Tetrahedron Vol. 36, pp. 3579 to 3584
Pergamon Press Ltd., 1980. Printed in Great Britain

0040-4020/80/1215 3579/$02.00/0

QUINOLINE ALKALOIDS—XXI[1]

THE ^{13}C NMR SPECTRA OF HEMITERPENOID QUINOLINE ALKALOIDS AND RELATED PRENYLQUINOLINES

N. M. D. BROWN,* M. F. GRUNDON, D. M. HARRISON and S. A. SURGENOR

School of Physical Sciences, The New University of Ulster, Coleraine, Northern Ireland

(*Received in U.K. 28 February* 1980)

Abstract – ^{13}C NMR spectra of twenty-five hemiterpenoid quinoline alkaloids and related prenylquinolines were determined; C-, O- and N-prenyl-quinolines and -quinolone derivatives, hydroxyisopropyldihydrofuroquinolones, hydroxydimethyldihydropyranoquinolones and furoquinolines are included. Chemical shifts were assigned by proton single-frequency and off-resonance decoupling and by comparison with model compounds.

During the last decade the structures of new hemiterpenoid quinoline alkaloids have been elucidated principally by spectroscopic methods.[2] The main problems in the case of the extensive group of tricyclic quinoline alkaloids are to distinguish between those with linear (4-quinolone) and angular (2-quinolone) annelation and between furo- and pyranoquinolines; IR,[3] UV,[4] ^{1}H NMR,[5,6] and mass spectroscopy[7] have been widely used to this end. The presence of OH, O- and N-Me, and prenyl groups in quinoline alkaloids is easily recognised, but the pattern of substitution is less readily established by spectroscopy alone. Since only a few isolated examples of the ^{13}C NMR spectra of these alkaloids have been reported previously[8,9] we were prompted to use the structural utility of ^{13}C NMR spectroscopy in the study of a representative group (25) of quinoline alkaloids and related compounds.

RESULTS AND DISCUSSION

The compounds in this survey fall into three structural types: (a) C-, O- and N-prenyl-quinoline and -quinolone derivatives, (b) tricyclic-, furo- or pyrano-quinolones, and (c) furo-quinolines. The origin of each sample is indicted in the Experimental section.

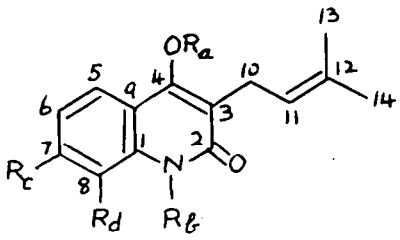
^{13}C NMR chemical shifts are given in Tables 1 and 2, or are incorporated in structural formulae **7**–**11** and **21**–**25**. The system of numbering C atoms is designed to facilitate data comparison between compounds. Poor solubility in $CDCl_3$ required the use of DMSO-d_6 in some cases; comparisons have been made between spectra obtained in different solvents in that any solvent-dependent shifts are small compared to those which are structural in origin. Assignments are based in the main on off-resonance decoupling experiments and on the chemical shifts reported for simple substituted quinolines and quinolones.[10]

(a) *Prenyl-quinoline and -quinolone derivatives.* Of the 3-prenyl-2-quinolones, **1**–**6**, only preskimmianine, **5**, from *Dictammus albus*, has been isolated from a natural source; assignments of chemical shifts are shown in Table 1. Resonances assigned to the *gem*-dimethyl carbons in compounds **1**–**6** occur in the ranges 17.8–18.1 ppm and 25.4–25.8 ppm, with those at 22.2–24.1 ppm assigned to methylene carbon. The olefinic carbon at C-11 resonates at 121.3–122.5 ppm and that of the tri-substituted olefinic carbon at 130.6–132.3 ppm in accord with the reported ^{13}C chemical shifts of isoprenyl carbons[11] with the isoprenyl methyls individually identified following specific assignments recently reported.[12] The assignment for C-11 was confirmed in compound **3** by single-frequency decoupling at the known position of the olefinic proton (τ 4.55).

The protonated aromatic C atoms of compounds **1**–**6** were identified by the characteristic doublets in the off-resonance spectra and the assignment followed comparison with published chemical shifts.[10] The ^{13}C NMR spectra of compounds **1**, **2** and **4** were completely assigned; however in compounds **5** and **6** not all the signals due to non-protonated C atoms were in fact observed (Experimental). The high frequency non-protonated carbons were readily identified as the CO carbon at C-2 (162.7–164.7 ppm) and the C atom at C-4 (156.8–162.0 ppm). In the latter examples we note that the presence of an OH group at C-4 in compounds **1**–**4** produces a signal at the low frequency end of the range given, whereas substitution by OMe in compounds **5** and **6** shifts the C-4 resonance to a higher frequency (160.4–162.0 ppm).

In compounds **2**, **4**, **5** and **6** resonances assigned to the C atoms of OMe groups occur in the range 56.0–61.7 ppm. The 3-prenylquinoline derivatives **3**, **4** and **6** and the quinoline alkaloids **8**, **10** and **12**–**21**, discussed below, contain N-Me groups that give resonances falling into distinct groups centred at *ca* 30 ppm and at *ca* 36 ppm. When the homocyclic ring of an N-Me quinoline derivative is unsubstituted at C-8 then the signal for the N-Me group appears at 29.0–31.2 ppm, but when an OMe group is present at that position the N-Me carbon resonates at lower field (35.5–36.5 ppm). In the only example studied of an N-methylquinolone with a substituent at C-8 other than an OMe group, the 7,8-methylenedioxy derivative, **6**, an intermediate value of 32.5 ppm for the N-Me resonance was observed. The position of substituents in quinoline alkaloids is not always readily deduced from their ^{1}H NMR spectra. This

Table 1. ^{13}C NMR chemical shifts of compounds **1**–**6** (δ values)[a]



1 $R_a=R_b=R_c=R_d=H$

2 $R_a=R_b=R_c=H$, $R_d=OMe$

3 $R_a=R_c=R_d=H$, $R_b=Me$

4 $R_a=R_c=H$, $R_b=Me$, $R_d=OMe$

5 $R_a=Me$, $R_b=H$, $R_c=R_d=OMe$

6 $R_a=R_b=Me$, $R_cR_d=OCH_2O$

Carbon	1	2	3	4	5	6
1	137.3	127.4	138.5	130.6	-	-
2	163.4	162.7	163.7	164.7	164.4	164.2
3	115.5	116.1	116.4	118.7	120.8	120.2
4	156.8	157.1	157.4	157.1	162.0	160.4
5	120.8	114.3	121.6	115.8	118.5	118.3
6	122.6	120.8	123.2	122.1	107.6	104.4
7	129.6	110.4	130.4	113.9	-	-
8	114.8	145.4	113.8	148.5	-	-
9	111.5	111.9	109.5	109.6	112.2	114.5
10	22.2	22.2	23.9	24.1	23.5	24.3
11	122.4	122.5	121.3	121.3	121.8	121.9
12	130.6	130.6	136.4	136.5	132.3	132.3
13	17.8	17.8	18.0	18.0	18.0	18.0
14	25.4	25.4	25.8	25.7	25.7	25.7
OMe		56.0		56.7	61.7	61.7
OMe					61.0	
OMe					56.3	
NMe			29.8	35.5		32.5
OCH_2O						101.0

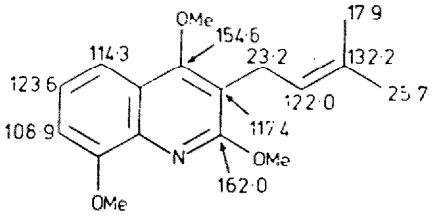
Compounds **1** and **2** were run in DMSO-d_6 solution, the others in $CDCl_3$.
[a]A dash indicates that the appropriate signal has not been detected (see Experimental).

^{13}C NMR criterion may therefore prove to be of general diagnostic value. While steric compression can lead to a shift of a ^{13}C NMR resonance of the magnitude observed for the 8-methoxyquinoline derivatives such shifts are always to lower frequency.[13] Spatial proximity is therefore not the explanation for the two distinct N-Me resonance locations found; the additional presence of the electronegative O atom of the OMe group may be significant. Chemical shifts for the 2,4,8-trimethoxy-3-prenylquinoline derivative, **7**, are unexceptional on the basis of the shifts assigned in compounds **1**–**6**. Again not all tertiary carbons are identified.

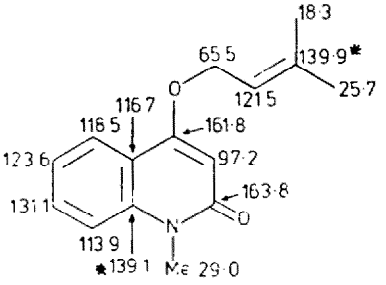
Complete assignments have been made for the O-prenylquinolone, ravenine **8**, and for the N-prenylquinolone **9**. The chemical shifts of C atoms of the prenyl group of ravenine are comparable to those of an O-prenylcoumarin.[14] Attachment of prenyl groups to O and to N results in high frequency shifts of the methylene C resonances by *ca* 42 ppm and by *ca* 17 ppm, respectively, compared with that for the group attached to carbon. The resonances of other carbons of the prenyl groups are relatively unaffected. Resonances for C-3 carbons in ravenine and in compound **9** appear at 97.2 and at 97.0 ppm, respectively. In compound **9**, the resonance at 105.2 ppm attributed to C-5 is consistent with that of an aromatic carbon *ortho* to an OMe group and agrees with the chemical shifts observed for the corresponding C atom of 2-methyl-6-methoxy-quinoline.[10]

The 1,2-dimethylallyl derivative, ravenoline **10**, has also been studied and the assignment of side-chain resonances made on the basis of expected chemical shifts and off-resonance multiplicity.

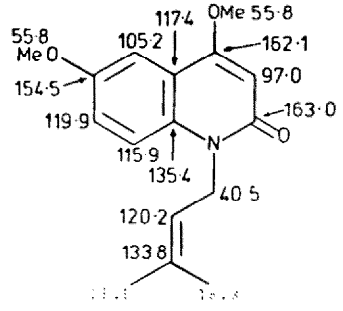
The ^{13}C NMR spectra of five quinoline alkaloids containing oxygenated 3-prenyl groups **11**–**15** have

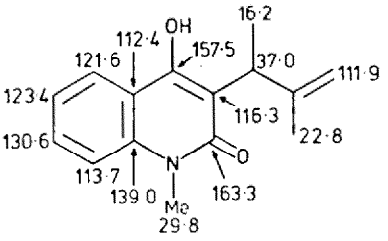


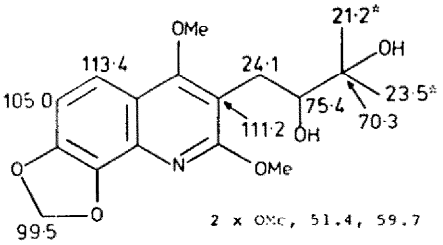
3 x OMe, 53.7, 56.4, 62.1



* Assignments may be reversed







2 x OMe, 51.4, 59.7

*Assignments may be reversed

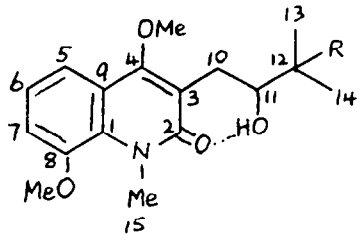
11

also been obtained (Table 2) but not all tertiary carbons were identified (Experimental). Chemical shifts for the C-3 substituent of orixine **11** are in agreement with those reported for xanthone derivatives with the same side-chain.[11] The most noteworthy feature of the spectra of balfourolone and lunacridine is the high frequency shift of *ca* 4 ppm of the 2-CO carbon resonance compared, for example, to the corresponding carbon of compounds **1**, **2**, **4**–**6** and **8**–**10**. This shift is due to intramolecular H-bonding between the CO oxygen and the side-chain OH group, as has been observed previously.[15] A clear demonstration of this effect is provided by a comparison of the ^{13}C NMR spectra of compounds **14** and **15**. Intramolecular H-bonding can occur in the alcohol **14** but not in the analogous methyl ether **15** as is indicated by a higher frequency chemical shift for the CO group carbon (Table 2) in the former with respect to that in the latter.

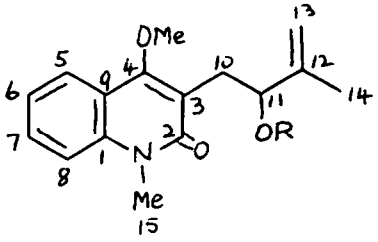
The side-chain carbon chemical shifts of balfourolone **12** compared to orixine **11** can also be attributed to the consequences of intramolecular H-bonding in the former; the differences for C-12, C-13 and C-14 in the case of lunacridine **13** simply reflect the absence of the second OH group at C-12.

(b) *Tricyclic quinolones.* The chemical shifts of hydroxyisopropyldihydrofuro-4-quinolone alkaloids, isoplatydesmine **16** and balfourodine **17** are compared with those of the 3-hydroxy-2,2-dimethyldihydropyrano-4-quinolone alkaloid, ribalinine **18** in Table 2. A feature in each of the three spectra is the weak signal at a position higher (171.5–175.2 ppm) than any observed for compounds already discussed. This we attribute to the carbon of the 4-CO group as part of a vinylogous tertiary amide system. For the furo derivatives **16** and **17** assignment of resonances at 25.0 ppm to Me carbons (C-13 and C-14), at 27.1–27.2 ppm to methylene carbon (C-10), at 90.6–91.1 to methine carbon adjacent to oxygen (C-11), and at 70.0–70.1 ppm to the non-protonated quarternary carbon (C-12) adjacent to oxygen was confirmed by off-resonance decoupling. The isomeric pyrano derivative **18** is similarly constituted. Comparison of the data of the furo system **16** and the pyrano analogue **18** reveals a large chemical shift difference between corresponding carbons e.g.

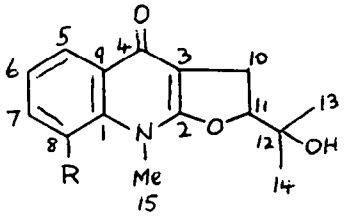
Table 2. ^{13}C NMR chemical shifts of compounds **12**–**20** (δ values)[a]



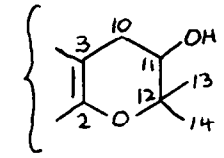
12 R=OH Balfourolone
13 R=H Lunacridine



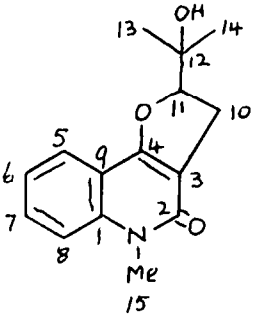
14 R=H
15 R=Me



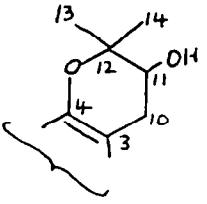
16 R=H Isoplatydesmine
17 R=OMe Balfourodine



18 R=H Ribalinine



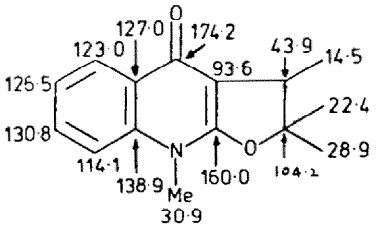
19 Araliopsine



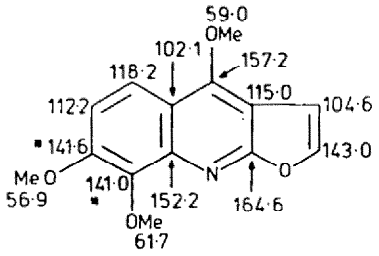
20 ψ-Ribalinine

Carbon atom	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
1	-	-	139.1	139.4	138.7	128.7	138.9	140.5	138.6
2	167.3	167.1	165.9	164.0	-	162.7	154.0	162.3	163.2
3	-	-	117.5	117.8	98.5	98.7	96.3	112.4	116.3
4	161.5	161.3	161.8	161.6	172.0	171.5	175.1	161.2	154.9
5	116.1	116.1	122.4	121.9	122.6	117.6	122.0	121.5	121.5
6	123.2	123.0	123.7	123.7	125.2	123.4	125.2	123.0	123.0
7	113.9	113.9	130.7	130.2	130.8	114.6	131.3	130.9	130.2
8	149.2	149.1	114.5	114.2	115.3	150.5	115.4	114.5	113.8
9	-	120.3	120.5	120.2	126.2	129.8	123.2	108.7	103.6
10	27.9	30.0	32.2	30.6	27.2	27.1	25.7	29.1	27.2
11	79.4	77.4	76.2	77.3	91.1	90.6	67.3	92.1	68.8
12	73.0	34.8	148.0	144.9	70.1	70.0	82.1	71.7	79.2
13	24.0	17.7	110.2	113.2	25.0	25.0	20.9	24.4	21.9
14	25.7	18.5	18.1	16.7	25.0	25.0	25.0	25.5	24.8
15(N-CH_3)	36.0	35.8	30.0	29.7	31.2	36.5	30.1	29.1	29.2
OMe at C-4	62.3	62.0	62.3	62.1					
OMe at C-8	56.7	56.7				56.9			
OMe at C-11				50.3					

Compounds **16** and **17** were run in DMSO-d_6 solution, the others in $CDCl_3$.
[a]A dash indicates that the appropriate signal was not observed (see experimental).

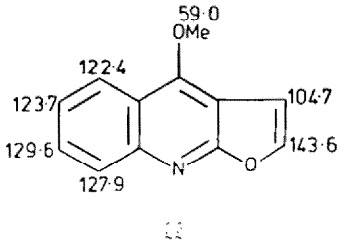


21

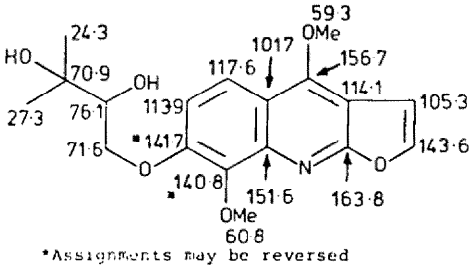


*Assignments may be reversed

22



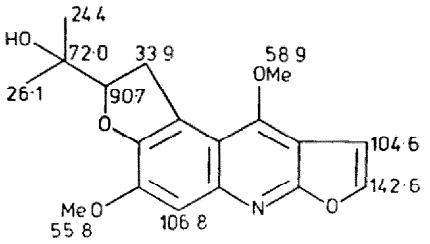
23



*Assignments may be reversed

Spectrum obtained in d_6-DMSO solution

24



Spectrum run at 325°K

25

+23.8 ppm between C-11 of compound **16** and C-11 of compound **18** and −12.0 ppm between C-12 of **16** and C-12 of **18**. Therefore ^{13}C NMR spectroscopy provides a most unequivocal method of characterising such furo- and pyrano-isomers.

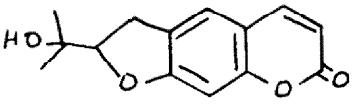
Chemical shifts for the isomeric angular tricyclic quinolone isomers, araliopsine **19** and ψ-ribalinine **20** are similar to those of the corresponding linear derivatives (Table 2); again the same distinction can be made between furo- and pyrano-derivatives. The one important difference between the angular compounds (2-quinolones) and the linear compounds (4-quinolones) is that the carbon of the CO group (C-2) in the angular derivatives has a chemical shift at lower frequency, by *ca* 10 ppm, with respect to that of the CO group (C-4) in the 4-quinolones. This criterion appears to provide a reliable method of distinguishing between angular and linear annelation in this group of compounds, and usefully supplements the existing methods using IR and ^{1}H NMR spectroscopy.

The ^{13}C NMR spectrum of the 1,2-dimethylallyl-quinolone derivative, lemobiline **21** [a cyclisation product of ravenoline **10**], has also been assigned completely. The low-frequency Me resonance at 14.5 ppm is attributed to the 3-Me group, while the other two Me substituents appear at 22.4 and 28.9 ppm; the methine carbon has a chemical shift of 43.9 ppm.

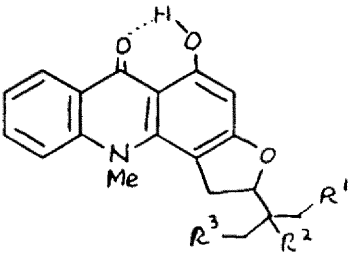
(c) *Furoquinolines.* Complete assignment of the ^{13}C NMR spectrum of skimmianine **22**, with lanthanide-induced shifts used to allocate OMe signals, has been reported already;[9] our data for the alkaloid differ by no more than 0.4 ppm. The spectra of three other furoquinoline alkaloids, dictamnine **23**, evoxine **24** and choisyine **25** have also been recorded and analysed by off-resonance decoupling and comparison with compounds discussed above. In the four furoquinolines high-intensity signals, well-separated from aromatic carbons bearing hydrogen, are observed for the furanoid α- and β-carbons. The α-carbons resonate in the range 142.6–143.6 ppm, while the β-carbons appear in the equally narrow range 104.6–105.3 ppm; these resonances seem to be characteristic of furoquinolines and arise at somewhat lower frequency than the corresponding chemical shifts in benzofuran and in furocoumarins, in which the furan ring is attached directly to a benzene ring.[14]

The carbon chemical shifts of the C-7 side-chain of evoxine are similar to those for the identical side-chains of orixine **11** and balfourolone **12**, the only important difference being that the methylene group of evoxine is adjacent to oxygen and therefore appears as expected at *ca* 45 ppm to higher frequency.

The resonances due to the hydroxyisopropyl-dihydrofuro moiety in the ^{13}C NMR spectrum of choisyine **25** were readily assigned following off-resonance decoupling. The chemical shifts are similar to those of other quinolines containing a hydroxy-isopropyldihydrofuro ring, for example compounds **16**, **17** and **19** and the coumarin[14] **26**, except that the



(26)



(27)

signal for the methylene group, is located at 33.9 ppm rather than at 27.1–29.1 ppm; signals for methylene groups in the related acridones **27** are at 37.6–37.9 ppm.[15] The difference may be due to the neighbouring OMe group at C-4 in compound **25** and to the adjacent Me group in the acridones **27**, and as in the case of the N-Me effect noted above, the shift to higher frequency is unlikely to be caused by steric compression.

Signals for the non-protonated C atoms of dictamnine **23** and of choisyine **25** were not detected in the spectra under the observational conditions used (Experimental).

EXPERIMENTAL

^{13}C NMR spectra were obtained for samples (70–150 mg, as available, at room temperature unless otherwise noted) in $CDCl_3$ except where indicated otherwise, with TMS as internal reference, on a Bruker WH-90 spectrometer operating at 22.63 MHz; 10 mm tubes were used and 8 K or 4 K to 4 K or 2 K Fourier transforms were employed. The spectrum of compound **3** was obtained with a JEOL FX-90Q instrument.

In a number of compounds (**5–7, 11–13, 16, 21, 23** and **25**) not all quaternary carbons have been identified; this is a consequence of low solubility signal: noise problems coupled with adverse relaxation characteristics which together demand unrealistically long accumulation times in these instances.

The following compounds were available from published syntheses: **1**,[16] **2**,[17] **3**,[18] **4**,[19] preskimmianine **5**,[20] **6**,[21] **7**,[20] ravenine **8** and ravenoline **10**,[18] orixine **11**,[21] balfourolone **12**,[22] lunacridine **13**,[17] **14** and **15**,[23] isoplatydesmine **16**,[6] balfourodine **17**,[19] ribalinine **18** and araliopsine **19**,[24] lemobiline **21**[18] and dictamnine **23**.[20] Compound **9** was obtained by reaction of 4,6-dimethoxy-2-quinolone with 3,3-dimethylallyl bromide;[25] ψ-ribalinine **20** was prepared by rearrangement of araliopsine.[27] Skimmianine **22**, evoxine **24** and choisyine **25** were isolated from *Choisya ternata*.[26]

Acknowledgement – We thank the Department of Education for Northern Ireland for a postgraduate studentship (to S.A.S.).

REFERENCES

[1]Part 20. J. L. Gaston and M. F. Grundon, *J. Chem. Soc.* Perkin I in press.
[2]M. F. Grundon, *The Alkaloids* (Edited by R. H. F. Manske and R. G. A. Rodrigo), Vol. XVII, p. 105. Academic Press (1979).
[3]N. J. McCorkindale, *Tetrahedron* **14**, 223, (1961); and refs quoted.
[4]H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.* **82**, 4395 (1960) and refs quoted.
[5]A. V. Robertson, *Aust. J. Chem.* **16**, 451 (1963).
[6]R. M. Bowman and M. F. Grundon, *J. Chem. Soc.* (C) 1504 (1966).
[7]J. Reisch, K. Szendrei, I. Novak and E. Minker, *Acta. Pharm. Hung.* **44**, 107 (1974); S. Hammerum, A. M. Duffield, R. A. Corral and O. O. Orazi, *Acta. Chem. Scand.* **B31**, 31, (1977).
[8]F. R. Stermitz and I. A. Sharifi, *Phytochemistry* **16**, 2003, (1977).
[9]A. Ahond, F. Picot, P. Potier, C. Poupat and T. Sévenet, *Ibid.* **17**, 166 (1978).
[10]L. F. Johnson and W. C. Jankowski, *Carbon-13 Nuclear Magnetic Resonance Spectroscopy. A Collection of Assigned, Coded and Indexed Spectra*, Wiley-Interscience, New York (1972); P. A. Claret and A. G. Osbourne, *Spectroscopy Letters* 167 (1976).
[11]J. S. E. Holker, R. D. Lapper and T. J. Simpson, *J. Chem. Soc.* Perkin I 2135 (1974); J. A. Ballantine, V. Ferrito, C. H. Hassall and M. L. Jenkins, *Ibid.* Perkin Trans 1, 1825 (1973).
[12]P. J. Nathan, C. Mejia and D. A. Bruno, *J. Am. Chem. Soc.* **101**, 1289 (1979).
[13]G. C. Levy and G. L. Nelson, *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*. Wiley-Interscience, New York (1972).
[14]M. H. A. Elgamal, N. H. Elewa, E. A. M. Elkhrisy and H. Duddeck, *Phytochemistry* **18**, 139 (1979).
[15]D. Bergeuthal, I. Mester, Zs. Rózsa and J. Reisch, *Ibid.* **18**, 161 (1979).
[16]R. M. Bowman and M. F. Grundon, *J. Chem. Soc.* (C) 1084 (1966).
[17]E. A. Clarke and M. F. Grundon, *Ibid.* 438 (1964).
[18]T. R. Chamberlain and M. F. Grundon, *Ibid.* (C) 910 (1971).
[19]E. A. Clarke and M. F. Grundon, *Ibid.* 4196 (1964).
[20]J. F. Collins, G. A. Gray, M. F. Grundon, D. M. Harrison and C. G. Spyropoulos, *Ibid.* Perkin Trans 1, 94 (1973).
[21]R. M. Bowman and M. F. Grundon *Ibid.* (C) 2368 (1967).
[22]R. M. Bowman, J. F. Collins and M. F. Grundon, *Ibid.* Perkin Trans 1, 626 (1973).
[23]M. F. Grundon, D. M. Harrison and S. A. Surgenor, *Tetrahedron Letters* 1713 (1979).
[24]M. F. Grundon and S. A. Surgenor, *J. Chem. Soc.* Chem. Comm. 624 (1978).
[25]J. F. Collins and M. F. Grundon, unpublished results.
[26]M. F. Grundon, D. M. Harrison and C. G. Spyropoulos, *J. Chem. Soc.* Perkin Trans. 1, 2181 (1974).
[27]M. F. Grundon and S. A. Surgenor, unpublished results.