SYNTHESIS OF CORTEXOLONE PHOSPHATE

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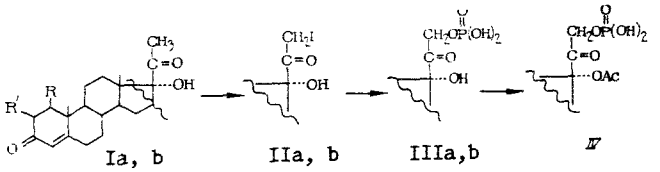
UDC 615.357.453.012.1

One of the important points in the synthesis of corticosteroids is the introduction of the 21-hydroxy, acyloxy, or other ester function into the 17β-acetyl side chain of the pregnanes. The object of the present work was the synthesis of cortexolone phosphate (IIIa) and its dehydro derivative (IIIb) from 17-hydroxyprogesterone; the microbiological hydroxylation of (IIIa) and (IIIb) leads to the isolation of hydrocortisone and prednisolone respectively.



Ia, IIa, IIIa, IV: R = R′ = H; Ib, IIb, IIIb: R + R′ = double bond.

The compounds (IIIa) and (IIIb) pertain to the water-soluble forms of the steroids which permit a significant increase in the concentration of the steroid in the culture liquid when they are employed as microbiological substrates [1].

The steroidal 21-phosphates are also utilized as intermediate compounds in the synthesis of the 17-acyl esters of the 17,21-dihydroxysteroids [3].

Methods for the synthesis of steroidal phosphates have been described in the literature; these involved the reaction of the 21-hydroxy compound either with pyrophosphoryl chloride [1] or with methanesulfonyl chloride with the subsequent treatment of the resulting mesylate with sodium iodide followed by the triethylamine–phosphoric acid (or K_2HPO_4) complex [5].

In our work, we obtained a quantitative yield of the 21-iodo derivative (IIa) of 17-hydroxyprogesterone by a known method [2] using the reaction of (Ia) with iodine in the presence of calcium oxide in the mixture of methylene chloride and methanol. We boiled the isolated iodo derivative, without purification, in the mixture of acetone and acetonitrile with the triethylamine–phosphoric acid complex. Performing the reaction in the mixture of solvents is preferable to the use of one of them, since the reaction time increases in pure acetone, and a decrease in the yield of 17α,21-dihydroxypregn-4-en-3,20-dione-21-phosphate is observed in acetonitrile. Depending on the method of isolation, we obtained the acid phosphate of cortexolone (IIIa) or its disodium salt in yields of 84 and 86.5%, respectively. We carried out the acetylation of the 17-hydroxyl group of compound (IIIa) in 64% yield with the mixture of AcOH, Ac_2O, and 57% perchloric acid as a catalyst.

We accomplished the analogous conversions with 17-hydroxydehydroprogesterone (Ib) and obtained a 72% yield of dehydrocortexolone phosphate (IIIb), from which prednisolone can be synthesized by microbiological hydroxylation. We obtained 17-hydroxydehydroprogesterone (Ib) by the dehydrogenation of 17α-hydroxypregn-4-en-3,20-dione (Ia) with the methyl ester of selenious acid in butyl acetate; the yield was 79.5%.

The scheme for the synthesis of cortexolone phosphate from 17-hydroxyprogesterone, which we have described, can be considered as a variant of the conversion to hydrocortisone.

S. Ordzhonikidze All-Union Scientific Research Institute of Pharmaceutical Chemisty, Moscow. Translated from Khimikofarmatsevticheskii Zhurnal, No. 1, pp. 68-70, January, 1987. Original article submitted September 18, 1985.

0091-150X/87/2101-0057$12.50

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer 575 instrument (Sweden); the substances were introduced in the form of a suspension in problem jelly. The UV spectra were taken in 96% ethyl alcohol on the model 599 instrument of the same firm. The control of the reaction was accomplished by the method of TLC in the 48:2 system of benzene–methodol and the 4:1 system of methanol–ammonia; the developer was the 10% solution of phosphomolybdic acid in ethyl alcohol.

21-Iodo-17α-hydroxypregn-4-en-3,20-dione (IIa). To a solution of 5 g of hydroxyprogesterone (Ia) in 40 ml of CH_2Cl_2 and 15 ml of methanol are added 3.8 g of CaO, ground in a mortar, with 0.25 ml of water. A solution of 6 g of iodine with 1.2 g of $CaCl_2$ in 30 ml of methanol is poured in at room temperature in a continuous stream. The temperature thereby rises by 10-12°C. The decolorization of the solution proceeds in 10-15 min, after which it is held for 30 min at room temperature. The reaction mass is cooled to 11°C; 50 ml of water are slowly added, watching to ensure that the temperature does not rise above 20°C. After stirring the solution for 10 min, it is filtered. The residue is washed with CH_2Cl_2. The layers are separated, and the aqueous layer is extracted with CH_2Cl_2 (three portions of 20 ml). The organic layers are combined, dried with sodium sulfate, and evaporated. The yield of the iodo derivative is 6.85 g (99.3%); it has mp 159-161°C. The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3410 (C–O), 1703 (C_{20}=O), 1660 (C_3=O), 1620 (Δ^4), and 560 (C–I).

The 21-Phosphate of 17α,21-Dihydroxypregn-4-en-3,20-dione (IIIa). To a suspension of 6.73 g of the iodo derivative of 17-hydroxyprogesterone (IIa) in the mixture of 50 ml of acetone and 50 ml of acetonitrile are added 6.7 ml of orthophosphoric acid and 20.1 ml of Et_3N. The mixture is boiled for 1.5 h and evaporated. The resulting oil is treated with 80 ml of acetone; the precipitated inorganic complex is filtered off, and the residue is washed with acetone. To the acetone mother liquor is added the solution of 2.5 g of $NaHCO_3$ in 34 ml of water. The aqueous acetone solution is concentrated up to the disappearance of the acetone. After filtering, the mother liquor is acidified to pH 2.0 to precipitate the phosphate (IIIa). The yield is 5.26 g (84%); the mp is 164-166°C (according to the literature data [1], the mp is 170°C). The UV spectrum is as follows: λ_{max} 242 nm, 15,800. The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3400 (C–O), 2640 (P–O), 1710 (C_{20}=O), 1673 (C_3=O), 1615 (Δ^4), and 1240 (P=O).

The 21-Disodium Phosphate of 17α,21-Dihydroxypregn-4-en-3,20-dione. To a suspension of 2 g of the iodo derivative of 17-hydroxyprogesterone (IIa) in the mixture of 20 ml of acetone and 20 ml of acetonitrile are added 2 ml of orthophosphoric acid and 6 ml of Et_3N. The mixture is boiled for 1.5 h and concentrated. To the residue are added 40 ml of water; the mixture is rendered alkaline with 5 N NaOH to pH 10.0. It is filtered, and the aqueous mother liquor is extracted with $CHCl_3$ (two portions of 10 ml). The aqueous layer, purified from by-products, is saturated with NaCl; 50 ml of isobutanol are added, and the mixture is acidified with 5 N HCl to pH 1.0-2.0. The layers are separated, and the butanol layer is concentrated in vacuo to the volume of 35 ml prior to filteration. The filtrate, diluted with 15 ml of acetone, is rendered alkaline with 7.5 N NaOH in methanol to pH 9.0. The residue is filtered off and washed with acetone. The yield is 1.78 g (86.5%); the product has $[\alpha]_D$ + 74.3° (c = 1, MeOH). The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3350 (C–O), 1720 (C_{20}=O), 1768 (C_3=O), 1615 (Δ^4), and 1240 (P=O).

The 21-Phosphate of 17α-Acetoxy-21-hydroxypregn-4-en-3,20-dione (IV). To a mixture of 37 ml of AcOH, 37 ml of Ac_2O, and 2.5 ml of 57% perchloric acid, cooled to 0°C, are added 7.05 g of the 21-phosphate of 17α,21-dihyroxypregn-4-en-3,20-dione (IIIa). The mixture is stirred for 3 h at room temperature. The reaction mass is poured into 300 ml of 0.1 N NaOH and washed with ether (six portions of 50 ml). The aqueous layer is salted out, acidified to pH 2.0, and extracted with chloroform. The chloroform extract is washed with a saturated aqueous solution of NaCl until a neutral reaction is obtained; the mixture is concentrated. The resulting oil is crystallized from ether and the crystals are filtered off. The yield of the 17-acetate-21-phosphate of cortexolone is 4.91 g (63.6%). The IR spectrum (ν_{max}, cm^{-1}) is as follows: 2680 (P–O), 1730 (C_{20}=O), 1670 (C_3=O). 1615 /Δ^4), and 1370 (P=O).

17α-Hydroxypregn-1,4-dien-3,20-dione (Ib). Hydroxyprogesterone (Ia) (15 g) is dissolved in 825 ml of butyl acetate with heating. The dehydrogenation mixture of 7.5 g of selenious acid, 11.3 ml of methanol, 7.4 ml of AcOH, and 73.4 ml of butyl acetate is added dropwise at the temperature of 117-118°C in the course of 3 h. At the same time, the butyl

acetate, methyl acetate, and water are distilled. The mixture is stirred for 3 h at 118-120°C prior to the cooling of the reaction mass. The mass is filtered from the selenium and washed with a triple salt solution (60 g of $Na_2S \cdot 9H_2O$, 31.5 g of Na_2SO_3 in 200 ml of water and 35 ml of ammonia) until the aqueous layer becomes the same color as the butyl acetate layer. The mixture is further treated with 10 ml of 30% H_2O_2 in the course of 2 h; it is washed with water until the absence of peroxide is achieved. The butyl acetate solution is concentrated to a low volume; the residue is filtered off, washed with cooled butyl acetate and ether, and dried. The yield of the mass is 11.83 g (79.5%); it has the mp 227-232°C. The residue is boiled in 15 ml of methanol and filtered. The mass, obtained in a yield of 10.9 g, has the mp 238-240°C (according to the literature data [4], the mp is 240-242°C). The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3408 (C—O), 1706 (C_{20}=O), 1670 (C_3=O), 1618 (Δ^4), and 1600 (Δ^1). The UV spectrum is as follows: λ_{max} 246 nm, ε 18,700.

21-Iodo-17α-hydroxypregn-1,4-dien-3,20-dione (IIb). Under the conditions described for the isolation of the iodo derivative of 17-hydroxyprogesterone (IIa), 3 g of dehydrohydroxyprogesterone (Ib) yield 3.96 g (95.5%) of (IIb). The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3400 (C—O), 1706 (C_{20}=O), 1677 (C_3=O), 1618 (Δ^4), 1600 (Δ^1), and 584 (C—I). The mp is 164-168°C.

The 21-Disodium Phosphate of 17α,21-Dihydroxypregn-1,4-dien-3,20-dione. Under the conditions described for the isolation of the disodium salt of cortexolone phosphate, 3.96 g of the iodo derivative (IIb) yield 3.05 g (75%) of the disodium salt of the 21-phosphate of dehydrocortexolone. The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3340 (C—O), 1720 (C_{20}=O), 1678 (C_3=O), 1619 (Δ^4), 1600 (Δ^1), and 1236 (P=O).

The 21-Phosphate of 17α,21-Dihydroxypregn-1,4-dien-3,20-dione (IIIb). The disodium salt of the 21-phosphate of 17α,21-dihydroxypregn-1,4-dien-3,20-dione (2.2 g) is dissolved in 15 ml of water. After the acidification with 5 N HCl to pH 1.0-2.0, the mixture is filtered. The mass of 1.8 g has the mp 176-178°C. It is crystallized from the 5:2 mixture of acetone—methanol. The compound (IIIb), with the mp 180-182°C, is obtained with the yield of 1.67 g. The IR spectrum (ν_{max}, cm^{-1}) is as follows: 3340 (C—O), 2700 (P—O), 1718 (C_{20}=O), 1670 (C_3=O), 1620 (Δ^4), 1600 (Δ^1), and 1240 (P=O). Found, %: C 59.26, H 6.72, and P 7.30. $C_{21}H_{29}O_7P$. Calculated, %: C 59.40, H 6.84, and P 7.30.

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