The activity of the compounds with respect to the investigated indices was lost when there was a propyl group in the 4 position.

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SYNTHESIS OF CHLODITANE METABOLITES AND THEIR ADRENOCORTICOLYTIC ACTIVITY

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1,1-Dichloro-2-o-chlorophenyl-2-p'-chlorophenylethane (chloditane) is used for treating various forms of hypercorticism and for modeling adrenocortical pathology under experimental conditions [1, 2].

At the Kiev Scientific-Research Institute of Endocrinology and Metabolism a search is being carried out for new effective inhibitors of steroidogenesis. In this aspect, the problem of chloditane metabolites and their corticolytic activity is very interesting, since the experimental data brought several authors to suggest that the adrenocorticolytic effect of chloditane is due to the action of its metabolites in the organism [3-6]. However, we believe that these conclusions are contradictory, since in the experiments *in vitro* the adrenocorticolytic properties of chloditane are manifested in the direct action of the preparation on the adrenal glands tissue [7-9]. We also found that chloditane accumulates in the adrenal glands both in dogs and humans sensitive to it, and in guinea pigs and ribbits resistant to it. The fact that the preparation accumulates in the adrenal glands is thus not important for the manifestation of its specific properties. It has also been suggested that the active metabolite is formed in the glands themselves, and its effect is observed there directly, while in the resistant animals it is not formed [10]. Some authors believe that the mechanism of formation of metabolites and their corticolytic action are similar to the hepatotoxic effect of carbon tetrachloride [11].

At present it has been found that in the organism chloditane can metabolize in three ways: by dehydrochlorination of the aliphatic part of the molecule [12], hydroxylation of the aromatic part [13], and dehydrogenation of the ethane group [14, 15].

In the present work, we report the synthesis of certain possible chloditane metabolites and studied their influence on the functional state of the adrenal glands.

The chloditane metabolites were synthesized by the scheme on the next page.

The structure of the compounds obtained was confirmed by their IR spectral data.

EXPERIMENTAL CHEMISTRY

The IR spectra of the compounds synthesized were taken in KBr tablets in a mineral oil suspension of the Specord IR-75 spectrophotometer (GDR).

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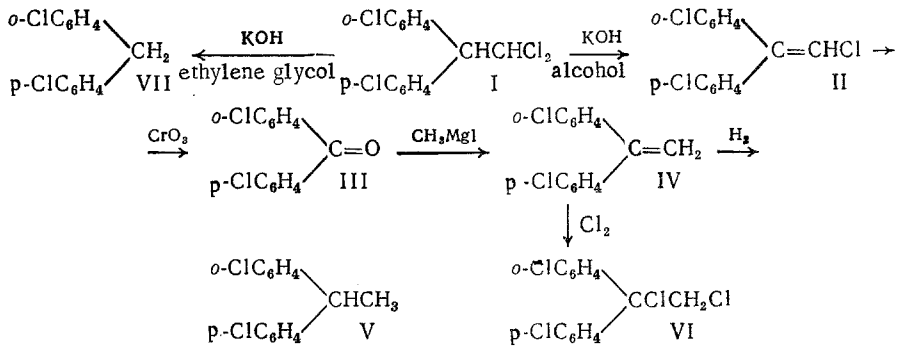

1-Chloro-2-o-chlorophenyl-2-p'-chlorophenylethylene (II). A solution of 1.4 g of potassium hydroxide in 40 ml of ethanol is added, with stirring, to a solution of 6.4 g (0.02 mole) of I in 30 ml of ethanol. The mixture is stirred for 2 h at 80-90°C, and when cool, 100 ml of cold water are added. The mixture is extracted by ether, and the ether extracts are washed with water and dried over sodium sulfate. Ether is evaporated and the residue is distilled *in vacuo*. Yield, 4.4 g (78%) of II, bp 148-149°C (3 mm Hg), d_4^{20} 1.3688, n_D^{20} 1.630, MR_D 73.71, calculated 73.78. IR spectrum: 1618 cm^{-1} (C=C). Found, %: Cl 37.51. $C_{14}H_9Cl_3$. Calculated, %: Cl 37.52.

o,p'-Dichlorobenzophenone (III). A mixture of 5.7 g (0.02 mole) of II and 6 g (0.06 mole) of chromic anhydride in 40 ml of glacial acetic acid is heated at 100°C for 1.5 h. When cool, the reaction mixture is poured into ice water, the precipitate is filtered, and recrystallized from methanol. Yield, 2.7 g (54%) of III, mp 65-66°C. IR spectrum: 1665 cm^{-1} (C=O). Found, %: Cl 28.27. $C_{13}H_8Cl_2O$. Calculated, %: C 28.29.

1-o-Chlorophenyl-1-p'-chlorophenylethylene (IV). A solution of 50 g (0.2 mole) of III in 200 ml of dry ether is added in the course of 1-1.5 h, with stirring, to a Grignard solution (0.35 mole of magnesium and 0.035 mole of methyl iodide in 150 ml of dry ether). The mixture is boiled for 1 h, cooled, and decomposed by 150 ml of 10% hydrochloric acid. The ether layer is separated, and the aqueous layer is extracted by ether (3 × 50 ml). The extracts are combined with the main ether layer, and dried over sodium sulfate. Ether is evaporated and the residue is distilled *in vacuo*. Yield 32.4 g (65%) of IV, bp 140-142°C (3 mm Hg), d_4^{20} 1.2913, n_D^{20} 1.6018, MR_D 68.82, calculated 68.92. IR spectrum: 1620 cm^{-1} (C=C). Found, %: Cl 28.36. $C_{14}H_{10}Cl_2$. Calculated, %: Cl 28.46.

1-o-Chlorophenyl-1,p'-chlorophenylethane (V). A solution of 24.9 g (0.1 mole) of IV in 100 ml of absolute ethanol is saturated with hydrogen with continuous shaking in the presence of 3 g of 5% palladium on carbon. After 30 min, the absorption of hydrogen ceases; the catalyst is filtered, alcohol is evaporated, and the residue is distilled. Yield, 19 g (80%)

TABLE 1. Functional State of Adrenal Cortex of Dogs after Receiving Chloditane Metabolites

Compound	No. of experiment	Concentration of 11-hydroxycorticosteroids in peripheral blood plasma, μg%					
		before the introduction of preparation		one week after introduction		two weeks after introduction	
		a	b	a	b	a	b
I	1	6,2	17,0	0,8	0,4	0	0
	2	7,8	17,0	0	0	0	0
II	3	9,8	13,7	3,2	10,1	5,5	3,1
	4	5,2	15,0	5,4	14,8	3,1	5,5
III	5	3,7	...	3,7	...	3,7	...
	6	4,8	...	4,2	...	4,2	...
IV	7	2,4	15,1	3,3	14,3	5,9	8,9
	8	3,8	17,1	2,6	13,3	7,9	8,6
V	9	4,4	17,8	4,3	15,0	7,1	18,0
	10	1,7	16,4	4,6	14,6	6,5	18,3
VI	11	5,9	18,0	10,0	11,8	4,0	15,1
o-$ClC_6H_4CH_2C_6H_4Cl$	12	2,6	15,3	3,6	14,6	6,1	9,1

Note. The chloditane metabolites were administered *per os* in a dose of 25 mg per 1 kg of body weight: a) before injection of ACTH; b) after injection of ACTH.

of V, bp 127-129°C (2 mm Hg), mp 56°C. Found, %: Cl 28.25. $C_{14}H_{12}Cl_2$. Calculated, %: Cl 28.23.

1,2-Dichloro-2-o-chlorophenyl-2-p'-chlorophenylethane (VI). A calculated amount of chlorine in carbon tetrachloride is added to a solution of 5 g (0.02 mole) of IV in 30 ml of dry carbon tetrachloride. After 24 h, the solvent is evaporated, and the residue is recrytallized from hexane. Yield, 4.8 g (76%) of VI, mp 67-68°C. Found, %: Cl 44.56. $C_{14}H_{10}Cl_4$. Calculated, %: Cl 44.37.

o-Chlorophenyl-p'-chlorophenylmethane (VII). A solution of 9.6 g (0.03 mole) of I is added, with stirring, to a solution of 22.4 g (0.4 mole) of potassium hydroxide in 250 ml of ethylene glycol. The reaction mixture is boiled for 6 h, cooled, poured into ice water, and extracted by chloroform. The ether extract is dried over sodium sulfate, and after evaporation of the solvent, the residue is distilled *in vacuo*. Yield, 4.7 g (68%) of VII, bp 137-140°C (0.4 mm Hg), mp 65-66°C. Found, %: Cl 29.67. $C_{13}H_{10}Cl_2$. Calculated, %: Cl 29.70.

EXPERIMENTAL PHARMACOLOGY

As most laboratory animals are resistant to the adrenocorticolytic action of chloditane, the investigations were carried out on dogs weighing 15-20 kg that were sensitive to the preparation. The chloditane metabolites were introduced into their food in a dose of 25 mg/kg for 7 and 14 days. The functional state of the adrenal cortex was judged from the level of 11-hydroxycorticosteroids in the peripheral blood plasma, and its change on intravenous administration of ACTH. The corticosteroids were determined by the fluorometric method [16].

The analysis of the data obtained (see Table 1) showed that a certain decrease in the concentrations of total 11-hydroxycorticosteroids was observed only on administration of 1-chloro-2-o-chlorophenyl-2-p'-chlorophenylethylene, while other chloditane metabolites did not change the functional state of adrenal cortex.

Hence, while the action mechanism of chloditane is based on its metabolism, its dehydrochlorination products do not participate in the adrenocorticolytic properties of the compound. It is probable that the specific action of chloditane is due to other reactions of its biotransformation in the organism.

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