STUDY OF THE ANTIGONAD PROPERTIES OF 1,2-BIS(METHYLSULFONYLOXY)ETHANE

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1,2-Bis(methylsulfonyloxy)ethane (I) possesses a unique ability to produce reversible atrophy of testes by inducing degradation of the Leydig's cells and disrupting spermatogenesis [1, 2]. In order to achieve this effect, the preparation is usually administered at high doses (100 mg/kg i.p.). We believe that, in lower doses, this agent can have a practical significance as a potential drug for the therapy of some androgen-dependent disorders (prostate cancer, hypersexuality of mentally ill men, etc.). In this connection, the purpose of our work was to re-synthesize compound I and study its antigonad activity under conditions of chronic or acute administration at low doses.

Compound I was obtained by interaction of methanesulfochloride with ethylene glycol in pyridine.

$$MeSO_2Cl + HOCH_2CH_2OH \xrightarrow{\text{pyridine}}$$

$$MeSO_2OCH_2CH_2OSO_2Me$$
I

1,2-Bis(methylsulfonyloxy)ethane appears as an odorless, non-colored low-melting crystalline substance, poorly soluble in water and soluble in organic solvents.

EXPERIMENTAL CHEMICAL PART

1,2-Bis(methylsulfonyloxy)ethane (I). To a mixture of 11.8 g (0.19 mole) of ethylene glycol in 55 ml of dry pyridine was added dropwise (over 25 min) 39.7 g (0.345 mole) of methanesulfochloride at 5 – 10°C. Then the reaction mixture was stirred for 1 h at room temperature, poured into 250 ml of ice-cold water, and allowed to stand for 1 h. The crystalline precipitate was separated by filtration, washed with water, and dried, first in air and then over phosphoric anhydride in a vacuum desiccator. Finally, the dry product was crystallized from an acetone – ether (1 : 3) mixture. Yield of compound I, 18 g (48%); m.p., 44 – 45°C; $C_4H_{10}O_6S_2$.

The melting temperature and the parameters of the IR absorption spectrum of compound I are identical with those of 1,2-bis(methylsulfonyloxy)ethane described in [3].

EXPERIMENTAL BIOLOGICAL PART

Experiments were performed on puberal male rats weighing 250 – 300 g. Compound I was introduced either by subcutaneous injections over 2 weeks at a dose of 10 or 25 mg/kg (in the form of a 5% solution in 25% aqueous DMSO) or by a single peroral administration at a dose of 25 or 50 mg/kg in the gel form (0.5% carbomethyl cellulose sodium salt, containing 0.9% sodium chloride, 0.4% sodium polysorbate, and 0.9% benzyl alcohol).

The antigonad activity of compound I was judged by (i) a decrease in the content of testosterone (T) in the blood plasma (as determined by the RIA techniques), (ii) variation in the weight of testes, epididymis, and accessory sexual glands, (iii) a change in the content of nucleic acids and proteins in the ventral lobe of prostate (VLP) [4], (iv) a change in the number of VLP cells [5], and a decrease in the amount of spermium in the epididymis [6].

The results of investigations showed that compound I produces a pronounced antigonad effect for the prolonged subcutaneous administration at a dose of 25 mg/kg. This was confirmed by a more than 5-fold drop in the content of T in the blood plasma, accompanied by a decrease in the weight of testes, epididymis, accessory sexual glands – VLP, coagulating glands, and seminal vesicles by a factor of 1.4, 1.6, 3.7, 2.6, and 1.6, respectively (Table 1). The drop of T in the blood leads to pronounced suppression of the morphological and functional state of VLP and epididymis. For example, the concentration of DNA in VLP is almost doubled, which is characteristic of the post-castration states and is related to the loss of the liquid cytoplasm fraction from the cells [7]. At the same time, the DNA and protein contents, and the RNA concentration and content in the organ markedly decrease (Table

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TABLE 1. Variation in the Weight of Testes, Epididymis, and Accessory Sexual Glands (mg / 100 g) and the Contents of Testosterone in the Blood (nmole / liter) in Rats Treated with Compound I

Experimental conditions	Number of animals *n*	Weight, mg / 100 g of accessory sexual glands					[T], nmole / liter
		testes	epididymis	VLP	coagulating glands	seminal vesicles	
Control	17	1138.0 ± 66.7	335.4 ± 16.7	111.4 ± 14.3	51.2 ± 6.2	92.8 ± 8.3	7.4 ± 2.0
I, 10 mg / kg, s.c., 14 days	5	901.1 ± 34.1	—	104.7 ± 18.1	48.3 ± 2.7	94.3 ± 4.3	5.2 ± 0.4
		($p < 0.01$)		($p > 0.5$)	($p > 0.5$)	($p > 0.5$)	($p > 0.5$)
I, 25 mg / kg, s.c., 14 days	7	812.5 ± 20.7	203.5 ± 13.0	30.0 ± 2.8	19.7 ± 3.3	56.3 ± 2.7	1.4 ± 0.5
		($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)
I, 25 mg / kg, p.o., single	7	1176.7 ± 34.7	356.7 ± 12.5	152.4 ± 14.0	64.9 ± 3.8	112.0 ± 7.3	
		($p > 0.5$)	($p > 0.5$)	($0.05 < p < 0.1$)	($p > 0.05$)	($p > 0.05$)	
I, 50 mg / kg, s.c., single	7	899.5 ± 32.8	174.7 ± 10.1	21.1 ± 2.3	19.5 ± 3.2	47.8 ± 2.4	
		($p < 0.01$)	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	

TABLE 2. Variation in the Contents of Nucleic Acids and Protein in VLP and Testes in Rats Treated with Compound I

Experimental conditions	Number of animals *n*	DNA		RNA		RNA / DNA	Protein	
		μg / mg tissue	μg / organ	μg / mg tissue	μg / organ		μg / mg tissue	μg / organ
Ventral lobe of prostate								
Control	6	3.37 ± 0.32	959.0 ± 133.0	2.72 ± 0.23	754.5 ± 97.9	0.82 ± 0.07	54.8 ± 4.1	15.1 ± 1.6
25 mg / kg, s.c., 14 days	7	6.67 ± 0.33	501.0 ± 58.2	1.61 ± 0.13	124.3 ± 22.5	0.24 ± 0.01	70.8 ± 3.3	5.3 ± 0.7
		($p < 0.001$)	($p < 0.01$)	($p < 0.01$)	($p < 0.001$)	($p < 0.001$)	($p < 0.05$)	($p < 0.001$)
Testes								
Control	6	3.36 ± 0.11	4993.0 ± 382.6	1.95 ± 0.06	2913.4 ± 254.8	0.58 ± 0.01	68.4 ± 2.2	101.9 ± 8.6
25 mg / kg, s.c., 14 days	7	3.90 ± 0.05	3897.0 ± 148.1	1.95 ± 0.02	1945.8 ± 70.3	0.46 ± 0.007	68.0 ± 1.4	68.1 ± 3.3
		($p < 0.001$)	($p < 0.05$)		($p < 0.01$)	($p < 0.001$)	($p > 0.5$)	($p < 0.01$)

2). Additional evidence of the atrophic changes in the organ is a pronounced decrease in the DNA / RNA ratio, which is probably indicative of the inhibited RNA biosynthesis. The contents of nucleic acids and proteins in the testes also tend to decrease (Table 2). The VLP of rats treated with compound I exhibits a sharp decrease in the number of cells: $(5.75 \pm 0.67) \times 10^7$ in the test versus $(11.02 \pm 1.53) \times 10^7$ in the control ($p < 0.001$). The epididymis shows a dramatic decrease in the amount of spermium: $(0.037 \pm 0.015) \times 10^7$ in the test versus $(6.97 \pm 0.25) \times 10^7$ in the control ($p < 0.001$). Both changes point to atrophic changes in the organs.

A single peroral administration of compound I leads to a pronounced antigonal effect for a dose of 50 mg / kg (Table 1). Here, the atrophic changes in the organs were identical with those observed for the subcutaneous introduction.

Thus, the results of our experiments showed that compound I exhibits a pronounced antigonad effect for both parenteral and peroral administration at small doses.

It was reported earlier that treatment with compound I leads to damage of the Leydig's cells, primarily by suppressing activity of the key enzymes of steroidogenesis, which results in decreasing content of T and increasing amount of gonadotrophins in the blood. The androgen function of testes is restored in 35 – 45 days after termination of the action of compound I [1, 2].

Taking into account the results presented above and some other data reported in the literature, we believe that compound I is worthy of further thorough investigation. This compound can be used in experiments as a model of primary hypogonadism, and in practical medicine as a castrating agent for some pathological states.

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