TRANSFORMED STEROIDS.

129. SYNTHESIS OF 6α-METHYL-16α,17α-CYCLOBUTANOPROGESTERONE

A. V. Kamernitskii, V. N. Ignatov, and I. S. Levina

UDC 542.91:547.92

We have already shown that the introduction of a substituent (F, Cl, CH_3) at the 6-position of the molecule of pregna-D_6'-pentaranes considerably increases the hormonal activity, in particular, progestagenic, and especially, contraceptive activity [1-3]. It was desirable to study the character of this influence also in the series of gestagenically active pregna-D_4'-pentaranes (16α,17α-cyclobutanoprogesterones) with no contraceptive activity. In the present article, we describe the synthesis of 6-methyl-substituted pregna-D_4'-pentaranes. We used our investigation on the introduction of the 6-methyl group into the molecule of 16α,17α-cyclohexanopregnanes [4], and carried out a similar sequence of reactions in the series of 16α,17α-cyclobutanopregnanes also.

As the starting material, we used the previously described [5] keto-acetate (I). Since the 20-carbonyl group of 16α,17α-disubstituted pregnanes is sterically hindered [4, 6], it appeared possible to introduce the CH_3 group into the 6-position via the opening of the 5α, 6α-oxide ring of compound (II) by the Grignard reagent without preliminary protection of the 20-ketone. We found that in the series of 16α,17α-cyclobutanopregnanes, the 20-carbonyl group enters the Grignard reaction. When a solution of (I) was heated with MeMgI for 1.5 h at 75°C, the corresponding derivative (VI) was formed. Therefore, the introduction of 6α-methyl required preliminary protection of the 20-carbonyl group in (I). The best method of protection is reduction, since during subsequent oxidation of the 3β-hydroxy group in (VII), a regeneration of the 20-ketone takes place simultaneously.

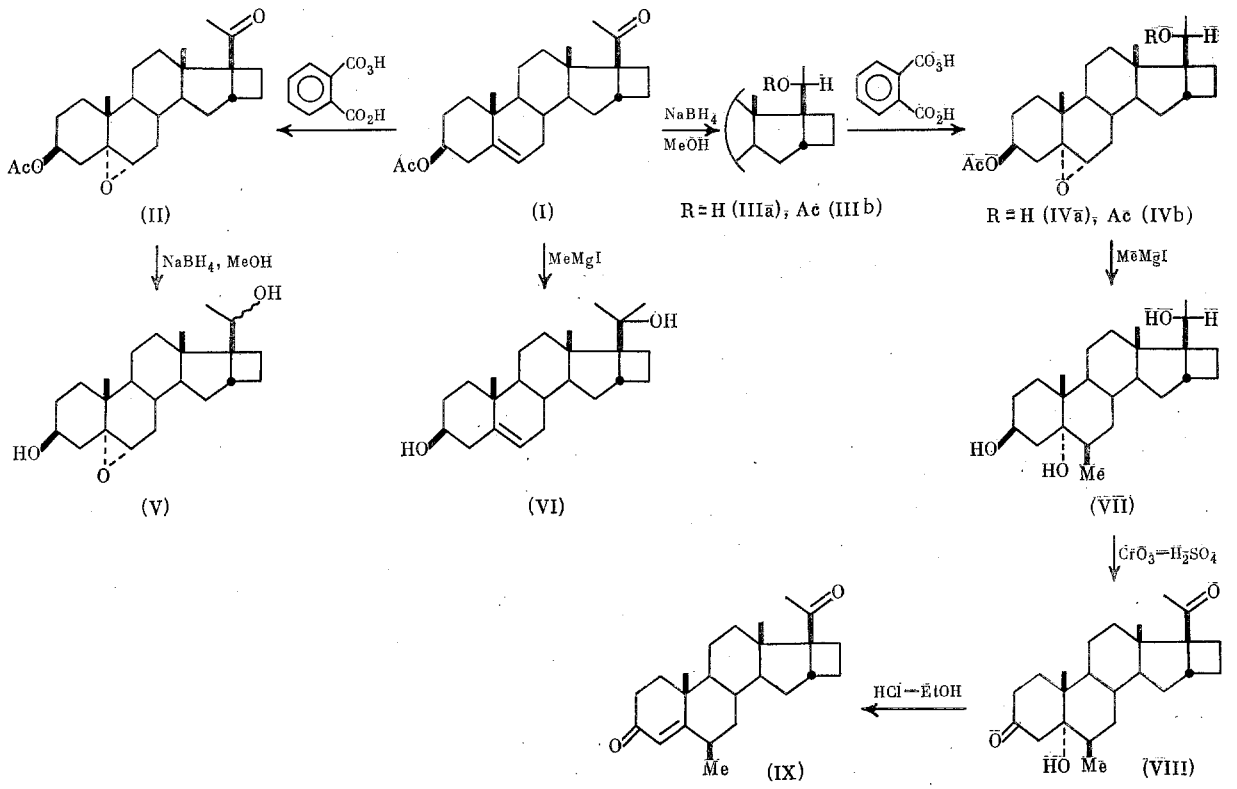
During reduction of (I) with $NaBH_4$ in methanol at 25°C, the hydroxy derivative (IIIa) was obtained in a high yield. The β-configuration was ascribed to this compound on the basis of the data in [7]. The high stereospecificity is due to steric hindrances from the side of the carbocyclic ring D'.

The epoxidation of the 5,6-double bond in the cyclobutenes studied was investigated in the case of (I), as well as its dehydro-derivative (IIIa). The use of monoperphthalic acid led to 5α,6α-oxides (II) and (IV), respectively, in yields of ∿80%. Their structure was confirmed spectrally. During epoxidation with p-carbomethoxyperbenzoic acid, a mixture of stereoisomeric epoxides was obtained in the ratio of 5,6α:5,6β ≃ 3:1 (according to PMR spectrum). The reduction of the 20-carbonyl group in 5α,6α-oxide (II) by $NaBH_4$ requires more severe conditions than the case of (I). Thus, products of reduction could be obtained only with a 30-fold excess of $NaBH_4$ and when the mixture was heated to 65°C for 2 h. A mixture of epimeric alcohols (V) was apparently obtained.

We took the above into consideration, and for the preparation of the end product (IX) in further reactions we used the 20β-hydroxy compound (IIIa). When oxide (IVa) was boiled with an excess of MeMgI, triol (VII) was obtained in a high yield. Its structure was confirmed spectrally. In the PMR spectrum there is a doublet of protons at C^6, δ 1.20 ppm and J = 6 Hz. Oxidation of (VII) with CrO_3 according to Jones leads to diketone (VIII) in a 90% yield. Boiling the latter in ethanol with concentrated HCl leads to the required end product, 6α-methyl-16α,17α-cyclobutanoprogesterone (IX). Under these conditions, splitting of the 5α-hydroxyl group is accompanied by epimerization at C^6 [6]. The structure of the end product (IX) was confirmed by using both physical and chemical data. In the IR spectrum there are absorption bands of an α,β-unsaturated ketone at 1610 and 1675 cm^{-1}. In the PMR spectrum there are singlets of protons of the angular and 21-CH_3 groups with δ 0.68, 1.12, and 2.07 ppm, respectively, a doublet of the 6-CH_3 group protons with δ 1.00 ppm and J = 6 Hz, and a multiplet signal of the proton at C^4 with a center at δ 5.72 ppm.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2151-2154, September, 1982. Original article submitted November 27, 1981.

0568-5230/82/3109-1901$07.50



The results of the pharmacological tests of (IX) will be published separately.

EXPERIMENTAL

The melting points were determined on a Koffler block. The IR spectra were measured on the UR-10 apparatus in KBr tablets. The PMR spectra were obtained on the Tesla BS-497 spectrometer in a $CDCl_3$ solution with reference to TMS. The mass spectra were obtained on the Varian MAT CH-6 apparatus. The TLC was carried out on microplates with brand L silica gel (5-40 μm). An iron-free brand KSK silica gel (200-250 mesh) was used for the column.

16α,17α-Cyclobutanopregn-5-ene-3β,20β-diol 3-Acetate (IIIa). A 1-g portion (26 mmoles) of $NaBH_4$ was added, with vigorous stirring, at 25°C to a solution of 1 g (2.6 mmoles) of (I) [5] in 40 ml of MeOH. The mixture was stirred for 1 h at 25°C, and then poured onto ice. The crystals were filtered, washed with water, and dried in air. Yield, 0.92 g of (IIIa) (92%), mp 158-161°C (petroleum ether—ether). IR spectrum (ν, cm^{-1}): 1260, 1725, 3550. PMR spectrum (δ, ppm): 0.70 s (3H, 18-CH_3), 0.98 s (3H, 19-CH_3), 1.31 d (3H, 21-CH_3, J = 6 Hz), 1.94 s (3H, 3-OAc), 5.32 m (1H, HC^6).

Diacetate (IIIb) — needles, mp 148-151°C (petroleum ether). IR spectrum (ν, cm^{-1}): 1250, 1730. PMR spectrum (δ, ppm): 0.59 s (3H, 18-CH_3), 0.96 s (3H, 19-CH_3), 1.37 d (3H, 21-CH_3, J = 6 Hz), 1.90 s and 1.95 s (6H, 3-OAc, and 20-OAc), 4.56 m (1H, HC^3), 5.11 q (1H, HC^{20}), 5.33 m (1H, HC^6). Found: C 75.14; H 9.21%. $C_{27}H_{40}O_4$. Calculated: C 75.60, H 9.41%.

16α,17α-Cyclobutano-5α,6α-epoxypregnane-3β,20β-diol 3-Acetate (IVa). A mixture of 0.8 g (2 mmoles) of (IIIa) in 15 ml of CH_2Cl_2 and 80 ml of an 8% ethereal solution of monoperphthalic acid was held for 20 h at 5-8°C. It was then diluted with 150 ml of ether, and treated with saturated Na_2CO_3 solution. The organic layer was washed with water and dried over $CaCl_2$. After removal of the solvent, the residue was crystallized from a mixture of hexane and ether to yield 0.73 g (87%) of (IVa), mp 156-160°C. IR spectrum (ν, cm^{-1}): 1250, 1730, 3450. PMR spectrum (δ, ppm): 0.64 s (3H, 18-CH_3), 1.04 s (3H, 19-CH_3), 1.32 d (3H, 21-CH_3, J = 6 Hz), 1.94 s (3H, 3-OAc), 2.86 d (1H, HC^6, J = 3.5 Hz).

Diacetate (IVb) — crystals, mp 136-142°C (petroleum ether—ether). IR spectrum (ν, cm^{-1}): 1248, 1730. PMR spectrum (δ, ppm): 0.52 s (3H, 18-CH_3), 1.03 s (3H, 19-CH_3), 1.36 d (3H, 21-CH_3, J = 6 Hz), 1.89 s, 1.96 s (6H, 3-OAc and 20-OAc), 2.87 d (1H, HC^6, J = 3.5 Hz).

Found: C 73.04; H 9.53%. $C_{27}H_{40}O_5$. Calculated: C 72.94; H 9.08%.

16α,17α-Cyclobutano-5α,6α-epoxypregnan-3β-ol-20-one Acetate (II). A 23-ml portion of an 8% ethereal solution of monoperphthalic was added to a solution of 1 g (2.6 mmoles) of (I) in 20 ml of CH_2Cl_2. The mixture was held for 20 h at 5-8°C, and then treated as described above. Yield, 0.62 g (60%) of (II), mp 214-217°C (ether—acetone). IR spectrum (ν, cm^{-1}): 1250, 1695, 1735. PMR spectrum (δ, ppm): 0.50 s (3H, 18-CH_3), 1.07 s (3H, 19-CH_3), 2.00 s (6H, 21-CH_3 and 3-OAc), 2.90 d (1H, HC^6, J = 4 Hz). Mass spectrum: M^+ 400. Calculated for $C_{25}H_{36}O_4$, mol. wt. 400.5.

16α,17α-Cyclobutano-5α,6α-epoxypregnane-3β,20ξ-diol (V). To a boiling solution of 1.45 g (2.4 mmoles) of (II) in 60 ml of MeOH, 2.7 g (70 mmoles) of $NaBH_4$ were added in small portions during 20 min. The mixture was boiled for 2 h, cooled, and poured onto ice. The precipitate was filtered, washed with water, and dried in air. Yield, 1.21 g (83%) of a mixture of isomers of (V), mp 172-183°C (ether—methanol). IR spectrum (ν, cm^{-1}): 3400. PMR spectrum (δ, ppm): 0.68 s (3H, 18-CH_3), 1.06 s (3H, 19-CH_3), 1.23 d (3H, 21-CH_3, J = 6 Hz), 2.90 d (1H, HC^6, J = 3 Hz), 3.90 m (2H, HC^3 and HC^{20}).

20-Methyl-16α,17α-cyclobutanopregn-5-ene-3β,20-diol (VI). An ethereal solution of MeMgI (prepared from 0.3 g of Mg and 5 ml of MeI in 40 ml of ether) was added in the course of 15 min at 36°C to a solution of 0.35 g (0.9 mmole) of (I) in 20 ml of toluene. The solution was concentrated to half its volume and held for 1.5 h at 75°C. It was then cooled to 5°C, and neutralized with saturated NH_4Cl solution. The organic layer was separated, washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was crystallized twice from an ether—petroleum ether mixture to yield 0.18 g (62%) of diol (VI), mp 178-181°C. IR spectrum (ν, cm^{-1}): 3400. PMR spectrum (δ, ppm): 0.82 s (3H, 18-CH_3), 0.99 s (3H, 19-CH_3), 1.18 s and 1.29 s (6H, 20 and 21-CH_3), 5.26 m (1H, HC^6). Found: C 80.43; H 10.96%. $C_{24}H_{38}O_2$. Calculated: C 80.39; H 10.68%.

6β-Methyl-16α,17α-cyclobutanopregnane-3β,5α,20β-triol (VII). An ethereal solution of MeMgI (prepared from 1 g of Mg and 20 ml of MeI in 100 ml of ether) was added in an Ar atmosphere to a solution of 0.8 g (2 mmoles) of oxide (IVa) in 80 ml of toluene. The mixture was treated as described above, and the organic layer was washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from a mixture of hexane and acetone to yield 0.57 g (76%) of triol (VII), mp 163-168°C. IR spectrum (ν, cm^{-1}): 1050, 3420. PMR spectrum (δ, ppm): 0.73 s (3H, 18-CH_3), 1.04 s (3H, 19-CH_3), 1.20 d (3H, $6CH_3$, J = 6 Hz), 1.34 d (3H, 21-CH_3, J = 6 Hz). Found: C 78.89; H 10.88%. $C_{24}H_{40}O_3$. Calculated: C 76.55; H 10.71%.

6β-Methyl-16α,17α-cyclobutanopregnan-5α-ol-3,20-dione (VIII). A 12-ml portion of the oxidizing mixture (prepared from 13.36 g of CrO_3, 11.5 ml of H_2SO_4 and H_2O to 50 ml total volume) was added dropwise at 0.5°C to a stirred solution of 0.5 g (1.3 mmole) of triol (VII). The mixture was held for 30 min, poured into water, and extracted with $CHCl_3$. The organic layer was washed with water to pH 7, and dried over $MgSO_4$. After removal of the solvent, 0.48 g (94%) of (VIII) was obtained, mp 224-228°C (from hexane—acetone). IR spectrum (ν, cm^{-1}): 1680, 1710, 3415. PMR spectrum (δ, ppm): 0.62 s (3H, 18-CH_3), 1.18 d (3H, 6-CH_3, J = 5 Hz), 1.23 s (3H, 19-CH_3), 2.03 s (3H, 21-CH_3). Found: C 77.83; H 9.31%. $C_{24}H_{36}O_3$. Calculated: C 77.37; H 9.71%.

6α-Methyl-16α,17α-cyclobutanopregn-4-ene-3,20-dione (IX). A 0.3-ml portion of concentrated HCl was added to a solution of 0.3 g (0.8 mmole) of (VIII) in 16 ml of alcohol. The mixture was held for 40 min at 50°C, cooled, poured into 100 ml of cold water, and extracted with $CHCl_3$. The organic layer was washed with water to pH 7, the solvent was evaporated, and the residue was chromatographed (SiO_2). Elution with a petroleum ether—acetone mixture (92:8) gave 0.09 g (33%) of (IX), mp 164-167°C (methanol). IR spectrum (ν, cm^{-1}): 1610, 1675, 1690. PMR spectrum (δ, ppm): 0.68 s (3H, 18-CH_3), 1.12 s (3H, 19-CH_3), 1.00 d (3H, 6-CH_3, J = 6 Hz), 2.07 s (3H, 21-CH_3), 5.72 m (1H, HC^4). Found: C 81.22; H 9.48%. $C_{24}H_{34}O_2$. Calculated: C 81.31; H 9.67%.

CONCLUSIONS

A synthesis of 6α-methyl-16α,17α-cyclobutanopregn-4-ene-3,20-dione was carried out by opening the 5,6α-oxide ring with a Grignard reagent, with preliminary protection of the 20-keto group.

LITERATURE CITED

1. A. V. Kamernitskii, L. E. Kulikova, I. S. Levina, V. V. Korkhov, A. A. Akhrem, G. V. Nikitina, and A. N. Poskalenko, Khim. Farm. Zh., No. 3, 61 (1977).
2. A. A. Akhrem, A. V. Kamernitskii, L. E. Kulikova, I. S. Levina, A. E. Terekhina, L. E. Lisitsa, and I. V. Ganina, Khim. Farm. Zh., No. 8, 24 (1977).
3. A. V. Kamernitskii, L. E. Kulikova, I. S. Levina, V. V. Korkhov, and G. V. Nikitina, Khim. Farm. Zh., No. 9, 72 (1980).
4. A. A. Akhrem, A. V. Kamernitskii, L. E. Kulikova, and I. S. Levina, Izv. Akad. Nauk SSSR, Ser. Khim., 444 (1978).
5. A. V. Kamernitskii, V. N. Ignatov, I. S. Levina, É. P. Serebryakov, G. V. Nikitina, and V. V. Korkhov, Khim. Farm. Zh., No. 10, 96 (1977).
6. R. Rakhit, R. Deghenghi, and C. R. Engel, Can. J. Chem., 41, 703 (1965).
7. L. F. Fieser and M. Fieser, Steroids, Reinhold (1959).