# STEROIDS. XXXVIII. SYNTHESIS OF THE ACETATE OF REICHSTEIN'S SUBSTANCE S

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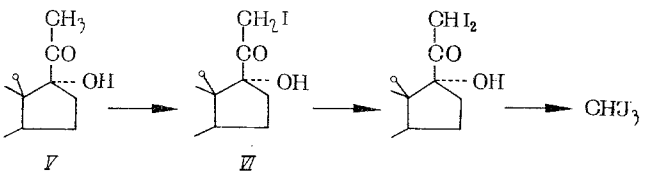
UDC 615.361.45.011+542.91

In the method published by us earlier of synthesis of the acetate of Reichstein's substance S from the acetate of dehydroprepnenolone, the method of direct iodination [1] of 16-α, 17-α-oxidoprogesterone (III) in the presence of calcium oxide and catalytic amounts of cumene hydroperoxide [2] was used to introduce the acetoxy group into position 21 of the steroid molecule. The acetate of Reichstein's substance S was obtained in 30% yield by this method. Because direct iodination proceeds better in the presence of a hydroxyl group in position 17, a method of direct iodination was developed for 17-α-hydroxyprogesterone (V) in the presence of cumene hydroperoxide which yielded the 21-iodo derivative, which upon further acetoxylation was converted into the acetate of Reichstein's substance S (VII) in 62% yield, calculated on (V) [3].

This communication describes a method of obtaining the acetate of Reichstein's substance S from the acetate of dehydropregnenolone (I) in which a new method is used for carrying out the direct iodination reaction of 17-α-hydroxyprogesterone under the influence of a cationic catalyst [4]. The iodination reaction proceeds in the presence of calcium oxide and catalytic amounts of salts [5] of alkali or alkali earth metals and hydrohalic or other acids (see Table 1).

An optimum regime of iodination is guaranteed by use of calcium chloride. Upon iodination without addition of salts, the time of decolorization of the iodine solution increases significantly and the yield of the acetate of Reichstein's substance S is decreased. Carrying out the reaction under the indicated conditions makes it possible to shorten the iodination time, increase the yield of the acetate of substance S to 70-72% calculated on 17-α-hydroxyprogesterone, and isolate 21-iodo-$\Delta^4$-pregnen-17-α-ol-3,20-dione (VI) [6] in an analytically pure form. Pure (VI) is stable upon storing in the dark and is easily reduced with sodium bisulfite into (V). From the mother solution after separation of (VI) was isolated the diiodide to which, on the basis of results of elementary analysis and IR spectrum, was assigned the structure of 21,21-diiodo-$\Delta^4$-pregnen-17-α-ol-3,20-dione. Iodoform, the reaction product of haloform cleavage of the hydroxyacetone grouping, was isolated upon exhaustive iodination of (VI) with excess iodine under conditions similar to iodination of (V). In this way, we isolated all products of consecutive iodination of 17-α-hydroxyprogesterone:




V VI

TABLE 1. Effect of Salts of Alkali and Alkali Earth Metals on the Iodination of 17-α-Hydroxyprogesterone.

| Salt | Time of decolorization of the $I_2$ solution (min) | Yield of acetate of Reichstein's substance S (%) |
|---|---|---|
| ZiCl | 23 | 66,5 |
| ZiBr | 11 | 63,5 |
| ZiI | 22 | 70,1 |
| KCl | 4 | 69,5 |
| KBr | 16 | 68,4 |
| KI | 60 | 71,3 |
| NaCl | 13 | 66,5 |
| NaBr | 14 | 71,5 |
| NaI | 54 | 71,5 |
| $CaCl_2$ | 13 | 73,5 |
| $KNO_3$ | 11 | 66,0 |
| $K_2CO_3$ | 9 | 65,8 |
| $Na_2SO_4$ | 134 | 62,9 |
| KOAc | Does not decolorize | — |
| — | 147 | 58,9 |

S. Ordzhonikidze All-Union Scientific-Research Chemicopharmaceutical Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 12, pp. 33-37, December, 1969. Original article submitted April 28, 1969.

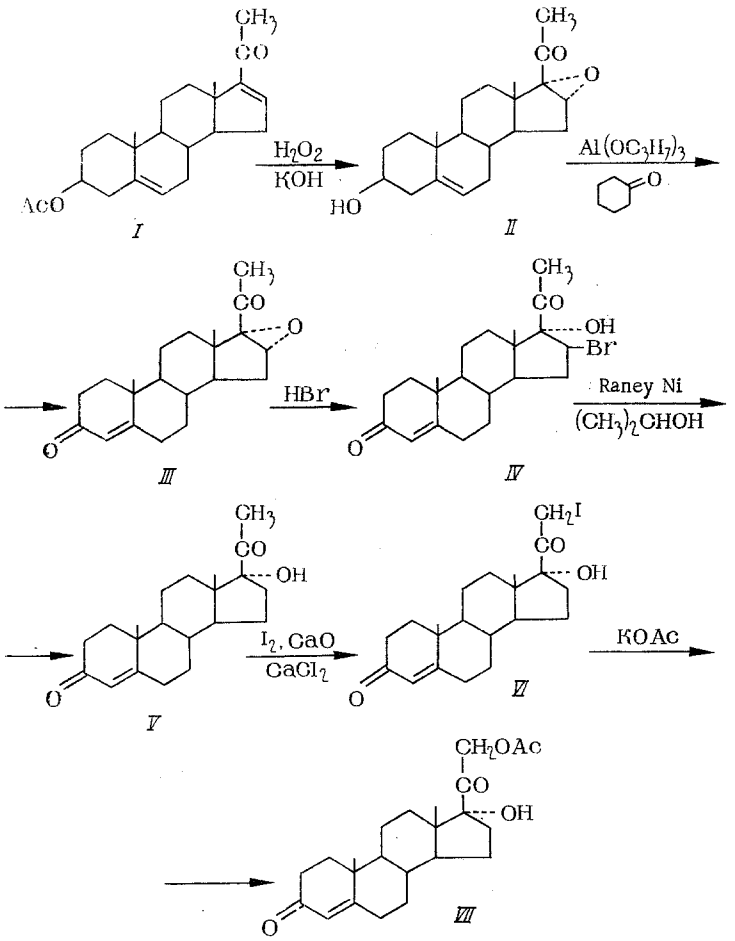
Conditions for the acetoxylation reaction with fused potassium and sodium acetates and acetic acid with triethylamine in dimethylformamide and acetone were studied on samples of analytically pure (VI). An optimum variation of acetoxylation was selected which guaranteed a yield of the acetate of Reichstein's substance S of 92-95% (fused potassium acetate in dimethylformamide at 60°C for 2 h) [4] and the reaction of nucleophilic substitution of iodine in position 21 was also studied on the example of (VI) [7].

Careful work-up of the separate stages of the indicated synthesis of the acetate of Reichstein's substance S, use of a new method to separate the aluminum compound in the Oppenauer reaction, and steam distillation in vacuum of the reaction products [8] obtained from (VI) by heating the latter in isopropyl alcohol at 50° with type $w_4$ Raney Ni catalyst, preliminarily washed with a 1% solution of acetic acid, in the presence of pyridine [9], and the rest made it possible to obtain the acetate of Reichstein's substance S in a yield of 49.5%, calculated on the acetate of dehydropregnenolone. The preference for the described method of synthesis of the acetate of Reichstein's substance S consists of the high economy of the process and also in the possibility of using 17-$\alpha$-hydroxyprogesterone as the starting compound for the preparation of 17-$\alpha$-hydroxyprogesterone capronate, an important medicinal preparation [10].

## EXPERIMENTAL

IR spectra were taken on a UR-10 instrument in mineral oil and UV spectra were taken on an SF-4 spectrophotometer in alcohol solution.

Chromatography was carried out on a thin layer on KSK silica gel fixed with gypsum in a system of chloroform–acetone in a 9.5:0.5 ratio (in the absence of indication of another system) with development with a saturated alcoholic solution of phosphomolybdic acid at 100° for 5 min.



Specific extinction coefficient $E^{1\%}_{1\,cm}$ was measured in ethanol.

16-α, 17-α-Oxido-$\Delta^5$-pregnen-3β-ol-20-one (16α, 17α-oxidoprogesterone) (II). To a suspension of 200 g of (I) in 4 liters of methanol at 10-14° were added simultaneously with energetic stirring 320 ml of a 19% solution of potassium hydroxide and 420 ml of a 27.5% solution of hydrogen peroxide over 30 min. The temperature of the reaction mixture increases to 18-20°. Stirring was continued for 24-26 h at the indicated temperature. To the reaction mixture cooled to 0° over 30 min was added 4 liters of cold water. The precipitate was filtered, washed with water, and dried at 80°. We obtained 178 g (96%) of technical (II) having mp 186-192° which was used for the subsequent step without purification.

16-α, 17-α-Oxido-$\Delta^4$-pregnen-3,20-dione (16α, 17α-oxidoprogesterone) (III). A solution of 17.8 g of (II) in 800 ml of toluene was heated to boiling and a certain amount of toluene was distilled until the appearance of a transparent distillate. To the hot solution was added 95 ml of cyclohexanone and the solvent was again distilled until the distillate became transparent. To the boiling reaction mixture over 10 min was added 8 ml of a 30% toluene solution of aluminum isopropoxide and the mixture was boiled with distillation of toluene for 30 min. The reaction mixture was cooled to 0° and to it with stirring was added dropwise 2.5 ml of water, 2.5 ml of a 15% solution of sodium hydroxide, and 7.5 ml of water; the mixture was stirred for 20 min, filtered, and the water-base layer was separated from the toluene layer. The latter was washed with water to a neutral reaction and subjected to steam distillation for 4 h. The reaction mixture was cooled and the precipitate was filtered and recrystallized from ethyl or isopropyl alcohol. We obtained 15.1 g of (III) (85.2%), mp 205-207°, $[\alpha]^{20}_D$ +163° (c 1.0, chloroform), $R_f$ 0.51 (chloroform-ethyl acetate, 9:1).

16β-Bromo-$\Delta^4$-pregnen-17α-ol-3,20-dione (Bromohydrin) (IV) [11]. We boiled 15 g of (III) in a solution of 75 ml of acetone for 3 h with stirring with 11 ml of 40% aqueous hydrobromic acid. The reaction mixture was cooled to 5° and to it was added 230 ml of water at such a rate that the temperature of the reaction mixture did not exceed 5°. The mixture was stirred for 15 min and the precipitate was filtered and washed with water to a neutral reaction. Weight of crude precipitate of (IV) was equal to 25-30 g with a moisture content of 40%; it was used in the subsequent reaction without purification. Content of (IV) in a dried sample was 95-99%.

$\Delta^4$-Pregnen-17α-ol-3,20-dione (17α-Hydroxyprogesterone) (V). To 30 g of crude (IV) were added 320 ml of isopropyl alcohol, 4.8 ml of pyridine, and a fivefold in relation to (IV) (calculated for 100%) amount of type $W_4$ Raney Ni catalyst (preliminarily washed with a 1% solution of acetic acid) and the mixture was heated at 50° for 5 h. The catalyst was filtered and washed with hot isopropyl alcohol. To the cooled alcohol solution were added 2250 ml of water and 9.6 ml of hydrochloric acid. The precipitate was filtered, washed with hot water, and dried. We obtained 13.3 g of (V) [88%, calculated on (III)], mp 212-215°, $E^{1\%}_{1\,cm}$ 480-490, $R_f$ 0.24. Recrystallization from isopropyl alcohol yielded 9.75 g of (V), mp 219-221°, $E^{1\%}_{1\,cm}$ 490-500, $\lambda_{max}$ 242 mμ. From the mother liquor was isolated 3.35 g of (V). Total yield of (V) was 13.1 g (86.6%). A Schöniger test for halogen was negative.

The amount of catalyst can be decreased threefold in relation to (IV). In this case, the catalyst must be preliminarily saturated with hydrogen. Yield of (V) amounts to 85-86%.

21-Iodo-$\Delta^4$-pregnen-17α-ol-3,20-dione (VI). To a solution of 10 g of (V) in a mixture of 75 ml of methylene chloride and 25 ml of methanol with stirring was added 0.5 ml of water and 7.6 g of calcium oxide. To the reaction mixture was added at 17-18°, a solution of 10 g of iodine and 1.7 g of calcium chloride (or other salt of an alkali or alkali earth metals) in 50 ml of methanol. The solution was added in one step during which a temperature increase to 28-30° was observed. The reaction mixture was cooled to 18-20° and stirred for 30 min. Decolorization began after 13-15 min. The calcium oxide was filtered and washed with methylene chloride and to the filtrate was added 80 ml of water. The methylene chloride layer was separated and the steroid was extracted from the water-methanol layer with methylene chloride. The combined extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to dryness in a vacuum at 30°. The crystalline residue of technical (VI) of weight 14.5-16 g was used for acetoxylation without additional purification. Upon two recrystallizations from methanol and ethanol from 14.5 g of technical (VI) was obtained 5.78 g of purified (VI), mp 158-160, $E^{1\%}_{1\,cm}$ 321, $[\alpha]^{20}_D$ + 129° (c 1.0, dioxane), $R_f$ 0.35. Found, %: I 27.62; $C_{21}H_{29}IO_3$. Calculated, %: I 27.80:IR spectrum: 3350 $cm^{-1}$ (OH), 1720 $cm^{-1}$ (C=O), 1650 $cm^{-1}$ (C=O, conjugated with a double bond), [1620 $cm^{-1}$ (C = C)].

From the mother solution was isolated 21,21-diiodo-$\Delta^4$-pregnen-17$\alpha$-ol-3,20-dione, mp 139.5° (dec., after repeated recrystallization from ethanol), $R_f$ 0.51. Found, %: I 43.58. $C_{21}H_{28}I_2O_3$. Calculated, %: I 43.7: IR spectrum: 3500 $cm^{-1}$ (OH), 1707 $cm^{-1}$ (C=O), 1670 $cm^{-1}$ (C=O, conjugated with a double bond), 1625 $cm^{-1}$ (C=C).

21-Acetate-$\Delta^4$-pregnen-17$\alpha$,21-diol-3,20-dione (Acetate of Reichstein's Substance S) (VII). Technical (VI) of weight 14.5-16 g was dissolved in 100 ml of dimethylformamide, 11.3 g of fused potassium acetate was added, and the mixture was heated for 2 h at 60°. The solid which precipitated after cooling was filtered, washed with dimethylformamide and water, and dried. We obtained 8.63 g (73.4%) of technical acetate of Reichstein's substance S (VII), mp 230-232°, $E^{1\%}_{1cm}$ 418 in which iodine is absent. Technical (VII) was dissolved in methylene chloride and treated with carbon at room temperature. The carbon was filtered, the solvent was evaporated to dryness, 45 ml of acetone was added to the residue, the mixture was boiled for 30 min, and after cooling the precipitate was filtered and dried. We obtained 8.44 g of (VII) (71.8%) calculated on (V), mp 235-238°, $E^{1\%}_{1cm}$ 423.

Iodination of 21-Iodo-$\Delta^4$-pregnen-17$\alpha$-ol-3,20-dione (VI). To 4 g of (IV) in 300 ml of methanol was added 4 g of calcium oxide and 1 ml of a 10% solution of calcium chloride in methanol, then at room temperature over 2 h was added a solution of 12 g of iodine in 30 ml of a 10% solution of calcium chloride in methanol. The reaction mixture was stirred at this temperature for $1^{1}/_{2}$ h. The calcium oxide was filtered, the solution was poured into 1 liter of ice water, and the precipitate was filtered, washed with a 1% solution of sodium bisulfite, water, and dried. The residue of weight 9 g was chromatographed on 100 g of silica gel. Methylene chloride eluted 0.43 g of iodoform; mp 120° (dec.), $R_f$ 0.88. Spot is of yellow color. Found, %: I 96.5 $CHI_3$. Calculated, %: I 96.8.

Reduction of 21-Iodo-$\Delta^4$-pregnen-17$\alpha$-ol-3,20-dione (VI). To a solution of 1 g of (VI) in 20 ml of methylene chloride was added 1 ml of a concentrated aqueous solution of sodium bisulfite. The suspension was stirred for 4 h and diluted with water. The methylene chloride layer was separated, washed with water, dried, and evaporated to dryness. We obtained 0.7 g of (V) (96).

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