SYNTHESIS AND BIOLOGICAL ACTIVITY OF 6-YLIDENE-THIAZOLIDINO[3,2-c]-1,2,4-TRIAZOL-5-ONES

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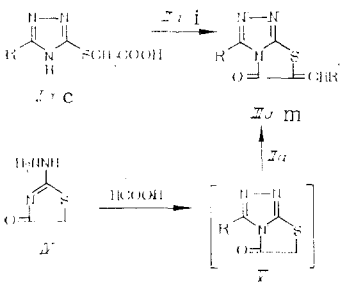
Continuing the search for biologically active substances in the 1,2,4-triazole series [3, 4], we have synthesized previously unreported ylidene derivatives of triazolidino-1,2,4-triazol-5-ones.

The 1,2,4-triazolyl-5-thioacetic acids (Ia-c) reacted readily with the aldehydes (IIa-i) on heating in a mixture of acetic acid and acetic anhydride (4:1), with the formation of 6-ylidenethiazolidino[3,2-c]-1,2,4-triazol-5-ones (IIIa-m) (Table 1).



Ia: R = H; Ib: R = CH_3; Ic: R = C_6H_5.

II: a – benzaldehyde: b – p-fluorobenzaldehyde; c – p-chlorobenzaldehyde; d – o-methoxybenzaldehyde; e – p-methoxybenzaldehyde; f – p-dimethyl aminobenzaldehyde; g – p-diethylaminobenzaldehyde; h – p-nitrobenzaldehyde; i – 5-nitrofuryl-acrolein.

III: a – R=H, R′=C_6H_5; b – R=H, R′=$C_6H_4N(CH_3)_2$-p; c – R-H, R′=$C_6H_4NO_2$-p; d – R=CH_3, R′=C_6H_4Cl-p; e – R=CH_3, R′$C_6H_4OCH_3$-p; f – R=CH_3; R′=$C_6H_4N(CH_3)_2$-p; g – R=CH_3, R′=$C_6H_4N(C_2H_5)_2$-p; h – R=R′=C_6H_5; i – R=C_6H_5, R′=C_6H_4F-p; j – R=C_6H_5, R′=C_6H_4Cl-p; k – R=C_6H_5; R′=$C_6H_4OCH_3$-o; l – R=C_6H_5, R′=$C_6H_4OCH_3$-p,m – R=C_6H_5; R′=2-(5-nitrofuryl-2)-ethylene-1-yl.

Thiazolidino ring closing can occur along edge "b" or along edge "c" of 1,2,4-thiazole to give 6-ylidenethiazolidino[3,2-b]-, 6-ylidenethiazolidino[3,2-c]-1,2,3-triazol-5-ones, or mixtures of the two. Thin-layer chromatography showed that after purification, the end products

TABLE 1. 6-Ylidenethiazolidino[3,2-c]-1,2,4-triazol-5-ones (IIIa-m)

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %				IR spectrum, cm^{-1}, νCO
			C	H	N	S		C	H	N	S	
III	88	193—195	57,8	3,0	18,2	14,0	$C_{11}H_6N_3OS$	57,9	2,7	18,4	14,1	1750
b	81,69	238—240	57,6	4,1	21,0	12,0	$C_{13}H_{11}N_4OS$	57,5	4,1	20,7	11,8	1725
c	39	223—225	48,5	2,0	20,2	12,0	$C_{11}H_5N_4O_3S$	48,3	1,8	20,5	11,7	1750
d	72	227—229	51,8	3,0	15,2	11,6	$C_{12}H_8ClN_3OS$	51,9	2,9	15,1	11,5	1735
e	69	199—200	56,9	4,3	15,5	11,6	$C_{13}H_{11}N_3O_2S$	57,1	4,1	15,4	11,7	1730
f	70	231—232	58,6	4,8	19,4	11,0	$C_{14}H_{14}N_4OS$	58,7	4,9	19,6	11,2	1740
g	64	180—182	61,1	6,0	18,2	9,9	$C_{16}H_{18}N_4OS$	61,1	5,8	18,0	10,1	1725
h	94	230—232	66,8	3,7	13,6	10,3	$C_{17}H_{11}N_3OS$	66,9	3,6	13,8	10,5	1740
i	93	204—206	63,3	3,1	13,2	9,9	$C_{17}H_{10}FN_3OS$	63,1	3,1	13,0	9,9	1740
j	83	256—258	60,0	3,2	12,7	9,2	$C_{17}H_{10}ClN_3OS$	60,1	2,9	12,4	9,4	1735
k	63	217—219	64,4	4,0	12,7	9,5	$C_{18}H_{13}N_3O_2S$	64,5	3,9	12,5	9,6	1735
l	89	132—134	64,2	4,3	12,8	9,8	$C_{18}H_{13}N_3O_2S$	64,5	3,9	12,5	9,6	1738
m	82	233—235	56,1	2,2	15,2	8,7	$C_{17}H_8N_4O_4S$	56,0	2,2	15,4	8,8	1735

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(IIIa-m) were single substances. Their structures were confirmed by reacting 2-hydroazinothiazolidone-4 (IV) [8] with formic acid in the presence of acetic anhydride to give thiazolidino[3,2-c]-1,2,4-triazol-5-one (V); without separation this was then reacted with the aldehyde IIf to give 6-p-dimethylaminobenzylidenethiazolidino[3,2-c]-1,2,4-triazol-5-one (IIIb), which has identical IR and UV spectra and R_f value and gave no melting-point depression with samples obtained from the acid Ia and aldehyde IIe.

The IR spectra of samples of compound IIIb show characteristic absorption bands: (cm^{-1}) 3100 – $\nu_{C-H_{arom}}$, 2920 – $\nu_{CH_{3as}}$, 2860 – $\nu_{CH_{3syn}}$, 2810 – ν_{CH_2}, 1725 – $\nu_{C=O}$, 1312 – $\nu_{CN_{arom}}$. The two samples of compound IIIb had identical mass-spectra, which contained a sharp peak corresponding to the molecular ion with m/z 272, in agreement with calculated data. The presence of peaks of ion fragments with m/z 172 $[O{\equiv}C{-}C{\equiv}C{-}N(CH_3)_2\text{-}p]^+$ (20.7%) and an ion with m/z 177 $[S{=}C{=}CH{-}C_6H_4{-}N{-}(CH_3)_2\text{-}p]$ (6.1%) confirms that the samples have the same structure.

Thus, the 1,2,4-triazolyl-5-thioacetic acids (Ia-c) react with aldehydes in an acetic acid–acetic anhydride mixture to give 6-ylidenethiazolidino[3,2-c]-1,2,4-triazol-5-ones.

EXPERIMENTAL CHEMISTRY

The purity of the compounds was checked by chromatography using Silufol (ChSSR) plates. IR spectra of the compounds in KBr pellets were taken on a Specord instrument. Mass spectra were recorded on a Varian MAT-311A under the usual conditions.

6-Ylidenethiazolidino[3,2-c]-triazol-5-ones (IIIa-m) (Table 1). A mixture of 10 mmoles of 1,2,4-triazolyl-5-thioacetic acids (Ia-c) and 10 mmoles of the aldehyde (IIa-i) in 10 ml of a mixture of acetic acid and acetic anhydride (4:1) were refluxed for 2 hours, cooled, the residue filtered and washed with ether. For analysis, the compounds were purified using dioxane (IIIb and g), n-propanol (IIIf), glacial acetic acid (IIId, e, and h-m), or a mixture of acetic acid and ethanol 1:1 (IIIa).

Compounds IIIa-m are yellow (IIIa, c-e, and h-l), orange (IIIb and f), violet (IIIg), or brown (IIIm) substances, insoluble in water, and soluble in organic solvents.

6-p-Dimethylaminobenzylidenethiazolidino[3,2-c]-1,2,4-triazol-5-one (IIIb). To a solution of 2.51 g (15 mmoles) of the hydrochloride of 2-hydrazinothiazolidone-4 (IV) [8] in 30 ml of a mixture of 85% formic acid and acetic anhydride (1:2) was added 1.02 g (15 mmoles) of sodium formate. This was refluxed for 6 hours, 2.23 g (15 mmoles) of p-dimethylaminobenzaldehyde added and heating continued for a further 2 hours. The mixture was cooled, poured into water, the precipitate filtered off and washed with water to give 2.8 g of IIIb (69%) with mp 238-240°C (decomp.), which on admixture with a sample obtained from the acid Ia and aldehyde IIf, melted at 238-240°C. R_f 0.86 (ethyl acetate–acetic acid, 19:1), 0.92 (benzene–acetic acid–water, 2:3:1), 0.85 (benzene–acetic acid–acetone, 17:1:2).

EXPERIMENTAL BIOLOGY

Compounds IIIa-m were tested for acute toxicity, antiinflammatory, neuroleptic, analgesic, antihypoxic, antimicrobial, and antifungal activity.

The antimicrobial and antifungal activities of the synthesized compounds were studied by the method of serial dilution in liquid nutrient media with 11 types of pathogenic bacterium and fungus. All the studied compounds IIIa-m proved to have little activity and suppressed microorganism growth only at a concentration of 500 μg/ml.

Acute toxicity was determined by V. B. Prozorov's method [5] (Table 2). The pharmacological data obtained was treated statistically [11].

The analgesic activity was determined from the increase in the threshold of pain sensitivity to thermal stimulus in mice [7]. It was shown that compounds IIIa, b, d, f, and k-m did not possess analgesic activity; compounds IIIc and h were weakly, and IIIe and i, moderately active. Compound IIIg was less active than analgin.

A study of the antihypoxic activity was carried out on male mice [7]; compounds IIIa, c, d, g, h-j, and l exhibited no antihypoxic activity, and compounds IIIb, e, f, k, and m showed weak activity.

The neuroleptic activity [2] of compounds IIIa-m was determined from the duration of sodium barbiturate sleep in white mice. The results are given in Table 2, which shows that compound IIIa possesses considerable neuroleptic activity. Substitution of the benzyl group

TABLE 2. Neuroleptic and Antiinflammatory Activity of 6-Ylidenethiazolidino[3,2-c]-1,2,4-triazol-5-ones (IIIa-m)

Compound	LD_{50}, mg/kg	Dose mg/kg	Duration of narcotic sleep		Antiinflammatory activity: increase in paw size, %		
			min	%	after 1 h	after 3 h	after 5 h
a	690	69	126±7,8	210	33±3,4	38±2,8	42±3,1
b	379	38	66±3,0	110	24±3,2	41±6,4	41±6,1
c	379	38	57±2,3	95	14±2,0	38±3,8	28±3,9
d	780	78	100±8,4	167	14±1,2	33±2,2	29±1,2
e	755	75,5	77±4,8	128	45±6,9	54±4,4	44±5,8
f	600	60	65±3,9	108	29±2,2	37±3,2	28±3,6
g	590	59	69±5,2	115	9±0,72	22±1,5	30±2,1
h	547	55	88±6,3	147	30±3,4	35±2,8	42±3,1
i	650	65	65±4,7	108	12±1,1	31±3,5	31±3,7
j	1630	163	145±9,4	242	17±2,6	29±3,3	29±2,4
k	1200	120	75±5,0	125	35±3,8	39±6,1	35±6,4
l	600	60	98±7,2	163	12±0,6	23±1,4	19±1,7
m	650	65	161±8,6	268	36±2,4	32±2,1	32±3,3
Sodium barbiturate		100	60±6,8	100	—	—	—
Aminazine		5	79±4,7	132	—	—	—
Butadione		—	—	—	24±10	37±13	31±10
Control		—	—	—	39±9	52±8	49±11

(IIIb and c) or 1,2,4-triazole ring leads to the disappearance or weakening of the neuroleptic activity. It should be noted that introduction of a p-chlorobenzylidene group (IIId and j) leads to an increase in the neuroleptic activity of the compounds. Analysis of the effect of 1,2,4-triazole ring substituents on the neuroleptic activity showed that the presence of a phenyl group at position 3 of the bicycle, as a rule, promotes an increase in the type of activity in question. Substitution of an aromatic aldehyde group by a β-(5-nitrofuryl-2)acrolein group leads to an increase in neuroleptic activity.

The antiinflammatory activity of compounds IIIa-m was studied on models of formalin inflammation [6]. The results of the study are given in Table 2, from which it can be seen that the strength and character of the antiinflammatory action is substantially affected by the substituents on the 1,2,4-triazole ring or benzene ring of the benzaldehyde. For example, compounds containing a benzaldehyde group (IIIa and h) possessed practically no antiinflammatory activity. Substitution of the benzaldehyde group by a p-chlorobenzaldehyde group (IIId and j) led to a sharp increase in antiinflammatory activity. The presence of a phenyl group at position 3 of the bicycle led to increased activity.

The work carried out thus confirms the expediency of examining the 6-ylidene substituted thiazolidino[3,2-c]-1,2,4-triazol-5-ones for antiinflammatory and neuroleptic activity.

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