# Cyclization of 3,3;20,20-Bis(ethylenedioxy)-*C*-nor-9,11-seco-5α-pregnane-9β,11-diol into 11-Oxa-5α,17α-pregnane-3,20-dione‡

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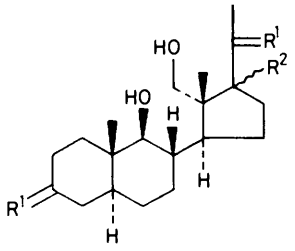
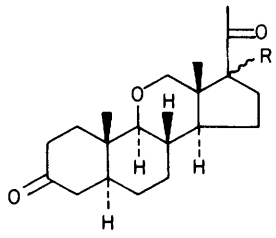
On refluxing with a catalytic amount of toluene-*p*-sulphonic acid in acetone, 3,3;20,20-bis(ethylenedioxy)-*C*-nor-9,11-seco-5α-pregnane-9β,11-diol (**1**) cyclized to give 11-oxa-5α,17α-pregnane-3,20-dione (**2**), *via* the transient formation of a hemiacetal.

There are a number of studies on the synthesis and physiological activity of heterocyclic steroids.[1] Among them, in view of the physiological significance of the 11-oxygen function in adrenocortical hormones, introduction of a heteroatom into the 11-position of the steroidal skeleton attracted our interest. In 1968 Engel and co-workers reported the synthesis of 11-oxaprogesterone from hecogenin acetate *via* 3,3;20,20-bis(ethylenedioxy)-*C*-nor-9,11-seco-5α-pregnane-9β,11-diol (**1**).[2] Further study on reactivity of the key intermediate (**1**) seemed of interest for the development of syntheses of 11-hetero steroids.

We now describe an unusual transformation of the diol (**1**) into 11-oxa-5α,17α-pregnane-3,20-dione (**2**) in connection with our recent study on the cyclization of the diol (**1**) into 17α-acetyl-11-oxa-*D*-homo-*C*-nor-5α-androstan-3-one (**3**).[3]

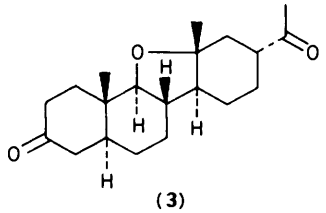


(**1**) $R^1$ = O, O, $R^2$ = α-H



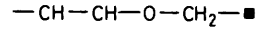
(**2**) R = β-H
(**4**) R = α-H

(**5**) $R^1$ = O, $R^2$ = α-H
(**6**) $R^1$ = O, $R^2$ = β-H



(**3**)

Treatment of the diol (**1**) with toluene-*p*-sulphonic acid (PTSA) in acetone under reflux for 6.7 h afforded a mixture of two diketones (**2**) and (**4**) in 92% yield [(**2**):(**4**) = 5:1, determined by $^1$H n.m.r. spectrum]. The more polar diketone (**4**), m.p. 213—215 °C, was identical with 11-oxa-5α-pregnane-3,20-dione.[2] Structural elucidation of the novel diketone (**2**) was performed as follows. The molecular formula ($C_{20}H_{30}O_3$) of the less polar diketone (**2**) was determined by its high-resolution mass spectrum ($M^+$, 318.2204). The i.r. and $^1$H and $^{13}$C n.m.r. spectra of compound (**2**) showed the presence of two carbonyl groups ($\nu_{max.}$ 1 710 cm$^{-1}$; $\delta_C$ 211.4 and 210.9), including an acetyl [$\delta_H$ 2.08 (3 H, s)], and two methyl groups [$\delta_H$ 1.06 (3 H, s) and 1.09 (3 H, s)]. Furthermore, the n.m.r. spectra revealed the presence of partial structure (A) in compound (**2**). The



(**A**)

■ denotes a quaternary carbon atom

similarity of the methylene- and methine-proton signals of the $CH_2$–O–CH group in the partial structure (A) to 12α-, 12β-, and 9α-proton signals of compound (**4**) (Table), and the nuclear Overhauser enhancement (n.O.e.) of the methine proton signal ($\delta_H$ 2.42) on irradiation of the doublet at $\delta_H$ 3.21, indicated the presence of a partial structure the same as the *B* and *C* rings of the diketone (**4**). The unusual high-field shifts of 9α-H in compounds (**2**) ($\delta_H$ 2.42) and (**4**) ($\delta_H$ 2.50) may be due to the five 1,3-diaxially oriented 1α-, 5α-, 7α-, 12α-, and 14α-hydrogen atoms around 9α-H.[4] The two-dimensional $^{13}$C–$^1$H shift-correlation spectrum of 5α-cholestan-3β-yl acetate showed the high-field-shifted 9α-H signal at $\delta_H$ 0.65 [$\delta_C$ 54.23 (C-9)[5a]]. Although in the $^1$H n.m.r. spectrum of compound (**4**) the 17α-H signal overlaps with others, the downfield-shifted methine proton signal C*H*COMe of compound (**2**) was observed at $\delta_H$ 2.83 (dd, *J* 8.2 and 2.3 Hz). Thus the diketone (**2**) was assumed to be the 17α-acetyl epimer of compound (**4**). The stereostructure of the *C* and *D* rings in the diketone (**2**) was further confirmed by the n.O.e. of 12β (equatorial)-H and 13β-Me signals induced by irradiation of 17β-H.

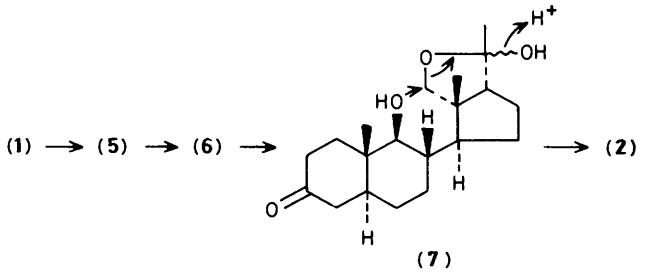
**Table.** $^1$H N.m.r. data (δ) (*J*/Hz) of diketones (**2**) and (**4**)[a]

| Proton | Compound (**2**) | Compound (**4**) |
|---|---|---|
| 9α-H | 2.42(d) (*J* 10.0) | 2.50(d) (*J* 9.5) |
| 12α-H | 3.21(d) (*J* 10.0) | 3.42(d) (*J* 10.2) |
| 12β-H | 3.90(d) (*J* 10.0) | 4.12(d) (*J* 10.2) |
| 17-H | 2.83(dd) (*J* 8.2, 2.3) | *b* |
| 10β-Me | 1.09(s) | 1.11(s) |
| 13β-Me | 1.06(s) | 0.77(s) |
| COMe | 2.08(s) | 2.06(s) |

[a] 270 MHz, in $CDCl_3$. [b] Overlapped by others.

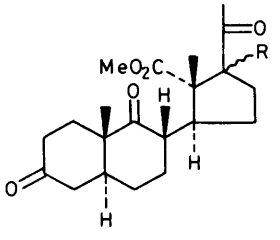
† Preliminary communication: H. Nagano, T. Iwadare, and M. Shiota, *J. Chem. Soc., Chem. Commun.*, 1985, 656.
‡ An additional example of the cyclization of 9,11-seco steroids *via* the transient formation of a hemiacetal, see Yu. P. Badanova and K. K. Pivnitsky, *Zh. Obsch. Khim.*, 1974, **44**, 2089. We thank Dr. Pivnitsky who informed us of this.

Finally, the structure of the diketone (**2**) was firmly established by converting compound (**2**) into the diketone (**4**). On being heated with PTSA in benzene under reflux, compound (**2**) epimerized to the 17β-acetyl isomer (**4**) and an equilibrium mixture of the diketones (**2**) and (**4**) (2:7) was obtained. Thus the diketone (**2**) was determined to be 11-oxa-5α,17α-pregnane-3,20-dione.




**Scheme 1.**

When the diol (**1**) was treated with PTSA at room temperature, only the diketone (**2**) and the deprotected diketo diol (**5**), m.p. 156—157 °C, were obtained. The absence of compound (**4**) in the reaction mixture, and the thermodynamic preference for the diketone (**4**) over the diketone (**2**), indicate that the epimerization at C-17 proceeded prior to the cyclic ether formation, *i.e.* the diketo diol (**5**) was converted into the diketone (**2**) *via* intermediate formation of the epimeric diketo diol (**6**) (Scheme 1). Base-catalysed epimerization of the triketo ester (**8**)[2] gave an equilibrium mixture of compound (**8**) and the epimeric triketo ester (**9**) [(**8**):(**9**) = 3:1].



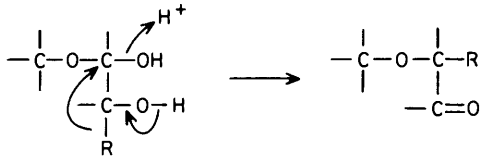
(**8**) R = α-H
(**9**) R = β-H

The occurrence of the smooth cyclization even under these mild conditions can be interpreted in terms of the formation of the hemiacetal (**7**). 18-Hydroxypregnan-20-ones are well known to exist in the hemiacetal form.[6] Elimination of water 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 the dioxo diol (**5**) to form a hemiacetal would prevent ring closure of compound (**5**) to give the diketone (**4**) under these conditions. In the reaction mixture neither compound (**6**) nor compound (**7**) was detected, showing that ring closure of compound (**6**) was extremely fast and the epimerization of the diketo diol (**5**) to the diketo diol (**6**) was the rate-determining step.

The reaction of the diol (**1**) with PTSA and ethylene glycol in benzene did not lead to the trapping of compound (**6**) or (**7**) as acetals. Although to ascertain the participation of the C-20 carbonyl group in the cyclization step conversion of the triketo ester (**9**) into 17α-ethyl derivative was attempted, reduction of the C-20 carbonyl in compound (**9**) to a methylene group was not achieved since the thioacetalization of the congested carbonyl did not proceed.

To the best of our knowledge few reactions of this type have been reported. Rearrangement reactions *via* transient formation of a hemiacetal as shown in Scheme 2 have been reported.[7]

The ready conversion of 3,3;20,20-bis(ethylenedioxy)-11β,18-dihydroxypregn-5-ene into 11β,18-epoxypregn-4-ene-3,20-dione in acidic medium[8] can also be interpreted by taking account of the participation of the 17β-acetyl group.



**Scheme 2.**

## Experimental

N.m.r. spectra were recorded on a JEOL GX-270 spectrometer for $CDCl_3$ solutions (unless otherwise stated) with $(Me)_4Si$ as internal standard. Mass (e.i.; 70 eV), and i.r. (KBr) spectra were taken on JEOL DX-300 and JASCO A-3 spectrometers, respectively. Optical rotations were determined on a JASCO DIP-181 polarimeter. M.p.s. were determined on a hot-block melting-point apparatus and are uncorrected. Pre-coated Merck Kieselgel 60 $F_{254}$ was used for general analytical purposes, and silica gel (Wakogel C-200) was used for column chromatography.

*Preparation of* 3,3;20,20-*Bis*(*ethylenedioxy*)-C-*nor*-9,11-*seco*-5α-*pregnane*-9β,11-*diol* (**1**).—The starting diacetal diol (**1**) was prepared from hecogenin acetate according to the reported method.[2] Its physical and i.r. and n.m.r. spectral data were in agreement with those described in Engel's report.[2]

*Cyclization of* 3,3;20,20-*Bis*(*ethylenedioxy*)-C-*nor*-9,11-*seco*-5α-*pregnane*-9β,11-*diol* (**1**) *into* 11-*Oxa*-5α,17α-*pregnane*-3,20-*dione* (**2**).—A solution of the diol (**1**) (23.5 mg) and PTSA monohydrate (7 mg) in acetone (7 ml) was heated under reflux for 6.7 h. After addition of aqueous sodium hydrogen carbonate, the acetone was evaporated off. The residue was extracted with diethyl ether and the extract was passed through a silica gel column [(1.0 g); eluant hexane–ethyl acetate (2:1)] to give a mixture of 11-oxa-5α,17α-pregnane-3,20-dione (**2**) and 11-oxa-5α-pregnane-3,20-dione (**4**) in 92% (17.1 mg) yield. The ratio (5:1) of these diketones was determined by the integration of $^1H$ n.m.r. spectrum. The isolation of these diketones [t.l.c., hexane–ethyl acetate (2:1); $R_F$ value of compound (**2**) 0.56, and $R_F$ value of compound (**4**) 0.52] was carried out by silica gel column chromatography [eluant hexane–ethyl acetate (4:1)] to afford 11-*oxa*-5α,17α-*pregnane*-3,20-*dione* (**2**) as plates, m.p. 157—158.5 °C (from hexane–ethyl acetate); $[\alpha]_D^{23}$ −45° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$ 1 710 $cm^{-1}$; $\delta_H$ (270 MHz) 1.06 (3 H, s, 13β-Me; a long-range spin coupling was observed between 12α-H and the methyl protons), 1.09 (3 H, s, 10β-Me), 2.08 (3 H, s, COMe), 2.42 (1 H, d, *J* 10.0 Hz, 9α-H), 2.83 (1 H, dd, *J* 8.2 and 2.3 Hz, 17β-H), 3.21 [1 H, d, *J* (−)10.0 Hz, 12α-H], and 3.90 [1 H, d, *J* (−)10.0 Hz, 12β-H]; $\delta_C$ (67.8 MHz) 10.40 (C-19), 20.40 (C-18), 24.40 (C-15 or -16), 25.28 (C-16 or -15), 28.14 (C-6 or -7), 29.27 (C-7 or -6), 32.09 (C-21), 36.44 (C-8), 37.11 (C-1), 37.21 (C-10), 37.81 (C-2), 43.88 (C-4), 44.46 (C-5), 45.82 (C-13), 48.45 (C-14), 59.46 (C-17), 76.19 (C-12), 89.97 (C-9), 210.96 (C-20), and 211.37 (C-3); these signals were assigned based on the completely decoupled, selectively decoupled, and INEPT spectra and by comparison of the chemical shifts with those of 5α-cholestan-3-one,[5a] 3α-hydroxy-5α-pregnan-20-one,[5b] and 11-hydroxyprogesterones;[5c] *m/z* 318 (rel. int. 25%, $M^+$), 300 (29, $M^+ - H_2O$), 275 (16, $M^+ - MeCO$), 257 (78, $M^+ - H_2O - MeCO$), 233 (75), and 107 (100) (Found: $M^+$, 318.2204. $C_{20}H_{30}O_3$ requires *M*, 318.2194).

Diketone (**4**) was obtained as plates, m.p. 213—215 °C (from ethyl acetate), and was identical with 11-oxa-5α-pregnane-3,20-dione in all respects [t.l.c., m.p., and i.r. and n.m.r. spectra (see Table)]; $\delta_C$ 10.49 (C-19), 12.86 (C-18), 22.81 (C-15 or -16), 23.89 (C-16 or -15), 28.10 (C-6 or -7), 28.99 (C-7 or -6), 30.90 (C-21), 36.18 (C-8), 37.19 (C-1), 37.29 (C-10), 37.83 (C-2), 43.91 (C-4), 44.26 (C-13), 44.59 (C-5), 54.54 (C-14), 59.82 (C-17); 79.12 (C-12), 90.33 (C-9), 208.30 (C-20), and 211.39 (C-3).

Cyclization of the diol (**1**) was carried out at room temperature also. A solution of the diol (**1**) (34.1 mg) and PTSA monohydrate (5 mg) in acetone (5 ml) was kept at 25 °C for 2 h. After work-up as described above the product was chromatographed on silica gel [(1.5 g); hexane–ethyl acetate (1:1)] to give the diketone (**2**) (6 mg, 23%) and 9β,11-*dihydroxy*-C-*nor*-9,11-*seco*-5α-*pregnane*-3,20-*dione* (**5**) (21 mg, 77%) as plates (from hexane–$CH_2Cl_2$), m.p. 156.0—157.0 °C; $\nu_{max.}$ 3 270, 1 710, and 1 690 $cm^{-1}$; $\delta_H$ ($CDCl_3$ + $D_2O$) 0.60 (3 H, s, 13β-Me), 1.09 (3 H, s, 10β-Me), 2.15 (3 H, s, COMe), 3.03 (1 H, d, *J* 10.6 Hz, 9α-H), 3.14 (1 H, t-like, *J ca.* 9 Hz, 17α-H), 3.51 [1 H, A part of an AB-type quartet, *J* (−)12.5 Hz, 12-H], and 3.57 [1 H, B part of an AB-type quartet, *J* (−)12.5 Hz, 12-H]. The stereochemistry of the acetyl group in the diketo diol (**5**) was defined by the lack of n.O.e. enhancement of the 13β-Me signal on irradiation of 17-H; *m/z* 336 (2%, $M^+$), 318 (28, $M^+ - H_2O$), and 95 (100) (Found: *m/z*, 318.2218. $C_{20}H_{30}O_3$ requires *m/z* 318.2195).

*Epimerization of* 11-*Oxa*-5α,17α-*pregnane*-3,20-*dione* (**2**) *into* 11-*Oxa*-5α-*pregnane*-3,20-*dione* (**4**).—A solution of the diketone (**2**) (5.8 mg) and PTSA monohydrate (4.4 mg) in benzene (3 ml) was heated under reflex for 7 h. Diethyl ether was then added to the reaction mixture and the resulting solution was washed successively with aqueous sodium hydrogen carbonate, water, and saturated brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a mixture of the diketones (**2**) and (**4**) in 93% yield. The ratio (2:7) of the diketones (**2**) and (**4**) in equilibrium was determined by the integration of the $^1H$ n.m.r. spectrum.

*Epimerization of Methyl* 3,9,20-*Trioxo*-C-*nor*-9,11-*seco*-5α-*pregnan*-11-*oate* (**8**) *into Methyl* 3,9,20-*Trioxo*-C-*nor*-9,11-*seco*-5α,17α-*pregnan*-11-*oate* (**9**).—To a methanolic solution of sodium methoxide, prepared from Na (39 mg) in dry methanol (3 ml), was added a solution of the triketo ester (**8**) (131 mg) in methanol (4 ml). The reaction mixture was heated under reflux for 2 h. After neutralization with dil. HCl, methanol was evaporated off, and the residue was extracted with diethyl ether. The ethereal solution was washed successively with water and saturated brine, and dried over anhydrous sodium sulphate. After methylation of the partly hydrolysed product with diazomethane the product was submitted to column chromatography [(6 g); eluant hexane–ethyl acetate (3:1)] to give the more polar *triketo ester* (**9**) (26.7 mg, 20%) as needles, m.p. 90.0—91.5 °C (from hexane–diethyl ether), and the starting material (**8**) (77.3 mg, 59% recovery). The spectral data of compound (**9**) were as follows; $\nu_{max.}$ 1 735 and 1 705 $cm^{-1}$; $\delta_H$ 1.13 (3 H, s, 13β-Me), 1.34 (3 H, s, 10β-Me), 2.11 (3 H, s, COMe), and 3.70 (3 H, s, $CO_2Me$); *m/z* 362 (11%, $M^+$), 344 (2, $M^+ - H_2O$), 259 (55, $M^+$ − COMe − $CO_2Me$ − H), and 43 (100, COMe) (Found: $M^+$, 362.2061. $C_{21}H_{30}O_5$ requires *M*, 362.2093.)

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