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THE REACTION OF STEROLS WITH DIMETHYLSULPHOXIDE AND ACETIC ANHYDRIDE

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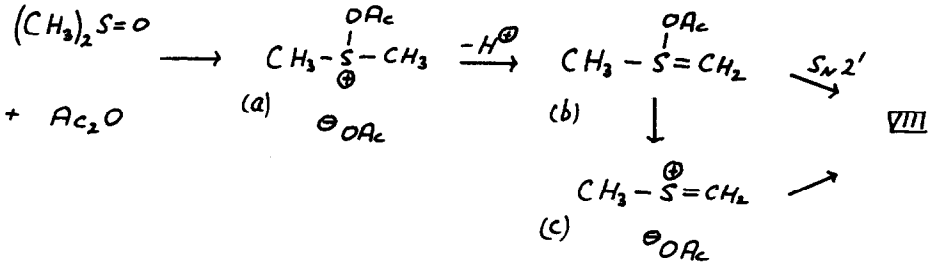
Dimethylsulphoxide - acetic anhydride mixtures (DMSO-Ac_2O) have been used to oxidise alcohols to ketones at room temperature[1] and methylthiomethyl ethers have been obtained as minor reaction products. Alkoxy dimethylsulphonium salts were suggested as intermediates in the oxidation. The oxidation of alcohols with dimethylsulphoxide-dicyclohexylcarbodiimide-acid mixtures (DMSO-DCC-$H^{\oplus}$) has also afforded methylthiomethyl ethers in low yield[2,3]. Jones and Wigfield[3] have suggested that in the formation of the methylthiomethyl ether (IVa) from 3β-hydroxyandrost-5-en-17-one (Ia), carbonium ion (IIIa) may be an intermediate, which reacts with DMSO to give the alkoxysulphonium ion (IIa). Torssell[4] has shown that salts $RCH_2O\overset{\oplus}{S}(CH_3)_2$ $BPh_4^{\ominus}$ will decompose in DMSO solution at 100° to give aldehydes, and that the reaction is speeded up by the addition of triethylamine, while the same salts are stable in DMSO - Ac_2O at room temperature. We report results that are pertinent to these discussions.

When cholesterol (Ib) is heated at 100° in DMSO - Ac_2O, the major steroidal product is the methylthiomethyl ether (IVb) formed in about 70% yield. The spectroscopic properties are analogous to those reported for compound (IVa)[3]. The other product identified was the acetoxymethyl ether (VII), obtained in about 5% yield. This structure follows from the infrared ($\nu_{max.}$ 1745, 1260, 1100 and 1020 $cm.^{-1}$ in CCl_4), the n.m.r. (τ 9.32 C_{18} - H_3; 9.19 and 9.09 $C_{21,26,27}$ - H_3; 8.99 C_{19} - H_3; 7.93 $COCH_3$; 6.53 3α-H; 4.67 O-CH_2-O; and 4.63 p.p.m. C_5-H in $CDCl_3$) and mass spectra (typical of cholest-5-ene with 3β-OCH_2X group), and from the hydrolysis to cholesterol. Two additional, but as yet unidentified, products were evident by thin layer chromatography. No evidence was obtained to suggest that cholest-4-en-3-one or cholest-5-en-3-one was formed. When 3β-hydroxy-5α-cholestane was treated under the same conditions, the only steroidal product found was the corresponding acetate (cf. ref. 4). Cholesterol acetate was unaffected by the reaction conditions. To test the possible participation of the 5,6-double bond in this reaction, i-cholesterol (Vb) was similarly treated,

when the same products, in the same yields, as those obtained from cholesterol were identified, and thin layer chromatography showed the same two unidentified minor products to be present. α-Acetoxymethyl methylsulphide (VIII) was also identified in all these reactions.

DMSO and Ac_2O probably form the sulphide (VIII) by one of the schemes below[5,6], so

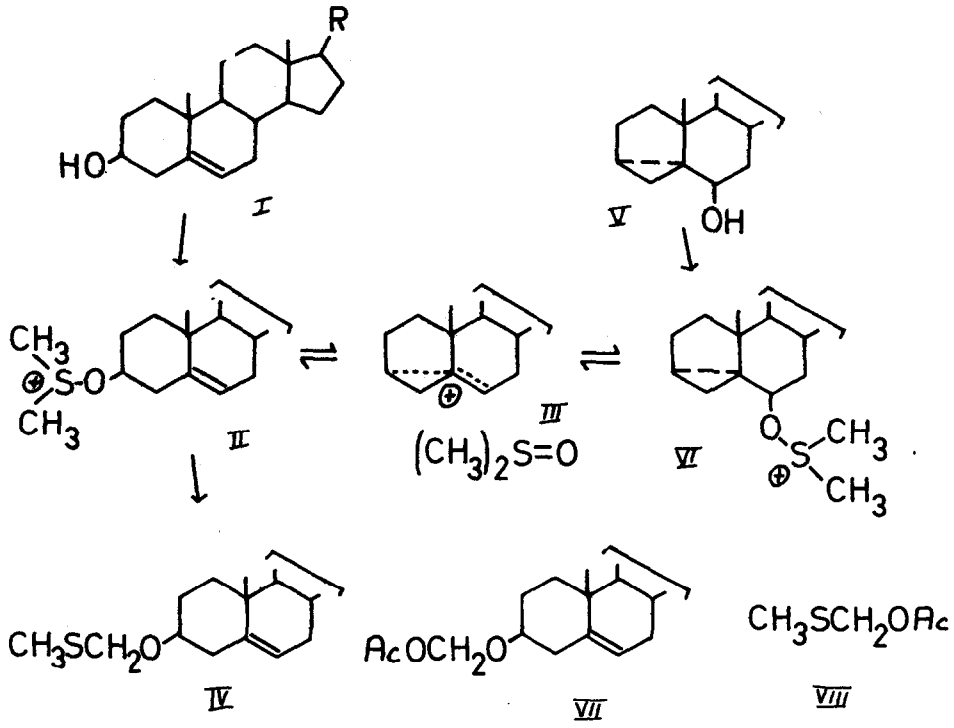


that (a), (b) and (c) are possible candidates for reaction with the sterol. The sterols are unchanged on being heated with the sulphide (VIII) in DMSO. Nucleophilic attack by oxygen on carbon of (b) or (c) would give a methylthiomethyl ether directly (implied in ref. 1), but this may be excluded in these cases since cholesterol and i-cholesterol would give different products. Attack by oxygen on sulphur of (a), (b) or (c) would give (after proton transfer) an alkoxydimethylsulphonium ion $ROS(CH_3)_2^{\oplus}$, which is thus the likely intermediate in the formation of these ethers. We then suggest that with the saturated alcohol, sulphonium ion formation is slower than acetylation, whereas the equilibrium involving the cholesteryl cation (IIIb) results in reaction of the sterols (Ib) and (Vb) with (a), (b) or (c) being faster than acetylation.

The formation of methylthiomethyl ether probably follows the mechanism suggested by Jones and Wigfield[3] and competition between formation of ether and ketone is presumably affected by the acidity of the α-proton that must be lost on oxidation[4] and on the steric environment of this centre. Some evidence on this point may be provided by current studies on 4,4-dimethyl steroids where formation of both ketone and methylthiomethyl ether has been observed.

It is to be noted that both cholesterol and 3β-hydroxy-5α-cholestane are both oxidised to ketones using DMSO-DCC-$H^{\oplus}$ conditions[2,7] and this supports the view of Torssell[4]

that free alkoxydimethylsulphonium ion is not an intermediate in these oxidations.



a, R= =O ; b, R = C_8H_{17}

Acknowledgement

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