Steroidal Analogues of Unnatural Configuration. Part XI.[1] Crystal and Molecular Structure of 3α,17α-Dihydroxy-4,4,14α-trimethyl-19-nor-10α-pregn-5-ene-11,20-dione and a Circular Dichroism Study of the Conformation of the Acetyl Side-chain of the 17-Hydroxy-isomers in Solution

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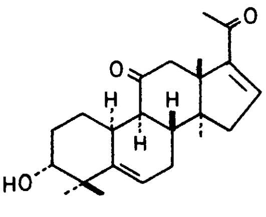
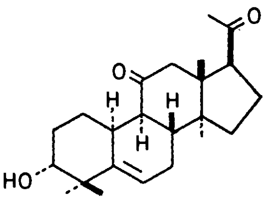
The crystal and molecular structure of the title compound (3) has been determined from three-dimensional, single-crystal *X*-ray analysis by direct methods, and refined by least squares methods to *R* 0.037. Crystals are monoclinic, space group $P2_1$, with $a = 12.80(1)$, $b = 7.52(1)$, $c = 10.81(1)$ Å, $\beta = 97.18(4)°$, $Z = 2$. Ring C is considerably distorted and the solvent-dependence of the 11-carbonyl chromophore c.d. spectra can be explained by conformational mobility of ring C.

The conformation of the 17β-acetyl side-chain in methanol is close to that found in the solid state but in non-polar solvents, c.d. studies showed that a second conformer, stabilized by intramolecular hydrogen bonding, exists. In the 17α-acetyl isomer only one conformation without intramolecular hydrogen bonding is observed in c.d. studies in both polar and non-polar solvents.

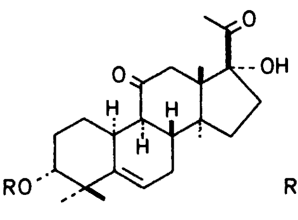
THE autoxidation of neutral $\Delta^{17(20)}$-enols derived from cucurbitacins gave 17-hydroperoxy-20-ketones which, upon reduction with triethyl phosphite, gave the corresponding 17-hydroxy-20-ketones in good yield.[2] This is still the only method available for 17-hydroxylation of these compounds with a methyl substituent at C(14). The hydroxylation method was studied in detail on 3α-hydroxy-4,4,14α-trimethyl-19-nor-10α-pregna-5,16-diene-11,20-dione (1), and a mixture of 17-hydroxy-isomers was obtained in good yield and in a ratio of 5 : 1. Only the major product, designated as ' probably the 17α-hydroxy-20-ketone ' was characterized. Dreiding molecular models showed, however, that because of the indeterminate steric influence of the 14α-methyl group, no unambiguous conclusions can be drawn as to which face of the intermediate enol is more prone to electrophilic attack. The product ratio shows, however, that one side is strongly favoured. The minor product has now been isolated and fully characterized.



(1)

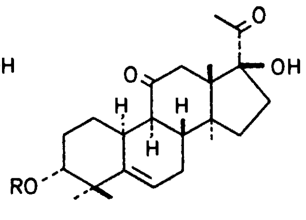


(2)



(3) R = H

(4) R = Ac



(5) R = H

(6) R = Ac

A comparison of the isomers revealed marked differences in their i.r., c.d., and n.m.r. spectra. The difficulties encountered in making unambiguous configurational assignments in the presence of the conformationally mobile 17-acetyl side-chain, prompted an *X*-ray crystallographic analysis of the major isomer and this confirmed the original 17β-acetyl-17α-hydroxy (3) assignment. The minor isomer must therefore be the 17α-acetyl-17β-hydroxy-compound (5). With the configurational problem solved, the other spectroscopic data allowed a description of the conformation of the 17-acetyl side-chain of both isomers in solution and in some detail.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Spectra were recorded in Merck Uvisol grade solvents as follows: i.r. spectra, Beckman IR 12 in dried (P_2O_5) carbon tetrachloride in 1 cm cells, concentration <0.001M; FT n.m.r., Varian XL 100 15 for solutions in carbon tetrachloride, $CDCl_3$, and deuteriomethanol; mass spectra, A.E.I. MS9; optical rotations, Bendix NPL automatic polarimeter for solutions in chloroform; c.d. spectra, JASCO J 20 instrument for solutions in carbon tetrachloride, hexane, and methanol in 0.2 cm cells, concentrations *ca.* 0.001M at 20 °C; *X*-ray crystallography, Phillips PW 1100 diffractometer, graphite-monochromated Mo-K_α radiation ($\lambda = 0.710\,7$ Å); for further details see later.

The crude crystalline product from the oxidation of the enol derived from compound (1)[2] showed on precoated silica gel F_{254} plates (0.25 mm; Merck) developed with 3% methanol in chloroform, a major component R_F 0.38 and a minor component R_F 0.28. Chromatography on a column of silica gel (0.05—0.2 mm; Merck; ratio 1 : 100) gave a clean separation of the two isomers and small quantities of the 16,17-dihydro-derivative (2).

3α,17α-*Dihydroxy*-4,4,14α-*trimethyl*-19-*nor*-10α-*pregn*-5-*ene*-11,20-*dione* (3).—The crude product was crystallized from chloroform–benzene and –methanol to give the 17β-acetyl-17α-hydroxy-compound (3), m.p. 247—250 °C (lit.,[2] 247—248 °C).

3α-*Acetoxy*-17α-*hydroxy*-4,4,14α-*trimethyl*-19-*nor*-10α-*pregn*-5-*ene*-11,20-*dione* (4).—Treatment of the dihydroxy-compound (3) with acetic anhydride–pyridine at 20 °C for 15 h, gave the 3α-*acetate* (4), m.p. 210—212 °C (from chloroform–methanol), $[\alpha]_D$ −159° (*c* 1.0), $\nu_{max.}$ 3 610 (unbonded 17α-OH), 3 495br (bonded 17α-OH), 1 738 (OAc),

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[1] Part X, J. R. Bull, J. Floor, and A. Tuinman, *Tetrahedron*, 1975, **31**, 2157.

[2] P. R. Enslin, *Tetrahedron*, 1971, **27**, 1909.

1 715sh (bonded 20-CO), and 1 704 cm^{-1} (11-CO), δ 0.66 (3 H, d, J 1 Hz, 13β-Me), 0.98 (Me), 1.06 (Me), 1.32 (14α-Me), 1.97 (Ac), and 2.22 (OAc) in carbon tetrachloride and δ 0.60 (3 H, d, J 1 Hz, 13β-Me), 1.02 (Me), 1.10 (Me), 1.29 (14α-Me), 2.03 (Ac), and 2.18 (OAc) in deuteriomethanol (Found: C, 72.0; H, 8.8. $C_{25}H_{36}O_5$ requires C, 72.1; H, 8.7%).

TABLE 1

Fractional co-ordinates with standard deviations

Atom	*x*	*y*	*z*
C(1)	0.345 6(3)	1.100 0	0.282 0(4)
C(2)	0.226 2(3)	1.102 7(6)	0.286 2(4)
C(3)	0.183 1(3)	0.915 7(6)	0.295 7(4)
C(4)	0.202 0(3)	0.798 0(5)	0.184 5(3)
C(5)	0.323 1(3)	0.795 0(5)	0.189 9(3)
C(6)	0.381 2(3)	0.654 0(6)	0.219 6(4)
C(7)	0.499 3(3)	0.650 0(6)	0.243 1(5)
C(8)	0.546 8(3)	0.834 9(5)	0.264 6(3)
C(9)	0.490 4(3)	0.958 4(5)	0.164 4(3)
C(10)	0.372 6(3)	0.976 5(5)	0.176 5(3)
C(11)	0.544 9(3)	1.135 5(5)	0.146 4(3)
C(12)	0.664 5(3)	1.144 2(6)	0.165 6(4)
C(13)	0.706 3(3)	1.037 7(5)	0.281 8(3)
C(14)	0.667 4(3)	0.840 9(5)	0.265 8(3)
C(15)	0.731 2(3)	0.752 8(6)	0.378 1(4)
C(16)	0.842 2(3)	0.836 5(6)	0.380 9(4)
C(17)	0.829 5(3)	1.015 8(5)	0.310 8(3)
C(18)	0.665 6(3)	0.131 2(6)	0.394 2(4)
C(20)	0.883 0(3)	1.168 8(6)	0.389 2(4)
C(21)	0.911 8(4)	1.333 2(7)	0.319 9(6)
C(30)	0.157 1(3)	0.610 3(7)	0.203 2(5)
C(31)	0.146 7(3)	0.869 1(7)	0.059 9(4)
C(32)	0.699 0(3)	0.7560 (7)	0.146 0(4)
O(20)	0.904 0(2)	1.157 0(5)	0.501 6(2)
O(17)	0.873 7(2)	1.013 7(4)	0.196 1(2)
O(11)	0.494 1(2)	1.266 4(4)	0.110 6(2)
O(3)	0.073 1(2)	0.927 5(4)	0.311 0(3)
H(1)	0.378(3)	1.049(5)	0.366(3)
H(2)	0.378(3)	1.221(5)	0.279(3)
H(3)	0.208(3)	1.174(5)	0.359(3)
H(4)	0.190(3)	1.159(5)	0.207(3)
H(5)	0.224(3)	0.861(5)	0.382(3)
H(6)	0.056(3)	0.863(5)	0.362(3)
H(7)	0.070(3)	0.617(5)	0.200(3)
H(8)	0.171(3)	0.539(5)	0.130(3)
H(9)	0.181(3)	0.568(5)	0.286(3)
H(10)	0.068(3)	0.888(5)	0.069(3)
H(11)	0.158(3)	0.785(5)	−0.014(3)
H(12)	0.179(3)	0.975(5)	0.039(3)
H(13)	0.350(3)	0.547(5)	0.228(3)
H(14)	0.516(3)	0.588(5)	0.321(3)
H(15)	0.526(2)	0.598(5)	0.180(3)
H(16)	0.527(3)	0.873(5)	0.350(3)
H(17)	0.654(3)	0.787(5)	0.064(3)
H(18)	0.776(3)	0.777(5)	0.133(3)
H(19)	0.677(3)	0.633(6)	0.144(3)
H(20)	0.699(3)	0.779(5)	0.458(3)
H(21)	0.733(3)	0.618(6)	0.365(3)
H(22)	0.876(3)	0.849(5)	0.465(3)
H(23)	0.890(3)	0.755(5)	0.339(3)
H(24)	0.950(3)	0.990(5)	0.215(3)
H(25)	0.861(3)	1.356(5)	0.255(3)
H(26)	0.989(3)	1.315(5)	0.297(3)
H(27)	0.927(3)	1.419(5)	0.381(3)
H(28)	0.583(2)	1.143(5)	0.382(3)
H(29)	0.693(2)	1.073(5)	0.482(3)
H(30)	0.695(2)	1.252(5)	0.405(3)
H(31)	0.692(2)	1.095(5)	0.086(3)
H(32)	0.684(3)	1.275(6)	0.176(3)
H(33)	0.497(3)	0.898(5)	0.081(3)
H(34)	0.339(3)	1.034(5)	0.099(3)

3α,17β-*Dihydroxy*-4,4,14α-*trimethyl*-19-*nor*-10α,17α-*pregn*-5-*ene*-11,20-*dione* (5).—The crude product was crystallized from chloroform–methanol to give the 17α-*acetyl*-17β-*hydroxy-compound* (5), m.p. 215—218 °C, $[\alpha]_D$ −151 °C (c 0.97) (Found: C, 74.0; H, 9.4. $C_{23}H_{34}O_4$ requires C, 73.8; H, 9.2%).

3α-*Acetoxy*-17β-*hydroxy*-4,4,14α-*trimethyl*-19-*nor*-10α,17α-*pregn*-5-*ene*-11,20-*dione* (6).—Treatment of the dihydroxy-compound (5) with acetic anhydride–pyridine at 20 °C for 15 h, gave the 3α-*acetate* (6), m.p. 173—175 °C (from methanol–ethyl ether), $\nu_{max.}$ 3 625 (unbonded 17β-OH), 1 737 (OAc), 1 720 (unbonded 20-CO), and 1 707 cm^{-1} (11-CO), δ 0.98 (Me), 1.00 (2 × Me), 1.07 (Me), 2.04 (Ac), and 2.22 (OAc) in $CDCl_3$ (Found: M^+, 416.256 8. $C_{25}H_{36}O_5$ requires M, 416.256 3).

TABLE 2

Bond lengths (Å) and angles (°) with standard deviations

(*a*) Distances			
C(1)–C(2)	1.534(5)	C(9)–C(11)	1.527(6)
C(1)–C(10)	1.543(5)	C(11)–O(11)	1.215(5)
C(2)–C(3)	1.518(6)	C(11)–C(12)	1.519(5)
C(3)–O(3)	1.440(4)	C(12)–C(13)	1.529(5)
C(3)–C(4)	1.536(6)	C(13)–C(14)	1.563(6)
C(4)–C(30)	1.546(7)	C(13)–C(17)	1.578(5)
C(4)–C(31)	1.537(6)	C(13)–C(18)	1.549(6)
C(4)–C(5)	1.544(5)	C(14)–C(15)	1.527(6)
C(5)–C(6)	1.312(6)	C(14)–C(32)	1.542(6)
C(5)–C(10)	1.518(6)	C(15)–C(16)	1.550(6)
C(6)–C(7)	1.501(5)	C(16)–C(17)	1.545(6)
C(7)–C(8)	1.525(6)	C(17)–O(17)	1.426(4)
C(8)–C(9)	1.536(5)	C(17)–C(20)	1.538(6)
C(8)–C(14)	1.542(5)	C(20)–C(21)	1.514(7)
C(9)–C(10)	1.535(5)	C(20)–O(20)	1.214(5)
(*b*) Angles			
C(10)–C(1)–C(2)	110.2(3)	O(11)–C(11)–C(12)	119.8(3)
C(1)–C(2)–C(3)	111.2(3)	C(9)–C(11)–C(12)	119.3(3)
C(2)–C(3)–C(4)	112.7(3)	C(11)–C(12)–C(13)	109.4(3)
C(2)–C(3)–O(3)	108.6(3)	C(12)–C(13)–C(14)	109.3(3)
O(3)–C(3)–C(4)	112.2(3)	C(12)–C(13)–C(17)	117.2(3)
C(3)–C(4)–C(5)	103.5(3)	C(12)–C(13)–C(18)	106.9(3)
C(3)–C(4)–C(10)	109.0(4)	C(14)–C(13)–C(17)	102.7(3)
C(3)–C(4)–C(31)	112.7(3)	C(14)–C(13)–C(18)	112.5(3)
C(30)–C(4)–C(5)	111.7(3)	C(17)–C(13)–C(18)	108.5(3)
C(31)–C(4)–C(5)	112.8(3)	C(13)–C(14)–C(15)	101.0(3)
C(30)–C(4)–C(31)	107.1(3)	C(13)–C(14)–C(8)	109.4(3)
C(4)–C(5)–C(6)	123.8(4)	C(13)–C(14)–C(32)	111.8(3)
C(4)–C(5)–C(10)	114.3(3)	C(8)–C(14)–C(15)	115.4(3)
C(10)–C(5)–C(6)	121.3(3)	C(8)–C(14)–C(32)	110.4(3)
C(5)–C(6)–C(7)	125.9(4)	C(15)–C(14)–C(32)	108.5(3)
C(6)–C(7)–C(8)	112.3(3)	C(14)–C(15)–C(16)	103.7(3)
C(7)–C(8)–C(9)	107.5(3)	C(15)–C(16)–C(17)	107.7(3)
C(7)–C(8)–C(14)	114.0(3)	C(16)–C(17)–C(13)	103.3(3)
C(14)–C(8)–C(9)	111.7(3)	C(16)–C(17)–C(20)	111.7(3)
C(8)–C(9)–C(10)	111.9(3)	C(16)–C(17)–O(17)	112.9(3)
C(8)–C(9)–C(11)	115.8(3)	C(13)–C(17)–C(20)	113.3(3)
C(10)–C(9)–C(11)	113.8(3)	C(13)–C(17)–O(17)	108.9(3)
C(9)–C(10)–C(1)	115.4(3)	C(20)–C(17)–O(17)	106.9(3)
C(9)–C(10)–C(5)	110.7(3)	C(17)–C(20)–C(21)	117.2(4)
C(1)–C(10)–C(5)	109.6(3)	C(17)–C(20)–O(20)	121.6(3)
C(9)–C(11)–O(11)	120.8(3)	C(21)–C(20)–O(20)	121.2(4)

X-*Ray Crystallography*.—Small needle-shaped crystals of the 17α-hydroxy-20-ketone (3) were obtained by slow crystallization from chloroform–methanol–benzene, with M = 374.50. Crystals were monoclinic, space group $P2_1$, a = 12.80(1), b = 7.52(1), c = 10.81(1) Å, β = 97.18(4)°, Z = 2, D_m = 1.20, and D_c = 1.21 g cm^{-3}. Data were collected for a crystal of dimensions 0.08 × 0.10 × 0.15 mm^3. A total of 1 563 independent reflections were measured by the ω—2θ scan mode, and data collected to $2\theta_{max.}$ 46°. Background was measured for half the total scan time on each side of the reflection. 148 reflections were considered to be unobserved with $I < 2\sigma$. The intensities were corrected for Lorentz and polarization factors but no absorption corrections were made.

The structure was solved by direct methods, by use of the multisolution approach as used in MULTAN 74,[3] and refined by full-matrix least-squares methods. Hydrogen atoms were located in a difference map and their positions refined. The thermal factors for the hydrogen atoms were kept constant at the value of the overall temperature factor estimated during structure-factor normalization. All other atoms were refined anisotropically. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ with $1/\sigma_F^2$ weights. The final R index is 0.037 (R' 0.039). The scattering factors of ref. 4 were used for the hydrogen atoms and those for all other atoms were generated from the analytical expressions of ref. 5. All the Fourier and refinement calculations were done with the crystallographic programmes of ref. 6. Final co-ordinates are listed in Table 1, bond distances and angles in Table 2. Standard deviations are based solely on the least-squares calculations. Structure factors, thermal parameters, and torsion angles are listed in Supplementary Publication No. SUP 21867 (16 pp., 1 microfiche).*

RESULTS AND DISCUSSION

Crystal and Molecular Structure of the 17α-*Hydroxy*-20-*ketone* (3).—The configuration of the molecule and the thermal vibration ellipsoids of the atoms are shown in Figure 1 which also shows the atom numbering system used in the X-ray analysis. The C–H distances are in the range 0.89—1.11 Å and the distances O(2)–H(24) and O(4)–H(6) are 0.99(4) and 0.78(4) Å, respectively.

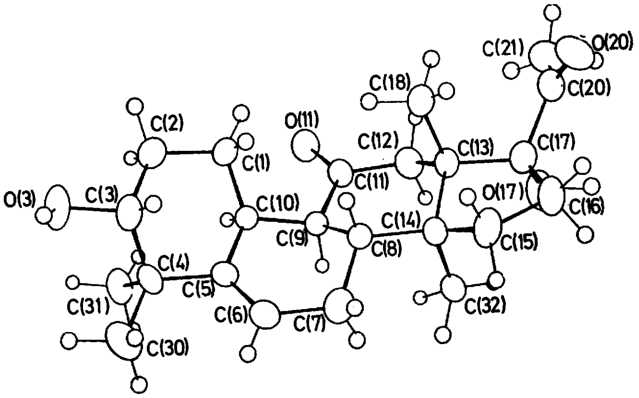

FIGURE 1 Structure and configuration of the refined model. The ellipsoids drawn for the non-hydrogen atoms represent surfaces enclosing 50% of the Gaussian thermal distributions

The torsion angles show that rings A and B have normal chair and half chair conformations, respectively. Ring C is a flattened chair. The distortion of ring C is compared with that found for other 11-oxo-steroids in Table 3 (see later). Ring D has a half chair conformation and the torsion angle C(12)–C(13)–C(14)–C(8) in ring C is opened to 66.9°, the corresponding angle C(17)–C(13)–C(14)–C(15) in ring D being closed to 45.8°. This observation is in agreement with the theoretical model of Bucourt and Hainaut.[7] The conformation of the 17β-acetyl side-chain is given by the torsion angle C(16)–C(17)–C(20)–C(21) of 158.4°, which is equivalent to θ 201.6° as defined by Allinger *et al.* (see later).

The hydrogen-bond network is centred on O(3), which is the donor in an O–H ··· O bond to atom O(20) at ($1 - x$, $\frac{1}{2} + y$, $1 - z$), length 2.860(5) Å, through H(6) and as an acceptor in a similar bond from atom O(17) at ($1 + x, y, z$), length 2.772(4) Å, through H(24).

Conformation of the 17β-*Acetyl Side-chain of the* 17α-*Hydroxy*-20-*ketone* (4).—The i.r. spectrum of the 3α-acetoxy- 17α-hydroxy-20-ketone (4) in dilute solution in carbon tetrachloride showed bands at 3 610 and 3 495 cm^{-1} (Δν 115 cm^{-1}) and the expected shift of the 20-carbonyl band to lower wavenumber giving clear evidence that the side-chain is present in an intramolecular hydrogen bonded and an unbonded form in a ratio of 1.5 : 1. Similar results have been obtained previously from 17α-hydroxypregnan-20-ones.[8,9]

Allinger *et al.*[10] calculated the conformational energy of the β-acetyl side-chain of pregnan-20-one as a function of the torsional angle θ formed by carbon atoms 16, 17, 20, and 21 (*cf.* diagram in ref. 10). Legrand[11] modified the conformational energies for 17α-hydroxypregnan-20-one. The most stable conformer corresponds to θ *ca.* 210°, a conclusion in good agreement with X-ray structure analysis[12] and the strong positive Cotton effect observed in o.r.d. and c.d. spectra of 17α-hydroxypregnan-20-ones in polar solvents.[13,14] A second energy-minimum at θ *ca.* 60° is *ca.* 3.5 kcal mol^{-1} higher, but is stabilized by intramolecular hydrogen-bonding between the 17α-hydroxy-group and the 20-carbonyl-group which it eclipses. Octant projections predict a strong negative Cotton effect for this conformer. In non-polar solvents a mixture of both conformers is present and was observed in o.r.d.[9] and c.d.[11] studies. The c.d. curve of 3β-acetoxy-17α-hydroxypregnan-20-one in cyclohexane is a bisignate[15] (double-humped) curve with $\Delta\varepsilon_{max.}$ (315 nm) 0.59 and $\Delta\varepsilon_{max.}$ (280 nm) −1.04. In ethanol solution the intramolecular hydrogen-bond is broken and only a single c.d. curve, $\Delta\varepsilon_{max.}$ (300 nm) 2.92 was observed.[16]

The conformation of the 17β-acetyl side-chain of the 17α-hydroxy-20-ketone (4) in solution can be predicted.

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* See Notice to Authors No. 7. in *J.C.S. Perkin II*, 1975, Index issue.

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Dreiding molecular models show that the extra methyl group at C(14) and the 19-nor-10α-stereochemistry, is not expected to lead to any significant deviation from the Allinger–Legrand conformational energy–torsion angle θ relationships. Accordingly a stable conformer at θ *ca.* 210° and a less stable conformer at θ *ca.* 60° can be expected and the observation that the c.d. curve of the 17α-hydroxy-20-ketone (4) is bisignate in carbon tetrachloride (Figure 2) and hexane and a single positive curve in methanol, is compatible with the predicted conformations.

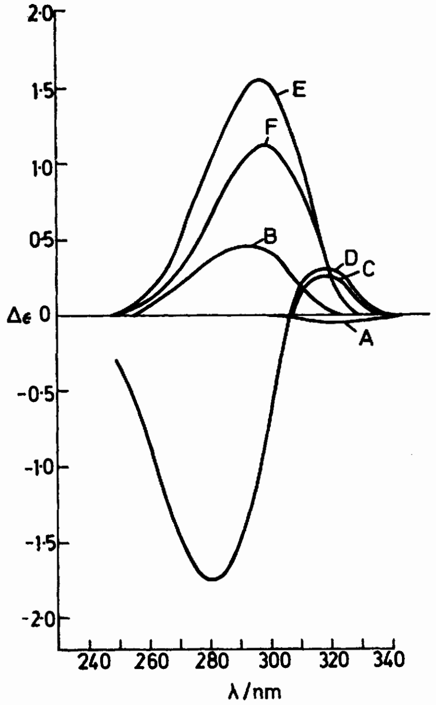

FIGURE 2 C.d. curves of: (A) 4,4,14α-trimethyl-19-nor-10α-pregn-5-en-11-one in carbon tetrachloride, (B) 4,4,14α-trimethyl-19-nor-10α-pregn-5-en-11-one in methanol, (C) 17α-hydroxy-11,20-dione (4) in carbon tetrachloride, (D) 17α-hydroxy-20-carbonyl chromophore in carbon tetrachloride, (E) 17α-hydroxy-11,20-dione (4) in methanol, and (F) 17α-hydroxy-20-carbonyl chromophore in methanol

The influence of solvent on the Cotton effect of the 11-carbonyl must, however, also be taken into consideration. The c.d. curve (Figure 2) of 4,4,14α-trimethyl-19-nor-10α-pregn-5-en-11-one showed $\Delta\varepsilon_{max.}$ (293 nm) 0.45 in methanol, $\Delta\varepsilon_{max.}$ (318 nm) −0.05 in carbon tetrachloride, and $\Delta\varepsilon_{max.}$ (292 nm) 0.31 in hexane, and therefore difference in amplitude and even in sign is evident. A solvent effect, but without change in sign, is also observed in the conformationally related 5α,6α-epoxy-4,4,14α-trimethyl-19-nor-10α-pregnan-11-one,[17] $\Delta\varepsilon_{max.}$ (292 nm) 0.79 in carbon tetrachloride and $\Delta\varepsilon_{max.}$ (290 nm) 1.23 in methanol. Although the values are relatively small compared to those observed for 11,20-diketones in this series (see later), a possible explanation for this solvent effect could be (*a*) asymmetric solvation of the 11-carbonyl chromophore or (*b*) a conformational change in ring C. In a detailed study[18] of steroidal ketones in methanol and hexane, only a small solvent effect was found for carbonyl groups in non-terminal rings, *e.g.* 5α-pregnan-11-one ($\Delta\varepsilon_{max.}$ 0.20 in methanol and 0.22 in hexane) and 5β-pregnan-11-one ($\Delta\varepsilon_{max.}$ 0.3 in methanol and 0.35 in hexane). Low-temperature studies have, however, suggested that ring C is conformationally mobile.[19] A study[20] of several 11-oxo-steroids differing in configuration at C(9) and C(10) showed that, on cooling solutions to −188 °C, the Cotton effect is altered towards that of the formal enantiomer; a change of sign is only observed if the Cotton effect at room temperature is rather small. The alteration in ellipticity was related to an equilibrium between different conformers in ring C, the non-bonded interaction between the 11-oxo-group and hydrogens at C(1) being relieved by a flattening of ring C.

A comparison of the internal ring C-torsional angles as determined by *X*-ray analysis of the 17α-hydroxy-20-ketone (3) with that of 16β-bromo-3β,17α-dihydroxy-5α-pregnane-11,20-dione[21] and a cucurbitacin (daticoside) derivative (Δ^5,9β-Me,11-ketone)[22] is shown in Table 3.

TABLE 3

Comparison of ring C internal torsional angles (°)

	(A)[a]	(B)[b]	(C)[c]
C(14)–C(8)–C(9)–C(11)	−53.2	−41	−38.1
C(8)–C(9)–C(11)–C(12)	54.0	43	33.0
C(9)–C(11)–C(12)–C(13)	−55.0	−52	−42.6
C(11)–C(12)–C(13)–C(14)	55.9	60	58.4
C(12)–C(13)–C(14)–C(8)	−62.2	−70	−66.9
C(13)–C(14)–C(8)–C(9)	59.9	59	55.1

[a] 16β-bromo-3β,17α-dihydroxy-5α-pregnane-11,20-dione.
[b] Daticoside derivative. [c] 19-Nor-10α,11-ketone (3).

This clearly shows that ring C is considerably more distorted in the 17α-hydroxy-20-ketone (3) than in the other two 11-ketones. A severe non-bonded interaction between the 11-oxo-group and the C(1)–αH is responsible for this conformational change and can be relieved by a change of torsional angles around C(9).

A computer-drawn octant projection of the *X*-ray structure of the 17α-hydroxy-11,20-dione (3) down the O=C(11) bond is shown in Figure 3. The flattening of ring C results in a molecule where most of the atoms are either cancelling or are near-nodal planes. A small positive Cotton effect can, however, be predicted since the C(13)-methyl group in a positive, upper left, rear octant has a stronger perturbing effect than the C(1)–C(10) bond in a negative, upper right, rear octant. It is evident that it requires only a small change in this conformation to change the balance in favour of a small

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[17] J. R. Bull, P. R. Enslin, and H. H. Lachmann, *J. Chem. Soc.* (*C*), 1971, 3929.

[18] D. N. Kirk, W. Klyne, and S. R. Wallis, *J. Chem. Soc.* (*C*), 1970, 350.

[19] Ref. 13, p. 125.

[20] G. Snatzke and D. Becher, *Tetrahedron*, 1964, **20**, 1921.

[21] J. M. Ohrt, A. Cooper, and D. A. Norton, *Acta Cryst.*, 1969, **B25**, 41.

[22] R. J. Restivo, R. F. Bryan, and S. M. Kupchan, *J.C.S. Perkin II*, 1973, 892.

negative Cotton effect. A change in solvent might well be responsible for such a change in a conformationally mobile system. A change of ring C conformation will also lead to a slightly different orientation of the Δ^5-bond relative to the 11-carbonyl group in terms of the pathway *via* the intervening C–C bonds (*cf.* Hudec and co-workers [23]) and this might also have an influence on the Cotton effect of the 11-carbonyl chromophore.

Whatever the exact conformation of ring C in solution may be and the reason for the solvent effect, the most important consideration is that observed 11-carbonyl Cotton effects are relatively small compared to those of the 20-carbonyl group. The c.d. spectra of the 11,20-dione (2) was determined in methanol and carbon tetrachloride and gave (after correction for the 11-carbonyl Cotton effect), $\Delta\varepsilon_{\max}$ (286 nm) 2.59 in methanol and $\Delta\varepsilon_{\max}$ (290 nm) 2.72 in carbon tetrachloride. It can thus be assumed with confidence that the 20-carbonyl group shows no abnormal solvent effect. In Figure 2 are also presented the c.d. curves of the isomeric 17-hydroxy-20-chromophores obtained by subtracting the c.d. curves of 4,4,14α-trimethyl-19-nor-10α-pregn-5-en-11-one.

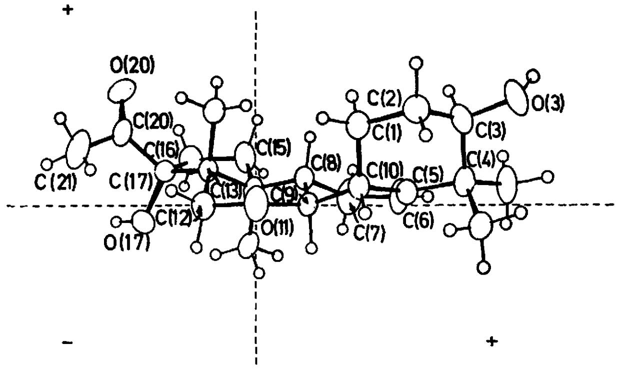

FIGURE 3 Octant projection of the *X*-ray structure of the 17α-hydroxy-11,20-dione (3) down the O=C(11) bond

The 17α-hydroxy-20-oxo-chromophore gave in methanol, $\Delta\varepsilon_{\max}$ (298 nm) 1.09. The positive Cotton effect is in close agreement with a side-chain conformation at θ *ca.* 210° and with the conformation determined by *X*-ray analysis. In carbon tetrachloride solution a bisignate curve, $\Delta\varepsilon_{\max}$ (319 nm) 0.31 and $\Delta\varepsilon_{\max}$ (280 nm) −1.77 is found. Similar results were obtained in hexane solution, *viz.*, $\Delta\varepsilon_{\max}$ (320 nm) 0.18 and $\Delta\varepsilon_{\max}$ (280 nm) −2.06. Intramolecular hydrogen bonding therefore, stabilizes a second conformer at θ *ca.* 60°. Compared with the values reported (see earlier) for 17α-hydroxypregnan-20-one, the population of the hydrogen bonded conformer is slightly higher in the 17α-hydroxy-20-ketone (4).

Conformation of the 17α-*Acetyl Side-chain of the* 17β-*Hydroxy*-20-*ketone* (5).—The calculations of Allinger *et al.*[10] for the conformational energy of 17α-acetyl-pregnan-20-one predicted an energy minimum between θ *ca.* 90 and 150°. A second energy-minimum at θ *ca.* 300° is expected to be sufficiently high in energy not to contribute to the dipole moment observed at room temperature for 5β,17α-pregnane-3,20-dione. The strongly negative Cotton effect of 17β-hydroxypregnan-20-ones [13] is consistent with a side-chain conformation between θ *ca.* 120 and 150°. The c.d. curve of the 17β-hydroxy-20-ketone (5) showed Cotton effects (Figure 2, corrected) of $\Delta\varepsilon_{\max}$ (290 nm) −0.75 in methanol and $\Delta\varepsilon_{\max}$ (295 nm) −1.28 in carbon tetrachloride. Octant projections predict a side-chain conformation in both polar and non-polar solvents of near θ 150° in which the non-bonded interaction between the C(14)-methyl and the C(20)-carbonyl groups is somewhat relieved. A second conformer at θ *ca.* 300° is clearly impossible as a result of the added high-energy C(21)(Me) ··· C(14)(Me) interaction on the α-face of the molecule. No evidence for such a conformer was therefore obtained from i.r. and c.d. spectra in different solvents.

Finally, the n.m.r. results of the two isomers is discussed briefly although it did not contribute to a solution of the conformational problem. In 4,4,14α-trimethyl-19-nor-10α-pregnan-11-one and the corresponding 11,20-dione the C(13)-methyl group resonates at δ 0.65 as a doublet, J 1 Hz, due to long-range coupling with the axial proton at C(12).[24] In the 17α-hydroxy-20-ketone (4) the methyl doublet is observed at δ 0.66 in carbon tetrachloride and δ 0.60 in deuteriomethanol. The near-identity of the C(13)-methyl resonances in the two solvents, despite 17-acetyl conformational differences, can be explained if the methyl group lies near the boundary of the shielding–deshielding cone of the carbonyl group, a result consistent with side-chain conformers at θ *ca.* 210 and 60°. The C(13)-methyl group ' observes ' in each conformer only a different face of the carbonyl π-system. The 17α-hydroxy-group is in a *quasi*-diaxial orientation to the C(14)-methyl group and is responsible for a downfield shift of the methyl resonance to δ 1.32. In the 17α-acetyl-17β-hydroxy-isomer the resonance of the C(13)-methyl group is shifted downfield to δ 1.00 by the 17β-hydroxy-group.

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[6/813 *Received*, 26*th April*, 1976]

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