

## Synthesis of Ring-A and -B Substituted 17 $\alpha$ -Acetoxypregnan-20-one Derivatives with Potential Activity on the Digitalis Receptor in Cardiac Muscle

John F. Templeton\* and V. P. Sashi Kumar

Faculty of Pharmacy, University of Manitoba, Winnipeg, Manitoba, Canada R3T 2N2

Ryungsoon S. Kim and Frank S. LaBella

Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada R3E 0W1

The synthesis of C-6 substituted (methyl, hydroxy, acetoxy, methoxy, ethoxy, methoxycarbonyloxy, ethoxycarbonyloxy, fluoro, chloro, bromo) 5 $\alpha$ ,5 $\beta$ ,C-4 unsaturated and C-4,6 unsaturated derivatives of 17 $\alpha$ -acetoxypregn-4-ene-3,20-dione (17 $\alpha$ -acetoxypregsterone) are reported. A convenient synthesis of 6 $\alpha$ -hydroxy derivatives by selective reduction of the 4-ene-3,6-dione system is described as is the formation of 6 $\alpha$ -alkoxycarbonyl derivatives. Synthesis of a 5 $\alpha$ -hydroxy-6-ketone *via* the 5 $\beta$ ,6 $\beta$ -epoxide with *N*-bromosuccinimide is reported. A new preparation of 3 $\alpha$ -hydroxy-5 $\alpha$ -derivatives from the 4-en-3-one group has been carried out. <sup>1</sup>H n.m.r. spectra are recorded. These compounds were synthesized to test for ouabain displacement activity on the digitalis receptor in cardiac muscle.

As part of an investigation<sup>1,2</sup> of the interaction of progestational steroids, derived from progesterone, with the digitalis receptor of cardiac muscle a structurally related series of ring A and B derivatives have been synthesized for binding studies on the heart muscle. Details of the chemical synthesis and <sup>1</sup>H n.m.r. spectra of these compounds, none of which proved to be as effective in the binding assay as 17 $\alpha$ -acetoxy-6-chloropregna-4,6-diene-3,20-dione (chlormadinone acetate) previously reported,<sup>1</sup> is given here.

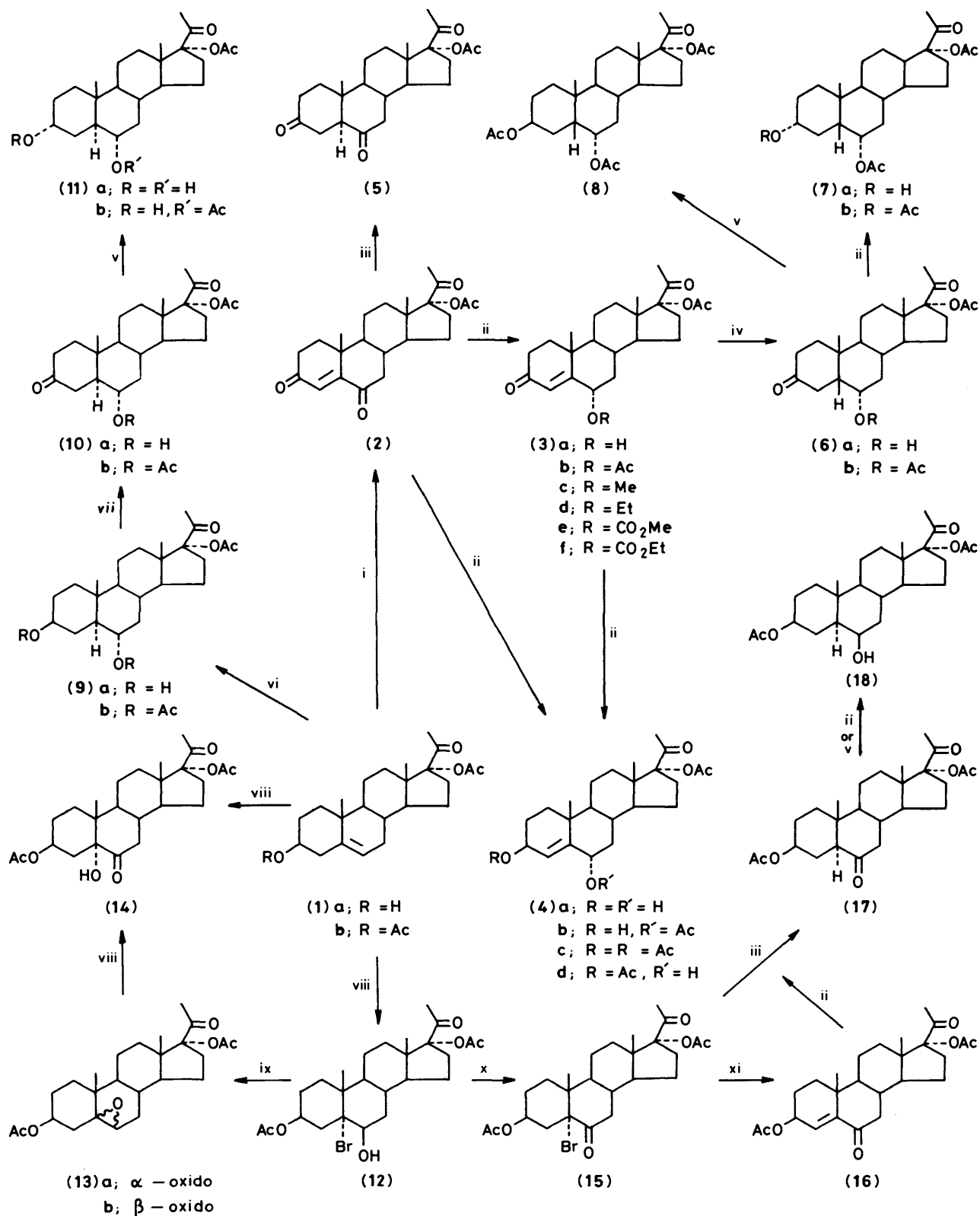
Some 5 $\alpha$ ,5 $\beta$  and C-4 unsaturated derivatives of progesterone were synthesized as shown in Scheme 1. Kiliani oxidation<sup>3</sup> of 17 $\alpha$ -acetoxy-3 $\beta$ -hydroxypregn-5-en-20-one (**1a**) gave the unsaturated 3,6,20-trione (**2**) which was selectively reduced by 1 equiv. of LTBA to the 6 $\alpha$ -alcohol (**3a**) from which the 6 $\alpha$ -acetate (**3b**) was prepared. The 3,6,20-trione (**2**) was further reduced more slowly to the unsaturated 3 $\beta$ ,6 $\alpha$ -diol (**4a**) with excess of reagent. From the 6 $\alpha$ -alcohol (**3a**) was prepared the 6 $\alpha$ -methoxy (**3c**) and 6 $\alpha$ -ethoxy (**3d**) derivatives with silver oxide and the corresponding iodoalkane in *N,N*-dimethylformamide.<sup>4</sup> The concomitant formation of the methoxycarbonyl (**3e**) and ethoxycarbonyl (**3f**) derivatives were previously unreported in this reaction. Reaction with iodomethane yielded the methoxycarbonyl derivatives as the major product whereas with iodoethane it was a minor product. Carbonate formation may occur through initial formylation of the alcohol by DMF followed by silver oxide oxidation to the hydrogen carbonate and alkylation. The greater yield of the methyl ester then results from the higher reactivity of iodomethane with the unstable hydrogen carbonate. Reduction of the unsaturated 3,6,20-trione (**2**) with zinc and acetic acid gave the 5 $\alpha$ -dione (**5**).<sup>5</sup> Catalytic reduction of the 6 $\alpha$ -alcohol (**3a**) with Pd/CaCO<sub>3</sub> in pyridine gave the 5 $\beta$ -derivative (**6a**) which on acetylation gave the 6 $\alpha$ -acetate (**6b**).<sup>6</sup> LTBA reduction of the 6 $\alpha$ -acetate (**6b**) gave the equatorial 3 $\alpha$ -alcohol (**7a**).<sup>7</sup> K-Selectride reduction of the 6 $\alpha$ -acetate (**6b**) followed by acetylation yielded the axial 3 $\beta$ -acetate (**8**).<sup>8</sup> LTBA reduction of the unsaturated ketone (**3b**) gave the 3 $\beta$ -alcohol (**4b**) which on acetylation gave the acetate (**4c**) (see below). Some 5 $\alpha$ -derivatives were readily obtained by hydroboration of 17 $\alpha$ -acetoxy-3 $\beta$ -hydroxypregn-5-en-20-one (**1a**) to give 17 $\alpha$ -acetoxy-3 $\beta$ ,6 $\alpha$ -dihydroxy-5 $\alpha$ -pregnan-20-one (**9a**).<sup>9</sup> Acetylation of the diol (**9a**) gave the triacetate (**9b**). Selective oxidation of the diol (**9a**) with silver carbonate on Celite<sup>10</sup> gave the C-3 ketone (**10a**) which on acetylation gave the diacetate (**10b**). LS-

Selectride reduction of the diones (**10a**) and (**10b**) gave 17 $\alpha$ -acetoxy-3 $\alpha$ ,6 $\alpha$ -dihydroxy-5 $\alpha$ -pregnan-20-one (**11a**) and the diacetate (**11b**) respectively.

Addition of 1 equiv. of *N*-bromosuccinimide<sup>11,12</sup> to the C-5 double bond of 3 $\beta$ ,17 $\alpha$ -diacetoxypregn-5-en-20-one (**1b**) rapidly gave the bromohydrin (**12**) whereas addition of an excess of NBS gave 3 $\beta$ ,17 $\alpha$ -diacetoxy-5 $\alpha$ -hydroxypregnan-6,20-dione (**14**). This product is probably formed *via* the 5 $\beta$ ,6 $\beta$ -epoxide (**13b**) which after ring opening to the diaxial diol is followed by oxidation of the 6 $\beta$ -alcohol.<sup>13</sup> Reaction of the bromohydrin (**12**) with alumina gave the 5 $\beta$ ,6 $\beta$ -epoxide (**13b**) which with NBS under the above conditions also yielded the hydroxy ketone (**14**). Chromic acid oxidation of the bromohydrin (**12**) yielded the C-6 bromo ketone (**15**). Dehydrobromination of the bromo ketone (**15**) in pyridine<sup>14</sup> gave the C-4 unsaturated ketone (**16**). LTBA reduction of this unsaturated ketone gave the 6 $\alpha$ -alcohol (**4d**) which was converted into the triacetate (**4c**). The triacetate (**4c**) was also prepared by acetylation of the diol (**4a**) and the alcohol (**4b**) (see above) but was not obtained crystalline from any source. The bromo ketone (**15**) on debromination with zinc in acetic acid yielded the 5 $\alpha$ -derivative (**17**) which on reduction with either LS-Selectride or LTBA gave the 6 $\beta$ -alcohol (**18**).

5 $\beta$ -Derivatives (Scheme 2) were prepared by catalytic hydrogenation over Pd/CaCO<sub>3</sub> in pyridine<sup>6</sup> of the 4-en-3-one system in 17 $\alpha$ -acetoxypregn-4-ene-3,20-dione (**19a**) and 17 $\alpha$ -acetoxy-6 $\alpha$ -methylpregn-4-ene-3,20-dione (**19b**) to give the saturated derivatives (**20a**) and (**20b**), respectively. Selective LTBA reduction of the C-3 ketone of the diones (**20a**) and (**20b**) gave the equatorial 3 $\alpha$ -alcohols (**21a**) and (**21b**) which were acetylated to give the diacetates (**21c**) and (**21d**). Similarly K-Selectride reduction of the diones (**20a**) and (**20b**) gave the axial 3 $\beta$ -alcohols (**22a**) and (**22b**) which on acetylation gave the diacetates (**22c**) and (**22d**).

Reduction products of the C-4 and C-4,6-unsaturated C-3 ketone are also shown in Scheme 2. Treatment of 17 $\alpha$ -acetoxy-6 $\alpha$ -methylpregn-4-ene-3,20-dione (**19b**) with either LS-Selectride or LTBA gave a mixture of the C-3 epimeric 3 $\alpha$ - and 3 $\beta$ -alcohols, (**23**) and (**24a**).<sup>15</sup> Catalytic reduction of the 3 $\alpha$ -alcohol (**24a**) with Rh/C gave a mixture of the 3 $\alpha$ ,5 $\alpha$ -alcohol (**25a**) and 3 $\beta$ ,5 $\alpha$ -alcohol (**25b**) derivatives. Reduction of the allylic alcohol to a mixture of C-3 epimers probably occurs through formation of the C-3 ketone (*via* initial addition of hydrogen to form the C-5 cation followed by a C-3 $\alpha$ H shift to C-5) which is known to yield the axial alcohol with rhodium



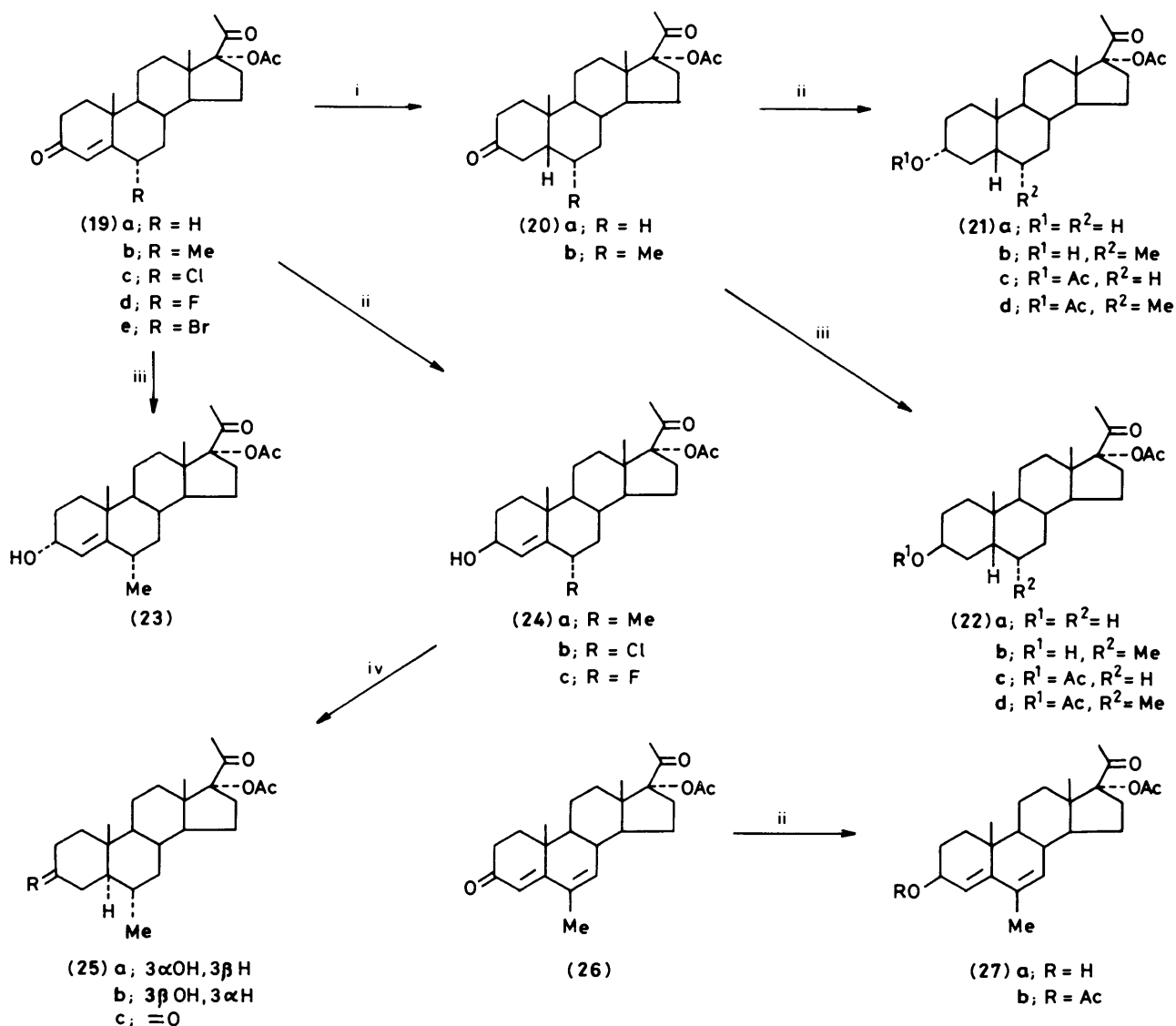
**Scheme 1.** Reagents: i, H<sub>2</sub>CrO<sub>4</sub>-HOAc; ii, LTBA; iii, Zn-HOAc; iv, Pd-CaCO<sub>3</sub>-pyridine; v, LS-Selectride; vi, B<sub>2</sub>H<sub>6</sub>; vii, Ag<sub>2</sub>CO<sub>2</sub>-Celite; viii, NBS; ix, Al<sub>2</sub>O<sub>3</sub>; x, Jones oxidation; xi, pyridine

catalyst.<sup>16</sup> This method of preparation of the axial alcohol in the 5 $\alpha$ -series is of value where, as in this case, initial reduction of the C-4 double bond is not readily achieved. Oxidation of the diol mixture gave the ketone (25c).

LTBA reduction of 17 $\alpha$ -acetoxy-6 $\alpha$ -chloropregn-4-ene-3,20-

dione (19c), prepared by the chlorination method of Mazac and Syhora<sup>17</sup> gave the 3 $\beta$ -alcohol (24b). LTBA reduction of the dienone (26) and acetylation gave the 3 $\beta$ -alcohol (27a) and 3 $\beta$ -acetate (27b).

The structures of the above compounds were established on



Scheme 2. Reagents: i, Pd-CaCO<sub>3</sub>-pyridine; ii, LTBA; iii, LS-Selectride; iv, Rh-C-H<sub>2</sub>

the basis of their <sup>1</sup>H n.m.r. spectra (see Table) which showed appropriate 10-methyl shifts and couplings for the CHOH protons at C-3 and C-6.

### Experimental

<sup>1</sup>H N.m.r. spectra are reported in the Table. H.p.l.c. was carried out in 1% ethanol-dichloromethane (unless stated otherwise) on a Waters  $\mu$ -Porasil (10  $\mu$ m) column using a Waters M45 instrument. Preparations, were monitored by t.l.c. on silica gel (Merck type 60 H) in 25–75% ethyl acetate-hexane followed by spraying with 4% concentrated sulphuric acid in ethanol and heating 5–10 min at 110 °C to produce a characteristic colour. Column chromatography was carried out on either neutral alumina or silica gel (Merck type 60 H for t.l.c.). M.p.s are uncorrected. Elemental analyses were performed by W. Baldeo, School of Pharmacy, University of London, England.

The following compounds were synthesized by the methods referenced below; structures were confirmed by m.p. and <sup>1</sup>H n.m.r. spectroscopy: 17 $\alpha$ -acetoxy-6 $\alpha$ -fluoropregn-4-ene-3,20-dione (19d), m.p. 261–264 °C (lit.,<sup>18</sup> m.p. 255–257 °C); 17 $\alpha$ -

acetoxy-6 $\alpha$ -fluoro-3 $\beta$ -hydroxypregn-4-en-20-one (24c), m.p. 144–146 °C (lit.,<sup>7</sup> m.p. 148–148.5 °C); 17 $\alpha$ -acetoxy-6 $\alpha$ -bromopregn-4-ene-3,20-dione (19e), m.p. 165–166 °C (lit.,<sup>19</sup> m.p. 163–166 °C);<sup>20</sup> 3 $\beta$ ,17 $\alpha$ -diacetoxy-5,6 $\alpha$ -epoxy-5 $\alpha$ -pregnan-20-one (13a), m.p. 225–229 °C (lit.,<sup>21</sup> m.p. 219–223 °C);<sup>22</sup> 3 $\alpha$ -6 $\alpha$ ,17 $\alpha$ -Triacetoxy-5 $\beta$ -pregnan-20-one (7b), m.p. 193–195 °C (lit.,<sup>23</sup> m.p. 196–199 °C) was prepared by acetylation of the triol obtained from Steraloids Inc., Wilton, NH, U.S.A.

*General Acetylation Procedure.*—To a 10% solution of the steroid in dry pyridine was added one-half the volume of acetic anhydride. After being set aside overnight at room temperature the reaction mixture was poured into ice-water and allowed to stand for 30 min; it was then acidified with dilute hydrochloric acid and extracted with ether.

17 $\alpha$ -Acetoxypregn-4-ene-3,6,20-trione (2).—17 $\alpha$ -Acetoxy-3 $\beta$ -hydroxypregn-5-en-20-one (1a) (1 g) was treated with Kiliani's reagent by the method previously reported by Ishige *et al.*<sup>3</sup> On t.l.c. a less polar component, which did not show fluorescence under u.v. radiation (5-en-3-one) rapidly formed and was converted into a more polar component in 2 h. The trione (4)

Table. <sup>1</sup>H Chemical shifts (*J* and *w*<sub>1</sub> in Hz)<sup>a</sup>

Compound	13-Me	10-Me	17-OAc	3-OAc	6-OAc	20-Ac	3-H	6-H	Other
(2)	0.70	1.18	2.07			2.12			2.73dd ( <i>J</i> 3.6, 15.6, 7β-H); 6.21d ( <i>J</i> 0.8, 4-H)
(3a)	0.67	1.19	2.04			2.11		4.36 ( <i>w</i> <sub>1</sub> 23)	6.19d ( <i>J</i> 1.7, 4-H)
(3b)	0.68	1.24	2.05		[2.13]	[2.10]		5.48ddd ( <i>J</i> 1.9, 5.5, 12.3)	5.93d ( <i>J</i> 1.8, 4-H)
(3c)	0.68	1.19	2.05			2.11		3.79ddd ( <i>J</i> 1.8, 5.3, 12.1)	3.41s (6-OMe); 6.13d ( <i>J</i> 1.8, 4-H)
(3d)	0.67	1.18	2.05			2.11		3.89ddd ( <i>J</i> 1.8, 5.3, 12.1)	1.23t ( <i>J</i> 7, 6-OCH <sub>2</sub> CH <sub>3</sub> ); 3.54m (6-OCH <sub>2</sub> CH <sub>3</sub> ); 6.15d ( <i>J</i> 1.8, 4-H)
(3e)	0.68	1.25	2.05			2.11		5.32ddd ( <i>J</i> 2, 5.5, 12.4)	3.81s (6-OCO <sub>2</sub> Me); 5.98d ( <i>J</i> 1.7, 4-H)
(3f)	0.68	1.24	2.05			2.11		5.31ddd ( <i>J</i> 2, 5.5, 12.4)	1.32t ( <i>J</i> 7.1, 6-OCO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ); 4.21ddd ( <i>J</i> 7.1, 14.3, 6-OCO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ); 5.99d ( <i>J</i> 1.7, 4-H)
(4a)	0.65	1.05	2.04			2.10	[4.22m]	[4.22m]	5.68d ( <i>J</i> 1.5, 4-H)
(4b)	0.63	1.08	2.02			2.10	4.17 ( <i>w</i> <sub>1</sub> 17)	5.31ddd ( <i>J</i> 2.2, 2.2, 4.8, 11.7) <sup>b</sup>	5.52d ( <i>J</i> 1.5, 4-H)
(4c)	0.63	1.10	2.03			2.10	5.35 ( <i>w</i> <sub>1</sub> 10)	5.27 ( <i>w</i> <sub>1</sub> 24)	5.46d ( <i>J</i> 1.4, 4-H)
(4d)	0.64	1.06	[2.03]	2.06		2.11	5.30 ( <i>w</i> <sub>1</sub> 20)	4.20d ( <i>J</i> 10)	5.62d ( <i>J</i> 1.5, 4-H)
(5)	0.97	0.66	2.06	[2.06]		2.13			
(6a)	0.64	1.02	2.04			2.14		4.13 ( <i>w</i> <sub>1</sub> 21)	
(6b)	0.65	1.08	[2.05]		[2.01]	2.14		5.18 sextet ( <i>J</i> 4.8, 4.8, 12.2)	
(7a)	0.61	0.98	[2.03]			2.16		5.15 sextet ( <i>J</i> 4.8, 4.8, 12.3)	
(7b)	0.61	0.99	2.02	[2.06]		2.15		5.16 ( <i>w</i> <sub>1</sub> 22)	
(8)	0.62	1.02	[2.03]	[2.02]		2.14		5.22 sextet ( <i>J</i> 4.8, 4.8, 12.1)	
(9a)	0.62	0.83	2.03			2.12		3.44 sextet ( <i>J</i> 5, 11, 11)	
(9b)	0.62	0.89	[2.04]	[2.03]		2.12		[4.65m]	
(10a)	0.69	1.07	2.08			2.16		3.56 septet ( <i>J</i> 5, 5, 11, 11)	
(10b)	0.69	1.13	[2.06]		[2.09]	2.15		4.79 sextet ( <i>J</i> 4.6, 11.0, 11.0)	
(11a)	0.66	0.84	2.07			2.16		3.43m	
(11b)	0.61	0.84	[2.03]		[2.02]	2.10		4.65 sextet ( <i>J</i> 4.6, 11.2, 11.2)	

(12)	0.64	1.33	[2.04]	2.14	5.49 septet ( $J$ 5, 5, 10.7, 10.7)	4.21d ( $J$ 0.8)	6.12t ( $J$ 1, 4-H)
(13a)	0.57	1.08	[2.01]	2.10	4.96 septet ( $w_{\ddagger}$ , 22)	2.92d ( $J$ 4.3)	6.40d ( $J$ 1.8, 4-H)
(13b)	0.60	1.01	[2.03]	2.11	4.78 ( $w_{\ddagger}$ , 27)	3.10d ( $J$ 2.1)	6.10t ( $J$ 0.9, 4-H)
(14)	0.61	0.83	[2.04]	2.13	5.05 septet ( $J$ 5, 5, 10.7, 10.7)		6.45d ( $J$ 1.8, 4-H)
(15)	0.62	1.00	2.06	2.17	5.34 septet ( $J$ 5, 5, 10.7, 10.7)		
(16)	0.66	1.03	[2.07]	2.12	5.33ddd ( $J$ 2.3, 6.5, 9.9)		
(17)	0.63	0.78	2.06	2.14	4.68 septet ( $J$ 5, 5, 10.7, 10.7)		
(18)	0.65	1.05	[2.04]	2.11	4.74 septet ( $J$ 5, 5, 10.7, 10.7)	3.82 ( $w_{\ddagger}$ , 8)	
(19c)	0.68	1.23	2.05	2.11		4.68ddd ( $J$ 1.9, 5.1, 12.8)	
(19d)	0.68	1.19	2.05	2.11		5.10ddd ( $J$ 2, 6, 12, 47.8)	
(19e)	0.68	1.23	2.05	2.11		4.88ddd ( $J$ 1.8, 7.1, 14.5)	
(20a)	0.65	1.03	2.04	2.14			
(20b)	0.65	1.02	2.04	2.13			
(21a)	0.61	0.92	2.03	2.15	3.68 ( $w_{\ddagger}$ , 27)		0.80d ( $J$ 8, 6-Me)
(21b)	0.60	0.91	2.02	2.15	3.63 septet ( $J$ 5, 5, 10.7, 10.7)		0.83d ( $J$ 6.9, 6-Me)
(21c)	0.61	0.94	[2.03]	2.15	4.76 ( $w_{\ddagger}$ , 27)		0.81d ( $J$ 6.8, 6-Me)
(21d)	0.60	0.93	[2.03]	2.15	4.74 septet ( $J$ 5, 5, 10.7, 10.7)		0.81d ( $J$ 7, 6-Me)
(22a)	0.61	0.97	2.03	2.13	4.14 ( $w_{\ddagger}$ , 7)		
(22b)	0.61	0.96	2.03	2.13	4.16 ( $w_{\ddagger}$ , 7)		
(22c)	0.62	0.99	[2.05]	2.14	5.10 ( $w_{\ddagger}$ , 10)		
(22d)	0.61	0.96	[2.06]	2.14	5.13 ( $w_{\ddagger}$ , 7)		
(23)	0.65	0.99	2.03	2.09	4.17 ( $w_{\ddagger}$ , 11)		
(24a)	0.65	1.05	2.02	2.08	4.17 ( $w_{\ddagger}$ , 20)		0.79d ( $J$ 6.9, 6-Me)
(24b)	0.65	1.09	2.04	2.09	4.24 ( $w_{\ddagger}$ , 18)		1.01d ( $J$ 6.6, 6-Me); 5.47dd ( $J$ 1.8, 5, 4-H)
(24c)	0.64	1.04	2.04	2.10	4.22 ( $w_{\ddagger}$ , 15)		5.28d ( $J$ 1.6, 4-H); 1.00d ( $J$ 6.5, 6-Me)
(25a)	0.62	0.80	2.03	2.11	4.08 ( $w_{\ddagger}$ , 9)		
(25b)	0.62	0.82	2.03	2.10	3.54 ( $w_{\ddagger}$ , 27)		
(25c)	0.64	1.01	2.03	2.10		4.58ddd ( $J$ 2.2, 2.2, 4.5, 12.1) <sup>b</sup>	5.68s (4-H)
(26)	0.72	1.09	2.06	2.09	4.25 ( $w_{\ddagger}$ , 16)		0.81d ( $J$ 7.3, 6-Me)
(27a)	0.69	0.97	2.04	2.07	5.41m		0.83d ( $J$ 6.3, 6-Me)
(27b)	0.69	0.99	[2.08]	(2.09)			0.81d ( $J$ 6.4, 6-Me)
							1.87s (6-Me); <sup>c</sup> 5.88s (4-H); 5.96s (7-H)
							1.80s (6-Me); <sup>c</sup> 5.49s (4-H and 7-H)
							1.79s (6-Me); <sup>c</sup> 5.44s (4-H and 7-H)

<sup>a</sup> Spectra were recorded in CDCl<sub>3</sub> (SiMe<sub>4</sub> internal standard) on a Bruker AM300 Instrument; chemical shift values in brackets are interchangeable or overlapping. The 16 $\beta$ H resonates in all compounds as a multiplet showing second order coupling at 2.90—3.00 p.p.m. <sup>b</sup> The C-6 $\beta$ H appears to be coupled to the 3 $\alpha$ H which was confirmed by decoupling and 2D experiments. <sup>c</sup> Allylic coupling.

(400 mg), m.p. 221—221.5 °C was recrystallized from dichloromethane–methanol (Found: C, 71.3; H, 7.7.  $C_{23}H_{30}O_5$  requires C, 71.5; H, 7.8%).

*17 $\alpha$ -Acetoxy-6 $\alpha$ -methoxy-(3c) and 17 $\alpha$ -Acetoxy-6 $\alpha$ -methoxycarbonyloxy-(3e) pregn-4-ene-3,20-dione.*—Silver oxide (1 g) was added to a solution of the 6 $\alpha$ -alcohol (3a) (200 mg) in *N,N*-dimethylformamide (5 ml) and iodomethane (5 ml) and the mixture was stirred for 24 h.<sup>4</sup> It was then filtered, diluted with ether, and the organic layer washed with water and evaporated to give a residue which was taken up in dichloromethane and chromatographed on silica. Elution with 2% acetone–dichloromethane gave the 6 $\alpha$ -methyl carbonate (3e) (148 mg) which was recrystallized from dichloromethane–ethyl acetate (110 mg), m.p. 198—200 °C (Found: C, 67.3; H, 7.8.  $C_{25}H_{34}O_7$  requires C, 67.2; H, 7.7%). Elution with 4% acetone–dichloromethane gave the 6 $\alpha$ -methoxy derivative (3c) (48 mg) which was recrystallized from ether–methanol (30 mg), m.p. 216—217 °C (Found: C, 71.45; H, 8.5.  $C_{24}H_{34}O_5$  requires C, 71.6; H, 8.5%).

*17 $\alpha$ -Acetoxy-6 $\alpha$ -ethoxy-(3d) and 17 $\alpha$ -Acetoxy-6 $\alpha$ -ethoxycarbonyloxy-(3f) pregn-4-ene-3,20-dione.*—The 6 $\alpha$ -ethyl ether (3d) was prepared from iodoethane and the 6 $\alpha$ -alcohol (3a) (200 mg) as described above for the 6 $\alpha$ -methyl ether (3c). Elution with 2% acetone–dichloromethane gave the non-crystalline 6 $\alpha$ -ethyl carbonate (3f) (52 mg) and 3% acetone–dichloromethane gave the 6 $\alpha$ -ethoxy derivative (3d) (126 mg) which was recrystallized from ether–methanol (100 mg), m.p. 216—217 °C (Found: C, 71.9; H, 8.7.  $C_{25}H_{36}O_5$  requires C, 72.1; H, 8.7%).

*3 $\beta$ ,6 $\alpha$ ,17 $\alpha$ -Triacetoxypregn-4-en-20-one (4c) from (4d).*—The 6 $\alpha$ -alcohol (4d) (228 mg) was acetylated to give the non-crystalline triacetate (4c) the <sup>1</sup>H n.m.r. spectrum of which was identical with that of the product obtained from the diol (4a) and the alcohol (4b).

*17 $\alpha$ -Acetoxy-5 $\alpha$ -pregnane-3,6,20-trione (5).*—A mixture of the unsaturated 3,6,20-trione (2) (100 mg), zinc dust (500 mg), and acetic acid (8 ml) was stirred and heated in an oil-bath (120 °C) for 30 min<sup>5</sup> when no starting material remained on t.l.c. Water (200 ml) was added and the mixture extracted with dichloromethane; the extract was then washed with water and aqueous sodium hydrogen carbonate and evaporated to give the saturated 3,6,20-trione (5) (56 mg), m.p. 232—233 °C from dichloromethane–acetone (Found: C, 71.3; H, 8.4.  $C_{23}H_{32}O_5$  requires C, 71.1; H, 8.3%).

*17 $\alpha$ -Acetoxy-6 $\alpha$ -hydroxy-5 $\beta$ -pregnane-3,20-dione (6a).*—The unsaturated ketone (3a) (3.6 g) and 5% Pd/CaCO<sub>3</sub> (1.0 g) in dry pyridine (150 ml) was stirred vigorously in a hydrogen atmosphere for 18 h.<sup>6</sup> The mixture was filtered, diluted with water, and extracted with dichloromethane to give the 5 $\beta$ -derivative (6a) (1.85 g), m.p. 203—206 °C from dichloromethane–ethyl acetate; recrystallization gave m.p. 205—207 °C (lit.,<sup>23</sup> m.p. 204—204.5 °C). Acetylation gave the 6 $\alpha$ -acetate (6b), m.p. 231—232 °C from dichloromethane–acetone (Found: C, 69.7; H, 8.3.  $C_{25}H_{36}O_6$  requires C, 69.4; H, 8.4%).

*17 $\alpha$ -Acetoxy-3 $\beta$ ,6 $\alpha$ -dihydroxy-5 $\alpha$ -pregnan-20-one (9a).*—To 17 $\alpha$ -Acetoxy-3 $\beta$ -hydroxypregn-5-en-20-one (1a) (1 g) in freshly distilled dry tetrahydrofuran (15 ml) in an argon atmosphere was added diborane (5.94 ml 1M solution in THF; 5.94 ml, 2.2 equiv.).<sup>9</sup> The mixture was stirred for 1 h at room temperature after which 10% aqueous NaOH was added and the mixture cooled in an ice-bath; hydrogen peroxide (30%; 3 ml) was then added dropwise and stirring continued for 1 h when the mixture was diluted with water and extracted with dichloromethane to give the 5 $\alpha$ -diol (9a) (456 mg) from

dichloromethane–ethyl acetate, m.p. 267—269 °C (Found: C, 70.2; H, 9.2.  $C_{23}H_{36}O_5$  requires C, 70.4; H, 9.2%). Acetylation gave the acetate (9b), m.p. 191—193 °C from ether–ethyl acetate (Found: C, 68.1; H, 8.45.  $C_{27}H_{40}O_7$  requires C, 68.0; H, 8.4%).

*17 $\alpha$ -Acetoxy-6 $\alpha$ -hydroxy-5 $\alpha$ -pregnane-3,20-dione (10a).*—A stirred solution of 17 $\alpha$ -acetoxy-3 $\beta$ ,6 $\alpha$ -dihydroxy-5 $\alpha$ -pregnan-20-one (9a) (1.5 g) in benzene (45 ml) was refluxed with silver carbonate/Celite for 1 h.<sup>10</sup> The mixture was filtered and evaporated and the residue recrystallized from dichloromethane–acetone to give the C-3 ketone (10a) (254 mg), m.p. 217—219 °C (Found: C, 71.0; H, 8.45.  $C_{23}H_{34}O_5$  requires C, 70.7; H, 8.8%). Acetylation gave the acetate (10b), m.p. 142—143/197—198 °C from ether–ethyl acetate (Found: C, 69.3; H, 8.6.  $C_{25}H_{36}O_6$  requires C, 69.4; H, 8.4%).

*3 $\beta$ ,17 $\alpha$ -Diacetoxy-5 $\alpha$ -bromo-6 $\beta$ -hydroxypregn-20-one (12).*—3 $\beta$ ,17 $\alpha$ -Diacetoxypregn-5-en-20-one (1b) (3.9 g) was treated with *N*-bromoacetamide (1.8 g) and perchloric acid (10% v/v; 15 ml) as described by Grenville *et al.*<sup>11</sup> and Bowers *et al.*,<sup>12</sup> to give the bromohydrin (12) (3.1 g), m.p. 191—192 °C (decomp.) from dichloromethane–acetone (lit.,<sup>24</sup> m.p. 184—186 °C). The same product was obtained without addition of perchloric acid.<sup>25</sup>

*3 $\beta$ ,17 $\alpha$ -Diacetoxy-5 $\beta$ ,6 $\beta$ -epoxy-5 $\beta$ -pregnan-20-one (13b).*—The bromohydrin (12) (1 g) in dichloromethane (50 ml) containing basic alumina (5 g) was stirred for 2 h at room temperature after which it was filtered to give a crystalline residue which on recrystallization from dichloromethane–acetone gave the 5 $\beta$ ,6 $\beta$ -epoxide (13b) (675 mg), m.p. 166—178 °C (lit.,<sup>21</sup> m.p. 168—173 °C).

*3 $\beta$ ,17 $\alpha$ -Diacetoxy-5 $\alpha$ -hydroxypregnane-6,20-dione (14).*—To a solution of 3 $\beta$ ,17 $\alpha$ -diacetoxypregn-5-en-20-one (1b) (2.1 g) in a mixture of dioxane (50 ml) and water (14 ml) was added *N*-bromosuccinimide (4.46 g, 5 equiv.). The mixture was stirred at room temperature for 22 h and then diluted with water and extracted with ether. The ether extract was washed with 10% aqueous sodium bisulphite and water to give a product which on recrystallization from dichloromethane–ethyl acetate yielded the 6,20-dione (14) (0.90 g), m.p. 277—279 °C (lit.,<sup>26</sup> m.p. 270—272 °C). Treatment of the 5 $\beta$ ,6 $\beta$ -epoxide (520 mg) under similar conditions gave the 6,20-dione (14) (340 mg), m.p. 269—273 °C.

*3 $\beta$ ,17 $\alpha$ -Diacetoxy-5 $\alpha$ -bromopregnane-6,20-dione (15).*—The bromohydrin (12) (2.5 g) in acetone cooled in an ice-bath was treated with an excess of 4M-chromic acid.<sup>12</sup> After 10 min methanol was added and the mixture diluted with water and extracted with dichloromethane to give the bromo ketone (15) (2.3 g), m.p. 195—197 °C (decomp.) from dichloromethane–methanol (Found: C, 58.7; H, 6.8; Br, 15.3.  $C_{25}H_{35}BrO_6$  requires C, 58.7; H, 6.9; Br, 15.6%).

*3 $\beta$ ,17 $\alpha$ -Diacetoxypregn-4-ene-6,20-dione (16).*—The bromo ketone (15) (500 mg) was treated with pyridine by the method of Magerlein *et al.*<sup>14</sup> to give, after passage through neutral alumina in 40% benzene–hexane, the unsaturated ketone (16) (405 mg), m.p. 195—200 °C from ethyl acetate. Recrystallization gave m.p. 203—204 °C (305 mg) (Found: C, 69.5; H, 7.8.  $C_{25}H_{34}O_6$  requires C, 69.7; H, 8.0%).

*3 $\beta$ ,17 $\alpha$ -Diacetoxy-5 $\alpha$ -pregnane-6,20-dione (17).*—Zinc dust (3 g) was added to a solution of the bromo ketone (15) (1 g) in acetic acid (15 ml) and the mixture stirred vigorously for 40 min. It was then diluted with water and extracted with dichloro-

methane: the extract upon evaporation afforded a residue which was recrystallized from dichloromethane-methanol to give the ketone (17) (703 mg), m.p. 248–250 °C (Found: C, 69.3; H, 8.25.  $C_{25}H_{36}O_6$  requires C, 69.4; H, 8.4%).

17 $\alpha$ -Acetoxy-6 $\alpha$ -chloropregn-4-ene-3,20-dione (19c).—The 6 $\alpha$ -chloro derivative (19c), m.p. 210–211 °C from dichloromethane-acetone (lit.,<sup>19</sup> m.p. 215–216 °C) was prepared by the method of Syhora and Mazac<sup>17</sup> for the analogous 16-methylene derivative.

17 $\alpha$ -Acetoxy-5 $\beta$ -pregnane-3,20-dione (20a).—17 $\alpha$ -Acetoxy-pregn-4-ene-3,20-dione (19a) (12 g) was dissolved in dry pyridine (50 ml) containing 10% Pd/CaCO<sub>3</sub> (1.35 g) and shaken in a hydrogen atmosphere for 24 h as described by Suvorov and Yaraslavtseva.<sup>6</sup> The reaction mixture was filtered and the residue recrystallized from dichloromethane-ethyl acetate to give the 5 $\beta$ -derivative (20a) (6.9 g), m.p. 211–212 °C (lit.,<sup>27</sup> m.p. 209 °C).

17 $\alpha$ -Acetoxy-6 $\alpha$ -methyl-5 $\beta$ -pregnane-3,20-dione (20b).—17 $\alpha$ -Acetoxy-6 $\alpha$ -methylpregn-4-ene-3,20-dione (19b) (8 g) in pyridine (40 ml) containing 10% Pd/CaCO<sub>3</sub> (1 g) was hydrogenated as described for 17 $\alpha$ -acetoxy-pregn-4-ene-3,20-dione (19a) above to give the 5 $\beta$ -derivative (20b) (6.9 g), m.p. 180–185 °C from dichloromethane-ethyl acetate (Found: C, 74.2; H, 9.4.  $C_{24}H_{36}O_4$  requires C, 74.2; H, 9.3%).

17 $\alpha$ -Acetoxy-3 $\alpha$ -hydroxy-(25a) and 17 $\alpha$ -Acetoxy-3 $\beta$ -hydroxy-6 $\alpha$ -methyl-5 $\alpha$ -pregnan-20-one (25b).—The olefin (24a)<sup>7</sup> (200 mg) in absolute ethanol (100 ml) containing glacial acetic acid (0.3 ml) and 5% rhodium on carbon catalyst was shaken in a hydrogen atmosphere for 48 h. The reaction mixture was then filtered and the filtrate concentrated, diluted with water, and extracted with dichloromethane. The organic layer was washed with aqueous sodium hydrogen carbonate and evaporated to yield a product which was chromatographed on silica in dichloromethane to give on elution with 2% acetone-dichloromethane a product (131 mg) which on h.p.l.c. separation yielded the 3 $\alpha$ ,5 $\alpha$ -derivative (2a) (47 mg), m.p. 173–176 °C from dichloromethane-methanol (Found: C, 73.75; H, 9.9.  $C_{24}H_{38}O_4$  requires C, 73.8; H, 9.8%) and the 3 $\beta$ ,5 $\alpha$ -derivative (25b) (36 mg), m.p. 229–230 °C from dichloromethane-methanol (Found: C, 73.8; H, 9.8.  $C_{24}H_{38}O_4$  requires C, 73.8; H, 9.8%). A similar mixture was obtained in the absence of acetic acid. Oxidation of the product mixture from hydrogenation with Jones' reagent gave the ketone (25c), m.p. 201–202 °C (dichloromethane-methanol) (Found: C, 74.0; H, 9.4.  $C_{24}H_{36}O_4$  requires C, 74.2; H, 9.3%). Similar hydrogenation of the dione (19b) gave a mixture of the following: 3 $\alpha$ ,5 $\alpha$ -alcohol (25a) (22%), 3 $\beta$ ,5 $\beta$ -alcohol (22b) (50%), 3 $\alpha$ ,5 $\beta$ -alcohol (21b) (14%), and 3 $\beta$ ,5 $\alpha$ -alcohol (25b) (14%) (by <sup>1</sup>H n.m.r.).

*Lithium Tri-*t*-butoxyaluminium Hydride Reduction: General Procedure.*—Unless otherwise stated the following procedure was used. To a solution of the steroid ketone (1 mmol) at 0 °C in either dry tetrahydrofuran (2% w/v) [for (3a), (4a), (4b), (7a), (24a), (24b), and (27a)] or dry ether (0.5% w/v) [for (4d), (18), (21a), or (21b)] was added LTBA (1.1 mmol). After 3–5 h reaction was complete (by t.l.c.), which showed two more-polar components than the starting ketone. The reaction was quenched with acetone followed by water and extracted with ether or dichloromethane.

(i) 17 $\alpha$ -Acetoxy-6 $\alpha$ -hydroxy-pregn-4-ene-3,20-dione (3a). Treatment of the trione (2) for 1 h with LTBA (1.1 equiv.) gave the dione (3a), m.p. 253–254.5 °C (dichloromethane-acetone) (Found: C, 71.1; H, 8.4.  $C_{25}H_{32}O_5$  requires C, 71.1; H, 8.3%). Acetylation gave the acetate (3b), m.p. 220–221 °C (dichloro-

methane-acetone) (Found: C, 69.5; H, 8.0.  $C_{25}H_{34}O_6$  requires C, 69.7; H, 8.0%).

(ii) 17 $\alpha$ -Acetoxy-3 $\beta$ ,6 $\alpha$ -dihydroxy-pregn-4-ene-20-one (4a). Treatment of the trione (2) for 24 h with LTBA (3.2 equiv.) gave the ketone (4a), m.p. 214–217 °C (dichloromethane-acetone) (Found: C, 70.7; H, 8.9.  $C_{23}H_{34}O_5$  requires C, 70.7; H, 8.8%). Acetylation gave a non-crystalline product the <sup>1</sup>H n.m.r. spectrum of which was identical with that of the triacetate (4c).

(iii) 6 $\alpha$ ,17 $\alpha$ -Diacetoxy-3 $\beta$ -hydroxy-pregn-4-ene-20-one (4b). The crude reduction product from reduction of the dione (3b) was separated by h.p.l.c. to give the alcohol (4b), m.p. 205–206 °C (dichloromethane-acetone) (Found: C, 69.2; H, 8.3.  $C_{25}H_{36}O_6$  requires C, 69.4; H, 8.4%). Acetylation gave a non-crystalline product the <sup>1</sup>H n.m.r. spectrum of which was identical with that of the triacetate (4c).

(iv) 3 $\beta$ ,17 $\alpha$ -Diacetoxy-3 $\beta$ -hydroxy-pregn-4-ene-20-one (4d). Reduction of the dione (16) gave the ketone (4d), m.p. 198–198.5 °C (dichloromethane-ethyl acetate) (Found: C, 69.3; H, 8.25.  $C_{25}H_{36}O_6$  requires C, 69.4; H, 8.4%). Acetylation gave a non-crystalline product the <sup>1</sup>H n.m.r. spectrum of which was identical with that of the triacetate (4c).

(v) 6 $\alpha$ ,17 $\alpha$ -Diacetoxy-3 $\alpha$ -hydroxy-5 $\beta$ -pregnan-20-one (7a). Reduction of the dione (6b) gave the ketone (7a), m.p. 191–193 °C (ether-ethyl acetate) (Found: C, 69.3; H, 9.05.  $C_{25}H_{38}O_6$  requires C, 69.1; H, 8.8%).

(vi) 3 $\beta$ ,17 $\alpha$ -Diacetoxy-6 $\beta$ -hydroxy-5 $\alpha$ -pregnan-20-one (18). Reduction of the dione (17) gave the ketone (18), m.p. 220–221 °C (dichloromethane-methanol) (Found: C, 68.9; H, 8.65.  $C_{25}H_{38}O_6$  requires C, 69.1; H, 8.8%).

(vii) 17 $\alpha$ -Acetoxy-3 $\alpha$ -hydroxy-5 $\beta$ -pregnan-20-one (21a). Reduction of the dione (20a) gave the ketone (21a), m.p. 207–208 °C (dichloromethane-ethyl acetate) (Found: C, 73.2; H, 9.7.  $C_{23}H_{36}O_4$  requires C, 73.4; H, 9.6%). Acetylation gave the diacetate (21c), m.p. 127–128 °C (dichloromethane-methanol) (lit.,<sup>28</sup> m.p. 228–232 °C) (Found: C, 71.9; H, 9.3.  $C_{25}H_{38}O_5$  requires C, 71.7; H, 9.15%).

(viii) 17 $\alpha$ -Acetoxy-3 $\alpha$ -hydroxy-6 $\alpha$ -methyl-5 $\beta$ -pregnan-20-one (21b). Reduction of the dione (20b) gave the ketone (21b), m.p. 213–214 °C (dichloromethane-ethyl acetate) (Found: C, 73.8; H, 9.9.  $C_{24}H_{38}O_4$  requires C, 73.8; H, 9.8%). Acetylation gave the diacetate (21d), m.p. 186–187 °C (dichloromethane-methanol) (Found: C, 72.1; H, 9.45.  $C_{26}H_{40}O_5$  requires C, 72.2; H, 9.3%).

(ix) 17 $\alpha$ -Acetoxy-3 $\beta$ -hydroxy-6 $\alpha$ -methylpregn-4-ene-20-one (24a). Reduction of the dione (19b) gave the ketone (24a), m.p. 186–187 °C (ethyl acetate) (lit.,<sup>7</sup> m.p. 182–185 °C).

(x) 17 $\alpha$ -Acetoxy-6 $\alpha$ -chloro-3 $\beta$ -hydroxy-pregn-4-ene-20-one (24b). The chloro ketone (19c) gave the ketone (24b) m.p. 184–186 °C (dichloromethane-acetone) (Found: C, 67.6; H, 8.35; Cl, 8.8.  $C_{23}H_{33}ClO_4$  requires C, 67.6; H, 8.1; Cl, 8.7%).

(xi) 17 $\alpha$ -Acetoxy-3 $\beta$ -hydroxy-6-methylpregna-4,6-dien-20-one (27a). Reduction of the dione (26) gave the ketone (27a), m.p. 201–205 °C (dichloromethane-methanol) (lit.,<sup>29</sup> m.p. 190–205 °C) (Found: C, 74.3; H, 9.0.  $C_{24}H_{34}O_4$  requires C, 74.6; H, 8.9%). Acetylation gave the acetate (27b) m.p. 190–192 °C from ether-ethyl acetate (lit.,<sup>29</sup> m.p. 197–199 °C) (Found: C, 73.0; H, 8.6.  $C_{26}H_{36}O_5$  requires C, 72.9; H, 8.5%).

*K- and LS-Selectride Reduction: General Procedure.*—K-Selectride and LS-Selectride refer to a 1M-solution in tetrahydrofuran (Aldrich Chemical Co., Milwaukee, WI, USA) of potassium hydridotri-*s*-butylborate and lithium tris(1,2-dimethylpropyl)hydriodborate, respectively. To a stirred solution of the steroid ketone (1 mmol) in freshly distilled tetrahydrofuran (20 ml) at –78 °C (acetone-solid CO<sub>2</sub> bath) under nitrogen was added either K-Selectride (1.1 ml) [for (22a) or (22b)] or LS-Selectride (1.1 ml) [for (8), (11a), (11b), (18), or (23)]. Reaction was complete (by t.l.c.) in 1–2 h after which

time the mixture was allowed to reach room-temperature when it was treated with 0.1M HCl (35 ml) and extracted with dichloromethane.

(i)  $3\beta,6\alpha,17\alpha$ -Triacetoxy-5 $\beta$ -pregnan-20-one (**8**). Reduction of the dione (**6a**) followed by acetylation gave the triacetate (**8**), m.p. 212–215 °C (dichloromethane–ethyl acetate) (Found: C, 67.9; H, 8.5.  $C_{27}H_{40}O_7$  requires C, 68.0; H, 8.5%).

(ii)  $17\alpha$ -Acetoxy-3 $\alpha,6\alpha$ -dihydroxy-5 $\alpha$ -pregnan-20-one (**11a**). Reduction of the dione (**10a**) gave the ketone (**11a**), m.p. 148–149 °C (ethyl acetate) (Found: C, 70.3; H, 9.3.  $C_{23}H_{36}O_5$  requires C, 70.4; H, 9.2%).

(iii)  $6\alpha,17\alpha$ -Diacetoxy-3 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one (**11b**). Reduction of the dione (**10b**) gave, after h.p.l.c. separation, the ketone (**11b**), m.p. 196–198 °C (ether–methanol) (Found: C, 69.2; H, 8.8.  $C_{25}H_{38}O_6$  requires C, 69.1; H, 8.8%).

(iv)  $3\beta,17\alpha$ -Diacetoxy-6 $\beta$ -hydroxy-5 $\alpha$ -pregnan-20-one (**18**). Reduction of the dione (**17**) gave the ketone (**18**), m.p. 220–221 °C (dichloromethane–methanol) the  $^1H$  n.m.r. spectrum of which was identical with that of the product obtained from LTBA reduction.

(v)  $17\alpha$ -Acetoxy-3 $\beta$ -hydroxy-5 $\beta$ -pregnan-20-one (**22a**). Reduction of the dione (**20a**) gave the ketone (**22a**), m.p. 231.5–232.5 °C (dichloromethane–acetone) (Found: C, 73.3; H, 9.6.  $C_{23}H_{36}O_4$  requires C, 73.4; H, 9.6%). Acetylation gave the acetate (**22c**), m.p. 180–184 °C (dichloromethane–ethyl acetate) (lit.<sup>28</sup> m.p. 86–88 °C) (Found: C, 71.9; H, 9.3.  $C_{25}H_{38}O_5$  requires C, 71.7; H, 9.15%).

(vi)  $17\alpha$ -Acetoxy-3 $\beta$ -hydroxy-6 $\alpha$ -methyl-5 $\beta$ -pregnan-20-one (**22b**). Reduction of the dione (**20b**) gave the ketone (**22b**), m.p. 250–252 °C (dichloromethane–acetone) (Found: C, 73.5; H, 9.8.  $C_{24}H_{38}O_4$  requires C, 73.8; H, 9.8%). Acetylation gave the acetate (**22d**), m.p. 204–205 °C (dichloromethane–ethyl acetate) (Found: C, 72.1; H, 9.45.  $C_{26}H_{40}O_5$  requires C, 72.2; H, 9.3%).

(vii)  $17\alpha$ -Acetoxy-3 $\alpha$ -hydroxy-6 $\alpha$ -methylpregn-4-en-20-one (**23**). Reduction of the dione (**19b**) gave, after h.p.l.c. separation in 10% ethyl acetate–hexane, the 3 $\alpha$ -alcohol (**23**), m.p. 209–210 °C (dichloromethane–acetone) (Found: C, 74.0; H, 9.2.  $C_{24}H_{36}O_4$  requires C, 74.2; H, 9.3%).

### Acknowledgements

The authors thank the Manitoba Heart Foundation for financial support. We thank the Manitoba Health Research Council for financial support in the purchase of the Bruker AM300. The authors are grateful to Mr. R. F. Donnelly, Ms. Anne Friesen, Ms. D. Smith and Dr. C. C. Jackson, Faculty of Pharmacy for assistance in the syntheses and Mr. Kirk Marat, Department of Chemistry, University of Manitoba, for recording the  $^1H$  n.m.r. spectra.

### References

- 1 R. S. Kim, F. S. LaBella, H. Zunza, F. Zunza, and J. F. Templeton, *Mol. Pharmacol.*, 1980, **18**, 395.
- 2 F. S. LaBella, I. Bihler, J. F. Templeton, R. S. Kim, M. Hnatowich, and D. Rohrer, *Fed. Proceed., Fed. Am. Soc. Exp. Biol.*, 1985, **44**, 2806.
- 3 M. Ishige, M. Shiota, and F. Suzuki, *Can. J. Chem.*, 1976, **54**, 2581.
- 4 R. E. Beyler, U.S.P. 3,105,840/1963; 3,126,399/1964 (*Chem. Abstr.*, 1964, **60**, 3056a; 1965, **61**, 8369h).
- 5 A. Windaus, *Chem. Ber.*, 1906, **39**, 2249.
- 6 N. N. Suvorov and Z. A. Yaraslavtseva, *Zh. Obsch. Khim.*, 1961, **31**, 1372.
- 7 D. J. Marshall, P. F. Morand, C. Revesz, and R. Gaudry, *J. Medicin. Chem.*, 1964, **7**, 355.
- 8 G. Gondos and J. C. Orr, *J. Chem. Soc., Chem. Commun.*, 1982, 1239.
- 9 M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, 1964, **29**, 1120.
- 10 E. R. H. Jones, G. D. Meakins, J. Pragnell, W. E. Muller, and A. L. Wilkins, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2376.
- 11 V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 1957, 4105.
- 12 A. Bowers, E. Denot, L. C. Ibanez, M. E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, 1962, **27**, 1862.
- 13 A. V. Kamernitakii, E. I. Chernoburova, and I. G. Reshetova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 1437.
- 14 B. J. Magerlein, D. A. Lyttle, and R. H. Levin, *J. Org. Chem.*, 1955, **20**, 1709.
- 15 G. Ohloff, B. Maurer, B. Winter, and W. Giersch, *Helv. Chim. Acta*, 1983, **66**, 192.
- 16 N. Nishimura, M. Ishige, and M. Shiota, *Chem. Lett.*, 1977, 963.
- 17 K. Syhora and R. Mazac, *Collect. Czech. Chem. Commun.*, 1966, **31**, 2768.
- 18 A. Bowers, L. C. Ibanez, and H. J. Ringold, *J. Am. Chem. Soc.*, 1959, **81**, 5991.
- 19 H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *J. Am. Chem. Soc.*, 1959, **81**, 3485.
- 20 M. Numazawa and Y. Osawa, *Steroids*, 1979, **34**, 347.
- 21 J. C. Babcock, J. A. Campbell, and J. A. Hogg, U.S.P. 2,838,469/1959 (*Chem. Abstr.*, 1960, **54**, 4683f).
- 22 A. Bowers and H. J. Ringold, *Tetrahedron*, 1958, **3**, 14.
- 23 U. Eberhardt, *Pharmazie*, 1977, **32**, 146.
- 24 A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, 1962, **84**, 3204.
- 25 E. J. Corey and J. Das, *Tetrahedron Lett.*, 1982, **23**, 4217.
- 26 T. Kolek and I. Malunowicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 1972, **20**, 1009.
- 27 K. Junkmann and H. Witzel, *Z. Vitam. Horm. Fermentforsch.*, 1958, **9**, 97.
- 28 S. Honma, S. Iwamura, K. Iizuka, A. Kambegawa, and K. Shida, *Chem. Pharm. Bull.*, 1977, **25**, 2019.
- 29 P. B. Sollman, U.S.P. 3,136,789/1964 (*Chem. Abstr.*, 1964, **60**, 14576f).

Received 23rd June 1986; Paper 6/1262