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SHORT COMMUNICATION

ATTEMPT AT SPECIFIC ELIMINATION OF AXIAL HYDROGEN ON STEROID SKELETON

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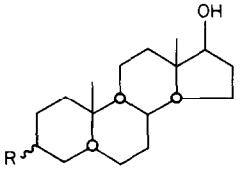
SUMMARY

Four derivatives of 5α-androstan-17β-ol having an ω-halogeno side chain of axial or equatorial configuration on C-3, in presence of boron trifluoride etherate, undergo a backbone rearrangement. There is some evidence that the elimination of the 1α or 5α hydrogen atoms by the electrophilic ω-methylene is the first step of the reaction.

As part of a general study of selective and stereospecific elimination of axial hydrogen atoms in some polycyclic compounds, this paper describes a reaction which probably occurs by removal of a 1α or 5α *hydrogen* in the 5α-androstane series.

We have tried to effect a stereospecific elimination by using an electrophilic reagent fixed at the end of a side chain of variable length and of α or β configuration, linked on C-3 of a steroid.

Four compounds I, II, III and IV with an ω-bromo methylene side chain at C-3, have prepared [1] using as starting material, for I, III and IV, the product of condensation of a 3β tosylate with sodium ethyl malonate according to Shoppee[2], and for II, the condensation of ethyl cyanacetate, according to Tsatsas[3].



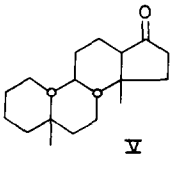
I R=$-CH_2-CH_2Br$ (3α)
II R=$-CH_2-CH_2Br$ (3β)
III R=$-CH_2Br$ (3α)
IV R=$-(CH_2)_2-CH_2Br$ (3α)

The reactivities of these four compounds in BF_3 etherate depends on the length and configuration of the side chain. The reaction products have been systematically analysed by g.l.c. (polyethylene glycol adipate (PEGA) on chromosarb G-AW, 80–100 mesh at 200°C) and t.l.c. (Kieselgel 60 Merck).

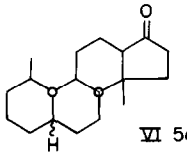
1. 0.3 mmol of the bromoalcohol I, when refluxed for 3 h with 1.6 ml freshly distilled BF_3 etherate and 0.4 ml anhydrous benzene give, with progressive elimination of the starting material, a mixture of non-polar products and three carbonyl compounds. The mixture is readily separated by t.l.c. on SiO_2 from the third ketone present only as traces, which has the same polarity as the ketone obtained by oxydation of the alcohol I.

Table 1. Circular dichroism data

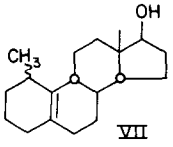
	Inflexion 289 nm	Max 297 nm	Max 305,7 nm	Max 318 nm
Ketone V	+ 1,46	+ 1,95	+ 2,05	+ 1,16
Ketones V + VI	+ 2,02	+ 2,79	+ 2.93	+ 1,66
Ketones IX + X + XI	+ 1,48	+ 1,83	+ 1,86	+ 1,10



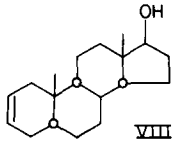
V



VI 5α or 5β



VII



VIII

The ketones V and VI result from the backbone rearrangement (i.e. inversion of the configuration of every spinal carbons atoms and *cis* 1–2 intramolecular transposition of their substituents), and concomitant elimination of the 3α side chain of I as shown by spectrometric results and chemical identification.

The ketone V (m.p. 145–6°C; $\alpha_D^{20} = +147°$; N.M.R. CH_3 (5β): 0.81δ;CH_3 (14β): 1.12δ; I.R. νCo: 1735cm^{-1}; C.D. cf. Table 1 is easily crystallized in methanol from the V + VI mixture. It is identical with a well known authentic sample, obtained by backbone rearrangement of 5-androsten-17β-ol [1, 4].

The ketone VI is obtained in the mother liquors as a mixture with V in the ratio 7:3. It can be separated from V only by g.l.c. using PEGA 5% at 200°C (N.M.R., by comparison with the spectra of V pure: CH_3 (1β) = 0,80 δ; doublet $J = 7$ Hz; CH_3 (14β) = 1,07 δ analytical data of the mixture VI(70%) + V(30%): I.R.νCo = 1735 cm^{-1}; C.D. cf. Table 1. VI is identical to:

1. a product of the backbone rearrangement of VII which is the χ-methyl-5(10)-estren-17β-ol [1]. This reaction gives mainly a mixture of two compounds: VI and its 1α-methyl epimer (N.M.R. 1α(CH_3) = 0,95δ doublet $J = 7$ Hz; 14β(CH_3) = 1,12 δ; m.p. of the mixture = 124–30°C).

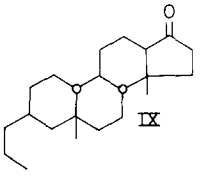
2. the product of the backbone rearrangement of the 2-androsten-17β-ol VIII in benzene-BF_3 etherate. This reaction leads for approximatively 40% to a mixture [1] analogous in N.M.R., g.l.c., and I.R. to the mixture V + VI, yet in a slightly different amount.

2. Under the same experimental conditions the compounds II and III give mainly deoxygenated products

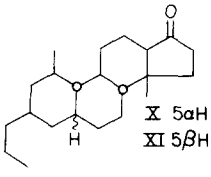
(75–80%), starting material (15–20%) and traces of ketones having the same polarity as the oxidation products of the starting materials. Neither backbone rearrangement nor side chain elimination occur in visible yield.

3. The bromoalcohol IV (prepared by extension of the side chain of I gives, under the same experimental conditions, deoxygenated products (75%) and a mixture (30%) of four others ketones: one of them, readily separated from the other by t.l.c. on SiO_2, has the same polarity as the direct oxydation product of the alcohol IV.

The three other ketones (νCo: 1735 cm^{-1} $CHCl_3$) are separable only by g.l.c. Their circular dichroïsm (Table 1), (identical with that of ketone [5]) favours a 14β-methyl hydrindanone motive as in [5]. Their analysis by coupled g.l.c. M.S. indicates essentially the same mass signals for each of them [M^+ = 316, M-15, M-18, M-33 (15 + 18), M-43 (loss of the propyl chain), M-57 (characteristic of 17 oxo-steroïds)]. Consequently these ketones result probably from a backbone rearrangement without loss of the side chain. They have the presumed structure IX, X and XI.



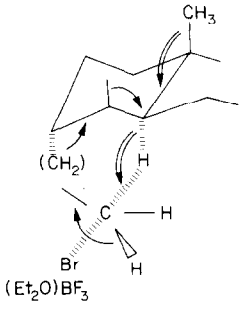
IX



X 5αH
XI 5βH

Thus, the backbone rearrangement in BF_3 etherate would only occur when the carbonium associated with the bromo-methylene group in BF_3 etherate is near the 5α (or 1α) hydrogen, as it is possible in compounds I and IV.

There is no reaction when the carbonium is far away from the axial hydrogen atom, as in II or III. Thus we suggest the following mechanism for elimination of the side chain and the backbone rearrangement.



The 1α (or 5α) hydrogen would be specifically attacked by the electrophilic methylene and the effect would be: either a cyclic transfer (single arrow) when a six atom pseudocycle can be formed (n = 1), leading to the backbone rearrangement (of the ethylenic intermediate) with the elimination of the side chain. Or the elimination of H^- without fragmentation of the side chain, giving only a backbone rearrangement (double arrow) when a six atom pseudocycle cannot be formed.

Direct elimination of the side chain which should occur indifferently for compounds I and II independently of their configuration is not retained, for II does not undergo this elimination.

The development of the backbone rearrangement, initiated by this hydride elimination, is very similar to what is generally observed with unsaturated steroids in strongly acidic media. But its postulated *initiation* (selective and stereospecific elimination of the axial hydrogen atom) is close to the postulated mechanism intitation of backbone rearrangements involved in terpene biosynthesis [5], and thus could be associated with "biometic reactions" [6].

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