SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SOME LACTAMS OF AMINOTHIENYLALKANE ACIDS AND OXIMES OF CYCLIC KETONES WHICH INCLUDE THE THIOPHENE RING

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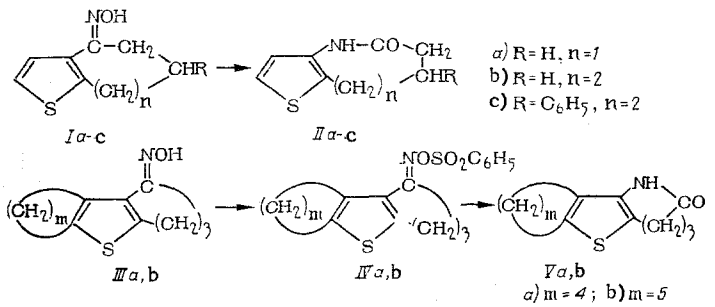
During recent years communications appeared on the presence of psychotropic activity in compounds with bi- and tricyclic structures containing one or two heteroatoms and having lactam and oxime groups. The most well known substances of such a type are the following: derivatives of dibenzodiazepine [1, 2], morphanthridine [3], substituted 5,6-dihydro-6-oxopyridobenzoxazepines [4], derivatives of aryldialkylaminoalkylbenzolactams [5], and benzothiazinelactams [6]; these possess antidepressive, anticonvulsive, antitremor, and psychosedative action. Some of the representatives of these classes, such as Noveril (dibenzodiazepine derivative) and Altinil (benzothiazepine derivative), have been used in medical practice as antidepressive agents.

The presence of activity in heterocyclic compounds including a lactam or an oxime group was used as a basis to carry out the present investigation on the synthesis and study of the pharmacological activity in the series of bi- and tricyclic lactams of aminothienylalkane acids and oximes of cyclic ketones, which include the thiophene ring.

An experimental study of the biological activity was carried out in the series of oximes of thienocycloalkanes of structure I and III, and lactams of structures II and V were derived from them by Beckmann rearrangement.



Earlier the synthesis of compounds Ia, Ib and IIa [7], IIb [8], and IIIa [9] were reported. Oximation of the corresponding ketones yielded new oximes Ic and IIIb. The Beckmann rearrangement of oxime Ic to lactam IIc was realized by the action of benzenesulfonyl chloride on the oxime solution in pyridine. Under these conditions, oximes III do not undergo rearrangement but do form benzenesulfonates of structure IV, which are converted to lactams V, under conditions given in [7], during prolonged boiling with sodium acetate solution in diluted alcohol. A proof of the structure of the resulting lactams containing the NH group, associated with the thiophene ring, was described earlier [7].

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TABLE 1. Comparative Activity in the Series of Lactams of Aminothienylalkane Acids and Oximes of Cyclic Ketones Which Include a Thiophene Ring

Compound	Potentiation of hexenal-induced sleep	Disturbance of oriented reactions	Disturbance of the coordination of movements
Ia	145 (121–167)	380 (237–607)	160 (143–179)
Ib	135 (96,4–189)	260 (162–416)	160 (123–200)
Ic	76 (21,1–273,6)	>800	>800
IIa	57 (45,6–71,4)	31 (24–39,9)	47 (43,27–51,0)
IIb	42 (34,7–50,82)	28.5 (24,6–33,1)	14 (10,8–21)
IIc	58 (50,2–67)	120 (98,3–142)	145 (85.3–230)
IIIa	66 (47,5–89,6)	>800	>800
IIIb	22 (19,3–25,6)	>800	600 (348.8–1032)
Va	20,5 (12,9–32,4)	185 (177–193,5)	151 (122,5–185,5)
Vb	25 (15,1–51,2)	350 (175–700)	260 (162–450)

Note. Numerals designate ED_{50} (in mg/kg) and reliability intervals at P = 0.05.

The pharmacological activity of these compounds was studied on mice of 18-20 g weight. The substances were introduced intraperitoneally. The study was carried out by the procedure usually used for the study of substances with psychotropic action [10]. Tests were made with hypodermic injection of Korazole [11], with maximum electroshock [12] to reveal the anticonvulsive activity, with the procedure which potentiates Hexenal-induced sleep, with the "climbing up a screen" method in order to study hypnosedative properties, and with the rotating rod to reveal the myorelaxant effect. Apart from this, the compounds varied the phenamine effects [13] and the tremor action of Arecoline, and caused catalepsy or eliminated the cataleptic action of triphthazine. The toxicity was determined during 24 h at constant temperature. The compounds were introduced intraperitoneally in a starch suspension. The result were treated statistically, and 50% effective doses (ED_{50}) were calculated by the method of [14].

The resulting data suggest that the spectrum of pharmacological activity of the compounds described in this study is characterized by a combination of moderately expressed sedative and myorelaxant action. All of them reveal the maximum activity of potentiation of Hexenal-induced sleep. For the most active compounds, the effective doses causing sleep in 50% of the animals were 20-25 mg/kg, under the myorelaxant action of ED_{50} = 30-35 mg/kg. The substances under study showed no anticonvulsive activity and no ability to eliminate Arecoline tremors. Also no ability was noted in lactams and oximes to eliminate or potentiate Phenomine stereotypy and also to cause catalepsy or eliminate the "cateleptogenic" action of Triphthazine. The toxicity of the derivatives under study is moderate and is within the range of 300-8000 mg/kg.

During the study of the relationship between the chemical structure and the pharmacological activity in the series of lactams of aminothienylalkane acids and oximes of cyclic ketones which include the thiophene ring, it was established that lactams possess high activity as compared with that of oximes (Table 1). At the same time a number of relationships can be pointed out in the manifestation of activity that depend on the characteristics of the chemical structure, both in the series of lactams and in the series of oximes. Of decisive significance for the activity in both series is, first of all, the transition from bicyclic to tricyclic structures, and also the size of the cycle containing the lactam or oxime group. The transition from bicyclic lactams and oximes (Ia, IIa) to tricyclic (IIIa, Va) is accompanied by a considerable decrease in the activity of compounds (3-6 fold) according to their ability to depress the oriented reaction and also according to their ability to disturb the coordination of movements (see Table 1). At the same time, the same changes in the structure of the substances involve some intensification in the activity on the potentiation of Hexenal-induced sleep. An increase in the supplementary carbocycle of tricyclic compounds by an additional methylene group (IIIb and Vb) also leads to a decrease in the oriented activity and myorelaxant properties. However, the activity of lactams with respect to the potentiation of Hexenal-induced sleep shows no marked variation, while the activity of oximes in this kind of action is even somewhat increased (see Table 1). Somewhat other relationships were noted in the variation in the activity in bicyclic structures containing oximes (1a-c) and lactam (Va-c) groups. As a result of expanding the ring containing these groups, the activity with respect to the disturbance of oriented reactions and the coordination of movements increases. The addition of a supplementary phenyl radical to the carbohydrate in position 7 of the lactam and in position 6 of the oxime leads to a considerable decrease in the activity of these kinds of action (see Table 1). The effectiveness of the compounds under study on the potentiation of Hexenal-induced sleep is essentially unchanged, either with the increase of the number of carbohydrate atoms in the ring or with the introduction of a phenyl radical.

Thus, the lactams of aminothienylalkane acids and oximes of cyclic ketones that include the thiophene ring, according to the spectrum of its pharmacological activity, can be relatd to substances with a moderate, overall irreconcilable, type of action. The resulting data indicate that the activity of the compounds under study mainly depends on the size of the ring containing the lactam or the oxime grouping, and on the addition of a supplementary carbocycle to the bicyclic compounds.

TABLE 2. Intermediate Substances in the Synthesis of Oximes Ic and IIIb

Compound	Yield,* %	Boiling point (degrees)	Melting point (degrees)†	Found, %			Empirical formula	Calculated, %		
				C	H	S		C	H	S
VI	84	195—8 (~2 mm)	82—4	66,90 67,04	5,77 5,56	11,16 10,93	$C_{16}H_{16}O_3S$	66,64	5,59	11,12
VII	90	—	112—3	68,80 68,75	6,41 6,57	12,01 12,12	$C_{15}H_{16}O_2S$	69,20	6,19	12,32
VIII	81	179—180 (~ 2 mm)		64,75 64,51	5,27 5,28	—	$C_{15}H_{15}ClOS$	64,62	5,42	—
IX	57	180—3 (~2 mm)	8—50	74,85 74,73	5,94 5,88	13,15 13,09	$C_{15}H_{14}OS$	74,35	5,82	13,23
X	90	—	72—3	65,45 65,20	7,67 7,72	—	$C_{13}H_{18}O_2S$	65,51	7,61	—
XI	74	157—9 (~2 mm)	55—6	70,74 70,76	7,32 7,29	—	$C_{13}H_{16}OS$	70,87	7,32	—

*The given yields are of purified substances.
† Compounds VI and VII are recrystallized from a mixture of toluene with heptane; IX, from heptane; X and XI, from hexane.

TABLE 3. Oximes, Benzenesulfonates of Oximes, and Lactams

Compound	Yield,* %	Melting point (degrees)†	Found, %				Empirical formula	Calculated, %			
			C	H	N	S		C	H	N	S
Ic	89	161—2	70,07 70,38	5,66 5,87	— —	12,32 12,21	$C_{15}H_{15}NOS$	70,00	5,88	—	12,46
IIIb	91	132—3	—	—	5,93 6,14	— —	$C_{13}H_{17}NOS$	—	—	5,95	—
IIc	67	171—2	70,19 70,29	5,89 5,88	— —	12,49 12,44	$C_{15}H_{15}NOS$	70,00	5,88	—	12,46
IVa	72	160—1	— —	— —	3,89 3,91	— —	$C_{18}H_{19}NO_3S_2$	—	—	3,88	—
IVb	73	143—4	60,74 60,68	5,46 5,58	— —	— —	$C_{19}H_{21}NO_3S_2$	60,77	5,64	—	—
Va	68	199—200	64,94 64,95	6,91 7,11	—	—	$C_{12}H_{15}NOS$	65,12	6,83	—	—
Vb	72	195—7	66,19 65,98	7,35 7,30	—	13,62 13,42	$C_{13}H_{17}NOS$	66,34	7,28	—	13,62

*The given yields are of purified substances.
† Compounds Ic, IIIb, Va, and Vb were recrystallized from diluted alcohol; IIc, from undiluted alcohol; IVa, from a mixture of ethyl acetate with heptane; IVb, from a mixture of ethyl acetate with hexane.

EXPERIMENTAL

6-Phenyl-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-4-onoxime (Ic). The synthesis was carried out by the method used to prepare similar compounds [7]. The methyl ester of 3-phenyl-4-(2-thienoyl)butyric aicd (VI) was obtained by acylating thiophene with the acid chloride of the monomethyl ester of β-phenylglutaric acid (bp 143-144° at ~ 2 mm) (prepared by boiling the monomethyl ester of β-phenylglutaric acid [15] with thionyl chloride for 2 h). This acid was reduced to 3-phenyl-5-(2-thienyl) pentanoic acid (VII). Cyclization of the acid chloride of this acid (VIII) in the presence of stannic chloride yielded 6-phenyl-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-4-one (IX). The constants of these compounds are given in Table 2.

Oximation of IX was carried out by the following method.* A mixture of 10 g of ketone, 7.2 g hydroxylamine hydrochloride, 8.3 g of sodium carbonate, 95 ml of water, and 165 ml of alcohol was boiled for

*Here and below, detailed conditions are given for the oximation of ketones, since a variation in these conditions yields products with different melting points associated with the variation in the syn- and anti-forms of the oximes.

7 h. Water was added to a hot solution until crystallization begins; the solution was cooled with ice. Compound Ic (9.5 g) was filtered off. The constants of the compounds, which were purified by recrystallization from diluted alcohol, are given in Table 3.

1,2,3,4,6,7,8,9-Octahydrodibenzothiophen-1-onoxime (IIIa). This compound was obtained by boiling for 3 h a mixture of 16.4 g of the corresponding ketone, 11 g of hydroxylamine hydrochloride, 32.6 g of crystalline sodium acetate, 190 ml of alcohol, and 125 ml of water. The yield of oxime recrystallized from diluted alcohol was 76% (mp 165-165.5°; according to literature data [9], mp 161°).

1,2,3,4,7,8,9,10-Octahydro-6H-benzo[b]cyclohepta[d]thiophen-1-onoxime (IIIb). This compound was obtained by a number of stages developed earlier for the synthesis of related compounds [5]: methyl ester of γ-oxo-γ-(5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2)butyric acid[16] was reduced by the Kizhner method to γ-(5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-2)butyric acid (X, see Table 2), which was heated with acetic anhydride in the presence of phosphoric acid to yield 1,2,3,4,7,8,9,10-octahydro-6H-benzo[b]-cyclohepta[d]thiophen-1-one (XI, see Table 2). Oximation was realized by boiling a mixture of 31.5 g of XI, 32.8 g of hydroxylamine hydrochloride, 39.6 g of potassium hydroxide, 145 ml of water, and 250 ml of alcohol for seven hours. Constants of IIIb and also of compounds mentioned below are given in Table 3.

Benzenesulfonate of 1,2,3,4,7,8,9,10-Octahydro-6H-benzo[b]cyclohepta[d]-thiophen-1-onoxime, (IVb). To a solution of 16 g of IIIb in 100 ml pyridine (purified by boiling with lithium hydride and distillation in the presence of benzenesulfonyl chloride) was added in one step a solution of 8.2 ml of benzenesulfonyl chloride in 25 ml of pyridine. On the following day the mixture was poured in 600 ml of 4 N hydrochloric acid solution saturated with sodium chloride; concentrated hydrochloric acid was then added until an acid reaction was shown with Congo, and the product was cooled by ice. The precipitate was filtered off, triturated in a mortar with diluted hydrochloric acid, and repeatedly washed with water. Yield, 21.6 g of IVb, recrystallized from a mixture of ethyl acetate with hexane.

Benzenesulfonate of 1,2,3,4,6,7,8,9 -octahydrodibenzothiophen- 1-onoxime (IVa) was prepared in an analogous manner.

The action of benzenesulfonyl chloride on oxime Ic under the given conditions caused at once the Beckmann rearrangement of this oxime, and lactam IIc was isolated from the reaction mixture.

1,3,4,5,7,8,9,10-Octahydro-2H-benzothieno (3,2-b) azepine-2-one (Va). A mixture of 12.2 g triturated into a powder, 84 g of sodium acetate, 400 ml of water, and 250 ml of alcohol was boiled for about 30 h. After conditioning in a refrigerator for 24 h, the precipitate was filtered off and recrystallized from diluted alcohol. Yield of Va, 5.1 g.

Compound Vb was obtained in a similar manner.

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