IMIDAZO[1,2-*a*]BENZIMIDAZOLE DERIVATIVES

V.* 3-AMINO DERIVATIVES OF 2,9-SUBSTITUTED IMIDAZO[1,2-*a*]BENZIMIDAZOLES

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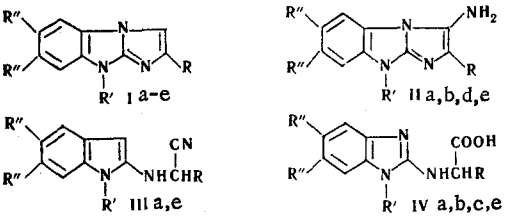
3-Amino derivatives of 9-alkyl(benzyl)-2-arylimidazo[1,2-*a*]benzimidazoles, obtained by the reduction of the appropriate 3-nitro(nitroso) derivatives, are extremely unstable, and the imidazole ring opens readily resulting in conversion to 2-(α-carboxybenzylamino)benzimidazoles. The reaction apparently proceeds through the intermediate formation of 2-(α-cyanobenzylamino)benzimidazole, which is a tautomeric form of the 3-amino compound and can react as such to form 3-acylamino derivatives and anils. If there is a methyl group in the 3-position of the ring, the amine is quite stable and can be isolated in free form.

As previously communicated in [2], the reduction of 3-nitro(nitroso)- and 3-areneazo derivatives of 9-methyl-2-phenylimidazo[1,2-*a*]benzimidazole (Ia) with stannous chloride in hydrochloric acid results in the formation of an unstable amine (IIa). The imidazole ring is opened during isolation from the tin complex, and 2-(α-carboxybenzylamino)-1-methylbenzimidazole (IVa), the structure of which was proved by means of the IR spectra and a number of transformations, is formed. Similar transformations are observed for the 3-nitroso derivative of the 9-benzyl compound (Ib).



I a-e

II a,b,d,e

III a,e

IV a,b,c,e

a R = C_6H_5, R′ = CH_3, R″ = H; b R = C_6H_5, R′ = $CH_2C_6H_5$, R″ = H;
c R = C_6H_5, R′ = C_2H_5, R″ = CH_3; d R = *p*-BrC_6H_4, R′ = CH_3, R″ = H;
e R = R′ = CH_3, R″ = H

It can be assumed that amine IIa exists in this case as a tautomeric form, viz., nitrile IIIa, which is a quite stable compound and is readily obtained by the reaction of 2-amino-1-alkylbenzimidazole with benzaldehyde, bisulfite, and sodium cyanide. The structure of IIIa was confirmed by the IR spectroscopic data. The compound is readily hydrolyzed to acid IVa, and reacts as the tautomeric amine (IIa) with acetic anhydride and benzaldehyde to form, respectively, 3-acetamido- (V) and 3-benzylideneamino derivatives (VI) of 9-methyl-2-phenylimidazo[1,2-*a*]benzimidazole. Thus, the peculiar form of ring-chain tautomerism previously described in the imidazo[1,2-*a*]pyridine series [3-5] (see scheme) occurs here.

The ring is cleaved in a different manner in the reduction of 3-nitro derivative Ia with sodium stannite: the compound is converted to 1-methyl-3-oximinophenacylbenzimidazolone (α-monoxime) through a step involving formation of a nitroso derivative [6].

The imidazole ring is opened to form an amino acid (IVc) in the reduction under the indicated conditions of 3-nitroso-6,7-dimethyl-2-phenyl-9-ethylimidazo[1,2-*a*]benzimidazole (VII). A product of more pro-

*See [1] for communication IV.

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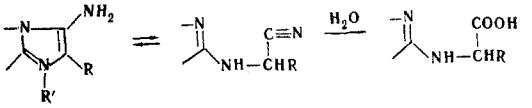


found cleavage (2-amino-1-methylbenzimidazole) is obtained from 3-nitroso-2-(p-bromophenyl)-9-methylimidazo[1,2-*a*]benzimidazole (VIII) on heating the tin complex with dilute alkali. However, the initially formed amine (IId) is somewhat more stable and can be isolated as the hydrochloride and picrate if the reduction of the nitroso compound is carried out with zinc dust in glacial acetic acid. Similar results are observed in the reduction of 3-nitroso-9-benzyl-2-phenylimidazo[1,2-*a*]benzimidazole (IX): the resulting amine can be isolated as the hydrochloride, pircrate, or acetyl derivative (X).

3-Amino-2,9-dimethylimidazo[1,2-*a*]benzimidazole (IIe) is the most stable compound in this series. It does not change on refluxing in dilute hydrochloric acid but is readily diazotized. We could not establish the possibility of the conversion of this amine to the tautomeric cyano form; on the other hand, nitrile IIIe, obtained by synthesis from 2-amino-1-methylbenzimidazole and acetaldehyde, is converted by the action of p-nitrobenzaldehyde to anil XI, which is identical to the compound formed from the amino form (IIe). This observation makes it possible to additionally establish that the amino group and, consequently, the nitro group in the starting compound are in the 3-position of the ring.

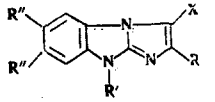
EXPERIMENTAL

2-(α-Carboxybenzylamino)-1-methylbenzimidazole (IVa). Stannous chloride (6.5 g) was gradually added with mechanical stirring to a suspension of 2.3 g (0.01 mole) of 3-nitro derivative Ia in 30 ml of concentrated HCl, and the mixture was refluxed until the red granules of the isonitroso derivative [6] in the precipitate vanished. The mixture was then cooled, and the snow-white precipitate of the tin complex of the amine was filtered to give 4.16 g of product. Found %: N 9.63. $C_{16}H_{14}N_4 \cdot SnCl_4 \cdot 2HCl$. Calculated %: N 9.41. The action of a 10% solution of sodium hypochlorite on a hot alcohol solution of the complex gave a dark-red azo compound which was chromatographed on aluminum oxide with chloroform as the eluant to give a product with mp 276-278° (from alcohol). The compound contained about 25% chlorine.

The complex (1.5 g) was refluxed for 10 min in a mixture of 40 ml of water and 3 ml of alcohol, and the precipitate of basic tin salts was filtered. Cooling of the filtrate precipitated 0.75 g of the colorless monohydrate of the hydrochloride of IVa with mp 153° (decomp., from alcohol–ether). Found %: N 12.7. $C_{16}H_{15}N_3O_2 \cdot HCl \cdot H_2O$. Calculated %: N 12.5. The product was dried in vacuo over P_2O_5 at 100° and again analyzed. Found %: N 13.2. $C_{16}H_{15}N_3O_2 \cdot HCl$. Calculated %: N 13.2. IR spectrum: $\nu_{C=O}$ 1740 cm^{-1}. At 170-190° the hydrochloride is decarboxylated to form a mixture of several compounds, one of which was chromatographically identical to 1-methyl-2-benzylaminobenzimidazole [7]. The free amino acid (IVa) precipitated from the hydrochloride solution in dilute ammonium hydroxide after evaporation of the ammonia to give snow-white, fine needles with mp 220° (decomp., from water or 50% aqueous alcohol). IR spectrum, cm^{-1}: $\nu_{C=O}$ 1665, ν_{C-O} 1360, ν_{NH} 3330, ν_{OH} 2600. On heating with dilute alkali the compound is cleaved to 2-amino-1-methylbenzimidazole. The action of 50% hypochlorite converted IVa to an azo compound, which was chromatographed on Al_2O_3 with chloroform as the eluant to give bright-orange needles with mp 285-286° (decomp., from alcohol), which were identical to genuine 1,1'-dimethyl-2,2'-azobenzimidazole [8]. In ether solution IVa forms an ester with diazomethane [2]. IR spectrum, cm^{-1}: $\nu_{C=O}$ 1746, ν_{C-O} 1225, ν_{NH} 3270.

2-(α-Cyanobenzylamino)-1-methylbenzimidazole (IIIa). A total of 2 ml [2.12 g (0.02 mole)] of benzaldehyde, 2.08 g (0.02 mole) of freshly prepared dry sodium bisulfite [10], and 15 ml of water was stirred for 0.5 h at 15-20°, 2.94 g (0.02 mole) of 1-methyl-2-aminobenzimidazole was added, and the mixture was heated on a boiling-water bath for 1 h. After the solids had gone into solution, a saturated solution of 2 g (0.04 mole) of sodium cyanide was added dropwise, and heating was continued for another 2-3 h. The next day, the precipitated nitrile was filtered to give 4.66 g (89%) of snow-white, shiny needles with mp 187-188° (decomp., from ethyl acetate) which were soluble on heating in alcohol. Found %: C 73.5; H 5.5; N 21.4. $C_{16}H_{14}N_4$. Calculated %: C 73.3; H 5.4; N 21.4. The valence vibrations of the C≡N group in the IR spectrum of III are displayed as a weak band at 2240 cm^{-1}, while the NH valence vibrations are displayed at 3155 cm^{-1}. Saponification of IIIa with dilute hydrochloric acid gave a quantitative yield of a compound with mp 153°, which was identical to the hydrochloride of IVa obtained by reductive cleavage of 3-nitroso-Ia. Compound IVa was obtained from the hydrochloride and had mp 218-219°.

TABLE 1. Imidazo[1,2-*a*]benzimidazole Derivatives



Compound	R	R′	R″	X	mp (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
							C	H	N	C	H	N	
VII	C_6H_5	C_2H_5	CH_3	NO	265 (DMFA)	$C_{19}H_{18}N_4O$	71,9	5,5	17,7	71,7	5,7	17,6	100
VIII	*p*-BrC_6H_4	CH_3	H	NO	244 (decomp., DMFA)	$C_{16}H_{11}BrN_4O$*	53,8	3,4	15,6	54,1	3,1	15,8	83,5
IX	C_6H_5	$C_6H_5CH_2$	H	NO	215 (alcohol + DMPA)	$C_{22}H_{16}N_4O$	74,8	4,5	16,0	75,0	4,6	15,9	94
VI	C_6H_5	CH_3	H	N=CHC_6H_5	137—138 (alcohol)	$C_{23}H_{18}N_4$	78,9	5,3	16,2	78,8	5,2	16,0	97
V	C_6H_5	CH_3	H	$NHCOCH_3$	235 (decomp., %alco.)	$C_{18}H_{16}N_4O$	70,8	5,4	18,2	71,1	5,3	18,4	91
IId·HCl	*p*-BrC_6H_4	CH_3	H	NH_2	211 (decomp., aqueous alcohol)	$C_{16}H_{13}BrN_4 \cdot HCl$	51,1	3,7		50,9	3,7		
IId, picrate	*p*-BrC_6H_4	CH_3	H	NH_2	280-281,5 (decomp., CH_3COOH)	$C_{16}H_{13}BrN_4 \cdot C_6H_3N_3O_7$			17,3			17,2	
IIb, picrate	C_6H_5	$C_6H_5CH_2$	H	NH_2	188 (decomp. CH_3COOH)	$C_{22}H_{18}N_4 \cdot C_6H_3N_3O_7$	59,0	4,0		59,3	3,7		
IIb·HCl	C_6H_5	$C_6H_5CH_2$	H	NH_2	217 (decomp., aqueous alcohol)	$C_{22}H_{18}N_4 \cdot HCl$*	70,4	5,5		70,1	5,1		
X	C_6H_5	$C_6H_5CH_2$	H	$NHCOCH_3$	212—213 (aqueous alcohol)	$C_{24}H_{20}N_4O$			14,5			14,7	
IIe·2HCl·H_2O	CH_3	CH_3	H	NH_2	297 (decomp., alcohol + ether)	$C_{11}H_{12}N_4 \cdot 2HCl \cdot H_2O$*	45,8	5,6	19,3	45,5	5,6	19,2	
IIe·2HCl	CH_3	CH_3	H	NH_2	297 (decomp., abs. alcohol + ether)	$C_{11}H_{12}N_4 \cdot 2HCl$*	48,2	5,4	20,5	48,3	5,2	20,5	
XI	CH_3	CH_3	H	N=$CHC_6H_4NO_2$-*p*	230—232 (alcohol)	$C_{18}H_{15}N_5O_2 \cdot H_2O$	61,8	4,8	19,9	61,5	4,9	19,9	78,2

*The composition of the compound was additionally confirmed by determining the percentage of halogen.

3-Benzylidieneamino-9-methyl-2-phenylimidazo[1,2-*a*]benzimidazole (VI). A mixture of 0.26 g (1 mmole) of IIIa and 0.12 g (1.2 mmole) of benzaldehyde was heated to 130° and held at this temperature for 5-7 min. The melt (which gave one spot on the thin-layer chromatogram) was cooled and triturated with petroleum ether, and the resulting precipitate was filtered and washed with petroleum ether to give bright-orange, strongly electrifiable, silky needles. Bands characteristic for IIIa have vanished in the IR spectrum of VI, and an intense $\nu_{C=N}$ band appears at 1632 cm^{-1}.

3-Acetamido-9-methyl-2-phenylimidazo[1,2-*a*]benzimidazole (V). This was obtained by the action of acetic anhydride on IIIa on heating the mixture to the boiling point and was isolated as shiny colorless plates.

1-Methyl-3-oximinophenacylbenzimidazolone (α-Monoxime). A solution of sodium stannite (from 0.47 g of $SnCl_2 \cdot 2H_2O$ in 5 ml of 10% sodium hydroxide) was added to a suspension of 0.3 g of 3-nitro-Ia in 30 ml of ethanol, and the mixture was refluxed for 4 h. The nitro compound dissolved, and tin salts precipitated. The tin salts were filtered, the filtrate was acidified with concentrated HCl to pH 1, diluted with water, and the resulting precipitate was filtered to give 0.15 g of a product with mp 226-227° (decomp., from alcohol). This product did not depress the melting point of the product of ring opening of the nitroso compound in alkali [6].

3-Nitroso-6,7-dimethyl-2-phenyl-9-ethylimidazo[1,2-a]benzimidazole (VII). Glacial acetic acid (2-3 ml) was added to an alcohol solution of 0.3 g (1 mmole) of Ic [1], followed by the dropwise addition of an aqueous solution of 0.07 g (1 mmole) of sodium nitrite to give dark-green, shiny needles which were slightly soluble in alcohol, ether, and acetone.

2-(α-Carboxybenzylamino)-5,6-dimethyl-1-ethylbenzimidazole (IVc). Derivative VII (0.8 g) was thoroughly ground with powdered tin, dilute hydrochloric acid (20 ml of 3:1) was added, and the mixture was refluxed until complete decoloration of the red oil. The solution was decanted, and the oil was treated with ethyl acetate; the ethyl acetate was evaporated, and the residue was refluxed for 5-10 min with a small amount of dilute ammonium hydroxide and filtered. The filtrate was allowed to stand in air until the odor of ammonia vanished, during which IVc precipitated to give 0.57 g (70%) of a product with mp 242° (decomp., from dilute acetic acid). Found %: C 70.3; H 6.5; N 13.1. $C_{19}H_{21}N_3O_2$. Calculated %: C 70.6; H 6.5; N 13.0. IR spectrum, cm^{-1}: $\nu_{C=O}$ 1662, ν_{C-O} 1349, ν_{NH} 3310, ν_{OH} 2620.

Methyl Ester of IVc. This was obtained by the action of an ether solution of diazomethane on a suspension of IVc in alcohol. The oil remaining after evaporation crystallized in a vacuum desiccator over P_2O_5 to give 75% of fine, strongly electrifiable needles with mp 136° (from hexane). Found %: C 71.3; H 6.7; N 12.5. $C_{20}H_{23}N_3O_2$. Calculated %: C 71.2; H 6.9; N 12.5. IR spectrum, cm^{-1}: $\nu_{C=O}$ 1750, ν_{C-O} 1220, ν_{NH} 3220.

3-Nitroso-2-(p-bromophenyl)-9-methylimidazo[1,2-*a*]benzimidazole (VIII). A solution of 0.5 g (7.5 mmole) of sodium nitrite in 3 ml of water was added dropwise to a hot solution of 1.63 g (5 mmole) of Id in 20 ml of ethanol and 10 ml of glacial acetic acid, and the mixture was heated at 70-80° for 15-20 min. The mixture was cooled, and the bright-green precipitate of VIII was filtered and washed with water and alcohol.

A tin complex was formed in the reduction of VIII with stannous chloride in hydrochloric acid and was heated with excess 5-10% NaOH and extracted with hot benzene. After evaporation of the benzene, the residue was refluxed with acetone and filtered, and the acetone was evaporated to give a product with mp 200-201° (from alcohol). The compound was identical to an authentic sample of 1-methyl-2-aminobenzimidazole.

3-Amino-2-(p-bromophenyl)-9-methylimidazo[1,2-*a*]benzimidazole (IId). A suspension of 1 g of VIII in 10 ml of glacial acetic acid was shaken with zinc dust at room temperature until the solution was completely decolorized (2-2.5 h). The excess zinc dust and zinc salts were filtered and washed on the filter with glacial acetic acid, and several drops of concentrated H_2SO_4 were added to the filtrate. After 30-40 min the resulting precipitate was filtered and washed with acetic acid. A suspension of it in water was made alkaline with 22% ammonium hydroxide, and the amine was extracted with chloroform. The amine was unstable, and the solution rapidly turned red. For this reason, concentrated HCl was added immediately to it, and the resulting precipitated hydrochloride of IId was filtered and washed with acetone to give colorless, fibrous, strongly electrifiable needles.

3-Nitroso-9-benzyl-2-phenylimidazo[1,2-*a*]benzimidazole (IX). This was obtained in the same way as 3-nitroso-Ia [6] as shiny, dark-green plates. Treatment of IX with concentrated HCl gave a red hydrochloride of IX with mp 194-195°. Found %: N 14.5. $C_{22}H_{16}N_4O \cdot HCl$. Calculated %: N 14.4.

2-Imino-1-benzyl-3-oximinophenacylbenzimidazoline. The hydrochloride of IX was readily hydrolyzed with moist air to 2-imino-1-benzyl-3-hydroximinophenacylbenzimidazoline hydrochloride [6] as colorless prisms with mp 199-200° (from alcohol). Found %: N 13.6. $C_{22}H_{18}N_4O_2 \cdot HCl$. Calculated %: N 13.8. The crystal hydrate of the base was isolated by means of ammonia from the hydrochloride as pale-yellow plates with mp 117.5° (from alcohol). Found %: C 70.0; H 5.1. $C_{22}H_{18}N_4O_2 \cdot \frac{1}{2}H_2O$. Calculated %: C 69.6; H 5.1. The compound was unstable and was converted to IX during drying.

3-Amino-9-benzyl-2-phenylimidazo[1,2-*a*]benzimidazole (IIb). This was obtained in the same way as IId with the difference that the precipitate ($ZnSO_4$) resulting after acidification of the acetic acid solution with concentrated H_2SO_4 was immediately filtered; the amine sulfate gradually crystallized out from the mother liquor and was filtered after 1 h. The picrate of IIb was obtained by the addition of an alcoholic solution of picric acid to an aqueous alcohol suspension of the sulfate and heating the mixture.

The free amine was obtained by the action of sodium acetate on a suspension of the sulfate in water, but it changed rapidly. The action of alcoholic HCl converted it to hydrochloride of IIb as snow-white, silky needles.

The 3-acetamido derivative (X) was obtained as silky, shiny needles by brief refluxing of IIb with acetic anhydride.

3-Amino-2,9-dimethylimidazo[1,2-*a*]benzimidazole (IIe). The reduction of 3-nitro-Ie was carried out with stannous chloride in alcoholic HCl via the method proposed in [10] for 1-nitro-3-phenylimidazo[5,1-b]-benzothiazole to give 61.6% of snow-white scales which darkened slightly during drying and had mp 192.5° (from benzene). Found %: N 27.8. $C_{11}H_{12}N_4$. Calculated %: N 28.0. IR spectrum, cm^{-1}: ν_{NH} 3380, 3487; δ_{NH_2} 1643, ν_{C-N} 1280, $\nu_{C\equiv N}$ 2143 (see [11]).

Refluxing IIe with dilute hydrochloric acid gave the dihydrochloride of IIe as a crystal monohydrate; the yellowish-white, fine needles lost water at 110-120°.

3-(p-Nitrobenzylideneamino)-2,9-dimethylimidazo[1,2-*a*]benzimidazole (XI). This was obtained in 78.2% yield by refluxing an alcohol solution of IIe with p-nitrobenzaldehyde. The product was dark-orange needles. An identical substance was formed by refluxing an alcohol solution of nitrile IIIe with p-nitrobenzaldehyde.

3-(2-Hydroxynaphthylazo)-2,9-dimethylimidazo[1,2-*a*]benzimidazole. The diazonium solution, obtained in the usual way from 0.15 g (0.75 mmole) of IIe, was poured into an alkaline solution of 0.11 g (0.75 mmole) of β-naphthol. The precipitate was chromatographed with a column filled with aluminum oxide with chloroform as the eluant to give 0.2 g (75%) of dark cherry-red needles with mp 235-236° (from alcohol). Found %: C 71.1; H 5.0; N 19.8. $C_{21}H_{17}N_5O$. Calculated %: C 71.0; H 4.8; N 19.7.

2-(α-Cyanoethylamino)-1-methylbenzimidazole (IIIe). This was obtained, like IIIa, from 2.94 g (0.02 mole) of acetaldehyde. The viscous oil obtained was extracted with chloroform. The residue after evaporation of the chloroform was washed with ethyl acetate and recrystallized from a small amount of benzene to give 1.6 g (40%) of snow-white, fine needles with mp 139-140°. Found %: N 28.0, 27.9. $C_{11}H_{12}N_4$. Calculated %: N 28.0. IR spectrum: $\nu_{C\equiv N}$ 2230 cm^{-1}.

2-(α-Carboxyethylamino)-1-methylbenzimidazole (IVe). Compound IIIe (0.40 g) was refluxed for 2 h with 4 ml of aqueous HCl (1 : 1). The mixture was then allowed to stand to precipitate the hydrochloride of IVe as 0.41 g (80%) of snow-white needles with mp 237-238° (decomp., from alcohol–ether). Found %: C 51.7; H 5.7; N 16.5; Cl 13.4. $C_{11}H_{13}N_3O_2 \cdot HCl$. Calculated %: C 51.7; H 5.5; N 16.4; Cl 13.9. The hydrochloride was very hygroscopic and readily formed a monohydrate.

The IR spectra of mineral oil suspensions were obtained with a UR-20 spectrometer.

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