SYNTHESIS AND REACTIONS OF 1-BENZYLIDE NEAMINO-IMIDAZO[1,2-a]IMIDAZOLES

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The method of synthesizing condensed imidazo-heterocyclic systems has been extended to the production of N-benzylideneaminoimidazo[1,2-a]imidazoles (VI, VII), the successive hydrolysis and treatment with nitrous acid of which has enabled N-substituted imidazo[1,2-a]-imidazoles to be obtained. A by-product of the synthesis is 1,2-dibenzylideneamino-4-phenyl-5-n-propylimidazole (VIII), the condensation of the reduction product of which with isatin leads to a tetracyclic system.

The most promising way of synthesizing imidazo-heterocyclic systems is a method [1] consisting in the condensation of a 2-amino-heterocycle with α -halogeno carbonyl compounds.

This method has been used for the synthesis of imidazo[1,2-a]pyridine [2], imidazo[1,2-a]imidazole [3], and other systems.

We have investigated the possibility of cyclizing 2-amino-1-benzylideneaminoimidazoles with α bromovalerophenone (I). The reaction of (I) with 2-amino-1-benzylideneamino-4-phenylimidazole (IV) in dimethylformamide in the presence of sodium bicarbonate gave 1-benzylideneamino-3,6-diphenyl-5-npropylimidazo[1,2-a]imidazole (VI).

It is known [4] that the reaction of benzaldehyde amidinohydrazone (III) with aryl bromomethyl ketones forms 2-amino-1-benzylideneaminoimidazoles, the hydrolysis or reduction of which leads to 1,2-diaminoimidazoles. The reaction of (I) with (III) gave 1-benzylideneamino-3,6-diphenyl-2,5-di-n-propylimidazo-[1,2-a]imidazole (VII). As a by-product of this reaction we isolated 1,2-dibenzylideneamino-4-phenyl-5-npropylimidazole (VIII). Initially, apparently, 2-amino-1-benzylideneamino-4-phenyl-5-n-propylimidazole (V) is produced, as in the formation of (IV) from (II) and (III) [4]. However, under the conditions used, (V) reacts with a second molecule of (I) and the benzaldehyde liberated by the partial hydrolysis of (III) forming (VII) and (VIII), respectively.



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The PMR, IR, and UV spectra of (VI) and (VII) show that they have similar structures.

The PMR spectra of (VI) and (VII) each have, in addition to the signals characteristic for phenyl and alkyl protons, a strong signal of the proton of an azomethine group. The IR spectra of (VI) and (VII) lack the absorption bands characteristic for CO and NH_2 groups, which shows the closure of the second imidazole ring. The IR spectra of (VI) and (VII) (Table 2) show absorption maxima at 245, 290, and 345 nm.

The acid hydrolysis of (VII) gave 1-amino-3,6-diphenyl-2,5-di-n-propylimidazo[1,2-a]imidazole (IX), the reaction of which with nitrous acid led to 3,6-diphenyl-2,5-di-n-propyl-1H-imidazo[1,2-a]imidazole (X). The IR spectrum of (X) has the absorption maximum at 3470 cm^{-1} that is characteristic for an NH group.



 $\begin{aligned} \mathbf{X} \ \mathbf{R}^{1} &= \mathbf{C}_{6}\mathbf{H}_{5}, \ \mathbf{R}^{2} = n \cdot \mathbf{C}_{3}\mathbf{H}_{7}, \ \mathbf{R}^{1} = \mathbf{N}\mathbf{H}_{2}; \quad \mathbf{X} \ \mathbf{R}^{1} = \mathbf{C}_{6}\mathbf{H}_{5}, \ \mathbf{R}^{2} = n \cdot \mathbf{C}_{3}\mathbf{H}_{7}, \ \mathbf{R}^{3} = \mathbf{H}_{7}; \\ \mathbf{X}\mathbf{I}, \ \mathbf{X}\mathbf{I} \ \mathbf{R}^{1} = \mathbf{C}_{6}\mathbf{H}_{5}, \ \mathbf{R}^{2} = n \cdot \mathbf{C}_{3}\mathbf{H}_{7}, \end{aligned}$

Compound (VIII) was reduced by hydrazine hydrate in ethylene glycol to 1,2-diamino-4-phenyl-5-npropylimidazole (XI), which reacted with isatin to form the tetracyclic system (XII). The individuality of (XII) was confirmed by thin-layer chromatography; however, we have not established which of the possible isomers was obtained: 2-phenyl-3-n-propyl-6H-imidazo[1',2':2,3][1,2,4]triazino[5,6-b]indole (XII-A) or 2-phenyl-3-n-propyl-10H-imidazo[1',2':2,3][1,2,4]triazino[6,5-b]indole (XII-B). The IR spectrum of (XII) has an absorption maximum with a fine structure in the 2750-3200 cm⁻¹ region which is characteristic for an associated NH bond.

EXPERIMENTAL

The UV spectra were taken on an SF-4A instrument in ethanolic solutions with concentrations of 10^{-4} - 10^{-5} M at a layer thickness of 1 cm. The IR spectra* were taken on a UR-20 instrument in chloroform. The PMR spectra were taken on a Varian A-60A instrument (60 MHz) in CDCl₃ with tetramethylsilane as internal standard.

The initial compounds were obtained by known methods, as indicated: benzaldehyde amidinohydrazone (III) and 2-amino-1-benzylideneamino-4-phenylimidazole (IV) - [4]; and α -bromovalerophenone (I) - [5].

<u>1-Benzylideneamino-3,6-diphenyl-5-n-propylimidazo[1,2-a]imidazole (VI)</u>. A mixture of 4.0 g (16.6 mmoles) of (I), 4.35 g (16.6 mmoles) of (IV), and 1.39 g (16.6 mmoles) of sodium bicarbonate in 15 ml of dimethylformamide was boiled with stirring for 3 h. The reaction mixture was poured into water, the aqueous layer was separated off, and the oil was allowed to stand until it solidified, after which it was washed with 10 ml of ethanol, filtered off, and dried. The yield of (VI) was 1.34 g (20%). Soluble in ethanol, benzene, and chloroform. Faintly yellowish needles. The results of analysis and the constants are given in Table 1.

<u>1-Benzylideneamino-3,6-diphenyl-2,5-di-n-propylimidazo[1,2-a]imidazole (VII) and 1,2-Dibenzyl-ideneamino-4-phenyl-5-n-propylimidazole (VII)</u>. A mixture of 35.2 g (0.217 mole) of (III) and 35.4 g (0.147 mole) of (I) in 30 ml of dimethylformamide was boiled for 2 h. The precipitate that deposited on cooling was filtered off, washed on the filter with ethanol (3×5 ml) and dried. Yield of (VII), 9.7 g (30%). Soluble in ethanol, benzene, and chloroform. Yellow needles. After 10 days, the precipitate that had deposited from the mother solution was filtered off, washed on the filter with 5 ml of ethanol, and dried. Yield 1.3 g (2.3%) of (VIII). Soluble in ethanol, benzene, and chloroform. Yellow prisms.

^{*}We express our gratitude to Yu.S. Ryabokobylko for taking the IR and PMR spectra.

Compound	mp, °C (solvent for crystallization)	Empirical formula	Found, %			Calculated, %			Yield,
			с	н	N	с	н	N	%
I II IX X XI XI XII	142,5—143,5 (ethanol) 176,5—177,0 (ethanol) 137,5—138,5 (ethanol) 218,5—219,5 (ethanol) 143,0—144,0 (benzene) 140,5—141,5 (benzene) 288,0—289,0 (ethanol)	$\begin{array}{c} C_{27}H_{24}N_4\\ C_{30}H_{30}N_4\\ C_{26}H_{24}N_4\\ C_{23}H_{26}N_4\\ C_{23}H_{25}N_3\\ C_{12}H_{16}N_4\\ C_{20}H_{17}N_5 \end{array}$	79,3 80,3 79,2 77,0 80,4 66,6 73.4	6,2 6,8 6,2 7,3 7,5 7,4 5,3	13,9 12,6 14,4 15,6 12,2 25,9 21,7	80,2 80,7 79,6 77,1 80,4 66,6 73,4	6,0 6,8 6,2 7,3 7,3 7,5 5,2	13,8 12,6 14,3 15,6 12,2 25,9 21,4	20,0 30,0 2,3 95,0 45,0 61,0 79,0

TABLE 1. Characteristics of the Compounds Obtained

TABLE 2. UV Spectra of the Substances Synthesized in Ethanol

Compound	$\frac{\text{Concentration,}}{\times 10^{-5} \text{ M}}$	λ_{\max} , nm (log ε)						
VI VII VIII IX XI XII XII	1,73,66,65,610,01,52,2	$\begin{array}{cccccccccccccccccccccccccccccccccccc$						

<u>1-Amino-3,6-diphenyl-2,5-di-n-propylimidazo[1,2-a]imidazole (IX)</u>. A mixture of 4.77 g (0.01 mole) of (VII), 17 ml of ethanol, 17 ml of hydrochloric acid, and 8 ml of water was boiled for 6 h, after which it was poured into water and neutralized with 25% ammonia. Yield 3.4 g (95%). Soluble in ethanol, chloro-form, and acetic acid, sparingly soluble in dilute mineral acids. Colorless fibrous needles.

3,6-Diphenyl-2,5-di-n-propyl-1H-imidazo[1,2-a]imidazole (X). With stirring at room temperature, a solution of 1.8 g of sodium nitrite in 24 ml of water was added to a solution of 6.2 g (17.3 mmoles) of (IX) in 120 ml of acetic acid and 11 ml of hydrochloric acid. The mixture was left to stand overnight, and then 300 ml of water and 30 ml of 25% ammonia were added. The precipitate that deposited was filtered off, washed with water, and dried. Yield 2.7 g (45%). Soluble in ethanol, benzene, chloroform, and acetic acid; sparingly soluble in dilute mineral acids. Small yellow needles.

<u>1,2-Diamino-5-n-propyl-4-phenylimidazole (XI)</u>. A mixture of 14.0 g (36.6 mmoles) of (VIII), 20 ml of hydrazine hydrate, and 60 ml of ethylene glycol was boiled for 2 h, after which it was poured into water. The precipitate that deposited was filtered off, washed with water, and dried. Yield 4.7 g (61%). Soluble in ethanol, benzene, chloroform, and dilute mineral acids. Colorless fibrous needles.

2-Phenyl-3-n-propyl-6H-imidazo[1',2':2,3][1,2,4]triazino[5,6-b]indole or 2-Phenyl-3-n-propyl-10Himidazo[1',2':2,3][1,2,4]triazino[6,5-b]indole (XII). A mixture of 1.25 g (5.8 mmoles) of (XI) and 0.85 g (5.8 mmoles) of isatin in 25 ml of benzene was boiled for 2 h. The precipitate that deposited on cooling was filtered off and dried. Yield 1.5 g (79%). Soluble in ethanol and chloroform; sparingly soluble in dilute mineral acids. Red fibrous needles. The thin-layer chromatography of (XII) was performed on alumina of activity grade II, chloroform, benzene, and carbon tetrachloride being used as the mobile phase. The .chromatography showed that an individual tetracyclic system had been obtained and not a mixture of isomers.

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