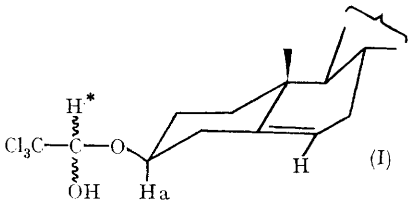
The Nuclear Magnetic Resonance Structure Determination of Sterols by using their Chloral Alcoholates

By I. McCLENAGHAN and P. J. SYKES*
(*Department of Chemistry, West Mains Road, Edinburgh* 9)

THE change in the chemical shift of characteristic peaks in the n.m.r. spectra of steroids on formation of derivatives often has valuable implications in their structure elucidation.[1,2] When, however, the n.m.r. spectrum of a compound can be determined and then a derivative rapidly prepared *in situ* followed by an immediate re-run of the spectrum, the time saved in structure determination may be considerable. We find that chloral, trichloroacetaldehyde, reacts extremely rapidly at room temperature with certain hydroxy-steroids to give products which display characteristic changes in chemical shifts. The asymmetry of the chloralate (I) formed leads to two products, presumably the *R* and *S* configurations in varying ratios, each with a sharp singlet at between τ 4·70 and 5·20, due to the tertiary proton (H*) in the chloralate. The separation (Δ) and τ values of this singlet pair are found to be fairly constant for a number of different sterols hydroxylated in the same position.

Chemical shifts (p.p.m.)

Steroid	H*	ΔH*	Vinylic H	C-19	C-18
3β-Hydroxycholest-5-ene (I)	—	—	4·63	9·00	9·33
(I) + chloral	4·74, 5·05	0·31	4·63	8·98	9·31
3β-Hydroxycholest-4-ene (II)	—	—	4·73	8·95	9·31
(II) + chloral	4·74, 5·02	0·28	4·63	8·93	9·30
3β-Hydroxyandrost-5-en-17-one (III) ..	—	—	4·60	8·96	9·11
(III) + chloral	4·74, 5·02	0·28	4·59	8·96	9·12
3β,17β-Dihydroxyandrost-5-ene (IV) ..	—	—	4·61	8·97	9·23
(IV) + chloral	4·72, 5·03 (C-3)	0·31	4·61	8·96	
	5·09, 5·15 (C-17)	0·06			9·16, 9·19
3β,17β-Dihydroxyandrost-4-ene (V) ..	—	—	4·70	8·95	9·25
(V) + chloral	4·72, 5·01 (C-3)	0·29	4·60	8·93	
	5·11, 5·17 (C-17)	0·06			9·16, 9·19



(I)

Thus for the five 3β-hydroxy-steroids listed in the Table, the addition of an excess of freshly distilled chloral gave rise to two singlets at approximately τ 4·74 and 5·05 with a separation of about 0·3 p.p.m. Two 3β,17β-dihydroxy-steroids also showed these signals but in addition showed a pair of singlets at approximately τ 5·10 and 5·16 with a separation of 0·06 p.p.m. due to the 17β-alcoholate. Thus, 3β-hydroxylation (Δ 0·3 p.p.m.) and 17β-hydroxylation (Δ 0·06 p.p.m.) may readily be distinguished by this method.

For the two 3β-hydroxy-Δ^5-steroids described, there is a negligible shift in the signals due to the C-19 methyl and the C-6 vinylic protons on the addition of chloral. However, in the case of the two 3β-hydroxy-Δ^4-steroids mentioned the C-4 vinylic proton signal is observed to shift downfield by 0·10 p.p.m. This therefore enables the allylic and homoallylic alcohols which are frequently obtained during the transformation of 3-keto-Δ^4-steroids to their 3β-hydroxy-Δ^5-counterparts,[3] to be readily distinguished.

In the case of the two 17β-hydroxy-steroids which are described, there is again a negligible shift in the signal from the C-19 methyl protons but the signal from the C-18 methyl group appears as two peaks with a separation of 0·03 p.p.m. upon the addition of chloral. These two peaks are in addition shifted downfield by an average of 0·05 to 0·08 p.p.m. The two C-18 methyl signals, which result upon the addition of chloral, are again presumably due to the chloralate group at C-17 having *R* and *S* configurations.

At present, this investigation is being extended to the n.m.r. spectra of chloral alcoholates of a range of steroid alcohols. The combination of the changes observed in the chemical shift of the tertiary alcoholate proton (H*), the tertiary alcohol proton (H_a) and the angular methyl groups when taken together with the concomitant changes in the form of the signals from the angular methyl groups has been found to be characteristic for many steroid alcohols. These results will be reported shortly.

We thank the Medical Research Council for financial support (I.M.).

(*Received, May* 13*th*, **1968**; *Com.* 599.)

---

[1] N. S. Bhacca and D. H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry", Holden Day, San Francisco, **1964**, p. 77.

[2] I. R. Trehan and C. Monder and A. K. Bose, *Tetrahedron Letters*, 1968, **67**.

[3] R. W. Kelly, I. McClenaghan and P. J. Sykes, *J. Chem. Soc.* (*C*), 1967, **2375**.