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SYNTHESIS OF 21-ESTERS OF HYDROCORTISONE WITH GLYCINE AND GLUTAMIC ACID AND STUDY OF THEIR PHARMACOLOGICAL ACTIVITY

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Hydrocortisone, which is an adrenal cortex hormone, is widely used in medical practice, as an effective anti-inflammatory agent [3]. On prolonged use when treating chronic diseases, like many other glucocorticosteroids, hydrocortisone may cause side effects, including the retention of sodium and water in the organism, increase in the elimination of potassium, development of edemas, increase in arterial pressure (the Itsenko–Cushing syndrome) hyperglycemia (steroid diabetes), may display an immunodepressive action, cause impairment of growth, and suppression of the adrenal cortex function. The above enumerated effects complicate the use of hydrocortisone in medical practice.

Great progress has recently been made in research on the transformation of natural corticosteroids and their analogs in order to obtain therapeutic agents with a directed action. Compounds have been described in the literature which are condensation products of glucocorticosteroids – hydrocortisone, prednisolone, dexamethasone, etc. – with various amino acids [6, 7]. In particular, 21-esters of hydrocortisone with glycine and glutamic acid which have a free or a protected amino group have quite recently become known [6]. However, the authors do not provide experimental data on the biological activity of these compounds, but suggest the possibility of their use as ointments, lotions, pomades, i.e., as local anti-inflammatory agents.

To produce water-soluble derivatives of hydrocortisone, the use of which would enable development of new medicinal forms and broaden indications on the application of the preparation, we carried out the synthesis of the hydrochlorides of 21-aminoacetoxy- and 21-α-L-glutamyloxy-11β,17α-dihydroxypregn-4-ene-3,20-dione (Ia and Ib, respectively), and carried out a comparative examination of their pharmacological properties in order to find out how

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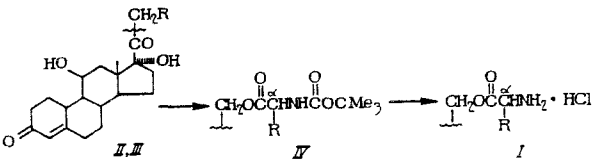
TABLE 1. Influence of Compounds Ia and Ib on the Inhibition of Paw Edema of Rats, Induced by Introducing Carrageenin, and Toxicity

Compound	Inhibition of a carrageenin induced edema in rats, %	Toxicity (LD_{50} mg/kg) in mice
Hydrocortisone	37±5,1*	>500
Ia	42±7,2*	>500
Ib	46±12,5*	>500

Note. Here and in Tables 2-4, asterisk – $p < 0.05$, compared with control.

the introduction of amino acid residues influences the biological properties of the glucocorticosteroid.

The method of preparation of hydrochlorides Ia and Ib is based on the known reaction by which esters are formed [1] by the



R=H(Ia, IVa), OSO_2Me(II), J (III), $(CH_2)_2COOH$(Ib), $(CH_2)_2COOCMe_3$(IVb)

reaction of the corresponding iodo derivative (III), obtained from hydrocortisone according to [8], with potassium salts of amino acids, the nitrogen acid of which is protected by the tert-butyloxycarbonyl (Boc) group. In the case of glutamic acid, in order to carry out the reaction selectively at the α-carboxylic group, the γ-carboxylic group was protected in the form of a tert-butyl ester, the hydrolysis of which proceeded simultaneously with the removal of the Boc protection of the amino group by the action of a solution of HCl in dioxane [9].

EXPERIMENTAL (CHEMICAL)

The elemental analysis data obtained matched the calculated values.

11β,17α,21-Trihydroxypregn-4-ene-3,20-dione 21-Mesylate (II). A 2 ml portion (22 mmoles) of methylsulfonyl chloride was added at 0°C to a solution of 2 g (5.5 mmoles) of hydrocortisone in 20 ml of pyridine. After 30 min, the mixture was poured into water, the precipitate was filtered off, washed with water, and dried. Yield 2.31 g (94.7%) of compound II, mp 185-187°C (dec.) [according to the literature data [5], mp 186-187°C (dec.)]. Mass spectrum: 440, 422, 407, 361, 343, 328.

11β,17α-Dihydroxy-21-iodopregn-4-ene-3,20-dione (III). A solution of 2.31 g (15.4 mmoles) of NaI in 30 ml of acetone was added to a solution of 2.31 g (5.25 mmoles) of compound II in 100 ml of acetone. The mixture was boiled for 15 min, and then was evaporated. The residue was stirred with a Na_2SO_3 solution, filtered, washed with water, and dried. Yield, 2.3 g of compound III (93%), mp 145-148°C (dec.) [according to the literature data [4], mp 148-150°C (dec.)]. IR spectrum, ν_{max}, cm^{-1}: 3380 (OH), 1705 (C_{20}=O), 1660 (C_3=O), 1620 (Δ^4), 580 (C-I).

21-(N-tert-butyloxycarbonyl)aminoacetoxy-11β,17α- dihydroxypregn-4-ene-3,20-dione (IVa). A solution of 1.92 g (5.9 mmoles) of the potassium salt of Boc-glycine in 10 ml of DMFA (for its preparation, 1.43 g of Boc-glycine and 0.45 g of KOH were dissolved in 5 ml of water, and the solution was evaporated with dioxane) was added to a solution of 2.3 g (4.9 mmoles) of the iodo derivative III in 7 ml of DMFA. After 4 h, the reaction mixture was poured into water, the precipitate was filtered, washed with water, and dried. Yield,

TABLE 2. Influence of Compounds Ia and Ib on Weight of Raw and Dry Granuloma, Increase in Body Weight, Weight of Adrenal Glands and Corticosterone Content in Blood Plasma (M ± m)

Compound	Weight of raw granuloma, mg	Weight of dry granuloma, mg	Increment in body weight, g	Weight of adrenal glands, mg	Corticosterone content, μg/100 ml
—	166,7±13,13	26,4±1,5	31,7±1,9	16,1±0,6	26,5±1,5
Ia	116,8±8,3*	19,0±1,2*	29,0±2,3	16,2±0,8	16,3±1,2*
Ib	125,0±9,0*	19,6±1,0*	13,8±3,0*	16,5±1,1	10,5±1,5*
Hydrocortisone	148,9±11,4	24,1±1,7	29,4±2,1	16,3±1,3	15,2±1,2*

TABLE 3. Glucocorticoid, Thymolytic, and Anti-inflammatory Activity of Compounds Ia and Ib under the Conditions of a Four-Day Course of Administration to Adrenalectomized Male Rats (M ± m)

Experimental conditions	Daily dose, mg/kg	Glycogen content in liver, g %	Glucose level in blood, mg %	Weight of thymus, mg per 100 g body weight	Weight of dry inflammation granuloma, mg
—	—	0,5±0,04	46,4±0,8	381,0±22,7	21,3±0,9
Hydrocortisone	10	5,2±0,3*	67,9±2,5*	130,6±15,0*	13,9±0,8*
Ia	10	0,6±0,08	49,9±2,1	381,4±28,4	14,5±0,5*
Ib	10	0,7±0,08*	60,9±3,7*	330,4±16,2	14,7±0,5*
—	—	0,5±0,04	49,0±1,4	359,2±46,3	23,7±0,8
Hydrocortisone	5	2,6±0,1*	65,7±1,8*	227,3±28,2*	15,9±0,7*
Ia	5	0,6±0,06	50,9±1,4	335,1±53,4	15,4±0,7*
Ib	5	0,7±0,1	54,4±4,2	337,3±27,9	18,5±1,1*
—	—	0,7±0,04	49,9±4,5	359,2±46,3	23,1±1,2
Hydrocortisone	2,5	1,0±0,1*	54,5±2,7	318,9±19,5	22,6±0,8
Ia	2,5	0,8±0,07	54,4±4,3	315,1±20,1	22,8±1,2
Ib	2,5	0,7±0,07	57,8±2,1	320,8±4,6	21,7±1,0

Note. In a group of 12-13 animals.

2.22 g (78% based on hydrocortisone) of compound IVa, mp 126-129°C. IR spectrum, CH_2Cl_2, ν_{max}, cm^{-1}: 3600 (OH), 3450 (NH), 1755 (COOR), 1715 (C_{20}=O), 1665 (C_3=O, amide I) 1615 (Δ^4), 1505 (amide II). PMR spectrum, $CDCl_3$, δ, ppm: 0.92 s (3H, 18-CH_3), 1.41 s (3H, 19-CH_3), 1.43 s (9H, $C(CH_3)_3$), 4.05 d (2H, α-CH_2, J ~ 5.54 Hz), 4.48 s (11-H), 5.02 centr. AB system (2H, 21-CH_2, J ~ 17 Hz), 5.16 t (1H, NH, J ~ 3.5 Hz), 5.68 s (4H). $C_{28}H_{41}NO_8$.

21-Aminoacetoxy-11β,17α-dihydropregn-4-ene-3,20-dione Hydrochloride (Ia). A 9 ml portion (12.8 mmoles) of a 3 N solution of HCl in dioxane was added to a solution of 2.22 g (4.28 mmoles) of compound IVa in 5 ml of dioxane. After 1 h, the precipitate was filtered off and washed with cold dioxane and hexane, and dried in a desiccator over an alkali. Yield, 1.94 g (77.5% based on hydrocortisone) of compound Ia in the form of white crystals, mp 180-184°C. IR spectrum, ν_{max}, cm^{-1}: 3480 and 3300 (OH, NH) 2660 broad band (hydrochloride), 1760 (COOR), 1720 (C_{20}=O), 1660 (C_3=O), 1615 (Δ^4), 1235 (COOR). PMR spectrum, $(CD_3)_2SO$, δ, ppm: 0.78 s (3H, 18-CH_3), 137 s (3H, 19-CH_3), 4.31 br. s (2H, α-CH_2), 4.48 d (11-H, J ~ 4 Hz), 5.08 centr. AB system (2H, 21-CH_2, J ~ 18 Hz), 5.56 s (4H), 8.52 br. s (2H, NH_2). $C_{23}H_{34}ClNO_6$.

21-(N-tert-Butyloxycarbonyl)-(γ-tert-butyl ester)-α-L-glutamyloxy-11β,17α-dihydroxypregn-4-ene-3,20-dione (IVb) was obtained under the conditions of the preparation of compound IVa, from 2.65 g (5.6 mmoles) of the iodo derivative III by the reaction with 2.15 g (6.73 mmoles) of the potassium salt of Boc-L-glutamic acid γ-tert-butyl ester (a solution of 1.812 g of Boc-L-glutamic acid γ-tert-butyl ester and 0.335 g of KOH in 10 ml of water and 4 ml of dioxane was evaporated in vacuo). Yield 3.41 g (82.7%, based on hydrocortisone) of compound IVb, mp 82-88°C. IR spectrum, CH_2Cl_2, ν_{max}, cm^{-1}: 3600 (OH), 3440 (NH), 1735 (COOR), 1710 (C_{20}=O), 1670 (C_3=O, amide I), 1625 (Δ^4), 1505 (amide II). PMR spectrum, $CDCl_3$, δ, ppm: 0.93 s (3H, 18-CH_3), 1.44 s (9H, tert-butyl ester), 1.45 s (3H, 19-CH_3), 1.46 s (9H, Boc), 4.41 br. d (1H, α-CH, J ~ 4.9 Hz), 4.48 br. s (11-H), 5.01 centr. AB system (1H, 21-CH_2, J ~ 18 Hz), 5.26 d (1H, NH, J ~ 8.8 Hz), 5.68 s (4H). An analytical sample was obtained by the chromatography on a column with silica gel, using $CHCl_3$ as eluent, mp 88-90°C, $C_{35}H_{53}NO_{10}$.

21-α-L-glutamyloxy-11β,17α-dihydroxypregn-4-ene-3,20-dione Hydrochloride (Ib). Compound Ib was obtained in the form of white crystals using the conditions of the preparation of compound Ia, from 3.4 g (5.25 mmoles) of compound IVb and 18 ml of a 3 N solution of HCl in dioxane (25.6 mmoles). Yield 2.8 g (82%, based on hydrocortisone). After recrystallization from an MeOH–ether (1:7) mixture, 2.4 g (71.5%, based on hydrocortisone) was obtained, mp 160-162°C. IR spectrum, ν_{max}, cm^{-1}: 3460 (OH, NH), 2640 and 2600 (hydrochloride), 1735 broad band (COOR, COOH), 1710 (C_{20}=O), 1680 (C_3=O), 1630 (Δ^4), 1230 (COOR). PMR spectrum, CD_3OD, δ, ppm: 0.92 (3H, 18-CH_3), 1.50 s (3H, 19-CH_3), 4.29 t (1H, α-CH, J ~ 6.7 Hz), 4.43 d (11-H, J ~ 3 Hz), 5.20 centr. AB system (2H, 21-CH_2, J ~ 18 Hz), 5.68 s (4H).

EXPERIMENTAL (BIOLOGICAL)

The synthesized compounds were examined by pharmacological methods to characterize their influence on acute exudative and chronic proliferative inflammatory reactions and evaluated according to side effect parameters, characteristic for glucocorticosteroids. The experiments were carried out on intact and adrenalectomized animals. The compounds studied were administered subcutaneously in aqueous solution.

The acute inflammation was induced by subplantary administration of 0.1 ml of a 1% solution of carrageenin to rats of both sexes weighing 150 g each. The ability of the compounds studied (in a dose of 10 mg/kg subcutaneously, 1 h after the injection of carrageenin) to decrease paw edema, measured pletismometrically 3 h after the administration of carrageenin, served as the indication of the anti-inflammatory activity of the compound studied [16]. The ability of the studied compounds to suppress the chronic inflammation, which was produced at the site of implantation of wadded or felt globules in male rats weighing 80-100 g with intact adrenal glands and after adrenalectomy (animal weight 120-140 g) was evaluated according to the inhibition of the growth of the inflammation granuloma [14]. To evaluate the side effects of the synthesized compounds in the same experiments on intact animals, their influence on the increment in the body weight, the weight of the adrenal glands, and the corticosterone content in the blood plasma was determined. The concentration of corticosterone was determined according to [17].

In experiments on adult adrenalectomized rats, the thymolytic, glucocorticoid, and mineral corticoid activity of the synthesized compounds, as well as anti-inflammatory activity was studied. The thymolytic effect was evaluated from the decrease in weight of the thymus [15]. The glucocorticoid effect was evaluated from the increase in the glycogen content in the liver, and of glucose in the blood [10]. Glycogen was determined by means of anthrone reagent [13], and glucose by the ortho-toluidine method [2]. The mineralocorticoid effect of the compounds was examined in a dose of 5 mg/kg from the influence on the excretion of sodium and potassium ions with urine [11]. The content of sodium and potassium in the urine was determined by flame photometry. The gestagenic effect was studied according to the stimulation of secretory changes in the endometrium in immature rabbits, each weighing 800-900 g on administration of the tested compounds for 6 days in a daily dose of 0.4 mg/kg [12]. The toxicity was determined by a single subcutaneous administration to mice, each weighing 16-18 g.

The activity and toxicity of compounds Ia and Ib was compared with those of hydrocortisone. The data obtained were processed statistically. The reliability of the differences was determined by means of the Student criterion at a significance level of $p = 0.05$.

Table 1 shows the data on the influence of the synthesized compounds on carageenin-induced paw edema of rats, and the LD_{50} value in mice. It is seen that the above compounds are not different from hydrocortisone in their anti-exudative effect on rats by subcutaneous administration in a dose of 10 mg/kg; the suppression of the edema reaction to carrageenin is 37-46%, and the difference between the magnitude of the effects is statistically insignificant. At a single subcutaneous administration in a dose of 500 mg/kg, neither the tested preparations studied nor hydrocortisone caused the death of the animals or changes in their general state and behavior.

Table 2 shows that when administered subcutaneously to the rats in a daily dose of 10 mg/kg for 7 days, compounds Ia and Ib decrease the weight of the dry and raw granuloma by 25-30%. Hydrocortisone has no anti-inflammatory activity on this model. Compound Ib inhibits increase in the body weight by a factor of two, while Ia and hydrocortisone do

TABLE 4. Study of the Influence of Compounds Ia and Ib under Subcutaneous Administration Conditions in a Dose of 5 mg/kg on the Excretion with Urine of Sodium and Potassium Ions in Adrenalectomized Rats, Compared with the DOCA and Hydrocortisone Effect (M ± m)

Compound	Na^+	K^+	Na^+/K^+
	mg after 3 h		
—	2,1±0,2	1,9±0,3	1,2±0,2
DOCA	0,6±0,1*	3,3±0,4*	0,2±0,04*
Hydrocortisone	2,1±0,4	2,9±0,3*	0,7±0,09*
Ia	2,0±0,4	2,0±0,5	1,1±0,3
Ib	2,7±0,5	2,3±0,5	1,1±0,2

Note. In a group of 10 animals.

not influence this parameter. The two compounds as well as hydrocortisone, while not influencing the weight of the adrenal glands, decreased the content of corticosterone in the blood plasma by a factor of 1.5-2.

Table 3 gives data on the anti-inflammatory action, glucocorticoid and thymolytic effects of the synthesized compounds. It was found that when the tested compounds and hydrocortisone are administered for four days in a daily dose of 10 mg/kg to adrenalectomized rats, they decrease the weight of the inflammation granuloma by 32-35%, while hydrocortisone increases the glycogen content in the liver by 10 times, increases the glucose level in the blood by 45% and lowers the weight of thymus by 65%. Compound Ia does not influence the content of glycogen in the liver, the glucose in blood, the weight of the thymus, while compound Ib causes an increase in the glycogen content by 40%, of glucose by 30%, and does not change the weight of the thymus. With decrease in the daily dose to 5 mg/kg, the anti-inflammatory effect of Ia and hydrocortisone practically does not decrease, while compound Ib has somewhat lower anti-inflammatory action, causing a decrease in weight of the inflammation granuloma by 20%. Only hydrocortisone under these conditions has any considerable thymolytic and glucocorticoid effect. When introduced in a daily dose of 2.5 mg/kg, all the tested compounds, including hydrocortisone, were found to be ineffective with respect to the above parameters.

Table 4 shows that compounds Ia and Ib do not display any appreciable mineralocorticoid activity in adrenalectomized rats: on a subcutaneous administration in a dose of 5 mg/kg, they did not influence the excretion of sodium and potassium ions in the urine. Hydrocortisone in this dose does not influence the content of sodium ions in the urine, but increases the elimination of potassium somewhat. For comparison, the effect of DOCA in a dose of 0.5 mg/kg on the above parameters is shown in Table 4.

In the study of the gestagenic activity it was found that in contrast to hydrocortisone, administration of Ia and Ib to rabbits in a daily dose of 0.4 mg/kg does not produce an effect. Hydrocortisone in the same dose stimulates the secretory changes of endometrium, evaluated as 3.5 points on the McPhail scale.

None of the compounds studied displayed androgenic, anabolic, estrogenic, antiandrogenic, antiestrogenic, and antimineralocorticoid activity.

Thus, on a single administration to rats with intact adrenal glands, the synthesized compounds did not differ from hydrocortisone with respect to the anti-inflammatory activity; on prolonged application, in contrast to hydrocortisone, compounds Ia and Ib suppressed the proliferative inflammatory reaction, without differing appreciably from hydrocortisone in the influence on the function of the adrenal glands. The ability was observed of compound Ib of inhibiting the body weight increase of the animals.

It was also found that on administration to adrenalectomized animals, the synthesized compounds practically do not differ in their anti-inflammatory activity from the reference preparation hydrocortisone and have an advantage over it in the selectivity of this effect, but no glucocorticoid, thymolytic, and gestagenic effects were observed, which are characteristic for hydrocortisone.

The data obtained show the practicability of a further search in the series of glucocorticosteroids and amino acids for effective anti-inflammatory agents, having good tolerability and minimal side effects.

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EXPERIMENTAL STUDY OF THE EFFECTS OF 12-CROWN-4 AND 15-CROWN-5 ON CARDIO- AND HEMODYNAMICS

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Crown ethers and their derivatives have attracted the attention of pharmacologists as potential cardiovascular drugs, the mode of action of which involves interference with the transport of sodium and calcium ions through biological membranes [1, 2]. There have been literature reports of their antiarrhythmic and antiischemic activity [2, 4, 5, 9]. However, these studies examined the effects of derivatives of crown ethers, and no data on the effects of the crown ethers themselves on cardio- and hemodynamics were given.

The object of the present study was to assess the effects of 12-crown-4 and 12-crown-5 on the cardiovascular system.

EXPERIMENTAL

Tests were carried out on 17 narcotized cats (pentobarbital sodium, 50 mg/kg) weighing 2.5-3.5 kg using electromagnetic fluorimetry and recording the contractile activity of the myocardium [3]. The following cardio- and hemodynamic indices were recorded: arterial pressure (AP), pressure in the left ventricle of the heart (PLV), the rate of contraction and relaxation of the myocardium (+dp/dt and −dp/dt), the Veragut contraction index, the F. Z. Meerson relaxation index, the instant blood volume (IBV), pulse volume (PV), overall peripheral resistance (OPR), cardiac contraction frequency (CCF), and venous return (VR) of blood to the heart via the posterior vena cava. Recordings were made on an N-388-8 autorecorder. The compounds were administered intravenously as their aqueous solutions.

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