STUDIES ON DERIVATIVES OF IMIDAZO[1,2-a]BENZIMIDAZOLE

II*. ALDEHYDES AND STYRYL-SUBSTITUTED IMIDAZO[1,2-a]BENZIMIDAZOLES

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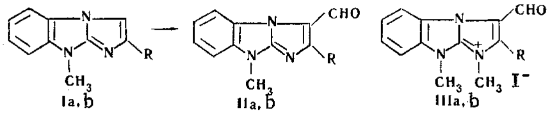
UDC 547.785.5+547.571+542.953.4

It has been found that 9-methyl-2-phenyl- and 2,9-dimethylimidazo[1,2-a]benzimidazoles undergo direct formylation at position 3. The formyl derivatives obtained take part in a series of condensations characteristic for aldehydes, but they do not undergo the Cannizzaro disproportionation.

Continuing a study of the electrophilic substitution reactions of imidazo[1,2-a]benzimidazole [1], we have established that the direct Vilsmeier formylation of 9-methyl-2-phenylimidazo[1,2-a]benzimidazole (Ia) takes place at position 3 of the imidazole ring attached to the benzimidazole system. The position of entry of the aldehyde group was established by means of the independent synthesis of this aldehyde from the 3-bromo derivative obtained previously [1] via the organolithium compound. 2,9-Dimethylimidazo-[1,2-a]benzimidazole (Ib), which was synthesized by a method described previously [2] from 2-amino-1-methylbenzimidazole and bromoacetone, also takes part in the formylation reaction. The structures of the aldehydes (IIa,b) obtained by formylation are confirmed by their IR spectra, which contain the absorption bands at 1638 and 1640 cm^{-1} that are characteristic for aldehydes of this type [3].



I–III a $R = C_6H_5$, b $R = CH_3$

Under the action of aromatic amines, IIa,b are converted into anils (Table 1), and they condense with nitro compounds and react with hippuric acid and acetic anhydride to form azlactones. Compounds IIb react more readily than IIa.

However, these aldehydes cannot take part in the Cannizzaro reaction, including cross-sections of this type, under very diverse conditions and in the presence of catalysts (active silver, freshly prepared silver oxide). An attempt to carry out this transformation by the action of sodium amide in liquid ammonia led to the deformylation of IIa with the formation of the initial Ia in almost quantitative yield.

On prolonged heating with methyl iodide, compounds II form methiodides which are unstable to heating in an alkaline medium: the 2-methyl derivative (IIIb), losing methyl iodide, is converted into the initial aldehyde, and the phenyl derivative (IIIa) undergoes deformylation, as well.

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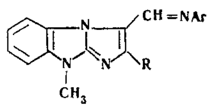
*For Communication I, see [1].

Rostov-on-Don State University. Translated from Geterotsiklicheskikh Soedinenii, Vol. 6, No. 6, pp. 838-841, June, 1970. Original article submitted July 28, 1968.

TABLE 1. Azomethines of the Imidazo[1,2-a]benzimidazole Series



Compound	R	Ar	Mp, °C (solvent for crystallization)	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
IVa	CH_3*	C_6H_4OH-*o*	292 (decomp. DMFA)	$C_{18}H_{16}N_4O$	71,28	5,54	18,34	71,04	5,30	18,42	83
IVb	C_6H_5*	C_6H_4OH-*o*	245 (benzene)	$C_{23}H_{18}N_4O$	75,60	4,79	15,40	75,39	4,95	15,29	38
IVc	CH_3*	$C_6H_4NO_2$-*p*	142 (ethanol)	$C_{18}H_{15}N_5O_2 \cdot H_2O$‡	61,48	5,04	20,03	61,53	4,88	19,93	98
IVd	C_6H_5†	$C_6H_4NO_2$-*p*	230 (benzene)	$C_{23}H_{17}N_5O_2$	69,64	4,29	17,96	69,86	4,32	17,72	76

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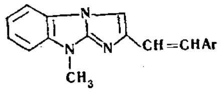
*Obtained by boiling equimolecular amounts of the starting materials in ethanol: IVa for 2 h, IVb for 9-10 h, and IVc for 3 h.

†Obtained by fusion at 150°C for 5 h and chromatography of the melt on a column of alumina (chloroform).

‡The compound does not lose water even on drying in vacuum over phosphorus pentoxide at 100°C.

TABLE 2. 9-Methyl-2-styrylimidazo[1,2-a]benzimidazoles



Compound	Ar	Mp, °C (solvent for crystallization)	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
1	C_6H_5	215(ethanol)	$C_{18}H_{15}N_3 \cdot H_2O$	74,47	5,55	14,24	74,21	5,28	14,42	90
2	*p*-$O_2NC_6H_4$	221(decomp., DMFA)	$C_{18}H_{14}N_4O_2 \cdot H_2O$	64,46	4,79	16,65	64,24	4,80	16,66	71,5
3	*o*-HOC_6H_4	297(DMFA)	$C_{18}H_{15}N_3O$	74,63	5,39	14,81	74,72	5,32	14,52	98
4	2,4-$(OH)_2C_6H_3$	307(DMFA)	$C_{18}H_{15}N_3O_2$	70,79	4,95	13,85	70,82	4,95	13,76	41
5	*p*-$(CH_3)_2NC_6H_4$	282(ethanol)	$C_{20}H_{20}N_4$	75,94	6,50	17,97	75,92	6,37	17,71	63

We were unable to convert Ib into an aldehyde by oxidizing the methyl group in position 2 with selenium dioxide: a complex mixture of conversion products was formed from which it was impossible to isolate the aldehyde. The oxidation of Ib by potassium permanganate in a neutral medium led to the opening of the imidazole ring attached to the benzimidazole system with the formation of 1,1'-dimethyl-2,2'-azobenzimidazole [4].

In spite of the fact that the methyl group in position 2 of IIb is not conjugated with the pyridine nitrogen atom of the imidazole ring, the mobility of the hydrogen atoms in this group is very high: condensation with aromatic aldehydes takes place very readily with the formation of 2-styryl derivatives (Table 2). The IR spectra of these compounds each has an absorption band at 1575 cm^{-1}, the presence of which shows the conjugation of the double bond with the aromatic ring. This is also shown by the shift of λ_{max} in the UV spectra by 10-15 nm in the long-wave direction (Fig. 1) as compared with I. All the styryl derivatives synthesized fluoresce in UV light.

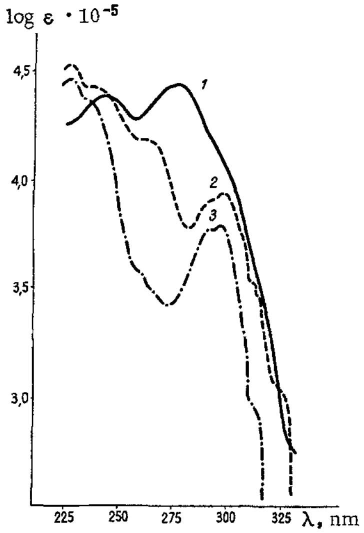


Fig. 1. UV absorption spectra of imidazo[1,2-a]benzimidazole derivatives (methanol): 1) 9-methyl-2-phenylimidazo[1,2-a]benzimidazole; 2) 2-(p-dimethylaminostyryl)-9-methylimidazo-[1,2-a]benzimidazole; 3) 9-methyl-2-styrylimidazo[1,2-a]benzimidazole.

EXPERIMENTAL

3-Acetonyl-2-imino-1-methylbenzimidazoline Hydrobromide. A hot ethanolic solution of 1.47 g (1 mmole) of 2-amino-1-methylbenzimidazole was mixed with 0.83 ml (1 mmole) of bromoacetone and the mixture was left overnight in a dark place. Ether was added, and the precipitate was filtered off and was washed with acetone and ether. Yield 2.42 g (85.5%). Snow-white needles with mp 287°C (decomp. from water). Found, %: C 46.64; H 4.55; Br 28.28; N 15.03. $C_{11}H_{13}N_3O \cdot HBr$. Calculated, %: C 46.49; H 4.97; Br 28.12; N 14.79.

3-Acetonyl-2-imino-1-methylbenzimidazoline. The base was isolated from an aqueous solution of the hydrobromide by means of a saturated solution of sodium carbonate with almost quantitative yield. Colorless needles, mp 110-111°C (from aqueous alcohol). Found, %: C 64.95; H 6.77; N 20.64. $C_{11}H_{13}N_3O$. Calculated, %: C 65.01; H 6.45; N 20.68.

The compound is unstable and gradually cyclizes, forming Ib, on storage.

2,9-Dimethylimidazo[1,2-a]benzimidazole (Ib). The hydrochloride of Ib was obtained with a yield of 88% by boiling (2 h) a solution of the imine or its hydrobromide in concentrated hydrochloric acid. Colorless needles with mp 200°C (decomp.). Found, %: N 18.66. $C_{11}H_{11}N_3 \cdot HCl$. Calculated, %: 18.95.

The salt was dissolved in ethanol and converted into the base by the addition of ammonia. Snow-white fibers. mp 94°C (from ethanol)*. Found, %: C 70.98; H 5.99; N 23.02. $C_{11}H_{11}N_3$. Calculated, %: C 71.31; H 5.99; N 22.69.

3-Formyl-2,9-dimethylimidazo[1,2-a]benzimidazole (IIb). With vigorous stirring, 1 ml of phosphorus oxychloride was slowly added to a solution of 0.93 g (6 mmoles) of Ib in 10 ml of anhydrous DMFA. The mixture was stirred in the cold for another half hour and in the boiling water bath for 15-20 min. After cooling, ice was added and the pH was brought to 7 by the addition of potassium acetate solution. The precipitate that deposited was filtered off and washed with water. Yield 0.75 g (70%). Yellowish-white needles soluble on heating in ethanol, dioxane, and water. mp 186°C (from methanol). Found, %: C 67.95; H 5.19; N 19.50. $C_{12}H_{11}N_3O$. Calculated, %: C 67.59; H 5.20; N 19.71. 2,4-Dinitrophenylhydrazone of IIb. Black crystals with mp 288°C (from DMFA). Found, %: C 55.04; H 4.02; N 24.67. $C_{18}H_{15}N_7O_4$. Calculated, %: C 54.96; H 3.84; N 24.93. Oxime of IIb. White strongly electrifying needles with mp 265°C (from aqueous ethanol). Found, %: C 62.93; H 5.35; N 24.76. $C_{12}H_{12}N_4O$. Calculated, %: C 63.14; H 5.30; N 24.55.

Methiodide of IIb (IIIb). This was obtained in 60% yield by boiling a solution of 1 mmole of the aldehyde and 3 mmoles of methyl iodide in absolute ethanol for 15-20 h. Slightly yellowish needles with mp 246-247°C (from ethanol containing ether). Found, %: C 44.20; H 4.09; N 12.21. $C_{13}H_{14}IN_3O$. Calculated, %: C 43.96; H 3.97; N 11.83. Compound IIIb is unstable. On storage and on heating with 10% KOH solution it decomposes, forming the initial IIb.

3-Formyl-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (IIa). a) This was obtained by the formylation of Ia by the method described for Ib, but the heating in the boiling water bath was performed for 2 h. Yield 88%. Snow-white silky needles with mp 147°C (from dioxane). Found, %: C 74.25; H 4.77; N 14.93. $C_{17}H_{13}N_3O$. Calculated, %: C 74.16; H 4.76; N 15.26.

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*After some days, the melting point fell to 74°C. According to analysis and IR spectroscopy, on storage hydration took place and the substance was partially reconverted into the initial imine.

b) In a current of nitrogen, a solution of 2 g of 3-bromo-9-methyl-2-phenylimidazo[1,2-a]benzimidazole in 70 ml of absolute toluene was added in portions to an ethereal solution of n-butyllithium (0.36 g of lithium and 15 ml of absolute ether) cooled to −75°C, and the mixture was stirred at this temperature for 5 h. The resulting mixture was treated with a mixture of 6 ml of DMFA in 70 ml of absolute ether, and stirring was continued at −75°C for 1 h and at 20°C for 3 h. Then the mixture was treated with 12 ml of aqueous acetic acid (1:1) and the ethereal solution was separated off. The residue from the evaporation of the ether was triturated with dioxane and the mixture was filtered. Yield 1.37 g (81%). mp 147°C. The compound was identical chromatographically (Al_2O_3; chloroform; bright blue spot revealed with iodine) and in its melting point with the product obtained by method (a). A mixture gave no depression of the melting point. 2,4-Dinitrophenylhydrazone of IIa. Dark red needles with mp 304°C (from DMFA). Found, %: C 60.43; H 3.91; N 21.46. $C_{23}H_{17}N_7O_4$. Calculated, %: C 60.65; H 3.76; N 21.53. Oxime of IIa. Colorless needles, mp 235°C (from aqueous ethanol). Found, %: C 70.31; H 5.05; N 19.28. $C_{17}H_{14}N_4O$. Calculated, %: C 70.33; H 4.86; N 19.30.

Methiodide of IIa (IIIa). An ethanolic solution of IIa (1 mmole) and methyl iodide (4 mmoles) was boiled for 35-40 h. After cooling, the precipitate was filtered off. Snow-white needles with mp 232-233°C (decomp. from ethanol). Yield 40%. Found, %: C 51.62; H 4.04; I 30.12; N 10.19. $C_{18}H_{16}IN_3O$. Calculated, %: C 51.81; H 3.87; I 30.41; N 10.07. When the substance was heated with 10% KOH solution, an oil was formed which crystallized on cooling, giving colorless needles with mp 118-119°C (from aqueous ethanol), identical chromatographically with the initial Ia. A mixture with an authentic sample gave no depression of the melting point.

4-(2',9'-Dimethylimidazo[1,2-a]benzimidazol-3'-ylmethylene)-2-phenyloxazolin-5-one. A mixture of 0.21 g (1 mmole) of IIb, 0.19 g (1.2 mmoles) of hippuric acid, 0.15 g (2 mmoles) of fused sodium acetate, and 1 ml of acetic anhydride was boiled for 1 min. The resulting solution was heated in the boiling water bath for 3 h, and then water (17 ml) was added and it was left overnight. The precipitate that had deposited was filtered off and washed with water. Yield 0.22 g (62%). Dark orange crystals with mp 252.5°C (from DMFA). Found, %: C 70.33; H 4.88; N 15.78. $C_{21}H_{16}N_4O_2$. Calculated, %: C 70.77; H 4.52; N 15.72.

4-(9'-Methyl-2'-phenylimidazo[1,2-a]benzimidazol-3'-ylmethylene)-2-phenyloxazolin-5-one. This was obtained in a similar manner to the preceding azlactone with a yield of 24%. Small orange needles with mp 252°C (from DMFA). Found, %: N 13.32. $C_{26}H_{18}N_4O_2$. Calculated, %: N 13.39.

9-Methyl-3-(β-nitrovinyl)-2-phenylimidazo[1,2-a]benzimidazole. A mixture of 0.28 g (1 mmole) of IIa, 0.09 g (1 mmole) of anhydrous of ammonium acetate, and 3 ml of nitromethane was boiled for 40 h and, after chromatography on a column (Al_2O_3; chloroform), the nitrovinyl derivative was isolated in the form of bright orange needles soluble in benzene, chloroform, and ethanol. Yield 0.15 g (47%). mp 189-189.5°C (from ethanol). Found, %: C 68.08; H 4.38; N 17.92. $C_{18}H_{14}N_4O_2$. Calculated, %: C 67.91; H 4.43; N 17.60.

Action of Potassium Permanganate on Ib. With heating in the boiling water bath and stirring, a saturated aqueous solution of 2.1 g of potassium permanganate was added to 0.7 g of Ib in 10 ml of water, and heating was continued for 2 h. After cooling, the precipitate was filtered off, and the reaction product was extracted from it with chloroform. After the evaporation of the chloroform, 0.46 g of a dark orange substance was left. Chromatography on a column containing alumina yielded bright orange needles of 1,1'-dimethyl-2,2'-azobenzimidazole with mp 283-284°C. There was no depression of the melting point in a mixture with an authentic sample.

Styryl Derivatives of Ib. These were obtained by fusing equimolecular amounts of Ib and the corresponding aldehydes at 65-100°C for 5-10 min. The melts were triturated with ether, and the products were filtered off and recrystallized (Table 2).

In the fusion with benzaldehyde, the reaction took place in the presence of catalytic amounts of boric acid. With 2,4-dihydroxybenzaldehyde, the condensation took place when the starting materials were heated in ethanol.

LITERATURE CITED

1. A. M. Simonov and V. A. Anisimova, KhGS [Chemistry of Heterocyclic Compounds], 4, 1102, 1968.
2. A. M. Simonov and P. M. Kochergin, KhGS [Chemistry of Heterocyclic Compounds], 1, 316, 1965.
3. V. V. Avidon and M. N. Shchukina, KhGS [Chemistry of Heterocyclic Compounds], 2, 295, 1966.
4. A. F. Pozharskii, E. A. Zvezdina, and A. M. Simonov, KhGS [Chemistry of Heterocyclic Compounds], 3, 184, 1967.