Ring-c Aromatic Steroids. Part 4.† The c-Aromatic Analogue of Progesterone

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The ring-c aromatic analogue of progesterone, 18-norpregna-4,8,11,13-tetraene-3,20-dione (2), was formed together with its 17-epimer (3) when 9α,11α-epoxy-20ξ-hydroxy-3-oxopregn-4-eno-18,20-lactone (14) was subjected to oxidative decarboxylation, and the resulting products treated with boron trifluoride. The precursor (14) was synthesised as follows. 11α-Hydroxyprogesterone (4) was dehydrated, and the product then selectively reduced (by two routes) to 20β-hydroxypregna-4,9(11)-dien-3-one (9). The latter was functionalised at C-18 to give 3-oxopregna-4,9(11)-dieno-18,20-lactone (10) which was oxidised, after opening of the lactone ring, to the corresponding lactol (12). The latter was converted into the required lactol epoxide (14). Internal displacement on the 9α,11α-epoxide occurred when the lactol epoxide (14) was treated with acid, yielding 9α-hydroxy-3,20-dioxopregn-4-eno-18,11β-lactone (16).

Earlier we carried out the synthesis of ring-c aromatic steroids of the 17β-methyl-18-norpregnane series by migration, to C-17, of the methyl group at the c/d junction of a 17-hydroxy steroid,[1,2] or of a 16α,17-epoxy steroid.[3] Two members of this group of ring-c aromatic steroids, *viz.* (1; R = H) and its 20-epimer, showed remarkably different corticoid activities in rodents. For structure–activity relationship studies it is desirable to produce c-aromatic C_{21} steroids devoid of a 17β-methyl group. In this paper, we report, as a first step in this direction, the synthesis of the ring-c aromatic analogue of the hormone progesterone, *viz.* 18-norpregna-4,8,11,13-tetraene-3,20-dione (2), and of its 17-epimer (3). Both are currently being evaluated for potential hormonal activity.

Instead of a Wagner–Meerwein rearrangement used previously, the removal of the methyl group from the c/d junction is achieved by a Barton-type functionalisation [5] followed by oxidative decarboxylation,[6] a reaction sequence used by Phillipou and his co-workers to form 18-norsteroids.[7] As in our earlier work [1-3] the synthetic strategy calls for the generation of the requisite degree of unsaturation at ring c prior to the removal of the methyl group at the c/d junction. In this case the 9α,11α-epoxy group serves as the precursor for two units of unsaturation, while oxidative decarboxylation provides the third unit of unsaturation.

The first synthetic objective is 20β-hydroxypregna-4,9(11)-dien-3-one (9) which has suitably placed double-bond and hydroxy groups required for epoxidation and functionalisation reactions respectively. This was obtained from 11α-hydroxyprogesterone (4) by two routes, both starting with dehydration to give $\Delta^{9(11)}$-progesterone (5). In an early study of the action of boiling collidine on the toluene-*p*-sulphonate of 11α-hydroxyprogesterone, Rosenkranz *et al.*[8] obtained, in 74% yield, a dehydrated product of m.p. 127—128 °C which they considered to be $\Delta^{9(11)}$-progesterone (5). In our hands, the pure toluene-*p*-sulphonate (see Experimental section) gave, in a similar yield, a product of the same m.p. which consisted of (by ^{1}H n.m.r. analysis, see Table 1) a 7 : 3 mixture of $\Delta^{9(11)}$- and Δ^{11}-progesterone (5) and (6). Smaller amounts of the Δ^{11}-isomer were obtained in dehydrations using either phosphoryl trichloride in pyridine,‡ or *N*-bromosuccinimide (NBS) and sulphur dioxide in pyridine.[9] We consider the last is the method of choice as it is superior in overall yield and in content of the desired $\Delta^{9(11)}$-product; a small amount of the Δ^{11}-product was removed in the course of subsequent reactions.

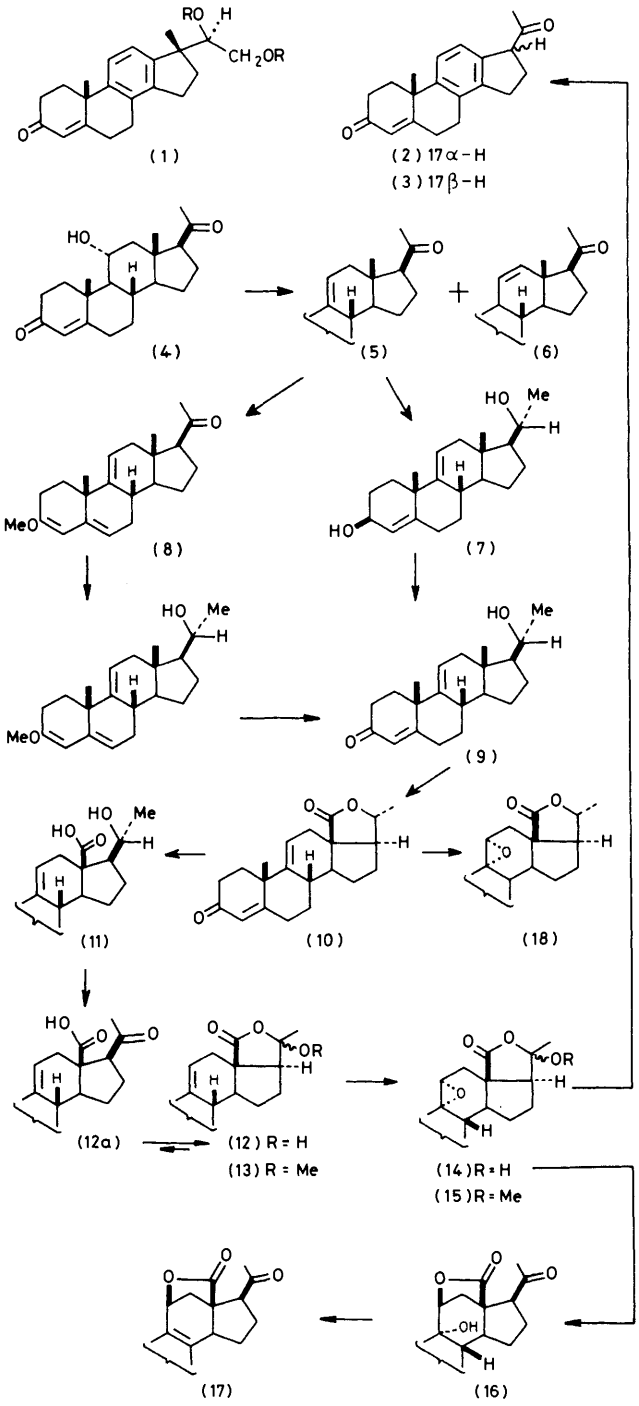
In the first route to 20β-hydroxypregna-4,9(11)-dien-3-one (9), $\Delta^{9(11)}$-progesterone (5) (from the $POCl_3$ method) was reduced by sodium borohydride. Fractional crystallisation removed the contaminating Δ^{11}-isomer, and the resulting 3β,20β-diol (7) ($J_{3,4}$ *ca.* 1 Hz, see Table 1) was selectively oxidised by manganese dioxide to give the required hydroxy ketone (9). More conveniently, the Δ^4-3-one function of the dione (5) (from the NBS–SO_2 method) was protected by conversion into the methyl dienol ether (8). After removal of the contaminating Δ^{11}-isomer by chromatography over silica, the pure dienol ether (8) was reduced to the corresponding 20β-alcohol (not isolated), followed by deprotection to give 20β-hydroxypregna-4,9(11)-dien-3-one (9) in 46% overall yield from 11α-hydroxyprogesterone (4).

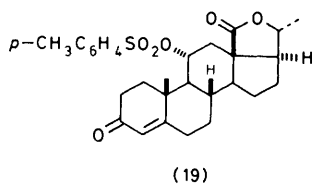
Functionalisation at C-18 of the 20β-alcohol (9) so obtained was carried out as described by Heusler *et al.*[10] using lead tetra-acetate followed by Jones oxidation to yield the 18,20β-lactone (10).[11] The α configuration of the methyl group at C-20 is shown by the <1 Hz coupling of 20β-H and 17α-H in the ^{1}H n.m.r. spectrum, thus confirming the presence of a 20β hydroxygroup in its precursors. Jones oxidation of the lactone (10) to the lactol (12) was carried out *via* the hydroxy acid (11), obtained on vigorous alkaline hydrolysis. The lactol (12) was soluble in aqueous alkali, confirming its partial existence in the open carboxylic acid form (12a),[7] but on treatment with methanolic hydrochloric acid was converted into the methylated lactol (13), which was insoluble. That the former compound exists partially in the open form (12a) even in chloroform solution is evident from the ^{1}H n.m.r. spectrum (Table 1). In contrast with its methyl ether (13), the lactol (12)/(12a) shows minor n.m.r. signals for an acetyl methyl (21-H_3), singlet at δ 2.15, and a 10-Me (19-H_3) singlet at δ 1.28 [the latter at the same position as the corresponding signal in the acid (11)].

Both the lactol (12) and its methyl ether (13) were smoothly converted by *m*-chloroperbenzoic acid into the corresponding 9α,11α-epoxides (14) and (15), respectively. The partial existence of the former epoxide as an open carboxylic acid caused some problems in its work-up when attempts were made to remove *m*-chlorobenzoic acid with alkali. The difficulty was overcome in two ways as described in the Experimental section. In attempting to devise yet another solution to this practical problem, we tried generating the lactol epoxide (14) from its methylated analogue (15). However, even 0.1M hydrochloric acid at room temperature resulted in the opening of the 9α,11α-epoxide ring, and the formation of an 18,11β-lactone. This reaction is discussed further below.

† Part 3, reference 4.

‡ This reagent was considered undesirable when a Δ^4-3-keto group is present [8] (see also P. R. Graber, A. C. Haven, and N. L. Wendler, *J. Am. Chem. Soc.*, 1953, **75**, 4722).





The oxidative decarboxylation of the lactol epoxide (14) was carried out using lead tetra-acetate in the presence of pyridine and copper(II) acetate.[12] The crude reaction mixture gave, in the methane chemical-ionisation mass spectrum, an MH^+ ion of m/z 313, corresponding to the loss of HCO_2H from the lactol epoxide (14). The reaction product was treated with boron trifluoride–diethyl ether complex in benzene. When carried out under reflux the product consisted of (by ^1H n.m.r. analysis, see Table 1) a 1 : 1 mixture of the progesterone analogue (2) (*viz.* 18-norpregna-4,8,11,13-tetraene-3,20-dione) and its 17-epimer (3). The product ratio changed to *ca.* 2 : 1 when the reaction was repeated at 0 °C or at 23 °C. It is evident that epimerisation at the α and benzylic carbon C-17 was taking place, and that the minor component at <23 °C was the epimerised compound (3). By preparative high-pressure liquid chromatography (h.p.l.c.) pure crystalline samples of the two C-aromatic products (2) and (3) were obtained from the 23 °C reaction in overall yields (two steps) of 11.4 and 5.6%, respectively. The poor yield was not significantly affected by a change of reaction temperature, the bulk of the by-products being apparently polymeric.

In an effort to increase the yield of the C-aromatic product, the oxidative decarboxylation of an 18,11β-lactone [*viz.* (17)] was investigated. While the epoxides (14) and (15) were stable when worked up under conditions in which acids were excluded, the lactol epoxide (14) was found to isomerise when recrystallised without special care. This transformation was repeated using methanolic hydrochloric acid, giving the 9α-hydroxy-18,11β-lactone (16) in 70% yield. This S_N2-type displacement on C-11 of the protonated epoxide by the C-18 carboxylic acid group is reminiscent of the related displacement reaction on the 11α-toluene-*p*-sulphonate (19) as observed by Heusler *et al.*[10] The structure of the hydroxy lactone (16) was confirmed by its ^1H and ^{13}C n.m.r. data (Tables 1 and 2), which showed a methyl signal at δ 2.18, a signal for 11α-H at δ 4.65 ($J_{11,12\beta}$ 5.5, $J_{11,12\alpha}$ <1 Hz) and *three* carbonyl signals at δ_C 176.5 (lactone), 199.0 (C-3),* and 207.5 p.p.m. (17-acetyl).*

The α configuration of the 9-hydroxy group, inferred from its mode of formation, is confirmed by the observed strong steric γ-*gauche* effects of this group on carbons 1,7, and 14 (*ca.* 7 p.p.m.) [see Table 2, progesterone *vs.* (16)]. In support, ready dehydration occurred when the hydroxy lactone (16) was exposed to thionyl chloride in pyridine at −10 °C. The resulting Δ^8-lactone (17) showed an 11α-H signal ($J_{11,12\beta}$ 5.5, $J_{11,12\alpha}$ <1 Hz) 0.3 p.p.m. to lower field than in its precursor, in agreement with its allylic nature. The 12β-H signal appears at the unusually downfield position of δ 3.15 and shows spittings by 11α-H and 12α-H (Table 1). Models show that 12β-H is co-planar with the Δ^8-double bond.

We investigated the possibility of oxidative decarboxylation of the Δ^8-lactone (17). However, neither it nor the derived hydroxy acid was decarboxylated under conditions which were successfully applied to the lactol epoxide (14). The Δ^8-lactone (17) was recovered in each case.

^{13}C *N.M.R. Results.*—^{13}C N.m.r. data shown in Table 2 are in full accord with the structures of the products. The ^{13}C signals are assigned by consideration of chemical shift theory, the number of attached hydrogen [from single-frequency off-resonance decoupled, or attached-proton test[14] (APT) spectra], internal consistency, and comparison with model compounds. Thus, the signals for $\Delta^{9(11)}$-progesterone (5) were assigned by applying to progesterone[13] the known shift effect of $\Delta^{9(11)}$-unsaturation on the androstane skeleton;[15] and the $\Delta^{9(11)}$-steroids (9), (10), and (12) were compared with the other $\Delta^{9(11)}$-steroids (20) and (21) prepared in connection with other work.[2] Among the $\Delta^{9(11)}$-steroids, the 18-carboxy compounds (10) and (12) are characterised by a decreased γ-*gauche* shielding (*ca.* 2.5 p.p.m.) of C-8 and C-15 by C-18, when compared with their 18-methyl counterparts (9), (20),

* The corresponding signals in progesterone (Table 2) appear at δ_C 198.5 and 208.3 p.p.m. (ref. 13).

Table 1. ^{1}H N.m.r. data [a]

Compd.	3-H	4-H	11-H	12-H	18-H	19-H	20-H	21-H	Other protons
(5)	—	5.75d [b]	5.5m [c]		0.62	1.33	—	2.14	
(6) [d]	—	5.75d [b]	*ca.* 5.65	6.3br d	0.76	1.16	—	2.22	
(9)	—	5.75d [b]	5.5m [c]		0.74	1.33	3.7m	1.14d [h]	
(7)	4.15m ($\Sigma J_{3,2}$ 13)	5.3d [b]	*ca.* 5.35m		0.75	1.20	3.75m	1.15d [h]	
(11)	—	5.75d [b]	5.55m [c]		—	1.30	3.6m	1.17d [h]	
(8)	—	5.2	5.5m		0.62	1.14	—	2.14	3.6 (OMe) *ca.* 5.3m (6-H)
(10)	—	5.8d [b]	5.5m		—	1.46	4.4q ($J_{20\beta,21}$ 6.5, $J_{17\alpha,20\beta} < 1$)	1.38d [h]	
(12) [and (12a)]	—	5.8d [b]	5.5m		—	1.42 [1.28]		1.63 [2.15]	
(13)	—	5.8d [b]	5.5m		—	1.43	—	1.53	3.3 (OMe)
(14)	—	5.8d [b]	3.3d ($J_{11,12}$ 5, <1)			1.49	—	1.49	
(18)	—	5.8d [b]	3.2d ($J_{11,12}$ 4.5, <1)		—	1.50	4.3q (J 6.5)	1.28d [h]	
(16)	—	5.9d [b]	4.65d ($J_{11,12}$ 5.5, <1)	2.65—2.9m [e]	—	1.22	—	2.18	
(17)	—	5.8d [b]	4.95d [f] ($J_{11,12}$ 5.5, <1)	1.9d [f] (α) 3.15dd [g] (β) ($J_{12,12}$ 10.5, $J_{11,12\beta}$ 5.5)	—	1.40	—	2.20	
(2)	—	5.95	7.2	7.2	—	1.58	—	2.23	4.1t [i] (17α-H)
(3)	—	5.95	7.2	7.2	—	1.58	—	2.20	4.1t [i] (17β-H)

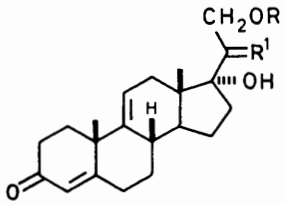
[a] Chemical shifts in p.p.m. downfield from $SiMe_4$ in $CDCl_3$ (to $\pm$0.01 p.p.m. for Me and to $\pm$0.05 p.p.m. for other signals) and, in parentheses, coupling constants J in Hz. For compound (11), CD_3OD was added to increase solubility. [b] J *ca.* 1 Hz; for (7) signal becoming singlet (and half-height width decreasing by *ca.* 0.5 Hz) on irradiation of 3-H. [c] Half-height width *ca.* 10 Hz. [d] Data extracted from spectrum of a mixture of compounds (5) and (6). [e] Signal shape affected by irradiation at δ 4.65. [f] Collapsed to singlet when irradiated at δ 3.15. [g] Collapsed to doublet when irradiated at δ 4.65. [h] J 6—6.5 Hz. [i] X of ABX, with $J_{17,16\alpha}$ and $J_{17,16\beta}$ = 13.5 Hz in (2), and 14.5 Hz in (3).

Table 2. ^{13}C N.m.r. chemical shifts [a]

Carbon atom	Compound: Progesterone [13]	(5)	(9)	(20) [b]	(21) [b]	(10)	(12)	(14)	(18)	(16)	(2)	(3)	(1, R = Ac) [c]
1	35.6	34.4 *	34.3 *	34.2 *	34.3 *	34.2 *	33.9 *	27.3 #	27.6 #	28.2 #	37.2	37.1	37.1
2	33.8	34.0 *	33.8 *	33.8 *	33.9 *	33.8 *	33.5 *	33.9 *	34.2 *	33.5 *	34.7	34.8	34.8
3	198.5	199.1	199.6	199.6	199.3	199.2	200.0	199.2	198.7	199.0	198.7	198.7	198.7
4	123.7	124.0	123.6	123.8	124.1	123.8	123.5	126.0	126.0	127.0	124.2 [f]	124.3 [f]	124.1 [f]
5	169.8	169.5	170.9	170.5	169.6	169.8	170.9	167.7	167.3	168.1	169.4	169.3	169.5
6	32.6	32.3 *	32.4 *	32.3 *	32.3 *	32.4 *	32.1 *	32.7 *	33.4 *	31.6 *	30.6	30.6	30.6
7	31.8	32.9 *	33.0 *	33.0 *	32.9 *	32.7 *	32.6 *	28.2 #	28.6 #	25.6 #	28.4	28.4	28.3
8	35.4	37.4	37.2	37.8	37.7	35.4	35.8	35.1	33.5	40.3	131.3	131.3	130.9
9	53.5	145.2	144.2	143.7	144.4	147.3	146.3	68.6	69.2	75.6	143.1 *	143.2 *	143.0
10	38.5	40.7	41.0	41.0	41.1	41.2	41.0	40.3	40.4	44.1	39.3	39.2	39.2
11	21.0	118.4	119.6	119.6	118.6	115.3	116.0	54.0	53.3	77.3	124.8 [f]	124.9 [f]	124.8 [f]
12	38.5	40.8	41.6	34.0 *	34.8	36.0	35.0	33.3 *	33.8 *	36.4	123.2	123.2	121.9
13	43.7	42.4	41.0	46.3	47.3	51.4	53.8	52.7	*d*	54.0	138.3	138.5	144.4
14	55.9	53.0	52.3	46.6	47.9	52.1	51.5	46.0	46.6	45.6	142.8 *	142.8 *	141.3
15	24.2	25.6	25.7 #	25.0	24.6	28.2	27.7 #	26.7 #	27.3 #	25.1 #	30.6	30.5	29.2
16	22.8	23.0	25.5 #	33.2 *	32.1 *	33.1 *	26.0 #	26.7 #	32.7 *	24.4 #	28.1	28.3	34.8
17	63.3	63.5	58.2	84.1	88.9	50.9	54.3	54.0	51.0	54.0	58.7	58.8	50.0
18	13.2	13.1	11.9	14.8	15.0	178.3	178.3	179.1	179.5	176.5	—	—	24.8
19	17.3	26.2	26.1	26.1	26.3	25.9	25.7	20.9	21.1	19.9	27.7	27.8	27.8
20	208.3	209.0	69.8	73.0	212.1	82.3	106.1	*d*	82.9	207.5	208.6	208.6	76.4
21	31.3	31.3	23.8	67.3	67.3	22.9	24.2 [e]	*d*	23.2	28.9	28.1	27.8	63.8
CH_3CO				21.0									20.6, 21.0
CH_3CO				171.5									170.4, 170.6

*, # Assignments within a vertical column may be reversed.

[a] In p.p.m. downfield from $SiMe_4$ in $CDCl_3$, with δ ($CDCl_3$) 77.1 p.p.m. [b] Data taken from ref. 2. [c] Data taken from ref. 1; δ ($SiMe_4$) 0 p.p.m. [d] Not observed due to interconversion with open form. [e] Broad. [f] C-11 is distinguished from C-4 by comparison of the residual couplings in the single-frequency off-resonance decoupled spectrum.



(20) R = Ac, R^1 = H, β-OH

(21) R = H, R^1 = O

and (21), and of course by appropriate large shift changes at C-13 and C-18.

It is instructive to make a ^{13}C n.m.r. comparison of the $\Delta^{9(11)}$-compounds (12) and (10) and their respective 9α,11α-epoxy analogues (14) and (18) (for the latter, see Experimental section) which are conformationally similar. For steroids, an epoxide causes increased shielding of those γ carbon atoms which have an axial hydrogen *cis* to it.[16] In the case of the 9α,11α-epoxides, the shielding effects on carbons 1,7, and 14 are *ca.* 5 p.p.m. On the other hand, when the lactones (10) and (18) are compared with the lactols (12) and (14), an extra hydroxy group at C-20 gives rise to γ-shielding of C-16 (*ca.* 6 p.p.m.) and β-deshielding of C-17 (*ca.* 3 p.p.m.). The low magnitude of the latter effect may reflect that in deuteriochloroform the lactols (12) and (14) are in equilibrium with significant amounts of the open forms [*cf.* (12a)] (see above).

^{13}C N.m.r. signals of the C-aromatic progesterone analogues (2) and (3) are assigned by comparison with our data on 17β-methyl C-aromatic steroids such as (1; R = Ac).[1] The derivation of the earlier assignments have been thoroughly discussed.[1] The ^{13}C n.m.r. data of the 17-epimers (2) and (3) differ significantly only in the shieldings of C-21. This carbon is 0.3 p.p.m. more shielded for the (17βH)-isomer (3) than for the (17αH)-isomer (2), possibly reflecting a higher degree of γ-interaction with C-16.

Experimental

N.m.r. data for compounds described herein are given in Tables 1 (^1H) and 2 (^{13}C). These were collected using a JEOL FX-90Q spectrometer operating at 89.6 and 22.5 MHz, respectively, in the Fourier-transform mode. *All mass spectral data refer to chemical ionisation* using methane as reagent gas and carried out on a Finnigan 3200E quadrapole mass spectrometer with the associated 6110 data system. Column chromatographic separations were carried out under *ca.* 30 Torr pressure using t.l.c.-grade silica gel. In the work-up procedures, washing and drying refer to the use of water or saturated sodium chloride and anhydrous sodium sulphate, respectively, and evaporation was performed under reduced pressure. M.p.s were uncorrected. Light petroleum refers to that fraction boiling in the range 40—60 °C.

Dehydration of 11α-*Hydroxyprogesterone* (4).—(*a*) A solution of 11α-hydroxyprogesterone (4) (1.0 g) and NBS (1.08 g) in pyridine (10 ml) was stirred under nitrogen and in the dark for 1 h at 25 °C. Sulphur dioxide was bubbled through the stirred mixture which was maintained at <25 °C until a negative test with acidified potassium iodide–starch resulted. After a further 10 min at 25 °C, water (15 ml) was added at such a rate that the temperature was kept <30 °C, followed by 5M hydrochloric acid (15 ml). The mixture was stirred at 12 °C for 30 min and then kept at 5 °C overnight. The precipitated product (0.61 g, 65%), m.p. 116—122 °C (from benzene–light petroleum), consisted of pregna-4,9(11)-diene-3,20-dione (5) contaminated with 5% of the Δ^{11}-isomer (6) (^1H n.m.r., Table 1).

(*b*) Phosphoryl trichloride (25 ml) was added to a solution of 11α-hydroxyprogesterone (4) (25 g) in pyridine (160 ml) at 0 °C. The mixture was heated to 100 °C for 10 min, cooled, poured onto ice, and acidified with 2M hydrochloric acid. The precipitate collected was crystallised from aqueous ethanol to give a 5 : 1 mixture of pregna-4,9(11)-diene-3,20-dione (5) and its Δ^{11}-isomer (6) (^1H n.m.r. analysis, see Table 1). Chromatography over silica resulted in a product (58% yield) with decreased content of the Δ^{11}-product. A sample crystallised from acetone–light petroleum melted at 116—124 °C, *m/z* 341 (10%, $M + C_2H_5^+$), and 313 (100, MH^+).

(*c*) 11α-Hydroxyprogesterone toluene-*p*-sulphonate,[8] m.p. 154—155 °C (lit.,[8] 154—155 °C); $\delta_H(CDCl_3)$ 0.63 and 1.34 (18-H and 19-H), 1.86 (Ac), 2.44 ($CH_3C_6H_4$), 5.08 [d of X of ABX (*J* 11, Σ*J* 15 Hz),11β-H], 5.79 (4-H), and 7.38 and 7.83 (each d, *J* 8 Hz, C_6H_4), was treated with collidine and worked up as described by Rosenkranz *et al.*[8] to give, on crystallisation from acetone–light petroleum, a 7 : 3 mixture of $\Delta^{9(11)}$- and Δ^{11}-progesterone (5) and (6), m.p. 127—128 °C (76%) (^1H n.m.r. analysis).

Pregna-4,9(11)-*diene*-3β,20β-*diol* (7).—Impure pregna-4,9(11)-diene-3,20-dione (5) (13.6 g), prepared by the dehydration method (*c*) above, was dissolved in a 3 : 1 mixture of methanol–tetrahydrofuran (THF) (200 ml) at 0 °C and sodium borohydride (2.55 g) was added during 2 h. After the addition of acetic acid (2.5 ml), water (600 ml) was added. The white precipitate formed was collected and dissolved in ethyl acetate (500 ml). Evaporation of the washed and dried ethyl acetate solution gave a solid (12.2 g) which was fractionally crystallised from chloroform to yield the $\Delta^{9(11)}$-diol (7) (8.8 g) as needles, m.p. 163—165 °C.

3-*Methoxypregna*-3,5,9(11)-*trien*-20-*one* (8).—Pregna-4,9(11)-diene-3,20-dione (5), contaminated with 5% of the Δ^{11}-isomer (6) (see above) (350 mg) was dissolved in 2,2-dimethoxypropane (3.25 ml) and an equal volume of *N,N*-dimethylformamide. Toluene-*p*-sulphonic acid monohydrate (10 mg) and methanol (0.12 ml) were added and the mixture was refluxed for 2.5 h, cooled, and sodium hydrogen carbonate (50 mg) was added. All solvent was removed by distillation under reduced pressure and the residue was chromatographed over silica (30 g) with ethyl acetate–light petroleum (10—60%) as eluant, each 100 ml containing 1 drop of triethylamine. This gave firstly 3-methoxypregna-3,5,11-trien-20-one (11 mg), then 3-methoxypregna-3,5,9(11)-trien-20-one (8) (230 mg, 78%), and finally recovered (5) (52 mg). A sample of the latter dienol ether (8) was recrystallised from acetone–light petroleum to give *needles*, m.p. 107—110 °C (Found: C, 80.8; H, 9.05. $C_{22}H_{30}O_2$ requires C, 80.95; H, 9.25%); *m/z* 367 (5%, $M + C_3H_5^+$), 355 (10, $M + C_2H_5^+$), and 327 (100, MH^+).

20β-*Hydroxypregna*-4,9(11)-*dien*-3-*one* (9).—(*a*) A solution of pregna-4,9(11)-diene-3β,20β-diol (7) (8.8 g) in freshly distilled dry chloroform (65 ml) at room temperature was stirred with freshly activated manganese dioxide washed thoroughly with hot chloroform. The residue obtained on evaporation of the combined chloroform solutions was chromatographed over silica gel to give the hydroxy ketone (9) as *needles* from benzene (6.8 g, 78%), m.p. 144—146 °C (Found: C, 80.1; H, 9.35. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%); *m/z* 355 (5%, $M + C_3H_5^+$), 343 (15, $M + C_2H_5^+$), 315 (100, MH^+), and 297 (15, $MH - H_2O^+$).

(*b*) To a solution of the dienol ether (8) (200 mg) in 1 : 1 methanol–THF (10 ml) was added sodium borohydride (20 mg) during 30 min at 0 °C. The mixture was then stirred for 30 min at this temperature, 5M hydrochloric acid was added

until the pH reached 4, and the mixture was stirred at 23 °C overnight before being neutralised with 2M NaOH. Solvents were partially removed under reduced pressure, water (10 ml) was added, and the mixture was extracted with ethyl acetate. The combined extracts were washed, dried, and evaporated to give the hydroxy ketone (9) (178 mg, 92%) which crystallised from acetone–light petroleum as needles, m.p. 142—146 °C.

(20R)-3-*Oxopregna*-4,9(11)-*dieno*-18,20-*lactone* (10).—A solution of the hydroxy ketone (9) (1.50 g), lead tetra-acetate (recrystallised) (10.3 g), and iodine (1.37 g) in cyclohexane (200 ml) was refluxed under irradiation with a 500-W tungsten lamp. When the iodine colour disappeared (1.5 h) the mixture was cooled, filtered, and the residue was washed with benzene. The combined filtrate and washings were washed twice with 5% aqueous sodium thiosulphate and then with water. The organic phase was treated with triethylamine (0.2 ml), dried, and evaporated. The oily residue was dissolved in acetone (30 ml) at 0—5 °C and was treated with Jones' reagent [18] (2.2 ml). After 30 min, sodium acetate (15.4 g) in water (45 ml) was added, and the solution was extracted with diethyl ether (3 × 150 ml). Evaporation of the washed and dried extract and crystallisation from diethyl ether gave needles of the lactone (10) (0.70 g, 45%), m.p. 224—226 °C (recrystallised from acetone–light petroleum) (lit.,[10] 225—228 °C); *m/z* 367 (5%, $M + C_3H_5^+$), 355 (15, $M + C_2H_5^+$), and 327 (100, MH^+).

20β-*Hydroxy*-3-*oxopregna*-4,9(11)-*dien*-18-*oic Acid* (11).—The lactone (10) (1.8 g) was heated under reflux in 20% methanolic potassium hydroxide for 3 h. The mixture was poured into ice–water and the solution was brought to pH 5 with sulphuric acid and extracted with chloroform and diethyl ether. The extracts were separately washed and dried, then combined and evaporated. Trituration of the residue with ethyl acetate followed by crystallisation from methanol gave the *hydroxy acid* (11) as an amorphous solid (1.37 g), m.p. 208—209 °C (decomp.) (Found: C, 73.4; H, 8.25. $C_{21}H_{28}O_4$ requires C, 73.25; H, 8.2%); *m/z* 385 (10%, $M + C_2H_5^+$), 345 (100, MH^+), 327 (35, $MH - H_2O^+$), 301 (5, $MH - CO_2^+$), and 299 (10, $327 - CO^+$).

20ξ-*Hydroxy*-3-*oxopregna*-4,9(11)-*dieno*-18,20-*lactone* (12).—A solution of the hydroxy acid (11) (100 mg) in acetone (30 ml) at 0 °C was treated with a slight excess of Jones reagent.[18] After the addition of water and partial removal of acetone, the solution was worked up to give the lactol (12) (75 mg) as *plates* from acetone–light petroleum, m.p. 170—172 °C (Found: C, 73.65; H, 7.5. $C_{21}H_{26}O_4$ requires C, 73.65; H, 7.65%); *m/z* 371 (10%, $M + C_2H_5^+$), 343 (100, MH^+), 325 (15, $MH - H_2O^+$), and 297 (15, $297 - CO^+$).

20ξ-*Methoxy*-3-*oxopregna*-4,9(11)-*dieno*-18,20-*lactone* (13).—A solution of the lactol (12) (200 mg) in methanol (10 ml) was treated with 10M hydrochloric acid (0.05 ml) at room temperature. After 4.5 h the mixture was poured into cold 0.5M sodium hydrogen carbonate (30 ml) and extracted with chloroform. The residue obtained on evaporation of the washed and dried chloroform solution was crystallised from methanol to give needles of the *methylated lactol* (13) (150 mg), m.p. 164—169 °C (decomp.) (Found: C, 73.85; H, 7.65. $C_{22}H_{28}O_4$ requires 74.15; H, 7.9%); *m/z* 397 (5%, $M + C_3H_5^+$), 385 (20, $M + C_2H_5^+$), 357 (100, MH^+), 325 (10, $MH - CH_3OH^+$), and 297 (10, $325 - CO^+$). It was reconverted into the lactol (12) when kept overnight at 18 °C in 4 : 1 methanol–0.1M hydrochloric acid.

9α,11α-*Epoxy*-20ξ-*hydroxy*-3-*oxopregn*-4-*eno*-18,20-*lactone* (14).—(*a*) To a solution of the lactol (12) (3.1 g, 9.1 mmol) in freshly distilled chloroform (50 ml) was added *m*-chloroperbenzoic acid (2.0 g, 11.6 mmol) in chloroform (20 ml) during 10 min. After the mixture had been stirred at room temperature for 50 min light petroleum (500 ml) was added and the mixture was kept overnight at 4 °C. After the organic solution was decanted, the solid remaining was washed with chloroform–light petroleum, and all solvent remaining was blown off with nitrogen to leave an oil (3.4 g). This was crystallised from acetone–light petroleum containing a few drops of triethylamine at 0—5 °C to give the lactol epoxide (14) (1.33 g). Solvent was removed from the mother liquor and the resulting oil was chromatographed over silica gel, with light petroleum–ethyl acetate (containing 1 drop of triethylamine per 100 ml of solvent) as eluant to give a further crop of the lactol epoxide (14) (0.87 g) (total yield 68%). A sample crystallised from acetone–light petroleum as *plates*, m.p. 200—203 °C (decomp.) (Found: C, 70.15; H, 7.25. $C_{21}H_{26}O_5$ requires C, 70.35; H, 7.3%); *m/z* 399 (10%, $M + C_3H_5^+$), 387 (20, $M + C_2H_5^+$), 359 (100, MH^+), and 341 (10, $MH - H_2O^+$).

(*b*) A solution of the lactol (12) (175 mg, 0.51 mmol) and *m*-chloroperbenzoic acid (100 mg, 0.58 mmol) in freshly distilled chloroform (10 ml) was kept at room temperature for 20 min by which time t.l.c. showed the reaction to be complete. After dilution with chloroform (30 ml), the solution was shaken with 5% aqueous sodium hydrogen sulphite until negative to iodide–starch test, and was then washed in turn with water, 1% aqueous sodium hydrogen carbonate (7.7 ml, 0.92 mmol), and finally water. The residue obtained on evaporation of the dried solution was crystallised from acetone–light petroleum or from methanol to give plates of the lactol epoxide (14) (90 mg, 49%). The yield was reduced when the sodium hydrogen carbonate used to extract the *m*-chlorobenzoic acid was stronger than 1% (see text).

9α,11α-*Epoxy*-20ξ-*methoxy*-3-*oxopregn*-4-*eno*-18,20-*lactone* (15) *and* (20R)-9α,11α-*Epoxy*-3-*oxopregn*-4-*eno*-18,20-*lactone* (18).—The methylated lactol (13) (300 mg) was converted into the epoxide (15) as described immediately above [procedure (*b*)], but (as the product is not alkali-soluble) using an excess of *m*-chloroperbenzoic acid, and 5% sodium hydrogen carbonate in the work-up. The epoxy lactol (15) (250 mg, 79%) crystallised from methanol as *plates*, m.p. 193—198 °C (decomp.) (Found: C, 71.0; H, 7.55. $C_{22}H_{28}O_5$ requires C, 70.95; H, 7.6%); *m/z* 413 (10%, $M + C_3H_5^+$), 401 (20, $M + C_2H_5^+$), 373 (100, MH^+), 355 (10, $MH - H_2O^+$), and 341 (15, $MH - CH_3OH^+$).

Upon similar epoxidation of the lactone (10), the epoxy lactone (18) was obtained as *needles*, m.p. 285 °C (decomp.) (Found: C, 68.75; H, 7.35. $C_{21}H_{26}O_4 \cdot 1.5H_2O$ requires C, 68.25; H, 7.9%).

9α-*Hydroxy*-3,20-*dioxopregn*-4-*eno*-18,11β-*lactone* (16).—A solution of the lactol epoxide (14) (50 mg) in a mixture of methanol (2.5 ml) and 0.1M hydrochloric acid (5 ml) was kept at 60 °C for 1 h. After neutralisation with 0.1M sodium hydroxide and evaporation of methanol, the solution was extracted with chloroform. The crude product (35 mg) obtained on evaporation of the washed and dried extract was crystallised from acetone–light petroleum to yield needles of the *hydroxy lactone* (16), m.p. 216—219 °C (Found: C, 70.7; H, 7.4. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%); *m/z* 399 (5%, $M + C_3H_5^+$), 387 (10, $M + C_2H_5^+$), 359 (100 MH^+), and 341 (5, $MH - H_2O^+$).

3,20-*Dioxopregna*-4,8-*dieno*-18,11β-*lactone* (17).—A solution of the hydroxy lactone (16) (100 mg) and thionyl chloride (0.3 ml) in pyridine (1 ml) at −10 °C was kept for 1 h after

which t.l.c. showed completion of reaction. The mixture was poured onto ice–water (20 ml), acidified (pH 5), saturated with sodium chloride, and extracted repeatedly with chloroform. The combined extracts were washed with 0.1M hydrochloric acid until the washings were acidic, and were then washed with water, dried, and evaporated. Crystallisation of the residue gave *plates* of the Δ^8-lactone (17), m.p. 183—186 °C; *m/z* 381 (5%, $M + C_3H_5^+$), 369 (20, $M + C_2H_5^+$), 341 (100, MH^+), 323 (35, $MH - H_2O^+$), and 295 (35, 323 $- CO^+$) [Found: M^+ (electron-impact m.s.), 340.166. $C_{21}H_{24}O_4$ requires *M*, 340.167].

(17αH)- *and* (17βH)-18-*Norpregna*-4,8,11,13-*tetraene*-3,20-*dione* (2) *and* (3).—A mixture of 9α,11α-epoxy-20ξ-hydroxy-3-oxopregn-4-eno-18,20-lactone (14) (1.70 g), lead tetra-acetate (3.4 g), copper(II) acetate [12] (136 mg), and pyridine (1.5 ml) in benzene (300 ml) was refluxed under nitrogen for 30 min. The mixture was cooled to 25 °C, filtered, and the residue was washed with benzene. The combined filtrate and washings were washed with water until neutral, dried, and the solvent was evaporated to give the decarboxylated products as a brown oil (1.50 g).

To the above product dissolved in benzene (150 ml) was added boron trifluoride–diethyl ether complex (1.5 ml) at 4 °C. After being stirred at 23 °C for 24 h the mixture was diluted with benzene (100 ml) and washed in turn with phosphate buffer (100 ml) at pH 6.8 and water. The dried solution was evaporated and the brown oil (0.87 g) was chromatographed over silica (30 g) with ethyl acetate–light petroleum (5—20%) as eluant to give a mixture of (17αH)- and (17βH)-18-norpregna-4,8,11,13-tetraene-3,20-dione (2) and (3) (275 mg). The two isomers were separated by preparative h.p.l.c. on a Partisil M9 10/60 column in 20 mg lots, with 10% ethyl acetate–dichloromethane as eluant, to give pure (17αH)-isomer (2) (the C-aromatic analogue of progesterone) (160 mg), recrystallised from acetone–light petroleum as *needles*, m.p. 125—126.5 °C, and pure (17βH)-isomer (3) (78 mg), recrystallised from acetone–light petroleum as *needles*, m.p. 116—117.5 °C [Found for (2): C 81.2; H, 7.35. Found for (3): C, 81.15; H, 7.5. $C_{20}H_{22}O_2$ requires C, 81.6; H, 7.55%]. Both showed *m/z* 335 (5%, $M + C_3H_5^+$), 323 (15, $M + C_2H_5^+$), 295 (100, MH^+), and 251 (10, $M - CH_3CO^+$).

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