SYNTHESIS AND TRANSFORMATIONS OF 2,3-DIOXO-2,3-DIHYDROIMIDAZO[1,2-a]-BENZIMIDAZOLE DERIVATIVES

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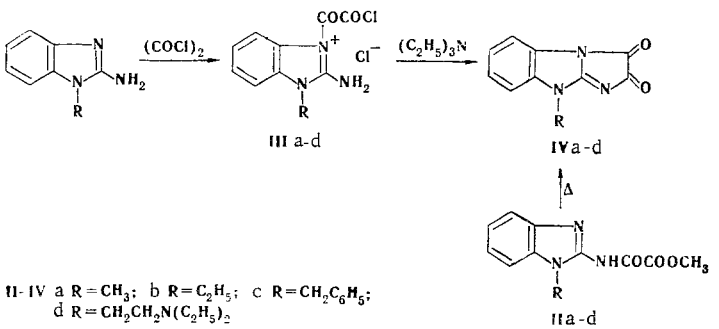
9-(H)Alkyl-2,3-dioxo-2,3-dihydroimidazo[1,2-a]benzimidazoles were synthesized by the action of oxalyl chloride on 2-amino-1(H)alkylbenzimidazoles and subsequent cyclization of the resulting 2-amino-1-(H)alkyl-3-chlorooxalylbenzimidazolium chlorides in the presence of triethylamine. The behavior of the synthesized benzimidazoles with respect to the action of alkalis, lithium aluminum hydride, and ethylmagnesium bromide was studied.

In order to obtain the previously undescribed 2,3-dioxo derivatives of imidazo[1,2-a]benzimidazole, we subjected 1-methyl-2-oxalylaminobenzimidazole (I) and 1-alkyl-2-methoxalylbenzimidazoles (II) to cyclization. Attempts to cyclize I by the action of various reagents (acetic anhydride, PCl_3, $POCl_3$, etc.) did not give positive results. When 2-methoxalylamino derivatives II are heated to 240-250°C, they split out an alcohol molecule and are converted to 9-alkyl-2,3-dioxo-2,3-dihydroimidazo[1,2-a]benzimidazoles (IV). However, the yields of these compounds do not exceed 27% because of pronounced resinification of the reaction mixture.

As in the case of monobasic acid chlorides [1], the ring nitrogen atom undergoes attack during the reaction of 2-amino-1-alkylbenzimidazoles with oxalyl chloride in acetone or dioxane in the cold to give 2-amino-3-chlorooxalyl-1-alkylbenzimidazolium chlorides (III) in almost quantitative yields. The absorption bands of two carbonyl groups show up at 1726-1753 and 1782-1812 cm^{-1} in the IR spectra of mineral oil suspensions of chlorides III; the absorption band of an amino group is observed at 3230-3495 cm^{-1}.



II-IV a R = CH_3; b R = C_2H_5; c R = $CH_2C_6H_5$; d R = $CH_2CH_2N(C_2H_5)_2$

When chlorides III are refluxed in dioxane in the presence of triethylamine or methylmorpholine for 2 h, an imidazoline ring is formed to give 2,3-dioxo derivatives of imidazo[1,2-a]benzimidazoles (IV).

The IR spectra of IV contain two absorption bands of C=O groups at 1694-1705 and 1748-1767 cm^{-1}. Since the order of the C=O bond in the 3 position (1.884) is higher than in the 2 position (1.841), the band in the higher-frequency region can be assigned to the $\nu_{C_{(3)}=O}$ vibrations, and the absorption at lower frequency can be assigned to the $\nu_{C_{(2)}=O}$ vibrations.

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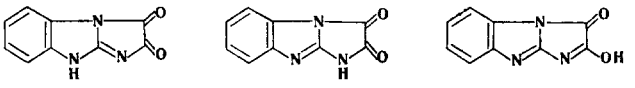
TABLE 1. 2-Amino-1(H)alkyl-3-chlorooxalylbenzimidazolium Chlorides (III and V)

Compound	R	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
				Cl	N	Cl	N	
V	H	225—227 (dec.)	$C_9H_7Cl_2N_3O_2$	27.7	16.0	27.3	16.1	99
IIIa	CH_3	191—192 (dec.)	$C_{10}H_9Cl_2N_3O_2$	26.1	15.1	25.9	15.3	56
IIIb	C_2H_5	160 (dec.)	$C_{11}H_{11}Cl_2N_3O_2$	24.9	14.4	24.6	14.6	65
IIIc	$CH_2C_6H_5$	154 (dec.)	$C_{16}H_{13}Cl_2N_3O_2$	20.7	12.0	20.3	12.0	78
IIId	$CH_2CH_2N(C_2H_5)_2$	156 (dec.)	$C_{15}H_{20}Cl_2N_4O_2$	20.1	15.3	19.8	15.6	82

NH-Unsubstituted 2,3-dioxo-2,3-dihydroimidazo[1,2-a]benzimidazole (VI), for which the following tautomeric forms are possible, was obtained by the action of oxalyl chloride on 2-aminobenzimidazole in the presence of triethylamine:

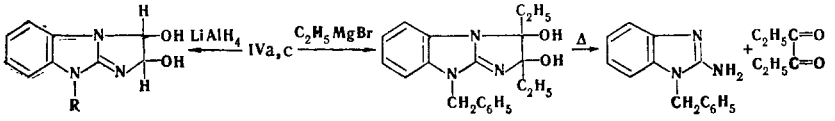


VI A VI B VI C

To ascertain the structure of this compound we recorded the IR spectra of VI, IVc, and 1-benzyl-2,3-dioxo-2,3-dihydroimidazo[1,2-a]benzimidazole (VII); the latter was obtained by reaction of equimolar amounts of 2-benzylaminobenzimidazole with oxalyl chloride in the presence of triethylamine.

The IR spectra of IVc and VII, in which tautomerism is impossible, contain two bands at 1705 and 1758 (IVc) and at 1764 and 1799 cm^{-1} (VII). Bands at 1690 and 3329 cm^{-1}, which can be assigned to the stretching vibrations of the C=O and OH groups, respectively, are observed in the spectrum of VI. It can therefore be assumed that 2,3-dioxo-2,3-dihydroimidazo[1,2-a]benzimidazole exists in the crystalline state in the form of enol (lactim) form VIC.

Imidazo[1,2-a]benzimidazole 2,3-dioxo derivatives IV are relatively resistant to the action of acids and alkalis in the cold, but when IVa is refluxed with 20% sodium hydroxide solution, its imidazoline ring is cleaved. 1-Methyl-2-oxaloaminobenzimidazole (I) was isolated after acidification of the solution to pH 3-4. When IVa,c are treated with lithium aluminum hydride in ether, both carbonyl groups undergo reduction to give 9-alkyl-2,3-dihydroxy-2,3-dihydroimidazo[1,2-a]benzimidazoles (VIII). The reaction of IVc with ethylmagnesium bromide in tetrahydrofuran (THF) leads to 9-benzyl-2,3-dihydroxy-2,3-diethyl-2,3-dihydroimidazo[1,2-a]benzimidazole (IX).



VIII IX

TABLE 2. 2-Methoxalylamino-1-R-benzimidazoles (II) and 2,3-Dioxo-9-R-2,3-dihydroimidazo[1,2-a]benzimidazoles (IV and VI)

Compound	R	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %	
				C	H	N	C	H	N	method A	method B
IIa	CH_3	193 (dec., aqueous alcohol)	$C_{11}H_{11}N_3O_3$	56.3	4.4	18.1	56.6	4.7	18.0	96	75
IIb	C_2H_5	218 (dec., aqueous alcohol)	$C_{12}H_{13}N_3O_3$	58.1	5.2	17.3	58.3	5.3	17.0	96	80
IIc	$CH_2C_6H_5$	193—194 (dec., aq. alcohol)	$C_{17}H_{15}N_3O_3$	65.8	4.5	13.7	66.0	4.9	13.6	85	70
VI	H	324—325 (acetic acid)	$C_9H_5N_3O_2$	57.4	2.4	22.1	57.7	2.7	22.4	66	—
IVa	CH_3	295 (alcohol)	$C_{10}H_7N_3O_2$	59.8	3.6	21.0	59.7	3.5	20.9	90	25
IVb	C_2H_5	269 (aqueous alcohol)	$C_{11}H_9N_3O_2$	61.0	4.5	19.1	61.4	4.2	19.5	67	27
IVc	$CH_2C_6H_5$	172—173 (alcohol)	$C_{16}H_{11}N_3O_2$	69.1	4.1	15.0	69.3	4.0	15.1	66	20
IVd	$CH_2CH_2N(C_2H_5)_2$	155—156 (hexane + benzene)	$C_{15}H_{18}N_4O_2$	63.3	6.5	19.8	62.9	6.3	19.6	46	—

Whereas dihydroxy derivatives VIII are quite stable compounds, dihydroxy derivative IX is decomposed to 2-amino-1-benzyl benzimidazole and dipropionyl (3,4-hexanedione) when it is heated in dioxane or other solvents; the formation of dipropionyl was confirmed by its conversion to diethylglyoxime [2].

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. Quantum-chemical calculations were carried out by the Hückel MO method with the Pullman parameters [3]. The molecular weight of IVa was determined cryoscopically in nitrobenzene.

2-Amino-1-alkyl-3-chlorooxalylbenzimidazolium Chlorides (III). A suspension of 2 mmole of 2-amino-1-alkylbenzimidazole in 20 ml of absolute acetone was added in portions to a solution of 0.51 g (4 mmole) of oxalyl chloride in 10 ml of acetone at 15-20°. After 1 h, the resulting precipitate was removed by filtration and washed with acetone and ether (see Table 1).

2-Amino-1H-2-chlorooxalylbenzimidazolium Chloride (V). This compound was obtained by the method described above by treatment of 2-aminobenzimidazole with an equimolar amount of oxalyl chloride.

2-Methoxalylamino-1-methylbenzimidazole (IIa). A) A solution of 1.47 g (0.01 mole) of 2-amino-1-methylbenzimidazole in 3.7 g (31 mmole) of dimethyl oxalate was refluxed for 5 h, after which it was cooled and triturated with ether. The solid material was removed by filtration, and the preceding operation was repeated three times. The product was washed with ether and dried at 100° to give 2.2 g of IIa. IR spectrum, cm^{-1}: 1660, 1710 (C=O), 3310 (NH).

B) A mixture of 1.47 g (0.01 mole) of 2-amino-1-methylbenzimidazole and 1.18 g (0.01 mole) of dimethyl oxalate in 25 ml of glacial acetic acid was refluxed for 3 h, after which the precipitate was removed by filtration and washed successively with acetic acid and ice water to give 1.7 g of IIa.

2-Methoxalylamino-1-ethylbenzimidazole (IIb) and 1-Benzyl-2-methoxalylaminobenzimidazole (IIc). These compounds were obtained by methods A and B above.

2,3-Dioxo-9-methyl-2,3-dihydroimidazo[1,2-a]benzimidazole (IVa). A) A solution of 1.47 g (10 mmole) of 2-amino-1-methylbenzimidazole in 50 ml of absolute dioxane was added in the course of 25 min to a solution of 1.9 g (15 mmole) of oxalyl chloride in 25 ml of dioxane at 15-20°. After 1 h, the mixture was heated to 60-70°, a solution of 6.1 g (30 mmole) of dry triethylamine in 10 ml of dioxane was added, and the mixture was refluxed for 30 min. The triethylamine hydrochloride was removed from the hot solution by filtration, and the filtrate was allowed to stand at room temperature for 10-12 h. The resulting precipitate was removed by filtration, washed with dioxane and hot water, and dried to give 1.8 g of IVa. Found: M 207. Calculated: M 201. IR spectrum, cm^{-1}: 1694, 1748 (C=O).

B) A 0.93-g (2 mmole) sample of 2-methoxalylamino-1-methylbenzimidazole (IIa) was heated at 240-250° for 8 h, after which the melt was dissolved in chlforoform and purified by chromatography on aluminum oxide with elution by acetone–chloroform (1 : 1) to give 0.2 g of IVa.

2,3-Dioxo-2,3-dihydroimidazo[1,2-a]benzimidazole (VI). This compound was similarly obtained (method A), except that 2-aminobenzimidazole was treated with an equimolar amount of oxalyl chloride. IR spectrum, cm^{-1}: 1690 (C=O), 3329 (OH).

2,3-Dioxo-9-ethyl-2,3-dihydroimidazo[1,2-a]benzimidazole (IVb). A) The method used to prepare IVa was used to obtain this compound from 2-amino-1-ethylbenzimidazole, but the reaction product was isolated from the reaction solution by the addition of water. IR spectrum, cm^{-1}: 1700, 1760 (C=O).

B) A 0.86-g (3 mmole) sample of 2-methoxyalylamino-1-ethylbenzimidazole (IIb) was heated at 180-200° for 5 h, after which the melt was triturated with ether and purified on aluminum oxide (elution with chloroform) to give 0.2 g of IVb.

2,3-Dioxo-9-benzyl-2,3-dihydroimidazo[1,2-a]benzimidazole (IVc). A) The method used to prepare IVb was used to obtain this compound, except that the reaction product was precipitated from the filtrate by the addition of hexane. IR spectrum, cm^{-1}: 1705, 1758 (C=O).

B) This compound was obtained from IIc by the method used to prepare IVb.

2,3-Dioxo-9-diethylaminoethyl-2,3-dihydroimidazo[1,2-a]benzimidazole (IVd). This compound was obtained by the method used to synthesize IVc (method A). IR spectrum, cm^{-1}: 1703, 1767 (C=O).

The properties of II, IV, and VI are presented in Table 2.

1-Benzyl-2,3-dioxo-2,3-dihydroimidazo[1,2-a]benzimidazole (VII). A solution of 0.67 g (3 mmole) of 2-benzylaminobenzimidazole [4] in 50 ml of dioxane was added to a solution of 0.57 g (4.5 mmole) of oxalyl chloride in 25 ml of dioxane previously cooled to 10-15°, and the mixture was allowed to stand at room temperature for 1 h. It was then heated to 60-70° and treated with 0.91 g (9 mmole) of triethylamine, after which the mixture was refluxed for 10 h. It was then cooled, and the precipitated triethylamine hydrochloride was removed by filtration. The solvent was removed from the filtrate by vacuum distillation, and the oily residue was triturated with hexane to give 0.48 g (58%) of pale-yellow crystals with mp 110° (from octane). IR spectrum, cm^{-1}: 1764, 1799 (C=O). Found: C 69.1; H 4.2; N 15.5%. $C_{16}H_{11}N_3O_2$. Calculated: C 69.3; H 4.0; N 15.1%.

2,3-Dihydroxy-9-methyl-2,3-dihydroimidazo[1,2-a]benzimidazole (VIIIa). A suspension of 1.0 g (5 mmole) of IVa in 50 ml of ether was added to a solution of 0.5 g (0.01 mole) of lithium aluminum hydride in 50 ml of absolute ether, and the mixture was refluxed for 4 h. It was then cooled and treated with 4-5 ml of water, and the ether layer was separated. Compound VIIIa was extracted from the aqueous layer with chloroform. The chloroform extract was dried with magnesium sulfate, the solvent was removed by distillation, and the residue was crystallized from alcohol to give 0.6 g (60%) of colorless needles with mp 235-236°. IR spectrum, cm^{-1}: 3130-3490 (OH). Found: C 58.1; H 5.7; N 20.2%. $C_{10}H_{11}N_3O_2$. Calculated: C 58.5; H 5.4; N 20.5%.

9-Benzyl-2,3-dihydroxy-2,3-dihydroimidazo[1,2-a]benzimidazole (VIIIb). This compound was similarly obtained in 70% yield as colorless crystals with mp 184° (from alcohol). IR spectrum, cm^{-1}: 3100-3370 (OH). Found: C 68.6; H 5.2; N 14.5%. $C_{16}H_{15}N_3O_2$. Calculated: C 68.3; H 5.4; N 14.9%.

9-Benzyl-2,3-dihydroxy-2,3-diethyl-2,3-dihydroimidazo[1,2-a]benzimidazole (IX). A solution of 0.83 g (3 mmole) of IVc in 10 ml of tetrahydrofuran (THF) was added with stirring in the course of 15 min to ethylmagnesium bromide obtained from 0.18 g (7 g-atom) of magnesium and 1.4 g (7 mmole) of ethyl bromide in 8 ml of ether, and the mixture was refluxed for 1 h. It was then cooled and treated with 2 ml of water and 2 ml of saturated ammonium chloride solution. The layers were separated, and the organic layer was dried with magnesium sulfate and vacuum distilled, and the oily residue was refluxed with hexane. The insoluble material was removed by filtration to give 0.8 g (52%) of colorless crystals with mp 112° (from chloroform–petroleum ether). IR spectrum, cm^{-1}: 3300-3380 (OH). Found: C 70.9; H 6.5; N 12.3%. $C_{20}H_{23}N_3O_2$. Calculated: C 71.2; H 6.9; N 12.5%.

1-Methyl-2-oxaloaminobenzimidazole (I). A) A solution of 0.5 g (3 mmole) of 2-amino-1-methylbenzimidazole and 0.27 g (3 mmole) of oxalic acid in 15 ml of alcohol was refluxed for 3 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with alcohol and ether to give 0.5 g (68%) of a product with mp 205° (dec., from alcohol). Found: C 54.4; H 4.0; N 19.5%. $C_{10}H_9N_3O_3$. Calculated: C 54.8; H 4.1; N 19.2%.

B) A 0.4-g (2 mmole) sample of IVa was refluxed for 10 min with 5 ml of 20% sodium hydroixde solution, after which the mixture was acidified with 10% hydrochloric acid to give 0.3 g (72%) of a substance with mp 205° (dec.). No melting point depression was observed for a mixture of this product with a sample obtained by method A.

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