SHORT PAPER

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The preparation of 21,21-dimethylprogesterone†

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The kinetically controlled alkylation of pregnenolone acetate has been used to prepare the 21,21-dimethyl analogue which was then converted into 21,21-dimethylprogesterone.

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The introduction of alkyl groups onto the steroid framework has for many years, been a useful strategy in the enhancement of biological activity. This is exemplified by the increased progestational activity shown by 17-methylprogesterone.[1] In this paper we describe the preparation of 21,21-dimethylprogesterone. There has been relatively little interest in the C-21 alkylation of progesterone since early studies[2] with the homologues of progesterone, 21-methyl and 21-ethylprogesterone, showed that they had little progestational activity on the proliferation of the endometrium of test aninlals. Subsequent studies[3-5] have concentrated on the preparation of 17α-alkyl and 16α, 17α -dialkylpregnanes in which 21-methylated pregnanes were unwanted by-products. However, a 19-nor-steroid promegestone, 17α, 21-dimethyl-19-norpregna-4,9-diene-3, 20-dione,[6] has attracted interest because it binds to the progestin receptor.

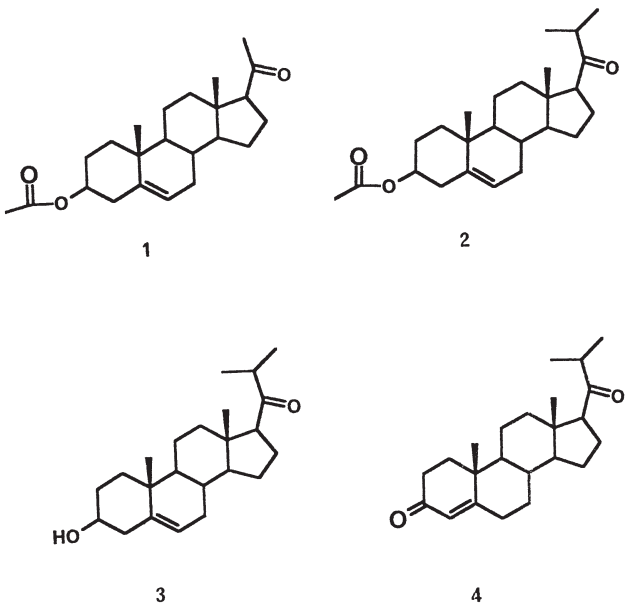
The alkylation at C-17 was achieved by the generation of the intermediate 17-enolate anion through reduction of a 16-dehydropregn-20-one[3] or by the conjugate addition of methylmagnesium halide to the unsaturated ketone.[4,5] This was followed by quenching the anion with methyl iodide. The higher homologues of progesterone were prepared[2] by a malonic ester synthesis from the 20-carboxylic acid chloride.

The regioselective alkylation in the α-position to a steroidal ketone has been thoroughly studied in the context of the alkylation of ring A.[7] The role of kinetic and thermodynamic control in the alkylation of ketones is well established. In the enolisation of pregn-20-ones, the more heavily-substituted 20(21)-enolate is the thermodynamic enolate whilst the less-highly substituted 20(21)-enolrate is the kinetic product. Hence if the kinetic enolate is generated in the presence of an excess of methyl iodide, alkylation should take place at C-21. This proved to be the case and it was possible to obtain the 21,21-dimethyl compound **2** from pregnenolone acetate **1** by generation of the anion with sodium hydride and quenching with a large excess of methyl iodide. The product **2** showed two additional methyl group doublets in the ^{1}H NMR spectrum (δ_H 0.92 and 0.94, J 7.1 Hz) The ^{13}C NMR spectrum of the corresponding alcohol **3** retained the characteristic low field methine signal at δ_C 61.0 assigned to C-17 whilst there was a new methine signal at δ_C 41.2 assigned to C-21 (see Table 1). Hence the alkylation had taken place at C-21. On occasions the product was contaminated by a trimethyl analogue but this was not obtained pure.

Hydrolysis of the 3β-acetate **2** with methanolic potassium carbonate gave the 3β-alcohol **3**. Oxidation of this alcohol using the Oppenauer method with aluminium isopropoxide and cyclohexanone, gave the ketone and brought about the isomerisation of the Δ^5-double bond to give 21,21-dimethylprogesterone **4** in satisfactory yield. The ^{13}C NMR spectrum (see Table 1) confirmed the structure.

Table 1 ^{13}C NMR data (determined in $CDCl_3$ at 75 MHz)

Carbon atom	3	4
1	36.5	35.7
2	31.5	33.9
3	71.6	199.4
4	42.23	12.3.9
5	141.1	171.0
6	121.3	31.9
7	31.5	32.7
8	32.1	35.5
9	49.9	53.6
10	36.4	38.5
11	21.1	21.0
12	38.9	38.7
13	44.5	44.4
14	56.9	56.0
15	23.4	23.4
16	24.6	24.5
17	61.0	60.8
18	13.7	13.7
19	17.1	17.1
20	214.4	215
21	41.2	41.1
21-Me	19.0,19.4	17.3,19.2



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

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80°C. ^{1}H and ^{13}C NMR spectra were determined at 300 and 75 MHz respectively in deuteriochloroform. IR spectra were determined as nujol mulls. Extracts were dried over sodium sulfate.

Methylation of pregnenolone acetate **1**: Pregnenolone acetate **1**, prepared by acetylation of pregnenolone with acetic anhydride in pyridine, had m.p. 146-148^{0}C (lit.,[8] 146–147°C). Sodium hydride (2 g) was washed with light petroleum and suspended in dry tetrahydrofuran (30 cm^3) under nitrogen. Pregnenolone acetate (3 g) in dry tetrahydrofuran (120 cm^3, was carefully added to the ice-cold suspension. Methyl iodide (18 cm^3) was then added by a syringe and the mixture was left for 38 h. The proceress of the reaction was monitored by TLC. The mixture was cooled ancl concentrated under vacuum. The residue was diluted with ether (250 cm^3). The extract was washed with water and aqueous soduim hydrogen carbonate, brine and dried. The solvent was evaporated to give 3β-acetoxy-21,21-dimethylpregn-5-en-20-one **2** (2.05 g) which crystallised from methanol as needles, m.p.125–127°C (Found:M^+ 386.285 $C_{25}H_{38}O_3$ requires 386.282), ν_{max}/cm^{-1} 1735, 1708: δ_H 0.64(3H, s, 18-H) 0.92 and 0.94 (each 3H, d, *J* 7.1 Hz, 21-Me), 1.02 (3H, s 19-H), 2.03 (3H, s, OAc), 0.95-2.20 (21H, overlapping multiplets), 4.50 (1H, tt, *J* 11 and 5 Hz, 3-H), 5.26 (1H, d 5 Hz, 6-H).

*Hydrolysis of the 3*β*-acetate* **2**: 3β-Acetoxy-21. 21-dimethylepregn-5-en-20-one (2 g) in methanol (60 cm^3) was treared with a solution of potassium carbonate (4 g) in water (20 cm^3) for 1 h at room temperature. Acetic acid (6 cm^3) ws added and the methanol was evaporated in vacuo. The residue was extracted with ethyl acetate. The extract was washed with water, dried and the solvent evaporated to give 21,21-dimethyl-3β-hydroxypregn-5-en-20-one 3 (1.44 g), m.p. 145–147°C, (Found:M^+ 345.278 $C_{23}H_{36}O_2$ + H^+ requires 345.279), ν_{max}/cm^{-1} 3415, 1708: δ_H 0.62 (3H, s, 18-H), 1.02 (3H, s, 19-H), 1.03 and 1.03 (each 3H,d, *J* 6.8 Hz, 21-Me), 0.95–2.20 (21H, overlapping multiplets), 3.53 (1H,m,3-H), 5.36(1H,d, *J* 4 Hz, 6-H).

*Oxidation of the 3*β*-alcohol* **3**: 21,21-Dimethyl-3β-hydroxypregn-5-en-20-one (1 g) and cyclohexanone (6 cm^3) were dissolved in toluene (50 cm^3) and a portion of the toluene (15 cm^3) was distilled. Aluminium isopropoxide (4 g) in toluene (10 cm^3) was added and the toluene was distilled over a period of 4 h. Saturated sodium tartrate (5 cm^3) was added. Water (50 cm^3) was then added and the mixture was steam distilled until 75 cm^3 of distillate had been collected. The residue was cooled and extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate, water and brine and dried. The solvent was evaporated to give 21,21-dimethylpregn-4-ene-3,20-dione (21,21-dimethylprogesterone) **4** (587 mg) which crystallised from ethyl acetate:light petroleum as needles, m.p. 120–210°C, (Found: M^+ 343.262 $C_{23}H_{34}O_2$ + H^+ requires 343.263) υ_{max}/cm^{-1} 1708, 1698; δH 0.65(3H,s,28-H), 1.02 and 1.05 (each 3H, d, *J* 6.8 Hz, 21-Me), 1.20(3H,s, 19-H), 0.95–2.30(21H, overlapping multiplets), 5.74 (1H,s, 4-H).

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