SYNTHESIS AND PHARMACOLOGICAL STUDY OF 3-INDOLYLPHENYLACETIC ACID TROPINE ESTER AND N,N-DIETHYLAMINOETHYLAMIDE

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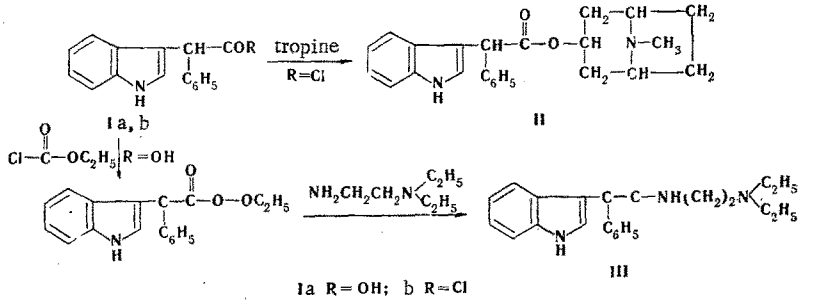
The synthesis of 3-indolylphenylacetic acid tropine ester and N,N-diethylaminoethylamide is described. The tropine ester has a pronounced spasmolytic effect.

Replacement of one of the phenyl groups in alkamine esters of diphenylacetic acid by an indole grouping leads to an appreciable reduction in the peripheral and central cholinolytic activity, but the spasmolytic effect of compounds of this sort is close to that of spasmolytin [1]. It is known that diphenylacetic acid tropine ester (tropacine) has pronounced central cholinolytic activity [2], and we therefore synthesized the tropine ester (II) of 3-indolylphenylacetic acid (Ia).

The method of mixed anhydrides proved to be unsuitable for this synthesis, probably because of the large volume of the tropine molecule (the starting acid and a small amount of the ethyl ester of acid I were isolated). We were able to obtain ester II by the action of tropine on acid chloride Ib:



The N,N-diethylaminoethylamide of acid Ia was synthesized by the method of mixed anhydrides.

The peripheral m-cholinolytic acitivity was estimated from the weakening of the acetylcholine ($2 \cdot 10^{-6}$)-induced spasm of an isolated section of the intestine of a rabbit. The central m- and n-cholinolytic effect was estimated from the effect on hyperkinesis in white mice induced by subcutaneous injection of nicotine (10 mg/kg) or arecoline (15 mg/kg). The spasmolytic activity was investigated in sections of rabbit intestine. The LD_{50} values were determined from intravenous injection of white mice. The calculations were made by the Kerber method.

It was found that with respect to peripheral m-cholinolytic activity preparation II (in the form of the acid adipate) is inferior to tropacine by a factor of ~20 (an acetylcholine spasm was relieved by the preparation in concentrations of $1 \cdot 10^{-5}$ g/ml, whereas $5 \cdot 10^{-7}$ g/ml of tropacine was effective). In doses in which tropacine considerably weakens and, in a number of experiments, completely prevents the development of arecoline hyperkinesis in mice (20-30 mg/kg intravenously), preparation II has no effect and dis-

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plays only a very slight protective effect with respect to nicotine-induced spasms. The spasmolytic activity of preparation II is comparable to that of tropacine: in concentrations of $1 \cdot 10^{-5}$-$2 \cdot 10^{-5}$ g/ml they both reduce by 50% the amplitude of the pendulum-like contractions of segments of rabbit intestine. In toxic doses, both preparations induced the same pattern of poisoning, which is characterized by adynamia, dyspnea, tremor, and clonic-tonic spasms. The LD_{50} value for preparation II is 86 mg/kg, as compared with 74 mg/kg for tropacine.

Thus replacement of a diphenylacetic acid residue in tropacine by a 3-indolylphenylacetic acid residue leads to a sharp decrease in the peripheral and central cholinolytic activity, but the spasmolytic properties and toxicity remain unchanged.

Compound III (the adipate) does not affect experimentally induced arhythmias induced by aconite in rats or induced by electrical current stimulation of the right auricle of the heart in urethane-narcotized cats during artificial respiration.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. For this, we used synthetic tropine, which was kindly provided us by Doctor of Chemical Sciences R. G. Glushkov, for which the authors are deeply grateful.

3-Indolylphenylacetic Acid Tropine Ester (II). A 2.46-g (11.8 mole) sample of PCl_5 was added at 0° to a solution of 2.96 g (11.8 mole) of 3-indolylphenylacetic acid (Ia) [3] in 50 ml of absolute ether, and the mixture was stirred while gradually raising the temperature to room temperature in the course of 2.5 h. The resinous impurities were removed by rapid filtration, and the ether was removed by vacuum distillation (water aspirator). Absolute benzene (50 ml) was added, and the solvent was again removed by distillation to remove traces of $POCl_3$. Absolute benzene (30 ml) was added to the residue, and a solution of 1.67 g (0.012 mole) of tropine in 20 ml of absolute benzene was added to the resulting solution in the course of 10 min. The mixture was then stirred for 1 h and allowed to stand at room temperature for 12 h. The resulting precipitate was removed by filtration and dissolved in alcohol. An alcohol solution of alkali was added, and the precipitated NaCl was removed by filtration and washed with alcohol. The solvent was removed from the filtrate by distillation, and the residue was triturated with water. The resulting solid was recrystallized from alcohol to give 2.8 g (64%) of the tropine ester with mp 174-176°. Found: C 77.1; H 7.1; N 7.7%. $C_{24}H_{26}N_2O_2$. Calculated: C 77.0; H 7.0; N 7.5%. IR spectrum: 1710 (C=O), 3120-3170 (N-H) cm^{-1}.

Adipate of Tropine Ester II. A solution of 0.33 g (0.002 mole) of adipic acid in 4 ml of absolute alcohol was added to a solution of 0.75 g (0.002 mole) of tropine ester II in 6 ml of absolute alcohol, and the mixture was allowed to stand for 12 h. The resulting precipitate was removed by filtration to give 0.88 g of the acid adipate with mp 143-144°. Found: C 69.3; H 7.0; N 5.5%. $C_{30}H_{36}N_2O_6$. Calculated: C 69.3; H 6.9; N 5.4%.

3-Indolylphenylacetic Acid N,N-Diethylaminoethylamide (III). A 0.7-ml (0.005 mole) sample of triethylamine was added with stirring at 0° to a solution of 1.25 g (0.005 mole) of acid Ia in 20 ml of absolute tetrahydrofuran (THF), after which the mixture was stirred for 10 min, and 5 ml of a 1 M solution of ethyl chlorocarbonate in absolute THF was added at the same temperature. The mixture was stirred for 15 min, after which 0.68 ml (0.005 mole) of N,N-diethylaminoethylamine in 3 ml of absolute THF was added. The mixture was then stirred at room temperature for 1 h, the precipitated triethylamine hydrochloride was removed by filtration, and the solvent was removed by distillation. Methylene chloride (15 ml) was added to the residue, and the solution was washed with sodium bicarbonate solution and water and dried with $MgSO_4$. The product was isolated by precipitation from an ether solution by the addition of cyclohexane to give 1.1 g (63%) of amide III with mp 105-106° (ether-cyclohexane). Found: C 75.3; H 7.6; N 11.8%. $C_{22}H_{27}N_3O$. Calculated: C 75.6; H 7.8; N 12.0%. IR spectrum: 1640 (amide C=O) and 3280 (indole N-H) cm^{-1}.

Adipate of Amide III. A solution of 1 g (2.9 mmole) of amide III in 10 ml of absolute alcohol was added to a solution of 0.43 g (2.9 mmole) of adipic acid in 20 ml of absolute alcohol, and the mixture was allowed to stand for 12 h. The acid adipate was precipitated by the addition of absolute ether to give 1.33 g (93.6%) of a product with mp 140-142°. Found: C 68.0; H 7.6; N 8.5%. $C_{28}H_{37}N_3O_5$. Calculated: C 67.8; H 7.5; N 8.5%.

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