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SYNTHESIS AND BIOLOGICAL PROPERTIES OF DERIVATIVES OF 4-HETERYLMERCAPTOQUINAZOLINE

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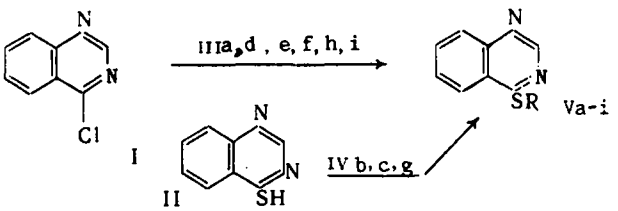
There is great interest in derivatives of quinazoline, among which are compounds having hypotensive, sedative, soporific, anticonvulsive, and antiinflammatory activities [2, 5, 7] and which have a broad spectrum of chemotherapeutic properties [3, 7]. All this attests to the obvious interest in the synthesis and investigation of the pharmacological properties of new quinazoline derivatives, for example those in the structure of which are introduced other heterocyclic radicals that are linked with the quinazoline nucleus through a sulfur atom in the 4-position.

For this purpose we reacted 4-chloroquinazoline (I) with 2-mercaptoquinoline (IIIa), 2-methoxy-9-mercaptoacridine (IIId), 2-ethoxy-9-mercaptoacridine (IIIe), 2-chloro-9-mercaptoacridine (IIIf), 2-methoxy-6-nitro-9-mercaptoacridine (IIIh), and 4-methoxy-6-nitro-9-mercaptoacridine (IIIi), or we reacted 4-mercaptoquinazoline (II) with 4-methoxy-9-chloroacridine (IVg), 5-nitro-8-chloroquinoline (IVb), and 2,6-dichloro-7-methylpurine (IVc) to obtain 4-heteryl-mercaptoquinazolines (Va-i, Table 1).



Va: R = quinolyl-2; Vb: R = 5-nitroquinolyl-8; Vc: R = 2-chloro-7-methylpurinyl-6; Vd: R = 2-methoxyacridinyl-0; Ve: R = 2-ethoxyacridinyl-9; Vf: R = 2-chloroacridnyl0; Vg: R = 4-methoxyacridinyl-9; Vh: R = 2-methoxy-6-nitroacridinyl-9; Vi: R = 4-methoxy-6-nitroacridinyl-9.

The synthesized compounds Va-i were isolated as the free bases and are yellow (Va, c, f), yellowish green (Ve), orange (Vb, g), red (Vd), or red-brown (Vh, i) crystalline compounds, insoluble in water and soluble in organic solvents. The infrared spectra of these compounds show vibration bands that are characteristic for the C—S—C bond in the region 770-750 cm^{-1}, for the C—N bond in the region 1610-1590 cm^{-1}, and for the C—O—C bond in the region 1110-1100 cm^{-1} (Vd-i). In the region 3430-3000 cm^{-1} some absorption bands related to stretching vibrations of the N—H bond (Vc) are present.

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TABLE 1. 4-Heterylmercaptoquinazolines (Va-i)

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	S		C	H	N	S
Va	57	169—170	66,3	3,9	13,2	10,3	$C_{17}H_{11}N_3S\cdot H_2O$	66,4	4,3	13,7	10,4
Vb	93	234—236	61,0	3,3	17,0	9,3	$C_{17}H_{10}N_4OS$	61,1	3,0	16,8	9,6
Vc *	67	183—185	47,6	3,1	24,2	9,4	$C_{14}H_9N_6ClS\cdot H_2O$	48,5	3,2	24,2	9,2
Vd	95	186—188	70,9	4,6	10,9	9,2	$C_{22}H_{15}N_3OS$	71,5	4,1	11,4	8,7
Ve	76	192—194	72,3	5,0	10,6	8,1	$C_{23}H_{17}N_3OS$	72,0	4,5	10,9	8,3
Vf †	78	180—184	67,0	3,8	11,4	8,3	$C_{21}H_{12}N_3ClS$	67,5	3,2	11,2	8,6
Vg	75	206—208	70,8	5,0	11,6	8,4	$C_{22}H_{17}N_3OS$	71,1	4,6	11,3	8,6
Vh	51	176—178	63,9	4,0	13,0	7,5	$C_{22}H_{14}N_4O_3S$	63,8	3,4	13,5	7,7
Vi	58	212—214	63,5	3,6	13,0	7,7	$C_{22}H_{14}N_4O_3S$	63,8	3,4	13,5	7,7

*Found, %: Cl 10.2; calculated, %: Cl 10.2.
†Found, %: Cl 9.2; calculated, %: Cl 9.4.

TABLE 2. Analgesic Activity of Compounds Va-i

Compound	Dose, mg/kg	Time of experiment, min					
		30	60	90	120	150	180
		Change of the pain threshold, %					
Va	17	117±5,0	141±13,4	154±9,9	141±11,0	127±13,4	124±6,3
Vb	43	130±14,1	172±14,2	193±11,3	195±15,0	189±14,0	185±10,7
Vc	10	123±24,4	143±18,6	162±20,6	167±15,2	144±16,6	132±20,2
Vd	8	141±13,7	218±23,2	217±24,0	178±2,0	169±10,6	168±18,1
Ve	13	125±6,5	162±11,1	172±12,5	157±14,1	134±11,4	124±12,1
Vf	12	136±9,6	176±14,9	199±12,0	186±13,8	189±14,6	186±17,1
Vg	23	104±4,3	112±5,7	115±9,7	109±7,2	112±6,4	110±5,7
Vh	35	131±9,6	180±14,8	203±19,5	190±31,1	159±24,9	137±20,1
Vi	37	117±11,2	146±15,5	153±15,4	138±17,9	117±18,7	99±12,8
Analgin	200	137±20,0	165±40,0	179±32,0	155±35,2	150±20,2	127±2,6

Investigation of the pharmacological activities showed that compounds Va-i have analgesic and antiinflammatory activities and exert an influence on the duration of hexenal-induced sleep (Tables 2 and 3). The strength and character of the action is influenced by both the heteryl radical and the substituents on it. Thus, replacing quinoline by 5-nitroquinoline (Vb) (see Table 2) results in a sharp increase of the analgesic effect, and replacing quinoline by various acridine derivatives (Vd-i) leads to an increase as well as a decrease of the effect, which confirms the influence of the substituents at the acridine nucleus on the magnitude of the pharmacological action. The most active compounds are those that contain an acridine ring having a substituent at the 2-position (Vd, e, f, h); here the compounds Vd and Vh, having a methoxy group, are the most active and Vf is the least active. Substituting the methoxy group by an ethoxy group (Ve) and shifting the methoxy group to the 4-position (Vg) result in lowering of the analgesic activity. Introducing a nitro group at the 6-position leads to an increase (Vh) or a decrease (Vi) of the activity in comparison with the original compounds.

Replacement of quinoline by 5-nitroquinoline leads to a sharp lowering of the toxicity (Vb), and replacement of quinoline by derivatives of acridine with a substituent in the 2-position ambiguously influences the toxicity: the latter increases with methoxy and ethoxy groups and chlorine (Vd, e, f). The most toxic compound is Vd, containing a methoxy group. Changing the position of the methoxyl on the acridine nucleus leads to a sharp decrease in toxicity (Vg, i).

As concerns the antiinflammatory activity of compounds Va-i (Table 3), the most active one is compound Vc, which contains a purine moiety. Substitution of 5-nitroquinoline for quinoline leads to an increase in the antiinflammatory activity (Vb), and in the compounds containing an acridine group (Vd-i) the extent of the influence is dependent on the substituent at the acridine nucleus.

Investigation of the influence on the duration of hexenal-induced sleep (Table 3) showed that introduction of a quinoline radical in 4-mercaptoquinazoline (Va) considerably prolongs sleep, and introduction of 5-nitroquinoline (Vb) considerably shortens it. Compound Vc, con-

TABLE 3. Antiinflammatory Activity of Compounds Va-i and Their Influence on the Duration of Hexenal-Induced Sleep

Compound	LD_{50} for mice, mg/kg	Dose, mg/kg	Duration of hexenal-induced sleep		Antiinflammatory acitivity – increase in volume of leg of rats, %		
			min	%	after 1 h	after 3 h	after 5 h
Va	172	17	123±10,4	205,0	30±2,3	45±3,7	50±4,4
Vb	435	43	11±3,5	18,3	40±3,8	36±4,2	28±3,1
Vc	96	10	64±11,5	106,6	23±1,7	27±2,4	18±1,6
Vd	76	8	120±8,4	200,0	11±1,1	33±2,4	41±3,7
Ve	129	13	62±10,7	103,3	50±3,1	59±4,7	68±5,1
Vf	120	12	56±5,0	93,3	21±1,8	29±2,3	25±3,1
Vg	230	23	80±5,8	133,3	24±1,7	32±2,4	30±2,6
Vh	346	35	75±8,1	125,0	29±3,1	42±5,1	46±6,0
Vi	372	37	54±7,2	90,0	16±1,2	28±2,4	32±2,6
Hexenel	—	100	60±6,8	100,0	—	—	—
Aminazine	—	5	79±4,7	131,6	—	—	—
Caffeine	—	10	42±2,4	70,0	—	—	—
Butadione	—	100	—	—	24±10	37±13	31±10

taining the purine group, has little influence on the duration of medically induced sleep. In the series of compounds containing an acridine group (Vd-i) the following relationship is found: compound Vd, having a methoxy group in the 2-position, prolongs hexenal-induced sleep considerably. Replacing methoxy by ethoxy (Ve) or shifting the methoxyl to the 4-position (Vg) or introduction of a nitro group in the 6-position (Vh) leads to a sharp decrease in the duration of sleep. Replacing methoxyl by chlorine (Vf) and also shifting that group to the 4-position and simultaneously introducing a nitro group in the 6-position (Vi) results in a shortening of hexenal-induced sleep in comparison with the control group.

Compounds Va-i have distinct antimicrobial and antifungal activities with regard to *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and anthracoid and yeastlike molds. The most active compound is Va, which has bacteriostatic activities against the strains of microorganisms mentioned in concentrations of 250, 250, 250, 7.8, and 62.5 μg/ml, respectively.

EXPERIMENTAL (CHEMICAL)

The individuality of the synthesized compounds was confirmed by TLC on Silufol UV-254 plates (Czechoslovakia). IR spectra were taken on a UR-20 apparatus (GDR) on KBr disks.

4-Heterylmercaptoquinazolines (Va-i). Method A. A 10-mmole portion of the appropriate mercaptoheteryl (IIIa, d, e, f, h, i) was dissolved in 20-30 ml of 50% aqueous DMF containing 0.56 g (10 mmoles) KOH, and 1.65 g (10 mmoles) of 4-chloroquinazoline (I) was added. The reaction mixture was refluxed for 1-5 h (until neutral reaction) and cooled; then 70-80 ml water was added, and the precipitate was filtered off, washed with water, and dried. Compounds Va, d, e, f, h, i were obtained.

Method B. A 1.61-g portion (10 mmoles) of 4-mercaptoquinazoline (II) was dissolved in 30-40 ml of 30% ethanol containing 10 mmoles of KOH or NaOH, and 10 mmoles of the appropriate haloheteryl (Vb, c, g) was added; further procedures are as in method A. For analysis all compounds were purified by precipitation from 50% aqueous DMF.

EXPERIMENTAL (BIOLOGICAL)

Investigations of the antimicrobial and antifungal activity were carried out by the method of series dilutions on a liquid culture medium. For cultivation of the bacteria, aminopeptides diluted twice with distilled water of pH 7.2 were used. The microbial load was $2.5 \cdot 10^5$ cells of an aminopeptidic 18-h-old culture in 1-ml medium. Molds were grown on Sabouraud's culture medium (pH 6.0-6.8). The load was $5 \cdot 10^5$ reproductive corpuscles per ml.

Investigation of the analgesic and antiinflammatory activity and the influence on hexenal-induced sleep of compounds Va-i was carried out with white rats of the Wistar strain weighing 160-180 g and with mice weighing 18-20 g. The compounds were first dissolved in Tween 80 and diluted with water. The acute toxicity was determined by the method of Prozorovskii [4]. The

data of pharmacological investigations were processed by the method of mathematical statistics [1]. Data on the acute toxicity of the compounds are shown in Table 3.

To study the analgesic activity use was made of the "hot plate" method: the compound was administered 30 min before the first determination of the pain threshold. The analgesic activity was judged by the change in the threshold of sensitivity of the animals on thermal irritation. First we determined the initial reaction of the mice (the time of beginning of licking the hind legs) upon placing them on a metal plate with a temperature of 55°C, and then we followed the pace of this reaction in seconds every 30 min during 3 h after administering the preparation. Analgin was used as the standard for analgesic activity. The results of the investigations are shown in Table 2.

The influence of the compounds under investigation on the duration of hexenal-induced sleep was studied with 6 groups of animals (7 mice in each group). The animals of the first, second, and third group were injected subcutaneously with the compounds under investigation 1 h before administering the hexenal. The animals of the fourth group served as controls and received hexenal, the fifth group was administered aminazine, and the sixth, caffeine. The duration of sleep of the control group was taken as 100%. Data of the investigations are shown in Table 3.

The antiinflammatory activity of the preparations was studied using inflammation by formalin as a model. In the aponeurosis of the hind leg of the rats 0.1 ml of 2% formaldehyde solution was injected. The size of the edema was determined volumetrically 1, 3, and 5 h after injecting the inflammatory agent. The investigated compounds were administered 1 h before injecting the formalin. Butadione served as the standard. The results of the experiments are shown in Table 3.

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