Synthesis and X-ray crystal structure of 3-oxo-23, 24-dinorchol-4-ene-22-cyanohydrin

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(22R) and (22S) 3-Oxo-23,24-dinorchol-4-ene-22-cyanohydrin have been synthesised from 3-oxo-23,24-dinorchol-4-ene-22-al and the crystal structure of the (22R) epimer has been determined by X-ray crystallography.

Keywords: steroids, X-ray crystallography, epimers

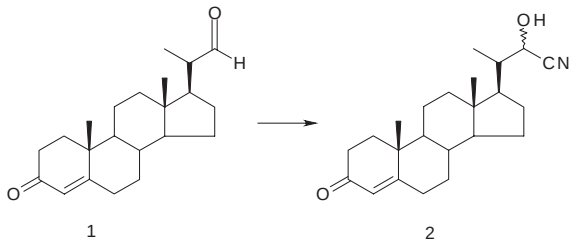
The molecular structures of steroids have been studied extensively by X-ray crystallography and head-to-tail intermolecular hydrogen bonding is a common feature.[1] Where only one donor and one acceptor are present, typically near positions 3 and 17 in the nucleus, this produces a continuous chain of molecules. The possibility of intermolecular coil formation in steroids has been reported[2] but most X-ray studies have concentrated on the isolated molecule rather than the supramolecular structure. For the novel chol-4-ene steroid described in this work the chain of molecules forms a helix in the direction of the *a* axis of the crystal unit cell.

3-Oxo-23,24-dinorchol-4-ene-22-cyanohydrin (2) was synthesised from 3-oxo-23,24-dinorchol-4-ene-22-al (1) using a method different from that described by Heyl and Herr.[3] Its crystal structure was determined (see Fig. 1).

Experimental

3-Oxo-23,24-dinorchol-4-en-22-al (**1**), KCN and NH_4Cl were purchased from Aldrich and used as received. The purity of the product was supported by TLC performed on silica gel (Merck type 60) and visualised under UV illumination and/or by I_2 vapour. The compound was purified by VLC using TLC grade silica (Kiselgel 60 PF_{254}). Melting points of the products were determined on a Gallenkamp melting point apparatus. Infrared spectra (wavenumbers in cm^{-1}) were recorded on an ATI Mattson Genesis FTIR spectrophotometer as KBr pellets. NMR spectra were recorded on a Varian Unity INOVA 400 MHz NMR spectrometer. Chemical shifts are reported in ppm downfield from TMS, using the middle resonance of CD_3OD (3.30 ppm for ^1H and 49.15 ppm for ^{13}C) as an internal standard and coupling constants (*J*) in Hz. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet) coupling constant (*J*), integration and peak assignment.

Synthesis of 3-oxo-23,24-dinorchol-4-ene-22-cyanohydrin **(2):** To a stirred solution of 3-oxo-23,24-dinorchol-4-en-22-al (1, 150 mg, 0.46 mmol) in MeOH (5 ml), KCN (28 mg) and NH_4Cl (38 mg) were added and the mixture was refluxed for 6h. Then dil. HCl was added to the reaction mixture, extracted with $CHCl_3$ and washed with H_2O. The crude solid was purified by VLC (40% EtOAc in pet-ether) and a mixture of the (22R) and (22S) forms of (2) were obtained (90 mg, yield: 82%). The epimers (70 mg) were separated by preparative reversed-phase HPLC using a LUNA C_{18} preparative column (250 mm × 21.2 mm, 10 Bm) eluted with a linear gradient: 45–100% acetonitrile in water (40 mins) followed by 100% acetonitrile (10 mins), flow rate = 20 ml/min, monitored by a photo-diode-array detector. The purified (22S)-cyanohydrin was obtained as a white amorphous solid (29 mg, 32%), m.p.: 188–190 °C. ^1H NMR (400 MHz): δ 0.76 (s, 3H, 18-Me), 1.09 (d, *J* = 6.5 Hz, 3H, 21-Me), 1.19 (s, 3H, 19-Me), 4.48 (d, *J* = 4.1 Hz, 1H, 22-CH), 5.67 (s, 1H, -CH=C). ^{13}C NMR (100 MHz): δ 35.5 (C-1), 33.9 (C-2), 199.7 (C-3), 123.9 (C-4), 171.3 (C-5), 32.8 (C-6), 31.9 (C-7), 35.6 (C-8), 52.0 (C-9), 38.5 (C-10), 20.9 (C-11), 39.3 (C-12), 42.8 (C-13), 53.6 (C-14), 24.2 (C-15), 27.4 (C-16), 55.3 (C-17), 12.1 (C-18), 17.4 (C-19), 41.1 (C-20), 13.2 (C-21), 65.2 (C-22), 118.4 (C-23). ESIMS *m/z*: 356 $[M+H]^+$. The purified (22R)-cyanohydrin was obtained as crystals (41 mg, 46%), m.p.: 230 °C (lit. m.p.[3]: 200-202 °C). IR ($CHCl_3$): ν_{max} cm^{-1} 3336br (O-H), 2945s (C-H), 287os (O-CH_2), 2235w (C≡N), 1670vs (C=O), 1616s (C=C), 1448w, 1379w, 1254m, 1072m, 935m, 847m and 756m. ^1H NMR (250 MHz): δ 0.75 (s, 3H, 18-Me), 1.13 (d, *J* = 7.3 Hz, 3H, 21-Me), 1.19 (s, 3H, 19-Me), 4.53 (d, *J* = 4.1 Hz, 1H, 22-CH), 5.67 (s, 1H, -CH=C). ^{13}C NMR (62.5 MHz): δ 35.5 (C-1), 33.9 (C-2), 199.7.3 (C-3), 123.9 (C-4), 171.3 (C-5), 32.8 (C-6), 31.8 (C-7), 35.6 (C-8), 52.0 (C-9), 38.5 (C-10), 21.0 (C-11), 39.3 (C-12), 42.8 (C-13), 53.6 (C-14), 24.2 (C-15), 27.4 (C-16), 55.3 (C-17), 12.2 (C-18), 17.4 (C-19), 41.1 (C-20), 13.2 (C-21), 64.9 (C-22), 122.4 (C-23). FABMS *m/z*: 356 $[M+H]^+$; 378 $[M+Na]^+$



Scheme 1

Crystal data and X-ray structure determination

X-ray crystallography: All crystallographic measurements were performed with a Nonius KappaCCD diffractometer using graphite-monochromated Mo-Kα radiation. The programs DENZO[4] and COLLECT[5] were used in data collection and cell refinement. $C_{23}H_{33}NO_2$, *M* = 355.50, *T*=120(2) K, λ = 0.71073Å, Orthorhombic, $P2_12_12_1$, *a* = 7.3975(2), *b* = 11.5777(2), *c* = 22.7737(6) Å, *U*=1950.48(8)Å^3, *Z*= 4, Density (calculated) = 1.211 Mg/m^3, μ = 0.076 mm^{-1}, F(000) = 776, Crystal size = 0.15 × 0.15 × 0.10 mm, θ range for data collection = 3.27 to 27.47°, Index ranges: –9<=*h*<=7, –12<=*k*<=15, –29<=*l*<=25, reflections collected = 11149, independent reflections = 2543 [*R*(int) = 0.0750], observed reflections [($I>2\sigma$] = 1925, number of parameters= 242, Goodness-of-fit on F^2 (*S*) = 1.020 , final R_1 [$I>2\sigma$] = 0.0475, R_2 (all data) = 0.1077. The structure was solved with SIR-97[6] and refined with SHELX-97.[7]

Plots and molecular geometries were obtained with PLATON.[8] Full crystallographic data, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC should quote the full literature citation and the reference number CCDC 209442.

Discussion

Compound **(2)** was identified by IR, MS and NMR analysis but a m.p. comparison with published data suggested that acetone may have been incorporated into the crystal lattice of the original product.[3] The IR, MS, NMR and crystallographic data for **(2)** have not been published previously.

The bond lengths and angles are normal for this type of molecule. As no heavy atom is present the absolute stereochemistry of the molecule has not been determined by the X-ray study and is assumed to correspond to that of progesterone. The chiral centres in the molecule (Fig.1) then become R at C8, C10, C17 and C22 and S at C9, C13, C14 and C20. Ring conformations are: A (C1α, C2β half-chair), B (chair), C (chair), D (C13 envelope). Intermolecular hydrogen bonding, O2–H2...O1, is present where O2–H2 = 0.94(4)Å, O2...O1^I = 2.745(3)Å (I = symmetry operation –0.5+*x*,0.5–*y*,2–*z*), H2...O1^I = 1.82(4)Å and O2-H2...O1 = 167(3)°. This hydrogen bonding links the molecules head-to-tail in a helical arrangement as shown in Fig. 2.

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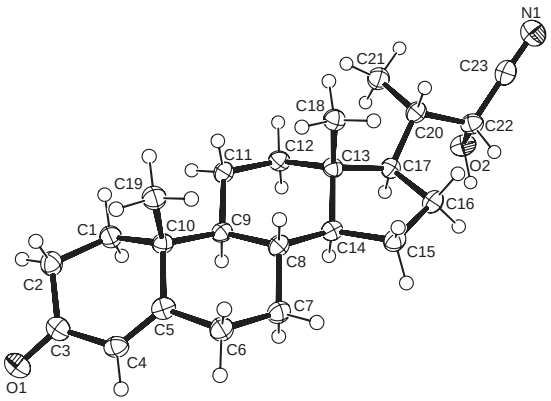

Fig. 1 The atomic arrangement in the molecule.

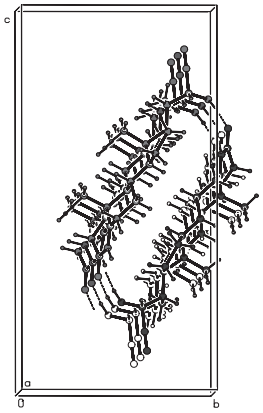

Fig. 2 A partial packing diagram showing the helical arrangement of molecules.

The β face of the steroid, as indicated by the angular methyl groups, together with the cyanide group are located on the outside of the helix. The axial hydrogens on the α face of the steroid (*e.g.*, H14, H17) are on the inside of the helix. The left-handed helix forms a column down the *a* axis of the unit cell.

A much weaker, non-classical, intermolecular hydrogen bond C20–H20...O1 is also present. Here C20–H20 = 1.0Å, C20...O1^{II} = 3.488(3)Å (II = symmetry operation 1.5–*x*, –*y*, –0.5+*z*), H20...O1^{II} = 2.55Å. For each complete rotation along the 7.3975(2)Å crystallographic axis the helix is loosely held to four other identical helices by the C–H...O hydrogen bonds. The non-bonded separation between O1 and O2 is 12.383(2)Å and the C17–C20–C22–O2 torsion angle is 76.6(3)°.

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