.75 br d	2.75 br d	3.02 ddd	3.00 ddd
H-6β	2.87 ddd	2.66 br d	2.93 ddd	2.73 br d	3.00 ddd	3.02 ddd	2.63 br d	2.60 br d
H-9	7.42	7.47	7.44	7.45	7.47	7.46	7.48	7.46
H-10[a]	7.05	7.08	7.05	7.07	7.09	7.07	7.11	7.09
H-11[a]	7.10	7.14	7.10	7.12	7.14	7.12	7.17	7.15
H-12	7.24	7.35	7.24	7.28	7.30	7.28	7.40	7.37
H-14α	2.50 dt	2.13 br	2.50 dt	1.74 td	3.22 dt	3.17 dt	3.21 dt	3.11 dt
H-14β	1.52 q	3.04 br t	1.83 q	3.10 br d	1.32 q	1.26 q	1.70 td	1.59 td
H-15	2.76 dt	2.74 br	2.79 dt	3.06 br s	2.45 tdd	2.38 tdd	1.98 tdd	1.94 tdd
H-17	7.55 d	7.55 d	7.50 d	7.63 d	7.54 d	7.56 d	7.51 d	7.50 d
H-18 (Me)	1.38 d	1.36 d	1.43 d	1.36 d	1.18 d	1.36 d	0.92 d	1.34 d
H-19	4.48 dq	4.46 qd	4.40 qd	4.14 br q	4.43 qd	3.86 dq	4.33 qd	3.55 dq
H-20	1.68 br d	1.86 br t	2.22 br s	2.29 br d	2.14 tt	1.75 qd	2.08 tt	1.61 br q
H-21α	2.72 dd	2.98 dd	2.77 dd	3.00 dd	2.25 t	2.20 t	2.56 t	2.48 t
H-21β	3.08 dd	2.62 dd	2.87 dd	2.36 t	2.97 dd	3.11 dd	2.67 dd	2.77 dd
CO_2Me	3.74 s	3.76 s	3.72 s	3.75 s	3.74 s	3.74 s	3.73 s	3.70 s
NH	7.86 br s	7.89 br s	8.77 br s	7.90 br s	7.98 br s	8.06 br s	8.35 br s	8.18 br s

Coupling constants

2 : $J_{3,14\alpha}$ = 3 Hz; $J_{3,14\beta}$ = 12 Hz; $J_{5\alpha,5\beta}$ = 12.5 Hz; $J_{5\alpha,6\alpha}$ = 4 Hz; $J_{5\alpha,6\beta}$ = 11 Hz; $J_{5\beta,6\alpha}$ <1 Hz; $J_{5\beta,6\beta}$ = 6 Hz; $J_{6\alpha,6\beta}$ = 15 Hz; $J_{14\alpha,14\beta}$ = 12 Hz; $J_{14\alpha,15}$ = 4 Hz; $J_{14\beta,15}$ = 12 Hz; $J_{15,17}$ = 0.5 Hz; $J_{15,20}$ = 4 Hz; $J_{18,19}$ = 6.5 Hz; $J_{19,20}$ = 12 Hz; $J_{20,21\alpha}$ = 5 Hz; $J_{20,21\beta}$ = 3 Hz; $J_{21\alpha,21\beta}$ = 12 Hz.

3 : $J_{3,14\alpha} \sim 9$ Hz; $J_{3,14\beta} \sim 4$ Hz; $J_{5\alpha,5\beta} = 12$ Hz; $J_{5\alpha,6\alpha} = 6$ Hz; $J_{5\alpha,6\beta} < 1$ Hz; $J_{5\beta,6\alpha} = 12$ Hz; $J_{5\beta,6\beta} = 4$ Hz ; $J_{6\alpha,6\beta} = 15$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} = 6$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{15,17} < 0.3$ Hz; $J_{15,20} \sim 6$ Hz; $J_{18,19} = 7$ Hz; $J_{19,20} = 6$ Hz; $J_{20,21\alpha} = 5$ Hz; $J_{20,21\beta} = 7$ Hz; $J_{21\alpha,21\beta} = 12$ Hz.

4 : $J_{3,14\alpha} = 3$ Hz; $J_{3,14\beta} = 12$ Hz; $J_{5\alpha,5\beta} = 12$ Hz; $J_{5\alpha,6\beta} = 12$ Hz; $J_{5\beta,6\alpha} < 1$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{6\alpha,6\beta} = 15$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} = 4$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{15,17} = 0.5$ Hz; $J_{15,20} = 4$ Hz; $J_{18,19} = 7$ Hz ; $J_{19,20} = 6$ Hz; $J_{20,21\alpha} = 5$ Hz; $J_{20,21\beta} = 3$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz.

5 : $J_{3,14\alpha} = 12$ Hz; $J_{3,14\beta} = 3$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\beta} < 1$ Hz; $J_{5\beta,6\alpha} = 11$ Hz; $J_{5\beta,6\beta} = 4.5$ Hz; $J_{6\alpha,6\beta} = 15$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} = 4$ Hz; $J_{14\beta,15} = 2$ Hz; $J_{15,17} = 1$ Hz; $J_{15,20} = 1$ Hz; $J_{18,19} = 6$ Hz; $J_{19,20} = 1$ Hz; $J_{20,21\alpha} = 4$ Hz; $J_{20,21\beta} = 11.5$ Hz; $J_{21\alpha,21\beta} = 11.5$ Hz.

6 : $J_{3,14\alpha} = 3$ Hz; $J_{3,14\beta} = 12$ Hz; $J_{5\alpha,5\beta} = 12$ Hz; $J_{5\alpha,6\alpha} = 4$ Hz; $J_{5\alpha,6\beta} = 11$ Hz, $J_{5\beta,6\alpha} < 1$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{6\alpha,6\beta} = 16$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} = 3$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{15,17} = 1.5$ Hz; $J_{15,20} = 12$ Hz; $J_{18,19} = 6$ Hz; $J_{19,20} = 3$ Hz; $J_{20,21\alpha} = 12$ Hz; $J_{20,21\beta} = 3$ Hz; $J_{21\alpha,21\beta} = 12$ Hz.

7 : $J_{3,14\alpha} = 3$ Hz; $J_{3,14\beta} = 12$ Hz; $J_{5\alpha,5\beta} = 12$ Hz; $J_{5\alpha,6\alpha} = 4$ Hz; $J_{5\alpha,6\beta} = 11$ Hz; $J_{5\beta,6\alpha} < 1$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{6\alpha,6\beta} = 16$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} = 3$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{15,17} = 1.5$ Hz; $J_{15,20} = 12$ Hz; $J_{18,19} = 6$ Hz; $J_{19,20} = 12$ Hz; $J_{20,21\alpha} = 12$ Hz; $J_{20,21\beta} = 3$ Hz; $J_{21\alpha,21\beta} = 12$ Hz.

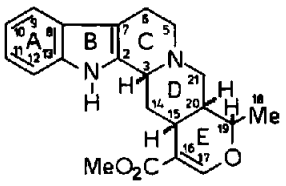
8 : $J_{3,14\alpha} = 2$ Hz; $J_{3,14\beta} = 4$ Hz; $J_{5\alpha,6\alpha} = 8$ Hz; $J_{5\alpha,6\beta} < 1$ Hz; $J_{5\beta,6\alpha} = 10$ Hz; $J_{5\beta,6\beta} = 4$ Hz; $J_{6\alpha,6\beta} = 16$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} = 2$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{15,17} = 1$ Hz; $J_{15,20} = 12$ Hz; $J_{18,19} = 6$ Hz; $J_{19,20} = 3$ Hz; $J_{20,21\alpha} = 12$ Hz; $J_{20,21\beta} = 3$ Hz; $J_{21\alpha,21\beta} = 12$ Hz.

9 : $J_{3,14\alpha} = 2$ Hz; $J_{3,14\beta} = 4$ Hz; $J_{5\alpha,6\alpha} = 8$ Hz; $J_{5\alpha,6\beta} < 1$ Hz; $J_{5\beta,6\alpha} = 10$ Hz; $J_{5\beta,6\beta} = 4$ Hz; $J_{6\alpha,6\beta} = 16$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} = 2$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{15,17} = 1$ Hz; $J_{15,20} = 12$ Hz; $J_{18,19} = 6.5$ Hz; $J_{19,20} = 12$ Hz; $J_{20,21\alpha} = 12$ Hz; $J_{20,21\beta} = 3$ Hz; $J_{21\alpha,21\beta} = 12$ Hz.

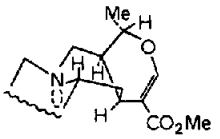
Spectra were run in $CDCl_3$ at 400 MHz. Values are in ppm (TMS = 0), s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, br, broad. The sample temperatures used were 20°C for compounds 2, 5, 6, 7, 8, and 9, and 60°C for compounds 3 and 4. The coupling constants between the aromatic protons are not included.

[a] Assignments can be interchanged.

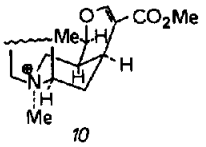
[b] Partly masked.



1

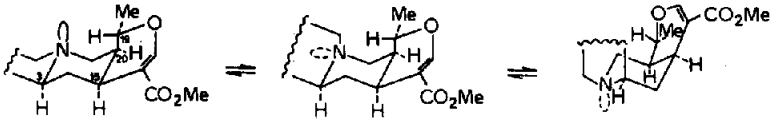


3d



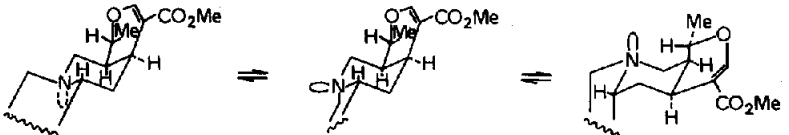
10

Group A
allo, C (19)-Me *α*
Tetrahydroalstonine *2*



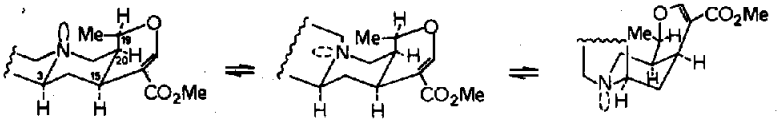
2a *2b* *2c*

Group B
epiallo, C (19)-Me *α*
Akuammigine *3*



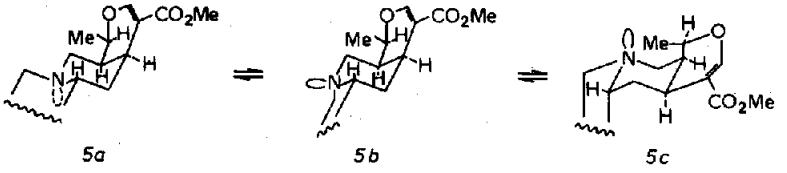
3a *3b* *3c*

Group C
allo, C (19)-Me *β*
Rauniticine *4*



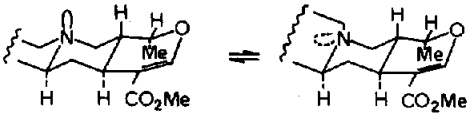
4a *4b* *4c*

Group D
epiallo, C (19)-Me *β*
3-Isorauniticine *5*



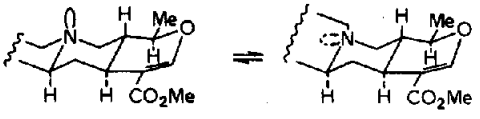
5a *5b* *5c*

Group E
normal, C (19)-Me *α*
Ajmalicine *6*



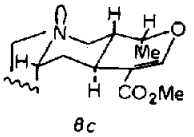
6a *6b*

Group F
normal, C (19)-Me *β*
19-Epiajmalicine *7*



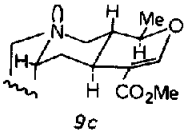
7a *7b*

Group G
pseudo, C (19)-Me *α*
3-Isoajmalicine *8*



8c

Group H
pseudo, C (19)-Me *β*
3-Iso-19-epiajmalicine *9*



9c

Scheme 1.

3-isorauniticine **5**, ajmalicine **6** and 19-epiajmalicine **7**, respectively. The contribution of conformer **b** can be considered to be negligible. The *trans* diequatorial juncture in quinolizine itself has been shown to be 10.9 kJ/mol (2.6 kcal/mol) more stable than the *cis* juncture.[14] The coupling constants and especially the (H–3) chemical shifts found (Table 1) for 3-isoajmalicine **8** and 3-iso-19-epiajmalicine **9** support their presentation as **8c** and **9c**, respectively.

It has been proposed[13] that akuammigine **3** exists in $CDCl_3$ solution in an equilibrium of conformers **3a** and **3c** (Scheme 1). However, the present results (Table 1), especially $J_{14\beta,15} = 12$ Hz, $J_{19,20} = 6$ Hz and $J_{20,21\alpha} = 5$ Hz, suggest, that the contribution of a third conformer to the conformational equilibrium of akuammigine **3** has to be taken into account. It seems to us reasonable to assume that this third conformer might be represented by **3d**, (equatorial C(19) CH_3-group), where the *D* ring of akuammigine **3** occupies a slightly deformed boat conformation. A supplementary argument favouring the contribution of conformer **3d** to the conformational equilibrium of akuammigine **3** is found by ^{13}C NMR spectroscopy. The apparently anomalously low shift value (25.7 ppm) found for C–15[13] can be explained by an interaction between nitrogen (N_b) lone pair and H–15 in **3d**. A boat conformation has been proposed *inter al.* for the D ring of geissoschizine.[15,16] However, in that case the *C/D* ring juncture is *cis*, whereas in **3d** it is *trans*.

The present results (Table 1) also suggest, that, although conformer **4a** is by far the most important one for rauniticine **4**, a certain contribution of conformer **4c** (equatorial C(19)CH_3-group) has to be taken into account. It has been shown[17] that the methylation of raunitidine (11-methoxyrauniticine) by methyliodide leads to a methiodide which structure is **10** (see also Ref. 13, note 47).

The NMR data presented permit a rapid distinction between the eight basic heteroyohimbine alkaloids and can be expected to be useful also for substituted analogues. In the cases of *C*, *D* and/or *E* ring substituted analogues, however, caution is needed in the interpretation of the results, especially in the "allo" and "epiallo" series, where the substituents can have a strong influence on the conformational equilibrium.

EXPERIMENTAL

All eight basic heteroyohimbine alkaloids (*vide supra*) used in the present investigation were available in the sample collections at ICSN as natural products. However, as the amount of the natural 3-iso-19-epiajmalicine **9** was very small, most of the NMR measurements concerning this heteroyohimbine base were executed using a synthetic sample prepared from 19-epiajmalicine **7** by the classical procedure,[11,18,19] dehydrogenation [$Hg(OAc)_2$], followed by reduction (Zn-acid) (yield 10%).

All the samples used were purified by repeated crystallizations from MeOH. The uniformity of the samples prior to their use in NMR experiments was checked by TLC (silica gel; $CHCl_3$/MeOH, 98/2).

Compound	Rf
Tetrahydroalstonine **2**	0.54
Akuammigine **3**	0.20
Rauniticine **4**	0.10
3-Isorauniticine **5**	0.25
Ajmalicine **6**	0.36
19-Epiajmalicine **7**	0.40
3-Isoajmalicine **8**	0.12
3-Iso-19-epiajmalicine **9**	0.14

Instrumentation. The NMR spectra enabling attribution of individual protons to the molecules under study were obtained from a laboratory-built 400 MHz ^{1}H high resolution spectrometer (I.E.F. 400). The spectrometer operates in Fourier transform mode using a Texas Instruments 980A computer which perform the 8K complex data point calculations in less than 6 sec. Normal NMR line resolution is 0.5 Hz per point for a 10 ppm spectrum. Frequency resolution enhancement can be assured by FT interpolation of part of the spectrum.[20] The persistent mode superconducting magnet is made from Nb-Ti multifilamentary wires cooled down to 2.17°K to produce a stable homogeneous field. No field-frequency lock was needed throughout the experiments. However, a 61.4 MHz deuterium automatic pulsed lock[21] has been incorporated for very long accumulations. The I.E.F. 400 spectrometer incorporates all the features such as single or multi-line decoupling, difference spectra, deconvolution, etc., indispensable for detailed analysis of complex molecules. The NMR spectra were run collecting 8–64 free induction decay signals for ~0.01 M solutions of the samples in 450 μl of $CDCl_3$.

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REFERENCES

[1]E. Wenkert, B. Wickberg and C. L. Leicht, *J. Am. Chem. Soc.* **83**, 5037 (1961).
[2]M. Shamma and J. M. Richey, *J. Am. Chem. Soc.* **85**, 2507 (1963).
[3]E. Winterfeldt, A. J. Gaskell, T. Korth, H.-E. Radunz and M. Walkowiak, *Chem. Ber.* **102**, 3558 (1969).
[4]J. Gutzwiller, G. Pizzolato and M. Uskokovic, *J. Am. Chem. Soc.* **93**, 5907 (1971).
[5]R. T. Brown and A. A. Charalambides, *Tetrahedron Letters* 1649 (1974).
[6]L. A. Djakouré, F. X. Jarreau and R. Goutarel, *Tetrahedron* **31**, 2695 (1975).
[7]J. Melchio, A. Bouquet, M. Païs and R. Goutarel, *Tetrahedron Letters* 4731 (1976).
[8]J. Boivin, M. Païs and R. Goutarel, *Tetrahedron* **33**, 305 (1977).
[9]E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81** 1474 (1959).
[10]J. S. Bindra, *The Alkaloids* (Edited by R. H. F. Manske), Vol. XIV, p. 95. Academic Press, New York (1973).
[11]J. D. Phillipson and S. R. Hemingway, *Phytochemistry* **14**, 1855 (1975).
[12]G. A. Morrison, *Fortschritte der Chemie Organischer Naturstoffe* (Edited by L. Zechmeister), Vol. 25, p. 290. Springer-Verlag, Vienna and New York (1967).
[13]E. Wenkert, C.-J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King and K. Orito, *J. Am. Chem. Soc.* **98**, 3645 (1976).
[14]H. S. Aaron and C. P. Ferguson, *Tetrahedron Letters* 6191 (1968).
[15]G. Rackur and E. Winterfeldt, *Chem. Ber.* **109**, 3837 (1976); See also H. Hammer, M. Rösner, U. Rosentreter and E. Winterfeldt, *Chem. Ber.* **112**, 1889 (1979).
[16]M. Damak, A. Ahond, P. Potier and M.-M. Janot, *Tetrahedron Letters* 4731 (1976).
[17]T. M. Moynehan, K. Schofield, R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.* 2637 (1962).
[18]E. Wenkert and D. K. Roychaudhury, *J. Org. Chem.* **21**, 1316 (1956).
[19]E. Wenkert and D. K. Roychaudhury, *J. Am. Chem. Soc.* **80**, 1613 (1958).
[20]P. Gonord, S. Kan and M. Sauzade, *J. Magn. Res.* **24** 457 (1976).
[21]S. Kan, P. Gonord, M. Fan, M. Sauzade and Courtieu, J. *Rev. Sci. Instrum.* **49**, 785 (1978).