THE SYNTHESIS OF NEW DERIVATIVES OF APHYLLIC ACID

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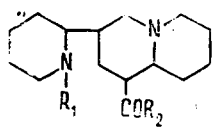
Aphyllic acid (AA) (I) possesses bronchospasmolytic properties [1], inhibits the transmission of impulses from the vagus nerve to the heart [2], and attenuates the toxic action of anticholinesterase substances [3]. In the present paper we give the results of the synthesis of a number of derivatives of AA containing functional groups characteristic for spasmolytic drugs [4]. The compounds synthesized were derivatives at the nitrogen atom and at the carboxyl group. When AA was condensed with diethylaminoethanol in the presence of thionyl chloride, the main product formed was aphylline (75%), and the yield of the diethylaminoethyl ester of AA (II) did not exceed 25%.

To increase its yield, (II) was synthesized from the β-chloroethyl ester of AA (III). The action on (III) of diethylamine in an autoclave at 120-140°C formed (II) (yield 30-35%). The β-chloroethyl ester of AA (III) was obtained by the action of dichloroethane on the sodium salt of AA in the presence of methanol (10 : 1). Yield 56%.

The condensation of N-methyl-AA with diethylaminoethanol and with piperidine in the presence of thionyl chloride gave the β-diethylaminoethyl ester of N-methyl-AA (IV) and N-methylaphylloylpiperidine (V), respectively. The condensation of N-nitroso-AA with β-diethylaminoethanol and with piperidine in the presence of phosphorus pentoxide at 130-140°C [5] yielded the β-diethylaminoethyl ester of N-nitroso-AA (VI) and N-nitro-



I. R_1=H; R_2=OH;
II. R_1=H; R_2=$OCH_2CH_2N(C_2H_5)_2$
III. R_1=H; R_2=OCH_2CH_2Cl;
IV. R_1=CH_3; R_2=$OCH_2CH_2N(C_2H_5)_2$
V. R_1=CH_3; R_2=NC_5H_{10}
VI. R_1=NO; R_2=$OCH_2CH_2N(C_2H_5)_2$
VII. R_1=NO; R_2=NC_5H_{10}

TABLE 1

Compound	Empirical formula	mp, °C	bp, °C (mm)	R_f^*	System	Yield, %
Diethylaminoethyl ester of AA (II)	$C_{21}H_{39}N_3O_2$	—	195—197 (8)	0,31	2	25
β-Chloroethyl ester of AA (III)	$C_{17}H_{29}N_2ClO_2$	69—70	—	0,50	2	56
Diethylaminoethyl ester of N-methyl-AA (IV)	$C_{22}H_{41}N_3O_2$	—	199—200 (7)	0,22	2	60
N-Methylaphylloylpiperidine (V)	$C_{21}H_{38}N_2O$	144—142	—	0,47	2	60
Diethylaminoethyl ester of N-nitroso-AA (VI)	$C_{21}H_{38}N_4O_3$	—	222—22 (4)	0,74	2	50
N-nitrosoaphylloylpiperidine (VII)	$C_{20}H_{35}N_4O_2$	—	235—236 (4)	0,95	1	45

*TLC, system 1, acetone; PC, system 2, butanol—acetic acid—water (100 : 13.5 : 27).

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soaphylloylpiperidine (VII). The physicochemical constants of the compounds obtained are given in Table 1. The results of the pharmacological investigation will be published separately.

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ISOLATION OF THE ALKALOID LINDELOFINE FROM *Lindelofia anchusoides* BY AN ION-EXCHANGE METHOD

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The alkaloid lindelofine is widely distributed in plants of the family Boraginaceae and has been detected in various species – Rindera cyclodonta, Lindelofia anchusoides, L. stylosa, and others [1-4].

The existing method of obtaining lindelofine by extraction with chloroform is comparatively laborious and uses large amounts of expensive solvent.

We have studied the possibility of using ion-exchange resins for the isolation of the alkaloid lindelofine from aqueous extracts of the epigeal part of L. anchusoides and, in particular, the processes of the extraction, sorption, and desorption of the combined alkaloids. Experiments have shown the economic desirability of using water to extract the alkaloids, the sorption of the latter on KU-1 cation-exchange resin, and the desorption of the alkaloids from the resin by a 2% solution of ammonia in 80% ethanol.

The comminuted raw material (50 kg), collected on April 4, 1974 in Chimgan (Tashkent oblast) in the budding phase was charged into a battery of two extractors and was extracted continuously with water. The aqueous extract of the alkaloids was passed through a battery of adsorbers consisting of four columns filled with KU-1 cation-exchange resin in the H form (2.2-2.5 kg each). The rate of flow of the extract was 600-700 liters/h · m^2.

After the complete extraction of the alkaloids from the raw material, they were desorbed from the cation-exchange resin with a 2% solution of ammonia in 80% ethanol. The rate of flow of the eluent was 200 liters/h · m^2. The ethanolic solution was concentrated, the aqueous residue was made alkaline with 25% ammonia solution, and the alkaloids were exhaustively extracted with chloroform. The N-oxide forms of the alkaloids were reduced with zinc dust and extracted with chloroform. The chloroform extract was concentrated in vacuum to dryness. This gave 1511 g of combined alkaloids, or 302% of the weight of the raw material.

From the combined alkaloids by treatment with acetone we isolated 702 g of lindelofine with mp 105-106°C (1.4% of the weight of the raw material).

Thus, we have developed a simple and economically favorable method of obtaining lindelofine from the epigeal part of L. anchusoides and have established the epigeal part of this plant in the budding stage as a basic source for the production of lindelofine.

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