BRIEF COMMUNICATIONS

2-AMINO-4-[2-(5-NITRO-FURYL)VINYL]THIAZOLE AND ITS DERIVATIVES

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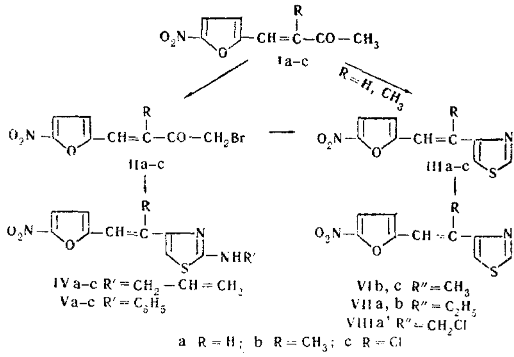
The reactions of 4-bromo-1-(5'-nitro-2'-furyl)but-1-en-3-one and its 2-methyl and 2-chloro derivatives with thiourea and its N-allyl and N-phenyl derivatives have yielded 2-amino-4-[β-5'-nitro-2'-furyl)-vinyl]thiazole and its α- and N-substituted derivatives. 2-Amino-4-[β-(5'-nitro-2'-furyl)vinyl]thiazole and its α-methyl derivative have also been prepared by the direct reaction of the corresponding α, β-unsaturated ketones with bromine and an excess of thiourea in chloroform, as was shown by a comparison of UV spectra. A series of N-acyl derivatives of the aminothiazoles has been obtained. UV and IR spectra are given.

2-Amino-4-[2-(5-nitro-2-furyl)vinyl]thiazole (**IIIa**) has been obtained previously by the reaction of 4-bromo-1-(5-nitro-2-furyl)but-1-en-3-one (**IIa**) with thiourea. By analogy with the synthesis of **IIa** we have for the first time prepared by the bromination of **Ib** and **Ic** the bromoketones **IIb** and **IIc**, their synthesis taking place more smoothly and with higher yields than that of **IIa** [2].

The reaction of **IIa–IIc** with thiourea and its N-allyl N-phenyl derivatives gave the aminothiazole derivatives **IIIa–IIIc–Va–Vc** (method A). Compounds **IIIb** and **IIIc** were isolated in the form of the hydrobromides. The latter are readily converted into the bases not only by the action of aqueous solutions of sodium acetate and ammonia but also by the action of water or by heating in ethanol.



We have established that the aminothiazoles **IIIa** and **IIIb** can also be prepared by the Dodson-King method, i.e., by the direct reaction of the corresponding α,β-unsaturated ketones **Ia** and **Ib** with bromine and two moles of thiourea in chloroform (method B). This was shown by a comparison of the UV spectra of samples of **IIIa** and **IIIb** prepared by both methods. The results obtained are of interest in view of the fact that, according to the literature [3, 4], the Dodson-King method has proved to be suitable for the synthesis of 2-amino-4-styrylthiazole and a derivative of it from benzylideneacetone and anisylideneacetone. In contrast to the synthesis of **IIIa** and **IIIb** the synthesis of **IIIc** by the Dodson-King method takes place with complications caused by the capacity for the chlorine in **Ic** for reacting with thiourea.

The hydrochlorides of **IIIb** and **IIIc** were prepared by the action of concentrated HCl on solutions of the bases in acetone. The hydrobromides of **IIIb** and **IIIc** were synthesized (**VI–VIII**). Data on the thiazoles are summarized in the table.

On the basis of the IR spectra of **IIIa**, **IIIc**, and **Vc** (in Nujol with an IKA-14 instrument), which contain bands with frequencies of 714, 715 cm^{-1} (cis form) and 973, 974 cm^{-1} (trans form), it may be concluded that the nitrofurylvinylaminothiazoles obtained are mixtures of geometrical isomers.

The UV spectra are specific for the groups of compounds **IIIa–IIIc**, **IVa–IVc**, and **Va–Vc** and also for the acyl derivatives **VI** and **VII**; however, all groups of compounds have a common band in the 400 nm region. For all the derivatives containing chlorine in the vinyl group, in this region there is a shift in the direction of short waves by approximately 15 nm.

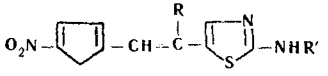
EXPERIMENTAL

4-Bromo-2-methyl-1-(5-nitro-2-furyl)but-1-en-3-one (IIb). With stirring and the passage of N_2, 16 g (0.1 mole) of bromine in 15 ml of CH_3COOH was added over 1 hr at 50–70° to 19.5 g (0.1 mole) of **Ib** in 120 ml of CH_3COOH, and the mixture was heated with the passage of nitrogen for a further 2 hr, after which it was poured with stirring into 600 ml of ice and water and, after a day, the precipitate was separated off. Yield 85%, mp 93–95° C (recrystallized three times from methanol). Found, %: C 39.70; H 3.00; N 5.24. Calculated for $C_9H_8BrNO_4$, %: C 39.44; H 2.94; N 5.11. λ_{max}, nm (log ε) in ethanol: 226 (3.91), 348 (4.25).

4-Bromo-2-chloro-1-(5-nitro-2-furyl)but-1-en-3-one (IIc) was prepared similarly with a yield of 95%, mp 116–118° C (from methanol). Found, %: C 32.78; H 1.96; Br+Cl 39.25. Calculated for $C_8H_5BrClNO_4$, %: C 32.62; H 1.71; Br+Cl 39.17. λ_{max}, nm (log ε) in ethanol: 231 (3.85), 346 (4.28).

Aminothiazoles. Method A. An alcoholic solution of 20 mM of thiourea (or, as the case might be, N-allyl- or N-phenylthiourea) was added to a solution of 20 mM of a bromoketone **II** in 20 ml of dioxane and 30 ml of ethanol, and the mixture was heated for 15 min. After a day the hydrobromides of **IIIa–IIIc** were filtered off, and an additional amount of the bases **IIIa–IIIc** was precipitated from the filtrates by the addition of aqueous sodium acetate or ammonia. Compounds **IIIa–IIIc** are also obtained from their hydrobromides by the action of water or by boiling with ethanol. Compounds **IVa–IVc** are precipitated by diluting the reaction mixture with water in the form of substances which are first resinous but harden during a day.

Method B. A solution of 30 mM of bromine in 10 ml of chloroform was added to 30 mM of the ketone **I** and 60 mM of thiourea in 150 ml of chloroform and the mixture was boiled for 6 hr. The precipitates



Compound	R	R′	Method	Mp, °C (decomp.)	Empirical formula	Found, %				Calculated, %				UV spectrum, λ_{max}, nm (log)	Yield, %
						C	H	N	S	C	H	N	S		
IIIa	H	H	A	(200—203) [b-d]	$C_9H_7N_3O_3S$	45.45	3.12	18.04	13.49	45.56	2.91	17.71	13.52	247(4.12), 300(4.09), 406(4.28) [h]	65
			B	(203—205) [c,d]	,,	45.66	2.90	17.69	13.46	45.56	2.91	17.71	13.52	246(4.15), 299(4.09), 405(4.27) [h]	70
IIIb	CH_3	H	A	180—182 [d]	$C_{10}H_9N_3O_3S$	48.01	3.81	—	12.94	47.80	3.61	—	12.76	251(4.10), 297(4.00), 405(4.24) [h]	83
			B	182—184 [d,e]	,,	48.00	3.66	—	13.09	47.80	3.61	—	12.76	249(4.09), 297(3.99), 405(4.22) [h]	38
IIIb· HBr	CH_3	H	A	(265—267)	$C_{10}H_9N_3O_3S \cdot \cdot HBr$	36.20	3.56	12.30	9.97	36.45	3.34	12.35	9.65		63
			C	(265)		36.30	3.48	12.55	—	36.45	3.34	12.35			
IIIb· HCl	CH_3	H	C	(263—265)	$C_{10}H_9N_3O_3S \cdot \cdot HCl$	41.83	3.64	14.55	—	42.09	3.47	14.61	—		
IIIc	Cl	H	A	215—217 [e]	$C_9H_7ClN_3O_3S$	39.50	2.15	14.55	12.16	39.79	2.23	15.47	11.80	251(4.08), 305(4.02), 390(4.28) [h]	89
														249(4.04), 302(3.97), 390(4.27) [i]	66
IIIc· HBr	Cl	H	A	(252—255)	$C_9H_7ClN_3O_3S \cdot HBr$	30.54	2.14	—	—	30.66	2.01	—	—		
IIIc. HCl	Cl	H	C	(255)	$C_9H_7ClN_3O_3S \cdot \cdot HCl$	34.76	2.49	13.43	—	35.08	2.29	13.64	—		
IVa	H	$CH_2—CH=CH_2$	A	121—122 [d]	$C_{12}H_{11}N_3O_3S$	51.88	4.17	14.90	—	51.97	3.99	15.16	—	253(4.19), 304(4.05), 410(4.21) [h]	77
IVb	CH_3	$CH_2—CH=CH_2$	A	120—121 [d]	$C_{13}H_{13}N_3O_3S$	52.23	4.65	14.51	—	53.59	4.50	14.43	—	255(4.21), 299(4.04), 410(4.26) [h]	90
IVc	Cl	$CH_2—CH=CH_2$	A	108—110 [d]	$C_{12}H_{10}ClN_3O_3S$	45.96	3.31	13.63	—	46.23	3.23	13.48	—	255(4.18), 308(4.02), 396(4.20) [h]	80
Va	H	C_6H_5	A	150—153 [d]	$C_{15}H_{11}N_3O_3S$	57.30	3.46	—	10.34	57.50	3.54	—	10.29	294(4.32), 416(4.18) [h]	90
Vb	CH_3	C_6H_5	A	146—147 [d]	$C_{16}H_{13}N_3O_3S$	58.69	4.27	—	9.49	58.70	4.00	—	9.80	295(4.46), 413(4.27) [h]	87
Vc	Cl	C_6H_5	A	180—182 [d]	$C_{15}H_{10}ClN_3O_3S$	51.60	2.87	12.03	—	51.80	2.90	12.08	—	294(4.47), 400(4.24) [h]	99
VIb	CH_3	$COCH_3$	D	(255—256) [f]	$C_{12}H_{11}N_3O_4S$	48.83	3.86	4.20	10.86	49.14	3.78	14.23	10.93	245(4.10), 280(4.16), 395(4.28) [h]	92
VIc	Cl	$COCH_3$	D	(242—245) [e]	$C_{11}H_8ClN_3O_4S$	42.24	2.50	—	10.10	42.12	2.57	—	10.21	246(4.03), 280(4.04), 381(4.20) [i]	87
														280(4.09), 370(4.24) [j]	
VIIa	H	COC_2H_5	D	(218—221) [e]	$C_{12}H_{11}N_3O_4S$	49.17	4.00	—	—	49.14	3.78	—	—		86
VIIb	CH_3	COC_2H_5	D	205—207 [e]	$C_{13}H_{13}N_3O_4S$	50.60	4.14	13.45	—	50.80	4.29	13.67	—	246(4,06), 281(4,14), 395(4.24) [h]	95
VIIIa	H	$COCH_2Cl$	E	(218—220) [e,f]	$C_{11}H_8ClN_3O_4S$	42.04	2.63	—	—	42.12	2.57	[g]	—		87

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[a] See Experimental. [b] Mp 188–190° C (decomp.) [1]. [c] From aqueous acetone. [d] From aqueous ethanol. [e] From aqueous dioxane. [f] From CH_3COOH. [g] Found, %: Cl 11.56. Calculated, %: Cl 11.30. [h] In ethanol. [i] In dioxane. [j] In CH_3COOH.

were separated off, triturated with aqueous sodium acetate solution, filtered off again, and washed with water.

Method C. Compounds **IIIb** and **IIIc** were triturated with acetone and concentrated HCl (or HBr) and washed with acetone.

Method D. A mixture of 5mM of **IIIa–IIIc**, 10 ml of a carboxylic acid, and 7.5 mM of its anhydride was boiled for 2 hr and was then diluted with water, and the precipitate was filtered off.

Method E. A solution of 6 mM of chloroacetyl chloride in 6 ml of dry benzene was slowly added to 5 mM of **IIIa** in 100 ml of dry benzene and the mixture was boiled for 4 hr; after a day the precipitate was filtered off.

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NEW α-(PYRIMID-4-YLAMINO)ACIDS

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The reaction of 4-methylthiothymine with amino acids has given α-(2-hydroxy-5-methylpyrimid-4-ylamino)acids. Similarly, 4-methylthiouracil forms α-(2-hydroxypyrimid-4-ylamino)acids the halogenation of which gives α-(5-halogeno-2-hydroxypyrimid-4-ylamino)acids.

In recent years, interest has arisen in the study of pyrimidylamino acids as possible anticarcinogenic substances [1, 2]. Some representatives of the α-(pyrimid-4-ylamino)acids such as, for example, N-(2-hydroxypyrimid-4-yl)α-alanine and its 5-halogeno derivatives have been described by Ueda and Fox [1].

We have synthesized a number of new N-substituted α-amino acid derivatives of uracil, thymine, and 5-halogenouracils. For the synthesis of the α-(2-hydroxypyrimid-4-ylamino)acids (I) and the α-(2-hydroxy-5-methylpyrimid-4-ylamino)acids (II) we used a recently developed method [1]—the reaction of 2-hydroxy-4-methylthiopyrimidine and 2-hydroxy-5-methyl-4-methylthiopyrimidine, respectively, with amino acids in an aqueous alkaline medium.

The products obtained are white crystalline substances with high melting points which are readily soluble in hot water, less readily in ethanol, and insoluble in ether and benzene.

The treatment of compound I with elementary bromine or N-bromosuccinimide in acetic acid gave the α-(5-bromo-2-hydroxypyrimid-4-yl)amino acids (**III**) and the reaction of compound I with elementary iodide in an aqueous alkaline medium yielded the α-(2-hydroxy-5-iodopyrimid-4-yl)amino acids (IV).

The compounds obtained were characterized by their UV absorption spectra, their R_f values in two systems of solvents, elementary analyses, and melting points.

We shall publish information concerning their antiblastic activity separately.

EXPERIMENTAL

Chromatography was carried out on paper of type "chromatograficheskaya B" ["chromatographic fast"] of the Volodarskii Leningrad mill by the ascending method. The following systems of solvents were used: n-butanol—acetic acid—water (4 : 1 : 5, upper layer) (system 1); n-butanol—water (86 : 14) (system 2); n-butanol—ethanol—water (4 : 1 : 5, upper layer) (system 3); n-butanol—saturated NH_3 (system 4). The substances were detected on the chromatograms by their absorption of UV light.

The UV absorption spectra were recorded on an SF-4 spectrophotometer in 0.1 N HCl, 0.1 N caustic soda, and water with concentrations of the order of 10^{-3} g-mole/*l*.

N-(2-Hydroxypyrimid-4-yl)valine (Ia). A mixture of 1.0 g (7 mM) of 4-methylthiouracil, 0.91 g (7.8 mM) of valine, 0.42 g (3.9 mM) of sodium acetate, and 20 ml of water was boiled for 22 hr. The cooled solution was acidified with dilute formic acid to pH 3 and was left overnight in the refrigerator. The precipitate that had deposited was filtered off, washed with water, and dried. Compounds **Ib** and **Ic** and **IIa–IId** were obtained similarly.

N-(5-Bromo-2-hydroxypyrimid-4-yl)glycine (IIIa). A solution of 0.32 g (4 mM) of bromine in 5 ml of acetic acid was added dropwise to a suspension of 0.34 g (2 mM) of N-(2-hydroxypyrid-4-yl)glycine in 15 ml of glacial acetic acid. After 30 minutes' stirring, the solid matter was dissolved, and the solution was left overnight at room