SHORT PAPER

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The conformation of the side chain of 21-alkylpregnanes†

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The X-ray crystal structures of some 21-alkylpregnanes have been determined and the effects of a 16α,17α-epoxide and 21-methyl group on the conformation of the side chain are discussed.

Keywords: 21-alkylpregnanes, 16α,17α-epoxide, 21-methyl

The conformation of the pregnane side chain relative to ring D is of considerable importance in the context of the steroid binding to the progestogen receptor.[1] In an analysis of 85 pregnane crystal structures it was found[2] that for 81 of these structures the C(16)–C(17)–C(20)–0(20) torsion angle lay between 0° and 46°. These angles were consistent with circular dichroism and NMR data suggesting that the crystal structure data also reflected the solution conformation. However, a small number of 16α,17α-epoxides have been examined[3–5] in which the pregnane side chain takes up a different conformation in which the carbonyl group has rotated about the C(17)–C(20) bond so that the C(20)–O(20) bond now almost eclipses the C(13)–C(17) bond and there is a large C(16)–C(17)–C(20)–O(20) torsion angle. There have been few studies on C–21 alkylated pregnanes possibly because early studies with 21-methyl and 21-ethylprogesterone showed that they had little progestational activity.[6] Further studies concentrated on 17α-alkyl and 16α,17α-dialkyl pregnanes. A 19-norsteroid, promegestone, 17α,21-dimethyl-19-norpregna-4,9-diene-3, 20-dione and its metabolite trimegestone, have recently attracted interest because of their binding to the progestogen receptor.[7]

In this paper, we report the influence of methylation at C-21 on the conformation of the pregnane side chain in steroids with and without a 16α,17α-epoxide. The substrates were prepared by the methylation of pregnenolone (**1**) and 16α,17α-epoxypregnenolone with excess sodium hydride and methyl iodide.[8] This gave 21,21-dimethyl-3β-methoxypregn-5-en-20-one (**2**), 21,21-dimethyl-16α,17-epoxy-3β-methoxypregn-5-en-20-one (**3**) and its 21,21,21-trimethyl analogue (**4**). The 21,21-dimethyl and 21,21,21-trimethyl-16α,17-epoxides were separated by chromatography. The 5,6-enes were epoxidised with the solid phase system potassium permanganate-ferrous sulfate to give the 5β,6β-epoxides (**5**) and (**6**).[9]

The crystal structures were determined and are shown in Figs 1–5. The conformation of the side chain reveals two interesting features. In the absence of the 16α,17α-epoxide the side chain took up a conformation in which there is a relatively low C(16)–C(17)–C(20)–O(20) torsion angle (see Table 1). On the other hand in the presence of the 16α,17α-epoxide the same angle is much larger and the carbonyl group takes up a conformation which is almost *trans* to the lone pairs of the epoxide oxygen. In both series the isopropyl group took up a conformation in which there was a gauche interaction between the carbonyl group and a methyl group with the isopropyl hydrogen lying *trans* to the carbonyl group. In **2** the torsion

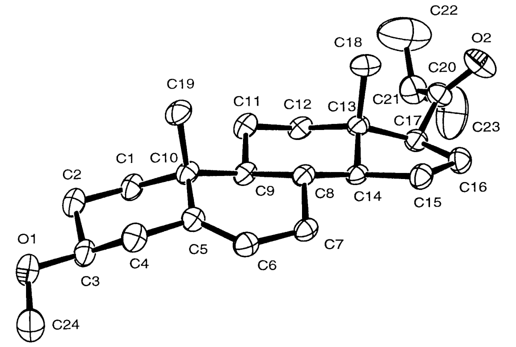

Fig. 1 X-ray crystal structure of compound **2**.

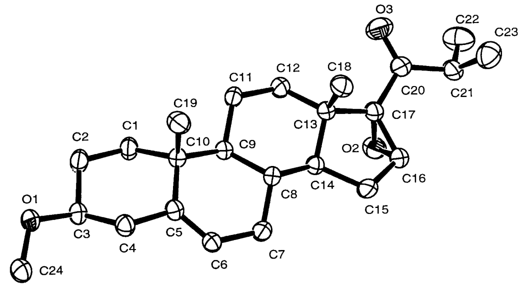

Fig. 2 X-ray crystal structure of compound **3**.

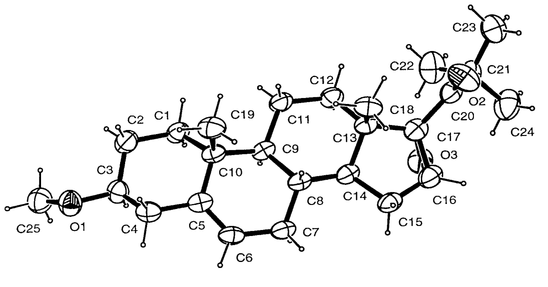

Fig. 3 X-ray crystal structure of compound **4**.

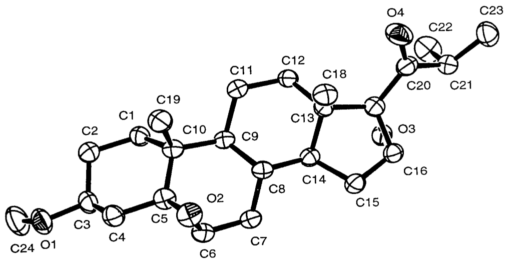

Fig. 4 X-ray crystal structure of compound **5**.

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* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

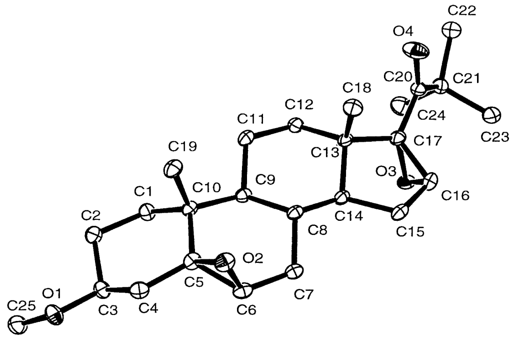


Fig. 5 X-ray crystal structure of compound **6**.

Table 1 Torsion angles (in degrees)

Compound	C(16)–C(17)–C(20)–O(20)	C(16)–C(17)–C(20)–C(21)
1	–27*	156*
2	–22	156
3	–167	13
4	–79	99
5	–128	55
6	–107	75

* The crystal structure of **1** was redetermined to obtain this figure.

angle H(21)–C(21)–C(20)–O(20) is –166° and in **3** it is –162°. The rotation of the isopropyl group has followed that of the carbonyl group.

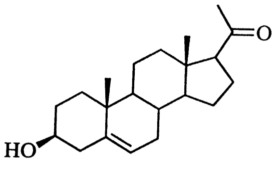
The geometry of isobutyraldehyde (2-methylpropanal) provides a simple model for this portion of the molecule.[10] Electron diffraction studies have shown that in the gas phase it predominantly (*ca*90%) adopts a conformation in which there is a gauche interaction between the carbonyl oxygen and a methyl group, *i.e.* a *trans* relationship between the hydrogen atom of the isopropyl group and the carbonyl oxygen. Although the original authors sought an explanation in terms of a methyl group:oxygen interaction, other rationalisations have been made[11] in terms of a hyperconjugative stabilisation involving an interaction between the C–H and the LUMO of the carbonyl group. A similar interaction might account for the steroid conformation. An interaction between the lone pairs of the epoxide oxygen and the carbonyl LUMO might favour the carbonyl group conformation which was observed in the presence of the 16α,17α-epoxide.

The conformation of ring A of the 5β,6β-epoxy steroids also provides a feature of interest. In the 5α-series a 3β-substituent is an equatorial substituent on ring A. However in a 5β-steroid with the normal steroidal A/B *cis* ring junction, it becomes an axial substituent on ring A. The X-ray structures of the 5β, 6β-epoxides show that the *cis* A/B ring junction adopts a non-steroid like conformation in which the 3β substituent retains an equatorial conformation comparable to that found for the 5α-steroids. It is possible that the strain imposed by the epoxide ring favours this conformation.

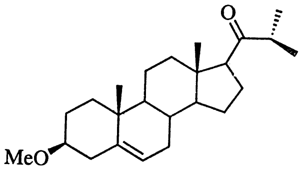
Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80°C. Extracts were dried over sodium sulfate. ^{1}H NMR spectra were determined at 300 MHz for solutions in deuteriochloroform. IR spectra were determined as nujol mulls. The preparation of compound **2** has been described previously.[8]

Methylation of 16α,17α-epoxypregnenolone: 16α,17α-Epoxy-pregnenolone (1.5g) in tetrahydrofuran (60 cm^3) was added to a suspension of sodium hydride (1g, 60% in mineral oil) in tetrahydrofuran (15 cm^3) and treated with methyl iodide (10 cm^3) at 0° for 14 h. The solution was then acidifed with dil. hydrochloric acid, concentrated in vacuo and the residue taken up in ether (300 cm^3). The extract was washed with water, aqueous sodium hydrogen carbonate, brine and dried. The solvent was evaporated and the residue chromatographed on silica.



1



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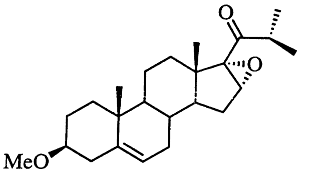

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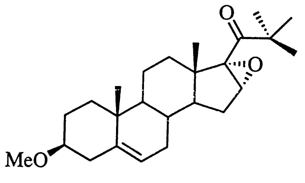

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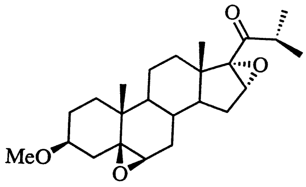

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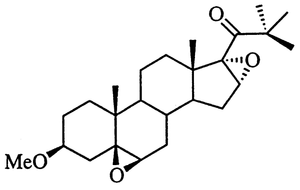

6

Elution with 2% ethyl acetate:light petroleum gave 21,21-dimethyl-16α,17α-epoxy-3β-methoxypregn-5-en-20-one (**3**) (420 mg) which crystallised from methanol as needles, m.p. 140–142°C, (Found M$^+$ 372.266 $C_{24}H_{36}O_3$ requires M$^+$ 372.266); ν_{max}/cm^{-1} 1692; δ_H 0.99 and 1.03 (each 3H, s, 18- and 19-H), 0.97 and 1.02 (each 3H, d, *J* 6.8Hz, 21-Me$_2$), 0.75–2.20 (17H, overlapping multiplets), 2.64 (1H, septet, *J* 6.8 Hz, 21-H), 3.03 (1H, tt, *J* 5.5 and 11 Hz, 3-H), 3.32 (3H, s, OMe), 3.60 (1H, s, 16-H), 5.32 (1H, m, 6-H). Further elution gave 16α,17α-epoxy-3β-methoxy-21,21,21-trimethylpregn-5-en-20-one (**4**) (500 mg) which crystallised from methanol as needles, m.p. 144–146°C, (Found: M$^+$ 386.285 $C_{25}H_{38}O_3$ requires 386.282); ν_{max}/cm^{-1} 1699; δ_H 0.98 and 1.01 (each 3H, s, 18- and 19-H), 1.14 (9H, s, 21-Me$_3$), 0.75–2.20 (17H, overlapping multipletes), 3.03 (1H, tt, *J* 5.5 and 11 Hz, 3-H), 3.32 (3H, s, OMe), 3.42 (1H, s, 16-H), 5.32 (1H, m, 6-H).

Epoxidation reactions: 21,21-Dimethyl-16α,17α-epoxide-3β-methoxypregn-5-en-20-one (**3**) (170 mg) in dichloromethane (5 cm^3) and *t*-butanol (0.5 cm^3) was added to a finely ground mixture of potassium permanganate (2 g) and ferrous sulfate (1 g) containing water (0.1 cm^3). The mixture was stirred for 2 h. filtered and the solvent evaporated. The residue was chromatographed on silica to give 5β,6β: 16α,17α-diepoxy-21,21-dimethyl-3β-methoxypregnan-20-one (**5**) (150 mg) as needles, m.p. 150–152°C, (Found: M$^+$ 388.262 $C_{24}H_{36}O_4$ requires 388.261); ν_{max}/cm^{-1} 1703; δ_H 0.97 and 0.98 (each 3H, s, 18- and 19-H), 0.95 and 0.98 (each 3H, d, *J* 6.8Hz, 21-Me$_2$), 0.75–2.10 (17H, overlapping multiplets), 3.04 (1H, d, *J* 3 Hz, 6-H), 3.21 (1H, tt, *J* 5.5 and 11 Hz, 3-H), 3.32 (3H, s, OMe), 3.61 (1H, s, 16-H). Under similar conditions 16α,17α-epoxy-3β-methoxy-21,21,21-trimethylpregn-5-en-20-one (**4**) (340 mg) gave 5β,6β: 16α,17α-diepoxy-3β-methoxy-21,21,21-trimethyl-pregnan-20-one (**6**) (310 g) as needles, m.p. 112–115°C, (Found: M$^+$ 402.278 $C_{25}H_{38}O_4$ requires 402.278); ν_{max}/cm^{-1} 1692; δ_H 0.97 (6H, s, 18- and 19-H), 1.13 (9H, s, 21–Me$_3$), 0.75–2.20 (17H, overlapping multiplets), 3.03 (1H, m, 6-H), 3.21 (1H, tt, *J* 5.5 and 11 Hz, 3-H), 3.30 (3H, s, OMe), 3.42 (1H, s, 16-H).

X-ray crystallographic data and structure determinations: Compound **2**, $C_{24}H_{38}O_2$, M_r 358.84, orthorhombic, space group $p2_12_12_1$ (No.19), a = 9.0979(10), b = 14.7270(9), c = 15.8362(17)Å, $\alpha = \beta = \gamma = 90°$, V = 2121.8(4)Å^3, z = 4, $D_{calc.}$ = 1.12 g cm^{-3}, μ = 0.07 mm^{-1}, F (OOO) = 792. Data were collected using a crystal of size 0.20 × 0.5 × 0.05 mm^3 on a kappaCCD diffractometer. A total of 11959 reflections were collected for $3.78 < \theta < 21.99°$ and $-9 \le h \le 9$, $-14 \le k \le 15$, $-16 \le l \le 15$. There were 2581 independent reflections and 1729 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refinded by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were $(I > 2\sigma(I))$ R_1 = 0.060, wR_2 = 0.149 and (all data) R_1 = 0.104, wR_2 = 0.178. The goodness-of-fit on F^2 was 0.926 and the largest difference peak and hole was 0.13 and –0.13eÅ^{-3}.

Compound **3**, $C_{24}H_{36}O_3$, M_r 372.53, orthorhombic, space group $P2_12_12_1$ (No.19), a = 6.2604(2), b = 13.5491(5), c = 24.6295(7)Å, $\alpha = \beta = \gamma = 90°$, V = 2084.1(1)Å^3, z = 4, $D_{calc.}$ = 1.18 g cm^{-3}, μ = 0.08 mm^{-1}, F(OOO) = 816. Data were collected using a crystal of size 0.30 × 0.30 × 0.20 mm^3 on a KappaCCD diffractometer. A total of 14044 reflections were collected for $3.90 < \theta < 27.87°$ and $-6 \le h \le 8$, $-17 \le k \le 16$, $-27 \le l \le 32$. There were 4961 independent reflections and 3626 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 Windows. The final R indices were $[I > 2\sigma(I)]$ R_1 = 0.054, wR_2 = 0.116 and (all data) R_1 = 0.084, wR_2 = 0.128. The goodness-of-fit on F^2 was 1.04 and the largest difference peak and hole was 0.20 and -0.19eÅ^{-3}.

Compound **4**, $C_{25}H_{38}O_3$, M_r 386.55, monoclinic, space group $P2_1$ (No.4), a = 1204088(12), b = 6.3434(4), c = 14.7810(16)Å, $\alpha = \gamma = 90°$, β = 108.642°, V = 1096.5(2)Å^3, z = 2, $D_{calc.}$ = 1.17 g cm^{-3}, μ = 0.08 mm^{-1}, F(OOO) = 424. Data were collected using a crystal of size 0.4 × 0.4 × 0.1 mm^3 on a KappaCCD diffractometer. A total of 6354 reflections were collected for $3.85 < \theta < 25.07°$ and $-14 \le h \le 13$, $-7 \le k \le 7$, $-15 \le l \le 17$. There were 3697 independent reflections and 3042 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawing used ORTEP-3 for Windows. The final R indices were $[I > 2\sigma(I)]$ R_1 = 0.052, wR_2 = 0.113 and (all data) R_1 = 0.069, wR_2 = 0.122. the goodness-of-fit on F^2 was 1.071 and the largest difference peak and hole was 0.14 and -0.14eÅ^{-3}.

Compound **5**, $C_{24}H_{36}O_4$, M_r 388.53, orthorhombic, space group $P2_12_12_1$ (No.19), a = 6.2520(3), b = 16.6018(8), c = 20.6191(13)Å, $\alpha = \beta = \gamma = 90°$, V = 2140.1(2)Å^3, z = 4, $D_{cala.}$ = 1.21 g cm^{-3}, μ = 0.08 mm^{-1}, F(OOO) = 848. Data were collected using a crystal of size 0.4 × 0.3 × 0.3 mm^3 on a KappaCCD diffractometer. A total of 7450 reflections were collected for $3.81 < \theta < 25.01°$ and $-7 \le h \le 6$, $-16 \le k \le 19$, $-24 \le l \le 21$. There were 3656 independent reflections and 2770 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were $[I > 2\sigma(I)]$ R_1 = 0.049, wR_2 = 0.108 and (all data) R_1 = 0.076, wR_2 = 0.121. The goodness-of-fit on F^2 was 1.016 and the largest difference peak and hole was 0.16 and –0.17eÅ^{-3}.

Compound **6**, $C_{25}H_{38}O_4$, M_r 402.55, orthorhombic, space group $P2_12_12_1$ (No.19), a = 6.3904(3), b = 15.6270(11), c = 22.7332(16)Å, $\alpha = \beta = \gamma = 90°$, V = 2270.2(2)Å^3, z = 4, $D_{calc.}$ = 1.18 g cm^{-3}, μ = 0.08 mm^{-1}, F(OOO) = 880. Data were collected using a crystal of size 0.3 × 0.2 × 0.2 mm^3 on a KappaCCD diffractometer. A total of 6333 reflections were collected for $3.75 < \theta < 22.97°$ and $-7 \le h \le 6$, $-15 \le k \le 17$, $-22 \le l \le 24$. There were 3099 independent reflections and 2564 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were $(I > 2\sigma(I))$ R_1 = 0.045, wR_2 = 0.102 and (all data) R_1 = 0.060, wR_2 = 0.11. The goodness-of-fit on F_2 was 1.018 and the largest difference peak and hole was 0.14 and -0.14eÅ^{-3}. The crystallographic data will be deposited with the Cambridge Crystallographic Data Centre.

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