6. A. V. Kamernitskii, V. A. Pavlov, I. G. Reshetova, and G. Snattske, Izv. Akad. Nauk SSSR. Ser. Khim., 2391 (1980).
7. A. V. Kamernitskii, I. G. Reshetova, N. M. Mirsalikhova and F. G. Umarova, Biokhimiya, 47, No. 6 (1982).
8. A. V. Kamernitskii, I. G. Reshetova, and K. Yu. Chernyuk, Izv. Akad. Nauk SSSR, Ser. Khim., 184 (1978).
9. A. V. Kamernitskii, V. G. Levi, I. G. Reshetova, V. S. Bogdanov, V. A. Pavlov, and E. G. Cherepanova, Khim. Prir. Soedin., 63 (1982).
10. R. Tschesche, G. Ludke, and G. Wulf, Chem. Ber., 102, 1253 (1969).

SYNTHESIS OF NEW ANTIATHEROMATOUS DRUGS.

STUDY OF THE ESTERIFICATION OF 17β-HYDROXY-5α-ANDROSTAN-3-ONE

L. N. Volovel'skii, V. N. Koryukina,
N. V. Popova, I. A. Rastrepina,
and L. K. Borozenets

UDC 615.857.06.088.8)

The acylation of dihydrotestosterone with propionyl and p-chlorophenoxyisobutyryl chlorides leads to the formation of dihydrotestosterone esters and the 3-enol acylates of the dihydrotestosterone esters. The acid hydrolysis of the 3-enol acylates converts them into the corresponding dihydrotestosterone esters.

The use of derivatives of p-chlorophenoxyisobutyric acid as antiatheromatic drugs normalizing the lipid metabolism started at the beginning of the 60's, when ethyl p-chlorophenoxyisobutyrate was tested and used [1]. The search for biologically active agents among the aroxyalkanecarboxylic acids is continuing [2, 3]. During the last 15 years, studies have appeared [4-6] showing that some androgens and their metabolites — in particular, dihydrotestosterone — possesses a hypolipoproteinemic action. However, dihydrotestosterone is inactivated and excreted from the organism in a relatively short time. Some dihydrotestosterone esters exhibiting hypolipoproteinemic properties, and 17β-hydroxy-5α-androstan-3-one p-chlorophenoxyacetate and p-chlorophenoxyisobutyrate, which prevent the development of disturbances to the lipid metabolism, have been synthesized. With these, the protective effect was expressed even after 30 days and was retained during the whole time of observation. These esters are obtained by the reaction of dihydrotestosterone with the chlorides of the acids mentioned in pyridine solution at −5-10°C.

A study of the reaction products in the production of dihydrotestosterone p-chlorophenoxyisobutyrate showed that another compound was formed in addition to the desired product.

Thin-layer chromatography showed the presence of two spots with R_f ~ 0.53 and ~0.65, the compound with R_f ~ 0.53 being dihydrotestosterone p-chlorophenoxyisobutyrate. The formation of enol acetates in the esterification with acetic anhydride of Δ^4-3-ketosteroids has been described in the literature [8-10].

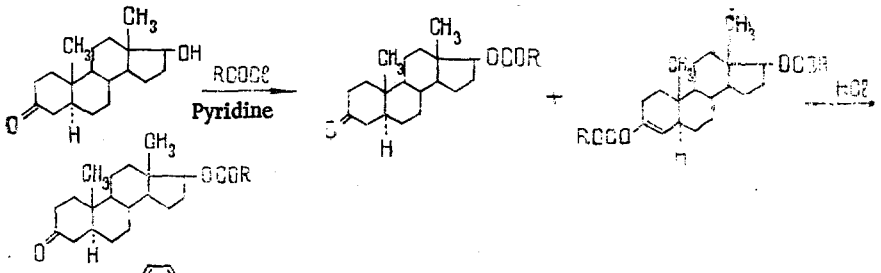
Similar results were obtained in the acetylation of 17α-hydroxyprogesterone [9]. No such reactions have been described for androstan hydroxyketones having no conjugated ethylenic bond in the ring. A distinguishing feature of the process that we are introducing is acylation at a temperature of ~0°C, while in the known cases this process takes place on heating. We have suggested that the spot with R_f ~ 0.65 belongs to 5α-androstene-3,17β-diol 3,17-bis(p-chlorophenoxyisobutyrate). The reaction product that we isolated from the filtrate contained no CO absorption band at 1705 cm^{-1} that is characteristic for a carbonyl CO group at C_3. The absence of this band from the IR spectrum and the presence of bands at 1720 cm^{-1} corresponding to a carboxylic CO group, and at 1650 cm^{-1}, corresponding to Δ^3-enol, may serve as a proof of the formation of an enol acetate.

Khar'kov Scientific-Research Institute of Endocrinology and Hormone Chemistry. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 473-476, July-August, 1983. Original article submitted November 16, 1982.

 0009-3130/83/1904-0444$07.50

This reaction was investigated with the use of the acylation of dihydrotestosterone with propionyl chloride as a model. On TLC, the mixture of reaction products obtained gave two spots with R_f ~ 0.69 and 0.53 when the chromatogram was run twice. But since it was impossible to isolate an enol propionate from this mixture, we made use of the properties of enol acetates of readily undergoing hydrolysis in the presence of a small amount of acid [9], when the esterified hydroxyl at C_{17} is unaffected. The experiments showed that when the mixture was heated in the presence of a small amount of hydrochloric acid dihydrotestosterone propionate (R_f ~ 0.53) was formed quantitatively.

On investigating the products of the esterification of dihydrotestosterone with p-chlorophenoxyisobutyryl chloride, we found that after the separation of the bulk of the dihydrotestosterone p-chlorophenoxyisobutyrate, a mixture of substances was isolated from the filtrates in which the main product was a compound with R_f ~ 0.65, with a small amount of one with R_f ~ 0.53 corresponding to dihydrotestosterone p-chlorophenoxyisobutyrate. Partial hydrolysis under the conditions described above converted the product obtained into dihydrotestosterone p-chlorophenoxyisobutyrate. On the basis of the results obtained, it may be assumed that the esterification of dihydrotestosterone with acid chlorides at temperatures below 0°C takes place in accordance with the following scheme:



1. R = Cl-C$_6$H$_4$-O-C(CH$_3$)$_2$CO-

2. R = C_2H_5CO-

EXPERIMENTAL

Dihydrotestosterone Propionate. With stirring and cooling to −(10-12)°C, 50 ml of freshly distilled propionyl chloride was added to a solution of 56 g of dihydrotestosterone in 350 ml of freshly distilled dry pyridine in such a way that the temperature did not rise above −10°C. After the end of the addition of the acid chloride, stirring was continued at the same temperature for another 2 h, and the mixture was poured into 3 liters of ice water containing 140 ml of sulfuric acid. The resulting precipitate was separated off and was dissolved in 600 ml of ether. The ethereal solution was washed successively with 150 ml of 5% hydrochloric acid, 300 ml of water, 150 ml of 5% sodium carbonate solution, and 300 ml of water and was dried over anhydrous sodium sulfate for 2 h, and then it was separated off and evaporated to dryness. The residue was crystallized from methanol, giving 57.7 g of a substance with mp 110-113°C. Recrystallization did not raise the melting point. On a chromatogram, two spots were formed with R_f ~ 0.53 and ~0.65 (C_6H_6–C_2H_5OH (95:5)), TLC on Silufol UV-254, spots were revealed with a 1% solution of vanillin in 10% perchloric acid). IR spectrum, ν_{max}^{KBr}, cm^{-1}: 1720 (carboxylic CO), 1200 (C–O–C).

The mixture of substances obtained (57.7 g) was boiled with 800 ml of benzene, 25 ml of concentrated hydrochloric acid, and 25 ml of water for 30 min and was then cooled and was diluted with 200 ml of water, and the benzene layer was washed successively with 150 ml of 5% caustic soda solution and with water to neutrality. The benzene solution was separated off and dried over anhydrous sodium sulfate. Then it was evaporated to dryness and the residue was crystallized from 100 ml of methanol. This gave 52.6 g (78.7% of theoretical) of dihydrotestosterone propionate with mp 119-123°C. On chromatogram it gave one spot with R_f ~0.53.

IR spectrum, ν_{max}^{KBr}, cm^{-1}: 1720 (carboxylic CO); 1705 (CO at C-3); 1200 (C–O–C).

Dihydrotestosterone p-Chlorophenoxyisobutyrate. With stirring at a temperature of −(2-5)°C, 60 ml of p-chlorophenoxyisobutyryl chloride was added to a solution of 20 g of dihydrotestosterone in 100 ml of freshly distilled dry pyridine in such a way that the temperature

did not rise above −2°C. Stirring at −(2-5)°C was continued for another 3 h, and then 250 ml of benzene and 150 ml of water were added. The benzene layer was separated off and the aqueous layer was extracted with benzene (2 × 100 ml). The combined benzene extracts were washed successively with 100 ml of saturated sodium chloride solution, 100 ml of 5% sodium chloride solution, and 150 ml of water. Then they were dried over anhydrous sodium sulfate and the benzene was distilled off completely. The residue was crystallized from methanol, giving 25 g (74.5% of theoretical) of dihydrotestosterone p-chlorophenoxyisobutyrate with mp 159-162°C.

The methanolic filtrate after evaporation yielded 4.7 g of a mixture of substances with mp 128-130°C (TLC on Silufol UV-254; visualization with a 1% solution of vanillin in 10% perchloric acid; (C_6H_6–C_2H_5OH (95:5); R_f ~ 0.65 and 0.53). The reaction products (4.7 g) were dissolved in 120 ml of benzene and then 2.5 ml of hydrochloric acid (1:1) was added and the mixture was boiled for 0.5 h. It was diluted with water, and the benzene layer was separated off and washed with 5% caustic soda solution (20 ml) and with water to neutrality. The benzene layer was separated off again, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from 20 ml of methanol, giving 3.5 g of a substance, $C_{29}H_{39}O_4Cl$, with mp 159-162°C. Total yield: 28.5 g (85% of theoretical) of dihydrotestosterone p-chlorophenoxyisobutyrate with mp 159-162°C.

IR spectrum, ν_{max}^{KBr}: 1705 (CO at C-3); 1720 (carboxylic CO): 1250 (C–O–C) cm^{-1}.

SUMMARY

1. It has been shown that the acylation of dihydrotestosterone with propionyl and p-chlorophenoxyisobutyryl chlorides leads to the formation of the dihydrotestosterone esters and the 3-enol acylates of the dihydrotestosterone esters.

2. The acid hydrolysis of 3-enol acylates of the dihydrotestosterone esters converts them into the corresponding dihydrotestosterone esters.

LITERATURE CITED

1. W. Clinne, M. Jones, I. M. Thorp, and W. Z. Waring, British Patent No. 860,303 (1961).
2. K. K. Deloery, Japanese Patent No. 53-19,570 (1978).
3. Shell International Research Maatschappii B. V., French Patent No. 2,371,414 (1978).
4. I. N. Sharkevich and S. D. Fisun, The Physiology, Biochemistry, and Pathology of the Endocrine System [in Russian], Kiev, Vol. 3 (1973), p. 87.
5. I. R. Dingmann and W. A. Jenkins, Metabolist, 11, 273 (1962).
6. I. N. Sharkevich, Patol. Fiziol. Éksp. Ter., 15, 79 (1971).
7. L. N. Volovel'skii, V. V. Natarov, I. S. Chekman, V. A. Tumanov, Z. P. Shchechenko, and S. A. Korotkov, USSR Inventor's Certificate No. 575,097; Byull. Izobr., No. 37, 28 (1977).
8. L. Ruzicka, and W. H. Fischer, Helv. Chim. Acta, 19, 806, 1371 (1936).
9. K. Junkmann and G. Suckowsky, Arzneimittel-Forschung, 12, 214 (1962).
10. H. H. Inhoffen, Chem. Ber., 69, 2141 (1936).