INVESTIGATION OF 1,2,4-TRIAZINO[6,5-b]INDOLE DERIVATIVES

I. SYNTHESIS AND TRANSFORMATIONS OF 3-MERCAPTO-1,2,4-TRIAZINO[6,5-b]INDOLES

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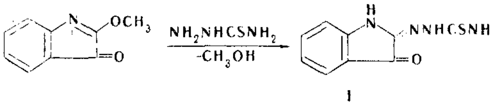
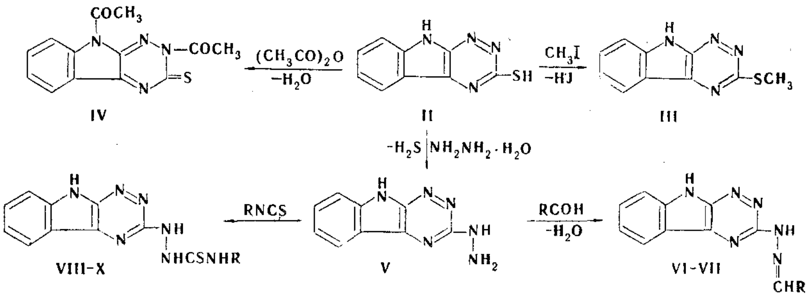
A method was developed for the preparation of isatin 2-thiosemicarbazone free of admixed 3-isomer. The method made it possible to shorten the time required for it to cyclize to 3-mercapto-1,2,4-triazino[6,5-b]indole from 9 h to 30 min. New 1,2,4-triazino[6,5-b]indole derivatives were obtained.

Many compounds of the 1,2,4-triazino[5,6-b]indole series have high physiological activity [1-3]. In this connection, it seemed of interest to synthesize a number of new derivatives of the little studied isomeric heterocyclic 1,2,4-triazino[6,5-b]indole system [4].

We obtained isatin 2-thiosemicarbazone (I), the starting material for the synthesis of 3-mercapto-1,2,4-triazino[6,5-b]indole (II) [4], in pure form by reaction of the O-methyl ether of isatin with thiosemicarbazide in the cold, which made it possible to carry out the cyclization of I in refluxing alkaline solution in 30 min instead of heating at 50° for 9 h [4].



The synthesis of the new 1,2,4-triazino[6,5-b]indole derivatives (III-X) is presented in the scheme below:



VI R=C$_6$H$_5$; VII R=p-NO$_2$C$_6$H$_4$; VIII R=C$_6$H$_5$; IX R=p-BrC$_6$H$_4$; X R=p-NO$_2$C$_6$H$_4$

Data on the compounds obtained are presented in Table 1.

EXPERIMENTAL

Isatin 2-Thiosemicarbazone (I). A saturated aqueous solution of an equimolecular amount of thiosemicarbazide was added to a solution of the O-methyl ether of isatin in benzene, obtained by the method

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TABLE 1. 1,2,4-Triazino[6,5-b]indole Derivatives

Compound	Mp, °C (crystallization solvent)	Empirical formula	N, %		Yield, %
			found	calc.	
III	213–214 (ethanol)	$C_{10}H_8N_4S$	25,5	25,9	65
IV	290–292 (DMF – ethanol*)	$C_{13}H_{10}N_4O_2S$	20,3	19,9	85
V	253–254	$C_9H_8N_6$	41,9	41,6	72
VI	>280 darkens, >330 (water – methanol)	$C_{16}H_{12}N_6$	28,8	29,2	95
VIa	>250 darkens, >330 1 *N* aque. HCl	$C_{16}H_{12}N_6 \cdot HCl$†	25,5	25,9	93
VII	>300 darkens, >330 (nitrobenzene)	$C_{16}H_{11}N_7O_2$	29,1	29,4	96
VIII	>250 darkens, >330 (water – methanol)	$C_{16}H_{13}N_7S$	28,1	27,9	85
IX	>230 darkens, >330 (DMF – water)	$C_{16}H_{12}BrN_7S$	23,2	23,0	75
X	>330 (DMF – water)	$C_{16}H_{12}N_8O_2S$	28,3	28,6	80

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*DMF is dimethylformamide.

†Found: Cl 11.4%. Calculated: Cl 10.9%.

in [5], and the mixture was shaken vigorously in a separatory funnel for 10 min. The resulting precipitate was removed by filtration, washed with water and alcohol, and dried to give 70% of a product with mp 218-219° (from aqueous ethanol) (mp 222° [4], 216-217° [6]). Found: N 25.5%. $C_9H_8N_4OS$. Calculated: N 25.4%.

3-Mercapto-1,2,4-triazino[6,5-b]indole (II). A 10-g sample of I was dissolved by heating in 150 ml of 1 N sodium hydroxide solution, and the solution was refluxed for 30 min. The hot solution was filtered, cooled to room temperature, and acidified with concentrated hydrochloric acid. The precipitate was removed by filtration, washed with boiling water, and dried at 105° to give 87-90% of dark-red crystals that melted above 330° (from dimethylformamide). Found: C 53.5; H 3.0; S 15.7%. $C_9H_6N_4S$. Calculated: C 53.5; H 3.0; S 15.9%.

The IR spectrum of the compound did not contain the carbonyl and amino group absorption bands observed in the spectrum of I at 1690 and 3450 cm^{-1}, respectively.

3-Methylthio-1,2,4-triazino[6,5-b]indole (III). This compound was obtained via a method similar to that used to prepare 3-methylthio-1,2,4-triazino[5,6-b]indole [7].

2,9-Diacetyl-3-thioketo-2,3-dihydro-1,2,4-triazino[6,5-b]indole (IV). This compound was obtained by refluxing II with excess acetic anhydride for 20 min. The reaction mixture was cooled and diluted with water, and the precipitate was removed by filtration, washed with water, and dried.

3-Hydrazino-1,2,4-triazino[6,5-b]indole (V). A solution of 4 g of II in 40 ml of hydrazine hydrate (99.5%) was refluxed on an oil bath until hydrogen sulfide evolution ceased (~2 h), and the hot mixture was filtered. The mixture was allowed to stand for 2 h, and the long yellow needles that formed were removed by filtration, washed with water, and dried in vacuo over calcium chloride at room temperature to constant weight. The product was soluble in nitrobenzene, dimethylformamide, and hot acetic acid, slightly soluble in alcohol and dioxane, and insoluble in benzene.

3-Benzylidenehydrazino-1,2,4-triazino[6,5-b]indole (VI). A suspension of equimolecular amounts of V and benzaldehyde in ethanol was refluxed on a water bath for 2 h. The resulting precipitate was removed by filtration, washed with alcohol, and dried. The reaction was markedly accelerated in the presence of hydrochloric acid, and, for example, in the case of the preparation of VI, the reaction was complete in 10 min. Compound VI was isolated as the hydrochloride (VIa), which was readily hydrolyzed in aqueous solvents.

3-(p-Nitrobenzylidenehydrazino)-1,2,4-triazino[6,5-b]indole (VII). This compound was obtained by a method similar to that used to prepare VI. Compounds VI and VII are crystalline substances that are soluble in dimethylformamide, acetic acid, pyridine, and dioxane, slightly soluble in alcohol, and insoluble in water, benzene, and chloroform. Compound VI is yellow, while VII is brown.

3-4'-Phenylthiosemicarbazido-1,2,4-triazino[6,5-b]indole (VIII). A suspension of equimolecular amounts of V and phenyl isothiocyanate in absolute ethanol was refluxed on a water bath for 4 h. The precipitate was removed by filtration, washed with a small amount of alcohol, and dried.

3-4'-(p-Bromophenyl)thiosemicarbazido-1,2,4-triazino[6,5-b]indole (IX) and 3-4'-(m-Nitrophenyl)-thiosemicarbazido-1,2,4-triazino[6,5-b]indole (X). These compounds were obtained via a method similar to that used to prepare VIII. Compounds VIII-X are yellow, crystalline substances that are soluble in dimethylformamide, acetic acid, and dioxane, slightly soluble in alcohol, and insoluble in water, ether, and benzene.

The IR spectra of potassium bromide pellets of I and II were recorded with a UR-20 spectrophotometer.

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