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CARBON-13 NMR SPECTRA OF STEROIDAL EPOXIDES.
CONFIGURATIONAL ASSIGNMENT OF AN EPOXY GROUP ON SIX-MEMBERED RING BY CARBON-13 NMR SPECTROSCOPY[1]

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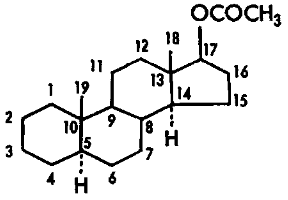
In the structure elucidation of epoxide-containing natural products,[2] we have been confronted with the problem of assignment of configuration of the three-membered ring. Although the relatively high field resonance of epoxide carbons has already been noticed,[3] no systematic study has been made on the influence of an epoxide ring on the chemical shifts of neighbouring carbons. We report here ^{13}C NMR shift correlations of various steroidal A-ring epoxides and demonstrate the utility of this technique for the assignment of configuration of a three-membered ring of this type.†

It is well known that upon introduction of a double bond into a six-membered ring the allylic carbons may be slightly shielded or deshielded, while the homoallylic carbons are either strongly shielded[5] or, in some cases, little affected.[6] In view of this, and also because of the conformational similarities of an unsaturated compound and its related epoxide, spectral comparison of these two sets of compounds has to be made. Thus, the ^{1}H-decoupled natural abundance ^{13}C FT NMR spectra of several unsaturated and epoxy derivatives[7] (1-6) of 17β-acetoxy-5α-androstane (7) have been examined in CDCl$_3$. Application of chemical



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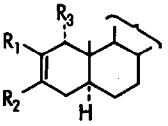
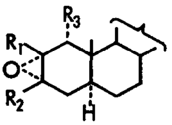
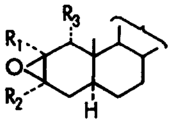
† A comprehensive study of ^{1}H NMR spectra of various steroidal epoxides and episulphides has already been reported.[4]



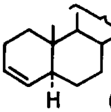
(1a: $R_1 = R_2 = R_3 = H$)
(1b: $R_1 = CH_3$; $R_2 = R_3 = H$)
(1c: $R_1 = R_3 = H$; $R_2 = CH_3$)
(1d: $R_1 = R_2 = H$; $R_3 = CH_3$)



(2a: $R_1 = R_2 = R_3 = H$)
(2b: $R_1 = CH_3$; $R_2 = R_3 = H$)
(2c: $R_1 = R_3 = H$; $R_2 = CH_3$)
(2d: $R_1 = R_2 = H$; $R_3 = CH_3$)



(3a: $R_1 = R_2 = R_3 = H$)
(3b: $R_1 = CH_3$; $R_2 = R_3 = H$)
(3c: $R_1 = R_3 = H$; $R_2 = CH_3$)
(3d: $R_1 = R_2 = H$; $R_3 = CH_3$)



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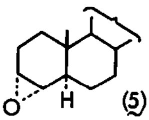

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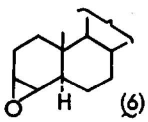

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shift rules,[3] single-frequency off-resonance decoupling (SFORD) experiments,[3] and/or comparison of the spectra of the structurally related compounds led us to the ^{13}C signal assignments shown in the Table, which also lists the differences in chemical shifts between the epimeric pairs of epoxides examined.

Inspection of the Table indicates that upon introduction of an epoxide into a six-membered unsaturated ring the following effects can be observed: the allylic carbon (β from oxygen) is slightly shielded (1-2 ppm), although the C-5 signals in 5 and 6 move slightly downfield with respect to those in 4.

The variation in chemical shift of the homoallylic carbon (γ from oxygen) bearing an axial hydrogen atom is strongly dependent upon the configuration of the epoxide ring. This observation has structurally diagnostic value. If the epoxide oxygen and the axial hydrogen in the γ position are *cis* to one another, the carbon atom bearing the hydrogen is always strongly shielded (3.5-6 ppm). However, in the case of a *trans* relationship, the chemical shift of the γ carbon is only slightly affected. This steric γ effect[3] is reflected in the chemical shift changes of C-5 from 1 to 2 and 3, and in those of C-1 from 4 to 5 and 6. A similar effect was observed for C-6 in 5 and 6, though to a lesser extent. On the contrary, a homoallylic quaternary C-10 seems to be only slightly shielded owing to the lack of hydrogens on it, even though it becomes the γ carbon of an α-epoxide oxygen. Another effect of diagnostic value, although of more limited use in configurational assignments of epoxides, could be the greater shielding of the 1α-methyl carbon of 2d (δ 10.6: 1,2-*cis* interaction) with respect to 3d (δ 12.1: 1,2-*trans* interaction); this is also due to a steric γ effect.[3]

It should be emphasized that two appreciable long-range δ effects[8] were observed for the C-19 and C-9 signals in all epimeric pairs of the epoxides examined (see the Table). The C-19 resonances in the β-epoxides appear at fields lower by about 1 ppm than those for the corresponding α-epoxides (*syn-axial* interaction);[8] the

TABLE

^{13}C Chemical Shift Data on the Steroids Examined (δ_C)[a] and Differences in Chemical Shifts between Epimeric Pairs of the Epoxides (in ppm)[b] in $CDCl_3$

Compounds	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-19	CH_3
1a	39.9	125.6	125.6	30.3	41.5	28.7	31.3	35.4	54.0	34.6	12.0	-
2a	38.2	50.4[d]	51.7[d]	29.0	36.2	28.2	31.1	35.4	53.5	33.6	12.9	-
3a	38.1	52.6[d]	51.5[d]	28.4[e]	41.2	28.2[e]	31.3	34.7	55.3	34.3	14.0	-
(3a)-(2a)	-0.1	+2.4	-0.2	-0.6	+5.0	0.0	+0.2	-0.7	+1.8	+0.7	+1.1	-
1b	45.0	132.4	119.6	30.5	41.4	28.5	31.5	35.5	54.2	35.0	11.8	24.1
2b	43.7	56.4	59.4	29.7	35.9[e]	28.1	31.2	35.5[e]	53.6	34.1	12.6	25.7
3b	43.4	57.7	58.9	29.3	41.6	28.1	31.4	34.8	55.6	34.8	13.4	24.2
(3b)-(2b)	-0.3	+1.3	-0.5	-0.4	+5.7	0.0	+0.2	-0.7	+2.0	+0.7	+0.8	-1.5
1c	40.1	119.7	132.3	35.2	41.9	28.5	31.3	35.4	54.0	34.4	12.0	23.0
2c[c]	39.1	58.3	57.2	34.2	37.3	28.2	31.1	35.4	53.5	33.9	13.0	23.0
3c[c]	38.8	60.1	57.2	33.7	41.7	28.2	31.3	34.8	55.3	33.7	13.8	24.6
(3c)-(2c)	-0.3	+1.8	0.0	-0.5	+4.4	0.0	+0.2	-0.6	+1.8	-0.2	+0.8	+1.6
1d	38.6	132.8	123.8	31.1	34.6	28.8	31.1	35.5	47.9	36.9	13.8	15.7
2d	35.4	55.9	53.1	29.9	30.8	28.5	30.8	35.4	46.5	36.1	14.5	10.6
3d[c]	34.0[e]	58.6	50.4	28.7	35.6[e]	28.4	31.0	34.6	49.1	36.1	15.7	12.1
(3d)-(2d)	-1.4	+2.7	-2.7	-1.2	+4.8	-0.1	+0.2	-0.8	+2.6	0.0	+1.2	+1.5
4	34.2	23.5	124.9	130.9	45.9	27.5	32.2	35.6	53.9	35.0	11.8	-
5	30.4	21.3	51.9	55.6	46.7	26.7	31.4	35.3	52.6	34.0	13.4	-
6	33.6	21.2	50.3	57.6	46.2	25.3	31.8	35.4	54.7	35.7	14.0	-
	+3.2	-0.1	-1.6	+2.0	-0.5	-1.4	+0.4	+0.1	+2.1	+1.7	+0.6	-
7	38.8	22.3	26.9	28.4	47.2	28.4	31.8	35.5	54.8	36.5	12.2	-

[a] ^{13}C NMR spectra were recorded on a Bruker HX-90E FT NMR (at 22.63 MHz) and/or a Varian NV-14 FT NMR spectrometer (at 15.09 MHz). Samples were dissolved in $CDCl_3$ containing TMS as an internal standard (δ_C 0); concentrations were about 1 mole/l for SFORD experiments, otherwise they were very low. Chemical shifts (accuracy, about ±0.1 ppm) of the following carbons were only slightly affected by the structural changes in the A-ring:[9] C-11 (δ 20.5±0.3); C-12 (36.9±0.2); C-13 (42.5±0.1); C-14 (50.8±0.3); C-15 (23.5±0.1); C-16 (27.6±0.1); C-17 (82.7±0.2); C-18 (12.0±0.2); $\underline{C}OCH_3$ (170.6±0.5); $CO\underline{C}H_3$ (21.0±0.2). [b] Plus sign denotes a downfield shift. [c] The spectra of these compounds were not examined by SFORD experiments owing to lack of sufficient materials. [d] These assignments have been confirmed by taking the spectra of the 3-deuterio derivatives (unpublished results). [e] These assignments may be reversed although those given here are preferred.

C-9 signals of the α-epoxides resonate at fields higher by about 2 ppm than those of their β counterparts.

Comparison of the various spectra indicates some further effects which will be helpful in assignment problems concerning epoxide-containing compounds. Upon introduction of a methyl group into a six-membered ring attached to an epoxide (from 2a to 2b and 2c, and from 3a to 3b and 3c), the carbons α, β, and γ from the methyl are characteristically deshielded by about +5∼+6, +5.3 (+7.5, oxymethine carbon), and +0.5∼1 ppm, respectively, if the substitution site is at the oxymethine carbon. A remarkable difference between the methyl effects upon the unsaturated steroids and their epoxides is seen in the shift values for the β carbons; the unsaturated β carbon in the former is shielded by about -6 ppm whereas the oxymethine β carbon in the latter is deshielded as described above. Comparison of the spectra of 2d and 3d with those of 2a and 3a, respectively, shows that both C-5 and C-9 are strongly shielded by a full 1,3-diaxial interaction (steric γ-effect).[3] On the other hand, due to the half-chair conformation, C-3 (γ carbon) is only slightly shielded in 3d, while in 2d this carbon is deshielded.

The present preliminary study should be extended to other types of epoxide-containing molecules before all the above stated observations can be accepted as rules; further investigations are now in progress in these laboratories.

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