Tetrahedron, 1964, Vol. 20, pp. 2585 to 2592. Pergamon Press Ltd. Printed in Northern Ireland

TERPENOIDS—IV

THE NUCLEAR MAGNETIC RESONANCE STUDY OF METHYL GROUP SIGNALS IN THE CUCURBITANES[1,2]

D. LAVIE, B. S. BENJAMINOV[3] and Y. SHVO
The Daniel Sieff Research Institute
The Weizmann Institute of Science, Rehovoth, Israel

(*Received* 10 *July* 1964)

Abstract—The methyl group region in the NMR spectra of several cucurbitane derivatives have been studied.

IN THE past few years a number of studies have been made in connection with methyl group signals in the NMR spectra of triterpenoid molecules.[4] In a previous paper a relationship was sought between various signals in the NMR spectra and the methyl groups in the euphane and isoeuphane series.[4] In the present paper such a relationship is described for a number of cucurbitane derivatives. The method used in this study has been to arrange selected compounds and their derivatives in a sequence that permitted the least amount of structural and stereochemical variation between consecutive members of that sequence. Cross checking by comparing specific segments of different molecules contributed to increasing the reliability of the study; however, it should be kept in mind that slight changes could still be introduced in the signal allocations.

The NMR data were divided into two major groups. These are presented and discussed separately. For the first of these two groups, we have selected derivatives with shortened side chain thus affording a smaller number of methyl groups, while in the second tabulation compounds with the complete structure are presented.

By first considering compounds 1 and 2 in Table 1 we notice only one structural difference between the two substances, namely the substituents at C-2. Indeed, while there is a good agreement between most of the methyl group signals, there is one, related to the group at C-4 which has now changed from 68 to 56 c/s. A comparable change is apparent for one of the methyl groups at C-4 for the subsequent compounds 2, 3 and 4. In compound 6, however, where ring A is identical to that of 1, the 68 c/s signal reappears, while the second signal changes slightly to 70 c/s. Compounds 2 and 3, however, differ only in the configuration of ring E which in 2 is α-oriented and in 3 β-oriented with respect to ring D. The slight changes in the signals of both 21- and 23-methyl groups are indicative of these changes.

Consideration of compound 4 shows two signals at much lower field (86 and 84 c/s)

---

[1] This investigation was supported by a research grant CA-2810 from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

[2] D. Lavie, E. Glotter and Y. Shvo, *Israel J. Chem.* **1**, 109 (1963).

[3] This author gratefully acknowledges the National Cancer Institute Fellowship (CA-19,319) of the National Institutes of Health, U.S. Public Health Service and the leave of absence from Rose Polytechnic Institute, Terre Haute, Indiana, U.S.A.

[4] D. Lavie, Y. Shvo and E. Glotter, *Tetrahedron* **19**, 2255 (1963) and the references cited therein.

Table 1. Positions of nmr signals of methyl groups (in c/s)

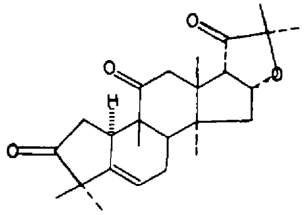
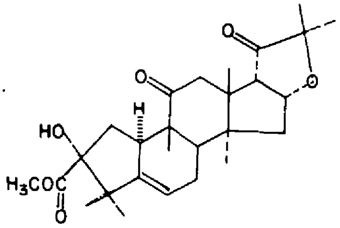
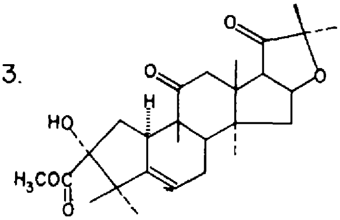
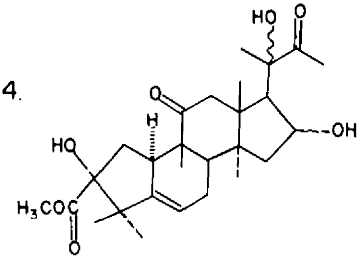
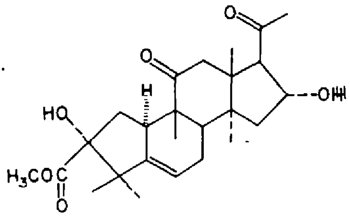
No.	Compound	At 4,4	At 9	At 13	At 14	21	23	$COCH_3$	OCH_3
1.		68, 68	68	53	65	75	81	/	/
2.		56, 68	68	56	63	75	81	/	228
3.		56, 68	68	58	63	73	77	/	227
4.		57, 70	63	60	84	86	/	141	229
5.		57, 70	62	42	84	/	/	130	/

TABLE 1 (*contd.*)

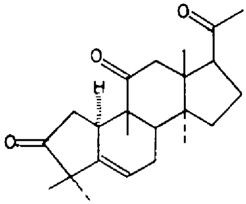
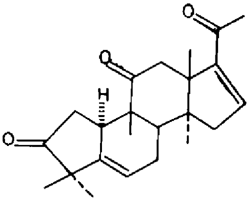
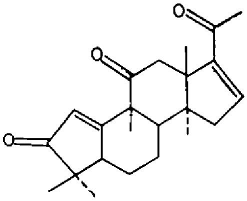
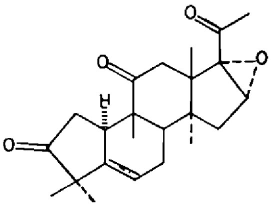
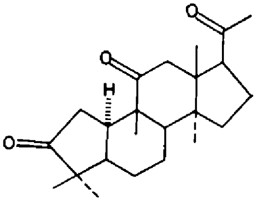
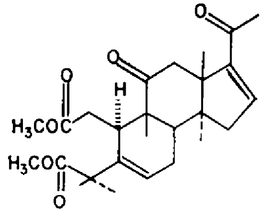
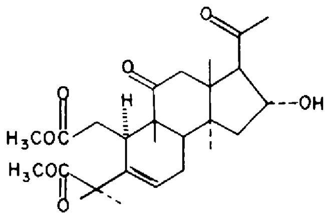
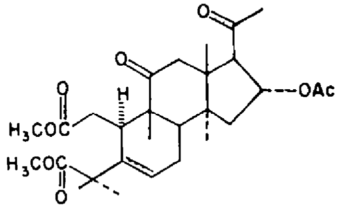
No.	Compound	At 4,4	At 9	At 13	At 14	21	23	$COCH_3$	OCH_3
6:		68, 70	64	43	64	/	/	128	/
7.		68, 72	68	61	64	/	/	139	/
8.		58, 66	92	60	66	/	/	138	/
9.		62, 66	62	56	77	/	/	121	/
10.		67, 70	62	41	64	/	/	126	/

TABLE 1 (*contd.*)

No.	Compound	At 4,4	At 9	At 13	At 14	21	23	COCH$_3$	OCH$_3$
11.		77, 79	70	58	70	/	/	135	217 217
12.		78, 81	66	37	86	/	/	128	216 216
13.		78, 79	66	35	85	/	/	128	218 218

which are assigned, one to the 21-methyl group due to the deshielding influence of the adjacent hydroxyl group, and the other to the C-14 methyl group which is deshielded through a 1,3-interaction between the α-oriented methyl group and the 16, α-hydroxyl group.[5] Comparing this compound (No. 4) with No. 5 reveals that the signal of the methyl group at C-14 remains unaltered, whereas the one at C-13 is greatly affected; it is now at the expected high field location of 42 c/s which is also consistent in compound 6 (43 c/s). The same group in compound 4, however, is found in lower field (60 c/s) due to an interaction with the 20-hydroxyl group.

It is noteworthy that whenever the signal related to the C-13 methyl group could be observed as a separate peak it invariably appeared broad, an average width of 3·5 c/s at half height. This is associated with a four-bond spin interaction between this group and the neighboring C-12 α-proton. A similar broadening was observed for the doublet of the C-12 α-proton which is part of an AB system in compounds 1–3. By having removed the 16-hydroxyl group in compound 6, we have also eliminated its deshielding effect (by the 1,3-interaction) described above, and hence the signal associated with

---

[5] Additional support for the 1,3-diaxial-interaction is found in J. N. Schoolery and M. T. Rogers, *J. Amer. Chem. Soc.* **80**, 5125 (1958); and R. F. Zürcher, *Helv. Chim. Acta* **46**, 2054 (1963).

the methyl group at C-14 resumes a position at 64 cps which is in good agreement with the corresponding signals in compounds 1, 2 and 3.

By introducing a double bond (Δ^{16}) in ring D, as shown in compound 7, the signal of the methyl group at C-13 is found in lower field (61 c/s) by virtue of its proximity to the double bond while some of the remaining signals suffer only slight changes.

A striking change was observed in the case of compound 8 in which the double bond was shifted to ring A thus greatly affecting the signal of the methyl group at C-9. While this signal has maintained a rather constant value in all preceding compounds (62–68 c/s), in compound 8 it is found at 92 c/s, a change of 24 units as compared to that of 7.[6] Indeed, the latter is in excellent agreement with the shift of 18 c/s observed in the signal of the substituent at C-13 when compounds 6 and 7 are compared. Since the two methyl groups at C-4 in compound 8 are now farther away from the double bond, (previously located in ring B) their signals also shifted to higher field by 10 and 6 c/s. In the following compounds 9–13 the signal associated with the C-9 methyl group resumes its normal location.

A deshielding effect through a 1,3-interaction can also be observed in compound 9 in which the α-epoxy group induces a downfield shift (as compared to No. 6) of the methyl group signal at C-14; a similar shift is also recorded for the C-13 methyl signal (cf. Ref. 18). As we proceed to compound 10 the signal for the methyl group at C-14 is observed to return to the 64 c/s position which is indeed the same position as that in No. 6.

In compounds 11, 12 and 13 ring A has been cleaved. While the values for the methyl groups at C-9 and C-14 have remained rather constant, a substantial shift to lower field of the *gem*-dimethyl signals is observed. The signals assigned to the methyl groups at C-13 and C-14 in compounds 12 and 13 assume values comparable to the corresponding groups in compound 5, whereas in 11 the C-13 methyl group is found in lower field due to the vicinal double bond (cf. compounds 7 and 8).

The signals of the protons in the methyl-ketone groupings follow a similar pattern as the other signals listed in the first tabulation. Compounds 7, 8 and 11 which have a similar ring D, display close values for these protons, whereas 5, 6, 12 and 13 display signals in somewhat higher field. The slightly lower field signal of 141 c/s in compound 4 may be explained by the presence of an additional hydroxyl group on the side chain. It is noteworthy that the signals of the methoxy protons are consistent in their positions in the NMR spectra.

Table 2 represents a compilation of methyl group signals associated with elatericin A, B, elaterin, and a number of their derivatives. The first change involves the hydrogenation of elatericin A (compound 14) to the dihydro derivative (compound 15) in which only the double bond on the side chain is reduced. The 26- and 27-methyl group signals are shifted to a higher field by 6 c/s due to the reduction of the double bond which eliminated its deshielding influence on these two groups. A similar shift is observed in the case of the compounds 18 and 19. An examination of compounds 16 and 17 which also contain reduced side chain reveal signals of similar values that

---

[6] W. J. Wechter, *J. Org. Chem.* **29**, 163 (1964), reported for 1α-methylcortisone a signal at 82 c/s for the 19-methyl group which is allylic to a double bond of an α,β-unsaturated ketone. A comparable system is found in ring A of compound 8 for the methyl group at C-9. However, in this case the 11-carbonyl group contributes further to the deshielding of the protons of this methyl group (92 c/s). A similar observation was made by Zürcher, see Ref. 5.

Table 2. Positions of nmr signals of methyl groups (in c/s)

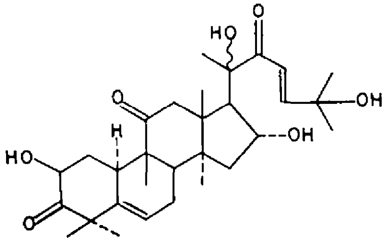
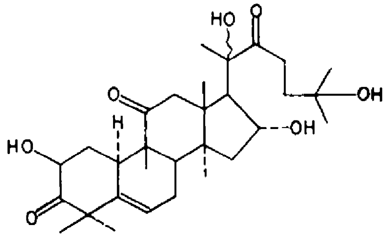
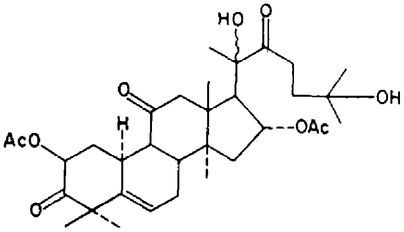
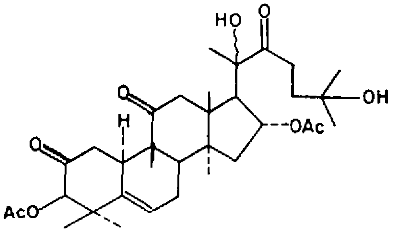
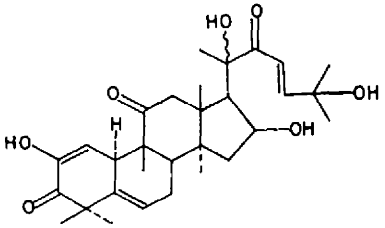
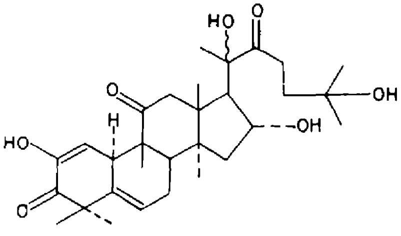
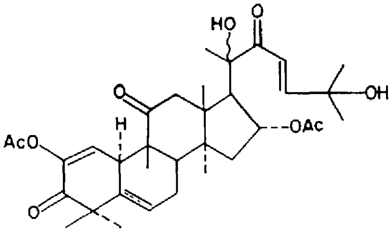
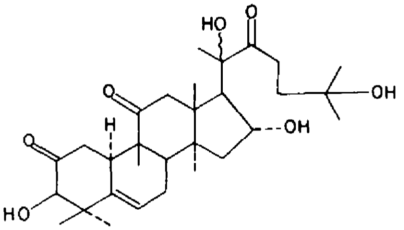
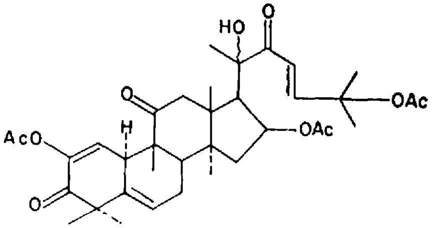
No.	Compound	At 4,4	At 9	At 13	At 14	21	26,27	OAc
14.		78 80	64	58	80	84	80, 80	/
15.		77 81	65	59	81	86	74, 74	/
16.		76 80	67	62	80	88	76, 76	117 129
17.		72 75	61	58	75	87	75, 75	117 132
18.		75 83	62	60	80	84	81, 81	/

TABLE 2 (*contd.*)

No.	Compound	At 4,4	At 9	At 13	At 14	21	26,27	OAc
19.		77 82	64	58	81	85	74, 74	/
20.		77 80	63	63	77	86	84, 84	110 132
21.		74 77	61	50	77	88	80, 83	/
22.		78 78	63	63	78	85	94, 94	112 121 132

could be related to these methyl groups. It should be pointed out that the lower field positions of these methyl groups as compared to other tetracyclic triterpenes[4] is attributable to the 25-hydroxy group present in these compounds. Moreover, in compound 22, in which the 25-hydroxyl group is acetylated, even lower field signals (94 c/s) were assigned.

In Table 1 it was noticed that a low-field signal (86 c/s) was allocated to the 21-methyl group in compound 4 due to the vicinal 20-hydroxyl group, and that all compounds containing a similar group in Table 2 display signals for the 21-methyl groups within the same range (84–88 c/s). In regard to the methyl groups at C-14, it was felt that due to the deshielding effect of the 16-hydroxy group already observed in compounds 4, 5, 12 and 13, low field positions had to be assigned (75–81 c/s).

In both tabulations the highest field signals (lowest c/s values) were assigned to the methyl groups at C-13 which are situated at the junction between a five and a six membered ring. The methyl groups at C-14 are also situated at such a junction but, unlike those at C-13, appear to be enveloped by the molecule due to the *cis*-fusion of rings B and C (Ref. 11 for a view of the model). The methyl group at C-14 is expected therefore, to be deshielded to a larger extent, whereas the one at C-13 which appears to emerge freely from the molecule, is at higher field.

The methyl groups at C-9 in Table 2 show signals that are in good agreement with those included in Table 1. The signals allocated to the *gem*-dimethyl groups at C-4 are not identical in their values due to their different orientation. However, in several cases in which there is a five-membered ring A there exists a certain degree of symmetry resulting in very close or identical signal values.

EXPERIMENTAL

The spectra were recorded on a Varian A-60 spectrometer; they were determined in $CDCl_3$ solutions of about 5–10% concentration and contained tetramethylsilane as the internal standard. Measurements are within ±1 c/s.

The names of the compounds included in the two Tables are listed below according to their corresponding numbers:

1. Methyl A(3)-nor-elaterate[7]
2. Methyl elaterate[7]
3. Methyl isoelaterate[7]
4. Methyl ecballate[8,9]
5. Methyl bisnor-ecballate[10]
6. 16-Desoxy-A(2)-nor-hexanor-elatericin A[8,10]
7. Δ^{16}-Desoxy-A(2)-nor-hexanor-elatericin A[8,11]
8. A(2)-Nor-hexanor-1(10), 16-cucurbitadiene-3,11,20-trione[11]
9. 16,17-Epoxy-A(2)-nor-hexanor-elatericin A.[12] M. p. 193–8°; ν_{max} 1742, 1700 cm^{-1}
10. A(2)-Nor-hexanor-cucurbitan-2,11,20-trione[11]
11. 2,3-Seco-Δ^{16}-hexanor-elatericin-A-2,3-dimethyl carboxylate[13]
12. 2,3-Seco-16-hydroxy-hexanor-elatericin-A-2,3-dimethyl carboxylate[13]
13. 2,3-Seco-16-acetoxy-hexanor-elatericin-A-2,3-dimethyl carboxylate.[13]
14. Elatericin A[14]
15. Dihydroelatericin A[15]
16. Elatericin A diacetate[15]
17. Tetrahydro-*iso*elatericin B diacetate[16]
18. Elatericin B[14]
19. Dihydroelatericin B[14]
20. Elatericin B diacetate[17]
21. Tetrahydro-*iso*elatericin B[16]
22. Elaterin diacetate[9]

[7] D. Lavie, B. S. Benjaminov and Y. Shvo, *J. Chem. Soc.* in press (1964).

[8] D. Lavie, Y. Shvo, O. R. Gottlieb and E. Glotter, *J. Org. Chem.* **27**, 4546 (1962).

[9] D. Lavie and S. Szinai, *J. Amer. Chem. Soc.* **80**, 707 (1958).

[10] D. Lavie and D. Willner, *J. Amer. Chem. Soc.* **82**, 1668 (1960).

[11] D. Lavie and B. S. Benjaminov, *Tetrahedron* **20**, 2665 (1964).

[12] Sample kindly supplied by Mr. E. Glotter from our laboratory.

[13] D. Lavie and B. S. Benjaminov, *J. Org. Chem.* in press.

[14] D. Lavie and D. Willner, *J. Amer. Chem. Soc.* **80**, 710 (1958).

[15] D. Lavie and Y. Shvo, *J. Amer. Chem. Soc.* **81**, 3058 (1959).

[16] D. Lavie and B. S. Benjaminov, *J. Org. Chem.* In press.

[17] D. Lavie and Y. Shvo, *J. Amer. Chem. Soc.* **82**, 966 (1960).

[18] K. Tori, T. Komeno and T. Nakagawa, *J. Org. Chem.* **29**, 1136 (1964); even larger deshielding effects are reported for compounds XV and XVII.