prepared auricles were placed in a dish (30 ml) of Tirode's solution, and oxygenated with oxygen at 30°C. The auricular contractions were recorded isometrically by means of an F-50 sensor and a Narco Bio-Systems physiograph (USA). The test compounds were dissolved in ethanol at an initial concentration of 10^{-2} M. Subsequent dilution was carried out with Tirode's solution. The effects of the compounds were assessed, starting at a concentration of 10^{-9} M.

Acute toxicities were determined in male white mice weighing 19-23 g, by the intraperitoneal route. Each dose was tested on six mice, which were kept under observation for ten days following dosing. The acute toxicities were calculated by the method of Litchfield and Wilcoxon.

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PREPARATION AND BIOLOGICAL ACTIVITY OF ANDROSTANE 17β-CARBOXYLIC ACIDS

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Some androstanecarboxylic acids are known to be biologically active, with a wide spectrum of action, notably antiinflammatory activity [3, 4].

We have previously synthesized some fluorinated 17β-carboxylic acids, and examined their hormonal activity [1].

We have now examined the antiinflammatory activity of some 5α-androstane and Δ^4-androstene acids. As in the earlier report [1], these compounds were obtained by the oxidative cleavage of the pregnane side chain in 20-ketosteroids of general formula (I) with atmospheric oxygen in caustic alkali, to give acids of structure (II).

These compounds (II) were examined as their water-soluble sodium salts, which were more convenient to use, and were obtained by treating a solution of the acid in dichloromethane with 10% sodium carbonate solution, followed by filtration of the crystalline salts which separated.

The structures of the products were confirmed by mass spectrometry. The spectra of all the test compounds showed molecular ion peaks of low intensity, in the case of (IIe), vanishingly small ($I_{M^+} < 0.1\%$). Breakdown of the fluorinated compounds under electron impact re-

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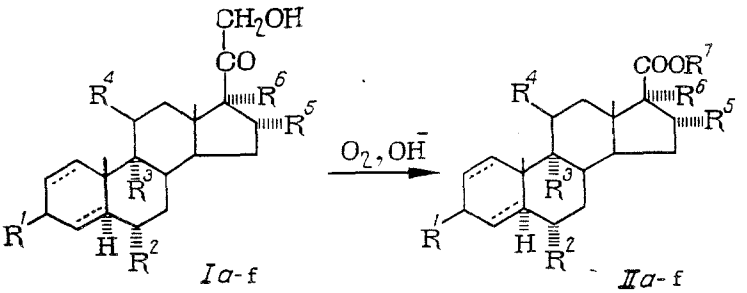
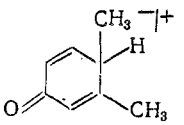


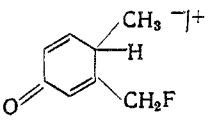
Ia-f *IIa-f*

I, II: R^1 = OH (a), O(b-f); R^2 = H (a-e), F (e); R^3 = H(a-c), F (d-f); R^4 = H (a,b), OH (c-f); R^5 = H(a-c), CH_3 (d); $R^5 + R^6$ = —$OC(CH_3)_2O$— (e,f); R^6 = OH (a-d); R^7 = H, Na(a-f); 5αH (a,b); $\Delta^{1,4}$ (d-f).

sulted in the elimination of a molecule of hydrogen fluoride with the formation of the stable $[M - HF]^+$ ion. The peak maximum intensity was that for the ion with m/z 122, with the following structure:



This molecular fragment is characteristic of $\Delta^{1,4}$-3-ketosteroids. In the case of (IIf), this fragment was the peak with m/z 139 (100%), with the structure:



The object of the pharmacological examination was to assess the effects of the compounds on acute (exudative) and chronic (proliferative) inflammatory reactions. The reference compounds used were the starting 20-ketosteroids (prednisolone, triamcinolone acetonide, dexamethasone, and sinaflan), which are used for the treatment of inflammatory and allergic conditions.

The tests showed that the androstanecarboxylic acids (II) display weak antiexudative activity, a subcutaneous dose of 5 mg/kg resulting in suppression of carrageenin edema by no more than 10-20%. In contrast, prednisolone, triamcinolone acetonide, dexamethasone, and sinaflan had a considerable antiinflammatory effect in this model, suppressing the edematous reaction by 48 ± 2.6, 64 ± 0.9, 73 ± 1.3 and 88 ± 1.8% ($P < 0.05$) respectively.

Table 1 shows the results of tests for local antiinflammatory and systemic effects (effects on the mass of the thymus and body weight in rats) of the compounds synthesized and the reference compounds. It will be seen that on local treatment in a dose of 600 μg per animal, the formation of granular inflammatory tissue was suppressed by dexamethasone (by 33%) and sinaflan (by 68%) only. Thymolytic effects were greatest in sinaflan, which reduced the mass of this organ by 92%, followed in order of decreasing activity by dexamethasone, triamcinolone acetonide, (IIe), (IIb), (IIa), prednisolone, and (IId). Compounds (IIc) and (IIf) caused no reduction in the mass of the thymus. In their ability to retard the increase in body weight of the animals, (IIa) was superior to dexamethasone, and (IIf) was comparable with it.

No compounds with high antiinflammatory activity have therefore been found amongst these androstanecarboxylic acids.

EXPERIMENTAL (CHEMISTRY)

Melting points were determined on a Boetius apparatus (East Germany). The specific rotations were measured in methanol–chloroform (1:1) on an FEP-02 apparatus (USSR). Mass spectra were obtained on a Varian MAT-112 (direct introduction of the sample into the source), ionization chamber temperature 180°C, ionizing electron energy 70 eV. IR spectra were obtained on a Perkin-Elmer spectrometer (Sweden) in suspension in Vaseline grease.

3β,17α-Dihydroxy-5α-androstan-17β-carboxylic Acid (IIa). To a solution of 6 g of (Ia) in a mixture of 75 ml of methanol and 75 ml of dichloromethane was added 3 g of NaOH in 40

TABLE 1. Antiinflammatory Activity and Systemic Effects of Androstane-17β-Carboxylic Acids on Local Application in Rats

Compound	Dry mass of granuloma, mg	Mass of thymus, g	Increase in body weight, g
Control	28.6±0.6	0.83±0.03	35.6±4.8
IIa	25.4±1.1	0.51±0.04*	11.2±2.7
IIb	29.4±0.9	0.48±0.05*	30.9±4.7*
IIc	23.7±1.3	0.75±0.06	34.7±3.2
IId	26.5±2.7	0.63±0.07*	30.2±2.9
IIe	26.2±0.9	0.43±0.05*	26.4±3.2
IIf	23.5±0.7	0.81±0.08	21.7±2.3*
Prednisolone	29.9±1.9	0.57±0.06*	41.5±4.5
Triamcinolone acetonide	22.7±2.3	0.35±0.09*	24.2±7.5
Dexamethasole	19.3±0.7*	0.21±0.03*	21.7±2.3*
Sinaflan	9.1±1.7*	0.07±0.01*	−1.4±4.0*

*Significantly different from the control at $P < 0.05$.

ml of methanol. A stream of air was passed through the solution for 3 h at room temperature. The mixture was then treated with 150 ml of water, the organic layer separated, and the aqueous layer acidified with hydrochloric acid to pH 2, and extracted with dichloromethane (2 × 75 ml). The extracts were combined, washed with water to pH 6.0, dried over sodium sulfate, the solvent removed under reduced pressure to a volume of 20 ml, and hexane added until crystallization commenced. The solid was filtered off and washed with a mixture of dichloromethane and hexane to give 4.89 g (95%) of (IIa), mp 250-252°C (methanol), $[\alpha]_D$ −5.98°. IR spectrum, ν_{max}, cm^{-1}: 3250–3600, 1700. $C_{20}H_{32}O_4$, m/z: 336 (M^+).

The method described above was used to obtain (IIb-f) in yields of 82% (IIb), 84% (IIc), 80% (IId), 78.5% (IIe), and 77.6% (IIf). Compounds (Ia) and (Ib) have been reported previously [2].

17α-Hydroxy-3-oxo-5-α-androstan-17β-carboxylic Acid (IIb). mp 254-256°C (chloroform), $[\alpha]_D$ + 29.4°, IR spectra, ν_{max}, cm^{-1}: 3480-3520, 1700-1720. ^1H NMR spectrum in $CDCl_3$, δ, ppm: 0.8 s (18-CH_3), 1.03 s (19-CH_3). $C_{20}H_{30}O_4$. Mass spectrum, m/z: 334 (M^+).

11β,17α-Dihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (IIc). mp 265°C (chloroform), lit. mp [5] 264-266°C, $[\alpha]_D$ + 67.5°, IR spectrum, ν_{max}, cm^{-1}: 3500, 3460, 2720-2400, 1725, 1650, 1580. Mass spectrum*, m/z: 346 (M^+) (8%), 225 (37%), 122 (100%), 121 (79%).

11β,17α-Dihydroxy-16α-methyl-3-oxo-9α-fluoroandrosta-1,4-diene-17β-carboxylic Acid (IId). mp > 260°C (chloroform), $[\alpha]_D$ 42.4°. IR spectrum, ν_{max}, cm^{-1}: 3540, 2700-2500, 1690, 1645, 1595. Mass spectrum, m/z: 378 (M^+) (3%), 360 (5%), 358 (21%), 122 (100%), 121 (69%).

Lit. mp [5] > 258°C (decomp.), $[\alpha]_D$ + 46.6° (dioxane), ν_{max}, nm: 238; ε 15,800.

11β-Hydroxy-16α,17α-isopropylidenedioxy-3-oxo-9α-fluoroandrosta-1,4-diene-17β-carboxylic Acid (IIe). mp 305.5°C (chloroform), $[\alpha]_D$ + 81.7°. IR spectrum, ν_{max}, cm^{-1}: 3520-3300, 2660-2340, 1710, 1655, 1590. Mass spectrum, m/z: 420 (M^+) (0.1%), 405 (4%), 400 (26%), 122 (100%), 121 (65%).

Lit. [7] mp 302.5-303.5°C, $[\alpha]_D$ + 81°, ν_{max}, nm: 238, ε 15,180.

11β-Hydroxy-16α,17α-isopropylidenedioxy-3-oxo-6α,9α-difluoroandrosta-1,4-diene-17β-carboxylic Acid (IIf). mp 298-299°C (chloroform), $[\alpha]_D$ + 57.4°. IR spectrum, ν_{max}, cm^{-1}: 3520-3260, 2740-2340, 1710, 1660, 1600. Mass spectrum, m/z: 438 (M^+) (9%), 423 (25%), 418 (13%), 398 (5%), 380 (3%), 139 (100%).

Lit. [6] mp 301-303°C (decomp.) (acetone–hexane). ^1H NMR spectrum in DMSO, δ, ppm: 0.93 s (18-CH_3), 1.14 s and 1.29 s [$C(CH_3)_2$], 1.48 s (19-CH_3), 4.15 d (11-H, J = 10 Hz), 4.96 m (6-H).

*In brackets are shown the intensities of the peaks with these m/z values, calculated relative to the intensity of the maximum peak.

EXPERIMENTAL (PHARMACOLOGY)

Exudative inflammation was induced in rats of both sexes weighing 140-160 g by subplantar injection (left rear extremity) of 0.1 ml of 1% carrageenin suspension in isotonic sodium chloride solution. Edema was measured with a Ugo Basile plethysmometer (Italy) 3 h after injection with carrageenin, and expressed as the difference between the volumes of the left and right paws. The test compounds were administered subcutaneously in a dose of 5 mg/kg one h before the injection of carrageenin. The effects of the compounds on proliferative inflammation were assessed by the method of Thalen et al. [8]. Felt pellets of mass 8 mg, containing 0.6 mg of the test compound, were implanted subcutaneously into adrenalectomized male rats weighing 80-100 g. Seven days later, the animals were killed, and the granulomas extracted, dried at 80°C, and weighed. The local antiinflammatory activity of the compounds was determined by their ability to reduce the mass of the "dry" granuloma. In the same tests, systemic effects were characterized by their effects on the mass of the thymus and the increase in body weight of the animals. The results were treated statistically, significant differences from the controls being established by the use of Student's t-test.

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PREPARATION AND PHARMACOLOGICAL ACTIVITY OF 1-ALKYL-5-ALKYLTHIO-2-ARYLIMIDAZOLE HYDROCHLORIDES

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Some mercaptoimidazole derivatives display high antiinflammatory activity [5-11]. It was of interest to establish whether 5-mercaptoimidazoles possessed this type of activity. These compounds have been little studied until recently, and only in the last few years have a small number of these compounds been obtained [3, 12, 13, 15-17].

We have developed a fairly general method of preparation of 1,2-disubstituted 5-alkylthioimidazoles from the corresponding imidazolylphosphonium salts (Ia-d), obtained in turn from reactants $ArCCl{=}NCH_2PPh_3Cl^-$ [12, 13]. Successive treatment of the phosphonium salts (Ia-d), first with caustic alkali, then with hydrogen chloride affords good yields of the water-soluble 1,2-disubstituted 5-alkylthioimidazole hydrochlorides (IIa-d) (Table 1). A similar method of cleavage of azolylphosphonium salts has been used previously for the preparation of functionally-substituted azoles, thiazoles, and selenazoles [1, 2], providing indirect confirmation of the structures of compounds (IIa-d). In order to show that the alkali and acid treatments did not cleave the imidazole ring, or affect the substituents in the 1-, 2-, and 5-positions, (IIa) was again treated with alkali to give 1-methyl-5-methylthio-2-phenylimidazole (III), isolated as its picrate (IV). In the PMR spectrum of the latter, two signals were present at high field, at 2.45 and 3.83 ppm, assigned to the $S{-}CH_3$ and $N{-}CH_3$ groups respec-

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