SYNTHESIS AND DIURETIC ACTIVITY OF PHENOXYACETIC ACID AND ANISOLE DERIVATIVES

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It is known ethacrynic acid, or 4-(2-methylenebutyryl)-2,3-dichlorophenoxyacetic acid (I), has high diuretic activity [1]. At present, definite interest has been shown in the search for diuretics among compounds with a structure similar to that of I. As the result of investigations among the derivatives of I, very effective diuretics have been found [3-7, 12, 15, 16]. Like I, most of these contain two chlorine atoms and an OCH_2COOH group in their molecule, and they differ from one another in the structure of the substituent at the 4-position of the benzene ring.

In several papers on the action mechanism of I, it was shown that it blocks the sulfhydryl groups of enzymes of kidney epithelium [9, 11], and in particular, the Na-K dependent ATP-ase (adenine triphosphatase) [13]. The blocking of the sulfhydryl groups may be due to either their addition to the α,β-enone group of the molecule of I, or to nucleophilic substitution of a chlorine atom at the 3-position of the molecule of I, or due to these two factors together.

Among the derivatives of I, compounds have been found which have no α,β-enone group in the structure, but nevertheless have a high diuretic activity [14]. It was interesting to study the influence of the chlorine atoms and the OCH_2COOH group on the diuretic activity of derivatives of I. We therefore synthesized 2-chlorophenoxyacetic acid (IIa), 2-chloro-4-acetylphenol (IIb), 4-acetylphenoxyacetic acid (IIc), 2-chloro-4-acetylanisole (IId), 2-chloro-4-acetylphenoxyacetic acid (IIe) and its ethyl ester (IIf), 2-amino-4-(3-chloro-4-methoxyphenyl)thiazole (IIg), and 2-amino-4-(3-chloro-4-carboxymethoxyphenyl)thiazole (IIh). Compounds IIa-c have been described in the literature [2], but we were the first to study their diuretic activity.

Compound IId was obtained by the acetylation of 2-chloroanisole by acetyl bromide in the presence of $SnCl_4$. Compound IIf was obtained by the action of ethyl bromoacetate on IIb by the method in [8]; its hydrolysis gave acid IIe. It should be noted that we were unable to obtain IIe by the acetylation of IIa with acetyl chloride, in the presence of either $SnCl_4$ or anhydrous $AlCl_3$. In bromination of IId,f by bromine in $CHCl_3$, bromomethyl 3-chloro-4-methoxyphenyl ketone (IIi) and bromomethyl 3-chloro-4-carboethyxymethoxyphenyl ketone (IIj) were isolated; their condensation with thiourea in ethanol led to the formation of IIg and IIh, respectively.

The individuality and the structure of the compounds obtained were confirmed by the data of TLC, IR spectroscopy, and elemental analysis.

Compounds IIb-f, h-j have the following bands in the IR absorption spectra (in cm^{-1}): IIb-f,i,j — 1630-1680 (C=O), IIe,f,h — 1750-1790 (COOR), IId-j — 795-800 (C—Cl).

EXPERIMENTAL CHEMICAL PART

The IR spectra were run on the Spectromom-2000 spectrophotometer (Hungary) in KBr tablets.* The course of the reaction and the purity of the compounds obtained were controlled by TLC on Silufol UV-254 plates (Czechoslovakia) in the benzene—ether (1:1) system.

2-Chloro-4-acetylanisole (IId). A mixture of 71.3 g (0.5 mole) of 2-chloroanisole and 67.6 g (0.55 mole) or AcBr is added dropwise at 30-35°C, with vigorous stirring, to 120 ml

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TABLE 1. Influence of Compounds IIa-h in a Dose of 24 mg/kg of Diuresis and Natriouresis in White Mice

Compound	Diuresis after 4 h, ml	Natriouresis after 4 h, μeq
IIa	4.3±0.35	150±20
IIb	2.5±0.3	95±10
IIc	2.0±0.3	105±21
IId	1.9±0.2	90±12
IIe	5.1±0.4	258±30
IIf	2.8±0.3	96±14
IIg	2.0±0.3	85±10
IIh	4.8±0.4	209±32
Ethacrynic acid	6.0±0.45	360±40
Control	2.1±0.2	80±20

of $SnCl_4$. The reaction mixture is left to stand for 20 h at ∿20°C, treated by dilute HCl with ice cooling, and steam distilled. Yield, 65.5 g (71%) of white crystalline product, mp 74-76°C (from ethanol). Found, %: Cl 19.1. $C_9H_9ClO_2$. Calculated, %: Cl 19.2.

Ethyl 2-chloro-4-acetylphenoxyacetate (IIf). A mixture of 34.1 g (0.2 mole) of IIb, 36.7 g (0.22 mole) of $BrCH_2COOEt$, 41.4 g (0.3 mole) of K_2CO_3, and 400 ml of acetone is boiled for 3 h. After 300 ml of acetone have been distilled off, the residue is cooled, 0.5 liter of water is added, the mixture is stirred to dissolution of salts, and then filtered. The precipitate is washed with water, dried, and crystallized from 1.5 liters to heptane. Yield, 40.1 g (78%) of white crystalline product, mp 73-74°C. Found, %: Cl 14.0. $C_{12}H_{13}ClO_4$. Calculated, %: Cl 13.8.

2-Chloro-4-acetylphenoxyacetic Acid (IIe) is obtained similarly without preliminary isolation of IIf. After distillation of acetone, 1 liter of 5% NaOH is added to the mixture (based on the above amount of Ib), the mixture is boiled for 1 h, treated with activated carbon, and filtered, and the filtrate is acidified. The precipitate is filtered, washed with water, and dried. Yield, 38.4 g (84%) of a white finely crystalline product, mp 150-151°C (from water). Found, %: Cl 15.6. $C_{10}H_9ClO_4$. Calculated, %: C 15.5.

Bromomethyl 3-chloro-4-methoxyphenyl Ketone (IIi). A solution of 3.2 g (0.02 mole) of Br_2 in 5 ml of $CHCl_3$ is added dropwise at ∿20°C to a solution of 3.7 g (0.02 mole) of IId in 20 ml of $CHCl_3$. The reaction mixture is held for 20 min, and then $CHCl_3$ is distilled in a water pump vacuum. The residue is crystallized from 120 ml of petroleum ether to yield 3.7 g (72%) of white crystalline product, mp 97-98°C. Found, %: Br 30.6; Cl 13.3. $C_9H_8BrClO_2$. Calculated, %: Br 30.3; Cl 13.5. Compound IIj is obtained in a similar way. Yield 80%, mp 140-141°C (from petroleum ether). Found, %: Br 24.0; Cl 10.5. $C_{12}H_{12}BrClO_4$. Calculated, %: Br 23.8; Cl 10.6.

2-Amino-4-(3-chloro-4-methoxyphenyl)thiazole (IIg). A solution of 0.76 g (10 mmoles) of thiourea in 20 ml of ethanol is mixed with a solution of 2.64 g (10 mmoles) of IIi in 20 ml of ethanol, and the mixture is boiled for 30 min, then cooled, and poured into 100 ml of water. The mixture is made alkaline with a NH_3 solution. The precipitate is filtered, washed with water, and dried. Yield, 2.15 g (90%) of a light-yellow product, mp 179-181°C (from ethanol). Found, %: Cl 14.5; N 11.5. $C_{10}H_9ClN_2SO$. Calculated, %: Cl 14.7%; N 11.6.

2-Amino-4-(3-chloro-4-carboxymethoxyphenyl)thiazole (IIh). A solution of 0.76 g (10 mmoles) of thiourea in 20 ml of ethanol is mixed with a solution of 3.36 g (10 mmoles) of IIj in 20 ml of ethanol, and the mixture is boiled for 10 min. Then 100 ml of 10% NaOH is added, and the mixture is boiled to the disappearance of the oily product formed (about 30 min). Activated carbon is added, and the mixture is filtered. The filtrate is cooled, acidified to pH 1.0, and filtered again. The filtrate obtained is treated with Na_2CO_3 solution of pH 4.0; the precipitate is filtered, washed with water, and dried. Yield, 1.48 g (52%) of a light-yellow product, mp >230°C (dec) (from ethanol). Found, %: Cl 12.0; N 10.1. $C_{11}H_9ClN_2SO_3$. Calculated, %: C 12.5; N 9.8.

EXPERIMENTAL PHARMACOLOGICAL PART

The influence of compounds IIa-h on diuresis and excretion of sodium ions was studied in white mice and white rats by the method in [10]. The experiments were carried out on

white intact mice weighing 20-22 g each, and white intact rats weighing 200-250 g each. Each compound was introduced into 10 mice and 10 rats, and the same number of animals were studied in a control experiment. The compounds studied were introduced by means of a gastric tube in the form of a suspension with starch mucilage in a dose of 24 mg/kg. Starch mucilage was introduced to the control animals in the same amount (1 ml) as to the experimental group. The aqueous dose in the control and experimental groups of the animals was 2% of the body weight of the animal. The diuresis and excretion of sodium ions was determined 4 h from the beginning of the experiment. The concentration of sodium ions in the urine was determined by the method of flame photometry on the PAZh-1 apparatus. The diuretic action of the compounds studied was compared with that of ethacrynic acid, which was introduced to the animals similarly and in the same dose.

All the compounds IIa-h studied do not have any appreciable effect on diuresis and natriouresis of white rats. Data on the influence of compounds IIa-h on diuresis and excretion of sodium ions in white mice are listed in Table 1.

Table 1 shows that among the compounds studied, compound IIe has the highest diuretic effect, and under its influence diuresis is 2.4 times and excretion of sodium ions double that of the control. Compounds IIa,h also have a significant diuretic action; under their influence, diuresis increased 2 and 2.3 times and excretion of sodium ions 1.8 and 2.4 times, respectively. All these three compounds have a chlorine atom at the o-position with respect to the OCH_2CCOH group, as in the case of ethacrynic acid.

Removal of the carboxylic group from the molecule or its esterification sharply lower the diuretic activity (IIb,d,g). The nature of the substituent at the p-position with respect to the OCH_2COOH group does not have any marked influence on the diuretic activity of the compounds studied (IIa,e,h).

Thus, our investigation shows the prospects of further search for diuretics in the series of 2-chlorophenoxyacetic acids.

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