SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SUBSTITUTED 2-AMINOMETHYL-4H-[1]-BENZOTHIOPYRANO[3,4-d]-IMIDAZOL-4-ONES

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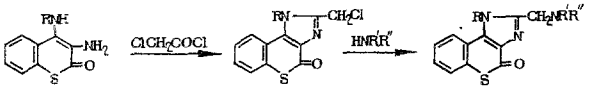
Because of the interest generated by condensed heterocyclic systems containing an imidazole ring as pharmacologically active compounds, we synthesized the previously unknown 2-aminomethyl-4H-[1]benzothiopyrano[3,4-d]imidazol-4-ones (Ia-m) in order to study their pharmacological activity.

As starting compounds we used 4-(N-R-amine)-3-aminothiocoumarins (IIa-e), which were synthesized by the previously described route [1]. Reaction of diamines II with chloroacetyl chloride gave 1-R-2-chloromethyl-4H-[1]benzothiopyrano[3,4-d]imidazol-4-ones (IIIa-e), which were transformed into compounds Ia-m by the action of the corresponding amines



IIa-e IIIa-e Ia-m

IIa-e, IIIa-e: a: R=H, b: R=CH_3, c: R-n-C_4H_9, d: R=$CH_2C_6H_5$, e: R=C_6H_5; Ia-m: a: R=H, R'+R''=$(CH_2)_5$; b: R=CH_3, R'+R''=$(CH_2)_5$; c: R=n-C_4H_9, R'+R''=$(CH_2)_5$; d: R=$CH_2C_6H_5$, R'+R''=$(CH_2)_5$; e: R=C_6H_5, R'+R''=$(CH_2)_5$; f: R=H, R'+R''=$CH_2CH_2OCH_2CH_2$; g: R=n-C_4H_9, R'+R''=$CH_2CH_2OCH_2CH_2$; h: R=$CH_2C_6H_5$, R'+R''=$CH_2CH_2OCH_2CH_2$; i: R=C_6H_5, R'+R''=$CH_2CH_2OCH_2CH_2$; j: R=n-C_4H_9, R'+R''=$CH_2CH_2N(CH_3)CH_2CH_2$; k: R=C_6H_5, R'+R''=$CH_2CH_2N(CH_3)CH_2CH_2$; l: R=n-C_4H_9, R'+R''=$CH_2CH_2N(C_6H_5)CH_2CH_2$; m: R=$C_6H_5$, R'+R''=$CH_2CH_2N(C_6H_5)CH_2CH_2$.

The structure of the compounds synthesized was confirmed by IR and mass spectroscopy data. As in the case of the more simple substituted 4H-[1]benzothiopyrano[3,4-d]imidazol-4-one derivatives [2], in the IR spectra of compounds Ia-m and IIIa-e, intense dependent vibrations of the carbonyl group are observed in the 1655-1615 cm^{-1} region, the stretching vibrations of the NH group in the spectra of compounds Ia, f and IIIa appear at 3140 cm^{-1} in the form of a broad band. In the mass spectra of compounds Ia-m and IIIa-e, low intensity peaks of molecular ions are recorded. The main direction of the fragmentation is determined by successive splitting of a substituent at the methylene group in the 2-position, and then of carbonyl.

EXPERIMENTAL (CHEMICAL)

The melting points of the compounds were determined on a microheater "Boetius" block. The IR spectra were run on the "Perkin-Elmer-580" spectrophotometer; the mass spectra were measured on a "Varian-MAT-11" apparatus with a system of direct introduction of the sample to the ion source, at a temperature of 100-120°C and an ionizing voltage of 70 eV. The course of the reaction and the purity of the compounds were controlled by TLC on Alufolien 60 F 254 plates, using chloroform as a solvent.

1-R-2-Chloromethyl-4H-[1]benzothiopyrano[3,4-d]imidazol-4-ones (IIIa-e). A suspension of 0.01 mole of diamines IIa-e in 20 ml of chloroacetyl chloride is boiled for 2 h and then cooled and diluted with a large amount of ether. The precipitate that separates is filtered, washed with ether, a sodium bicarbonate solution, and water, and then dried. Compounds IIIa-e are obtained, whose properties are listed in Table 1.

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TABLE 1. 1-R-2-Chloromethyl-4H-[1]benzothiopyrano[3,4-d]-imidazol-4-ones IIIa-e

Compound	Yield, %	Mp, °C [a]	R_f [b]	Found, %			Empirical formula	Calculated, %			M^+
				Cl	N	S		Cl	N	S	
IIIa	84	245—7 [c]	0	14,43	11,44	12,53	$C_{11}H_7ClN_2OS$	14,15	11,18	12,78	251
IIIb	61	210—2	0,21	13,24	10,65	12,01	$C_{12}H_9ClN_2OS$	13,40	10,59	12,12	265
IIIc	63	166—8	0,29	11,81	8,95	10,41	$C_{15}H_{15}ClN_2OS$	11,55	9,14	10,45	307
IIId	79	202—4	0,65	10,18	7,89	9,29	$C_{18}H_{13}ClN_2OS$	10,40	8,22	9,41	327
IIIe	91	245—7	0,60	10,66	8,49	9,79	$C_{17}H_{11}ClN_2OS$	10,85	8,57	9,81	341

a) Compound IIIa was recrystallized from a benzene–alcohol (8 : 2) mixture, IIIb, from 50% alcohol, IIIf from benzene, IIId, e from a benzene–heptane (5 : 1) mixture.
b) Alufol, eluent chloroform.
c) Solidifies at 252°C and melts again at 334-336°C.

TABLE 2. 1-R-2-(N-R'-N-R"-Aminomethyl)-4H-[1]benzothiopyrane[3,4-d]imidazol-4-ones Ia-m

Compound	Yield, %	Mp, °C [a]	R_f [b]	Found, %		Empirical formula	Calculated, %		M^+
				N	S		N	S	
Ia	89	180—2	0,28	14,06	10,64	$C_{16}H_{17}N_3OS$	14,03	10,70	299
Ib	81	162—4	0,26	13,45	10,21	$C_{17}H_{19}N_3OS$	13,41	10,23	313
Ic	93	184—6	0,49	11,81	9,05	$C_{20}H_{25}N_3OS$	11,82	9,02	355
Id	90	242—4	0,68	10,72	8,34	$C_{23}H_{23}N_3OS$	10,78	8,23	389
Ie	93	223—5	0,44	10,97	8,62	$C_{22}H_{21}N_3OS$	11,19	8,54	375
If	86	239—41	0,60	14,04	10,46	$C_{15}H_{15}N_3O_2S$	13,94	10,64	301
Ig	88	202—4	0,48	11,64	9,21	$C_{19}H_{23}N_3O_2S$	11,76	8,97	357
Ih	92	255—7	0,24	10,59	8,49	$C_{22}H_{21}N_3O_2S$	10,74	8,19	391
Ii	94	243—5	0,18	11,11	8,49	$C_{21}H_{19}N_3O_2S$	11,14	8,49	377
Ij	87	166—8	0,23	14,85	8,87	$C_{20}H_{26}N_4OS$	15,12	8,65	370
Ik	83	178—80	0,10	14,33	8,25	$C_{22}H_{22}N_4OS$	14,35	8,21	390
Il	86	129—31	0,42	12,97	7,39	$C_{25}H_{28}N_4OS$	12,95	7,41	432
Im	88	196—8	0,25	12,42	7,06	$C_{27}H_{24}N_4OS$	12,38	7,08	452

a) Compound Ia recrystallized from a benzene–hexane (8:2) mixture, Ib, f, j, *l*, from a benzene–hexane (1 : 1) mixture, Ic, e, g from alcohol, Ih, i, k, m from benzene.
b) Alufol, eluent chloroform.

1-R-2-(N-R'-N-R"-aminomethyl)-4H-[1]benzothiopyrano[3,4-d]imidazol-4-ones (Ia-m). To a suspension of 5 mmoles of compounds IIIa-e in 100 ml of absolute benzene, 11 mmoles of the corresponding amine are added. The mixture is boiled for 7-8 h, and after cooling, the precipitate is filtered and washed with benzene. The combined solution is washed with water and evaporated. Compounds Ia-m are obtained (in the case of compound Ie, and additional amount of product is isolated from the first precipitate by washing with water), whose properties are listed in Table 2.

EXPERIMENTAL (PHARMACOLOGICAL)

The general activity, the acute toxicity (the LD_{50} was determined), and the effect on the CNS of compounds Ia-m and IIIa-e were studied. The experiments were carried out on white mice, weighing 20-22 g each. Doses of a compound, corresponding to 1/10 LD_{50} were used.

The action on CNS was evaluated by the following tests: 1) effect on the movement coordination and muscle tonus were studied by the "rotating rod" test (frequency of rotation 8 rpm for 2 min); 2) effect on spontaneous movement activity (SDA) were studied on the "Animex" apparatus (from the firm LKB, Sweden); 3) effect of phenamine hyperactivity (PHA) – antagonism to phenamine (10 mg/kg intraperitoneally) – was studied on the "Animex" apparatus (from the firm LKB, Sweden); 4) effect on duration of the action of narcotic compounds was determined from the moment of the loss of the turning over reflex up to its restoration. To determine the prolongation of the action of narcotic compounds, thiopental sodium was introduced intravenously in a dose of 30 mg/kg; in the study of the potentiation of a subthreshold dose, thiopental sodium was introduced in a dose of 12.5 mg/kg; 5) antispasmodic action was studied by two tests: maximal electroshock (alternate current with a

strength of 50 mA, frequency 50 pulses/sec at an irritation duration of 0.2 sec) and the reaction with Corazol (subcutaneous administration in a dosage of 120 mg/kg); 6) analgesic action was determined by the Hafler method.

RESULTS AND DISCUSSION

It was found that compounds Ia-m and IIIa-e have neurotropic activity and are relatively slightly toxic. The LD_{50} with intraperitoneal administration was 500-1000 mg/kg for most of the compounds with the exception of compounds Ia, b, j, k and IIIa, b, whose LD_{50} is from 100 to 300 mg/kg.

In the series of compounds Ia-m, a certain dependence of the neurotropic action on the nature of the radicals attached to the nitrogen atom and to the methylene group has been established. The highest neurotronic activity was revealed in compounds containing a piperidine residue. Compound Ia decreases the SDA by a factor of 2-6, and the action of phenamine by a factor of 1.4-1.6. Replacement of hydrogen at the nitrogen atom by alkyl groups leads to increase in activity. Compound Ib decreases the SDA by a factor of 6-20 (depending on the time after introduction), decreases the PHA by a factor of 1.5-2, and prolongs the action of thiopental sodium by a factor of 1.6. Compound Ic was found to be the most active: it decreases the SDA by a factor of 30-40, decreases the PHA by a factor of 3-4, and prolongs thiopental-induced sleep in mice by a factor of 3-4; in 20% of mice a potentiation of the action of thiopental-sodium was observed. At the same time, this compound is less toxic (LD_{50} 1000 mg/kg), compared with compounds Ia and Ib (LD_{50} 100 and 220 mg/kg, respectively). Compound Id also has a depressant effect on CNS, decreasing the SDA and PHA by a factor of 1.3-1.5, and prolonging the action of thiopental-sodium twofold. In compound Ie, a two-phase action on the CNS is displayed: it increases the SDA by a factor of 1.7-2.4, but decreases the PHA by a factor of 1.6-1.8, and inappreciably increases (by a factor of 1.2) the duration of thiopental-induced sleep in mice.

Replacement of the piperidine residue by the morpholine or piperadine residues leads in general to a decrease in the depressant effect on the CNS. Compounds If-i decrease the SDA and PHA by a factor of 1.2-6 and 1.3-4, respectively, and they also prolong the action of thiopental-sodium. It is noteworthy that in this series of compounds compound Ig was found to be most active: it prolongs the action of thiopental-sodium by 18-23 times. At the same time, the action on the SDA (decrease by a factor of 3-6) and PHA (decrease by a factor of 2-4) models was most pronounced in compound If, which, however, only slightly prolongs the duration of the thiopental-induced sleep in mice.

In the series of compounds Ij-m, the most active is compound Il: It decreases the SDA and PHA by factors of 3-8 and 1.2-1.4, respectively, and prolongs the action of thiopental-sodium threefold.

For compounds IIIa-e, a pronounced effect on the duration of thiopental-sodium induced narcosis is most characteristic: They prolong sleep by 1.4, 1.8, 6.5, 8, and 3.4 times, respectively. It should be noted that on the SDA and PHA models these compounds exhibit differently directed effects. Thus, compounds IIIc and IIId which are most active in sleep prolongation, decrease the SDA by a factor of 2-6 and increase the PHA by a factor of 1.3-1.5.

All the compounds studied (in doses of 1/10 LD_{50}) do not exhibit muscle-relaxing, cataleptic, antispasmodic, and analgetic action.

Thus, the preliminary study of the pharmacological activity of the 4H-[1]benzothiopyrano[3,4-d]imidazol-4-one derivatives showed that they possess definite neurotropic activity, mainly of the depressant type, which encourages a search for more effective neutropic compounds in this series by a particular modification of the structure, i.e., selection of substituents at the nitrogen atom and the methylene group in the imidazole ring.

LITERATURE CITED

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