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NOVEL REARRANGEMENTS IN THE STEROID SERIES

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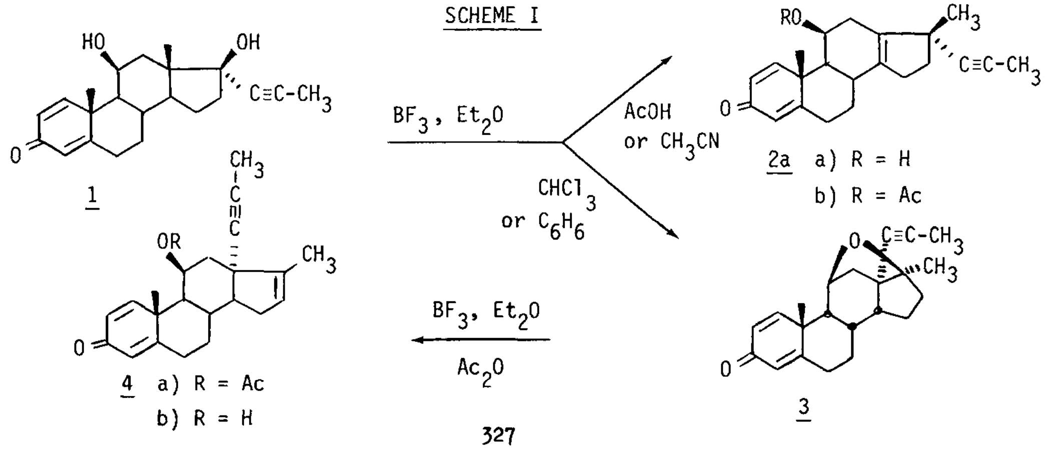
Abstract : *Two rearrangements in the steroid series involving a propynyl substituent are described. One of them yielded a fused cyclobutene derivative.*

It has been shown that 11β,17β-dihydroxy-17α-propynyl-androsta-1,4-dien-3-one 1, possesses a remarkable corticoid-like activity (1). When this compound was treated with BF_3 etherate in acetic acid or acetonitrile, the well-known rearrangement of the 18 methyl group to the 17-position (2) occurred, yielding 88% of 2a [MP 182°C, $(\alpha)_D^{20}$ + 113 ± 3.5° (0.5% $CHCl_3$) ^{1}H-NMR δ (3) : 1.19 (s, 17Me) 1.43 (s, 19Me) 1.73 (s, CH_3-C≡) 4.60 (m, H_{11}) 6.07 (bs, H_4) 6.28 (bd, J=10Hz, H_2) 7.28 (d, J=10Hz, H_1)]. However, when the solvent was changed to benzene, chloroform or CCl_4, the main reaction product became 3 (65%) as determined by further transformations, and finally confirmed by independent X-ray analysis (4). The physical characteristics of this compound are the following : MP 157°C, $(\alpha)_D^{20}$ - 1° (0.8% in $CHCl_3$).
^{1}H-NMR δ : 1.25 (s, 17Me) 1.30 (s, 19Me) 1.80 (s, CH_3-C≡) 4.48 (d, J=7Hz, H_{11}) 6.04 (bs, H_4) 6.23 (dd, J=2Hz and 10Hz, H_2) 7.08 (d, J=10Hz, H_1).
^{13}C-NMR δ : 154.2 (d, C_1) 127.1 (d, C_2) 185.4 (s, C_3) 124.3 (d, C_4) 157.0 (s, C_5) 73.4 (d, C_{11}) 93.5 (s, C_{17}) 79.0 and 79.5 (s, C≡C) 24.6 (q, 17Me) 19.0 (q, 19Me) 3.5 (q, $\underline{CH_3}$-C≡). Presence of 2 carbons α to oxygen (C_{11} and C_{17}). M^+ 322.

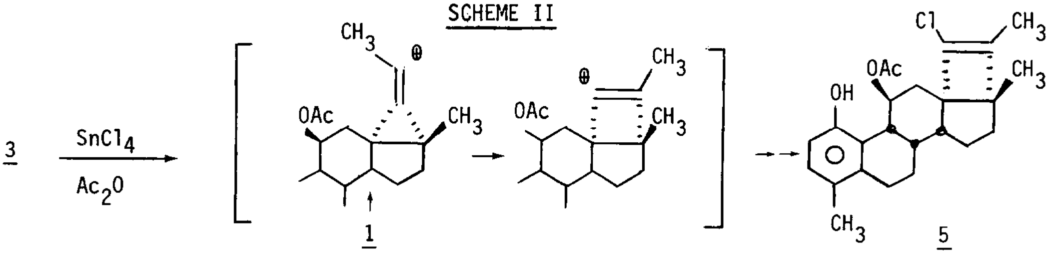
SCHEME I



It appears that a non-nucleophilic solvent favours the triple bond participation in the rearrangement, whereas nucleophilic solvents favour elimination of the 14α proton. As diethylether present in BF_3 etherate can be considered as a nucleophilic solvent, it was expected that the use of pure boron trifluoride in chloroform should increase the yield of compound 3 at the expense of the minor product 2. This was indeed the case, this procedure giving a 78% yield of 3.

To determine the structure of 3, this compound was treated with BF_3 etherate in acetic anhydride to effect the opening of the epoxy bridge, giving a 64% yield of the 11β acetoxy steroid 4a :
^{1}H-NMR δ : 1.08 (s, 19Me) 1.63 (bs, 17Me) 1.73 (s, CH_3-C≡) 2.03 (s, OAc) 5.3 and 5.5 (m, H_{11} and H_{16}) 6.07 (bs, H_4) 6.28 (dd, J=1.5Hz and 10Hz, H_2) 7.12 (d, J=10Hz, H_1). The 17Me is slightly coupled with the 15 methylene. Presence of two deshielded protons : H_{16} (ethylenic) and H_{11} (α to oxygen);
^{13}C-NMR δ : 153.9 (d, C_1) 127.9 (d, C_2) 185.4 (s, C_3) 123.2 (d, C_4) 167.8 (s, C_5) 68.2 (d, C_{11}) 122.7 (d, C_{16}) 142.8 (s, C_{17}) 75.0 and 83.5 (s, -C≡C-) 12.9 and 19.8 (q, 17 and 19Me) 3.6 (q, $\underline{CH_3}$-C≡). 21.5 and 169.9 (OAc : CH_3 and $\underset{\underset{O}{\|}}{\underline{C}}$). Presence of $>$CH - OAc and $-$CH = C$<$. This compound could be saponified to the corresponding 11β hydroxy steroid 4b (MP 195°C : $(\alpha)_D^{20}$ - 182°). Alternatively, when compound 3 was treated with $SnCl_4$ in acetic anhydride, followed by mild saponification, an extensively rearranged product was isolated in 78% yield. The structure of this compound was shown by X-ray diffraction analysis to be 5, (see below). The physical data are the following : MP 245°C : $(\alpha)_D^{20}$ + 44 ± 1° (1% in $CHCl_3$).
^{1}H-NMR δ : 1.06 (s, 17Me) 1.53 (s, CH_3-C=C) 1.81 (s, OAc) 2.13 (s, $\underline{CH_3}$-⌬) 6.38 and 6.79 (d, J=9Hz, H_2 and H_3) 6.5 (m, H_{11}) 5.86 (bs, OH). Absence of ethylenic proton. Presence of one phenolic OH.
^{13}C-NMR δ : 153.2 (s, C_1) 112.7 (d, C_2) 127.8 (d, C_3) 127.4 (s, C_4) 140.8 (s, C_5) 123.2 (s, C_{10}) 69.9 (d, C_{11}) 61.7 and 55.4 (s, C_{13} and C_{17}) 123.6 and 139.3 (s, >C=C<) 19.1 (q, 4Me) 7.9 and 18.3 (q, 17Me and Me on the double bond) 21.7 and 171.3 (OAc : CH_3 and C=O). 24 carbons are observed. Absence of triple bond. Presence of a tetrasubstituted double bond.

SCHEME II



As can be seen, this product arises from two independent molecular rearrangements :

- the well-known dienone-phenol rearrangement (5)
- the formation of a fused cyclobutene via triple bond participation.

This latter rearrangement most likely occurs through a vinyl cation intermediate of the type indicated in the scheme, followed by vinylidene-cyclobutene rearrangement. Such a rearrangement has already been observed in the aliphatic series (6).

Evidence for the postulated cyclopropylvinylidene cation intermediate arises from the fact that compound 5 can also be obtained in, albeit, low yield (15%), along with 2b, by direct treatment of 1 with acetic anhydride and $SnCl_4$.

SINGLE CRYSTAL X-RAY ANALYSIS OF 5 (RU 28950)

The compound was recrystallized from an acetone-ethanol mixture. A colourless single crystal of 0.5mm in mean dimension was mounted and set-up on a Philips PW 1100 automatic single crystal diffractometer. The stepscan technique was used with CuKα monochromatized radiation. Space group is monoclinic $P2_1$, Z=2 with a=11.650 (4), b=8.546 (3), c=11.185 (4)Å, β=97.51 (5)°. 2379 independant reflexions were measured, from which 1977 were considered as observed. No absorption correction was made. The structure was solved by the Multan (7) programme and refined with our local chain (8). Almost all the hydrogen atoms were located on difference fouriers. They were refined with the isotropic approximation for their thermal motion. However, one hydrogen atom of methyl M (C4) and one of the methyl M (C22) refine to inacceptable positions, so they were kept fixed(9).The final agreement indices were R=0.043 and Rω=0.042 for the 1977 reflexions, each with unit weight.

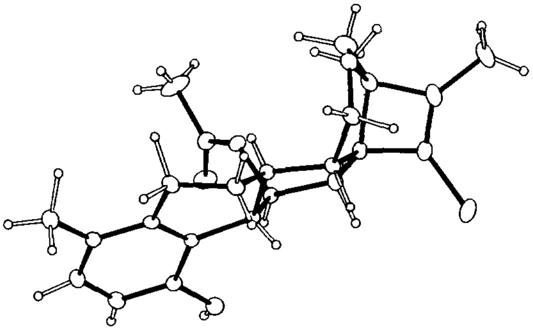
The X-ray analysis unambiguously shows that the studied compound corresponds to formula 5. The figure gives an illustration of its three-dimensional structure. As the chemical filiation allows the knowledge of the absolute hand, no attempt was made to deduce this information from a crystallographic study.

The mean precision for C-C type bond lengths is 0.006Å and that for C-C-C type valency angles is 0.7°. The mean observed C-H length is 0.92Å.

Few structural features appeared as significantly outside the common range as a consequence of large strains around C(13) and C(17). The following values are noticeable : C(13) - C(17) = 1.590 (5)Å, C(18) - C(19) = 1.297 (7)Å, C(18) - C(13) - C(17) = 82.8 (4)°, C(13) - C(17) - C(19) = 86.1 (5)°, C(18) - C(19) - M(C19) = 132.4 (1.2)°, C(12) - C(13) - C(17) = 121.2 (8)°.

Ring A is almost planar with deviations from the mean squares plane in the range 0.01 - 0.05Å, however, its substituents are slightly outside this plane : e.g. C(6) - 0.20Å, C(9) + 0.15Å, O(1) - 0.13Å. Ring D has a quasi symmetric conformation (cf. Figure), ring E is nearly planar with deviation < 0.01Å from the mean least squares plane. M(C19) lies in this plane but the chlorine atom is significantly outside (0.11Å). RU 28950 possesses a markedly twisted overall conformation which brings a low value (51°) for the dihedral angle between the mean planes of rings E and A.

The crystalline cohesion is assumed by an H-bond O(1) - H(O1) (x,y,z) ... O(21) (3-x, $y-{}^{1}/_{2}$, 1-3) : [O ... O = 2.825 (6)Å, O - H ... O = 163 (4)°] and by numerous van der Waals contacts. Of particular interest are H(C20) ... Cl(18) (2.88(4)Å), H(2) ... Cl(18) (3.00 (4)Å) and C - H ... π interactions.



Perspective view of 5 seen along the direction C(15) - middle of C(13) - C(17) drawn by the ORTEP programme (10).

REFERENCES AND NOTES

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3. ^{1}H-NMR Spectra were recorded on Bruker WH-90 and WP-60 spectrometers as solutions in CDCl$_3$. For ^{13}C-NMR experiments, both broad band proton noise decoupled and single frequency off resonance decoupled spectra were recorded on a Bruker WH-90 spectrometer operating at 22.63 MHz. Chemical shifts are in ppm downfield from internal TMS.

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9. The numbering of the steroid nucleus was performed in the usual way except for C$_{19}$ (sp$_2$ carbon of cyclobutene bearing a methyl) C$_{21}$ and C$_{22}$ (respectively sp$_2$ and sp$_3$ carbons of the 11β acetoxy chain).

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