SYNTHESIS OF 18,19-BISNOR-$\Delta^{1,3,5(10),13(17)}$-PREGNAPENTAEN-3-OL-20-ONE METHYL ETHER

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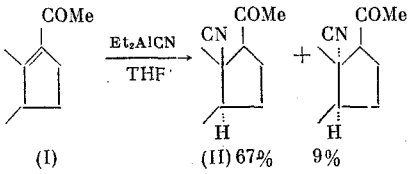
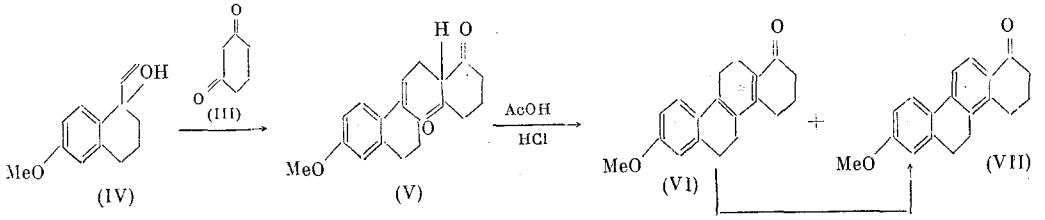
Modified steroidal compounds with functional substituents at C-18 possess a broad spectrum of physiological activity [1]. One of the paths for inserting a substituent in the C-18 position is the addition of HCN to 18-nor-$\Delta^{13(17)}$-steroids (I). According to [2], Et_2AlCN in THF can also be used instead of HCN; the main product is compound (II), which is obtained in high yield and has a natural configuration



(I) (II) 67% 9%

At the present time two methods are known for obtaining the starting 18-nor-$\Delta^{13(17)}$-steroids of type (I). The first method [3] starts with hydrophenanthrene derivatives, while the second method [4] starts with 18-nor-D-homosteroids. A general method was developed in our laboratory for the synthesis of D-homoestrane steroids, which was used to obtain the 18-nor-$\Delta^{13(17)}$-steroids in order to subsequently convert them them to either 18-oxygen or nitrogen-containing pregnane derivatives.

Previously it was established [5] that the condensation of dihydroresorcinol (III) with vinylcarbinol (IV) in the presence of either Triton B or alkali gives the desired secodiketone (V) in 6% yield. We found that when the reaction is run in CH_2Cl_2 in the presence of anhydrous borax the yield of (V) rises to 52%, while in the presence of Al_2O_3 (II-III activity) the yield is ~20%



(IV) (V) (VI) (VII)

The cyclization of secodiketone (V) by refluxing with 18% HCl in glacial CH_3COOH gives a mixture of compounds, from which ~10% of 3-methoxy-18-nor-$\Delta^{1,3,5(10),8,13}$-D-homoestrapentaen-17a-one (VI), with mp 115-116°, was previously isolated [5]. Under these conditions we obtained a mixture, from which by chromatographing on Al_2O_3 we were able to isolate only 3-methoxy-18-nor-$\Delta^{1,3,5(10),8(14),9(11),12}$-D-homoestrahexaen-17a-one (VII) with mp 124-125°. If the cyclization is run by refluxing with 18% HCl in methanol, then ketone (VI) is formed in 74% yield.

The development of a method for the synthesis of ketone (VI) made it possible to go to the 18,19-bisnorpregnane derivatives. The absorption of half of the theoretical amount of H_2 is observed when ketone (VI) is hydrogenated over Pd/$CaCO_3$ in ethyl acetate, after which the reaction stops. Employing preparative GLC it proves possible to isolate from the mixture of products, along with the starting ketone (VI),

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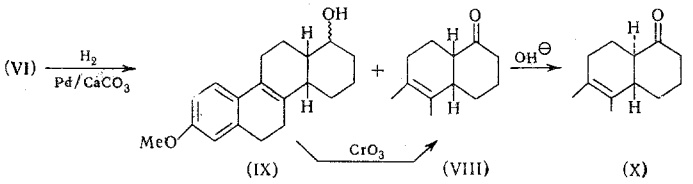
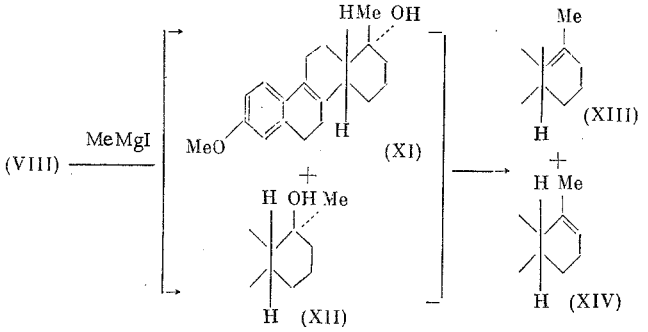
~35% of 3-methoxy-18-nor-$\Delta^{1,3,5(10),8}$-D-homo-13Hβ,14β-estratetraen-17a-one (VIII) and 7% of carbinol (IX)

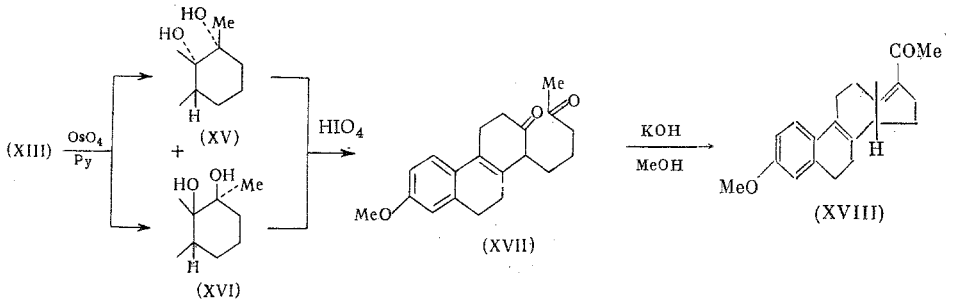


The hydrogenation of ketone (VI) in methanol goes practically to completion and gives 65% of ketone (VIII) and ~30% of carbinol (IX). The configuration of carbinol (IX) was not determined completely. However, since, when alcohol (IX) is oxidized by the Jones method, it changes to ketone (VIII), it is likely that both of these compounds can be assigned to the same steric series. In turn, ketone (VIII) when heated with alcoholic NaOH solution is easily isomerized to the known ketone (X), with a CD-trans coupling of the rings [6], and in this way can be assigned to the C/D-cis series.

A mixture of stereoisomeric tertiary alcohols (XI) and (XII) is formed when cis-ketone (VIII) is reacted with CH_3MgI, the recrystallization of which from methanol gave mainly the isomer with mp 156-158°. It is known that the Grignard reaction with cyclic ketones, containing a cis-decalone system, proceeds stereospecifically with an equatorial addition of the substituent [7]. This conclusion can also be made when examining the molecular model constructed for ketone (VIII). On this basis the main reaction product with mp 156-158° was assigned the structure of isomer (XI), with an axial OH group.

The dehydration of alcohol (XI), or of a mixture of (XI) and (XII), with $POCl_3$ in pyridine leads to the formation of 3-methoxy-17a-methyl-18-nor-$\Delta^{1,3,5(10),8,13(17a)}$-D-homoestrapentaene (XIII), which contains traces of its isomer at the double bond (XIV), which is indicated by the weak signal of an olefinic proton in the NMR spectrum of the dehydration product





cis-Hydroxylation of the $\Delta^{13(17a)}$ double bond, with the formation of two isomeric diols (XV) and (XVI), occurs when compound (XIII) is reacted with OsO_4 in pyridine. The oxidation of this mixture with HIO_4 led to the formation of the 13,17a-secodiketone (XVII), which when treated with alcoholic KOH solution underwent intramolecular crotonic condensation with the formation of 3-methoxy-18,19-bisnor-$\Delta^{1,3,5(10),13(17)}$-pregnapentaen-20-one (XVIII), the key compound in the synthesis of 18-cyanosteroids.

EXPERIMENTAL METHOD

Secodiketone (V). A solution of 40 g of 1-vinyl-6-methoxy-1-tetralol (IV) and 17 g of dihydroresorcinol (III) in 20 ml of CH_2Cl_2 was stirred at 20° in the presence of 11 g of finely ground anhydrous borax for a day. The precipitate was filtered, washed in succession with CH_2Cl_2 and water, and dried. We obtained

26.3 g of (V) with mp 158-162°; after recrystallization from methanol, mp 173-174° [5]. An additional 2.5 g of (V) was isolated from the mother liquor; the total yield of (V) was 52%. Infrared spectrum (KBr pellet, ν, cm^{-1}): 1632, 1604 (enol form of β-diketone), 1550 (aromatic double bond).

Cyclization of Secodiketone (V). a) A solution of 15 g of (V) in 450 ml of methanol and 150 ml of 18% HCl solution was refluxed for 1.5 h in an argon atmosphere. After distilling off the solvent and HCl in vacuo, the residue was dissolved in benzene, and the solution was washed in succession with water and $NaHCO_3$ solution. After the usual workup we obtained an oil which crystallized when rubbed with hexane. We isolated 9.7 g (69%) of ketone (VI) with mp 114-115° (from methanol); cf. [5]. Infrared spectrum (in Nujol, ν, cm^{-1}): 1638 $\left(\diagdown\!\!\diagup C=C-CO\right)$, 1605 and 1536 (aromatic double bond). NMR spectrum (in $CDCl_3$, δ, ppm): 3.8 (OCH_3), 2.55 ($-CH_2-$, multiplet), 7.0 (aromatic H atom); the signal of an olefinic proton is absent.

b) A solution of 0.37 g of (V) in a mixture of 3.7 ml of glacial CH_3COOH and 11 ml of 18% HCl solution was refluxed for 10 h. After cooling, the mixture was extracted with benzene. The extract was worked up in the usual manner to give an oil. The oil was subjected to TLC on Al_2O_3 (II-III activity), using benzene for elution, to give 100 mg of ketone (VIII) with mp 124-125° (from methanol), and R_f 0.63. Ultraviolet spectrum (in ethanol, λ_{max}, nm): 228 (ε 19,000), 280 (ε 21,900), and 326 (ε 27,000). Infrared spectrum (KBr pellet, ν, cm^{-1}): 1670 (CO, conjugated with an aromatic ring, 1608, 1582, and 1555 (aromatic double bonds). The data of the IR and UV spectra correspond to those given previously [8].

Hydrogenation of Ketone (VI). a) A solution of 2 g of (VI) in 200 ml of ethyl acetate was hydrogenated over 0.2 g of previously reduced 10% Pd/$CaCO_3$. After the absorption of 51% of the theoretical amount of H_2 the hydrogenation stopped and failed to renew itself when a fresh portion of catalyst was added. The catalyzate was subjected to TLC on SiO_2 in chloroform to give 0.58 g of the starting (VI) with R_f 0.3. From the zone with R_f 0.4 0.75 g (31%) of ketone (VIII), mp 110-112° (from methanol), was isolated. Infrared spectrum (KBr pellet, ν, cm^{-1}): 1705 (CO in six-membered ring), 1610, 1572, and 1508 (aromatic double bonds). Found: C 79.11; H 7.41%. $C_{19}H_{22}O_2 \cdot 0.5CH_3OH$. Calculated: C 79.02; H 7.48%. Dinitrophenylhydrazone of ketone (VIII), mp 176-178° (from $MeOH-CHCl_3$).

From the most polar zone, with R_f 0.1, by treatment with methanol we isolated 0.14 g (7%) of alcohol (IX) with mp 145-147°. Infrared spectrum (KBr pellet): 3340 cm^{-1} (OH). Ultraviolet spectrum (in ethanol): λ_{max} 262 nm ($\log \varepsilon$ 4.1).

b) A solution of 5 g of ketone (VI) in 160 ml of methanol was hydrogenated over 140 mg of 10% Pd/$CaCO_3$ until 1 mole of H_2 was absorbed. The hydrogenizate was chromatographed in the same manner as the preceding. We obtained 3.3 g (66%) of the cis-ketone (VIII) with mp 111-113°, and 1.5 g (30%) of carbinol (IX) with mp 140-145°.

Jones Oxidation of Carbinol (IX). To a solution of 50 mg of (IX) in 20 ml of acetone, cooled to 0°, three drops of Jones reagent was added, and after 20 min the mixture was poured into water and extracted with $CHCl_3$. The extract was worked up in the usual manner to give 15 mg of the cis-ketone (VIII) with mp 111-112° (from methanol), which failed to depress the mixed melting point with an authentic specimen.

Isomerization of cis-Ketone (VIII). A solution of 0.2 g of (VIII) in 12 ml of methanol was refluxed for 2 h with 0.1 g of NaOH and then allowed to stand overnight. The obtained crystals were filtered, washed with methanol, and dried. We obtained 0.18 g (90%) of the trans-ketone (X) with mp 148-150° [6]. Infrared spectrum (KBr pellet, ν, cm^{-1}): 1710 (CO in six-membered ring), 1621, and 1502 (aromatic double bonds).

Preparation of Alcohols (XI) and (XII). To a stirred solution of CH_3MgI (from 0.5 g of Mg and 2.3 g of CH_3I in 25 ml of absolute THF), cooled to 0°, 1 g of cis-ketone (VIII) in 35 ml of THF was added and the mixture was refluxed for 1 h. The mixture was decomposed at 0° with aqueous NH_4Cl solution, extracted with ether, and worked up to give 0.92 g of an oil that crystallized partially when treated with chilled methanol. We isolated 0.59 g of alcohol (XI), mp 156-158° (from MeOH), and 0.31 g of an oily mixture of isomers (XI) and (XII). Infrared spectrum of (XI) (KBr pellet, ν, cm^{-1}): 3350 (OH), 1818, and 1500 (aromatic double bonds). Found: C 80.57; H 8.91%. $C_{25}H_{26}O_2$. Calculated: C 80.49; H 8.48%.

Dehydration of Alcohols (XI) and (XII). A solution of 1.8 g of mixed (XI) and (XII), or of the pure (XI) isomer, in 20 ml of anhydrous pyridine was refluxed with 0.9 g of $POCl_3$ in a nitrogen atmosphere for 30 min, cooled, poured into a mixture of ice and water, and extracted with ether. We obtained 1.14 g (60%) of (XIII) as an oil, which was used subsequently without purification. Absorption bands in the 3200-3400 cm^{-1} region, characteristic for the OH group, are absent in its IR spectrum.

Hydroxylation of Compound (XIII). To a solution of 0.9 g of (XIII) in 9 ml of dry pyridine 0.83 g of OsO_4 in 5 ml of pyridine was added. The mixture was allowed to stand at ~20° in the dark for 4 days. The pyridine was removed in vacuo by codistillation with benzene. The obtained oil was dissolved in 30 ml of ethanol and added with stirring to a solution of 3 g of sodium hyposulfite in 50 ml of 50% alcohol. The mixture was refluxed for 3 h, and the obtained black precipitate was filtered and washed with hot alcohol. The filtrate was evaporated in vacuo and the residue was treated with 70 ml of water. The obtained oil was extracted with $CHCl_3$. The extract was worked up in the usual manner to give 0.81 g (80%) of an oil, which on standing deposited 160 mg of a product with mp 178-180°. Based on the TLC data this product was a mixture of (XV) and (XVI). Infrared spectrum (KBr pellet, ν, cm^{-1}): 3228 (broad band, OH), 1618, and 1510 (aromatic double bonds).

Based on the TLC data, the oily residue contained the same mixture of compounds.

Oxidation of Mixed Glycols (XV) and (XVI). To a solution of 0.7 g of mixed (XI) and (XVI) in 12 ml of methanol 5 ml of 20% HIO_4 solution was added, and the mixture was allowed to stand overnight. The mixture was poured into 50 ml of water and extracted with $CHCl_3$. After the usual workup we obtained 0.69 g of an oil, which, based on the TLC data, contained several substances. Preparative chromatographing on SiO_2 in the system: 4:1 hexane–chloroform, gave 0.45 g of the crude diketone (XVII) as an oil with R_f 0.4, in the IR spectrum of which absorption bands at 1706 (CO) and 1550 cm^{-1} (aromatic double bond) were observed. According to the data of the IR spectra, the other fractions were devoid of the keto compound.

Cyclization of Ketone (XVII). A solution of 0.35 g of KOH in 7 ml of water was added to a solution of 0.35 g of the above obtained (XVII) in 30 ml of alcohol. The mixture was allowed to stand for two days, neutralized with CH_3COOH, and diluted with water. Extraction with ether and the usual workup gave 0.14 g of an oil; from the oil, by preparative TLC on SiO_2 in chloroform, it was possible to isolate 68 mg (20%) of amorphous product (XVIII) with R_f 0.3, which, based on the data of the IR spectrum, contains the grouping $\diagdown\!\!\diagup C=C-CO$ (1695 cm^{-1}). Molecular weight of (XVIII) 294 (by mass spectrometry); 2,4-dinitrophenylhydrazone, mp 84-86.5° (from MeOH–$CHCl_3$), cf. [3].

CONCLUSIONS

A method was developed for the synthesis of 3-methoxy-$\Delta^{1,3,5(10),8,13}$-D-homoestrapentaen-17a-one, from which it was possible to obtain 3-methoxy-18,19-bisnor-$\Delta^{1,3,5(10),13(17)}$-pregnapentaen-20-one, a key compound in the total synthesis of 18-cyanosteroids.

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