Stereospecific and Regiospecific Addition to an Isolated, Acyclic (Steroidal) Olefinic Bond

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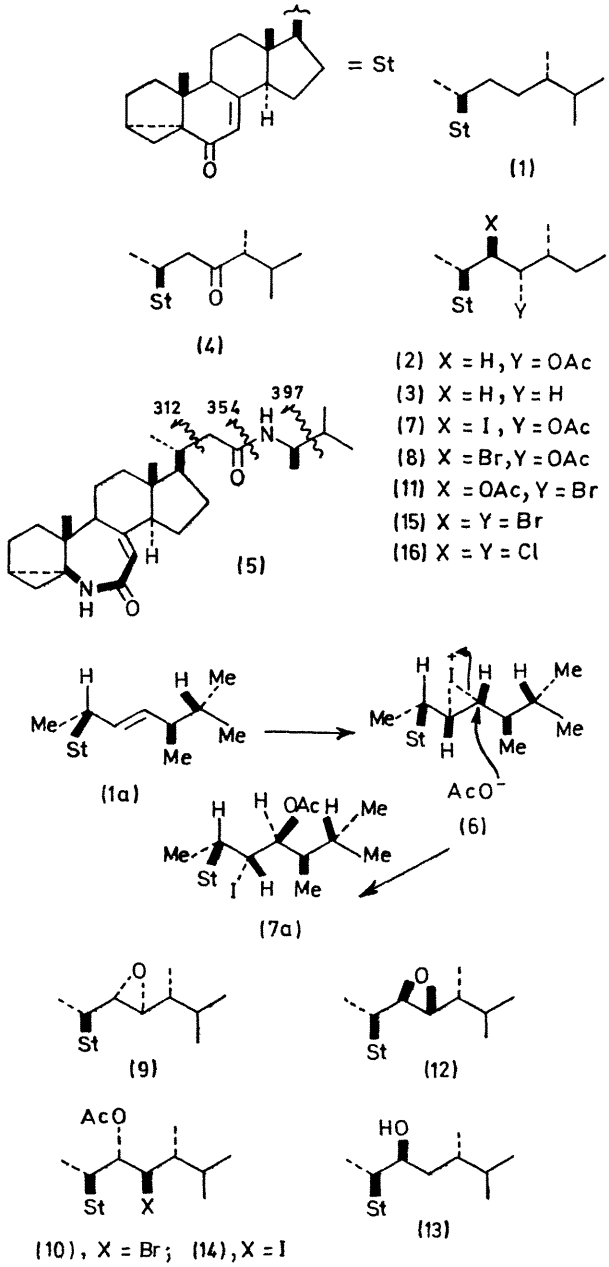
Summary The preferred stereospecific and regiospecific path for the addition of typical electrophilic reagents to the 22(23)-ethylenic linkage of the ergosterol side-chain has been established.

DURING an approach towards the synthesis of the insect moulting hormone ecdysone[1] it was noted that the side-chain olefinic bond of 3α,5α-cycloergosta-7,22-dien-6-one (**1**) yielded only one iodoacetate, m.p. 157—159·5°, $[\alpha]_D^{28}$ +53° (*c* 0·5, $CHCl_3$),† upon reaction with iodine and silver acetate in moist acetic acid.[2] No evidence could be found for the significant‡ co-formation of alternative isomers in the crude reaction mixture. This result represents an extremely selective mode of addition to an isolated, acyclic double bond flanked only by simple chiral centres and in the absence of directing functions, such as alcohol groups.[3]

The product was relatively stable and only underwent further solvolysis, to a mixture of hydroxy-acetates, after a period of several days. Optimum yields of the iodo-acetate (53%) were obtained under anhydrous conditions. Reduction of the iodo-acetate, with freshly distilled tributyltin hydride in tetrahydrofuran afforded an acetate (**2**), m.p. 147—150°, $[\alpha]_D^{25}$ +66° (*c* 0·5, $CHCl_3$), which was converted into the corresponding alcohol (**3**), m.p. 188—192°, $[\alpha]_D^{20}$ +54° (*c* 0·3, $CHCl_3$), by lithium aluminium hydride reduction followed by re-oxidation to the 6-ketone with manganese dioxide. Oxidation of the latter alcohol, with Jones' reagent, afforded the 23-ketone (**4**), m.p. 177—180°, $[\alpha]_D^{19}$ +52°. The position of the carbonyl function in the compound (**4**) was indicated by its mass-spectral fragmentation pattern and confirmed by Beckmann rearrangement[4] of the derived 6,23-dioxime, which yielded the amide (**5**), m.p. 123—127°, $[\alpha]_D^{31}$ +140° (*c* 0·3, $CHCl_3$), possessing the mass-spectral fragmentations indicated. Thus, the original iodo-acetate must have the iodo-substituent at position 22. Since the favoured conformation of the ergosterol-like side-chain of the starting material is probably similar to that in calciferol, which, for the solid state, has been defined by *X*-ray crystallography,[5] it can be represented as in (**1a**). Approach of the encroaching electrophile would be from the least hindered side of the double bond to form the iodonium ion (**6**). Attack of the conjugate acetate ion in the *anti*-sense, preferably at position 23, *i.e.* away from the bulky steroid substituent, leads to formulation of the adduct as the (22*R*)(23*S*)-22-iodo-23-acetoxy-isomer (**7**) (≡**7a**). The derived alcohol would then have the stereochemistry depicted in structure (**3**). This assignment was consistent with molecular rotation differences obtained between it and the isomeric 22- and 23-alcohols and which will be reported later. A subsequent *X*-ray crystallographic determination on the alcohol (**3**) confirmed this assignment. The latter, space group $P2_1$ possessed one molecule per asymmetric unit, $a = 8{\cdot}048$, $b = 20{\cdot}122$, $c = 7{\cdot}641$ Å; $\beta = 93{\cdot}92°$. The



† All new compounds had satisfactory microanalytical and spectral properties.
‡ Less than 5% isomers present by t.l.c. and ^1H n.m.r. analysis.

structure was solved by direct methods and the current R factor is 0·13 for 1800 reflections.§

The stereo- and regio-specific[6] nature of addition to the 23-olefinic bond of compound (**1**) appears to be general. Thus bromo-acetoxylation gave three, of the four possible, bromoacetates (ratio *ca.* 9:4:1). The major isomer (**8**), m.p. 166—169°, $[\alpha]_D^{24}$ +42° (*c* 0·5, $CHCl_3$), was reduced in the same manner as for the iodo-acetate (**7**) to give the alcohol (**3**). Furthermore, treatment of either the iodo-acetate (**7**) or the bromo-acetate (**8**) with methanolic potassium carbonate gave the epoxide (**9**), m.p. 179—182°, $[\alpha]_D^{25}$ +40° (*c* 0·8, $CHCl_3$), shown, as anticipated, to be identical to the *minor* epoxide produced by direct oxidation of the starting olefin (**1a**).

The two minor bromo-acetates from compound (**1**) were also characterised. The next most abundant isomer (**10**), m.p. 146—148° $[\alpha]_D^{25}$ +43° (*c* 0·4, $CHCl_3$), must form from the same bromonium ion as compound (**8**), but by attack at position 22, since this adduct afforded the same epoxide (**9**) by treatment with methanolic potassium carbonate. The least abundant isomer was shown to be (**11**), m.p. 152—153°, $[\alpha]_D^{25}$ +36° (*c* 0·1, $CHCl_3$) as follows. It gave the isomeric epoxide (**12**), m.p. 158—160° $[\alpha]_D^{27}$ +74° (*c* 0·5, $CHCl_3$), with methanolic potassium carbonate and, by reduction with tributyltin hydride followed by hydrolysis, afforded the alcohol (**13**), m.p. 204—208°, $[\alpha]_D^{25}$ +31° (*c* 0·3, $CHCl_3$). The latter alcohol was also derived from reduction of the corresponding 22-ketone, m.p. 182—184°, $[\alpha]_D^{20}$ +52° (*c* 0·2, $CHCl_3$) obtained from the bromo-acetate (**10**).

One further correlation of the structures of the bromo-acetates was also demonstrated. Heating either of the predominant bromo-acetate isomers (**8**) or (**10**) at 140—150° for several minutes established a 1:1 equilibrium of both compounds.[7] Similar thermal isomerisation of the least abundant isomer (**11**) also caused equilibration with formation of small quantities of a new compound, presumed to be the fourth bromo-acetate but which was not isolated. Thermal isomerisation of the iodo-acetate (**7**) also gave an equilibration with a more polar isomer (**14**), m.p. 138—141°, $[\alpha]_D^{25}$ +42° (*c* 0·1, $CHCl_3$), analogous to bromo-acetate (**10**).

The generality of the selective addition to the ergosterol 22(23)-double bond allows structural assignments to be made to other kinetically-controlled adducts, such as the dibromides (*e.g.* **15**) and dichlorides (*e.g.* **16**).[8,9]

(*Received, April 29th*, 1971; *Com.* 664.)

§ Carried out at Queen Mary College. Correspondence regarding the analysis should be directed to S.N.

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