Unusual Cyclization of 3,20-Bisethylenedioxy-9,11-seco-c-nor-5α-pregnane-9β,11-diol into 11-Oxa-5α,17α-pregnane-3,20-dione

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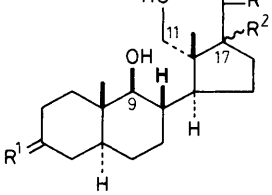
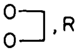
On refluxing with a catalytic amount of toluene-*p*-sulphonic acid in acetone 3,20-bisethylenedioxy-9,11-seco-c-nor-5α-pregnane-9β,11-diol (**1**) cyclized to give 11-oxa-5α,17α-pregnane-3,20-dione (**2**), *via* the transient formation of a hemiacetal.

We describe an unusual transformation of the diol (**1**)[1] into the oxa-steroid (**2**), in which the intermediately formed 17α-acetyl group participates in the ether ring closure.

Treatment of (**1**) with a catalytic amount of toluene-*p*-sulphonic acid (TsOH) in acetone under reflux afforded a diastereoisomeric mixture of (**2**), $C_{20}H_{30}O_3$ (M^+, *m/z* 318.2204), m.p. 157—158.5 °C (colourless plates from hexane–AcOEt), $[\alpha]_D^{23}$ −45° (*c* 0.8, $CHCl_3$), and (**3**)[1] in 92% yield [(**2**) : (**3**), 5 : 1]. The i.r., and ^1H and ^{13}C n.m.r. spectra of (**2**) showed the presence of two carbonyl groups ($\nu_{max.}$ 1710 cm^{-1}; δ_C 211.4 and 210.9) including an acetyl [δ_H 2.08 (s)], two methyl groups [δ_H 1.06 and 1.09 (s)], and an ether group, CH–CH–O–CH_2– [δ_C 89.9 (CHO) and 76.2 (CH_2O); δ_H 2.42 (d, *J* 10.0 Hz, CH–O), 3.21 (d, *J* 10.0 Hz, *H*CH–O), and 3.90 (d, *J* 10.0 Hz, HC*H*–O)]. The similarity of the methylene and methine proton signals of the CH_2–O–CH group in (**2**) to those in (**3**)† and the nuclear Overhauser enhancement (n.O.e.) of the methine signal (δ 2.42) on irradiation of the doublet at δ 3.21 suggested that the B and C rings in (**2**) are the same as in (**3**). The unusual high-field shifts of 9α-H in (**2**) (δ 2.42) and (**3**) (δ 2.50) may be due to the five 1,3-diaxially oriented 1α-, 5α-, 7α-, 12α-, and 14α-hydrogen atoms around 9α-H. Thus (**2**) was assumed to be the 17α-acetyl epimer of (**3**).

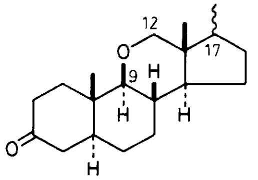
The stereostructure of the C and D rings in (**2**) was further confirmed by the n.O.e. of the 12β(equatorial)-H and 13β-CH_3 signals induced by irradiation of 17β-H. On heating



(**1**) R^1 = , R^2 = α-H

(**4**) R^1 = O, R^2 = α-H

(**5**) R^1 = O, R^2 = β-H



(**2**) R = α-COMe

(**3**) R = β-COMe

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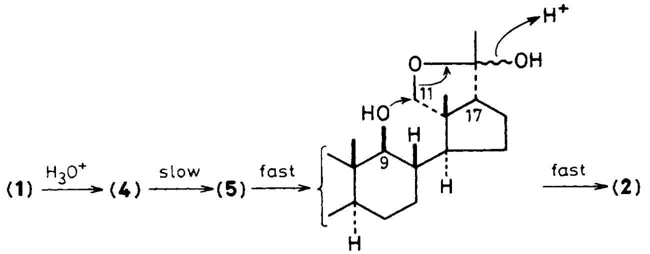
† ^1H N.m.r., 270 MHz, $SiMe_4$, $CDCl_3$ solutions, *J* in Hz, δ values for (**2**) [(**3**)]: 9α-H: d, 2.42 (*J* 10.0) [2.50 (*J* 9.5)]; 12α-H: d, 3.21 (*J* 10.0) [3.42 (*J* 10.0)]; 12β-H: d, 3.90 (*J* 10.0) [4.12 (*J* 10.2)]; 17-H: dd, 2.83 (*J* 8.2, 2.3) [overlapped by other signals for (**3**)]; 18-H; s, 1.06 [0.77]; 19-H: s, 1.09 [1.11]; 21-H: s, 2.08 [2.06].



(6)

Scheme 1

(2) with TsOH in benzene under reflux an equilibrium mixture of (2) and (3) (2:7) was obtained in 90% yield, and (2) was thus established to be 11-oxa-5α,17α-pregnane-3,20-dione.

When (1) was treated with TsOH at room temperature, only (2) and the dioxo-diol (4), m.p. 156—157 °C, were obtained; (3) was not detected. This result together with the thermodynamic preference for (3) over (2) indicates that the epimerization at C-17 proceeded prior to the cyclic ether formation, *i.e.* (4) was converted into (2) *via* the intermediate formation of (5) (Scheme 1). The occurrence of the smooth cyclization even under these mild conditions can be interpreted in terms of the formation of the hemiacetal (6).[2] Elimination of H_2O from the protonated hemiacetal with subsequent nucleophilic attack of the appropriately oriented 9β-hydroxy oxygen on C-11 would yield the cyclic ether (2). The inability of (4) to form a hemiacetal would prevent the ring closure of (4) into (3) under these conditions. In the reaction mixture neither (5) nor (6) was detected, showing that the ring closure of (5) was extremely fast and the epimerization of (4) to (5) was the rate-determining step.

The reaction of (1) with TsOH and ethylene glycol in benzene did not lead to the trapping of (5) or (6) as the acetals.

To the best of our knowledge few reactions of this type have been reported.[3]

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References

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2 18-Hydroxypregnan-20-ones are well known to exist in the hemiacetal form: see, for example, M. P. Li, M. K. Birmingham, and T. H. Chan, *J. Org. Chem.*, 1976, **41**, 2552.

3 The facile conversion of 3,20-bisethylenedioxy-11β,18-dihydroxypregn-5-ene into 11β,18-epoxypregn-4-ene-3,20-dione in acidic medium can also be interpreted by taking account of the participation of the 17β-acetyl group: D. N. Kirk and M. S. Rajagopalan, *J. Chem. Soc., Chem. Commun.*, 1976, 77, and references cited therein. A rearrangement reaction proceeding *via* the transient formation of a hemiacetal has been reported: D. Rabinovich, Z. Shakked, I. Kirson, G. Günzberg, and E. Glotter, *J. Chem. Soc., Chem. Commun.*, 1976, 461.