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RESEARCH ON IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES

XI.* SYNTHESIS OF 2-ARYLAMINO DERIVATIVES OF 9-METHYLIMIDAZO[1,2-a]BENZIMIDAZOLE

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UDC 547.785.5.07

2-Arylamino derivatives of 9-methylimidazo[1,2-a]benzimidazole were obtained by cyclization of the products of the reaction of 2-amino-1-methylbenzimidazole with chloroacetic acid anilides. The former undergo diazo coupling and acetylation in the 3 position of the system, and the amino groups of secondary amines are also acetylated.

The previously unknown 2-arylamino derivatives of 9-methylimidazo[1,2-a]benzimidazole (IIa-e) were synthesized from N-arylamides of 2-imino-1-methyl-3-benzimidazolylacetic acid (Ia-e) by closing of a new imidazole ring through the amide carbonyl group and the imino group.

Only extremely scanty information regarding the synthesis of such amines in a series of condensed imidazole systems is available. The only representative of this class of compounds – 2-acetamidoimidazo[1,2-a]pyridine – was obtained by heating the tosylimino derivative of 1-carbamoylmethyl-2-pyridoneimine [2] in acetic anhydride. We were unable to obtain unsubstituted 2-amino-9-methylimidazo[1,2-a]benzimidazole by a similar method, inasmuch as we were unable to convert 2-imino-3-carbamoylmethyl-1-methylbenzimidazoline (III) to the tosyl derivative. The action of acetic anhydride on imine III gives initially the N-acetyl derivative, and, as in the case of 3-carboxylmethyl-substituted compounds, 3-acetyl-2,9-dimethylimidazo[1,2-a]benzimidazole [3] is formed on prolonged heating in the presence of anhydrous sodium acetate. The use of phosphorus oxychloride as the condensing agent leads to resinification, possibly as a consequence of the instability of the resulting amino derivative.

As one would expect, we therefore undertook the synthesis of the more stable 2-arylamino-substituted imidazo[1,2-a]benzimidazoles. The starting N-arylamides (Ia-e) were obtained by heating 2-amino-1-methylbenzimidazole with chloroacetic acid anilides in acetone. The cyclization of Ia-e in phosphorus oxychloride proceeds smoothly, and the hydrochlorides (IIa-e) of the 2-arylamino derivatives are formed in 90-95% yields. The IR spectra of the latter do not contain the absorption band of a CO group at 1700-1705 cm^{-1} that is present in the spectra of the starting amides. In the free state, arylamines IIa-e are distinguished by high instability.

The structure adopted for IIa-e is in agreement with the chemical properties manifested by them. Stable diacetyl derivatives Ia, c-e are formed on treatment of secondary amines IIa, c-e (R = H) with acetic anhydride. Acetylation takes place at the amino group and in the 3 position of the three-ring system,

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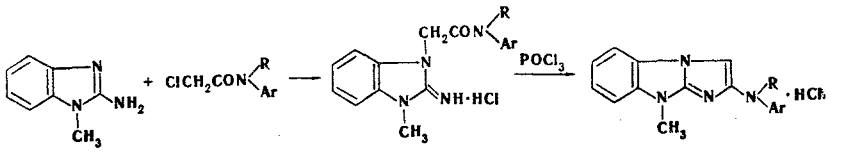
*See [1] for communication X.

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh, No. 10, pp. 1394-1398, October, 1975. Original article submitted December 16, 1974.

TABLE 1. 1-Methyl-2-imino-3-benzimidazolinylacetic Acid N-Arylamide Hydrochlorides (Ia-e)

Compound	R	Ar	mp, °C (solvent)	Empirical formula	Found, %				Calc., %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
Ia	H	C_6H_5	271 (alcohol)	$C_{16}H_{16}N_4O \cdot HCl$	60,6	5,4	11,0	17,5	60,7	5,4	11,2	17,7	95
Ib	CH_3	C_6H_5	257 (alcohol)	$C_{17}H_{18}N_4O \cdot HCl$	61,7	5,6	10,7	17,2	61,7	5,8	10,7	17,0	94
Ic	H	p-$NO_2C_6H_4$	292 (DMF)	$C_{16}H_{15}N_5O_3 \cdot HCl$	53,3	4,2	9,5	19,5	53,1	4,5	9,8	19,4	92
Id	H	p-ClC_6H_4	260 (alcohol)	$C_{16}H_{15}ClN_4O \cdot HCl \cdot H_2O$	51,4	5,2	19,4	15,6	52,0	4,9	19,2	15,2	66
Ie	H	p-$COOC_2H_5C_6H_4$	261 (alcohol)	$C_{19}H_{20}N_4O_3 \cdot HCl$	59,1	5,9	8,4	14,8	58,7	5,4	9,0	14,4	87

as confirmed by the presence in the PMR spectrum of IVa of three singlets of identical intensity at δ 3.80, 2.50, and 2.19 ppm. Tertiary amine IIb forms only C-acetyl derivative IVb.



Ia-e

IIa-e

I, II, a R=H, Ar=C_6H_5; b R=CH_3, Ar=C_6H_5; c R=H, Ar=p-$NO_2C_6H_4$; d R=H, Ar=p-ClC_6H_4; e R=H; Ar=p-$COOC_2H_5C_6H_4$

Amines IIa-e undergo diazo coupling in the 3 position which is typical for the imidazobenzimidazole system, to give azo compounds Va-e.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of Ia-e and IIa-e and of chloroform solutions of IVa-e wer recorded with a UR-20 spectrometer.

The PMR spectrum of a $CDCl_3$ solution of IVa was recorded with a Tesla BC 487C spectrometer with an operating frequency of 80 MHz and tetramethyldisiloxane as the internal standard. The δ values presented in this paper were converted with respect to the signal of tetramethylsilane.

2-Imino-3-carbamoylmethyl-1-methylbenzimidazoline (III). A solution of 2.54 g (0.01 mole) of 2-imino-3-methoxycarbonyl methyl-1-methylbenzimidazoline hydrochloride [4] in 25 ml of 22% ammonium hydroxide was heated to the boiling point, after which it was cooled, and the resulting precipitate was removed by filtration and washed with a small amount of water to give 1.6 g (80%) of colorless prisms with mp 226° (from water). Found: C 59.0; H 5.9; N 27.4%. $C_{10}H_{12}N_4O$. Calculated: C 58.8; H 5.9; N 27.4%.

2-Acetimido-3-carbamoylmethyl-1-methylbenzimidazoline. A 0.20-g sample of amide III was refluxed in 1 ml of acetic anhydride for 3-5 min, after which the mixture was cooled, and the resulting precipitate was removed by filtration and washed with ether to give 0.20 g (83%) of colorless needles with mp 223° (from alcohol). Found: C 58.8; H 5.7; N 22.9%. $C_{12}H_{14}N_4O_2$. Calculated: C 58.5; H 5.6; N 22.7%.

2-Imino-1-methyl-3-benzimidazolinylacetic Acid N-Arylamide Hydrochlorides (Ia-e, Table 1). A saturated solution of equimolecular amounts of 2-amino-1-methylbenzimidazole and chloroacetic acid N-arylamide in acetone was heated for 18-20 h, after which the solid material was removed by filtration and washed with acetone. The products were insoluble in cold water, chloroform, and ether.

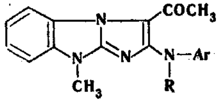
2-Arylamino-9-methylimidazo[1,2-a]benzimidazole Hydrochlorides (IIa-e). A 1-mmole sample of arylamide Ia-e was heated in 30 ml of phosphorus oxychloride until it had dissolved completely, after which the solution was heated for another 3 h. The solvent was then removed by vacuum distillation, and the dark viscous residue was treated with cold water; after 2-3 h, the precipitate was removed by filtration. (Hydrochloride IIb was soluble in water, and the solution obtained after decomposition of the $POCl_3$ was therefore neutralized with 22% ammonium hydroxide and extracted with benzene, and dry HCl was bubbled into the benzene solution after prior drying over potassium carbonate.) Hydrochlorides IIa-e are stable but were difficult to purify by the usual methods, and they were therefore used without additional purification

TABLE 2. Picrates of 2-Arylamino Derivatives of 9-Methylimidazo-[1,2-a]benzimidazole (IIa-e)

Compounds	R	Ar	mp, °C (solvent)	Empirical formula	Found, %			Calc., %		
					C	H	N	C	H	N
IIa	H	C_6H_5	226 (DMF + alcohol)	$C_{16}H_{14}N_4 \cdot C_6H_3N_3O_7$	53,7	4,0	19,8	53,7	3,7	19,9
IIb	CH_3	C_6H_5	162 (absolute alcohol	$C_{17}H_{16}N_4 \cdot C_6H_3N_3O_7$	54,9	4,0	19,8	54,7	3,8	19,4
IIc	H	p-$NO_2C_6H_4$	198 (glacial CH_3COOH)	$C_{16}H_{13}N_5O_2 \cdot C_6H_3N_3O_7$	49,0	2,7	20,8	49,2	3,0	20,9
IId*	H	p-ClC_6H_4	234 (DMF)	$C_{16}H_{13}ClN_4 \cdot C_6H_3N_3O_7$	50,0	3,4	18,4	50,0	3,7	18,7
IIe	H	p-$COOC_2H_5C_6H_4$	230 (DMF)	$C_{19}H_{10}N_4O_2 \cdot C_6H_3N_3O_7$	53,6	3,8	17,5	53,3	3,8	17,4

* Found: Cl 5.5%. Calculated: Cl 5.8%.

TABLE 3. Acetyl Derivatives of 2-Arylamino-9-methylimidazo-[1,2-a]benzimidazoles (IVa-e)

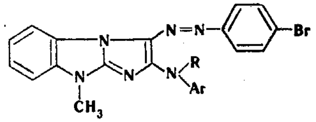


Compound	R	Ar	mp, °C (solvent)	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IVa	$COCH_3$	C_6H_5	171 (alcohol)	$C_{20}H_{18}N_4O_2$	69,6	5,2	16,2	69,3	5,2	16,2	76
IVb	CH_3	C_6H_5	158 (alcohol)	$C_{19}H_{18}N_4O$	71,5	5,4	17,7	71,7	5,7	17,6	78
IVc*	$COCH_3$	p-$NO_2C_6H_4$	271 (DMF)	$C_{20}H_{17}N_5O_4$	61,6	4,0	18,2	61,4	3,8	17,9	77
IVd†	$COCH_3$	p-ClC_6H_4	194 (heptane)	$C_{20}H_{17}ClN_4O_2$	63,0	4,4	14,3	63,1	4,5	14,7	84
IVe	$COCH_3$	p-$COOC_2H_5C_6H_4$	174 (alcohol)	$C_{23}H_{22}N_4O_4$	65,8	5,5	13,0	66,0	5,3	13,4	88

* Compound IV was isolated as yellow needles by cooling the reaction mixture. The needles were removed by filtration and washed successively with ether and water.

† Found: Cl 9.0%. Calculated: Cl 9.3%.

TABLE 4. 3-(4'-Bromophenylazo)-2-arylamino-9-methylimidazo[1,2-a]benzimidazoles (Va-e)



Compound	R	Ar	mp, °C (solvent)	Crystal color	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	Br	N	C	H	Br	N	
Va	H	C_6H_5	244 (alcohol)	Orange	$C_{22}H_{17}BrN_6$	59,2	4,1	18,2	19,2	59,3	3,9	18,0	18,9	67
Vb*	CH_3	C_6H_5	195 (alcohol)	Red	$C_{23}H_{19}BrN_6 \cdot H_2O$	57,5	4,2	16,8	17,7	57,9	4,4	16,7	17,6	54
Vc	H	p-$NO_2C_6H_4$	302 (DMF)	Brown	$C_{22}H_{16}BrN_7O_2$	54,2	3,4	16,0	20,3	53,9	3,3	16,3	20,0	92
Vd†	H	p-ClC_6H_4	193 (benzene)	Orange	$C_{22}H_{16}BrClN_6$	55,4	3,0		17,3	53,1	3,3		17,5	96
Ve	H	p-$COOC_2H_5C_6H_4$	245 (DMF)	Red	$C_{25}H_{21}BrN_6O_2$	58,5	4,4	16,0	15,6	58,0	4,2	15,5	16,1	87

* In the preparation of Vb, diazo coupling was carried out in aqueous solution.

† Combined Cl and Br contents. Found: 23.6%. Calculated: 24.0%.

in the subsequent transformations. Hydrochlorides IIa-e were converted to picrates for identification. Data for these compounds are presented in Table 2.

Nitrate Salts of IIa. Hydrochloride IIa was suspended in water, after which the suspension was made alkaline with 22% ammonium hydroxide, and the precipitated amine was separated rapidly and dried between sheets of filter paper. It was then dissolved in alcohol, the alcohol solution was treated with excess concentrated HNO_2, and the resulting precipitate was removed by filtration and washed with ether to give pale-yellow needles with mp 205° (from alcohol) that were soluble in water. Found: C 59.2; H 4.3; N 21.2%. $C_{16}H_{14}N_4 \cdot HNO_3$. Calculated: C 59.1; H 4.6; N 21.5%.

2-(N-Acetylphenylamino)-3-acetyl-9-methylimidazo[1,2-a]benzimidazole (IVa). A solution of 0.30 g (1 mmole) of hydrochloride IIa in 3 ml of acetic anhydride was refluxed for 3 h in the presence of 0.30 g of anhydrous sodium acetate, after which it was cooled and poured over ice. After the acetic anhydride had decomposed, the mixture was neutralized with sodium carbonate, and the liberated oil was extracted with chloroform. The chloroform extract was evaporated to the minimum volume, and the product was purified by column chromatography (with Al_2O_3 and elution by chloroform); the fraction with R_f 0.9 (according to TLC data) was collected. The product was readily soluble in benzene and acetone but insoluble in ether and water.

The properties of IVa and the other acetyl derivatives are presented in Table 3.

The stretching vibrations of the carbonyl groups in the IR spectra of IVa-e appear at 1630 ($COCH_3$) and 1680 ($N-COCH_3$) cm^{-1}.

3-(4'-Bromophenylazo)-9-methyl-2-phenylaminoimidazo[1,2-a]benzimidazole (Va). A solution of a diazonium salt obtained from 0.17 g (1 mmole) of p-bromoaniline and 0.07 g (1 mmole) of sodium nitrite by the usual method was added to 0.30 g (1 mmole) of hydrochloride IIa in 3 ml of glacial acetic acid containing 0.40 g of sodium acetate. After 1 h, the reaction product was removed by filtration and washed with water. The bright-orange azo compound was soluble in water, ether, and benzene and highly soluble in chloroform and acetone (see Table 4).

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