SYNTHESIS AND PHARMACOLOGICAL STUDY OF AMINOALKYL ESTERS OF INDOL-3-YLPHENYLACETIC ACID

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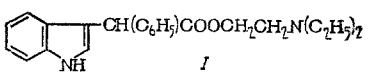
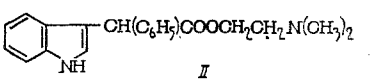
The esters of diphenylacetic acid and related carboxylic acids include compounds which have entered medical practice as cholinolytics and spasmolytics (adiphenine, amizil, etc.). Depending on the chemical structure of the individual compounds, this class possesses peripheral m- and n-cholinolytic activity, central cholinolytic activity or spasmolytic acitivity [1-5]. It is also known that replacement of one of the phenyl residues in the aminoalkyl diphenylacetates by a heteroaromatic residue gives compounds with a more pronounced pharmacological activity. Thus, the cholinolytic properties of esters of α-phenyl-α-(2-thienyl)-acetic acid are several times greater than those of the analogous diphenylacetic acid esters [6, 7].

In the present work, we will present the results of the synthesis and pharmacological study of two aminoalkyl esters of indol-3-ylphenylacetic acid, viz. the N,N-diethylaminoethyl ester (I), which can be regarded as the indole analog of adiphenine, and the corresponding N,N-dimethyl compound (II). Compound I was prepared by a mixed anhydride method, which involves treating a solution of the acid in tetrahydrofuran at 0° with a chloroformate ester in the presence of triethylamine and subsequently reacting the mixed anhydride formed with diethylaminoethanol. We synthesized compound II by reacting the sodium salt of indol-3-ylphenylacetic acid with dimethylaminoethyl chloride. For the pharmacological study, the aminoalkyl esters obtained were converted into their water-soluble hydrochlorides.



I



II

III

The pharmacological investigation of the compounds was conducted in comparison with adiphenine (the hydrochloride of 2-diethylaminoethyl 1,1-diphenylacetate, III). The peripheral m-cholinolytic activity was estimated from the decrease in the depressant reaction induced in urethane-narcotized cats by intravenous injection of acetylcholine (0.1 μg/kg), from the decrease in the spasm induced in an isolated section of rabbit intestine by acetylcholine ($2 \cdot 10^{-6}$), and from the mydriatic action obtained when solutions of the compounds were spotted onto the conjunctiva of cats. The effect on the parasympathetic and sympathetic ganglia was judged from the change in the depressant reaction induced by stimulation of the cervical cord of the vagus and from the change in the reactions on the part of the third eyelid, arterial pressure and respiration to the intravenous injection of cytisine (20 μg/kg) in narcotized cats (1 g/kg urethane, intraperitoneal). The effect on the n-cholinoreactive system was also estimated on the smooth muscle of the stomach of a frog from the change in its reaction to acetylcholine ($2 \cdot 10^{-6}$). The effect on the central n-cholinoreactive system was studied on muscles with experimental nicotine hyperkinesia. The compounds were injected subcutaneously 15 min before administering the nicotine in a dose of 10 mg/kg. The spasmolytic

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TABLE 1. Comparative Activity of Adiphenine (III) and Esters of Indol-3-ylphenylacetic Acid

Compound	Peripheral cholinolytic action						Dose relieving hyperkinesia after subcutaneous injection of nicotine (in mg/kg)	Concentration causing relaxation of rabbit intestine muscles	Rene index from 300 to 400 (in %)	LD_{50} intravenous (in mg/kg)
	dose decreasing the depressant reaction to the intravenous injection of acetylcholine (in mg/kg)	concentration decreasing the acetylcholine spasm in rabbit intestine by 50%	increase in pupil diameter	dose decreasing the depressant reaction to stimulation of the vagus by 50% (in mg/kg)	dose decreasing the cytisine-induced reaction by 50% (in mg/kg)	concentration decreasing the contraction of the smooth muscle of frog stomach by 50%				
I	5 (no effect)	10^{-5}	1% (no effect)	5	5	10^{-5}	75 (no effect)	2.10^{-6}	0.5	63
II	5 (no effect)	10^{-5}	1% (no effect)	5	5	10^{-5}	75 (no effect)	2.10^{-6}	0.1	63
III	5	2.10^{-6}	1% (twofold)	1	1	2.10^{-6}	75	2.10^{-6}	1	40
Activity in relation to III, taken as 1:										
I	-	0.2	-	0.2	0.2	0.2	-	1	2	-
II	-	0.2	-	0.2	0.2	0.2	-	1	10	-
III	1	1	1	1	1	1	1	1	1	-

activity was studied on sections of isolated rabbit intestine. The local anesthetic action on rabbits was determined by the Rene method. The LD_{50} (according to the Kerber method) was determined by intravenous injection in white mice. The data obtained are given in Table 1.

The investigation of pharmacological activity showed that compounds I and II are similar in the character and strength of their pharmacological action and compared with III (i.e., when one of the phenyl residues is replaced by indole) are considerably less active in relation to peripheral and central cholinolytic action, or are completely devoid of this action. In their ability to exert a spasmolytic action, the compounds under investigation are no different to III. In addition, they have a stronger local anesthetic action. Both compounds are less toxic than III.

EXPERIMENTAL

N,N-Diethylaminoethyl Indol-3-ylphenylacetate (I) Hydrochloride. Triethylamine (0.7 ml) is added at 0° to a stirred solution of 1.25 g indol-3-ylphenylacetic acid in 20 ml of absolute tetrahydrofuran. The

mixture is stirred for 10 min and 5 ml of a 1 M solution of chloroformate ester in absolute tetrahydrofuran added at the same temperature. After stirring for 15-20 min, 0.68 ml of diethylaminoethanol and 3 ml of absolute tetrahydrofuran are added. The mixture is stirred at room temperature for 1 h, the precipitate of triethylamine hydrochloride filtered off, the solvent distilled off, and the residue treated with 15 ml of methylene chloride, washed with sodium bicarbonate solution and water, and dried with magnesium sulfate. The substance is isolated in the form of its hydrochloride by adding an alcoholic solution of hydrogen chloride to a pH of 6.5. Yield 73%, mp 163-164° (decomp.). Found. %: C 68.36; H 7.20; Cl 9.26; N 6.97. $C_{22}H_{27}N_2O_2 \cdot HCl$. Calculated. %: C 68.30; H 7.0; Cl 9.16; N 7.24.

N,N-Dimethylaminoethyl Indol-3-ylphenylacetate (II) Hydrochloride. Solutions of 0.12 g of metallic sodium in 20 ml of absolute isopropanol and of 0.72 g of dimethylaminoethyl chloride hydrochloride in 20 ml of isopropanol are added at the same rate over 1 h to a stirred, boiling suspension of 1.36 g of sodium indol-3-yl-phenylacetate in 40 ml of absolute isopropanol. The mixture is stirred and boiled for 12 h, the isopropanol distilled off under vacuum, the residue treated with absolute ether (50 ml), the precipitate of sodium chloride separated, and the ether solution evaporated down to half under vacuum and poured into 100 ml of petroleum ether. The precipitate formed is filtered off and recrystallized from an ether–petroleum ether mixture. Compound II, mp 141-142°, is obtained in a yield of 1.45 g (90%). The substance is converted into its hydrochloride in the normal way, mp 182-183°. Found. %: C 67.45; H 6.31; Cl 9.89; N 7.97. $C_{20}H_{22}N_2O_2 \cdot HCl$. Calculated. %: C 67.50; H 6.50; Cl 9.98; N 7.86.

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