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TERPENOIDS—II

THE NUCLEAR MAGNETIC RESONANCE SPECTRA OF TETRACYCLIC TRITERPENES[1,2]

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Abstract—The methyl region in the NMR spectra of euphane and isoeuphane derivatives have been studied. Several signals were compared with data of other triterpenes of the dammarane and lupane series.

SEVERAL studies of the methyl signals in the NMR spectra of complex molecules of the sterol type have been published,[3] and the chemical shifts of the 18- and 19-methyl groups of numerous derivatives have been determined. The locations of these peaks have been studied in relation to various substituents introduced in the molecule. The side chain of the steroids has been studied separately and the various signals have been assigned, the results being applied for the identification of unknown steroids.[4] In triterpenes the problem is much more complex due to the large number of methyls. In pentacyclic triterpenes a relationship has been sought between certain clusters of peaks and certain compounds.[5] However a more definite relationship between peaks and specific methyl groups in the molecule has been described for the series of the lupane[6] and dammarane.[7]

In our investigations we have used compounds of the euphane[2] and isoeuphane series in order to determine a similar relationship. It is expected that through the collection of such data in several series of compounds it will be possible to reach a more subtle knowledge of the factors governing the specific locations of the resonance peaks of the methyl groups in the triterpenes.

The compounds studied differed by various substituents in ring A of the molecule. Those substituents which had a strong diamagnetic anisotropy were expected to induce, in a selective way, accessory fields of such intensity which should result in changes of the chemical shifts of the various methyl groups in the neighbourhood of ring A. The resonance lines of the methyl groups which were located in the other parts of the molecule were expected to remain in their original positions. Furthermore, the spectra were studied by performing other changes in the molecule, for example, the reduction of the double bond of the side chain. The changes which involved the euphane

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

[2] Part I. D. Lavie, E. Glotter and Y. Shvo, *Tetrahedron* **19**, 1377 (1963).

[3] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.* **80**, 5121 (1958); R. F. Zürcher, *Helv. Chim. Acta* 44, 1380 (1961); Yutaka Kawazoe, Yoshihiro Sato, Mitsutaka Natsume, Hiroko Hasegawa, Toshihiko Okamoto, and Kyosuke Tsuda, *Chem. and Pharm. Bull. Japan* 10, 338 (1962).

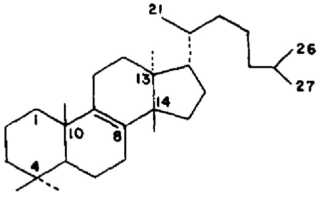
[4] G. Slomp and F. A. MacKellar, *J. Amer. Chem. Soc.* **84**, 204 (1962).

[5] M. Shamma, R. E. Glick and R. O. Mumma, *J. Org. Chem.* **27**, 4512 (1962).

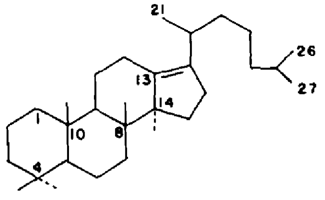
[6] J. M. Lehn and G. Ourisson, *Bull. Soc. Chim., Fr.* 1137 (1962).

[7] J. M. Lehn, *Bull. Soc. Chim., Fr.* 1832 (1962).

to the isoeuphane series (see Formulae) were connected with methyl migrations and a new location of the nuclear double bond, therefore our data of the isoeuphane series could be compared with the data of the dammarane and lupane series which were available in the literature.[6,7]



Euphene



Isoeuphene

The signals of 19 substances in the euphane series are shown in Table 1. The resonance spectra of substances 1, 3 and 6 were compared to the spectra of their respective dihydro-derivatives 2, 4 and 7, in which the side chain double bond is reduced. The peaks at about 98 and 103 c.p.s. of the first group do not occur in the spectra of the second group, while in the latter two new signals appeared at higher field at about 50 and 56 c.p.s. These signals can therefore be related to the 26,27-methyl groups of the isopropylidene and isopropyl derivatives respectively. During the reduction, the positions of the other peaks are virtually unaffected. By this identification it was possible to assign the two peaks of the 26,27-methyl groups in the spectra of all other dihydro-derivatives of this series. A similar observation has been reported by Lehn.[7] The signal of the secondary 21-methyl group, which should not be influenced by changes either in the side chain or in ring A, was expected to display part of an AB_3 system, in this case a peak with a shoulder at higher field of the spectrum.[8] Indeed such a signal was observed at 53·4–56·8 c.p.s. which was present throughout all the 19 substances. In order to assign the positions of the peaks of the methyl groups attached at C_{13} and C_{14}, the spectra of the isoeuphane derivatives presented in Table 2 had to be compared. The methyl group at C_{13} occurs at a junction between five and six membered rings and its signal was expected to be at the highest position of the spectrum as reported for steroids.[3] The peak which occurred therefore, between 44·4 and 48·2 c.p.s. was allocated to this methyl group and was missing in the isoeuphane derivatives. The methyl group attached at C_{14} β-orientation which is allylic to a double bond, was given the peak consistently present between 53·4 and 56·8 c.p.s. in the euphane series; it was also present in the isoeuphane derivatives though slightly shifted downfield. This methyl group now α-oriented was again in an allylic position as in the euphanes; a similar location has been attributed to this methyl group in the dammaranes,[7] in which no skeletal double bonds are present. By elimination, the remaining 3 peaks are related to the methyl groups of ring A.

The data found for the isoeuphane derivatives shown in Table 2, establish that the methyl groups of the side chain, 26,27, have almost the same chemical shifts as in the euphane derivatives, a slight displacement of about 2 c.p.s. to higher field being observed. The 21-methyl group in the iso-series, which is now neighbouring a double bond, is displaced downfield; it is centered between 61·2 and 62·2 c.p.s.,

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[8] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* p. 97. Pergamon Press, London (1959).

TABLE 1. POSITIONS OF NMR SIGNALS OF METHYL GROUPS

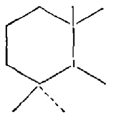
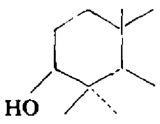
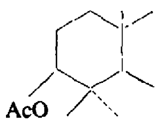
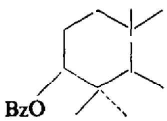
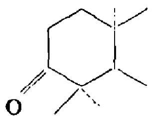
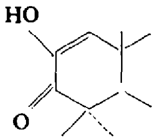
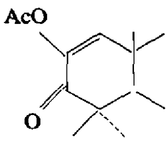
No.	Compound	at 4α, 4β, 10β			at 13α	at 14β	21	26,27	
1	3β-Hydroxy-8,24-euphadiene (Euphol)	61·7	58·8	49·2	46·9	54·2	54·2	102·9	98·5
2	3β-Hydroxy-8-euphene	62·0	59·5	50·0	47·0	54·7	54·7	56·9	50·0
3	3β-Acetoxy-8,24-euphadiene	59·8	53·5	53·5	46·0	53·5	53·5	103·0	98·8
4	3β-Acetoxy-8-euphene	60·2	53·9	53·9	46·4	53·9	53·9	56·3	50·5
5	3β-Benzoyloxy-8-euphene	63·5	63·5	59·2	48·0	56·6	55·3	56·6	50·9
6	8,24-Euphadiene-3-one	66·5	63·7	63·7	46·0	54·8	54·8	101·2	97·7
7	8-Euphene-3-one	68·1	65·6	65·6	47·1	56·8	56·8	56·8	51·1
8	8-Euphene	59·5	56·2	56·2	47·5	56·2	54·5	56·2	51·4
9	3-Hydroxy-euphene-2-one	73·4	55·9	48·4	44·4	55·9	54·1	55·9	50·1
10	3-Acetoxy-euphene-2-one	68·3	58·5	52·5	48·2	55·8	54·5	55·8	50·2
11	2-Hydroxy-1,8,24-euphatriene-3-one	74·3	74·3	68·0	45·6	56·1	56·1	103·6	99·0
12	2-Acetoxy-1,8,24-euphatriene-3-one	76·1	73·0	68·2	45·6	55·9	55·9	102·3	98·0
13	3-Hydroxy-2-oxa-euphadiene	66·9	57·2	53·4	46·4	53·4	53·4	102·5	98·0
14	3-Acetoxy-2-oxa-euphadiene	68·4	51·8	58·0	47·0	53·9	53·9	102·8	97·9
15	1-Hydroxy-2-oxa-euphadiene-3-one	80·5	75·5	67·0	48·0	55·0	55·0	103·0	98·9
16	1-Acetoxy-2-oxa-euphadiene-3-one	80·8	77·3	70·5	43·8	55·0	55·0	103·5	98·5
17	2-Oxa-euphadiene-3-one	80·3	75·8	68·4	47·1	55·9	55·9	104·3	99·3
18	Seco-euphene-2,3-dicarboxylic acid anhydride	84·9	78·8	69·8	49·6	56·0	56·0	56·0	50·3
19	Seco-A-2-nor-1,3-diacetoxy-euphadiene	67·0	67·0	61·1	47·2	55·0	55·0	102·2	97·2

TABLE 2. POSITIONS OF NMR SIGNALS OF METHYL GROUPS IN ISOEUPHANE DERIVATIVES

No.	Compound	at 4α, 4β 10β,			at 8β	at 14α	21 Centre of doublet	26,27	
20	3β-Hydroxy-13(17)-isoeuphene	60·3	51·5	47·3	51·5	51·5	61·6	55·0	49·5
21	3β-Acetoxy-13(17)-isoeuphene	51·3	51·3	51·3	51·3	51·3	61·2	54·1	48·8
22	13(17)-Isoeuphene-3-one	66·4	63·1	56·7	52·8	52·8	62·2	54·7	48·5

with a coupling constant averaging 6·3 c.p.s. The remaining signal which in all three compounds showed a double intensity at about the same position of the spectrum (51·3–52·8 c.p.s.) was assigned to the C_{14} methyl (*vide supra*) and to the C_8 β-oriented methyl group. The remaining three resonance peaks have been allocated to the methyl groups of ring A.

TABLE 3. POSITIONS OF NMR SIGNALS OF METHYL GROUPS IN RING A OF VARIOUS TRITERPENES

Ring A	Series	at 4α, 4β and 10β			
	Euphane	56·2	56·2	59·5	compd. 8
	Lupane	50·5	50·5	48·5	ref. 6 compd. 1
	Dammarane	51·5	51·5	49·5	ref. 7 compd. 2
	Euphane	49·2	58·8	61·7	compd. 1
	Isoeuphane	47·3	60·3	51·5	compd. 20
	Lupane	46–48	59	51·5	ref. 6 compd. 15
	Dammarane	47	58·5	51	ref. 7 compd. 14
	Euphane	53·5	53·5	59·8	compd. 3
	Isoeuphane	51·3	51·3	51·3	compd. 21
	Lupane	50·5–53·5	50·5–53·5	50·5–53·5	ref. 6 compd. 19
	Dammarane	51·5	51·5	51·5	ref. 7 compd. 18
	Euphane	59·2	63·5	63·5	compd. 5
	Lupane	60	56	55	ref. 6 compd. 23
	Dammarane	60·5	55–57·5	55–57·5	ref. 7 compd. 25
	Euphane	63·7	63·7	66·5	compd. 6
	Isoeuphane	63·1	66·4	56·7	compd. 22
	Lupane	62·5	65	56·5–58·5	ref. 6 compd. 5
	Dammarane	63	65·5	57·5	ref. 7 compd. 3
	Euphane	68·0	74·3	74·3	compd. 11
	Lupane	69	72·5	66·5–68	ref. 6 compd. 27
	Euphane	68·2	73·0	76·1	compd. 12
	Dammarane	67·5	72	69	ref. 7 compd. 43

In Table 3 are reported the signals related to the ring A methyl groups in the four series euphane, isoeuphane, dammarane and lupane. There is a general tendency of deshielding in the euphane series as compared to the other series which do not possess the nuclear Δ^8. This effect is weak with two signals while stronger with the third and runs from 7–11 c.p.s. This resonance signal can be tentatively attributed to the C_{10} methyl group which is in close proximity to the double bond. Indeed in the isoeuphane derivatives, in which the nuclear double bond is at $C_{13(17)}$, all ring A signals have practically identical chemical shifts with those found for the dammarane and lupane series. The introduction of a carbonyl group at C_3 results in a general deshielding effect of methyl groups in ring A (substances 5 and 6) while the most outstanding effect is observed with a lactol (15, 16), a lactone (17) and seven membered ring anhydride (18), signals being recorded at about 80 c.p.s.

EXPERIMENTAL

The spectra were recorded on a Varian A-60 spectrometer; they were determined in deuterated chloroform solutions of about 5-10% concentration and containing tetramethylsilane as internal standard. Measurements are within ±1 c.p.s.