Baeyer–Villiger Oxidation of 19-Substituted Steroidal Ketones: Structure of Rearranged Products Involving Participation of the 19-Substituent

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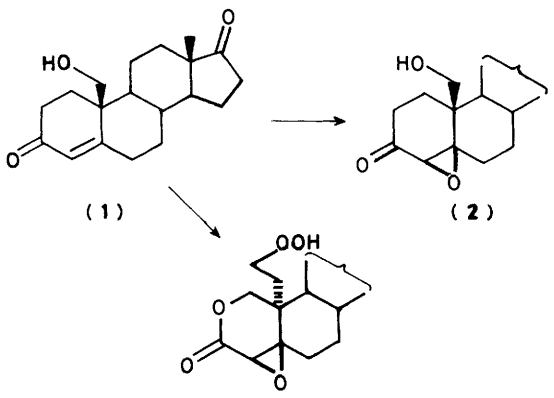
Baeyer–Villiger reactions of 19-hydroxy-4β,5-epoxy-5β-androstane-3,17-dione (**2**), 19-hydroxy-4α,5-epoxy-5α-androstane-3,17-dione (**13**), 17β,19-dihydroxy-5β-androstan-3-one (**18**), and 19-hydroxyandrost-4-ene-3,17-dione (**1**) are reported. When carbonyl functions are present at C-3 and C-17, Baeyer–Villiger rearrangement occurs preferentially at C-17. The rearrangement product obtained from the Δ^4-3-ketone (**1**) was found to be 5β-formyl-5,19-dihydroxy-17-oxo-A-nor-3,5-seco-5β-androstane-3-carboxylic acid 5,19(*R*) lactol 3,5-lactone (**27**).

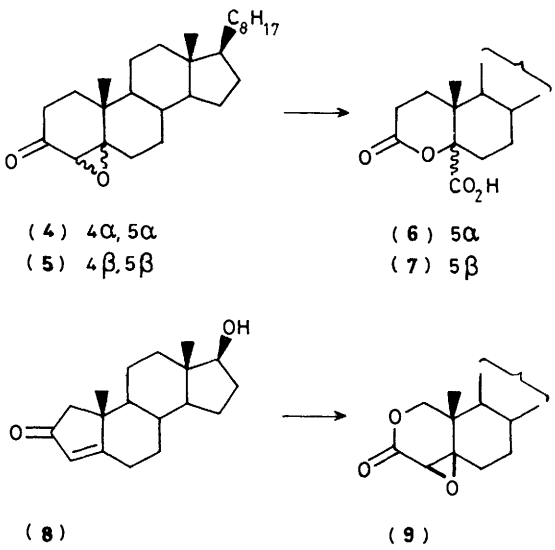
In a previous paper,[1] we reported that the reaction of 19-hydroxyandrost-4-ene-3,17-dione (**1**) with basic hydrogen peroxide in methanol led to the 4β,5β-epoxide (**2**) or to the hydroperoxide (**3**) depending on the reaction conditions used (Scheme 1). The formation of the hydroperoxide (**3**) is explained by the occurrence of a Baeyer–Villiger rearrangement



Scheme 1.

once the epoxide (**2**) has been formed. This reaction provides, in high yield and in one step, steroids with the unnatural[2] or 'retro' configuration (*i.e.* 9β, 10α). Such rearrangements with hydrogen peroxide have been reported in steroids which are unsubstituted at C-19. For example, Reusch and LeMahieu[3] reported that the oxidation of 4α,5-epoxy-5α-cholestan-3-one (**4**) or 4β,5-epoxy-5β-cholestan-3-one (**5**) with alkaline hydrogen peroxide gave the lactone carboxylic acids (**7**) and (**6**), respectively (Scheme 2). Levine[4] reported the formation of the epoxy lactone (**9**), as the major product on alkaline hydrogen peroxide oxidation of A-nor-17β-hydroxyandrost-4-en-3-one (**8**), presumably *via* the intermediate epoxy ketone (Scheme 2). Also, the oxidation of the propionate ester of testosterone with hydrogen peroxide in the presence of catalytic amounts of selenium dioxide was reported[5] to yield a 7-membered B-ring actone.

Since the Baeyer–Villiger reaction is highly dependent both on the nature of the ketone and of the oxidizing agent, we decided to study in more detail the influence of a 19-

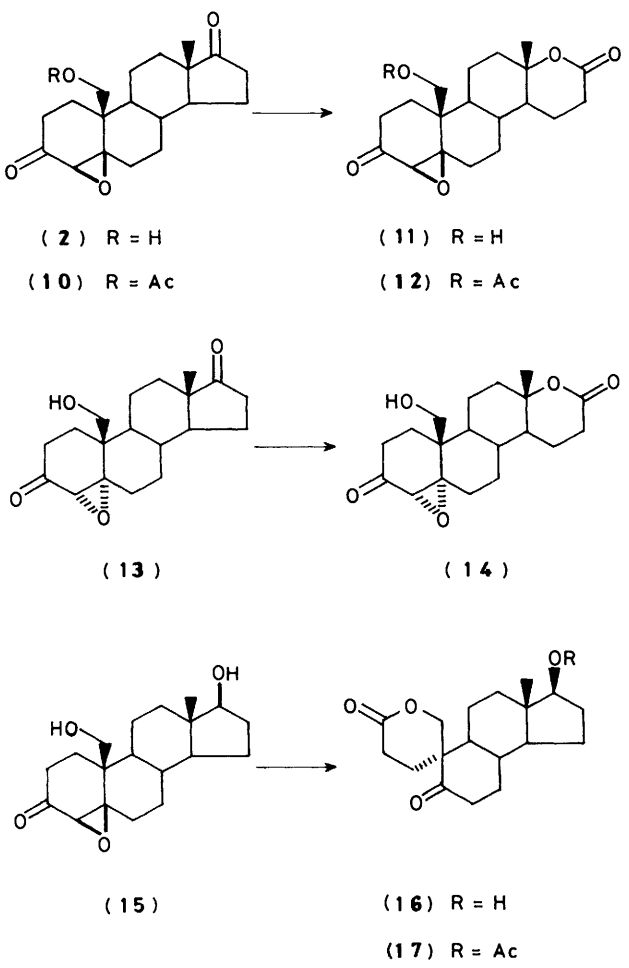


Scheme 2.

hydroxymethyl group in reactions with *m*-chloroperbenzoic acid (MCPBA). In this paper, we report on the influence of the 19-hydroxy group on the products of MCPBA (Scheme 3) oxidation of androgens with isomeric epoxide functions at C-4, C-5, a saturated A-ring, and unsaturation at C-4, C-5.

Results and Discussion

Reaction of C-4, C-5 *Epoxides* (**2**) *and* (**13**) *with MCPBA.*— Treatment of the 4β,5β-epoxy diketone (**2**) with MCPBA for 4 days afforded only one product (60% yield based on 29% recovery of starting material). This compound was identified as 19-hydroxy-4β,5-epoxy-17a-oxa-D-homo-5β-androstane-3,17-dione (**11**). Evidence for the insertion of an oxygen atom in the D-ring is as follows: the 18-methyl resonance in the ^{1}H n.m.r. spectrum is shifted downfield at δ 1.32, consistent with the insertion of an oxygen atom at the 17a position.[6] Similarly, the 18-methyl resonance in the ^{13}C n.m.r. spectrum is shifted downfield at δ 20.1, again in agreement with published data.[7] All 19 carbon atom resonances were assigned and they are summarized in the Table. Similarly, treatment of 19-acetoxy-4β,5-epoxy-5β-androstane-3,17-dione (**10**) with MCPBA afforded



Scheme 3.

19-acetoxy-4β,5-epoxy-17a-oxa-D-homo-5β-androstane-3,17-dione (**12**) in 89% yield. This structure was confirmed by the isolation of an alcohol, identical in all respects with the rearranged product (**11**), upon treatment with potassium carbonate.

The insertion of an oxygen atom in the D-ring was also observed when 19-hydroxy-4α,5-epoxy-5α-androstane-3,17-dione (**13**) was treated with MCPBA. In this case, 19-hydroxy-4α,5-epoxy-17a-oxa-D-homo-5α-androstane-3,17-dione (**14**) was isolated in 20% yield based on 24% recovery of starting material. The ^{1}H n.m.r. spectrum indicated a singlet at δ 1.31, integrating for three protons and assigned to the 18-methyl group[6] next to the 17a-oxygen atom. The above results indicate that the Baeyer–Villiger rearrangement is specific to the D-ring with the C-3, C-17 diketones (**2**), (**10**), and (**13**).

The same reaction was then repeated on 17β,19-dihydroxy-4β,5-epoxy-5β-androstan-3-one (**15**) which does not have a 17-carbonyl group. It was found that this diol (**15**) reacted very slowly with MCPBA. After 11 days, three products were detected by t.l.c. and some starting material was still present. The only compound which was isolated in pure form was found, by mass spectrometry, to have a molecular weight of 306. The elemental analysis agreed with the empirical formula $C_{18}H_{26}O_4$ and was consistent with loss of CH_2 from the starting epoxide (**15**). The ^{1}H n.m.r. spectrum showed resonances at δ 0.81 (18-CH_3) and 3.63 (17α-H) as well as a quartet integrating for two protons centred at δ 4.44. The i.r. spectrum was consistent with a 6-membered ring lactone (1 745 cm^{-1}) and a saturated 6-membered ring ketone (1 705 cm^{-1}). These functional groups were confirmed by resonances at δ 172.1 and 210.6, respectively in the ^{13}C n.m.r. spectrum. Based on these data, this product is proposed to be A-nor-3,5-seco-5-oxo-17β,19-dihydroxyandrostan-3-oic acid 3,19-lactone (**16**). In agreement with this structure, only one acetate group was introduced when (**16**) was treated with acetic anhydride in pyridine. The 17β-acetoxy derivative (**17**) shows a triplet resonating at δ 4.58 and integrating for one proton, in the ^{1}H n.m.r. spectrum, which is assigned to the 17α-hydrogen atom. As expected, the quartet integrating for two protons, assigned to the 19-methylene group, is centred at δ 4.42 as in the starting material (**16**). The 17-keto analogue of (**16**) has been reported[1] upon treatment of (**1**) with hydrogen peroxide and base in methanol.

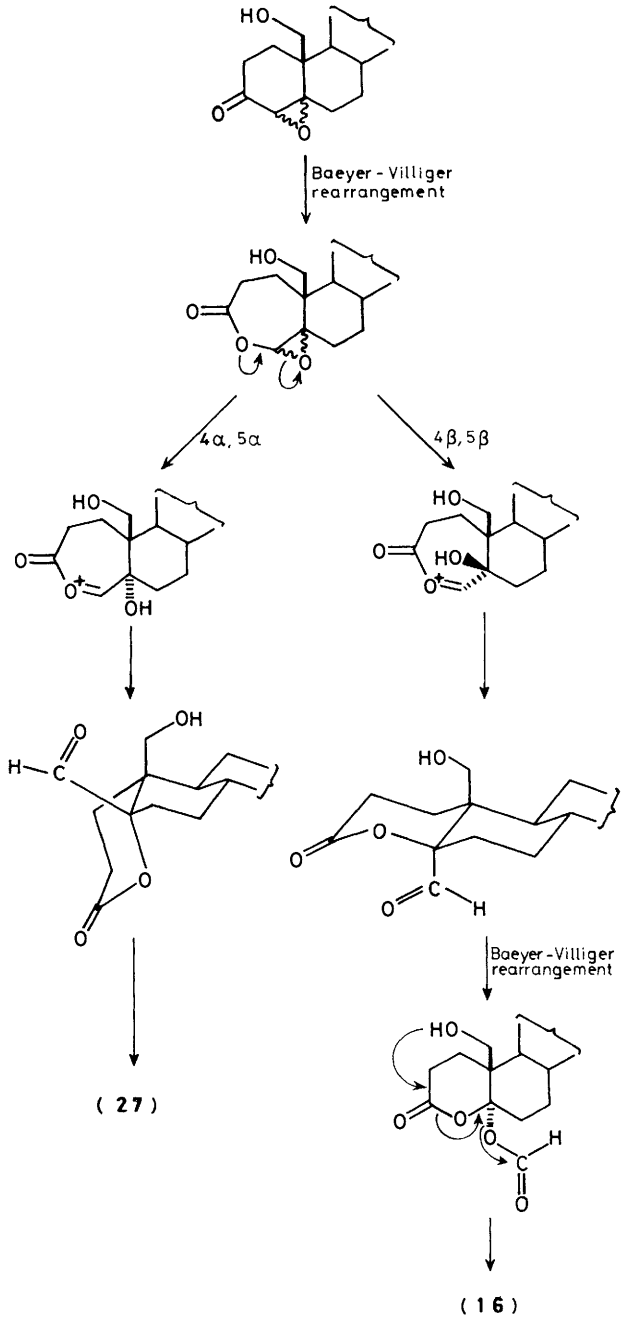
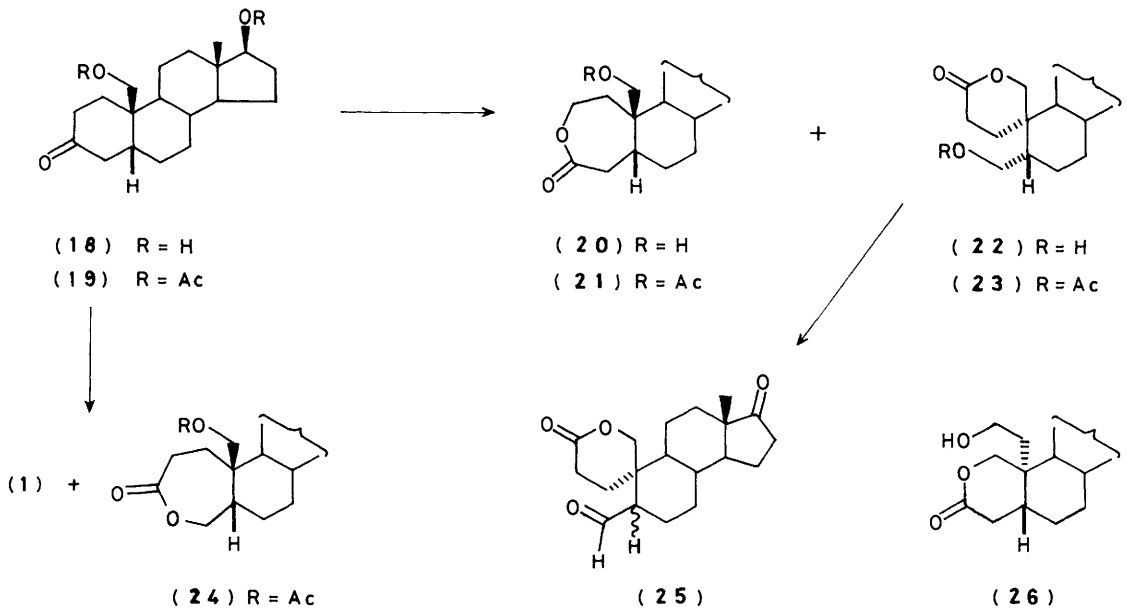


Figure 1. Proposed mechanism for the formation of (**16**) and (**27**)

A proposed mechanism for the formation of (**16**) is illustrated in Figure 1. Initial Baeyer–Villiger rearrangement occurs with



Scheme 4.

the 4β,5β-epoxide (**15**) resulting in the insertion of an oxygen atom at position 3a followed by opening of the epoxide to generate a 6-membered ring lactone with a formyl group at C-5. Baeyer–Villiger rearrangement of the latter results in insertion of a second oxygen atom. Participation of the 19-hydroxy group triggers the elimination of the resulting formate to give (**16**). A similar sequence of reactions was initially proposed by Pinhey and Schaffner[8] to explain the formation of Windaus acid in steroids having an intact 19-methyl group.

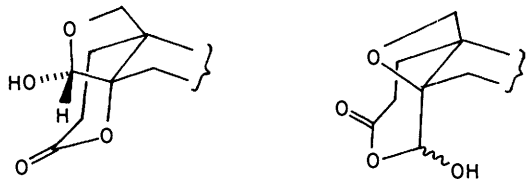
Reaction of 17β,19-*Dihydroxy*-5β-*androstan*-3-*one* (**18**) *and Its Diacetate* (**19**) *with MCPBA*.—The reaction of 17β,19-dihydroxy-5β-androstan-3-one (**18**) with MCPBA was carried out to determine whether insertion of an oxygen atom at the C-3a position would induce cyclization with the 19-hydroxy group as in compound (**16**). Treatment of the diol (**18**) with MCPBA afforded two products (Scheme 4) in yields of 46 and 35%, respectively. The elemental analysis of the first compound confirmed the addition of one atom of oxygen. The ^{1}H n.m.r. data indicated that the oxygen atom was adjacent to a methylene group because of the resonance of a multiplet centred at δ 4.16 which integrated for two protons. The 19-methylene group was still present as indicated by the quartet centred at δ 3.72. Since the ^{13}C n.m.r. chemical shift at δ 62.3 was in agreement with the chemical shift of δ 63.3 reported by Dave, Stothers, and Warnhoff[7] for A-homo-2a-oxa-5β-cholestan-3-one, it was concluded that the first product must be A-homo-17β,19-dihydroxy-2a-oxa-5β-androstan-3-one (**20**). On treatment of this compound with acetic anhydride in pyridine, the monoacetate (**21**) was obtained.

The elemental analysis of the second product gave the same empirical formula as for the first product. The presence of a lactone was indicated by the i.r. absorption at 1 730 cm^{-1}. In the ^{1}H n.m.r. spectrum, a quartet centred at δ 4.37 and integrating for two protons suggested a methylene group next to an oxygen atom. Also, a broad doublet at δ 3.72 integrating for two protons was present. The ^{13}C n.m.r. data (see Table 1) confirmed the presence of a lactone with resonances at δ 172.8 for the carbonyl group and δ 71.4 for the methylene group next to the oxygen atom. However, the methylene group at δ 60.9 was at higher field than normally found for a 19-alcohol (δ 64—66). Two hydroxy groups were still present since, upon treatment with acetic anhydride in puridine, the product obtained showed two singlet resonances integrating for three protons each at δ 2.01 and 2.04 in its ^{1}H n.m.r. spectrum. Based on the spectroscopic data and the involvement of the 19-hydroxy group, it was concluded that this compound must be either 4,17β,19-trihydroxy-3,4-seco-5β-androstan-3-oic acid 3,19-lactone (**22**) or the isomer (**26**).

Oxidation of the second product provided evidence for structure (**22**) since epimeric aldehydes (**25**) were isolated. The epimerizable hydrogen atom at the asymmetric C-5 carbon atom explains the formation of these epimers. Such an epimerizaton would not be observed upon oxidation with a structure like (**26**). Also, the ^{1}H n.m.r. spectrum of the oxidation product of (**26**) would have shown a triplet for the 19-methylene group next to the aldehyde group.

The reaction of 17β,19-diacetoxy-5β-androstan-3-one (**19**) with MCPBA was then carried out and a homogeneous product (by t.l.c.) was isolated in high yield. Analysis of the ^{13}C n.m.r. spectrum clearly showed that both isomers (**21**) and (**24**), corresponding to insertion of an oxygen atom at positions 2a and 3a respectively, had been formed in a ratio of *ca.* 1:1. The ^{13}C n.m.r. resonance at δ 69.9 for (**24**) was in agreement with the known value of δ 70.5 for the 3a-oxa isomer in the cholesterol series.[7]

Reaction of 19-*Hydroxyandrost*-4-*ene*-3,17-*dione* (**1**) *with MCPBA*.—The reaction of the unsaturated C-19 alcohol (**1**) with MCPBA resulted in the formation of a mixture of compounds. The major product (27%) isolated had a high resolution mass spectrum consistent with a molecular formula of $C_{19}H_{21}O_5$ corresponding to the addition of two oxygen atoms. The presence of a lactone was indicated by the i.r. absorption at 1 730 cm^{-1} and by the ^{13}C n.m.r. resonance at δ 171.4. Besides a quartet centred at δ 3.88, integrating for two protons and assigned to a methylene group next to an oxygen atom, the ^{1}H n.m.r. spectrum showed a doublet at δ 3.27, integrating for one proton (exchangeable upon addition of D_2O), which was assigned to a secondary alcohol. Finally, a very fine doublet at δ 4.97 became a singlet after the addition of D_2O, thus indicating that it was coupling with the hydroxy proton.



(27) (28)

Figure 2. Possible structures for the product obtained on oxidation of (**1**) with MCPBA

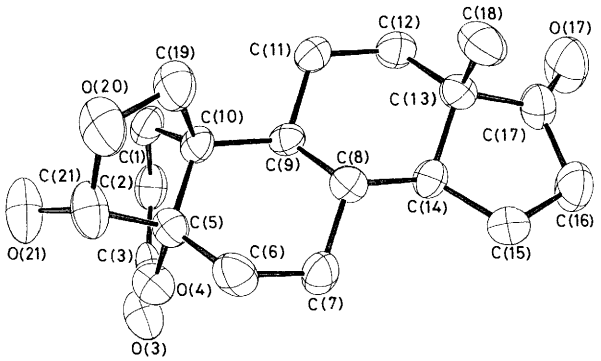


Figure 3. ORTEP Drawing of (**27**) with atomic numbering

Based on the ^{1}H n.m.r., i.r., and ^{13}C n.m.r. data, two possible structures could be proposed for this compound (see Figure 2). Upon acetylation, the product isolated was homogeneous by t.l.c. analysis but was found to be a mixture of epimers by ^{1}H n.m.r. analysis (*ca.* 1:1). In order to determine which of the two remaining structures was the correct one, the compound was carefully crystallized and an *X*-ray crystallographic analysis was performed. The correct structure was found to be (**27**) (see Figure 3; for details, see Experimental section).

Formation of the lactol (**27**) can be explained by a mechanism similar to the one proposed for the formation of (**16**) (see Figure 1). In this case the precursor is the 4α,5α-epoxide, and the 5β-aldehyde which forms, immediately cyclizes with the 19-hydroxy group to form the lactol (**27**) rather than undergoing a further Baeyer–Villiger rearrangement [*cf.* formation of (**16**)].

Experimental

M.p.s were determined with a Hoover Uni-melt apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter for solutions in chloroform. I.r. spectra were recorded on a Perkin-Elmer 783 infrared spectrophotometer using chloroform solutions unless otherwise specified. ^{1}H N.m.r. spectra were obtained with a Varian XL-300 instrument (with deuteriochloroform as solvent and internal standard). ^{13}C N.m.r. spectra were recorded with a Varian FT-80 instrument or on a Bruker AM-500 instrument (with deuteriochloroform as solvent and internal standard). The high-resolution and electron impact mass spectra were determined with a V.G. 7070-E double focusing instrument. Microanalyses were carried out by M-H-W Laboratories, Phoenix, AZ 85018, U.S.A. The reactions were monitored by t.l.c. using Merck pre-coated silica gel 60F-254 plates. For column chromatography Terochem Silica gel 1918 (equivalent to Merck 9385, 20-45 μm) was used. Work-up involved pouring the reaction mixture into water, extraction with methylene chloride and washing the extracts with water (with 5% HCl if pyridine was present). After the extracts were dried (Na_2SO_4), the solvents were removed under reduced pressure.

19-*Hydroxy*-4β,5-*epoxy*-17a-*oxa*-D-*homo*-5β-*androstane*-3,17-*dione* (**11**).—To a solution of 19-hydroxy-4β,5-epoxy-5β-androstane-3,17-dione (**2**)[9] (180 mg) in chloroform (4 ml) was added *m*-chloroperbenzoic acid (MCPBA) (180 mg). After the reaction mixture had been stirred for 32 h at room temperature, additional MCPBA (60 mg) was added. The reaction was terminated after 4 days. Work-up was followed by column chromatography eluted successively with methylene dichloride–ethyl acetate, 85:15, 4:1, and 7:3. Starting material (**2**) (53 mg, 29%) was recovered, and the 17a-*oxa-steroid* (**11**) (77 mg, 60% based on recovered starting material) was isolated. Transparent plates were obtained by slow evaporation of ethyl acetate, m.p. 252—253 °C (Found: M^+, 334.1774. $C_{19}H_{26}O_5$ requires M, 334.1773) (Found: C, 68.4; H, 7.85. $C_{19}H_{26}O_5$ requires C, 68.62; H, 7.84%); $\gamma_{max.}$ 3 660 and 3 440 br (OH), and 1 720 cm^{-1} (17-OCO and 3-CO); δ_H 1.32 (s, 3 H, 18-H_3), 2.93 (s, 1 H, 4α-H), and 3.90 (q, 2 H, δ_a 3.76, δ_b 4.04, J_{ab} 11.4 Hz, 19-H_2); *m/z* 334 (M^+, 5.4%), 319 (5.5), 316 (5.4), 306 (4.9), 304 (14.8), 303 (14.4), 275 (23), and 260 (52.7).

19-*Acetoxy*-4β,5-*epoxy*-17a-*oxa*-D-*homo*-5β-*androstane*-3,17-*dione* (**12**).—19-Hydroxy-4β,5-epoxy-5β-androstane-3,17-dione (**2**) (2.00 g) was treated with acetic anhydride in pyridine. Work-up afforded 19-acetoxy-4β,5-epoxy-5β-androstane-3,17-dione (**10**) as an oil. Crystals were obtained from methanol (2.15 g, 95%), m.p. 145—146 °C; $\gamma_{max.}$ 1 735 (17-CO and 19-$COCH_3$), and 1 710—1 700 sh cm^{-1} (3-CO); δ_H 0.87 (s, 3 H, 18-H_3), 2.11 (s, 3 H, 19-$COCH_3$), 2.90 (s, 1 H, 4α-H), and 4.40 (q, 2 H, δ_a 4.22, δ_b 4.57, J_{ab} 11.5 Hz, 19-CH_2); *m/z* 360 (M^+, 17%), 318 (1), 300 (9), 287 (7), and 259 (21); (Found: M^+, 360.1911. Calc. for $C_{21}H_{28}O_5$: M, 360.1929). To a solution of (**10**) (211 mg) in chloroform (8 ml) was added MCPBA (254 mg). The mixture was stirred for 70 h at room temperature, after which MCPBA (50 mg) was added. The reaction was terminated after 6 days. Column chromatography eluting successively with methylene chloride–ethyl acetate 9:1, 85:15, and 4:1, afforded starting material (**10**) (9 mg, 4%), a mixture of products (overlapping spots on t.l.c.) (16 mg), and 19-acetoxy-4β,5-epoxy-17a-oxa-D-homo-5β-androstane-3,17-dione (**12**) (196 mg, 89%), m.p. 69 °C (Found: C, 66.85; H, 7.3. $C_{21}H_{28}O_6$ requires C, 66.98; H, 7.50%); $[\alpha]_D$ +48° (*c* 0.21); δ_H 1.31 (s, 3 H, 18-H_3), 2.10 (s, 3 H, 19-$COCH_3$), 2.92 (s, 1 H, 4α-H), and 4.34 (q, 2 H, δ_a 4.18, δ_b 4.49, J_{ab} 11.4 Hz, 19-CH_2); *m/z* 376 (M^+, 36%), 348 (2), 334 (21), 333 (42), 316 (15), and 303 (14).

19-*Hydroxy*-4α,5-*epoxy*-17a-*oxa*-D-*homo*-5α-*androstane*-3,17-*dione* (**14**).—To a solution of 19-hydroxy-4α,5-epoxy-5α-androstane-3,17-dione (**13**)[10] (56 mg) in chloroform (3.5 ml) was added MCPBA (81 mg). After the clear solution had been stirred at room temperature for 1 day, additional MCPBA (61 mg) was added. The reaction was terminated after 6 days. Work-up was followed by column chromatography. Elution with methylene dichloride–ethyl acetate (7:3), afforded the starting material (**13**) (12 mg, 24%). Further elution with methylene dichloride–ethyl acetate (1:1), afforded the 17a-*oxa steroid* (**14**) (9.5 mg, 20%), m.p. 229—230 °C (Found: C, 67.8; H, 7.7. $C_{19}H_{26}O_5$ requires C, 68.22; H, 7.84%); $\gamma_{max.}$ 3 620 and 3 420br (OH), and 1 710 cm^{-1} (3-CO and 17-OCO); δ_H 1.31 (s, 3 H, 18-H_3), 3.15 (s, 1 H, 4β-H), and 3.90 (q, 2 H, δ_a 3.84, δ_b 3.95, J_{ab} 10.3 Hz, 19-H_2); *m/z* 334 (M^+, 3.6%), 316 (3.1), 306 (3.9), 305 (4.6), 304 (7.7), 261 (26.2), and 260 (16.4).

Preparation and Treatment with MCPBA of 17β,19-*Dihydroxy*-4β,5-*epoxy*-5β-*androstan*-3-*one* (**15**).—To a solution of 19-hydroxyandrost-4-ene-3,17-dione (**1**) (2.10 g) in methanol (80 ml), cooled in an ice–water bath, was added sodium borohydride (0.33 g). The reaction was terminated after 90 min by the addition of acetic acid (5 drops). The residue obtained after the removal of the solvent was dissolved in methanol (30

Table 1. ^{13}C n.m.r. chemical shifts[a,b]

Carbon Atom	(11)	(15)	(16)	(20)	(22)
1	21.6	21.8	[31.1]	33.7	[22.4]
2	32.1	32.2	36.4	62.3	36.7
3	205.5	206.2	172.1	176.2	172.8
4	60.2	59.9		36.4	60.9
5	68.5	69.1	210.6	41.1	39.8
6	28.4*	30.1	38.4	30.5	[25.4]
7	29.8	30.3	[23.2]	25.1	[27.4]
8	37.5	35.1	36.0	33.6	35.8
9	45.8†	46.8	51.5	35.6	45.8
10	41.3	41.7	51.7	40.9	37.0
11	22.9	21.3	22.9	20.9	21.3
12	32.9	36.5	[30.3]	37.1	30.4
13	82.4	43.0	43.0	43.0	42.7
14	46.0†	50.8	50.4	51.3	51.2
15	19.8	23.2	23.3	23.3	23.1
16	28.9*	30.0	[28.2]	29.0	[27.8]
17	171.0	81.4	81.1	81.6	81.5
18	20.1	11.1	11.3	11.2	11.1
19	64.8	64.9	69.0	65.2	71.4
	(25)[c]	**(21)**	**(24)**	**(27)**	**(10)**
1		37.1	28.8	26.2*	21.6
2		62.7	34.1	32.6	31.8
3		175.7	175.5	171.4	205.5
4	202.8	36.3	69.9		60.3
5	52.0	34.1	38.5	87.4	68.3
6		27.7*	27.7*	25.3*	29.6
7		26.5*	26.2*	23.8*	31.2
8	35.2	35.4	35.4	35.7	34.6
9	46.8	40.7	40.9	42.3	46.6
10	37.3 (44.4)	39.7	39.6	39.7	40.8
11	20.9	20.7	20.5	22.1	21.4
12	31.5	37.1	37.1	31.7	29.2
13	47.4	42.6	42.6	47.8	47.6
14	51.1	51.1	51.1	50.3	51.1
15	21.5	24.9	23.3	21.5	21.5
16	35.6	27.6	27.5	35.6	35.5
17	220.0	82.3	82.3	219.9	219.5
18	13.7	12.2	12.1	13.9	13.7
19	69.4 (69.0)	66.8	66.7	73.4	65.3
5a				101.1	
$COCH_3$		20.1	20.1		21.0
$COCH_3$		20.9	20.9		
$COCH_3$		171.1	171.1		171.0
$COCH_3$		171.1	171.1		

* or † Assignments within a vertical column may be reversed. [ ] Tentative assignments. [a] Data are in p.p.m. in $CDCl_3$ with $\delta(CDCl_3)$ 77.0 p.p.m. [b] The assignment of ^{13}C n.m.r. peaks in terms of number of attached hydrogen atoms has been made using the pulse sequence DEPT[17] (Distortionless Enhancement of n.m.r. signal by Polarization Transfer). [c] All the resonances are listed in the Experimental section.

ml) and cooled in an ice–water bath. Ice-cold 10% aqueous NaOH (10 ml) and 30% hydrogen peroxide (12 ml) were successively added and the reaction mixture was stirred for 30 min at 0—4 °C. Work-up and column chromatography eluted with methylene dichloride–ethyl acetate (65:35), afforded 17β,19-*dihydroxy*-4β,5-*epoxy*-5β-*androstan*-3-*one* (**15**) (1.05 g, 47%). Crystals were obtained from ether, m.p. 155—156 °C (lit.,[11] m.p. 150—153 °C); $[\alpha]_D$ +136° (*c* 0.275); $\gamma_{max.}$ 3 600 (OH) and 1 710 cm^{-1} (3-CO); δ_H 0.74 (s, 3 H, 18-H_3), 2.88 (s, 1 H, 4α-H), 3.62 (tr, 1 H, 17α-H), and 3.96 (q, 2 H, δ_a 3.73, δ_b 4.18, J_{ab} 11.4 Hz, 19-H_2); *m/z* 320 (M^+, 11%), 302 (16), 290 (30.6), 289 (30.8), 273 (29.7), and 93 (100). 17β,19-Dihydroxy-4β,5-epoxy-5β-androstan-3-one (**15**) (114 mg) was dissolved in chloroform (5 ml) and stirred at room temperature for 11 days in the presence of MCPBA (120 mg). The reaction mixture was purified by column chromatography. Elution with methylene dichloride–ethyl acetate (7:3, and 68.5:32.5), afforded a mixture of two compounds by t.l.c. (63 mg) which was repurified by column chromatography with methylene dichloride–ethyl acetate (73:27 and 72:28) as eluant. The least polar compound isolated was not identified but was found by ^{13}C n.m.r. to be a mixture of isomers (*ca.* 10:1) despite the fact that it was homogeneous on t.l.c. The second more polar compound, was not obtained in a pure form. Further elution of the first column with methylene dichloride–ethyl acetate (65:35), afforded a third compound (20 mg) homogeneous on the basis of t.l.c. but which could not be identified. Finally, the second compound was obtained in a pure form after repetition of the reaction of (**15**) (342 mg) with MCPBA. This compound eluted with methylene dichloride–ethyl acetate (73:27), was identified as 17β,19-*dihydroxy*-A-*nor*-3,5-*seco*-5-*oxo*-*androstane*-3-*carboxylic acid* 3,19-*lactone* (**16**) (68 mg, 21%). This product (**16**)

was recrystallized from ethyl acetate–ether, m.p. 162—163 °C (Found: C, 70.4; H, 8.45. $C_{18}H_{26}O_4$ requires C, 70.54; H, 8.56%); $\gamma_{max.}$ 1 745 (3-OCO) and 1 705 cm^{-1} (5-CO); δ_H 0.81 (s, 3 H, 18-H_3), 3.63 (tr, 1 H, 17α-H), and 4.44 (q, 2 H, δ_a 4.39, δ_b 4.48, J_{ab} 11.8 Hz, 19-H_2); *m/z* 306 (M^+, 28.3%), 288 (16.7), 279 (15.6), 278 (81), and 140 (100).

Treatment of 17β,19-*Dihydroxy*-5β-*androstan*-3-*one* (**18**) *with MCPBA*.—19-Hydroxyandrost-4-ene-3,17-dione (2.00 g) was treated with sodium borohydride, and the crude product obtained, 17β,19-dihydroxyandrost-4-en-3-one, was hydrogenated over 10% palladium on charcoal according to the literature procedure.[12] 17β,19-Dihydroxy-5β-androstan-3-one (**18**) (1.31 g, 65%) was obtained following elution of the column with methylene dichloride–ethyl acetate (3:2). M.p. 145 °C (ethyl acetate) (lit.,[12] m.p. 183—185 °C) (Found: M^+, 306.2201. $C_{19}H_{30}O_3$ requires *M*, 306.2187); $[\alpha]_D$ +25° (*c* 0.24) (lit.,[12] $[\alpha]_D$ +26°); $\gamma_{max.}$ 3 620 and 3 360br (OH) and 1 710 cm^{-1} (3-CO); δ_H 0.73 (s, 3 H, 18-H_3), 3.64 (tr, 1 H, 17α-H), and 3.80 (q, 2 H, δ_a 3.65, δ_b 3.95, J_{ab} 10.7 Hz, 19-H_2); *m/z* 306 (M^+, 17.4%), 288 (21), 277 (20.9), 276 (36.9), 275 (98.1), 274 (13.8), and 257 (100). To a solution of (**18**) (0.10 g) dissolved in chloroform (3 ml) was added MCPBA (0.10 g), and the reaction was stirred at room temperature for 2 days. After work-up, purification by column chromatography, eluted successively with methylene dichloride–ethyl acetate, 65:35, 60:40, 55:45, and 50:50 first afforded 17β,19-*dihydroxy*-5A-*homo*-2a-*oxa*-β-*androstan*-3-*one* (**20**) (48 mg, 46%), m.p. 199—200 °C (Found: C, 70.9; H, 9.35. $C_{19}H_{30}O_4$ requires C, 70.75; H, 9.38%); $[\alpha]_D$ +57° (*c* 0.12); $\gamma_{max.}$ 1 725 cm^{-1} (3-OCO); δ_H 0.72 (s, 3 H, 18-H_3), 3.72 (q, 2 H, δ_a 3.51, δ_b 3.94, J_{ab} 11.1 Hz, 19-H_2), 3.64 (t, 1 H, 17α-H), and 4.16 (m, 2 H, 2-H_2); *m/z* 322 (M^+, 4.9%), 304 (11.8), 292 (14.7), and 291 (30.1). The second compound eluted was 4,17β,19-*trihydroxy*-A-*nor*-3,4-*seco*-5β-*androstane*-3-*carboxylic acid* 3,19-*lactone* (**22**) (37 mg, 35%), m.p. 108—110 °C (Found: C, 70.6; H, 9.4. $C_{19}H_{30}O_4$ requires C, 70.75; H, 9.38); $[\alpha]_D$ +4° (*c* 0.10); $\gamma_{max.}$ 1 730br cm^{-1} (3-OCO); δ_H 0.71 (s, 3 H, 18-H_3), 3.61 (t, 1 H, 17α-H), 3.72 (br d, 2 H, 4-H_2), and 4.37 (q, 2 H, δ_a 4.28, δ_b 4.46, J_{ab} 11.8 Hz, 19-H_2); *m/z* 322 (M^+, 28.5%), 304 (20.9), 294 (5.4), 292 (18.2), 291 (17.4), 279 (20.1), and 274 (34.3).

17β,19-*Diacetoxy*-A-*homo*-2a-*oxa*-5β-*androstan*-3-*one* (**21**).—The A-*homo*-2a-*oxa steroid* (**20**) (4 mg) was dissolved in pyridine (0.5 ml). Acetic anhydride (1 ml) was added to the steroid solution, and the mixture was stirred overnight at room temperature. Work-up afforded 17β,19-*diacetoxy*-A-*homo*-2a-*oxa*-5β-*androstan*-3-*one* (**21**) (100%) as a sticky material; δ_H 0.77 (s, 3 H, 18-H_3), 2.02 (s, 3 H) and 2.06 (s, 3 H) 17β- and 19-acetates, 4.15 (q, 2 H, δ_a 3.91, δ_b 4.39, J_{ab} 11.5 Hz, 19-H_2), 4.18 (m, 2 H, 2-H_2), and 4.58 (t, 1 H, 17α-H); *m/z* 364 ($M^+ - CH_3CO$, 1.1), 346 (10.3), 304 (39.3), 291 (15.1), and 286 (25.9).

Oxidation of 4,17β,19-*Trihydroxy*-A-*nor*-3,4-*seco*-5β-*androstane*-3-*carboxylic Acid* 3,19-*Lactone* (**22**).—The oxidation of the A-*nor-steroid* (**22**) (40 mg) was carried out according to the procedure described by Ratcliffe.[13] Column chromatography with methylene dichloride–ethyl acetate (9:1) as eluant afforded 19-*hydroxy*-A-*nor*-3,4-*seco*-4,17-*dioxo*-5ξ-*androstane*-3-*carboxylic acid* 3,19-*lactone* (**25**) (9 mg, 22%), as a homogeneous compound on the basis of t.l.c. (Found: M^+, 318.1835. $C_{19}H_{26}O_4$ requires *M*, 318.1824); $\gamma_{max.}$(KBr) 1 735br cm^{-1}; δ_H 0.85 (s, 3 H, 18-H_3), 4.34 (q, 2 H, δ_a 4.31, δ_b 4.37, J_{ab} 11.7 Hz, 19-H_2), and 9.76 (s, 1 H, 4-CHO); δ_C 13.7 (CH_3, C-18), 20.9 (CH_2, C-11), 21.1 (CH_2), 21.5 (CH_2, C-15), 24.0 (CH_2), 25.4 (CH_2), 26.1 (CH_2), 28.2 (CH_2), 28.8 (CH_2), 29.4 (CH_2), 31.5 (CH_2, C-12), 35.2 (CH, C-8), 35.6 (CH_2, C-16), 37.3 (C, C-10), 44.4 (C), 46.8 (CH, C-9), 47.4 (C, C-13), 51.1 (CH, C-14), 52.0 (CH, C-5), 69.0 (69.4) (CH_2, C-19), 202.8 (CH, C-4), and 220.0 (C, C-17); *m/z* 318 (M^+, 21.6%), 300 (8.2), 290 (8.5), and 272 (10.2).

4,17β-*Diacetoxy*-19-*hydroxy*-A-*nor*-3,4-*seco*-4β-*androstane*-3-*carboxylic Acid* 3,19-*Lactone* (**23**).—The A-nor-3,4-seco steroid (**22**) (5 mg) was dissolved in pyridine (0.5 ml). Acetic anhydride (1 ml) was added to the steroid solution, and the mixture was stirred overnight at room temperature. Work-up afforded 4,17β-*diacetoxy*-19-*hydroxy*-A-*nor*-3,4-*seco*-4β-*androstane*-3-*carboxylic acid* 3,19-*lactone* (**23**) as a clear oil; δ_H 0.75 (s, 3 H, 18-H_3), 2.01 (s, 3 H) and 2.04 (s, 3 H) 4- and 17β-acetates, 4.16 (d, 2 H, 4-H_2), 4.37 (q, 2 H, δ_a 4.27, δ_b 4.47, J_{ab} 11.8 Hz, 19-H_2), and 4.55 (t, 1 H, 17α-H); *m/z* 406 (M^+, 6.5%), 364 (2.4), 346 (21.9), 318 (9.7), and 286 (33.6).

Treatment of 17β,19-*Diacetoxy*-5β-*androstan*-3-*one* (**19**) *with MCPBA*.—Acetylation (acetic anhydride and pyridine) of 17β,19-dihydroxy-5β-androstan-3-one (150 mg) afforded the diacetate[10] (**19**) (100%); δ_H 0.79 (s, 3 H, 18-H_3), 2.02 (s, 3 H) and 2.05 (s, 3 H) 17β- and 19-acetates, 4.24 (q, 2 H, δ_a 4.07, δ_b 4.40, J_{ab} 11.1 Hz, 19-H_2), and 4.59 (t, 1 H, 17α-H); *m/z* 390 (M^+, 0.4%), 331 (52.7), 330 (100), 317 (15.7), and 302 (22.9). To a stirred solution of the diacetate (**19**) (197 mg) in chloroform (5 ml) was added MCPBA (250 mg). The reaction was terminated after two days. Column chromatography with methylene dichloride–ethyl acetate, (92:8) as eluant afforded a homogeneous compound on the basis of t.l.c. which was found by ^{13}C n.m.r. to be a *ca.* 1:1 mixture of 17β,19-*diacetoxy*-2a-*oxa*-5β-*androstan*-3-*one* (**21**) and 17β,19-*diacetoxy*-3a-*oxa*-5β-*androstan*-3-*one* (**24**) (64%), m.p. 72—73 °C (Found: C, 68.15; H, 8.65. $C_{23}H_{34}O_6$ requires C, 67.93; H, 8.43%); $[\alpha]_D$ +28° (*c* 0.27); $\gamma_{max.}$ 1 735br cm^{-1} (3-OCO and 17β,19-acetates); δ_H 0.77 (s, 3 H, 18-H_3), 2.02 (s, 3 H) and 2.06 (s, 3 H) 17β- and 19-acetates, 4.11 (m, 2 H), 4.26 (br q, 2 H, δ_a 3.93, δ_b 4.59, 19-H_2), and 4.42 (t, 1 H, 17α-H); *m/z* 406 (M^+, 0.7%), 346 (12.8), 333 (11.2), 304 (20.8), 291 (10.5), 286 (22.1), and 273 (33.7).

Treatment of 19-*Hydroxyandrost*-4-*ene*-3,17-*dione* (**1**) *with MCPBA*.—To a solution of 19-hydroxyandrost-4-ene-3,17-dione (**1**) (0.52 g) in chloroform (10 ml, previously mixed with 10 ml of 35% $HClO_4$ and separated) was added MCPBA (0.53 g). The solution was stirred at room temperature for 2 days. Work-up was followed by column chromatography eluted successively with methylene dichloride–ethyl acetate, 90:10, 85:15, 82:18, and 70:30. Two compounds were first isolated (8 and 22 mg, respectively) but their structures could not be elucidated. Further elution afforded 5β-*formyl*-5,19-*dihydroxy*-17-*oxo*-A-*nor*-3,5-*seco*-5β-*androstane*-3-*carboxylic acid* 5,19(R) *lactol* 3,5-*lactone* (**27**) (153 mg, 27%), m.p. 248—249 °C (ethyl acetate) (Found: M^+, 334.1753. $C_{19}H_{26}O_5$ requires *M*, 334.1773) (Found: C, 68.3; H, 7.95. $C_{19}H_{26}O_5$ requires C, 68.22; H, 7.84); $[\alpha]_D$ +75° (*c* 0.32); $\gamma_{max.}$ 3 350br (OH) and 1 730 cm^{-1} (3-OCO and 17-CO); δ_H 0.88 (s, 3 H, 18-H_3), 3.27 (d, 1 H, *J* 4 Hz exchanges with D_2O, 5a-OH), 3.88 (q, 2 H, δ_a 3.77, δ_b 3.99, J_{ab} 8.5 Hz, 19-H_2), and 4.97 (d, 1 H, *J* 4 Hz becomes a singlet upon addition of D_2O, 5a-H); *m/z* 334 (M^+, 17.8%), 316 (2.9), 306 (2.5), 278 (7.7), 275 (33.5), and 260 (100). Finally, starting material (**1**) (65 mg, 12.5%) was eluted from the column.

X-*Ray Crystal Structure Analysis of* (**27**).—A suitable crystal for *X*-ray analysis was obtained by slow evaporation of a 95% ethanol solution.

Crystal data. $C_{19}H_{26}O_5$, M = 334.3, Monoclinic, a = 6.696 3(5), b = 12.093 9(13), c = 10.804 3(10) Å, β = 105.48(1)°. V = 843 $Å^3$ (by least-square refinement from the setting angles of 25 reflections with 2θ in the range of 35—40°, Mo-K_{α_1} = 0.709 32 Å), space group $P2_1$, Z = 2, D_x = 1.329 g cm^{-3}. Crystal size is *ca.* 0.07 × 0.2 × 0.3 mm, μ = 0.9 cm^{-1}.

Intensity data were collected on a CAD-4 diffractometer, with the NRCCAD[14] control program and profile analysis[15] in the $\theta/2\theta$-mode using graphite monochromatized Mo-K_α radiation. 3 102 Reflections were measured, $2\theta_{max.} = 50°$, $+h$, $+k$, $+l$, and $-h$, $+k$, $+l$ 1 547 unique, giving 1 060 with $I \geqslant 2.5\,\sigma(I)$: Friedel equivalents 1 394 unique and 942 with $I \geqslant 2.5\,\sigma(I)$. The intensity of three standard reflections was stable within $\pm 3\%$. The structure was solved by direct methods and refined (non-hydrogen atoms anisotropic, hydrogen atoms isotropic) by full matrix least-squares techniques and counting statistics weight using the NRCVAX[16] program system. Hydrogen atoms were located from the D-map. Final R_f and R_w values are 0.041 and 0.020. The final atomic parameters for non-hydrogen atoms are given in Table 2, whilst the atomic co-ordinates for the hydrogen atoms, the thermal parameters, and the bond lengths and angles are available as supplementary material (24 pages) from the Cambridge Crystallographic Data Centre.*

Acetylation of the Lactone (**27**).—To a solution of (**27**) (13 mg) in pyridine (0.5 ml) acetic anhydride (1 ml) was added and the mixture was stirred overnight at room temperature. Work-up afforded an epimeric mixture (*ca.* 1:1, by ^{1}H n.m.r.) of acetates (homogeneous on the basis of t.l.c.). M.p. 211—212 °C; $\gamma_{max.}$(KBr) 1 740—1 735 cm^{-1} (5a-acetate and 17-CO); δ_H 0.87 (0.88) (s, 3 H, 18-H_3), 2.06 (2.11) (s, 3 H, 4-$COCH_3$), 3.76 (4.14) (q, 2 H, δ_a 3.73, δ_b 3.79, J_{ab} 8.7 Hz, 19-H_2) (q, 2 H, δ_a 4.05, δ_b 4.24, J_{ab} 8.6 Hz, 19-H_2), and 5.84 (6.19) (s, 1 H, 5a-H); *m/z* 376 (M^+, 3.9%), 335 (12), 334 (58), 333 (49), 317 (14), and 305 (18).

Table 2. Atomic parameters *x*, *y*, and *z*. E.s.d.'s refer to the last digit printed

Atom	*x*	*y*	*z*
C(1)	0.227 7(6)	0.693 5(4)	0.473 4(4)
C(2)	0.082 8(6)	0.654 2(4)	0.552 3(3)
C(3)	0.086 3(5)	0.533 5(4)	0.577 9(3)
O(3)	−0.004 1(3)	0.490 48	0.649 68(20)
O(4)	0.186 2(3)	0.465 5(3)	0.519 09(19)
C(5)	0.283 3(4)	0.497 8(4)	0.418 3(3)
C(6)	0.224 9(6)	0.403 4(4)	0.320 6(4)
C(7)	0.002 0(6)	0.413 9(4)	0.240 8(4)
C(8)	−0.022 4(5)	0.520 9(4)	0.164 6(3)
C(9)	0.019 9(5)	0.620 8(4)	0.256 4(3)
C(10)	0.227 6(4)	0.614 0(4)	0.363 3(3)
C(11)	−0.000 5(6)	0.730 2(4)	0.181 6(4)
C(12)	−0.211 7(6)	0.741 3(4)	0.078 9(4)
C(13)	−0.253 5(5)	0.640 4(4)	−0.006 7(3)
C(14)	−0.237 7(4)	0.535 5(4)	0.074 4(3)
C(15)	−0.335 4(7)	0.445 6(4)	−0.020 3(4)
C(16)	−0.523 4(6)	0.506 4(5)	−0.110 5(4)
C(17)	−0.472 0(5)	0.628 5(4)	−0.094 7(3)
O(17)	−0.584 6(4)	0.702 4(3)	−0.144 02(24)
C(18)	−0.110 0(6)	0.636 9(5)	−0.097 8(4)
C(19)	0.417 0(5)	0.637 9(5)	0.310 6(3)
O(20)	0.586 8(3)	0.573 9(3)	0.389 91(22)
C(21)	0.520 3(5)	0.500 1(5)	0.472 4(3)
O(21)	0.577 2(4)	0.538 1(3)	0.597 44(23)

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* For details see 'Instructions for Authors' (1989), *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

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