IMPROVED METHOD FOR THE PREPARATION OF 21-ACETOXY DERIVATIVES OF STEROIDS OF THE PREGNANE SERIES

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A method including a step involving direct iodination at the 21-position and acetoxylation of the iodo derivative [1-3] is known for the preparation of 21-acetoxy derivatives of steroids of the pregnane series. In particular, the synthesis of the acetate of Reichstein's substance S (I), a major intermediate for the production of antiphlogistic corticosteroids, is carried out by direct iodination of 17α-hydroxyprogesterone (II) under cationic catalysis conditions [2, 4] in the presence of calcium chloride and calcium oxide and hydroxide. The resulting 21-iodo derivative of 17α-hydroxyprogesterone (III) is converted to I in 64% yield by the action of fused potassium acetate in dimethylformamide.

In accordance with this method, the reaction mass, after completion of the iodination, is poured into water, and the resulting mixture is filtered away from the solid phase, and III is extracted with methylene chloride and isolated by evaporation of the solvent. However, this method for the isolation of III has a substantial disadvantage. An alkaline medium, which promotes the occurrence of side reactions and, consequently, a decrease in the yield of the chief product, is formed on mixing of the reaction mass with water. A stable emulsion that hinders filtration and separation of the aqueous layer from the organic layer is often formed in the process; this increases the contact time of the reaction product with the alkaline medium and leads to mechanical losses. Other methods described for the isolation of 21-iodo derivatives of steroids of the pregnane series – by pouring the reaction mass into cooled 4% aqueous acetic acid [5] or into a mixture of acetic acid and sodium thiosulfate [3, 6] – also have the disadvantage associated with the possibility of the reduction of the reaction product.

We have found a method for the preparation of III that makes it possible to increase the yield. The method consists in pouring the reaction mixture, after completion of the iodination of II, into a cooled, aqueous sodium bicarbonate solution (pH ~ 7.5). Calcium carbonate is precipitated in the process and is readily separated from the liquid phase by filtration; the possibility of the formation of an alkaline emulsion that hinders filtration is eliminated. The subsequent isolation of the reaction product is carried out by separation of the organic layer from the aqueous layer and evaporation of the solvent. Technical III (a light-yellow, crystalline powder) is subjected, without subsequent purification, to acetoxylation with fused potassium acetate in dimethylformamide [2, 4].

The use of the proposed method for the isolation of III makes it possible to obtain I in a two-step yield of 69-70%. This method for the preparation of III can be successfully used to isolate other 21-iodo derivatives of steroids synthesized by direct iodination. For example, 95-98% of 21-iodo-16α,17α-epoxyprogesterone (V) is obtained from 16α,17α-epoxyprogesterone (IV); V is converted to 21-acetoxy-16α,17α-epoxyprogesterone (VI) in a two-step yield of 68-70% by the action of fused potassium acetate in acetone containing acetic acid and isopropyl alcohol [6].

EXPERIMENTAL

The iodination and acetoxylation processes were monitored by chromatography on plates in a thin layer of KSK silica gel fastened to gypsum [7] using methyl chloride–acetone (9:1 in the iodination of II) and ethyl

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acetate–cyclohexane (1:1 in the iodination of IV) systems with development with 50% phosphoric acid at 100-110°C for 6-7 min.

21-Iodo-17α-hydroxyprogesterone (III). A mixture of 8.5 g of calcium oxide and 0.56 ml of water was added with stirring to a solution of 11.16 g of II in 82 ml of methylene chloride and 28 ml of methanol. A solution of 11.16 g of iodine and 1.9 g of calcium chloride in 28 ml of methanol was then added at 18-20°. The solution was poured into a single receiver, and a temperature rise to 28° was observed. The reaction mixture was cooled to 25-26°, and stirring was continued for 50-55 min. Decoloration commenced after 10-15 min. Methylene chloride (75 ml) was added to the reaction mass, and the mixture was poured into a cooled (to 0-3°) sodium bicarbonate solution (50 g of salt in 600 ml of water). After 10-15 min, the mixture was filtered, and the precipitate was washed on the filter with ethylene chloride–methanol (4:1) and then with methylene chloride. The organic layer was separated from the aqueous layer. Evaporation of the solvent in vacuo at 30° gave 14.5-15 g (95-98%) of III as a light-yellow powder with mp 145° (dec.).

Acetate of Reichstein's Substance S [21-Acetate of Δ^4-Pregnene-17α,21-diol-3,20-dione (I)]. Powdered fused potassium acetate (14.4 g) was added to a solution of 14.5-15 g of III in 144 ml of dimethylformamide. The reaction mixture was stirred at 20-25° for 1 h, the temperature was gradually raised to 58-60° (in the course of 1 h), and the mixture was held at this temperature for 2 h. The mixture was then cooled to −7 to −10°, and the precipitate was filtered after 10-12 h. The precipitate was washed with cold dimethylformamide and then with cold and hot water. The product was dissolved in 90 ml of methylene chloride, and the aqueous layer was separated. Activated charcoal (0.3 g) was added to the organic layer, and the mixture was stirred for 15-20 min. The charcoal was removed by filtration and washed with methylene chloride. The solvent was evaporated to dryness, 10 ml of acetone was added to the residue, and the mixture was again evaporated to dryness. Acetone (45 ml) was added, and the mixture was refluxed with stirring for 20 min. The resulting suspension was cooled at −7 to −10° for 10-12 h. The resulting precipitate was filtered, washed with cold acetone, and dried at 65-70° to give 9.12-9.26 g of I (69-70% based on II) with mp 238-241° (mp 235-238° [2]).

21-Iodo-16α,17α-epoxyprogesterone (V). IV was iodinated by the method described above to give 4.5-4.8 g (95-98%) of V with mp 130-132° (dec.) from 3.7 g of starting compound. One recrystallization from methanol gave 2.8-3.0 g (56-60%) of a product with mp 134-137° (dec.) (mp 138-140° [6]).

21-Acetoxy-16α,17α-epoxyprogesterone (VI). Fused potassium acetate (7.1 g) and 7.1 ml of acetic acid were added with stirring to a solution of 4.5-4.8 g of V in 150 ml of acetone and 32 ml of isopropyl alcohol. The mixture was refluxed for 15-20 h, after which it was vacuum-evaporated at 45-50° to 50-60 ml. The residue was poured into a cooled (to 0-3°) solution of sodium chloride (25 g of salt in 300 ml of water). The precipitate was filtered, washed with water, and dissolved in 40 ml of methylene chloride. The aqueous layer was separated, and 0.1 g of activated charcoal was added to the organic layer. The organic layer was stirred for 20 min, the charcoal was removed by filtration, and the solvent was evaporated to dryness. The residue was dissolved in 12 ml of methanol by heating, and the solution was allowed to stand at −7 to −10° for 10-12 h. The product was removed by filtration, washed with cold methanol, and dried at 60-65° to give 2.90-2.92 g (66-67%) of VI with mp 164-166° (mp 168-170° [6]). Evaporation of the methanol mother liquor and crystallization of the residue gave an additional 0.1-0.15 g of a product with mp 163-166°. The overall yield of VI was 68-70% based on IV.

LITERATURE CITED

1. H. J. Ringold and G. Stork, J. Am. Chem. Soc., 80, 250 (1958).
2. L. V. Sokolova, L. I. Klimova, and Z. V. Yaroslavtseva, Khim.-Farmats. Zh., No. 12, 33 (1969).
3. E. J. Agnello et al., U. S. Patent No. 3,376,294 (1968).
4. L. V. Sokolova, N. N. Suvorov, L. I. Klimova, et al., USSR Author's Certificate No. 198,332 (1965); Byull. Izobr., No. 14, 18 (1967).
5. A. Bowers and H. J. Ringold, J. Am. Chem. Soc., 80, 3091 (1958).
6. N. N. Suvorov, O. K. Nikiforova, L. V. Sokolova, et al., Med. Prom. SSSR, No. 12, 9 (1960).
7. A. A. Akhrem and A. I. Kuznetsova, Thin-Layer Chromatography [in Russian], Moscow (1965), p. 22.