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

II.* SYNTHESIS AND PROPERTIES OF 3-SUBSTITUTED 1,2,4-TRIAZACARBAZOLES

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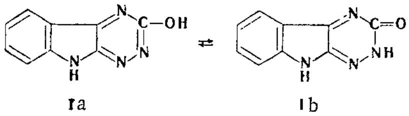
A method was worked out for the preparation of isatin α-semicarbazone, the starting material for the synthesis of 3-hydroxy-1,2,4-triazacarbazoles, and the structure of the latter was refined. Nucleophilic exchange of 3-chloro-1,2,4-triazacarbazole (which was obtained for the first time) with amines, hydrazines, and arylhydrazines was studied.

In a continuation of our research [1] involving a study of the properties of 1,2,4-triazacarbazole derivatives, we have investigated the structure of the recently obtained 3-hydroxy-1,2,4-triazacarbazole (I) [2] and have synthesized a number of new 3-substituted 1,2,4-triazacarbazoles, which are of interest as possible physiologically active substances.

The IR spectrum of I does not contain absorption bands at 1625-1800 cm^{-1} (CO) but does contain broadened absorption bands at 2600-3200 cm^{-1}, which should pertain to the absorption of OH and NH groups bonded by intermolecular hydrogen bonds [3].

In contrast to the thio analog, which readily forms a hydrazone under similar conditions [1], I does not undergo reaction with hydrazine hydrate. It dissolves in aqueous sodium hydroxide solutions to form a sodium salt (II) and reacts with phosphorus oxychloride to give 3-chloro-1,2,4-triazacarbazole (III).

On the basis of these results, of the two possible tautomeric froms (Ia and Ib), the hydroxy form Ia should be adopted for I.



Ia Ib

3-Chloro-1,2,4-triazacarbazole is of interest as a starting material for the synthesis of new 3-substituted derivatives of 1,2,4-triazacarbazole. As should have been expected in conformity with the aromatic structure of III, the halogen atom is less labile than in aliphatic compounds: it is not saponified by water on refluxing in aqueous dioxane solution for 10 h, and an amine residue does not exchange with the chlorine atom at temperatures below 100°, nor is it substituted by CN and N_3 groups under the conditions generally used. However, nucleophilic substitution does occur above 100° with aliphatic, aromatic, and alicyclic amines, hydrazine, and arylhydrazines. When III is refluxed in sodium hydroxide solution it is saponified to I. The data on the compounds obtained are presented in Table 1.

We have developed a simple method for the preparation of isatin α-semicarbazone (XI), the starting material for the preparation of I, by reaction of the O-methyl ether of isatin [4] with semicarbazide hydrochloride in the presence of an equimolecular amount of sodium acetate. The methods for the preparation

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*See [1] for communication I.

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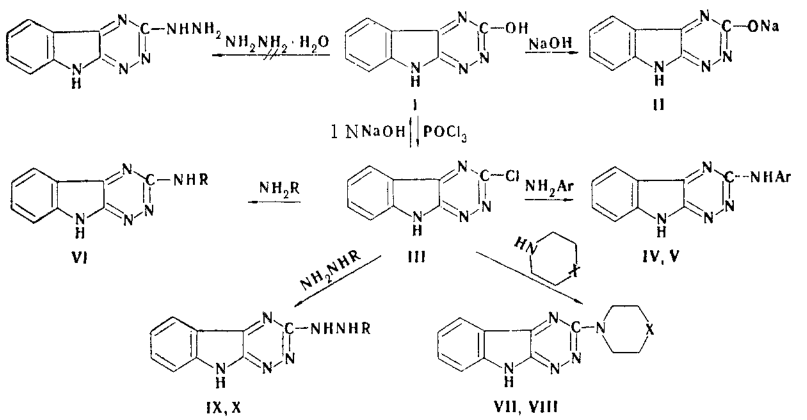
TABLE 1. 3-Substituted 1,2,4-Triazacarbazoles

Compound	Mp, °C (crystallization solvent)	Empirical formula	N, %		Yield, %
			found	calc.	
II	>330	$C_9H_5N_4NaO$	26,5	26,9	93
III	294—296	$C_9H_5ClN_4$*	26,9	27,4	52
IV	272—273 (isobutyl alcohol)	$C_{15}H_{11}N_5$	26,5	26,8	90
V	260—261 (isobutyl alcohol)	$C_{16}H_{13}N_5O$	23,7	24,0	91
VI	234—235 (dioxane)	$C_{11}H_{11}N_5O$	30,3	30,6	92
VII	290—292 (dioxane)	$C_{13}H_{13}N_5O$	26,8	27,4	81
VIII	210—211 (acetone - water, 1: 1)	$C_{14}H_{15}N_5$	27,4	27,7	68
IX	253—254	$C_9H_8N_6$	41,7	41,6	75
X	256—257 (nitrobenzene)	$C_{15}H_{12}N_6$	29,9	30,4	90

*Found: Cl 16.9%. Calculated: Cl 17.4%.

of XI described in [5, 6] include multistep syntheses of isatin α-anil or isatin α-imide, from which XI are obtained by transhydrazination reactions.



IV $Ar=C_6H_5$; V $Ar=C_6H_4OCH_3\text{-}o$; VI $R=CH_2CH_2OH$; VII $X=O$; VIII $X=CH_2$; IX $R=H$; X $R=C_6H_5$

EXPERIMENTAL

Sodium Salt of 3-Hydroxy-1,2,4-triazacarbazole (II). A 1-g sample of I was dissolved in 54 ml of boiling 0.1 N sodium hydroxide solution, and the solution was refluxed for 10 min. The water was evaporated, and the residue was dissolved in boiling ethanol. The ethanol solution was filtered, and the salt was precipitated by the addition of ether to give a yellow, crystalline substance that was soluble in water, slightly soluble in alcohol, and insoluble in ether, tetrahydrofuran, dioxane, and benzene.

3-Chloro-1,2,4-triazacarbazole (III). A total of 20 ml of phosphorus oxychloride was added to 10 g of I, 3 ml of dry triethylamine was added to the mixture, and the resulting mixture was heated to the boiling point on an oil bath and refluxed for 45 min. The mixture was cooled, and 200 g of ice was added to it with stirring. The precipitate was removed by filtration, washed with water until it gave a neutral reaction, and dried. Compound III was extracted from the precipitate with a large amount of tetrahydrofuran and chromatographed with a column filled with analytical grade aluminum oxide. The height of the aluminum oxide layer was 40 mm, and the diameter was 20 mm. The eluate was vacuum-distilled to a volume of 20 ml, and the resulting precipitate was removed by filtration, washed with ether, and dried. The reaction product was a yellow, crystalline substance that was sufficiently pure for analysis and further study and had mp 294-296° (mp 298-299°, from aqueous dioxane). The product was soluble in pyridine, dimethylformamide, dioxane and tetrahydrofuran, slightly soluble in alcohol and ether, and insoluble in benzene, chloroform, and water.

Hydrolysis of 3-Chloro-1,2,4-triazacarbazole. A 1-g sample of III was dissolved in 150 ml of 1 N aqueous sodium hydroxide solution, and the solution was refluxed for 7 h on a water bath. The solution was filtered and neutralized with concentrated hydrochloric acid (at the end with acetic acid), and the resulting precipitate was removed by filtration, washed with water until it gave a neutral reaction, and dried. The product melted above 330° and, according to its IR spectrum, was identical to I.

Reaction of III with Amines. A mixture of 1 g of III and a 10-fold amount (by weight) of amine was heated on an oil bath at 150-160° for 6 h. The hot solution was filtered, cooled, and treated with a sixfold amount of water (in the preparation of VI-VIII) or ether (in the preparation of IV and V). The resulting precipitate was removed by filtration, washed with water, dried, and crystallized from a suitable solvent. Compounds IV-VIII are yellow, crystalline substances that are soluble in alcohol, acetone, dioxane, and tetrahydrofuran, and slightly soluble in ether and benzene (except for VIII, which was readily soluble in these solvents).

Reaction of III with Hydrazine Hydrate and Phenylhydrazine. A mixture of 1 g of III and a 10-fold amount (by weight) of the appropriate hydrazine was refluxed on an oil bath for 2 h (in the preparation of IX) or heated at a bath temperature of 150-160° for 6 h (in the preparation of X). The mixture was cooled, and the resulting precipitate was removed by filtration, washed with water (IX) or ether (X), dried, and crystallized. Compounds IX and X are yellow, crystalline substances that are soluble in dimethylformamide, pyridine, and nitrobenzene, slightly soluble in alcohol, dioxane, and tetrahydrofuran, and insoluble in benzene, ether, and chloroform.

Isatin α-Semicarbazone (XI). This compound was obtained in 86.5% yield via a method similar to that used to prepare isatin α-thiosemicarbazone [1]. The IR spectrum of KBr pellets of I was recorded with a UR-20 spectrophotometer.

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