SYNTHESIS AND ANTICHOLINESTERASE ACTIVITY OF AMINES AND DIAMINES OF THE FURAN SERIES AND THEIR SALTS

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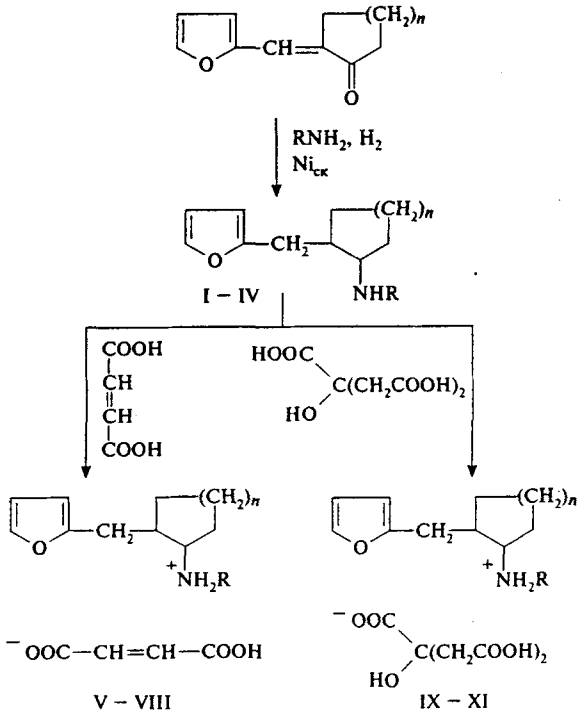
The pharmacological properties of furfurylcycloalkylamines and their isologues are almost unstudied. The are a few works devoted to the antimicrobial and antiphage activity of 2-(2-furfuryl)- and 2-(2-tetrahydrofurfuryl)cycloalkylamines in complexes with metal salts, including Pt(II), Pd(II), and Co(II) [1, 2].



I, V, IX: R = H, n = 1;
II, VI, X: R = Me, n = 1;
III, VII, XI: R = H, n = 2;
IV, VIII: R = Me, n = 2

The purpose of this work was to synthesize and characterize, with respect to the anticholinesterase (ACE) activity, the primary, secondary, and tertiary furfuryl-substituted cycloalkylamines, diamines, and their salts with organic and mineral acids. Interest in this study was stimulated by evidence [3] that amine salts are potential ACE inhibitors.

We have synthesized a series of 2-(2-furfuryl)cycloalkylamines (I – IV) by the method of catalytic hydroamination of furfurylidenecyclanones. The reactions were performed at a temperature of 100°C and a hydrogen pressure of 10 MPa in an alcohol solution of ammonia or methylamine in the presence of Raney nickel catalyst [4, 5].

Interaction of amines I – IV with organic acids in alcohol solutions led to maleates V – VIII and citrates IX – XI with yields 43 – 95% and 35 – 29%, respectively. The choice of acids was determined by the ability of maleates and citrates to be purified, their solubility in water, and their low hygroscopicity (compared to that of mineral acid salts).

Diamines of the furan series (XIV and XV) were synthesized with a yield of 76 – 79% proceeding from the primary amines I and III by reactions of cyanoethylation and catalytic reduction of intermediate aminonitriles XII and XIII.

The cyanoethylation of amines I and III was performed in the presence of catalytic amount of acetic anhydride and hydroquinone (acrylonitrile stabilizer).

The hydrogenation of aminonitriles XII and XIII (obtained at a yield of 82 – 85%) was carried out on Raney nickel catalyst (100°C; 7.5 MPa) in the presence of an 8 – 10-fold excess of ammonia necessary for suppressing the side reactions leading to the formation of secondary amines and hydrogenation of the furan ring.

For the passage to tertiary diamines XVI and XVII, compounds XIV and XV were subjected to reductive methylation by formaldehyde over Raney nickel catalyst at a temperature of 25 – 30°C and a hydrogen pressure of 7.5 MPa; diamines XVI and XVII were obtained at a yield of up to 79%.

The latter diamines were used for the synthesis of di(iodomethylate) XVIII and dihydrochloride XIX obtained with yields 78% and 98%, respectively.

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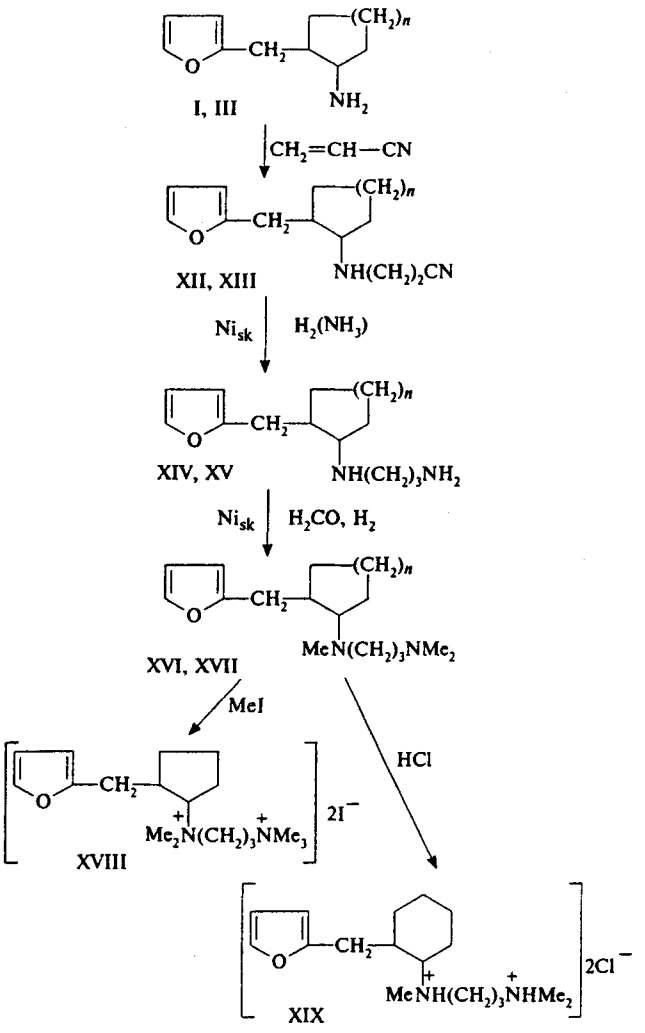

XII, XIV, XVI: $n = 1$; XIII, XV, XVII: $n = 2$

The proposed structures of the originally synthesized compounds V – XI and XVI – XIX were confirmed by IR spectroscopic data. Vibrations of the furan ring ($\nu_{=C-H}$) are manifested in the region of 3120 – 3160 cm^{-1}, the absorption bands due to $\nu^{as}_{CH_3}$ and $\nu^{s}_{CH_3}$ are observed at 2980 and 2885 cm^{-1}, and the bands of $\nu^{as}_{CH_2}$ and $\nu^{s}_{CH_2}$, at 2935 and 2860 cm^{-1}, respectively. The spectra of tertiary diamines XVI and XVII exhibit no absorption in the region of 3300 – 3500 cm^{-1} (ν_{NH} and ν_{NH_2}). The presence of the carboxylate anion in salts V – XI is confirmed by the absorption bands at 1550 – 1580 cm^{-1} (ν^{as}) and 1380 – 1400 cm^{-1} (ν^{s}). The residue of citric acid (compounds IX – XI) is manifested by the characteristic bands at 1760 ($\nu_{C=O}$) and 3400 – 3500 cm^{-1} ($\nu_{OHassoc}$), and that of maleic acid (compounds V – VIII) gives absorption bands at 1720 cm^{-1} ($\nu_{C=O}$), 1660 cm^{-1}($\nu_{C=C}$), and 3300 – 3450 cm^{-1} (ν_{OH}). The IR spectra of salts V, VII, IX, and XI display the bands of $\nu^{+}_{NH_3}$ (at 3300 cm^{-1}), while the spectra of VI, VIII, and X show the vibrations $\nu^{+}_{NH_2}$ (2670 – 2700 cm^{-1}), and the spectra of dihydrochloride XIX exhibit ν^{+}_{NH} (2700 cm^{-1}).

The synthesized compounds, including maleates V – VIII, citrate IX – XI, aminonitriles XII and XIII, diamines XIV – XVII, iodomethtylate XVIII, and dihydrochloride XIX were tested for the ability to inhibit the activity of acetylcholinesterase.

It was established that all compounds at concentrations $10^{-6} – 10^{-2}$ M possess anticholinesterase properties (Table 1).

As for the degree of ACE inhibition, compounds IX – XI and XIX exhibited comparably high activities, while the activity of maleate VII even slightly exceeded that of the known anticholinesterase drug galanthamine [3].

On the basis of data obtained, it was difficult to establish any relationship between the structure of compounds and their properties. Nevertheless, we should note certain correlation of the anticholinesterase activity, on the one hand, and the size of alicycle and degree of substitution of the ammonium nitrogen atom, on the other hand. Thus, cyclohexyl derivatives produce a stronger inhibiting action as compared to that of cyclopentane analogs (cf. V vs. VII, XII vs. XIII, and XVI vs. XVII). Introduction of the methyl substituent at the ammonium nitrogen has virtually no effect on the activity of the furfurylcyclopentylamine salts (cf. V vs. VI and IX vs. X), but reduces the inhibiting action in the series of N-cyclohxylammonium (in maleates VII and VIII). The nature of the anion (citrate vs. maleate) did not significantly affect the activity. Citrates IX and X are somewhat more active than maleates V and VI in the series of N-(2-furfurylcyclopentyl)ammonium salts, but their cyclohexane counterparts VII, VIII, and IX exhibit an opposite trend. Transition from diamines XVI and XVII to the corresponding salts XVIII and XIX enhances the inhibiting action.

TABLE 1. Anticholinesterase Activity of 2-(2-Furfuryl)cycloalkylamines and Their Salts

Compound	pI_{50}
V	4.6
VI	4.4
VII	5.3
VIII	4.5
IX	4.9
X	4.8
XI	5.0
XII	2.9
XIII	3.9
XIV	3.0
XV	2.8
XVI	2.8
XVII	3.8
XVIII	3.2
XIX	4.9
Galantamin	5.2

EXPERIMENTAL CHEMICAL PART

The IR spectra were recorded on the UR-20 and Specord M-80 spectrophotometers (Germany) using samples prepared as thin layers or suspensions in vaseline oil and hexachlorobutadiene.

The synthesis of 2-(2-furfuryl)cycloalkylamines I – IV was performed according to [4, 5]. Aminonitriles XII, XIII and diamines XIV, XV were obtained as described elsewhere [6].

N-[2-(2-furfuryl)cyclopentyl]ammonium maleate (V). A mixture of 2.5 g (0.015 mole) of amine I, 1.74 g (0.015 mole) maleic acid, and 4 ml ethanol was boiled on a water bath for 20 – 30 min. Then the solution was cooled and evaporated to 2/3 of the initial volume. Salt V was precipitated with ether and recrystallized from ethyl acetate to obtain 4.16 g (94%) of maleate V; m.p., 100 – 102°C.

Similar procedures were used to obtain maleates VI – VIII and citrates IX – XI.

Methyl(γ-dimethylaminopropyl)[2-(2-furfuryl)cyclopentyl]amine (XVI). A mixture of 15.54 g (0.07 mole) of diamine XIV, 6.3 g (0.21 mole) paraform, 0.5 g sodium acetate, 80 ml methanol, 10 ml water, and 1.5 g Raney nickel was placed in a 250-ml autoclave and treated at an initial hydrogen pressure of 7.5 MPa and a temperature of 25 – 30°C. The reaction was terminated after 6 – 7 h upon the absorption of a calculated amount of hydrogen (0.21 mole). The catalyst was separated from hydrogenizate, the solvent was distilled off, and the residue extracted with ether. The ether extracts were dried over KOH, the solvent (ether) evaporated, and the residue distilled in vacuum to collect the fractions with b.p., 138 – 140°C (2 Torr); n_D^{20}, 1.4940. Yield of diamine XVI, 8.7 g (47%).

A similar procedure was used for the synthesis of diamine XVII.

TABLE 2. Characteristics of Compounds V – XI and XVI – XIX

Compound	Yield, %	M.p., °C	Empirical formula
V	95	100 – 102	$C_{14}H_{29}NO_5$
VI	43	86 – 88	$C_{15}H_{21}NO_5$
VII	47	50 – 52	$C_{15}H_{21}NO_5$
VIII	58	139 – 141	$C_{16}H_{23}NO_5$
IX	39	76 – 78	$C_{16}H_{23}NO_8$
X	24	90 – 92	$C_{17}H_{25}NO_8$
XI	32	80 – 82	$C_{17}H_{25}NO_8$
XVI*	47	–	$C_{16}H_{28}N_2O$
XVII**	67	–	$C_{17}H_{30}N_2O$
XVIII	98	73 – 75	$C_{18}H_{34}I_2N_2O$
XIX	78	79 – 82	$C_{17}H_{32}Cl_2N_2O$

* Liquid product: b.p., 138 – 140°C (2 Torr); n_D^{20}, 1.4940.

** Liquid product: b.p., 150 – 153°C (2 Torr); n_D^{20}, 1.4980.

Methyl(γ-dimethylaminopropyl)[2-(2-furfuryl)cyclopentyl]amine di(iodomethylate) (XVIII). A mixture of 2.64 g (0.01 mole) of diamine XVI with a 5-fold excess of methyl iodide (7.1 g) was heated on a water bath for 3 h. Then the excess MeI was distilled off. The residue was cooled and poured over absolute ether to crystallize an oily product. Yield of iodomethylate XVIII, 5.37 g (98%); m.p., 73 – 75°C.

Methyl(γ-dimethylaminopropyl)[2-(2-furfuryl)cyclopentyl]amine dihydrochloride (XIX). To a solution of 1.39 g (0.005 mole) of diamine XVII in 8 ml of absolute ether was added a mixture of 20 ml of absolute ether with 0.55 g (0.015 mole) HCl. The white precipitate was filtered and washed with absolute ether to obtain 1.36 g (78%) of dihydrochloride XIX; m.p., 79 – 82°C.

The characteristics of compounds V – XI and XVI – XIX are listed in Table 2.

The data of elemental analyses for C, H, N in compounds V – XI and XVI – XIX agreed with the results of calculations according to the proposed formulas.

EXPERIMENTAL BIOLOGICAL PART

The anticholinesterase activity of the synthesized compounds was studied by the method of potentiometric titration. ACE was obtained from human blood erythrocytes. Experiments were performed with a purified water-soluble ACE preparation (acetylcholine acetylhydrogenase, [3.1.1.7] according to the IUPAC enzyme catalog) from human erythrocytes (purchased from the Research Institute of Vaccines and Sera, Perm) with a specific activity of 3.0 AC units/mg. The substrate was an acetylcholine iodide solution with a concentration of 2×10^{-3} M.

A mixture of aqueous solutions of ACE, acetylcholine iodide, buffer (pH 7.0), and inhibitors (at a concentration varied from 10^{-7} to 10^{-2} M) was placed in a controlled-temperature cell. The resulting acetic acid was titrated with 0.02 N sodium hydroxide solution.

The ACE activity was evaluated as pI_{50} (negative logarithm of the inhibitor concentration producing a 50% decrease in enzyme activity).

REFERENCES

1. V. I. Bystrenina, A. D. Shebaldova, A. P. Kriven'ko, et al., *Khim-Farm. Zh.*, **20**(11), 1316 – 1318 (1986).
2. V. I. Bystrenina, A. D. Shebaldova, T. G. Nikolaeva, et al., *Khim-Farm. Zh.*, **17**(2), 45 – 48 (1983).
3. S. N. Golikov and V. I. Rozengart, *Cholinesterases and Anticholinesterase Substances* [in Russian], Moscow (1964), pp. 72 – 76.
4. A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina, *Khim. Geterotsikl. Soedin.*, No. 5, 850 – 856 (1967).
5. A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina, *Khim. Geterotsikl. Soedin.*, No. 6, 787 – 790 (1970).
6. T. G. Nikolaeva and A. P. Kriven'ko, *Dep. VINITI*, No. 3451 – 76 (28.09.76), Moscow (1976); *Ref. Zh. Khim.*, 10Zh205 (1977).