TRANSFORMED STEROIDS

COMMUNICATION 56. SYNTHESIS OF 16α, 17α, 21ξ, 1'ξ-DIISOPROPYLIDENEDIOXYL-21-ETHYLPREGN-4-ENE-3,20-DIONE

A. A. Akhrem, A. V. Kamernitskii,
and I. G. Reshetova

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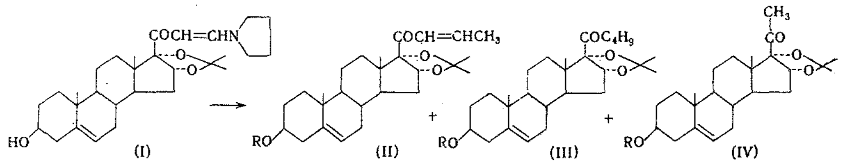
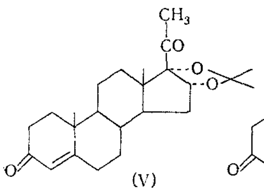
In continuation of a study of the synthesis of polyhydroxy steroids [1, 2] we ran the reaction of 16α-17α-isopropylidenedioxy-21-pyrrolidylmethylenepregn-5-en-3β-ol-20-one (I) with CH_3MgI. Here, as the result of 1, 4-addition [3], is formed 16α, 17α-isopropylidenedioxy-21-ethylidenepregn-5-en-3β-ol-20-one (II), while with a large excess of Grignard reagent we isolated 16α, 17α-isopropylidenedioxy-21-isopropylpregn-5-3β-ol-20-one (III) as a secondary product. With a slight excess of CH_3MgI, along with dienone (II), we detected 16α, 17α-isopropylidenedioxypregn-5-en-3β-ol-20-one (IV):

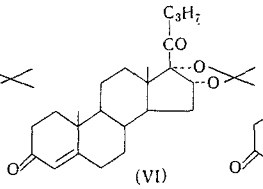


The reaction products could be separated by the fractional crystallization of the corresponding 3-acetates. The yield of dienone (II), which, depending on the reaction conditions, ranged from 45 to 70%, was estimated from the yield of the keto oxide that was obtained after the epoxidation of the mixture under alkaline conditions. The presence of the conjugated $\Delta^{21(1')}$-20-keto grouping in compound (II) was proved by ozonization. The NMR spectrum of dienone (II) has a multiplet of the protons of the CH=CH group in the 7.29-6.08 ppm region, the signals of the protons at C_6, C_3, and C_{16} in the 5.6-4.08 region, a singlet of the CH_3COO group at 1.85 ppm, two signals of the angular CH_3 groups at 1.33 and 0.47 ppm, and two partially overlapping singlets of the CH_3 groups of the isopropylidenedioxy grouping at 0.98 and 0.93 ppm. Based on the data of the circular dichroism (CD) and the intensity of the UV spectrum the conjugated $\Delta^{21(1')}$-20-keto chromophore in compound (II) was assigned the trans-configuration [4].

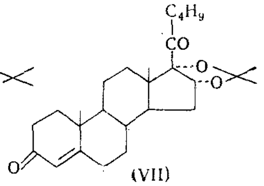
In a search for ways of separating the mixture, formed as a result of the Grignard reaction, the mixture was subjected to oxidation by the Oppenauer method. It unexpectedly proved that dienone (II) undergoes, along with oxidation of the 3β-hydroxyl group, also reduction of the $\Delta^{21(1')}$-bond that is conjugated with the 20-keto group. As a result a mixture of the acetonides of 16α, 17α-dihydroxyprogesterone (V), 16α, 17α-dihydroxy-21-ethylprogesterone (VI) and 16α, 17α-dihydroxy-21-isopropylprogesterone (VII) was obtained:



(V)



(VI)



(VII)

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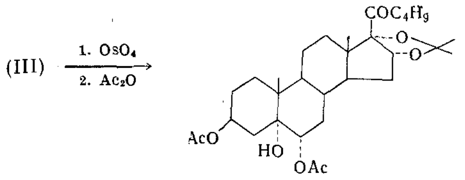
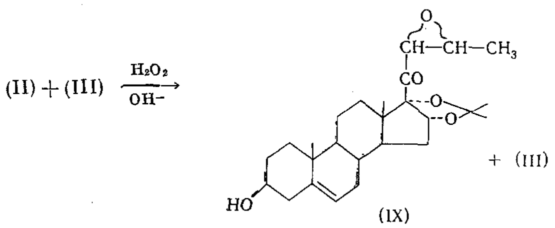
The structure of the 21-isopropyl-20-ketone (III) was established on the basis of the data of the IR and UV spectra. In the NMR spectrum the multiplet, corresponding to the protons of the CH=CH group, disappears; signals are present of the protons at C_6, C_3, and C_{16} in the 5.6-4.8 region, the singlet of the CH_3COO group at 1.89 ppm, and of the two angular CH_3 groups at 1.35 and 0.47 ppm, and the triplet of the protons of the CH_3 groups of the butyl radical appears at 0.95 ppm, which overlaps with the signals of the CH_3 groups of the isopropylidenedioxy grouping. Fragmentation under electron impact indicates the presence of the isopropyl keto grouping in the side chain. Oxidation of compound (III) by the Oppenauer–Jones method leads to the Δ^4-3-ketone (VII), while hydroxylation with OsO_4 and subsequent acetylation leads to 16α, 17α-isopropylidenedioxy-21-isopropylpregnane-3β, 5α, 6α-triol-20-one 3, 6-diacetate (VIII). The data of the IR, UV and mass spectra of compounds (VII) and (VIII) also corroborate the structure of ketone (III).



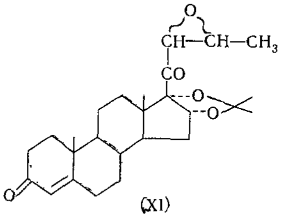
(VIII)

The presence in compound (II) of a reactive propenyl keto grouping made it possible to remove this product from the mixture that is obtained in the Grignard reaction with enamino ketone (I). As was to be expected, the epoxidation of a mixture of compounds (II) and (III) with H_2O_2 under alkaline conditions went only at the Δ^{21}-double bond, in which connection 21ξ, 1'ξ-epoxy-16α, 17α-isopropylidenedioxy-21-ethylpregn-5-en-3β-ol-20-one (IX) was formed in quantitative yield, which in its chromatographic mobility differs much more from (III) than do compounds (II) and (III) among themselves. Compound (IX) could be isolated by chromatographing on Florisil. The structure of epoxide (IX) and of its 3-acetate was corroborated by the data of the IR and mass spectra.



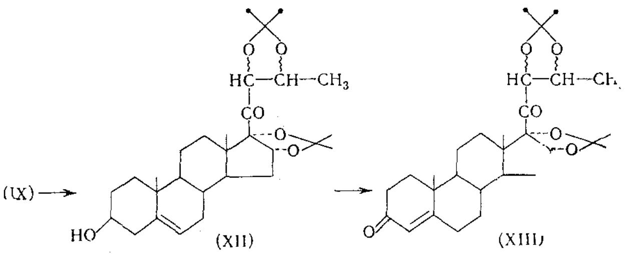
(IX)

The 21ξ, 1'ξ-epoxy-20-keto grouping also proved to be unstable under the conditions of oxidation by the Oppenauer method. The main reaction product in the attempted oxidation of keto oxide (IX) was not 16α, 17α-isopropylidenedioxy-21ξ, 1'ξ-epoxy-21-ethylpregn-4-ene-3,20-dione (XI), but instead the dihydroxyprogesterone acetonide (V).



(XI)

The desired 16 , 17 , 21ξ, 1'ξ-diisopropylidenedioxy-21-ethyl-pregn-4-ene-3,20-dione (XIII) was obtained by treating epoxide (IX) with BF_3 etherate in acetone, as described in [3] for 21ξ, 21a-oxides, and subsequent oxidation of the 3-hydroxy compound (XII) by the Oppenauer method.



METHOD

The melting points were determined on a Kofler block. The IR spectra were taken on a UR-10 instrument in KBr, the UV spectra were taken on a Unicam SP-700 instrument in ethanol, the mass spectra were taken on an LKV-9000 instrument, the NMR spectra were taken on a DA-60-IL instrument in CCl_4, while the GLC was run on an LKhM-7A instrument equipped with a flame-ionization detector. For the TLC we used microplates covered with Kieselguhr G and the solvent system: 8:2:0.5 hexane–ether–methanol.

Reaction of 16α, 17α-Isopropylidenedioxy-21-pyrrolidylmethylenepregn-5-en-3β-ol-20-one (I) with CH_3MgI. To the Grignard reagent, obtained from 1 g of Mg, 3 ml of CH_3I and 20 ml of absolute ether, was added a solution of 0.5 g of enamino ketone (I) in 50 ml of absolute THF at 10°C. The mixture was stirred under reflux for 5 h, allowed to stand overnight at 20°, and then decomposed with 20 ml of water and 1 ml of 1:1 HCl solution, and repeatedly extracted with ether. The extracts were washed in succession with $Na_2S_2O_3$ solution, $NaHCO_3$ solution and water, dried over Na_2SO_4, and evaporated. The low-polar products were extracted by refluxing in hexane; here we obtained 0.32 g of a mixture, the components of which are very close in chromatographic mobility. The mixture was acetylated with 0.5 ml of $(CH_3CO)_2O$ in 5 ml of pyridine (20°, 18 h). After the usual workup we obtained a mixture of two compounds, from which by a 6-fold recrystallization from MeOH we isolated 16α, 17α-isopropylidenedioxy-21-ethylidenepregn-5-en-3β-ol-20-one 3-acetate (II) with mp 188-189° (needles). Infrared spectrum (ν, cm^{-1}): 1730, 1690, 1620, 1380, 1250. Ultraviolet spectrum (λ_{max}, nm): 323 (ε 188), 233 (ε 6500). On ozonization we obtained CH_3COOH, which was identified by GLC.

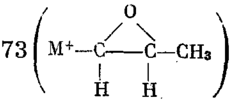
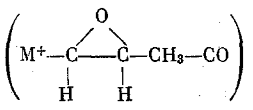
To the Grignard reagent, obtained from 1 g of Mg, as described above, was added 0.325 g of enamino ketone (I) in 20 ml of absolute THF. The mixture was stirred under reflux for 5 h, allowed to stand overnight, and worked up as described above. When the mixture was chromatographed on Florisil in the systems: hexane and hexane–ether (15, 30, 50, 100%) we isolated 0.13 g of unsaturated ketone (III) with mp 177-180° (from methanol). Infrared spectrum (ν, cm^{-1}): 3400, 1707, 1380. Found: C 75.29; H 9.97%. $C_{27}H_{42}O_4$. Calculated: C 75.30; H 9.77%. Mass spectrum (m/e): 430 (M^+); 373 ($M^+-C_4H_9$), 345 ($M^+-C_4H_9-CO$), 327 ($M^+-C_4H_9-CO-H_2O$).

3-Acetate (IIIb), mp 179-181° (from methanol). Infrared spectrum (ν, cm^{-1}): 1730, 1702, 1380, 1250. Found: C 73.98; H 9.74%. $C_{29}H_{44}O_5$. Calculated: C 73.73; H 9.32%. Mass spectrum (m/e): 472 (M^+), 412 (M^+-CH_3COOH), 387 ($M^+-C_4H_9-CO$).

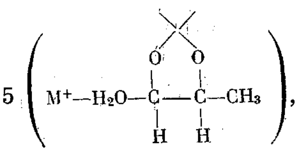
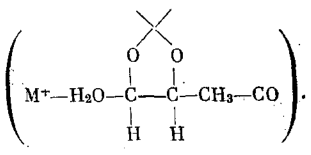
Oxidation of Mixture by Oppenauer Method. Here 0.7 g of the mixture, obtained from the reaction of enamino ketone (I) with CH_3MgI in 50 ml of absolute toluene, was heated for 1 h with 0.7 g of aluminum isopropylate and 7 ml of cyclohexanone. After the usual workup we obtained a mixture that was separated by chromatographing on Florisil in the systems: heptane and heptane–ether (10-100%). Here we isolated three compounds: 16α, 17α-isopropylidenedioxy-21-ethylpregn-4-ene-3, 20-dione (VI) [mp 163-165° (from hexane), mol. wt. 414 (by mass spectrometry); IR spectrum (ν, cm^{-1}): 1710, 1680, 1620, 1380-1370. UV spectrum: λ_{max} 240 nm (ε 17,600)]; dihydroxyprogesterone acetonide (V) with mp 204-206°; and Δ^4-3-ketone (VII) with mp 196-200°.

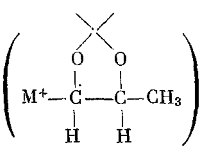
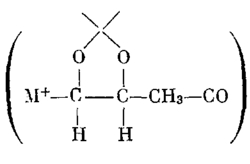
16α, 17α-Isopropylidenedioxy-21-isopropylpregnane-3β, 5α, 6α-triol-20-one 3, 6-diacetate (VIII). A mixture of 116 mg of ketone (IIIa), 71 mg of OsO_4 and 10 ml of pyridine was kept at 20° for 48 h. The obtained complex was decomposed by the addition of 0.76 g of $K_2S_2O_5$, 12.5 ml of H_2O and 3.5 ml of pyridine. The product was extracted with CH_2Cl_2, washed in succession with water, dilute HCl solution and water, dried over Na_2SO_4, and evaporated. The residue was acetylated in 1 ml of pyridine with 0.5 ml of $(CH_3CO)_2O$. After the usual workup the product was purified by chromatographing on two plates (13 × 18 cm) covered with SiO_2 in the system: 3:1 ether–petroleum ether. We obtained 80 mg of diacetate (VIII) with mp 211-212° (from hexane). Infrared spectrum (ν, cm^{-1}): 3480, 1735, 1730, 1710, 1380, 1270-1250. Found: C 67.36; H 8.85%. $C_{31}H_{48}O_8$. Calculated: C 67.78; H 8.75%. Mass spectrum (m/e): 548 (M^+), 491 ($M^+-C_4H_9$), 463 ($M^+-C_4H_9-CO$), 403 ($M^+-CO-CH_3COOH$), 343 ($M^+-C_4H_9-CO-2\cdot CH_3COOH$).

16α, 17α-Isopropylidenedioxy-21-isopropylpregn-4-ene-3, 20-dione (VII). With stirring, to 400 mg of ketone (III) in 50 ml of absolute acetone at 15° was added 0.9 ml of 8 N CrO_3 solution. After 5 min the mixture was diluted with water, extracted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and evaporated. The residue was dissolved in MeOH, 0.5 ml of 10% KOH solution was added, the mixture was heated at 100° for 5 min, and then it was neutralized with CH_3COOH, diluted with water, extracted with ether, washed with water, dried over Na_2SO_4, and evaporated. The residue was recrystallized from hexane, and then from MeOH. We obtained the Δ^4-3-ketone (VII) with mp 196-200°. IR spectrum (ν, cm^{-1}): 1710, 1680, 1620. UV spectrum: λ_{max} 247 nm (ε 11,900). Mass spectrum (m/e): 428 (M^+), 343 ($M^+ - C_4H_9 - CO$). Found: C 73.29; H 8.73%. $C_{27}H_{40}O_4 \cdot CH_3OH$. Calculated: C 73.00, H 9.50%.

21ξ, 1'ξ-Epoxy-16α, 17α-isopropylidenedioxy-21-ethylpregn-5-en-3β-ol-20-one (IX). To 0.4 g of the mixture of products, obtained from the Grignard reaction with 0.6 g of enamino ketone (I), in 50 ml of MeOH were added 1.5 ml of 4 N NaOH solution and 3 ml of 30% H_2O_2 solution. After 48 h the mixture was neutralized to pH 7, repeatedly extracted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and evaporated. The residue (0.4 g) was recrystallized from hexane. We obtained 0.25 g of epoxide (IX) with mp 188-190° (from methanol). Infrared spectrum (ν, cm^{-1}): 3530, 1710, 1380. Found: C 72.50, H 9.23%. $C_{26}H_{38}O_5$. Calculated: C 72.55; H 8.86%. Mass spectrum (m/e): 430 (M^+), 373  $\left(M^+-\underset{H}{C}\overset{O}{\frown}\underset{H}{C}-CH_3\right)$, 345  $\left(M^+-\underset{H}{C}\overset{O}{\frown}\underset{H}{C}-CH_3-CO\right)$. 3-Acetate (X), mp 240-241° (from hexane), mol. wt. 472 (by mass spectrometry).

Oxidation of 21ξ, 1'ξ-epoxy-16α, 17α-isopropylidenedioxy-21-ethylpregn-5-en-3β-ol-20-one (IX) by Oppenauer Method. From a solution of 900 mg of epoxide (IX) in 50 ml of absolute toluene and 7 ml of cyclohexanone was distilled 15 ml of toluene, after which a solution of 1 g of aluminum isopropylate in 5 ml of toluene was added. The mixture was refluxed for 1 h, cooled, treated with 50% CH_3COOH solution, extracted with CH_2Cl_2, washed in succession with water, $NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated. The residue was dissolved in hexane and chromatographed on Florisil in the systems: heptane (300 ml), and a petroleum ether–ether mixture (100-ml portions) ranging from 10 to 100%. We obtained 100 mg of an oily product that was pure when based on the R_f in various systems [IR spectrum (ν, cm^{-1}): 1710, 1680, 1630, 1380. UV spectrum: λ_{max} 240 nm (ε 21,100)]; 400 mg of progesterone acetonide (IV), mp 207-208° [IR spectrum (ν, cm^{-1}): 1710, 1680, 1620, 1380. UV spectrum: λ_{max} 242 nm (ε 15,900); mol.wt. 386 (by mass spectrometry)].

Reaction of 21ξ, 1'ξ-Epoxy-16α, 17α-isopropylidenedioxy-21-ethylpregn-5-en-3β-ol-20-one (IX) with Boron Trifluoride Etherate. A mixture of 300 mg of epoxide (IX), 20 ml of absolute acetone and 0.5 ml of $BF_3 \cdot Et_2O$ was refluxed for 30 min, and then it was kept at 20° for 24 h. After this it was treated with water, extracted with ether, washed with water, dried, and evaporated. The residue was dissolved in $CHCl_3$ and separated first on a plate (18 × 24 cm) covered with Al_2O_3 in ether, and then the obtained mixture (180 mg) was separated on a plate covered with SiO_2 in the system: 45:15:3 hexane–ether–methanol. We obtained 60 mg of 16α, 17α, 21ξ, 1'ξ-diisopropylidenedioxy-21-ethylpregn-5-en-3β-ol-20-one (XII) with mp 92-95° (from hexane). Infrared spectrum (ν, cm^{-1}): 3530-3320, 1715, 1380. Mass spectrum (m/e): 470 ($M^+ - H_2O$), 355  $\left(M^+-H_2O-\underset{H}{\overset{O}{C}}-\underset{H}{\overset{O}{C}}-CH_3\right)$, 327  $\left(M^+-H_2O-\underset{H}{\overset{O}{C}}-\underset{H}{\overset{O}{C}}-CH_3-CO\right)$.

16α, 17α, 21ξ, 1'ξ-Diisopropylidenedioxy-21-ethylpregn-4-ene-3, 20-dione (XIII). From a solution of 40 mg of the 3-hydroxy compound (XII) in 20 ml of absolute toluene and 2 ml of cyclohexanone was distilled 5 ml of toluene. After cooling, a solution of 0.2 g of aluminum isopropylate in 1 ml of toluene was added, and the mixture was refluxed for 1 h. After the usual workup and separation of the mixture on a plate (13 × 18 cm) covered with SiO_2 in hexane and hexane–ether (1:2) we obtained 12 mg of the Δ^4-3-ketone (XIII) with mp 212-214° (from hexane). Ultraviolet spectrum: λ_{max} 238 nm (ε 19,400). Infrared spectrum (ν, cm^{-1}): 1715, 1680, 1620, 1380, 1370. Mass spectrum (m/e): 371  $\left(M^+-\underset{H}{\overset{O}{C}}-\underset{H}{\overset{O}{C}}-CH_3\right)$, 343  $\left(M^+-\underset{H}{\overset{O}{C}}-\underset{H}{\overset{O}{C}}-CH_3-CO\right)$.

CONCLUSIONS

1. The reaction of 16α, 17α-isopropylidenedioxy-21-pyrrolidylmethylenepregn-5-en-3β-ol-20-one with methylmagnesium iodide leads to a mixture of the propenyl, isobutyl, and methyl ketones.

2. The epoxidation of this mixture, opening of the oxide ring with acetone in the presence of boron trifluoride etherate, and oxidation by the Oppenauer method gave 16α, 17α, 21ξ, 1'ξ-diisopropylidenedioxy-21-ethylpregn-4-ene-3, 20-dione.

LITERATURE CITED

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4. A. A. Akhrem, G. A. Kogan, A. V. Kamernitskii, I. G. Reshetova, T. N. Deshko, and I. S. Kovnatskaya, Izv. Akad. Nauk SSSR, Ser. Khim., 984 (1972).