SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF DERIVATIVES OF 2-DIMETHYLAMINOQUINOLINE AND 1,2,3,4-TETRAHYDRONAPHTHYRIDINE

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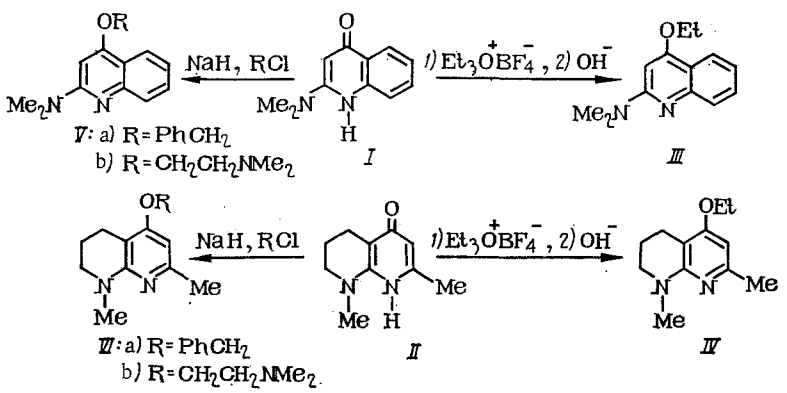
It was shown previously [1] that the products of alkylation of pyrrolo-, pyrido-, and azepino[2,3-c]quinoline derivatives possess neurotropic activity. In continuation of these investigations the interaction has been studied of 2-dimethylaminoquinol-4-one (I) and 1,7-dimethyl-1,2,3,4,5,8-hexahydronaphthyrid-5-one (II) with various alkylating agents. The obtained compounds were subjected to a pharmacological investigation. The interaction of I and II with triethyloxonium fluoborate led to the corresponding ethoxy derivatives (III and IV, respectively). The structure of III followed from its UV spectrum which differed significantly from the spectrum of the initial quinoline (I) (Fig. 1) and was closely similar to the spectrum of the previously described 1-methyl-4-methoxy-2,3-dihydropyrrolo[2,3-c]quinoline [2]. In the case of IV the UV spectrum also differed from the spectrum of II (Fig. 2). Furthermore a peak for a $(M-OC_2H_5)^+$ ion was observed in the mass spectrum of IV and is a characteristic of the fragmentation of compounds containing ethoxy groups. The fact that the alkylation of I and II with triethyloxonium fluoborate led to O derivatives was not unexpected since the high tendency of this reagent towards an O-alkylation reaction of the sodium salts of I and II with primary alkyl halides was to be expected to a significant extent over selective N-alkylation [4-6]. However on alkylating both I and II with benzyl chloride or with N,N-dimethylaminoethyl chloride in the presence of NAH the derivatives (Va, Vb, VIa, VIb) were obtained, the UV spectra of which were similar to the spectra of III and IV and differed appreciably from the spectra of I and II. Consequently an O-alkylation has taken place in these cases too (see Figs. 1, 2; Table 1). This circumstance obliged us to reconsider the structures of the products of alkylation of pyrrolo-, pyrido-, and azepinoquinolines which previously [1] had been assigned the structure of N-alkylated derivatives from literature data [4-6]. Analysis of the UV spectra of these compounds showed that they were all practically identical to the spectra of the corresponding O-ethyl derivatives [7] and thus were also products of O-alkylation.



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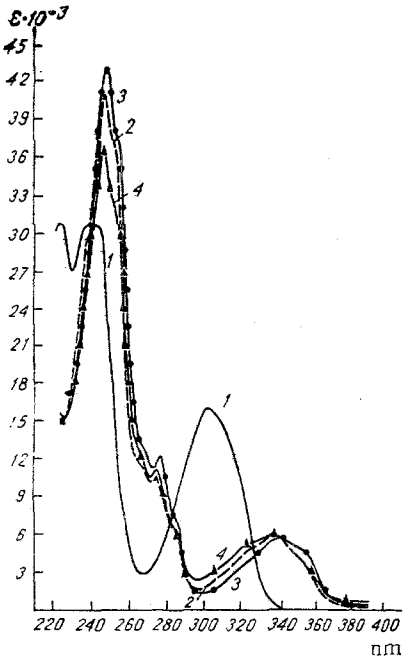


Fig. 1

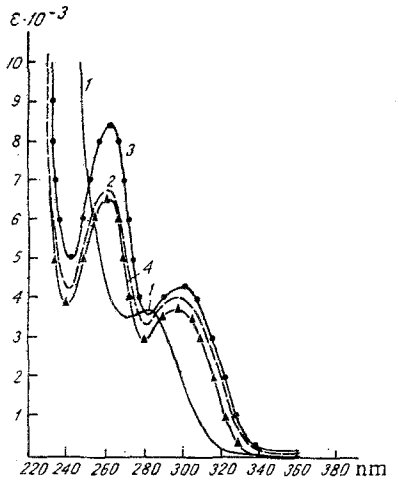
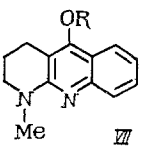


Fig. 2

Fig. 1. UV spectra in methanol. 1) I; 2) III; 3) Va; 4) Vb.

Fig. 2. UV spectra in a mixture of 20% ethanol + 80% 0.1 N sodium hydroxide. 1) II; 2) IV; 3) VIa; 4) VIb.

Proceeding from the fact that the products of alkylation of 1-methyl-5-hydroxypiperido-[2,3-b]quinoline (VII) possess neurotropic activity, a pharmacological study has been carried out of the derivatives of 2-dimethylaminoquinoline (Va, b) and 1,7-dimethyl-1,8-naphthyridine (VIa, b), which may be considered as bicyclic fragments of tricyclic (VII). The aim of elucidating to what extent the naphthyridine or quinoline portion of the (VII) molecule was responsible for the pharmacological activity of compounds of this type was pursued in this way.



VII

R = $PhCH_2$, $CH_2CH_2NMe_2$

EXPERIMENTAL

Pharmacology

An investigation of the obtained compounds (Va, Vb, VIa, VIb) was carried out in a series of pharmacological tests characterizing central and peripheral neurotropic activity. The effect of substances was studied on the effects of amphetamine (hyperthermia and group toxicity), L-DOPA, reserpine, apomorphine, and also on catalepsia caused by tryptazine. Also studied were the anticonvulsive action, interaction with soporific and analgesic agents, effect on arterial pressure and respiration, and the local anesthetic activity; the acute toxicities of compounds were determined.

It was established that the greatest central neurotropic activity was possessed by compound VIa.

On injecting VIa at a dose of 25-50 mg/kg subcutaneously simultaneously with amphetamine the body temperature of mice rose 1-1.5° more than on injecting amphetamine alone. On simultaneous injection of VIa (25 mg/kg subcutaneously) with amphetamine (7.5 mg/kg subcutaneously) 20% more mice died than on injecting amphetamine alone. By this criterion VIa joins

TABLE 1. UV Spectra of the Synthesized Compounds

Compound	λ_{max}, nm (log ε)
I	224 (4,48), 244 (4,49), 304 (4,21)
III	248*(4,61), 276*(4,03), 338*(3,74)
Va	248*(4,62), 277*(4,07), 340*(3,74)
Vb	248*(4,56), 276*(4,02), 337*(3,74)
II	226 (4,46) 228 (4,46), 284 (3,57)
IV	260 (3,3), 298 (3,61)
VIa	261 (3,92), 299 (3,64)
VIb	260 (3,82), 298 (3,57)

*In these spectra there was also a weak shoulder in addition to the indicated maximum.

TABLE 2. Derivatives of Quinoline and 1,2,3,4-Tetrahydronaphthyridine

Compound	Yield, %	Melting point,* °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	Cl		C	H	N	Cl
Va	67,5	155—6	77,6	6,6	10,5	—	$C_{18}H_{18}N_2O$	77,7	6,5	10,1	—
Va·HCl		164—6	64,8	6,3	8,7	10,8	$C_{18}H_{18}N_2O \cdot H_2O \cdot HCl$	65,0	6,3	84	10,7
Vb·HCl	67	243—4	51,0	7,1	11,6	20,4	$C_{15}H_{21}N_3O \cdot 1,25H_2O \cdot 2HCl$	50,8	6,9	11,8	20,0
VIa·HCl	69	126—8	63,2	7,1	8,4	11,2	$C_{17}H_{20}N_2O \cdot H_2O \cdot HCl$	63,3	7,1	8,7	11,0
VIb·HCl	50	240—1	52,2	7,8	—	21,5	$C_{14}H_{23}N_3O \cdot 2HCl$	52,2	7,8	—	22,0

*Compounds V and VI were crystallized from isopropanol.

those substances possessing antidepressant activity.

Compound Va was less active by this criterion and VIb and Vb even lower.

Compounds VIa and Va injected into mice at a dose of 50 mg/kg subcutaneously changed the hypothermal response to L-DOPA (200 mg/kg intraperitoneally) to a hyperthermal response.

The body temperature of mice 30 min after injection of L-DOPA on a background of the action of the preparations was 3-3.2° higher than on injection of L-DOPA alone.

Compound VIa (25-50 mg/kg subcutaneously) reduced the hypothermia caused by apomorphine (10 mg/kg into the abdominal cavity) by 1-1.5°.

In contrast to the majority of antidepressants the investigated compounds proved to have no appreciable effect on hypothermia and ptosis caused by reserpine (2 mg/kg subcutaneously) and also proved to have no anticataleptic action in experiments in rats (catalepsia was caused by the injection of tryptazine 6 mg/kg into the abdominal cavity).

A study of the effect of the preparations on convulsions showed that on injection of 25 mg/kg subcutaneously to mice the compounds proved to have no action on convulsions caused by an electric current. The convulsive action of corazole was enhanced. Thus, on injecting corazole into the abdominal cavity at a dose of 125 mg/kg the number of collapsed mice was 20% and after injection of Va, Vb, VIa, and VIb 60-80%.

No anesthetic activity was detected on implanting 1% solutions into the conjunctival sac of the rabbit eye.

In experiments on cats under urethane anesthesia it was established that compounds Vb and VIb (1-5 mg/kg intraveneously) caused a transient reduction of arterial pressure.

On administering Va and VIa at the same doses after the hypotensive phase a hypertensive reaction was recorded. On administering VIa a contraction of the third eyelid and depression of respiration was recorded. These phenomena were reduced by the adrenolytic tropaphen. Thus these compounds possess some adrenomimetic activity.

On subcutaneous injection in mice the LD_{50} of Va, Vb, VIa, and VIb were 350, 270, 175, and 250 mg/kg, respectively.

Thus derivatives of 1,2,3,4-tetrahydro-1,8-naphthyridine possessed the elements of antidepressant activity but were surpassed by known antidepressants.

As in the case of the tricyclic compounds VII, the most active was the compound carrying a benzyl substituent.

In comparison with aminoquinoline derivatives the naphthyridines (particularly VIa) were the most active. Compound VIa also possessed some peripheral adrenomimetic activity.

The studied compounds were less active when compared with known antidepressants and with modern adrenomimetic substances.

EXPERIMENTAL

Chemistry

UV spectra of solutions were taken on an EPS-3 spectrophotometer in methanol (compounds I, III, Va, and Vb) and in a mixture of 20% ethanol + 80% 0.1 N sodium hydroxide. The properties of compounds V and VI are given in Table 2.

2-Dimethylamino-4-ethoxyquinoline (III). A solution of triethyloxonium fluoborate (3.03 g) in methylene chloride (20 ml) was added to a solution of I (3 g) in methylene chloride (50 ml). The mixture was stored for 16 h at ~20° and III fluoborate (4.4 g: 91%) was filtered off, mp 270-273° (from alcohol). Found, %: C 51.6, H 5.5, N 9.2. $C_{13}H_{17}BF_4N_2O$. Calculated, %: C 51.3, H 5.6, N 9.2. The salt obtained was made alkaline in aqueous solution with 2 N sodium hydroxide and III was obtained, mp 104-107° (from petroleum ether). Found, %: C 72.3, H 7.3, N 13.9. $C_{13}H_{16}N_2O$. Calculated, %: C 72.2, H 7.4, N 13.0.

Compound IV was prepared in a similar manner in 58.5% yield and had mp 39-42° (from hexane). Found, %: C 69.8, H 8.7, 13.5. $C_{12}H_{18}N_2O$. Calculated, %: C 69.9, H 8.7, N 13.6.

2-Dimethylamino-4-(β-N,N-dimethylaminoethoxy)quinoline (Vb). Sodium hydride (0.92 g) was added in portions to a suspension of I (3.76 g) in anhydrous dimethylformamide (DMF; 40 ml) at 40° and the mixture was maintained at 90° for 2 h. A solution of β-(N,N-dimethylamino)ethyl chloride in anhydrous DMF (10 ml) was added dropwise to the mixture which was then heated at 100° for 3 h, and the DMF distilled off in vacuum. The residue was dissolved in water, the solution extracted with chloroform, the extract dried with anhydrous sodium sulfate, and the chloroform distilled off. The residue was dissolved in acetone, the solution was acidified with an alcoholic solution of hydrogen chloride, and Vb hydrochloride was obtained. Compounds Va, VIa, and VIb were obtained similarly (see Table 2).

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N-DERIVATIVES OF ANABASINE.

PREPARATION OF N-DERIVATIVES OF ANABASINE HAVING NICOTINOLYTIC PROPERTIES

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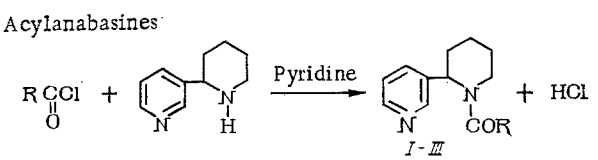
The alkaloid anabasine, which comprises 69.0-79.8% of the total alkaloid content of the plant *Anabasis aphylla* (central Asia) [1], has a whole series of nicotine-like biological properties. We have found [2] that certain N-aryl and N-alkyl derivatives of anabasine, containing bulky acyl or alkyl radicals on the nitrogen of the piperidine ring, display antinicotinic activity. Such substances can be of interest for conducting pharmacological investigations on experimental animals.

Our search for compounds which block nicotinic choline receptors in the substituted anabasine series was based, first of all, on the structural similarity between anabasine and nicotine; secondly, on the availability of a hydrogen atom on the nitrogen of the piperidine ring, which facilitates the synthesis of N derivatives; and, finally, on the fact that raw materials are readily available for native production of anabasine itself.

The synthesis of anabasine derivatives was carried out according to the following scheme:



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