SYNTHESIS AND CERTAIN PHARMACOLOGICAL PROPERTIES
OF 1-(INDOLYL-3')-2-ALKYLAMINOPROPANOLS

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It has been established that the substitution of the phenyl ring of phenylalkylamines by an indole ring leads to a change of the pharmacological activity. Thus, indopane [1-(indolyl-3')-2-aminopropane hydrochloride], the indole analog of phenamine, differs from the latter in a number of pharmacological properties [1].

In this connection it was of interest to study a series of derivatives of 1-(indolyl-3')-2-alkylaminopropanols since these compounds can be considered as ephedrine analogs which contain an indole ring in place of a phenyl ring.

Certain derivatives of indolylalkylaminopropanols were synthesized for this purpose. Compounds IV-VI are compounds of the erythro-series (studied as adipates), VII belongs to the threo-series and was obtained as the base (immediately prior to the experiment it was dissolved in hydrochloric acid).

The erythro-amino alcohols IV-VI were prepared by the reduction of the corresponding 3-α-alkyl(dialkyl)-aminopropionylindoles (I-III) with various reducing agents (NaBH₄, LiAlH₄, Raney nickel).

The threo-amino alcohol IV-VI were prepared by the isomerization of the corresponding erythro-amino alcohol (I) in 0.5 N HCl solution and was also isolated from the mixture of erythro- and threo-isomers obtained by the hydrogenation of 3-α-methylaminopropionylindole over Raney nickel. The assignment of the configurations was made on the basis of a study of the PMR spectra of the obtained amino alcohols and a comparison of these with the PMR spectra of ephedrine and β-ephedrine.

On the basis of the structural similarity of the compounds with ephedrine the pharmacological activity was studied in accordance with the specific characteristics for the latter.

The effect on arterial pressure was studied in urethane-narcotized cats with intravenous introduction of the compounds. In parallel with the recording of the arterial pressure, changes of the tone of the third eyelid were registered. The action on vessels was studied in rabbit's ears isolated according to Kravkov-Pisemskii. Broncholic activity was determined in urethane-narcotized cats by the T. M. Turpaev modification of the Konzett method [2]. Independent respiration in the animals was cut off with the help of Diplacin. The spasm of the bronchial muscles was induced by electrical stimulation of the vagus. The ability of the
compounds to alter the temperature of the body and the motor activity of animals served as an indication of central action. The experiments were conducted in white mice of weight 15-17 g introducing the compounds into the abdominal cavity. The temperature was measured with an electrothermometer. The motor activity was recorded by the method of Knoll and Vajnovszki [3].

Toxicity was determined on white mice of weight 15-17 g introducing the compounds into the abdominal cavity. Each dose was investigated in five animals. The LD50 was calculated according to the method of Litchfield and Wilcoxon [4].

The results of the investigations carried out indicated that the compounds containing a secondary amino group (IV, V, and VII) gave a pressor effect. Compound VI showed a hypotensive action which was also maintained after decapitation of the animals. All of the compounds increase the tone of the third eyelid. Compounds IV, V, and VII produce constriction of the vessels but to a lesser degree than ephedrine. Thus, at a dilution of 10^-7 ephedrine reduces the number of vessels flowing and the dripping from the ear by 60-65%; d,1-erythro-1-(3'-indolyl)-2-methylaminopropanol (IV) adipate reduces the dripping by 20-25%; d,1-erythro-1-(1'-methyl-3'-indolyl)-2-methylaminopropanol (V) adipate by 10-15%; d,1-threo-1-(3'-indolyl)-2-methylaminopropanol (VII) by 35-40%; d,1-erythro-1-(3'-indolyl)-2-dimethylaminopropanol (VI) adipate dilates the vessels by 15-20%.

All of the compounds investigated reduce the tone of the bronchial muscles; IV is the most active; in a series of experiments it reduced or prevented bronchoospasm at a dose of 10 mg/kg; however, according to the duration of the effect the compound is less effective than ephedrine. The rest of the compounds are weakly active in this respect.

In contrast to ephedrine not one of the compounds investigated showed any stimulatory action on the central nervous system or produced any hyperthermic effect. The derivative of the three-series (VII) at a dose 100 mg/kg reduces the motor activity of animals and produces a lowering of the body temperature in mice by 2°C.

The LD50 for IV-VII is respectively (in mg/kg) 390 (312-487), 220 (163-297), 350 (250-490), and 200 (138-265), for ephedrine it is 350 (301-406).

Thus, derivatives of 1-(indolyl-3')-2-alkylaminopropanols containing a secondary amino group, like ephedrine, show a peripheral sympathomimetic action.

In this respect IV, the indole analog of ephedrine, is the most active.

EXPERIMENTAL

3-(α-Methylaminopropionyl)indole (I). A mixture of 2.5 g of 3-(α-bromopropionyl)indole and 20 ml of 25% aqueous methylamine solution was heated until complete solution and the solution was maintained at 70-80°C for 1 h. On cooling a colorless crystalline precipitate separated. After recrystallization from water the yield was 1.67 g (84%) with mp 142-143°C. Found %: C 71.03; H 6.67; N 13.77. C12H14ON2. Calculated %: C 71.25; H 6.97; N 13.85.

1-(Indolyl-3')-2-methylaminopropanol-1 (IV). A. To a solution of 3.8 g of 3-(α-methylaminopropionyl)indole in 38 ml of absolute methanol was added in portions 3.8 g of sodium borohydride. After the addition of the NaBH4 the mixture was stirred for 2 h at room temperature; the solvent was then evaporated in vacuum. The substance crystallized on addition of water. The yield of erythro-l-(indolyl-3')-2-methylaminopropanol-1 was 2.58 g (69%). The mp was 129-130°C. Found %: C 70.61; H 7.94; N 13.61. C12H16ON2. Calculated %: C 70.55; H 7.89; N 13.71.

B. 3-(α-Methylaminopropionyl)indole (5 g) was dissolved in 250 ml of ethyl alcohol and hydrogenated for 10 h over 5 g of Raney nickel in an autoclave at 30 atm and 70°C. After separating the catalyst the solvent was evaporated; the residue was boiled with 100 ml of ether. The precipitate which was insoluble in ether was filtered off: 1.25 g (25%) of a colorless crystalline substance was obtained with mp 179-181°C from acetone; this was threo-1-(indolyl-3')-2-methylaminopropanol-1. A sample mixed with the sample obtained by the reduction of 3-(α-methylaminopropionyl)indole with NaBH4 gave a depression of mp. Found %: C 70.61; H 7.94; N 13.61. C12H16ON2. Calculated %: C 70.55; H 7.89; N 13.71.