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REARRANGEMENT OF PROPARGYL ENOL ETHERS OF KETOSTEROIDS. A ROUTE TO BENZO[d,e]STEROIDS

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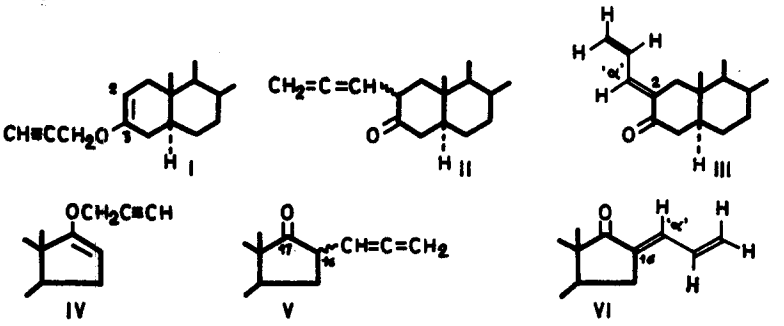
The supposed inability of the linear triple-bonded system to fit a six-centered geometry does not hinder the Claisen-like rearrangement of propargyl ethers[1]. The failure to isolate characterizable compounds from phenyl propargyl ethers was attributed to the ready polymerization of the allenylphenols or the benzofurans[1]. A survey of the literature reveals very few successful examples of rearrangement of non-phenolic propargyl enol ethers, all of which were derivatives of aldehydes[2,3].

In pursuing our studies on the Claisen rearrangement of allyl enol ethers of ketosteroids[4,5], we have examined the rearrangement of the propargyl enol ethers. The starting materials were prepared from the corresponding methyl or ethyl acetals or enol ethers by transetherification with propargyl alcohol (cf. [4,5,6]). In all cases rearrangement occurred readily in solvents boiling slightly above 100°C, showing no practical difference of reactivity between the rigid propargyl group and the more flexible allyl group.

The propargyl ether (I) of the Δ^2-enol of 17β-acetoxy-5α-androstan-3-one, m.p. 129-130°, $[\alpha]_D$ +49.5°[7], refluxed in toluene for 5 hours gave in 50% yield an epimeric mixture of 2-allenyl-3-ketones (II), from which 2α-allenyl-5α-androstan-17β-ol-3-one acetate, m.p. 147-149°, $[\alpha]_D$ -62°, could be isolated. The product was identified by the typical asymmetrical stretching vibration at 1960 cm^{-1} and hydrogenation to the known propyl derivative[4]. On refluxing in pyridine, II

was isomerized to 17β-acetoxy-2-allylidene-5α-androstan-3-one (III)[8], m.p. 182-184°, $[\alpha]_D$ +13.5° (Chf.), λ_{max} 277-278 mμ (ε 12.800), ν_{max} of the conjugated system 1678, 1619 and 1582 cm^{-1}. III was also obtained directly from I in 60% yield by carrying out the rearrangement in pyridine or butanol.



Similarly, dehydroepiandrosterone acetate propargyl enol ether (IV), m.p. 161-162°, $[\alpha]_D$ -30°, by refluxing in toluene, afforded in 65% yield the epimeric mixture of 16-allenes V, from which the main component, 16α-allenyldehydroepiandrosterone acetate, m.p. 129-132°, $[\alpha]_D$ -129°, was isolated by crystallization from methanol. By refluxing in pyridine, IV gave in quantitative yield 16-allylidenedehydroepiandrosterone acetate (VI)[8], m.p. 155-157°, $[\alpha]_D$ -73.5°, λ_{max} 278-279 mμ (ε 21.000), ν_{max} of the conjugated system 1706, 1621 and 1587 cm^{-1}.

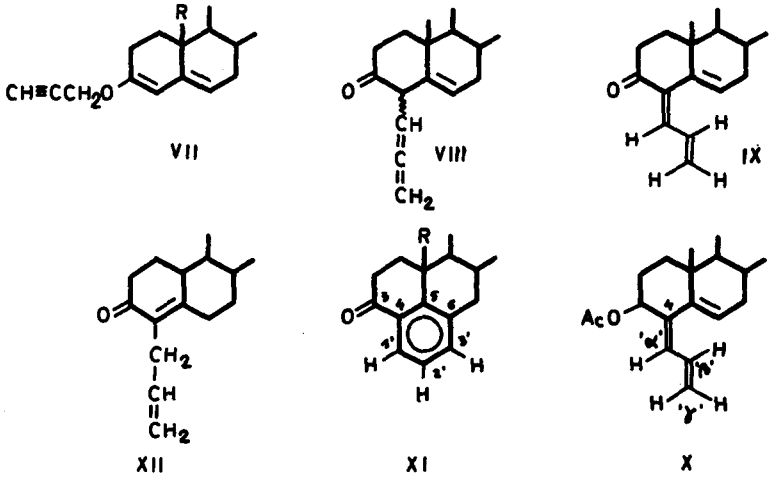
Propargyl enol ethers of Δ^4-3-ketones showed a more complex behaviour, because the rearrangement products can undergo further transformations.

Testosterone acetate propargyl enol ether (VIIa, R = CH_3), m.p. 149-151°, $[\alpha]_D$ -148°, refluxed in toluene for 5 hours, afforded in 70% yield a crystalline mixture of two products. Repeated crystallizations from methanol yielded a product, m.p. 135-137°, $[\alpha]_D$ +3°, recognized as 17β-acetoxy-4-[§]-allenylandrost-5-en-3-one (VIII)[9] on the basis of the allene band at 1960 cm^{-1} and in accordance with our previous findings on the corresponding allyl derivatives[4]. On the other hand, the reaction mixture on passage through an alumina column was con-

verted completely into the second reaction product, identified as the conjugated ketone (shift of the α,β double bond) 17β-acetoxy-4-allylideneandrost-5-en-3-one (IXa)[8] m.p. 130-133°, $[\alpha]_D$ -90°, λ_{max} 221 mμ (ε 11.000) and 297-298 mμ (ε 8.000), ν_{max} of the conjugated system 1676, 1632, 1604 and 1564 cm^{-1}.

Progesterone 3-propargyl enol ether (VIIb, R = CH_3), m.p. 157-158°, $[\alpha]_D$ -62°, treated as above, afforded directly in 60% yield, after recrystallization of the reaction mixture, 4-allylidenepregn-5-ene-3, 20-dione (IXb), m.p. 178-181°, $[\alpha]_D$ -26.5°, λ_{max} 222 mμ (ε 11.300) and 297-298 mμ (ε 8.300), ν_{max} of the conjugated system 1682, 1636, 1606 and 1570 cm^{-1}.

Further proof of the structure of allylideneketones (IX) was obtained by the NMR spectrum of the product[10] of $LiAlH_4$ reduction and acetylation of IXb, 4-allylidenepregn-5-ene-3β,20β-diol diacetate (X), m.p. 173-177°, $[\alpha]_D$ -159°, λ_{max} 255 mμ (ε 16.500). This showed for the side-chain at C-4 the multiplet of the 'β' proton centered at 6.85 ppm, the signals of the 'γ' protons between 5.0 and 5.3 ppm, of the 'α' proton at 6.02 ppm and the signals of the proton at C-6 (partially overlapped by the proton at C-3) between 5.4 and 5.7 ppm.



By refluxing enol ether VIIb for 3 hours in pyridine, a new compound recognized as benzo[d,e]pregn-4-ene-3,20-dione (XIb, R =CH_3)[11], m.p. 214-215°, $[\alpha]_D$ +53°, was obtained in 27% yield. The yield increased to 45% by working in the presence of palladium charcoal. Similarly enol ether VIIa, refluxed in pyridine in the presence of the catalyst, gave in 36% yield 17β-acetoxy-benzo[d,e]androst-4-en-3-one (XIa, R =CH_3)[11], m.p. 143-145°, $[\alpha]_D$ -14.5°. The same products were obtained also by refluxing VIII or IX in pyridine.

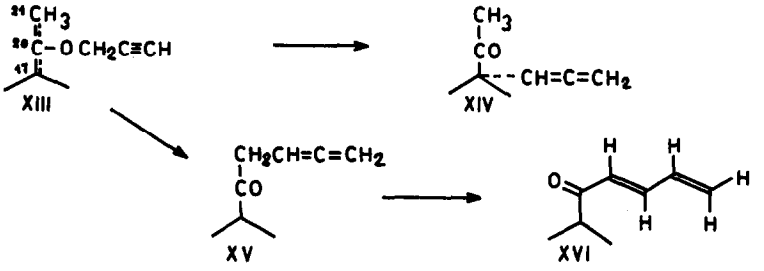
The structure of the pentacylic steroid analogs XI[12] was elucidated as follows. UV maxima at 219 mμ (ε 11.420), 259-260 mμ (ε 10.400) and 302-303 mμ (ε 2.260) and IR bands at 1675, 1582, 790 and 759 cm^{-1} were consistent with the presence of a 1-tetralone system[13] and a 1,2,3-trisubstituted benzene ring. NMR spectra showed the signals of the aromatic protons at C-3' and C-2' around 7.3 ppm and that of the C-1' proton at 7.85 ppm, due to the anisotropy of the C-3 carbonyl group.

3-Oxobenzosteroids XI underwent easy reduction and hydrogenolysis to 3-deoxo derivatives by hydrogenation at room temperature and atmospheric pressure in the presence of palladium catalyst. Thus XIa yielded benzo[d,e]androstene-17β-yl acetate, m.p. 102-104°, $[\alpha]_D$ -23°, λ_{max} 222-223 mμ (ε 6.400) and 265 mμ (ε 320), ν_{max} 1584, 777 and 762 cm^{-1}, aromatic proton signals around 6.9 ppm and benzylic proton signals around 2.85 ppm, in agreement with the attributed structure.

Since the isomerization of the allenes VIII is fast in the reaction conditions, benzosteroids XI arise from 4-allylideneketones IX by cyclodehydrogenation. The favourable effect of a hydrogenation catalyst, in pyridine or in other solvents[14], is evident, but the nature of the reaction is as yet unknown[15]. Addition of a hydrogen acceptor such as ethyl cinnamate did not increase appreciably the yield. However, some results seem to suggest that at least with certain compounds cyclization and aromatization occur partially by hydrogen disproportionation, the 4-allylideneketone acting as both hydrogen donor and

acceptor. Thus, 19-norandrost-4-ene-3,17-dione 3-propargyl enol ether (VIIc, R = H), m.p. 153-155°, $[\alpha]_D$ +101.5°, refluxed in pyridine in the presence of palladium charcoal, gave in 48% yield 19-norbenzo[d,e]androst-4-ene-3,17-dione (XIc, R = H), m.p. 209-211°, $[\alpha]_D$ +26°, λ_{max} 212 mμ (ε 21.500), 258 mμ (ε 10.900) and 302 mμ (ε 2.300). Chromatography of the mother liquor afforded in 5% yield 4-allyl-19-norandrost-4-ene-3,17-dione (XII), m.p. 176-179°, $[\alpha]_D$ +135° (Chf.), λ_{max} 250 mμ (ε 14.100), identical with the product prepared by rearrangement of the allyl enol ether according to the reported procedure[4].

The 20-propargyl enol ether of 3β-acetoxypregn-5-en-20-one (XIII), m.p. 118-120°, $[\alpha]_D$ -49°, was a mixture of 17(20)- and 20-enes [16]. On rearrangement, it gave the expected products XIV and, through XV,



XVI. 17α-Allenyl-3β-hydroxy-pregn-5-en-20-one (XIV), m.p. 151-153°, $[\alpha]_D$ +38°, was obtained in the highest yield (40%) after refluxing XIII in toluene or pyridine and saponifying the mixture with KOH[17]; hydrogenation to the 17α-propyl derivative, identical with the product prepared in a different manner[18], confirmed the structure allotted.

The allene XV was not isolated, whereas the corresponding conjugated ketone, 21-allylidene-3β-acetoxy-pregn-5-en-20-one (XVI)[8], m.p. 160-162°, $[\alpha]_D$ +52.5°, λ_{max} 265 mμ (ε 23.800), ν_{max} of the conjugated system 1678, 1615 and 1584 cm^{-1}, was obtained in about 30% yield after reaction in toluene and chromatography on alumina.

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7. Rotations are in dioxan, unless otherwise indicated. IR spectra were recorded in Nujol mull, UV spectra in ethanol. NMR spectra were recorded on the A-60 and H-100 spectrometer at the Varian Research Laboratory in Zürich. All new compounds gave satisfactory analytical results. We are indebted to Dr. S. Cairoli for the microanalyses and to Dr. C. Pedrali for IR spectra.
8. At the present we have no information on the stereochemistry of carbon 'a'.
9. For the probable change in conformation of ring A see ref. 4.
10. 4-Allylidene-3-ketones undergo ready polymerization, so that the preparation and preservation of pure samples are rather difficult.
11. There is as yet no official ruling about naming of benzo-steroids.
12. Substituted benzo[d,e]steroids have been prepared in other ways by R. Sciaky and U. Pallini, Tetrahedron Letters 1839 (1964) and J.M.H. Graves and H.J. Ringold, Steroids, suppl. I, 23 (1965).
13. Cf. T. Momose, Y. Ohkura and S. Goya, Pharm. Bull. 3, 401 (1955), Chem. Abst. 50, 13850 (1956).
14. In solvents such as n-butanol, n-pentanol, toluene, halobenzenes, ethyl cinnamate, cyclodehydrogenation hardly occurs at all except in the presence of the catalyst.
15. Autooxidative processes are not involved, since the reaction occurred also in the presence of antioxidants.
16. Cf. B. Belleau and T.F. Gallagher, J. Am. Chem. Soc. 74, 2816 (1952).
17. In these conditions, XVI polymerized to give a high melting unknown product, ν_{max} 1690 and 1655 cm^{-1}.
18. R. Vitali and R. Gardi, Gazz. Chim. Ital., in press.