SYNTHESIS OF 17-HYDROXY-20-OXOPREGNANES BY REACTION OF CYANOHYDRINS OF 17-OXOANDROSTENES WITH METHYL-LITHIUM

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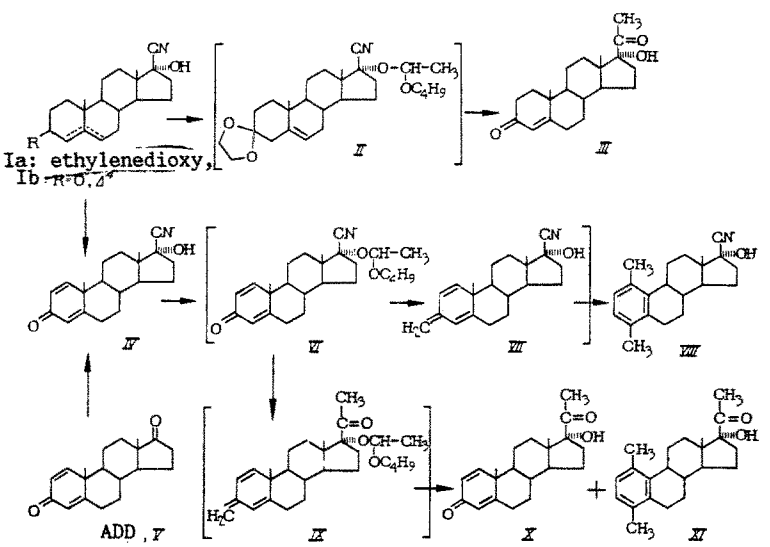
In the present work, which is a continuation of investigations already carried out in [1, 7], results are presented of a study of the reaction of 17α-hydroxy-3-oxoandrosta-1,4-diene-17β-carbonitrile (IV) with methyl-lithium. In the literature [5-10], similar reactions have been described for 17α-hydroxy-3-oxo-androst-4-ene-17β-carbonitrile (Ib). To selectively carry out nucleophilic addition reaction of methyl-lithium at the nitrile group and to obtain pregnane derivatives, the carbonyl group at C_3 is protected by the formation of ketals, enamines and enol ethers. In the case of cyanohydrin of androstadienedione IV, no effective protection for a "crosswise" congugated system was found in the literature [9]. These $\Delta^{1,4}$-ketones do not form ketals, thioketals, enamines and enol ethers. Although obtainable in high yields, 3-methoxyimines and semicarbazones cannot be used, since their hydrolysis is usually difficult and ineffective. It is known [2] that under Grignard reaction conditions, at low temperatures (-15 – 0°C) and at a minimal excess of methylmagnesium bromide, this dienone system is less reactive than the Δ^{16}-20-oxo group conjugated with the double bond. Thus, 6-methyl-steroids can be obtained without preliminary protection of the 3-keto group.

The aim of the present work was to compare the reactivities of the nitrile group and the dienone system under conditions of a condensation reaction with methyl-lithium to evaluate the possible use of androstadienedione (ADD, V) for preparing pregnanes by the method of a cyanohydrin synthesis.

To protect the 17α-hydroxy group, butoxyethyl ethers II and VI were prepared. In the reaction of the corresponding cyanohydrins Ia and IV with butyl vinyl ether, a mixture of diastereomers is formed, with, according to PMR spectroscopy data, practically equal contents of R- and S-isomers. This mixture was used without isolation at the condensation stage with an ether solution of methyl-lithium.

In the case of 17α-(1-butoxy)ethoxy-3,3-ethylenedioxyandrost-5-ene-17β carbonitrile (II), the nucleophilic addition reaction at the nitrile group was carried out under conditions milder than those described in [5, 10]. Low temperatures (−30°C) were used, while the acetal



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groups were hydrolyzed by HCl for 40 min at 20°C, in contrast to 1-hour heating at 110°C in CH_3COOH. 17α-Progesterone (III) was obtained in an 88.5% overall yield. It is an intermediate product in the production of gestagenic preparations: hydroxyprogesterone caproate and acetomepregenol.

Androstadienedione cyanohydrin IV was obtained by two methods; hydrocyanation of ADD (V) by the method described in [3] and dehydrogenation of compound Ib by the action of the methyl ester of selenious acid.

Due to the presence of a dienone system and the high solubility of ADD in polar solvents, the hydrocyanation reaction had to be carried out in a concentrated solution at a temperature of 10°C.

In the reaction of a minimal excess of methyl-lithium with 17α-(1-butoxy)ethoxy-3-oxoandrosta-1,4-diene-17β-carbonitrile (VI) at −30°C, the reaction proceeds only at the carbonyl group, without affecting the 17β-nitrile group. Thus, 17α-hydroxy-3-methylene-androsta-1,4-diene-17β-carbonitrile (VII) is formed, which is unstable, in particular in solutions, and during chromatography on silica gel readily rearranges into 17α-hydroxy-1,4-dimethylestra-1,3,5(10)-triene-17β-carbonitrile (VIII).

This methylene–benzene rearrangement is a general type of Wagner–Meerwein rearrangement with a rupture of the C-C bond and migration of the methyl group. The 1-3 shift as a result of this rearrangement and the formation of a p-disubstituted estratriene are indicated by the literature [8] and by PMR spectroscopy data. There is no signal of the 19-angular methyl group at C(10) in the spectrum. The resonance signals of the secondary group protons at the 1- and 4- carbon atoms of the steroid molecule at δ 2.22 and 2.37 ppm are shifted into a weaker field compared with the signal of the angular methyl group protons at C(13) (δ 0.905 ppm). The protons at C(2) and C(3) give singlets at δ 6.92 ppm in the region characteristic of aromatic protons. Their equivalence is confirmed by the formation of a p-sibstituted estratriene VIII.

If the condensation of compound VI with a large excess of methyl-lithium is carried out at 20°C, a product of addition at two functional groups is obtained with the formation of a methylene compound of the pregnane series (IX). We used the known [4] method of oxidation of methylene compounds by peracids, and obtained 17α-hydroxypregna-1,4-diene-3,20-dione (X) in an overall yeild of 22%, based on the initial cyanohydrin IV. The main product in the reaction was that of a methylene–benzene rearrangement, 17α-hydroxy-1,4-dimethyl-19-norpregna-1,3,5(10)-triene-2-one (XI). Its structure was confirmed by mass and PMR spectroscopy methods and by the data of elemental analysis.

We thus determined the conditions for the preparing 17α-hydroxy-3-oxoandrosta-1,4-diene-17β-carbonitrile (IV) in a high yield by hydrocyanation of ADD. We found that the reaction of ADD cyanohydrin in the form of its acetal with methyl-lithium proceeds mainly at the carbonyl group of the dienone system. However, when a large exceess of methyl-lithium is used, the nucelophilic substitution proceeds at the C(3) carbonyl and the 17β-cyano group, so that by carrying out an additional oxidation, 17α-hydroxypregna-1,4-diene-3,2--dione can be obtained.

EXPERIMENTAL

The IR spectra were run on a Perkin-Elmer-575 spectrophotometer (USA), the compounds were introduced in the form of a suspension in mineral oil; the mass spectra were measured on a MAT-112 spectrometer from Varian (GFR), PMR spectra on a XL-200 spectrometer from Varian (Switzerland) in a $CDCl_3$ solution (TMS).

17α-Hydroxypregn-4-ene-3,20-dione (III). A 1 ml portion of butyl vinyl ether is added to a solution of 1 g (2.8 mmoles) Ia and 20 mg of p-toluenesulfonic acid in 9 ml of THF. The mixture is stirred for 30 min, and made alkaline to pH 8.0 by triethylamine. At a temperature of −30°C in an N_2 current, 7 ml of 1.2 M (8.4 mmoles) of methyl-lithium are slowly added, and the mixture is stirred for 2 h, while the temperature is gradually raised to 20°C. A mixture of 2 ml of concentrated HCl, 2 ml of H_2O and 5 ml of MeOH is added, with cooling, up to pH 2.0. After 40 min, the reaction mixture is poured into H_2O, the precipitate is filtered, and washed with water. Yield 0.82 g, (88.5%) of III, mp 218-219°C (according to the literature data [11], mp 220-222°C). IR spectrum, ν_{max}, cm^{-1}: 1612 (Δ^4) 1670 (C_3 = O), 1700 (C_{20} = O), 3420 (C-O). UV spectrum, λ_{max} (C_2H_5OH): 240 nm (log ε 4.23).

17α-Hydroxy-3-oxoandrosta-1,4-diene-17β-carbonitrile (IV). A. A 5 g portion (16 mmoles) of Ib is dissolved, with heating in 250 ml of butyl acetate. At a temperature of 117-118°C, the dehydrogenating mixture, consisting of 2.57 g (20 mmoles) of selenious acid, 3.86 ml of MeOH, 2.57 ml of CH_3COOH and 25.7 ml of butyl acetate, is slowly added, while a mixture of butyl acetate, methyl acetate and H_2O is simultaneously distilled off. Two hours after the end of the addition, the reaction mixture is cooled and filtered. A 5 ml portion of 30% H_2O_2 is added to the mother liquor, which, after 2 h, is washed with water, 50 ml of a 1% sodium sulfite solution, and again with water to pH 7.0. The organic layer is dried and evaporated to a small volume. The precipitate is filtered, washed with butyl acetate, and ether. Yield, 4.28 g (86%) of IV, mp 200-204°C. After purification by acetonitrile, the weight is 3.41 g (68.7%), mp 216-220°C. IR spectrum, λ_{max}, cn^{-1}: 1590 (Δ^1), 1610 (Δ^4), 1650 (C_3 = O), 2220 (C≡N), 3250 (C—O). Mass spectrum: 311, 284, 266. PMR spectrum (CD_3OD+DCl), ppm: 1.01 s (3H, 18-CH_3), 1.30 s (3H, 19-CH_3), 6.07 m (4-H), 6.22 q (2-H), 7.31 d (1-H). Found, %: C 77.26; H 8.00; N 4.46. $C_{20}H_{25}No_2$. Calculated, %: 77.18; H 8.03; N 4.50.

B. A 13 g portion (45.7 mmoles) of V is dissolved in a mixture of 6 ml of MeOH and 4.25 ml (47 mmoles) of acetone cyanohydrin in the presence of 1 ml of H_2O and 0.8 ml of 1 N solution of sodium hydroxude in methanol (pH 9.0). The reaction mixture is cooled to 10°C, and 4 ml of H_2O are added slowly dropwise, up to the beginning of crystallization. At the end of the addition of H_2O, the temperature of the reaction mixture is raised to 20°C, and the mixture is stirred for nearly 20 h. A 2 ml portion of water is added slowly to the reaction mixture, which is then stirred for 4 h, another 10 ml of water are added (a total of 17 ml of H_2O), and the mixture is stirred for 4 more hours. The crystals that separate are filtered, washed with 12 ml of a MeOH — H_2O mixture (1;3) and then with H_2O until the disappearance of the cyanide ions in the wash waters. Yield, 11.74 g (82%) of IV. After the purification with ethyl acetate, the product contains 1.5-2% of the initial ADD with no isomeric 17β-hydroxy-17α-carbonitrile steroid. The yield at the purification stage is 80%. The products obtained by methods A and B have identical principal physicochemical characteristics.

17α-Hydroxy-1,4-dimethylestra-1,3,5(10)-triene-17β-carbonitrile (VIII). In the same way as in the synthesis of compound III, from 0.5 g (1.6 mmole) of IV, 0.59 g of an oil, decolorized by carbon, was obtained, which crystallized from hexane on cooling. Yield 0.39 g (78.5%) of VII. Chromatography on silica gel (eluent — benzene) gave 0.04 g of VIII, mp 150-153°C. IR spectrum, ν_{max} cm^{-1}: 800 (2H of benzene ring), 1600 (benzene ring), 2240 (C≡N), 3430 (C—O). Mass spectrum: 309, 282, 264, 225. PMR spectrum ($CDCl_3$), δ, ppm: 0.905 s (3H, 18-CH_3), 2.22 (3H, CH_3-C_1), 2.37 s (3H, CH_3-C_4), 6.92 s (2-H, 3-H). Found, %: C 81.62; H 8.70; N 4.56. $C_{21}H_{27}NO$ Calculated, %: C 81.57; H 8.73; N 4.53.

17α-Hydroxy-1,4-dimethyl-19-norpregna-1,3,5(10)-trien-2-one (XI) and 17α-Hydroxypregna-1,4-diene-3,20-dione (X). A 1.6 ml portion (12.8 mmoles) of butyl vinyl ether is added to a solution of 2 g (6.4 mmoles) of IV and 40 mg of p-toluenesulfonic acid in 12 ml of THF. After 30 min, the organic acid is neutralized by triethylamine and, in an N_2 current, 32 ml of 1.2 M (38.4 nmmoles) of methyl-lithium is slowly added, and the mixture is stirred for 1.5 h. Excess methyl-lithium is decomposed by aqueous methanol. The layers are separated, the organic layer is washed with a saturated solution of NH_4Cl and H_2O to pH 7.0. The aqueous layer is extracted by ether. The combined ether layers are dried over Na_2SO_4, and treated with 7 ml of an ether solution of perphthalic acid (a 0.917 M solution, 6.4 mmoles). The mixture is stirred for 17 h, and filtered. The ether mother liquor is washed with a 1% aqueous solution of $NaHCO_3$ and H_2O. Methanolic hydrochloric acid solution (1:1) is added to the organic layer, the mixture is stirred for 30 min, then washed with a 1% solution of $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated. Weight of the precipitate 2.14 g. Chromatography on silica gel have 1.13 g (54%) of XI, mp 176-180°C. IR spectrum, ν_{max}, cm^{-1}: 800 (2H of benzene ring), 1700 (C_{20} = 20), 3500 (C—O). Mass spectrum: 326, 308, 283, 225. PMR spectrum ($CDCL_3$), δ, ppm: 0.78 s (3H, 18-CH_3), 2.19 s (3H, CH_3-C_1), 2.29 s (3H, 21-CH_3), 2.33 s (3H, CH_3-C_4), 6.90 s (2-H and 3-H). UV spectrum, λ_{max}, nm (C_2H_5OH): 210 (ε 7800), 222 (ε 5100), 260 (ε 2000), 280 (ε 1800). Found, %: C 80.10; H 9.86. $C_{22}H_{30}O_2$. Calculated, %: C 80.99; H 9.20. On further elution, 0.46 g (22%) of X is isolted, mp 240-242°C (according to literature data [6], mp 240-242°C). IR spectrum, ν_{max}, cm^{-1}: 1600 (Δ^1), 1618 (Δ^4), 1663 (C_3 = O), 1706 (C_{20} = O), 3408 (C—O). UV spectrum, λ_{max} (C_2H_5OH): 246 nm (ε 18,900).

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