Cyclization Reaction of 3,20-Bis(ethylenedioxy)-9,11-seco-C-nor-5α-pregnane-9β,11-diol into 17α-Acetyl-11-oxa-C-nor-D-homo-5α-androstan-3-one

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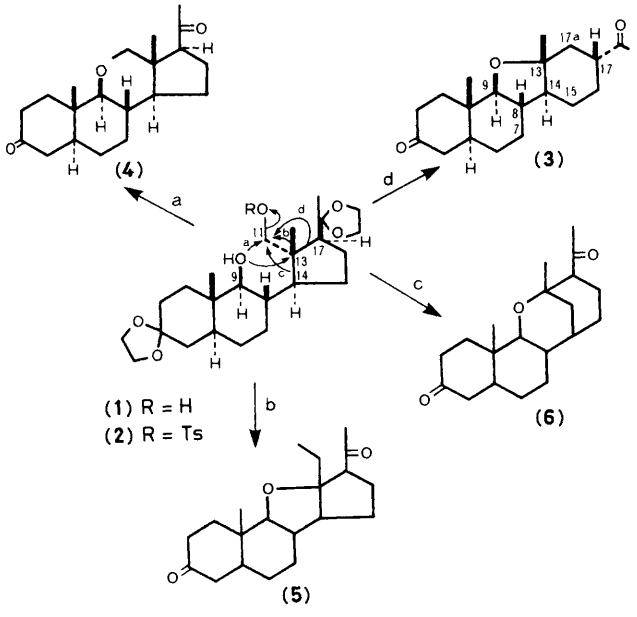
3,20-Bis(ethylenedioxy)-11-tosyloxy-9,11-seco-C-nor-5α-pregnane-9β-ol (**2**) on heating in dimethylformamide was converted into 17α-acetyl-11-oxa-C-nor-D-homo-5α-androstan-3-one (**3**).

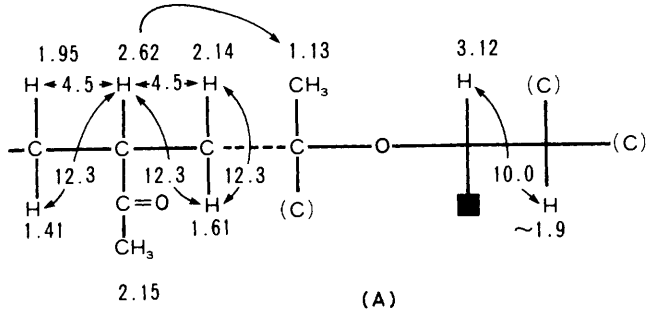
An intramolecular cyclization of 3,20-bis(ethylenedioxy)-9,11-seco-C-nor-5α-pregnane-9β,11-diol (**1**) leading to the 11-oxa-5α-pregnanes (path a) *via* the 11-toluene-*p*-sulphonate (**2**) has been reported by Engel and his co-workers.[1] In this paper we describe the conversion of (**1**) into an isomeric ether (**3**) and its structure elucidation.

Diol (**1**), when treated with toluene-*p*-sulphonyl chloride in pyridine at 5 °C gave the crude product (**2**) (m.p. 83.5—87.5 °C). Treatment of this unpurified (**2**) in dimethylformamide (DMF) at 70 °C followed by acid hydrolysis (toluene-*p*-sulphonic acid–acetone) gave a crystalline compound (**3**) m.p. 133—134 °C (colourless needles from CH_2Cl_2–hexane), $[\alpha]_D^{20}$ +23 (*c* 1.0, $CHCl_3$), in 43% yield, together with 11-oxa-5α-pregnane-3,20-dione (**4**)[1] in 32% yield from (**1**). The molecular formula of (**3**), $C_{20}H_{30}O_3$, was determined by its elemental analysis and mass spectrum in which the molecular ion peak appeared at *m/z* 318.2161. The i.r. (1705 cm^{-1}, KBr), ^1H n.m.r. (δ 3.12, d, *J* 10.0 Hz; $CDCl_3$) and ^{13}C n.m.r. (δ 210.87, 210.31, 93.21, and 82.41) spectra indicated the presence of two carbonyl groups and an ether (CH–O–C) group together with three methyl groups [δ_H 2.15 (s), 1.13 (s), and 1.08 (s)] in (**3**).

Based on the above evidence, it was assumed that (**3**) was an isomeric ether that was formed from tosyloxy elimination with subsequent C-13–C-18 (path b), C-13–C-14 (path c), or C-13–C-17 (path d) bond migration and nucleophilic attack of



Scheme 1



Arrows indicate spin-couplings and n.O.e. connectivity.

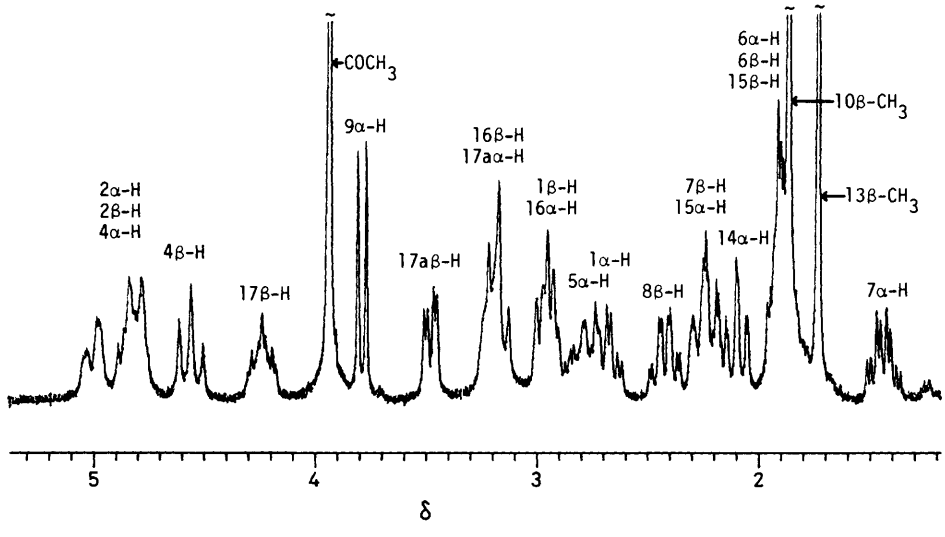


Figure 1. ^1H N.m.r. spectrum of (**3**) in the presence of $Eu(fod)_3$.

C-9 oxygen on C-13 as shown in Scheme 1. Structure (**5**) was excluded because of the absence of ethyl signals in the ^{1}H n.m.r. spectrum. The spin couplings of the 17-methine proton (δ 2.62, tt, *J* 12.3, 4.5 Hz) of the cyclic ether suggested the presence of the unit CH_2–$CH(COCH_3)$–CH_2, which excluded the structures (**5**) and (**6**). Furthermore, proton homonuclear decoupling and nuclear Overhauser enhancement (n.O.e.) experiments on (**3**) (400 MHz, $CDCl_3$) expanded the partial structure to (A).

To establish the structure of the cyclic ether (**3**) including its stereochemistry, a ^{1}H n.m.r. spectrum obtained in the presence of Eu(fod)$_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate) [270 MHz, $CDCl_3$; (**3**): Eu(fod)$_3$ 3:1 molar ratio] was analysed in detail (see Figure 1).

The doublet at δ 3.79 (*J* 10.0 Hz) was assigned unequivocally to 9α-H. The signal observed at δ 2.42 was spin coupled with 9α-H and assigned to 8β-H. Irradiation of 8β-H altered the signal patterns at δ 2.10 (td, *J* 12.2 and 2.3 Hz) and 1.44 (qd, *J* 12.0 and 4.7 Hz) to a broad doublet (*J* 12.0 Hz) and to a triplet of doublets (*J* 12.0 and 4.7 Hz), respectively. These signals were assigned to 14α-H and 7α(axial)-H, respectively. Further, 14α-H was spin-coupled with the 15-CH_2 protons, and the magnitude of spin couplings between 14α-H and 15β-H (*J* 12.2 Hz) and between 14α-H and 15α-H (*J* 2.3 Hz) revealed a *trans* C/D ring junction, since the dihedral angles of these vicinal protons expected from the observed coupling constants were around 180 and 60°. Such a spatial arrangement would be possible only in C/D *trans* configuration in a 11-oxa-C-nor-D-homo-steroid system. The axial nature of 17-H ascertained by its large coupling constant and the n.O.e. of 18-H induced by irradiation of 17-H revealed that 17-H and 13-CH_3 were 1,3-diaxially oriented on the chair D ring.

The β-configuration of 17-H indicated that configurational inversion at C-17 had occurred during the reaction. This inversion must have taken place through enolization of the 20-ketone yielded by hydrolysis of the 20-ethylenedioxy group.

Extensive proton homonuclear spin decoupling experiments starting from the unequivocally assignable 4β-H (t, *J* 15.0 Hz), 9α-H, and 17β-H revealed the spin network of all the protons in (**3**). The assignments are shown in Figure 1.

Thus the structure of the cyclic ether (**3**) was established to be 17α-acetyl-11-oxa-C-nor-D-homo-5α-androstan-3-one.

We thank Professor Motoo Tori, Tokushima Bunri University, for the 400 MHz ^{1}H n.m.r. spectra and Dr Kikuo Yasuda, Teikoki Hormone Mfg. Co., Ltd. for the high resolution mass spectral measurement. We also thank Dr. Kazuhiko Orito, Hokkaido University, for helpful discussions.

Received, 7th January 1984; Com. 040

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