SYNTHESIS OF ALDOSTERONE ANTAGONISTS

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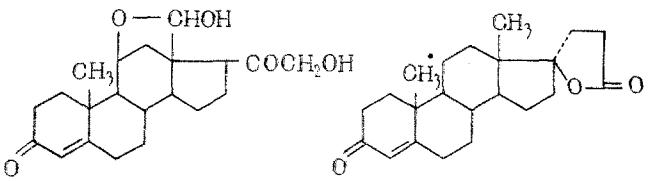
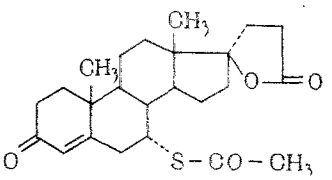
The main regulator of water-salt equilibrium in the organism is aldosterone (I), one of the hormones of the adrenal cortex.

In certain illnesses of the heart, liver, and kidney, in the majority of cases an elevated secretion of this hormone accompanying edema is observed, which causes an undesirable retention of sodium and chloride ions, and also of water, and increases secretion of potassium ions. Therefore, in curing the illnesses mentioned above, it is extremely important to suppress the effect of aldosterone with its antagonists, thus making possible excretion of salt and water from the organism and retention of potassium. To a certain degree, such an antagonist was found to be the γ-lactone of 3-(3-keto-17β-hydroxy-4-androsten-17α-yl)-propionic acid [1, 2], abbreviated to the so-called spirolactam SC-5233 (II), which is similar in chemical structure to aldosterone:



I

II



III

In the process of studying the properties of (II), the relation between certain changes in its structure and the effectiveness of the biological effect was established. Thus, expansion of the lactone ring to a six-membered ring leads to a significant decrease of activity [3], and closing the lactone at the 17α-hydroxyl group instead of the 17β-hydroxyl group involves complete loss of biological activity [4].

The same result was observed upon saturation of the Δ^4 double bond [3]. A sharp increase in the activity upon subcutaneous introduction was noted for the spirolactone devoid of the methyl group at C-10 [5]. However, upon a dose per os the biological effect of this compound is relatively small [6].

Of the antagonists of aldosterone known at the present time, of greatest interest is the 7α-thioacetic derivative of (II), the γ-lactone of 3-(3-keto-17β-hydroxy-7α-acetylthio-4-androsten-17α-yl)-propionic acid (III), called aldactone or SC-9420.

Upon subcutaneous introduction, (III) does not differ in activity from the spirolactone SC-5233; however, upon a dose per os it surpasses the latter by 50 times [6].

The valuable therapeutic effect of aldactone was also confirmed by foreign and domestic clinical practice in the curing of circulation deficiences, kidney edema, cirrhosis of the liver, and other illnesses [7]:

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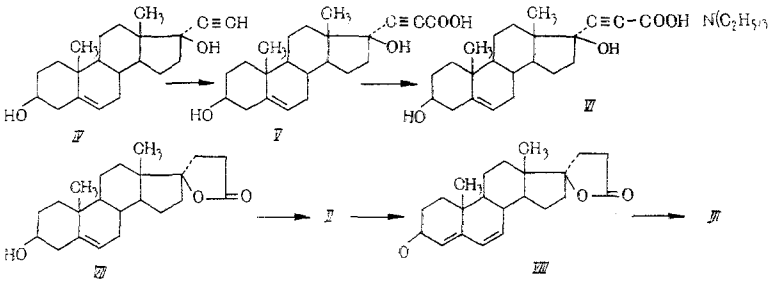

We accomplished the synthesis of (II) on the basis of the scheme of Cella and co-workers [1,3], with the only difference being that ethynyl androstenediol (IV) was used as the starting material, instead of dehydroepiandrostene acetate. In addition, technological changes were made at the separate stages.

The first stage of the synthesis consisted of reaction of (IV) with ethylmagnesium bromide, as a result of which the magnesium complex was easily formed, which was converted to the propiolic acid (V) by reaction with dry carbon dioxide gas. Since the carboxylation reaction occurred slowly and it was not possible to take it to completion, it was important to find a convenient method of purifying (V) from the starting material (IV). It was found to be most convenient to separate (V) from tetrahydrofuran in the form of its salt with triethylamine (VI). Selective catalytic hydrogenation on palladized carbon transformed the salt (VI) to lactone (VII), which upon Oppenauer oxidation gave the spirolactone SC-5233 (II). The latter upon reaction with chloranil gave the diene (VIII) [8], which was converted to aldactone (III) by reaction with thioacetic acid [9].

EXPERIMENTAL

Salt of Triethylamine and 3-(3β,17β-Dihydroxy-5-androsten-17α-yl)-propiolic Acid (VI). To a solution of 15 g of ethynylandrostenediol (IV) in 1 liter of dry toluene was added 60 ml of an ether solution of the Grignard reagent prepared from 25 g of ethyl bromide and 6 g of magnesium. Into the reaction mixture cooled to room temperature with agitation was passed carbon dioxide for 6 h. The next day to the flask was added a solution of 7 ml of concentrated H_2SO_4 in 60 ml of water. Toluene was then distilled from the reaction mixture with steam. The solid product was filtered, washed with water, and dried in air. Weight of technical acid was 15-16 g, mp 220-225°C. To obtain the pure product, (V) was heated for 2 h with 50 ml of tetrahydroruan and 4 ml of triethylamine. The formed salt of triethylamine, (VI), was filtered and dried: mp 235-237°, yield 10 g [about 46% based on starting material, without consideration of the amount of unreacted (IV)].

γ-Lactone of 3-(3β-17β-Dihydroxy-5-androsten-17α-yl)-propionic Acid (VII). A solution of 20 g of (VI) in 120 ml of methanol was hydrogenated at room temperature and normal pressure over 8 g of preliminarily prepared Pd/C catalyst. Absorption of hydrogen (2 moles) virtually ceased after 2 h. After separation of the catalyst, a portion of the solvent was distilled from the filtrate and a solution consisting of 12 ml of H_2SO_4, 9 ml of water, and 18 ml of methanol was added. After addition of 250 ml of water to the reaction mixture, the precipitate was filtered, washed with water, dried, and crystallized from ethyl acetate. Yield of lactone amounted to 11.5 g or 76.6% of theoretical. Mp 188-190°. Literature data [1]: mp. 190-191°.

γ-Lactone of 3-(-Keto-17β-hydroxy-4-androsten-17α-yl)-propionic Acid (Spirolactone SC-5233) (II). We placed 3 g of lactone (VII), 90 ml of toluene, and 30 ml of cyclohexanone in a round-bottom flask and distilled a portion of the solvent to completely remove moisture. To the flask was then added a solution of 3 g of aluminum isopropoxide in 15 ml of toluene and the mixture was boiled for one hour. After exhaustive distillation of the volatile material with steam, a solution of 5 ml of H_2SO_4 in 20 ml of water was added to the reaction flask and the mixture was extracted with chloroform; the chloroform solution was washed with water and the solvent was distilled. The residue was crystallized from ethyl acetate. Yield of spirolactone SC-5233 amounted to 2.3 g of about 78% theoretical. Mp 162-163°, which agrees with the literature data [1, 3].

γ-Lactone of 3-(3-Keto-17β-hydroxy-4, 6-androstadien-17α-yl)-propionic Acid (VIII). We dissolved 3 g of (II) in 120 ml of trimethylcarbinol, added 3 g of chloranil, and boiled the mixture for 6 h. The solvent was then distilled and the residue was heated with 15 ml of chloroform. The insoluble portion was

separated by filtration. The chloroform was distilled from the filtrate and the residue was dissolved in 0.5 liter of benzene. The solution was washed with 0.5% sodium hydroxide, then water, dried with Na_2SO_4, and the solvent was distilled. The residue was crystallized from ethyl acetate. We obtained 1.35 g (45%) of diene (VIII), mp 161-163°, instead of the yield of 26% and mp 149-151° indicated in the literature [8].

γ-Lactone of 3-(3-Keto-17β-hydroxy-7α-acetylthio-4-androsten-17α-yl)-propionic Acid (Aldactone) (III). A mixture of 1 g of (VIII) and 1.1 ml of thioacetic acid (IX) was heated at 100° for one hour. The excess (IX) was distilled in vacuum and the aldactone residue was crystallized from methanol. Yield 0.92 g (76%). In the determination of melting point, the product gets wet at 133-135° and melts at 201-203° ($[\alpha]_D^{20}$ = −34.2°, c 2, $CHCl_3$), which corresponds to the literature data [8] (m.p. 201–202°, $[\alpha]_D^{20}$ = −33.5°). Found, %: S 7.52. $C_{24}H_{32}O_4S$. Calculated, %: S 7.69.

CONCLUSIONS

Two antagonists of aldosterone were synthesized based on ethynyl androstenediol: the γ-lactone of 3-(3-keto-17β-hydroxy-4-androsten-17α-yl)-propionic acid (SC-5233) and its 7α-thioacetate (aldactone or SC-9420).

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