Tetrahedron Letters No. 8, pp 699 - 702, 1977. Pergamon Press. Printed in Great Britain.

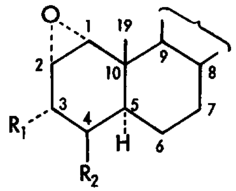
ANOMALOUS α-EFFECTS DUE TO METHYL SUBSTITUTION IN THE HALF-CHAIR CONFORMATION IN CARBON-13 NMR SPECTROSCOPY[1]

Malick Sangaré, Bernard Septe, Guy Bérenger and Gabor Lukacs*
Institut de Chimie des Substances Naturelles du C.N.R.S., 91190-Gif-sur-Yvette, France,
and
Kazuo Tori and Taichiro Komeno
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

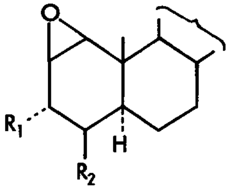
(Received in Japan 10 January 1977; received in UK for publication 26 January 1977)

In previous paper,[2,3] we have reported that ^{13}C NMR spectroscopy can be efficiently applied to the configurational assignment of epoxides and episulfides on six-membered rings. During these investigations,[2] we noticed an anomalous negative α-effect (an upfield shift) upon the 1α-Me substitution of a 5α-androst-2-ene derivative and its corresponding epoxides. This unexpected observation prompted us to examine the size of the α-effect of a Me group in the half-chair conformation, and in this communication we would like to present our results.

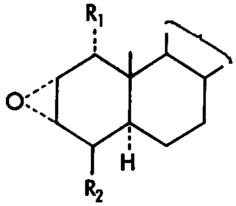
Various Me-substituted 5α-cholestane A-ring epoxides (**1**-**6**) were synthesized by 1,4-addition



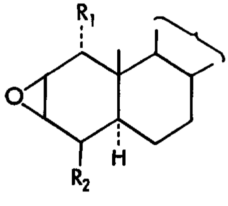
1a: $R_1 = R_2 = H$
1b: $R_1 = Me, R_2 = H$
1c: $R_1 = H, R_2 = Me$



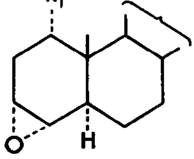
2a: $R_1 = R_2 = H$
2b: $R_1 = Me, R_2 = H$
2c: $R_1 = H, R_2 = Me$



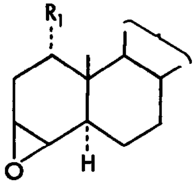
3a: $R_1 = R_2 = H$
3b: $R_1 = Me, R_2 = H$
3c: $R_1 = H, R_2 = Me$



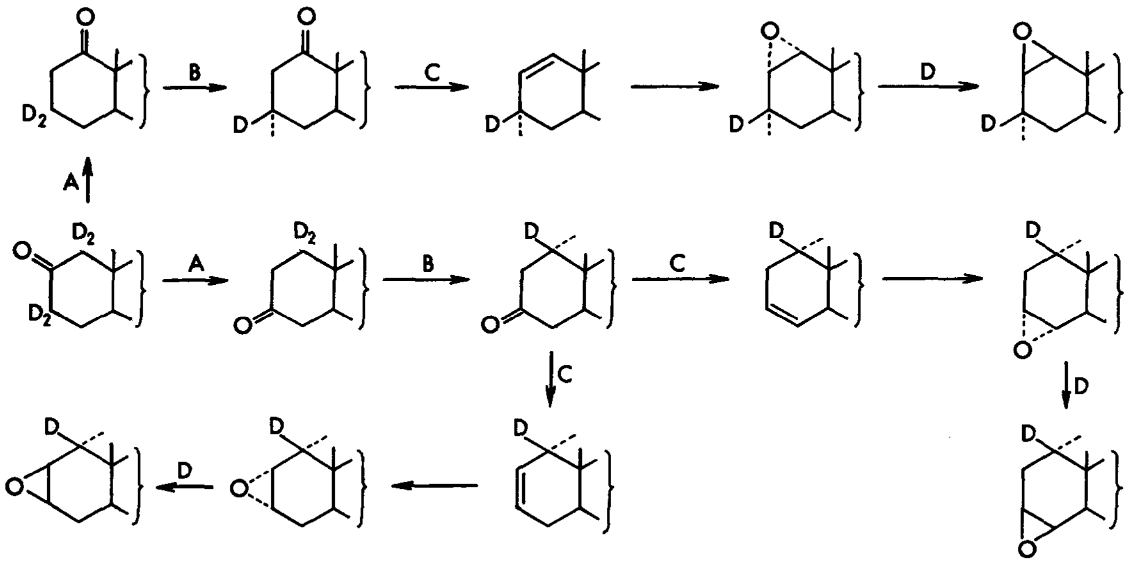
4a: $R_1 = R_2 = H$
4b: $R_1 = Me, R_2 = H$
4c: $R_1 = H, R_2 = Me$



5a: $R_1 = H$
5b: $R_1 = Me$



6a: $R_1 = H$
6b: $R_1 = Me$



Scheme. $\xrightarrow{A}$ Reduction, tosylation, elimination, epoxidation, reduction, oxidation (six steps).
$\xrightarrow{B}$ Bromination, elimination, Grignard reaction[4] (three steps).
$\xrightarrow{C}$ Reduction, tosylation, elimination (three steps).
$\xrightarrow{D}$ Epoxide inversion (three steps).

of MeMgI in the presence of CuCl to α,β-unsaturated ketones followed by the appropriate chemical transformation. The Grignard reactions were totally stereospecific affording the 1α-Me, 3α-Me, and 4β-Me derivatives.[4,5] Epoxidation of the intermediate unsaturated systems yielded the α-epoxides exclusively.[5]

The ^{13}C signals in 1a-6a, 3b, and 4b (see the TABLE) were readily assigned by comparison with reported data.[2,6] The signal assignment of the Me-substitution site was confirmed in six cases by recording the ^{13}C spectra of the following deuterated derivatives: 1b-3β-*d*; 2b-3β-*d*; 3b-1β-*d*; 4b-1β-*d*; 5b-1β-*d*; and 6b-1β-*d*. The deuterium-labeled α- and β-epoxides were prepared, respectively, in thirteen and sixteen steps from the known 2-cholestanone-1,1,3,3-d_4 according to the Scheme,[6] which also shows the procedure leading to all the compounds examined in this paper.

Inspection of the chemical shifts (δ_C) listed in the TABLE indicates that in the systems examined, the size of the α-effect due to Me-substitution is totally different from what would be expected for cyclohexanes assuming the chair conformation.† The steroidal epoxides studied have their A-ring in the half-chair cyclohexane conformation, causing the unexpected δ_C values.

The α-effect of 1α-Me is upfield (-2.7 and -2.4 ppm for 3b and 4b, respectively). When the

---

† Upon introduction of a methyl group into a six-membered ring attached to an epoxide, strong downfield α- and β-effects were found[2] when the Me-substitution site was the oxymethine carbon. The β-effects in the present examples are large positive (downfield) shift values ranging from +4.1 to +9.6 ppm for the hydrogen-bearing sites. Thus they are comparable to expected shift values in chair cyclohexanes.

TABLE. ^{13}C Chemical Shift Data for Steroidal Epoxides Examined, δ_C,[a] and Methyl Substitution Effects in ppm

No.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-19	Me
1a	59.4	52.8	23.5	28.1	37.2	28.1	31.7	35.5	48.9	36.5	21.2	11.4	--
1b	60.0	56.9	25.6	34.3	31.5	28.1	31.8	35.5	49.3	36.3	21.3	11.4	18.2
1c	59.3	52.6	33.1	26.5	43.4	23.2	31.7	34.8	48.9	36.8	21.3	12.1	19.4
2a	59.3	54.3	26.6	22.7	45.6	27.7	32.0	35.7	51.1	35.9	21.6	10.6	--
2b	59.8	58.9	28.4	30.0	39.6	27.7	32.0	35.8	51.2	36.0	21.6	10.8	17.5
2c	59.4	54.1	35.8	24.9	51.2	22.6	32.0	35.8	51.2	36.7	21.8	11.6	19.2
3a	38.2	50.4	51.7	29.0	36.2	28.2	31.1	35.4	53.5	33.6	20.9	12.9	--
3b	35.5	56.0	53.2	30.0	30.8	28.8	31.5	35.4	46.6	35.7	21.3	14.6	10.6
3c	38.2	51.9	57.4	31.8	43.2	24.8	31.8	35.2	53.6	34.5	20.9	13.8	16.2
4a	38.1	52.6	51.5	28.2[b]	41.2	28.4[b]	31.3	34.7	55.3	34.3	20.8	14.0	--
4b	35.7	58.8	50.6	28.7	34.0	28.7	31.5	34.8	49.1	36.1	20.5	15.7	12.1
4c	38.1	53.2	57.7	31.0[b]	48.9	25.7	31.9[b]	34.6	55.6	34.6	20.9	15.2	18.7
5a	30.4	21.3	51.9	55.6	46.7	26.7	31.4	35.3	52.6	34.0	21.3[d]	13.4	--
5b	32.8	28.5	52.5	56.3	38.5	27.0	31.8	35.3	47.9	36.7	20.3	15.5	16.3
6a	33.6	21.2	50.3	57.6	46.2	25.3	31.8	35.4	54.7	35.7	20.7[d]	14.0	--
6b	33.0	29.1	49.7[b]	57.3	38.7	25.0	32.2	35.4	49.3[b]	37.1	19.8	16.8[c]	14.7[c]
	1α-Me Substitution Effect												
3b-**3a**	-2.7	+5.6	+1.5	+1.0	-5.4	+0.6	+0.4	0.0	-6.9	+2.1	+0.4	+1.7	
4b-**4a**	-2.4	+6.2	-0.9	+0.5	-7.2	+0.3	+0.2	+0.1	-6.2	+1.8	-0.3	+1.7	
5b-**5a**	+2.4	+7.2	+0.6	+0.7	-8.2	+0.3	+0.4	0.0	-4.7	+2.7	-1.0	+2.1	
6b-**6a**	-0.6	+7.9	-0.6	-0.3	-7.5	-0.3	+0.4	0.0	-5.4	+1.4	-0.9	+2.7	
	3α-Me Substitution Effect												
1b-**1a**	+0.6	+4.1	+2.1	+6.2	-5.7	0.0	+0.1	0.0	+0.4	-0.2	+0.1	0.0	
2b-**2a**	+0.5	+4.6	+1.8	+7.3	-6.0	0.0	0.0	+0.1	+0.1	+0.1	0.0	+0.2	
	4β-Me Substitution Effect												
1c-**1a**	-0.1	-0.2	+9.6	-1.6	+6.2	-4.9	0.0	-0.7	0.0	+0.3	+0.1	+0.7	
2c-**2a**	+0.1	-0.2	+9.2	+2.2	+5.6	-5.1	0.0	+0.1	+0.1	+0.8	+0.2	+1.0	
3c-**3a**	0.0	+1.5	+5.7	+2.8	+7.0	-3.4	+0.7	-0.2	+0.1	+0.9	0.0	+0.9	
4c-**4a**	0.0	+0.6	+6.2	+2.8	+7.7	-2.7	+0.6	-0.1	+0.3	+0.3	+0.1	+1.2	

---

[a] ^{13}C FT NMR spectra were recorded on a Bruker HX-90E FT NMR spectrometer operating at 22.63 MHz in $CDCl_3$ containing TMS as an internal standard (δ_C 0) at an ambient temperature; accuracies of δ_C are about ±0.1. Chemical shifts for carbons from C-12 to C-18 and from C-20 to C-27 were only slightly affected by the structural changes in the A-ring and agree well with previous results.[6] [b,c] These signal assignments may be reversed within a horizontal line. [d] See ref 3.

1α-Me group is not situated at the carbon adjacent to the epoxide ring as in the cases of 5b and 6b, its α-effect causes a downfield shift for the former (+2.4 ppm, *syn*-relationship between epoxide and Me) and a slight upfield shift for the latter compound (-0.6 ppm, *anti*-relationship). The α-effect of 3α-Me and 4β-Me is downfield in the spectra of 1b, 2b, 3c, and 4c. However, the corresponding shift values of +2.1, +1.8, +2.8, and +2.8 ppm, respectively, are a little larger than the α-effect of an axial methyl group in a cyclohexane (+1.1 ± 0.2 ppm).[7] When the 4β-Me group is not attached to the carbon adjacent to the epoxide (1c and 2c), its α-effect causes an upfield shift for the former (-1.6 ppm, *anti*-relationship) and a downfield shift for the latter compound (+2.2 ppm, *syn*-relationship). The rather larger variation in the α-effects is attributable to the fact that the half-chair conformation of the epoxy cyclohexanes becomes more or less distorted as a result of steric hindrance with the extra methyl group.[‡,§]

The results presented here indicate that much care should be exercised in the structural analysis of natural products having cyclohexane rings in the half-chair conformation if the investigation is based on a ^{13}C NMR spectral study. The α-effect due to a methyl group might be negative in such systems.

REFERENCES

(1) Résonance Magnétique Nucléaire du ^{13}C de produtis Naturels et Apparantés, XXXII. For Part XXXI, see K. Tori, T. T. Thang, M. Sangaré and G. Lukacs, *Tetrahedron Lett.* to be published. This paper also constitutes Part XIX of NMR Studies on Steroids by the Shionogi Group.

(2) K. Tori, T. Komeno, M. Sangaré, B. Septe, B. Delpech, A. Ahond and G. Lukacs, *Ibid.* 1157 (1974).

(3) K. Tori, T. Komeno, J.-M. Takam and G. Lukacs, *Ibid.* 135 (1975).

(4) R. Wiechert, *Z. Naturforsch.* **19b**, 944 (1964); H. Mori, *Chem. Pharm. Bull (Tokyo)* **10**, 386 (1962); *Idem.*, *Ibid.* **12**, 1224 (1964); P. Bertin and J. Perronnet, *Bull. Soc. Chim. France* 2782 (1964); W. J. Wechter, G. Slomp, F. A. MacKellar, R. Wiechert and U. Kerb, *Tetrahedron* **21**, 1625 (1965).

(5) Characterization and structure proof of all the new compounds will be reported in a full paper.

(6) H. Eggert and C. Djerassi, *J. Org. Chem.* **38**, 3788 (1973).

(7) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York (1972).

[‡] The corresponding unsaturated steroids seem to exhibit α-effects due to Me-substitution which are similar to those of the epoxides studied.[2] However, precise spectral analysis of the unsaturated compounds is difficult because the synthetic scheme affords mixtures. The α-epoxides from these mixtures can be easily separated.

[§] It seems worthwhile to describe here the effects of 1α,2α- and 1β,2β-epoxide formations, since they have not been reported. The TABLE shows that the steric γ-effects of the epoxide rings[2] shield C-3, C-5, and C-9 in 1a, and C-4 and C-10 in 2a, and that the steric δ-effect of the β-epoxide ring[2] slightly but appreciably deshields C-11 in 2a.