Synthesis of 6α-methyl-16α,17α-cyclohexano-19-norprogesterone from a 19-methyl-6-desmethyl precursor

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After prolonged refluxing of 19-tosyloxy-16α,17α-cyclohexanopregn-5-en-3β-ol-20-one (**3**) with NaI in 2-propanol, the initially formed 19-iodo derivative (**4**) undergoes supraface migration of the CH_2I group from the C(10) atom to the C(6) atom, probably through involvement of a homoallyl cation. The resulting 6β-iodomethyl-16α,17α-cyclohexano-19-norpregn-5(10)-en-3β-ol (**5**) was transformed in three steps into 6α-methyl-16α,17α-cyclohexano-19-norprogesterone (6α-methyl-19-nor-D'_6-pentarane, **8**). The transformation of compound **5** into the target product **8** also gave a side product, a pentarane with aromatic ring *A* (**10**), which was isolated and characterized by spectroscopic methods.

Key words: 6-methyl-19-norpentaranes, synthesis, transformations; homoallylic rearrangement.

In a continuation of studies of the synthesis and structure—activity relationships of active 16α,17α-cyclohexanoprogesterones (D'_6-pentaranes)[1,2] we synthesized 6α-methyl-16α,17α-cyclohexano 19-norprogesterone (Scheme 1, **8**). It was shown previously[2] that the progestagenic activity of D'_6-pentaranes increases considerably when a 6-methyl group is introduced into the molecule. The purpose of the present work was to find out if a similar modification in a series of 19-nor-D'_6-pentaranes had the same effect. The first step involved the synthesis of these compounds.

We studied the possibility of obtaining compound **8** from 19-hydroxypentarane **1**, an intermediate product in the synthesis of 16α,17α-cyclohexano-19-norprogesterone,[3] through homoallylic rearrangement of its 19-substituted derivative[4] (see Scheme 1). It is known that solvolysis or nucleophilic substitution of 19-tosyl(or mesyl)oxy-3β-hydroxy(or acetoxy)-Δ^5-steroids can give, along with the corresponding 19-derivatives, 6-substituted 19-nor-$\Delta^{5(10)}$-steroids, 5β,19-cyclo-6-substituted steroids, and *B*-homo-$\Delta^{5,10}$-steroids. The direction of the reactions and the yields of the above reaction products depend on the conditions chosen for the process and are controlled by a combination of kinetic and thermodynamic factors.[5—9]

It was found that refluxing 19-tosylate **3** (obtained by alkaline hydrolysis of 3β-acetate **2**) with NaI in 2-propanol in an argon atmosphere, followed by chromatographic purification of the reaction mixture resulted in formation of 19-iodide **4** in >50% yield. The structure of compound **4** follows from its ^{1}H NMR spectrum, which contains apart from two singlets of the 18-Me and 21-Me groups (δ 0.80 and 2.14, respectively), a two-proton AB-system of signals of the 10-iodomethyl group (δ 3.28, 3.58, J = 11 Hz)* and a signal of the olefinic proton at C(6) with δ 5.62.

On the other hand, prolonged (>30 h) refluxing of tosylate **3** with excess NaI in 2-propanol resulted in a rearrangement product, *i.e.*, 6β-iodomethyl-$\Delta^{5(10)}$-steroid **5**; the ^{1}H NMR spectrum of the reaction mixture did not reveal the presence of the substitution product **4**. Similar results were obtained when the reaction was carried out in acetonitrile. The structure of compound **5** was confirmed spectroscopically. The ^{1}H NMR spectrum contains singlets of protons of the 18-Me and 21-Me groups with δ 0.71 and 2.13, respectively, whereas the signal of the olefinic proton at C(6) with δ 5.62 is not observed. The presence of a 6-iodomethyl group is indicated by the presence of a two-proton AB-system (δ 3.08, 3.48, J = 11 Hz).

The transformation of the 19-iodo-Δ^5 derivative **4** into compound **5** was also observed when pure iodide **4** was heated in 2-propanol for 7—10 h (^{1}H NMR spectral data). This transformation is most likely to occur as a homoallylic-cyclopropylcarbinylic rearrangement.[5]

The β-configuration at the C(6) atom in the molecule of iodide **5** was assigned because this rearrangement product is formed *via* a homoallyl cation.[5,6]

Reduction of the 6β-iodomethyl product **5** with lithium aluminum hydride in ether gave a mixture of 6β-methyl-3β,20-diols **6**, which was oxidized by pyridinium chlorochromate (PCC) or by the Jones reagent in CH_2Cl_2 to afford 6β-methyl-$\Delta^{5(10)}$-3,20-diketone

* The corresponding signals in the spectrum of tosylate **3** are located at δ 3.96 and 4.10.

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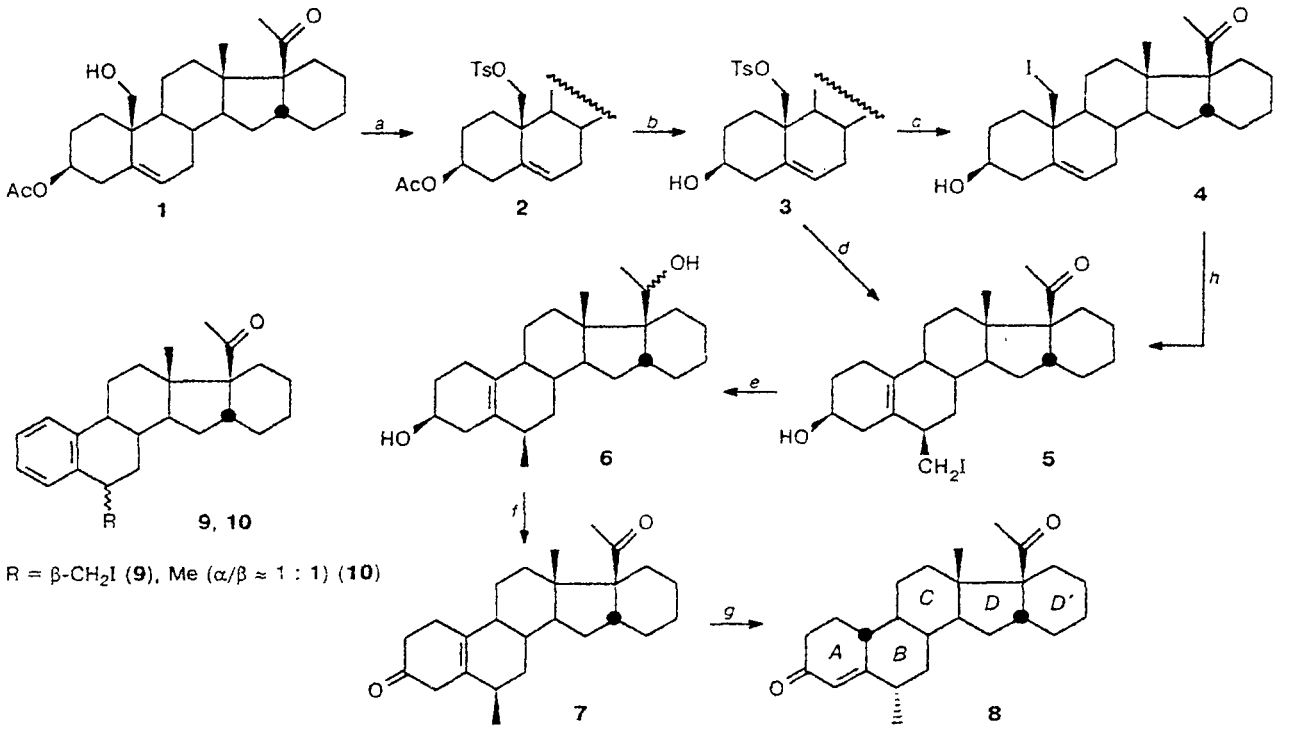
Scheme 1



Reagents and conditions: *a.* TsCl—Py, 20 °C, 48 h; *b.* NaOH—MeOH—dioxane; *c.* NaI—Pr^{i}OH, refluxing, 3 h, Ar; *d.* NaI—Pr^{i}OH, refluxing, 32 h; *e.* $LiAlH_4$—ether, refluxing, 10 h; *f.* PCC, CH_2Cl_2 (or Jones reagent); *g.* MeOH—KOH (or MeOH—HCl); *h.* Pr^{i}OH, refluxing.

7. The structure of the latter follows from its ^{1}H NMR spectrum, which contains a doublet of methyl group protons at C(6) with δ 1.05 and J = 6.8 Hz, as well as singlets of angular 18-Me group and 21-Me group with δ 0.73 and 2.17, respectively. Short-term boiling of diketone **7** with aqueous-methanolic alkali resulted in the final product, 6α-methyl-16α,17α-cyclohexano-19-norprogesterone (**8**), in 60% yield (after chromatographic purification). Similar results were obtained by acidic isomerization of compound **7**.

The structure of 6α-methyl-19-norpentarane **8** follows from the following data: its ^{1}H NMR spectrum contains singlets of an angular 18-Me group at δ 0.75 and a 21-Me group at δ 2.15, a doublet of a Me group at the C(6) atom with δ 1.19, as well as a multiplet of the 6-methine proton at δ 2.69 and an olefinic proton signal at C(4) with δ 5.85. The most intense peak in the mass spectrum of enedione **8** is that of its molecular ion $[M]^+$ with m/z 368; the two weaker peaks with m/z 353 and 325 correspond to elimination of methyl and acetyl groups from the molecular ion.

The 6α-configuration of the methyl group in molecule **8** was assigned because the more thermodynamically favorable 6-equatorial substitution in the steroid series[1,10] is usually preferable.

Column chromatography of the mixture obtained by oxidation of diketone 7 gave, in addition to the target compound **8**, a nonpolar product (yield 20%), to which the structure of steroid **10** with aromatic ring *A* was assigned, based on mass spectral as well as ^{1}H and ^{13}C NMR spectroscopic data.

The fact that product **10** is a mixture of C(6) epimers in ~1 : 1 ratio is first of all indicated by the fact that its ^{1}H NMR spectrum (in C_6D_6) contains two singlets of the 18-Me group at δ 0.53 and 0.57, which have nearly equal intensities and whose overall intensity corresponds to three protons, and two doublets of the 6-Me group with centers at δ 1.22 and 1.25. The ^{1}H NMR spectrum in $CDCl_3$ contains doubled signals of the 18-Me and 6-Me groups (δ 0.80, 0.76 and 1.37, 1.39, respectively), two singlets of the 21-Me group at δ 2.22 and 2.23, and a multiplet from four aromatic protons (δ 7.15—7.40). The region characteristic of the HC(16) angular proton contains a multiplet from two protons with a center at δ 3.08 corresponding to HC(16) and HC(6), which is observed in the spectrum of compound **10** in C_6D_6 as two multiplets (1 H each) at δ 2.86 and 3.08.

The ^{13}C NMR spectrum of product **10** in the region of δ 19—65 displays 33 (of 36) signals corresponding to the doubled number of C atoms in the steroid skeleton

and the methyl groups, 12 signals of C atoms in the aromatic ring in the regions of δ 124—129 and 139—142, and a single signal of the C atom in the 20-carbonyl group at δ 212.5. Of the 12 signals of the aromatic ring, eight signals correspond to =CH groups (δ 124.6, 124.9, 125.5, 125.6, 125.7, 125.8, 127.4, 128.7), while four signals correspond to quaternary aromatic C atoms (δ 139.8, 139.9, 141.4, 141.8), thereby indicating the nature of aromatic ring *A* and the presence of two isomeric forms.

The mass spectrum of compound **10** contains a molecular ion peak $[M]^+$ with *m/z* 350.

Apparently, the aromatic steroid **10** is formed as iodide **9** during the transformation of iodide **4** into **5** but it was isolated only in the step of oxidation of the main product **6**.

Thus, 6α-methyl-16α,17α-cyclohexano-19-norprogesterone (**8**) was synthesized from the 19-methyl-6-desmethyl precursor.

Experimental

Melting points were determined on a Boetius heating micro stage. Mass spectra were obtained on a Varian CH-6 MAT mass spectrometer with 70 eV energy of ionizing electrons and using direct injection of the samples into the ion source. ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer (250.13 MHz), while ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (75.47 MHz) in $CDCl_3$. Qualitative analyses of mixtures were carried out by TLC on DC Alufolien Kieselgel 60_{254} plates (Merck); the chromatograms were visualized with a solution of cerium sulfate in 10% H_2SO_4 followed by heating of the plates. Preparative chromatography was performed on columns with Woelm silica gel.

3β-Acetoxy-19-*p*-toluenesulfonyloxy-16α,17α-cyclohexanopregn-5-en-20-one (2). A solution of alcohol **1** (3 g) (see Ref. 3), TsCl (6 g), and dimethylaminopyridine (DMAP) (10 mg) in anhydrous pyridine (30 mL) was kept at 20 °C for 48 h. The reaction mixture was poured onto ice, and the precipitate that formed was filtered off, washed repeatedly with water on the filter, and dried in air to give 3.42 g (89%) of compound **2**, which was used in the next step without further purification. An analytical sample of compound **2** had m.p. 167—168 °C (CH_2Cl_2—petroleum ether).

3β-Hydroxy-19-*p*-toluenesulfonyloxy-16α,17α-cyclohexanopregn-5-en-20-one (3). A solution of compound **2** (1.14 g) in dioxane (30 mL) was mixed with a solution of NaOH (0.46 g) in water (5 mL) and methanol (35 mL) and kept at 20 °C for 3 h. The reaction mixture was then poured onto ice and extracted with ether. The extract was washed with water, dried with Na_2SO_4, and concentrated *in vacuo*. The solid precipitate was recrystallized from a CH_2Cl_2—petroleum ether mixture to give 0.84 g (80%) of tosylate **3**. An analytical sample had m.p. 147—148 °C (acetone—hexane). ^{1}H NMR, δ: 0.57 (s, 3 H, 18-Me); 2.11 (s, 3 H, 21-Me); 2.43 (s, 3 H, CH_3—C_6H_4); 3.05 (m, 1 H, HC(16)); 3.50 (m, 1 H, HC(3)); 3.96, 4.10 (m, 2 H, $H_2C(19)$); 5.58 (m, 1 H, HC(6)); 7.31, 7.70 (dd, 4 H, A_2B_2 system, J_{AB} = 8 Hz).

3β-Hydroxy-19-iodo-16α,17α-cyclohexnopregn-5-en-20-one (4). A solution of compound **3** (0.2 g) and NaI (0.1 g) in 2-propanol (25 mL) was refluxed for 3 h in an argon flow. The reaction mixture was concentrated *in vacuo* to 1/3 of its volume, poured into ice water, and extracted with ether. The ethereal extract was washed with water and dried with Na_2SO_4. The oily residue that formed after removal of the solvent was chromatographed. Elution with a petroleum ether—ether mixture (65 : 35) gave 0.10 g (54.5%) of iodide **4**. ^{1}H NMR, δ: 0.80 (s, 3 H, 18-Me); 2.14 (s, 3 H, 21-Me); 2.98 (m, 1 H, HC(16)); 3.28, 3.58 (dd, 2 H, $H_2C(19)$, J = 11 Hz); 3.54 (m, 1 H, HC(3)); 5.62 (m, 1 H, HC(6)).

3β-Hydroxy-6β-iodomethyl-16α,17α-cyclohexano-19-norpregn-5(10)-en-20-one (5). A mixture of compound **3** (1.67 g) and NaI (1.5 g) in 2-propanol (90 mL) was refluxed for 32 h with stirring. The major part of the solvent was removed *in vacuo*, and ice water (150 mL) was added to the residue. The resulting precipitate was filtered off, washed with water, and dried in air to give 1.43 g (85.6%) of 6β-iodomethyl-19-norpentarane **5** as an amorphous powder. ^{1}H NMR, δ: 0.71 (s, 3 H, 18-Me); 2.13 (s, 3 H, 21-Me); 2.98 (m, 1 H, HC(16)); 3.08 (m, 1 H, $H_2C(6)$); 3.48 (m, 1 H, $H_2C(6)$); 3.98 (m, 1 H, HC(3)).

6β-Methyl-16α,17α-cyclohexano-19-norpregn-5(10)-ene-3β,20ξ-diol (6). A suspension of iodide **5** (1.43 g) and $LiAlH_4$ (0.5 g) in dry ether (135 mL) was refluxed for 10 h with stirring. The reaction mixture was then decomposed with water and treated with 5 *N* NaOH. The ethereal layer was separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with water, dried with Na_2SO_4, and concentrated *in vacuo* to give 1.3 g of compound **6** (oil). ^{1}H NMR, δ: 0.80, 0.92 (both s, 3 H, 18-Me); 1.05 (d, 3 H, 6-Me, J = 6.8 Hz); 4.0 (m, 2 H, HC(3), HC(20)).

6β-Methyl-16α,17α-cyclohexano-19-norpregn-5(10)-ene-3,20-dione (7). A solution of diol **6** (2.3 g) in CH_2Cl_2 (25 mL) was stirred with PCC (5.3 g) at 0—5 °C for 1 h. The reaction mixture was passed through a column with silica gel, and the latter was additionally eluted with ether (100 mL). The solvents were removed *in vacuo*, and the residue was chromatographed. Elution with a heptane—acetone mixture (98 : 2 → 97 : 3) gave 0.46 g of minor component **10** as an oil. The analytical sample of compound **7** was obtained by adding hexane to the oily product **7** followed by recrystallization from hexane, m.p. 138—142 °C. ^{1}H NMR, δ: 0.73 (s, 3 H, 18-Me); 1.05 (d, 3 H, 6-Me, J = 6.8 Hz); 2.16 (s, 3 H, 21-Me); 2.68 (m, 1 H, HC(6)); 2.98 (m, 1 H, HC(16)).

6α-Methyl-16α,17α-cyclohexano-19-norpregn-4-ene-3,20-dione (8). A solution of compound **7** (0.2 g) in MeOH (5 mL) and 10% aqueous KOH (0.2 mL) was refluxed for 30 min. After cooling, the reaction mixture was acidified with dilute HCl to pH 7, the methanol was removed *in vacuo*, water was added to the residue, and the mixture was extracted with ether. The oily residue obtained after removal of the ether was then chromatographed. Elution with a hexane—AcOEt mixture (98 : 2) gave 0.12 g (60%) of enedione **8**, m.p. 178—181 °C (ether—hexane). ^{1}H NMR, δ: 0.75 (s, 3 H, 18-Me); 1.19 (d, 3 H, 6-Me, J = 7.2 Hz); 2.15 (s, 3 H, 21-Me); 2.69 (br. quint, 1 H, HC(6)); 2.97 (m, 1 H, HC(16)); 5.85 (s, 1 H, HC(4)). MS, *m/z* (I_{rel} (%)): 368 $[M]^+$(100), 353 $[M-Me]^+$ (17), 325 $[M-MeCO]^+$ (30). Calculated for $C_{25}H_{36}O_2$: M = 368.54.

6ξ-Methyl-17β-acetyl-16α,17α-cyclohexanogona-1,3,5(10)-triene (10). The nonpolar product isolated from the reaction mixture after oxidation of diol **6** with PCC (0.46 g, oil), was dissolved in hexane. The crystalline precipitate that formed upon cooling had m.p. 111—114 °C. ^{1}H NMR (C_6D_6), δ: 0.53, 0.57 (both s, 3 H, 18-Me); 1.22, 1.25 (both d,

3 H, 6-Me, J = 6.6 Hz); 1.86 (s, 3 H, 21-Me); 2.86, 3.08 (m, 2 H, HC(6), HC(16)); 7.12, 7.25 (m, 4 H, H arom.). MS, m/z (I_{rel} (%)): 350 $[M]^+$ (39), 307 $[M-43]^+$ (58), 226 $[M-124]^+$ (41), 212 $[M-138]^+$ (100). Calculated for $C_{25}H_{34}O$: M = 350.54.

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