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AN N. M. R. STUDY OF 4-ETHYLTHIO-4-EN-3-OXO STEROIDS: THE UNIQUE DESHIELDING EFFECT OF A THIO-FUNCTION*

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Much attention has recently been focused on the magnetic anisotropy effect of hetero atoms such as tertiary nitrogen (1), halogen and oxygen (2-7), regarding the analytical application of proton magnetic resonance spectroscopy to the structure and stereochemistry of complex molecules. In the present communication we wish to report an unusually large long-range deshielding effect of a polar thio-function observed in 4-thio-4-en-3-oxo steroids.

Three of us (M. T., M. I. and T. F.) and their colleagues have succeeded in a convenient synthesis of 4-ethylthio-4-en-3-oxo steroids, i. e. 4-ethylthiocholest-4-en-3-one (I), 17β-acetoxy-4-ethylthioandrost-4-en-3-one (II) and 16α, 17-epoxy-4-ethylthiopregn-4-ene-3, 20-dione (III)**, by the polyphosphoric acid-catalyzed ring opening of their corresponding

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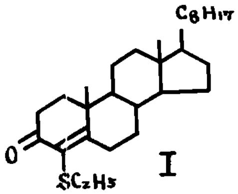
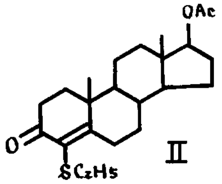
** These new thiosteroids gave correct analyses and showed the expected spectral characteristics. The structures of the compounds were further confirmed by chemical evidences. They will be published elsewhere. All other known compounds used for the present n. m. r. study were obtained according to the literature with which their physical properties were consistent.



I



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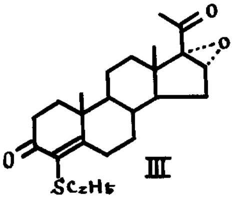

III

4, 5-epoxy-3-oxo derivatives with ethylmercaptan.

In the n. m. r. spectra (Fig. 1) of these thiosteroids taken at 60 MC on a Varian A-60 N. M. R. spectrometer, a doublet with J=14.5 c. p. s., centered at τ6.22*, was observed. We eventually assigned the signal to the allylic C_6-hydrogen of α- or equatorial configuration under the deshielding effect of a polar sulfur function at C-4. We reason for the assignment as follows.

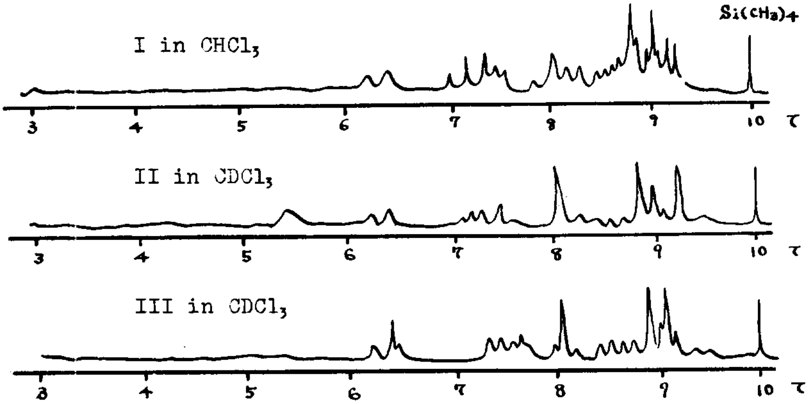

Fig. 1

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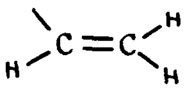
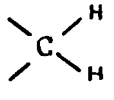
* We have taken the center of the doublets as the position of the signal. If the doublets being, as we conclude, the A part of AB-type spectra, the exact position of the signal should be shifted upfield from the center. However, the correction for it was calculated and found to be smaller than 0.02 p. p. m.

1)That the splitting of the signals is due to spin-spin coupling and not to chemical shift was proved by the intensity of the signals being exactly proportional to one proton, and that in the spectrum of II (Fig. 2) taken at 40 MC on a Japan Electronic Optics Laboratory J. N. M. 3 high resolution spectrometer, the signal in question also appeared as a doublet with J=14.4 c. p. s.

Fig. 2

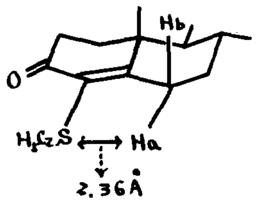


IV



V

2)The information that such a large magnitude of spin-spin coupling constant as 14.5 c. p. s. is characteristic to the structural types of either IV or V (8), coupled with the fact that the magnetic anisotropy effect of neighboring functional groups can cause a downfield shift to the hydrogen resonance, suggested that the signals could be assigned to a hydrogen of cyclic methylenes* under a spatial interaction with such neighboring groups in the compounds.



3)A Dreiding stereomodel (VI) exhibiting the stereochemistry around the ring-A and B in I, II or III being constructed, the distance between the nonbonded sulfur and allylic hydrogen (Ha, α- or equatorial configuration) atoms was calculated to be 2.36 Å which is even 0.15 Å shorter than that between 1, 3-diaxial hydrogens in a cyclohexane ring (10), suggesting a possible spatial interaction between these atoms**.

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* The hydrogens of this type usually give rise to signals higher than τ 8.0 (9).

** The calculated distance between the sulfur and Hb (β- or axial configuration) atoms was found to be 3.36 Å.

4)The signal of the $C_6\alpha$-H should appear as a doublet of AB-type (Fig. 3) due to the spin-spin coupling with the $C_6\beta$-H with a J of such a large magnitude as 14.5 c. p. s. and furthermore each peak of the doublet should be expected to appear as a triplet with a J of ca. 2-3 c. p. s. due to the spin-spin coupling with the $C_7\alpha$- and $C_7\beta$-hydrogens. This was proved to be the case as follows: the doublet of II (Fig. 4), for instance, does not show a hyperfine structure, however, a)the peaks are broad, b)the observed half width in average of the peaks at lower and higher fields of the doublets of I and II[*] are 7.0 and 6.0 c. p. s. respectively[**], and c)the relative intensity of these peaks of I and II are 1:1.8 and 1:1.4 respectively.

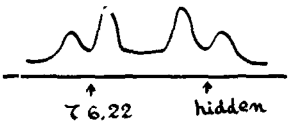

Fig. 3

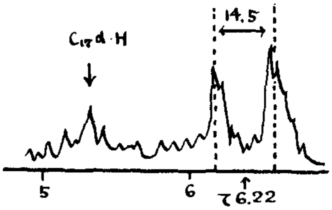

Fig. 4

All these data led us to conclude that the signals in question come from the quartet of AB-type due to the C_6-methylene group, and that the other doublet of the quartet appearing at higher field could not be detected as a hidden signal being buried in the back ground due to cyclic methylenes in the compounds.

In order that the assumed spatial interaction between the C_4-sulfur function and $C_6\alpha$-hydrogen in the 4-en-3-oxo system

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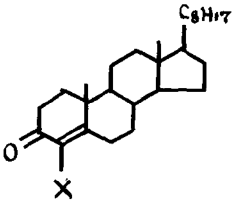
[*] III Was omitted for the present calculation as the doublet of III is overlapped with the signal, singlet, of $C_{18}\beta$-H and the calculation would then be erroneous.

[**] The observed value of less than 7 c. p. s. could prove the equatorial character of the hydrogen responsible for the doublets; if the hydrogen be of axial character, the half width would be, in rough calculation, larger than 10 c. p. s. (11).

might further be confirmed, we examined the n. m. r. spectra of cholest-4-en-3-one (VII) (12), the reference compound, and its 4-substituted analogs, 4-methyl- (VIII) (13), 4-hydroxy- (IX) (14), 4-methoxy- (X) (15), 4-acetoxy- (XI) (16), 4-chloro- (XII) (17), 4-bromo- (XIII) (18), 4-mercapto- (XIV)[*], and 4-acetylthio- (XV)[*] -cholest-4-en-3-ones, and bis-{cholest-4-en-3-on-4-yl}-disulfide (XVI)[*] and -sulfide (XVII)[*], taken at 60 Mc on the Varian spectrometer. As is shown in Table 1, the similar signals under varying deshielding effects were found in the spectra of IX, X, XII, XIII, XV, XVI and XVII; the intensities of these signals, doublet with J=14.5 c. p. s., were proved to be proportional to one proton. The fine structure of the signals of, for instance, IX, XII and XV are shown in Fig. 5.

Table 1

In $CDCl_3$



C_4-Substituents (X)	C_6 α-H (τ)
H (VII)	> 7.58
CH_3 (VIII)[**]	7.21 ?
OH (IX)	6.96
OCH_3 (X)	6.93
$OCOCH_3$ (XI)[**]	7.28 ?
Cl (XII)	6.74
Br (XIII)	6.72
SH (XIV)[**]	7.22 ?
$SCOCH_3$ (XV)	6.86
S-S-$C_{27}H_{43}O$ (XVI)	6.43
S-$C_{27}H_{43}O$ (XVII)	6.42

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[*] Prepared according to the procedure of J. M. Krämer, K. Brüchner, K. Irmscher and Karl-Heinz Bork, *Ber.*, **96**, 2803 (1963). They will be published elsewhere.

[**] We could not be certain about the exact positions of these signals appearing at higher field than τ 7; the signals were obscure being almost buried in the back ground.

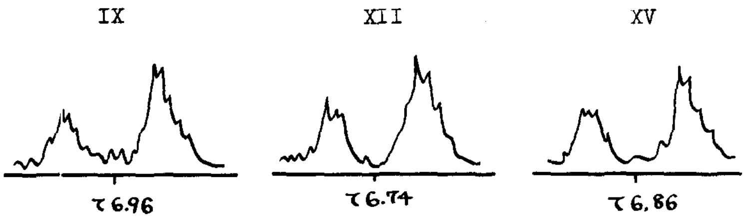

Fig. 5

Meanwhile Collins, Hobbs and Sternhell (19) and Wittstruck, Malhotra and Ringold (20) have reported a series of n. m. r. data on the allylic spin-spin coupling in 6-substituted-4-en-3-oxo steroids, from which we abstract the following valuable data (Table 2) suggesting the presence of a spatial interaction between the olefinic C_4-H and C_6 α-substituents in the 4-en-3-oxo system. These data coupled with a proof for the

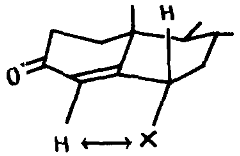

Table 2

In CCl_4

C_6 α-Substituents (X)	C_4-H (τ)
H	4.45
CH_3	4.35 (4.36)*
OH	3.81 (4.38)*
$OCOCH_3$	4.29 (4.19)*
F	3.95
Br	3.78 (4.25)*

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* The data in parentheses are those of the corresponding C_6 β-substituted derivatives.

presence of such an interaction between the C_4-H and C_6 α-substituents in 4, 5-epoxy-3-oxo steroids established by Collins, Hobbs and Sternhell (21) would be a further support for our argument.

On the basis of the evidence we have obtained coupled with those reported in the literatures cited above, we can finally deduce that the order of the long-range deshielding effects of polar functions is the following and that the

$$H < CH_3,(SH) < OCOCH_3 < F < OH.OR < SCOCH_3 < Cl \approx Br < SR$$

effect of the alkylthio function is the largest among all in inducing the downfield shift of more than 1 p. p. m.

We are not certain yet about the nature of the large deshielding effects by the alkylthio group and other polar functions to proton magnetic resonance. We might suggest, however, that as the order of the effects is almost parallel to that of the atomic polarizability of hetero atoms reported by Ingold (22), i. e. $F < O < (C) < Cl < Br < S$, the ease of distortion of the electron clouds of such hetero atoms could cause a paramagnetic anisotropy effect to the hydrogen in their vicinity.

We are also not certain why the SH group does not give such effect nearly at all. However, it is an interesting fact that acetylation of the mercapto group (XIV → XV) did regenerate the effect, which is that the acetylation effect* worked in this case in the reverse or downward direction. The usual acetylation (upfield) shift has also been observed in the conversion of the diosphenol (IX) to the acetate (XI).

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* The acetylation effect found by Kawazoe et al. (4) was to reduce the long-range deshielding effect of hydroxyl group in proton magnetic resonance.

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