AZACYCLOALKANES

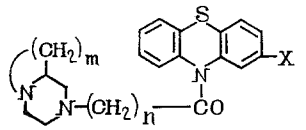
XXI. DEPENDENCE BETWEEN STRUCTURE AND ANTIANGINAL PROPERTIES OF 1,4-DIAZABICYCLO [4,m,0]ALKANYL DERIVATIVES OF 10-ACYLPHENOTHIAZINES

L. S. Nazarova, A. M. Likhosherstov,
G. A. Markova, G. G. Chichkanov,
N. V. Kaverina, and A. P. Skoldinov

UDC 615.224:547869.2]015.11

Over the course of several years we have conducted research on the synthesis of condensed systems of piperazine–1,4-diazabicyclo[4,m,0]alkanes [1,2] and the preparation from them of substances exhibiting various physiological activity. It has been found, for example, that butyrophenone derivatives of such bicyclic amines possess neurotropic properties [3]. It seemed promising to also screen the phenothiazine derivatives of these compounds.

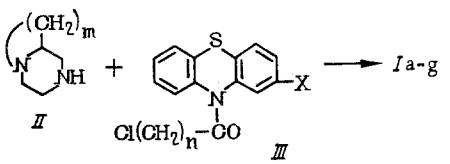
It was found earlier in our institute that going from the 10-dialkylaminoalkyl derivatives of phenothiazine to the corresponding 10-dialkylaminoacyl derivatives led to a change in the spectrum of pharmacological activity of the compounds, namely, to a loss of their neuroleptic properties, to an increase in their cholinolytic and spasmolytic activity, and to the appearance of antianginal* activity (see, e.g., [4]). In this connection we have conducted research on the structure dependence of antianginal properties for the series of 10-[ω-N-(1,4-diazabicyclo[4,m,0]alkanyl)acyl]phenothiazines of the general formula



I

where n = 1,2,3; m = 3,5; X = H, Cl, CF_3.

The phenothiazine derivatives I were synthesized by alkylation of 1,4-diazabicyclo[4,m,0]alkanes (II) with 10-(ω-chloroacyl)phenothiazines (III).



II III

a n = 1, X = Cl, m = 3; e n = 2, X = CF_3, m = 3;
b n = 2, X = Cl, m = 3; f n = 2, X = Cl, m = 5;
c n = 3, X = Cl, m = 3; g n = 2, X = CF_3, m = 5.
d n = 2, X = H, m = 3;

The starting 10-(ω-chloroacyl)phenothiazines III were obtained by acylation of the corresponding 2-subsituted phenothiazines with chloroacetyl chloride, β-chloropropionyl chloride, or γ-chlorobutyryl chloride. Compounds III (n = 1,2) were obtained by previously described methods [5-8]. Compound III (n = 3) was prepared by an analogous method. The amines II were synthesized by a method previously described by us [2].

The reaction was conducted by heating a mixture of II and III components at boiling in dry toluene at molar excess of amine II. The acylation products I were mainly high-boiling oils, giving single spots during

*Antianginal properties indicates the aggregate cardiovascular effects determining the possible effectiveness of the preparation for treating ischemic diseases of the heart (angina pectoris).

Institute of Pharmacology of the Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 6, pp. 84-89, June, 1978. Original article submitted December 29, 1977.

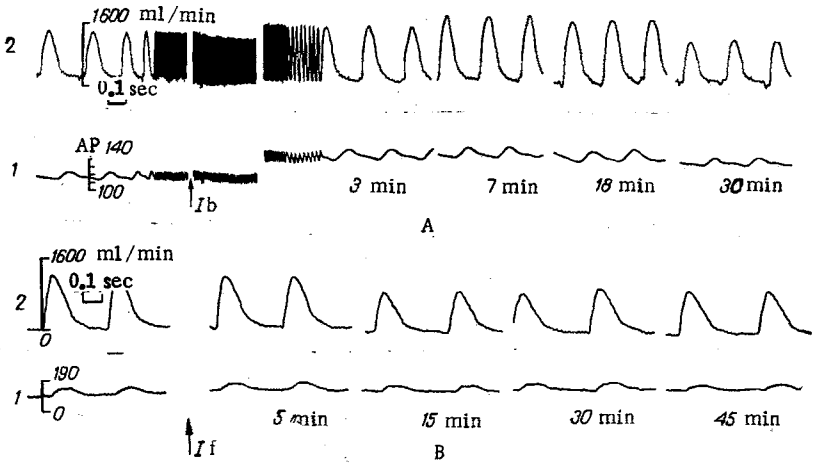


Fig. 1. Influence of the preparations Ib (A) and If (B) on arterial pressure in the femoral artery (1) and phase blood flow in the aorta (2). Dose, 5 mg/kg intravenously. From left to right: background and curves taken after various time periods after administration of the preparation.

thin-layer chromatography on alumina; compound Ia was a crystalline substance. All of the obtained I products were isolated as the dihydrochlorides which were crystalline salts, readily soluble in water and aqueous alcohol. Many of them were hygroscopic and gave up moisture with difficulty on drying. Ib was treated with excess methyl iodide to give the corresponding diquaternary salt IV.

Physical constants, yields, and analytical data for the dihydrochlorides of I compounds are given in Table 1.

The homologous compounds Ia-c were used to investigate the influence of acyl chain length on several hemodynamic parameters. The tests conducted showed that the most active compound was Ib (n = 2), which significantly increased coronary blood flow, led to a simultaneous increase in the contractile function of the myocardium, and did not cause development of tachycardia. Although an increase in the coronary blood flow is observed also on shortening the chain (e.g., Ia), this sharply decreases the duration of the effect. Other indicators such as palpitations, contractile capacity of the myocardium, cardiac output were not changed during the action of this substance Under the influence of the butyryl derivative Ic, all of the mentioned functions were unchanged and the coronary blood flow increased insignificantly in comparison to the initial level. Thus, the optimal effect in the series of compounds studied was developed in the presence of a β-aminopropionyl radical.

Compounds Ib, d, and e containing a 1,4-diazabicyclo[4,3,0]nonanyl radical (m = 3) and a propionyl chain (n = 2) bonding the amine and phenothiazine nuclei, with X = Cl, H, or CF_3, served as examples for studying the influence of the substituent in position 2 of the phenothiazine ring on the antianginal properties. All of the compounds of this group were capable of increasing the cardiac blood supply. The increase in cardiac blood flow for compounds Ib, d, and e can be expressed by the ratio 1 : 0.6 : 0.7. The duration of this effect was the same for Ib and d, but the effect of Ie lasted twice as long.

Finally, the dependence between pharmacological properties and structure of the diazabicyclic fragment of the molecule (variable m) was studied for the compounds Ib, f (n = 2; X = Cl) and Ie (n = 2; X = CF_3). A comparison of the influence of the compounds studied on the cardiac blood supply and hemodynamic parameters showed that compound If (m = 5), while it increases the cardiac blood flow, differs from Ib (m = 3) in that the former causes a decrease in the contractile function of the myocardium (Fig. 1). Analogous compounds with a trifluoromethyl group in position 2 (Ie, g) exhibit similar effects.

Thus the structure of the diazabicyclic portion of the molecules exerts an essential effect on the nature of the pharmacological activity: For example, on going from a 1,4-diazabicyclo[4,3,0]nonane system to a 1,4-diazabicyclo[4,5,0]undecane system, a depressor influence on the myocardium appears.

On studying the diiodomethylate of 10-[β-N-(1,4-diazabicyclo-[4,3,0]nonanyl)propionyl]-2-chlorophenothiazine (IV), prepared from Ib, it was established that the diquaternary salt has no expressed influence on the cardiac blood supply or arterial pressure.

TABLE 1. Dihydrochlorides of 10-Acylphenothiazine Derivatives of 1,4-Diazabicyclo[4,m,0]alkanes

Compound	Yield, %	mp, °C*	Found, %						Molecular formula	Calculated, %					
			C	H	N	S	Cl, total	Cl′		C	H	N	S	Cl, total	Cl′
Ia	62	188—9,5 (decomp.)	—	—	—	—		14,57	$C_{21}H_{22}ClN_3OS \cdot 2HCl$	—	—	—	—	—	14,99
Ib	70	215—6	53,98	5,53	8,54	—	21,80	14,38	$C_{22}H_{24}ClN_3OS \cdot 2HCl$	54,26	5,38	8,63	—	21,85	14,56
Ic	50,4	224—6	54,99	5,59	8,21	—	21,03	13,79	$C_{23}H_{26}ClN_3OS \cdot 2HCl$	55,15	5,63	8,38	—	21,23	14,16
Id	61,5	190—1,5	58,66	6,08	9,01	7,10	15,38	—	$C_{22}H_{25}N_3OS \cdot 2HCl$	58,40	6,02	9,29	7,09	15,67	—
Ie	69,7	222—3	53,50	4,94	8,12	6,23	—	13,38	$C_{23}H_{24}F_3N_3OS \cdot 2HCl$	53,08	5,04	8,07	6,16	—	13,62
If	72,5	206—7,5	55,78	6,22	8,30	6,21	20,59	—	$C_{24}H_{28}ClN_3OS \cdot 2HCl$	55,97	5,99	8,16	6,21	20,65	—
Ig	64	162—4	—	—	7,25	5,68	—	12,45	$C_{25}H_{30}F_3N_3OS \cdot 2HCl \cdot H_2O$	—	—	7,14	5,66	—	12,51

*Compounds 1b-e were crystallized from absolute alcohol, If from alcohol, and Ig from an alcohol–ether mixture.

Based on the pharmacological study conducted, the two most interesting members of the series studied are compounds Ib and Ie.

Results of the investigation show also that in the series of 10-N-substituted phenothiazine derivatives, the pharmacological properties essentially depend on details of the chemical structure. In addition to highly active neuroleptics, antidepressants, and antiarrhythmic preparations, active antianginal compounds were also discovered in this series of compounds.

EXPERIMENTAL

Chemical

10-[α-N-(1,4-Diazabicyclo[4,3,0]nonanyl)acetyl]-2-chlorophenothiazine (Ia). 1,4-Diazabicycle[4,3,0]nonane (0.02 mole) was added to a solution of 0.01 mole chloroacetyl-2-chlorophenothiazine in 40 ml dry toluene and the reaction mixture was refluxed for 6 h. On cooling, the toluene solution was decanted, washed with water, and treated with a 7% solution of HCl to pH 1.0. The aqueous solution was separated, basified with 20% NaOH solution, and extracted with ether. The ether was evaporated and the residue crystallized. Yield 2.97 g (74%), mp 132.5°C. Found, %: C 63.04, H 5.57, N 10.35, Cl 8.90. $C_{21}H_{22}ClN_3OS$. Calculated, %: C 63.05, H 5.55, N 10.51, Cl 8.87.

The dihydrochloride of Ia was prepared by mixing a solution of 2 g of the base in absolute alcohol and an ether solution of HCl (see Table 1).

Dihydrochloride of 10-[β-N-(1,4-Diazabicyclo[4,3,0]nonanyl)propionyl]-2-trifluoromethylphenothiazine (Ie) (typical preparation). A solution of 0.02 mole 10-(β-chloropropionyl)-2-trifluoromethylphenothiazine in 40 ml dry toluene was mixed with a solution of 0.04 mole of amine II in 30 ml dry toluene and refluxed for 3 h. At the end of heating, the reaction mixture was cooled and the toluene solution decanted, washed with water, and treated with 7% HCl solution to pH 1.0. The water-acid solution was heated at 60-70°C for 10-15 min in the presence of activated carbon, filtered, basified with 20% NaOH solution, and I was extracted with ether. An ether solution of HCl was added to the ether solution of I and the precipitating salt was filtered off, washed with absolute ether, dried, and crystallized (see Table 1).

The dihydrochlorides of Ib, d, f, and g were obtained analogously.

Diiodomethylate of 10-[β-N-(1,4-Diazabicyclo[4,3,0]nonanyl)propionyl]-2-chlorophenothiazine. A mixture of methanolic solutions of 0.02 mole IIb and 0.03 mole methyl iodide was refluxed for 12 h, the methanol removed, and the residue crystallized from a 1:4 isopropanol-ethanol mixture to give the product with mp 146-148°C. Yield 46%. Found, %: I 36.52. $C_{24}H_{30}Cl_2N_3OS$. Calculated, %: I 36.38.

10-(γ-Chlorobutyryl)-2-chlorophenothiazine. γ-Chlorobutyric acid hydrochloride (5.08 g, 0.036 mole) was added dropwise to a solution of 7.02 g (0.03 mole) 2-chlorophenothiazine in 50 ml dry toluene. The reaction mixture was refluxed for 2 h and evaporated to dryness. The crystallized residue was dissolved in 35 ml absolute isopropanol, heated for 30 min with 1 g activated carbon, and filtered. On cooling, a crystalline substance precipitated out, with mp 110-111°C. Yield 8.38 g (82.5%). Found, %: 56.90, H 3.71, Cl 20.70, S 9.37. $C_{16}H_{13}Cl_2NOS$. Calculated, %: C 56.82, H 3.87, Cl 20.96, S 9.48.

10-(γ-N-(1,4-Diazabicyclo[4,3,0]nonanyl)butyryl]-2-chlorophenothiazine (Ic). 1,4-Diazabicyclo[4,3,0] nonane (0.04 mole) solution in 20 ml dry toluene was added dropwise to a solution of 0.02 mole 10-(γ-chlorobutyryl)-2-chlorophenothiazine in 50 ml dry toluene, the mixture heated under stirring for 15 h, the toluene solution decanted, and the residue washed with 10 ml dry toluene. The combined toluene solutions were washed with water, treated with 7% HCl solution to pH 1.0 and the aqueous solution heated with activated carbon, filtered, and basified with 40% NaOH solution. The product was extracted with ether. The dihydrochloride was obtained by the usual method (see Table 1).

Pharmacological

A complex of procedures were used to ascertain the antianginal properties of the compounds. Tests were conducted on cats of weight 3-4 kg, narcotized with urethane (600 mg/kg) and chloralose (40 mg/kg). The volume rate of cardiac blood flow was determined by withdrawing blood from the coronary sinus of the heart using a pump deliverer [9]. To study the influence of the series of compounds studied on the activity of the heart and on hemodynamic parameters, an electromagnetic method was used for measuring the blood flow in the ascending part of the aortic arch with the aid of a domestic blood-flow measuring device RKE-1. In conducting a phase analysis of the blood in the aorta, the following parameters of heart activity and hemodynamics were registered: arterial pressure, pulse rate, and cardiac output.

The contractile function of the heart of mice was ascertained from the change in the maximum acceleration of blood flow in the aorta. The preparations were administered intraveneously in doses of 5 mg/kg.

LITERATURE CITED

1. A. M. Likhosherstov, L. S. Nazarova, and A. P. Skoldinov, Zh. Org. Khim., 6, 1729-1734 (1970).
2. L. S. Nazarova, A. M. Likhosherstov, K. S. Raevskii, et al., Khim. Farm. Zh., No. 1, 88-92 (1976).
3. L. S. Nazarova, A. M. Likhosherstov, K. S. Raevskii, et al., Khim. Farm. Zh., No. 4, 49-55 (1976).
4. Yu. I. Vikhlyaev, in: New Data on the Pharmacology and Clinical Picture of Phenothiazine Derivatives [in Russian], Moscow (1958), pp. 27-46.
5. R. Dahlbom and T. Ekstrand, Acta Chem. Scand., 5, 102 (1951).
6. S. V. Zhuravler and A. N. Gritsenko, Zh. Obsch. Khim., 26, 3386-3388 (1956).
7. A. N. Gritsenko and S. V. Zhuravlev, Zh. Obsch. Khim., 30, 2642-2644 (1960).
8. A. N. Gritsenko, Z. I. Ermakova, S. V. Zhuravlev, et al., Khim. Farm. Zh., No. 6, 18 (1971).
9. N. V. Kaverina, Farmakol. Toksikol., No. 1, 39-43 (1958).

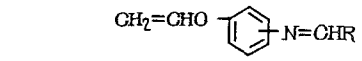
ANTIMICROBIAL ACTIVITY OF VINYLOXYPHENYL-AZOMETHINES

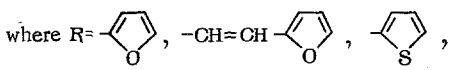
G. N. Pershin, S. N. Milovanova, O. O. Makeeva, B. I. Vishnevskii, L. N. Ertevtsian, G. G. Skvortsova, and Z. M. Garashchenko

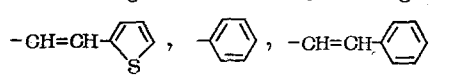
UDC 615.281: 547.37'564.4

Nitrogen-containing aromatic compounds have served as the basis for synthesizing a series of important drug preparations which exhibit for example, analgesic, antibacterial, sedative, antipyretic, and anti-inflammatory activity. It is also known that the C = N group can impart valuable biological properties to a compound [1-3]. The interest in azomethine compounds has grown even more since the discovery that this class of substances and the intracomplexes formed by them play an important role in various biochemical and chemical processes [4-6].

The aim of the present study is to establish the biological activity of N-substituted vinyloxyanilines of the general type







with respect to the structure of the substituent on the azomethine group.

The following compounds were studied: furfurylidene-p-vinyl-oxyaniline (I), β-(2-furyl)acrylidine-o-, -m-, -p-(vinyloxy or ethoxy)anilines (II-V), thienylidene-m-, p-(vinyloxy)anilines (VI, VII), β-(2-thienyl) acrylidene-p-(vinyloxy or ethoxy)anilines (VIII, IX), benzylidene-p-(vinyloxy or ethoxy)anilines (X, XI), and N-cinnamylidene-p-(vinyloxy or ethoxy)anilines (XII, XIII). Their synthesis and structure elucidation, with the exception of compound X, has been described previously [7-10]. Testing for antimicrobial activity of the synthesized azomethines was conducted in the Chemotherapy Division of the All-Union Pharmaceutical Chemistry Research Institute (VNIKhFI) and in the divisions of laboratory Diagnostics and Experimental Therapy and Pathomorphology of the Leningrad Research Institute for Tuberculosis (LNIIT). The results of the study show that the investigated compounds have weak fungistatic activity and high tuberculostatic activity. They are of interest for study during experimental tuberculosis of laboratory animals.

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific-Research Institute, Moscow. Leningrad Scientific-Research Institute for Tuberculosis of the Ministry of Health of the RSFSR. Irkutsk Institute of Organic Chemistry of the Siberian Branch of the Academy of Sciences of the USSR.

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 6, pp. 89-92, June, 1978. Original article submitted December 7, 1977.