evaporated. Bases XV-XXI were separated from nitrogen-free impurities by extraction with hexane. Compound XIV was converted into the hydrochloride by the action of dilute HCl.

Hydromethylamination of pyrylium tetrafluoroborates VIII-XIV, XXII was carried out under conditions similar to the hydroamination of the 1,5-diketones. Compound XXIII was isolated in the form of a tetrafluoroborate, which was converted into an iodide by the action of KI.

EXPERIMENTAL (BIOLOGICAL)

The antiviral properties were determined in experiments on tissue cultures, infected with smallpox vaccine, herpes simplex type I, the classical fowl plague, vesicular stomatitis, the equine Venezuela encephalomyelitis, respiratory syncytial, and "ECHO-6" viruses by the "screening test" method [4], with subsequent determination of the antiviral action by the plaque reduction method under agar coating, as described previously in [1].

With the ECHO virus, the investigations were carried out on single layer cultures of passivated skin-muscular cells of a human embryo, with respiratory-syncytial virus on a grafted culture of rabbit lung cells, and with the remaining cultures on primarily trypsinized chicken embryo fibroblasts.

The determination of the quantitative characteristics of the antiviral action was preceded by finding the maximally tolerated concentration of the compounds studied for noninfected tissue cultures after a 96 h incubation in their presence. The chemotherapeutic index (CTI) was calculated as the ratio of the maximally tolerated concentration to the minimal concentration, decreasing the titer of the virus by the value of 1.25 log PFU/ml.

LITERATURE CITED

1. V. I. Votyakov, E. I. Boreko, G. V. Vladyko, et al., Primary Investigation of Antiviral Properties of Synthetic and Natural Compounds. Method, Recommendations [in Russian], Minsk (1986).
2. A. J. Jones and M. M. A. Hassan, J. Org. Chem., 37, 31-43 (1972).
3. A. J. Jones, A. F. Casy, and K. M. McErlan, Can. J. Chem., 51, 1782-1789 (1973).
4. P. Link, E. Rada, and D. Blaskovic, Ann. N.Y. Acad. Sci., 130, 31-43 (1965).
5. J. A. Van Allan and G. A. Reynolds, J. Org. Chem., 33, 1102-1107 (1968).
6. F. Vierhapper and E. L. Eliel, J. Org. Chem., 42, 51-61 (1977).

ANTIANDROGENIC ACTIVITY OF CERTAIN STEROID SPIROLACTONES

I. M. Gella, L. Yu. Sergienko, and A. N. Cherevko

UDC 615.254.1.017:[615.357:577.175.62].015.25].07

Cyprosterone acetate (CPA) is widely used in clinical practice for treating androgen-dependent diseases, either by itself (the androur preparation), or in combination with estrogens (the dian preparation) [1]. However, the variety of pathological states for which use of antiandrogens has been indicated demands considerable extension of the arsenal of these agents.

Several authors [7, 8, 11, 16, 17] have studied the antiandrogenic properties of spironolactone Ia and the possibilities of its use in clinical practice for treating certain androgen-dependent diseases. In experiments with a tissue culture it was found that Ia has a greater affinity to androgenic receptors than CPA [10]. At the same time, in a systemic administration, CPA displays a more pronounced antiandrogenic action than Ia [6, 7].

The last fact is attributed to the possible transformation of spironolactone in the organism into the slightly active antiandrogen canrenone (II) [6]. This indicates that derivatives of spironolactone which do not undergo a rapid metabolic deactivation and which retain a fairly high affinity to androgen receptors may be of a considerable practical interest.

Kharkov Scientific Research Institute of Endocrinology and Hormone Chemistry.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 12, pp. 29-31, December, 1990. Original article submitted January 3, 1990.

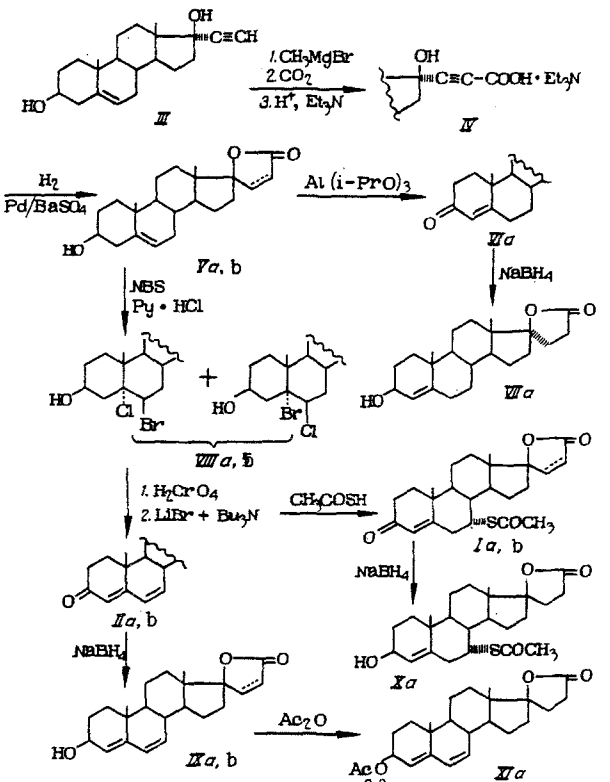
0091-150X/90/2412-0892$12.50

Numerous investigations, the main aim of which was to obtain new antimineralocorticoid preparations, showed that the introduction of 1,2-, 6,7-, 15,16-methylene groups, a 9(11)-epoxy group, or double bonds into the molecule of Ia and the replacement of the 7a-acetylthio group by other substituents, does not much influence the antiandrogenic activity, and essentially lowers it somewhat [9, 12, 15].

The present investigation gives the results of the synthesis of certain steroid spirolactones with a reduced 3-keto group and of screening for their antiandrogenic activity.

As in [3], ethylandrostenediol III was selected as the starting material for the synthesis of the compounds studied. A preliminary protection of the hydroxyl groups in III by means of butyl vinyl ether during the carboxylation of the ethynyl group made it possible to increase the yield of salt IV by 1.8 times, compared with [3]. A complete or partial hydrogenation of the triple bond in IV over $Pd/BaSO_4$, followed by lactonization, led to lactones Va,b in a practically quantitative yield. A chlorobromination of lactones Va, b by a modified method [5] gives a mixture 5α-Cl, 6β-Br- and 5α-Br-6β-Cl-lactones: according to the PMR spectrum data (400 MHz), for VIIIa, the ratio of the isomers is 2:1. Lactones VIIIa,b, without being purified, were oxidized by Jones reagent to the corresponding ketones and dehydrohalogenated to the corresponding 4,6-dienes by means of $LiBr-Bu_3N$ in DMFA according to [4]. Oxidation of Va according to Oppenauer and the addition of CH_3COSH to IIa,b was carried out according to [3].

The desired 3β-hydroxy derivatives were obtained by the reduction of spirolactones Ia, IIa,b, VIa by means of $NaBH_4$ in methanol, followed by chromatographic purification and crystallization. The properties of the compounds obtained are given in Table 1.



Everywhere the δ-Δ^{20}-derivatives

EXPERIMENTAL (CHEMICAL)

The IR spectra were run in KBr on a UR-20 spectrophotometer, and the PMR spectra were recorded in $CDCl_3$ on XL-200 ("Varian," USA) and WH-400 ("Bruker," GFR) spectrometers. The specific rotation was measured on a "Polamat A" polarimeter (GDR) in $CHCl_3$.

γ-Lactone of 17α-Pregna-4,6-dien-17β-ol-3-one-21-carboxylic Acid (IIa). A 12-ml portion of dry pyridine in 150 ml of acetone was saturated by dry HCl in the presence of Thymol Blue until the color of the indicator converted from yellow-green to rose, and then pyridine was

TABLE 1. Physicochemical Properties of Compounds Obtained

Compound	Mp, °C	578 degrees	IR spectrum, cm^{-1}	PMR spectrum, ppm
Ia	204—6	—36		
Ib	218—20	+50	1760 (lactone CO), 1692(7-CH_3CO), 1675(CO), 1690(C=C)	1,03s(18-CH_3), 1,17s(19-CH_3), 2,3s(7-CH_3CO), 5,64s(4-H), 5, 79d(21-H), 7, 45d(20-H)
IIa	163—5	+27,5		
IIb	231—2	+172	1765 (lactone CO), 1660(CO), 1620, 1590(C=C)	1,07s(18-, 19-CH_3), 5, 62s(4-H), 6,07m(5-, 6-H), 5,9d(21-H), 7,38d(20-H), 0,95s(18-CH_3)
VIIa	152—3	+25	3490(OH), 1760(lactone CO)	0,95s(18-CH_3), 1,07s(19-CH_3), 4,15m(3α-H), 5,3m(4-H)
VIIIa	144—8	—73	3510(OH), 1765(lactone CO)	5α-Cl, 6β-Br:0,98s(18-CH_3), 1,4s(19-CH_3), 4,42m(3α-H), 4,62m(6α-H); 5α-Br, 6β-Cl:0,99s(18-CH_3), 1,45s(19-CH_3), 4,3m(3α-H), 4,52m(6α-H)
VIIIb	136—40	—36	3500(OH), 1760(lactone CO)	
IXa	178—80	—59	3500(OH), 1760(lactone CO)	0,93s(18-, 19-CH_3), 4,2m(3a-H), 5,33s(4-H), 5,52d(6-H), 5,58d(7-H)
IXb	199—01	+22,5	3400(OH), 1755(lactone CO) 1630(C=C)	1,01s(18-CH_3), 1,11s(19-CH_3), 4,16m(3α-H), 5,4d(4-H), 5,62dd(6-H), 5,97dd(7-H), 5,95d(21-H), 7,4d(20-H)
Xa	179—91		3540(OH), 1770(lactone CO) 1695(7-CH_3CO)	0,95s(18-CH_3), 1,1s(19-CH_3), 2,34s(7-CH_3CO), 3,78m(7-H), 3,92m(3α-H), 5,32m(4-H)
XIa	169—70	—85	1780(CO (lactone CO), 1745(CH_3CO)	

Note. Ia) lit. [3] mp 201-3°C. $[\alpha]_D$ −34.2; IIa) lit. [3] mp 161-3°C, $[\alpha]_D$ +24.5; IXa) lit [4], mp 179-81°C, $[\alpha]_D$ − 71; IXa) lit. [4] mp 165-6°C, $[\alpha]_D$ − 91.

TABLE 2. Antiandrogenic Properties of New Steroid Derivatives of Spirolactones

Compound	Dose, mg per day	% of weight inhibition	
		P	T
Ia	0,66	5	28
	2,0	33	51
	3,3	57,3	66
Ib	0,66	5	5
	2,0	18,4	42,7
VIIa	0,66	31,4	39,7
	2,0	22,3	5
IXa	0,66	44,4	42
	2,0	33,2	32
	3,3	40	46
IXb	0,66	34,7	5
	2,0	5,6	8,3
Xa	0,66	19,8	8,3
	2.0	27,4	19,7
XIa	0,66	5	8
	2,0	23,6	27
	3,3	24,1	42

added dropwise up to a reversible transition of the indicator color. A 24-g portion of lactone Va was added to the mixture obtained, which was then cooled to 6-8°C, and 20 g of bromosuccinimide was added in portions over a period of 10 min. The mixture was then stirred for 1 h at room temperature, and then 90 ml of a dilute hydrochloric acid (1:2) and 400 ml of water were added over a period of 30 min; the mixture was cooled to 5°C and the precipitated VIIIa was filtered off. The air-dried VIIIa was dissolved in 300 ml of acetone, cooled to 6-8°C, and Jones reagent, prepared from 9 g of CrO_3, was added at the same temperature over a period of 30 min. At the end of the oxidation, the excess of the oxidant was decomposed by isopropanol, and the product was precipitated by adding 500 ml of water, filtered, and dried in a vacuum desiccator over $CaCl_2$. The dry product was dissolved in 100 ml of dry dimethylformamide and the solution was added over a period of 75 min at 150-155°C to a solution of 12 g of anhydrous LiBr and 50 ml of tributylamine in 350 ml of dry dimethylformamide. The mixture was stirred for another 30 min, and 350 ml of the solvent was distilled off from the reaction mixture. The residue was cooled to 40-50°C, 50 ml of dilute HCl (1:8) was added, and then 300 ml of water was added slowly, and the mixture was stirred for 40 min at 10°C. The precipitated product was filtered; the yield of IIa was 13.6 g (87%). In subsequent reactions IIa was used without purification; an analytical sample was obtained by crystallization from ethanol.

γ-Lactone of 17α-Pregna-4,6-diene-3β-,17β-diol-20-carboxylic Acid (IXa). Sodium borohydride $NaBH_4$ (0.75 g) was added in small portions to a solution of 5.7 g of IIa in 100 ml of methanol, and the mixture was stirred for 6 h and allowed to stand overnight. Compound IXa

that separated out was filtered off, dried in air and chromatographed on a column with SiO_2 using the mixture of $CHCl_3$ and CH_2Cl_2 (1:1) as eluent. After crystallization from ethanol, 3.2 g (56%) of analytically pure IXa was obtained.

γ-Lactone of 3β-acetoxy-17α-pregna-4,6-dien-17β-ol-20-carboxylic acid (XIa). A 2.4 g portion of IXa was dissolved in 20 ml of dry pyridine, 5 ml of acetic anhydride was added and the mixture was allowed to stand overnight. The reaction mixture was then poured onto ice, the precipitated product was separated, and after crystallization from methanol, 1.8 g (68%) of IXa was obtained.

EXPERIMENTAL (BIOLOGICAL)

The investigation of compounds Ia,b, VIIa, IXa,b, Xa, XIa for the antiandrogenic activity on a systemic application was carried out by a generally accepted procedure of testing compounds with an assumed antiandrogenic activity [15]. The experiments were carried out on male rats of the Wistar line, each weighing 180-200 g, castrated two weeks before carrying out the experiments. The compounds tested were introduced daily for 7 days in a dose of 0.66, 2.0, and 3.3 mg per 100 g of body weight of the animals in combination with an oily solution of testosterone propionate (TSP) in a dose of 0.2 g per 100 g of body weight. The rats in the control groups received either TSP only, or mineral oil in equivalent dose and volume.

The animals were killed by decapitation 24 h after the 1st injection (the killing was effected using an ether-Rausch narcosis); the prostate (P) and the testes (T) were removed and weighed.

The percent of inhibition of the androgenic effect of TSP, calculated by the method in [2], served as the indication of the antiandrogenic activity. The degree of manifestation of the antiandrogenic effect of the compounds studied was evaluated by comparison with the antiandrogenic effect of Ia.

Table 2 shows that the antiandrogenic activity of most of the spirolactone derivatives tested is dependent on the dose and increases with increase in the amount of the compound administered, i.e., the observed effect is dose dependent. Thus, it can be seen that both the introduction of a double bond into the lactone ring of Ib, IXb and the acetylation of the OH group (XIa) leads to a decrease in the antiandrogenic activity. The reduction at C(3) of spirolactone VIa to VIIa sharply increases the activity in a dose of 0.66 mg per day (up to 31.4% of inhibition, compared with 5% of inhibition by spironolactone), but in a dose of 2 mg per day, this compound is inferior to spironolactone. A similar pattern is observed with the reduction of spirolactone Ia to derivative Xa.

A steady result of pronounced increase in the antiandrogenic activity in all doses studied was obtained with reduction of canrenone to compound IXa. This compound most significantly surpasses the parameters of Ia and other compounds tested even in a dose of 0.66 mg per day, while in doses of 2 mg and 3.3 mg per day, its effect is comparable to the effect of Ia. A distinct characteristic of this compound is its steady antiandrogenic action on the testes, which indicates that the interaction of this compound with androgen receptors oversteps the dependence of the latter on the specificity of organs, which means that a similarly high activity of the compound can also be expected with respect to other androgen-sensitive organs and tissues, similarly as characteristic for compound Ia [3].

LITERATURE CITED

1. Androgens and Antiandrogenic Therapy [Russian translation], S. L. Jeffco (ed.), Moscow (1965).
2. T. I. Ivanenko, Probl. Endokrinol., 24, No. 4, 86-91 (1978).
3. G. I. Kipryanov, N. I. Moleva, and A. T. Veitsman, Khim.-farm. Zh., No. 1, 10-13 (1969).
4. US Patent 3107241 (1963); Chem. Abstr., 60, 3041 g (1964).
5. US Patent 3682894 (1972); Ref. Zh. Khim., No. 10N 391P (1973).
6. D. Armaini, J. Kabowiak, A. Goi, et al., Clin. Endocr., 23, No. 4, 341-347 (1985).
7. P. D. Brouclie and L. Starka, Endokrinologie, 68, No. 1, 35-39 (1976).
8. P. Corvol, A. Michaud, J. Menard, et al., Endocrinology, 97, No. 1, 52-59 (1975).
9. M. de Gasparo, U. Hess, H. P. Ramjoue, et al., J. Pharmacol. Exp. Ther., 240, No. 2, 650-656 (1987).
10. C. Eil and S. K. Edelson, J. Clin. Endocr., 59, No. 1, 51-55 (1984).
11. A. Goodfellow, J. Alaghband-Zaden, G. D. Carter, et al., Br. J. Derm., 111, 209-214 (1984).

12. W. Losert, D. Bittler, M. Buse, et al., Arzneimittelforsch., 36, No. 11, 1583-1600 (1986).
13. F. Neumann, Methods in Drug Evaluation, Milano (1965), pp. 547-573.
14. K. Nickisch, D. Bittler, J. Casals-Stenzel, et al., J. Med. Chem., 28, No. 5, 546-550 (1985).
15. K. Nickisch, D. Bittler, H. Laurent, et al., J. Med. Chem., 30, No. 8, 1403-1409 (1987).
16. G. Shapiro and S. Evron, J. Clin. Endocr., 55, No. 3, 423-433 (1980).
17. A. Weisman, J. Bowden, B. L. Frank, et al., Arch. Derm., 121, No. 1, 57-62 (1985).

SYNTHESIS OF AROYLBENZOFURANS

V. I. Shvedov, S. A. Zotova, and T. M. Korneeva

UDC 615.224:547.722.1].012.1

Materials possessing coronary dilation [1, 5], anesthetic [3], and spasmolytic [1] properties are found among the acylated derivatives of benzofurans. The discovery of compounds possessing antiviral effects among the bis-benzofuranyl ketones also has been communicated [4]. Further, the aroylbenzofurans are convenient starting compounds for the synthesis of benzofuranylarylcarbinols showing hypocholesterolemic action [7] and are useful for treatment of cardiovascular disease [6]. Taking into account the above, we continued to investigate the synthesis of new derivatives of benzofuranyl ketones with the aim of studying their pharmacological activity.

Condensation of 2-methyl-3-bromoacetyl-5-methoxybenzofuran [2] with salicylaldehyde or its 5-methoxy-, 5-bromo-, or 5-nitro-derivative gave a series of 2-methyl-5-methoxybenzofurans containing a 2'-benzoylfuroyl group in position 3. This enabled the preparation of 3-(benzofuroyl-2')-(I), 3-(5'-methoxybenzofuroyl-2')-(II), 3-(5'-bromobenzofuroyl-2')-(III), and 2-methyl-3-(5'-nitrobenzofuroyl-2')-5-methoxybenzofuran (IV).

Compounds I-IV were successfully reduced with $NaBH_4$ to the corresponding carbinols VI-VIII in yields of 71-86%. In experiments to synthesize hydroxy group derivatives of IV-VIII such as aminoalkyl esters of carbamates, we obtained either the starting materials or polymers. Experiments to demethylate compounds I-IV with the help of HBr or $AlCl_3$ also were unsuccessful. To obtain 2-methyl-3-(5'-R-benzofuroyl-2')-5-hydroxybenzofurans and its derivatives we used salicylaldehyde and its derivatives, and instead of 5-methoxy-2-methyl-3-bromoacetylbenzofuran, the corresponding 5-acetoxybenzofuran (IX). The latter was prepared by bromination of 2-methyl-3-acetyl-5-acetoxybenzofuran with dioxane dibromide. The products of condensation of compound IX with salicylaldehyde and its derivatives were the 2-methyl-3-(5'-R-benzofuroyl-2')-5-acetoxybenzofurans which were deacylated without isolation by boiling in the presence of concentrated HCl. These paths synthesized 3-(benzofuroyl-2')-(X), 3-(5'-methoxybenzofuroyl-2')-(XI); 3-(5'-bromobenzofuroyl-2')-(XII); and 2-methyl-3'-(5'-nitrobenzofuroyl-2')-5-hydroxybenzofuran (XIII).

Aminomethylation of compounds X-XIII by the action of bis-dimethylaminomethane gave the corresponding 4-dimethylaminomethyl derivatives (XIV-XVII).

The method that we used for the synthesis of 3-benzofuroylbenzofurans was applied to prepare other 3-heteroyl derivatives such as 2-methyl-3-(4',5'-diphenylthenoyl-2')-5-methoxybenzofuran (XVIII). The compound was obtained in 60.9% yield by boiling 2-methyl-3-bromoacetyl-5-methoxybenzofuran with 1,2-diphenyl-2-mercaptoacrolein in the presence of K_2CO_3.

On the basis of the 3-bromoacetyl derivative we also synthesized 3-(imidazol-1-ylacetyl)-XIX and 2-methyl-3-isopropylaminoacetyl-5-methoxybenzofuran, characterized as the hydrochloride (XX)(cf. Table 1).

The interaction of 2-bromomethyl-3-carboethoxy-5-methoxybenzofuran with imidazole gave 2-(imidazol-1-ylmethyl)-3-carboethoxy-5-methoxybenzofuran (XXI) in 75% yield.

The synthesized compounds XIV-XVI and XVIII-XX were surveyed for their pharmacological activity in the Pharmacological Laboratory, and compounds XIX and XXI for their antibacterial

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 12, pp. 31-33, December, 1990. Original article submitted January 3, 1990.

 0091-150X/90/2412-0896$12.50