RESEARCH ON BENZIMIDAZOLE DERIVATIVES. XXXV.*

SYNTHESIS AND TRANSFORMATIONS OF 1-ALKYL-3-(2'-PROPYNYL)-2-IMINOBENZIMIDAZOLINES

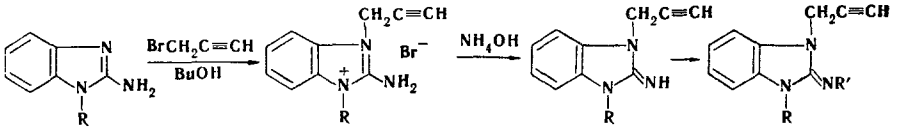
I. I. Popov, P. V. Tkachenko, and A. M. Simonov

UDC 547.785.5.07:542.952

Several transformations of 1-alkyl-3-(2'-propynyl)-2-iminobenzimidazolines involving the imino group and the triple bond were studied. It is shown that they are readily isomerized in the presence of bases to allenes, which are then converted to 2-methylimidazo[1,2-a]benzimidazole derivatives by intramolecular cyclization. 1-Alkyl-3-(β-bromoallyl)-2-iminobenzimidazolines can be used for the synthesis of the latter.

It has been shown that 2-amino derivatives of heterocycles that contain a "pyridine" nitrogen atom are quaternized by propargyl bromide at the ring heteroatom, and the resulting quaternary salts can be smoothly converted to condensed imidazole derivatives by the action of bases [2, 3]. In this connection, the synthesis of imidazo[1,2-a]benzimidazole derivatives, among which there are physiologically active compounds [4], seemed of interest.

We subjected 1-alkyl-2-aminobenzimidazoles (Ia-c) to reaction with propargyl bromide, and the optimum yields of salts IIa-c were obtained when n-butyl alcohol was used as the solvent. Salts IIa-c are readily converted to 1-alkyl-3-(2'-propionyl)-2-iminobenzimidazolines (IIIa-c) by the action of concentrated ammonium hydroxide. The data from the IR spectra of IIIa-c confirm their structures: 3310 (≡C–H) and 3360 cm^{-1} (=N–H).



I II III IV-VI

I-VI a $R=CH_3$; b $R=C_2H_5$; c $R=CH_2C_6H_5$; IV a-c $R'=CH_3$; V a-c $R'=COCH_3$; VI a-c $R'=CH_2OH$

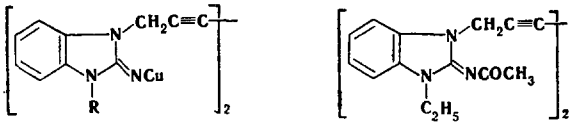
The peculiarity of the chemical transformations of 2-iminobenzimidazolines IIIa-c is due to the presence of two reaction centers (=NH and C≡CH) in these compounds. A study of their properties showed that the imino group first undergoes attack by electrophilic reagents. Thus the alkylation of IIIa-c with methyl iodide (1 mole) in liquid ammonia in the presence of sodium amide (1 mole) proceeds with the formation of N-methyl derivatives IVa-c. The action of acetic anhydride on IIIa-c gives N-acetyl derivatives Va-c, as attested to by the appearance in the IR spectra of an amide band at 1620 cm^{-1} (C=O). Refluxing IIIa-c with formalin in methanol gives only N-hydroxymethyl derivatives VIa-c, the IR spectra of which do not contain a band at 3360 cm^{-1} (=NH), but a band does appear at 3600 cm^{-1} (OH).

Only the copper salts of diynes (VIIa,b) were isolated from the Glaser oxidative dimerization of imines IIIa,b. When acetyl derivative Vb was used in this reaction, diyne

*See [1] for communication XXXIV.

Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 396-400, March, 1975. Original article submitted April 15, 1974.

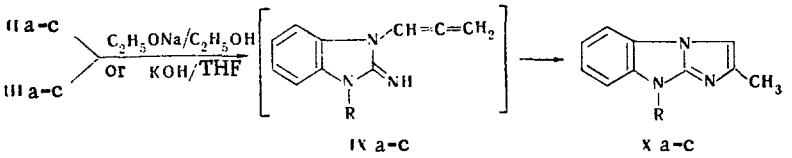
VIII was obtained. However, we were unable to isolate the free diynes from VIIa,b or VIII by the action of dilute mineral acids, and resinification was observed.



VII VIII

VII a R = CH_3; b R = C_2H_5

The reaction of IIIa-c with nucleophilic reagents takes place at the acetylene group. Thus when these compounds are refluxed in an alcohol solution of sodium ethoxide or are treated with potassium hydroxide in THF at room temperature they undergo prototropic rearrangement to allenes IX, which are cyclized to give 2-methylimidazo[1,2-a]benzimidazole derivatives (Xa-c). The latter can be obtained under the same conditions from salts IIa-c.

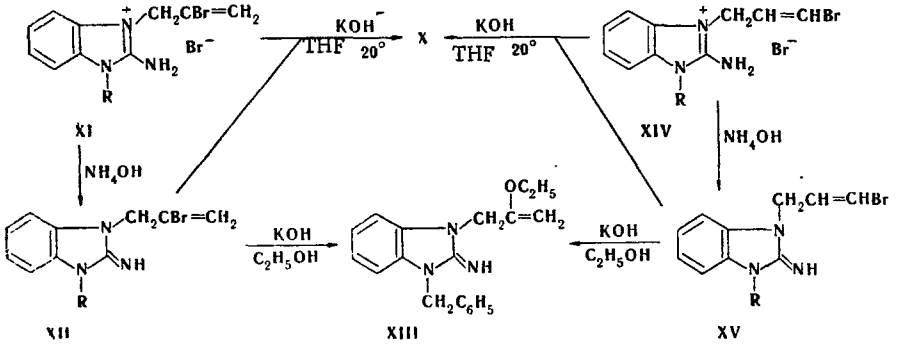


IX a-c X a-c

II, III, IX, X a R = CH_3; b R = C_2H_5; c R = $CH_2C_6H_5$

Intermediately formed allenes IX can be isolated in some cases. For example, IXc, which is unstable in the presence of bases and on storage, was obtained by treatment of IIc or IIIc with potassium hydroxide in THF at 0°. The absorption at 1090 and 1970 cm^{-1} in the IR spectrum of IXc and the absence of a band at 3310 cm^{-1} (≡C–H) attest to the allene structure. The PMR spectrum of IXc (in $CDCl_3$) contains the signal of protons of an allene group (–CH=C=CH_2) at σ 5.61 ppm (doublet) [5].

Because of the high rate of the acetylene–allene rearrangement of imines IIIa-c under the conditions of the Favorskii reaction, ethynylcarbinols are not formed.



XI, XII a R = C_2H_5; b R = i-C_3H_7; c R = $CH_2C_6H_5$

Compound X was synthesized in good yield by treatment of benzimidazolines XIIa-c or salts XIa-c, obtained by quaternization of amines I with 2,3-dibromo-1-propene in n-butyl alcohol, with potassium hydroxide in THF at room temperature. On the other hand, the reaction of XIIc with alcoholic potassium hydroxide at 20° gives β-ethoxyallyl derivative XIII. Under the described conditions, benzimidazoline XV or salt XIV behave like XIIc and also form Xc and XIII. It might be assumed that allenes IX are formed intermediately and then readily add nucleophilic reagents. Allene IXc can also be obtained by the action of potassium hydroxide in THF at 0° on XIIc and XV and also from imine IIIc.

EXPERIMENTAL

The IR spectra of chloroform solutions of the compounds were obtained with a UR-20 spectrometer. The NMR spectra of deuterochloroform solutions were obtained with a BS 487C spectrometer (80 MHz). Activity III (Brockmann classification) aluminum oxide was used for chromatography.

TABLE 1. 1-Alkyl-3-(2'-propynyl)-2-iminobenzimidazolines and Their Derivatives

Compound	R	R'	mp, °C*	Empirical formula	Found, %				Calc., %				Yield, %
					C	H	Br	N	C	H	Br	N	
IIa	CH_2	H	248—250	$C_{11}H_{11}N_3 \cdot HBr$	49,9	4,5	29,9	15,5	49,6	4,5	30,1	15,8	72
IIb	C_2H_5	H	239—240	$C_{12}H_{13}N_3 \cdot HBr$	51,5	5,0	28,6	15,4	51,5	5,0	28,5	15,0	80
IIc	$CH_2C_6H_5$	H	296—298	$C_{17}H_{15}N_3 \cdot HBr$	59,2	4,9	23,3	12,4	59,6	4,7	23,4	12,3	72
IIIa	CH_3	H	110—111	$C_{11}H_{11}N_3$	71,6	6,0	—	22,7	71,3	5,9	—	22,7	96
IIIb	C_2H_5	H	83—84	$C_{12}H_{13}N_3$	72,0	7,0	—	21,4	72,3	6,6	—	21,1	97
IIIc	$CH_2C_6H_5$	H	120—121	$C_{17}H_{15}N_3$	77,8	6,1	—	16,3	78,2	5,8	—	16,0	95
IVa	CH_3	CH_3	236—237	$C_{12}H_{13}N_3 \cdot C_6H_3N_3O_7$	50,2	3,9	—	19,7	50,5	3,7	—	19,6	80
IVb	C_2H_5	CH_3	223—224	$C_{13}H_{15}N_3 \cdot C_6H_3N_3O_7$	49,2	4,1	—	19,1	48.9	4,1	—	19,0	78
IVc	$CH_2C_6H_5$	CH_3	185—186	$C_{18}H_{17}N_3 \cdot C_6H_3N_3O_7$	57,0	4,0	—	16,8	57,2	4,0	—	16,7	72
Va	CH_3	$COCH_3$	135—136	$C_{13}H_{13}N_3O$	68,5	5,8	—	18,7	68.7	5,7	—	18,5	85
Vb	C_2H_5	$COCH_3$	131—132	$C_{14}H_{15}N_3O$	69,9	6,5	—	17,2	69,7	6,2	—	17,4	83
Vc	$CH_2C_6H_5$	$COCH_3$	141—143	$C_{19}H_{17}N_3O$	74,9	5,6	—	14,1	75,2	5,6	—	13,8	80
VIa	CH_3	CH_2OH	161—162	$C_{12}H_{13}N_3O \cdot C_6H_3N_3O_7$	50,2	3,9	—	19,8	50,5	3,7	—	19,6	62
VIb	C_2H_5	CH_2OH	154—155	$C_{13}H_{15}N_3O \cdot C_6H_3N_3O_7$	51,3	4,2	—	19,4	51,6	4,1	—	19,0	58
VIc	$CH_2C_6H_5$	CH_2OH	140—141	$C_{18}H_{17}N_3O \cdot C_6H_3N_3O_7$	57,0	4.2	—	16,2	57,2	4,0	—	16,6	60

*The compounds were purified for analysis by crystallization: IIIa-c and Va-c from heptane, and IIa-c, IVa-c, and VIa-c from ethanol.

1-Alkyl-3-(2'-propynyl)-2-iminobenzimidazoline Hydrobromides (IIa-c, Table 1). A solution of 0.01 mole of N-alkyl-substituted 2-aminobenzimidazoles Ia-c in 5 ml of n-butylalcohol was refluxed with 12 mmole of propargyl bromide for 1 h, after which the mixture was cooled, and the resulting precipitate of the quaternary salt was removed by filtration and washed with n-butyl alcohol and ether. The colorless crystalline products were quite soluble in water but less soluble in alcohol.

1-Alkyl-3-(2'-propynyl)-2-iminobenzimidazolines (IIIa-c, Table 1). A 0.01-mole sample of salt IIa-c was triturated thoroughly with 10 ml of concentrated ammonium hydroxide, and the resulting solid was removed by filtration and washed with water. The colorless crystalline products, which were insoluble in water, turned red on storage.

1-Alkyl-2-N-methylimino-3-(2'-propynyl)benzimidazolines (IVa-c, Table 1). A solution of 6 mmole of IIIa-c in 5 ml of absolute ether was added to a solution of 6 mg-atom of sodium metal in 50 ml of liquid ammonia. After 30 min, 6 mmole of methyl iodide in 3 ml of absolute ether was added dropwise, after which the mixture was stirred at −70° for 2 h and allowed to stand at room temperature until the ammonia had evaporated. The residue was treated with 20 ml of water, and the mixture was extracted with chloroform. The solvent was removed by distillation, and the product was purified by chromatography with a column filled with Al_2O_3 (elution with ether) to give colorless oils that were soluble in organic solvents but insoluble in water.

1-Alkyl-2-acetamino-3-(2'-propynyl)benzimidazolines (Va-c, Table 1). A 5-mmole sample of IIIa-c was dissolved in 20 ml of acetic anhydride, and the solution was allowed to stand at room temperature for 4 h. Water (20 ml) was then added, and the solution was neutralized with potassium carbonate. The precipitated acetyl derivative was removed by filtration, washed with water, dried, and crystallized from heptane to give colorless crystals that were soluble in chloroform, alcohol, acetone, and ether but insoluble in water.

1-Alkyl-2-(N-hydroxymethyl)-imino-3-(2'-propynyl)benzimidazolines (VIa-c, Table 1). A mixture of 2 mmole of IIIa-c and 5 ml of formalin was refluxed in 5 ml of methanol for 3 h, after which the mixture was cooled, diluted with 25 ml of water, and extracted with chloroform. The solvent was removed by distillation, and the residue was chromatographed

TABLE 2. 9-Alkyl-2-methylimidazo[1,2-a]benzimidazoles and 1-Alkyl-3-(β-bromoallyl)-2-iminobenzimidazolines

Compound	R	bp, °C*	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	Br	N	C	H	Br	N	
Xa	CH_3	94[6]	$C_{11}H_{11}N_3$	—	—	—	—	—	—	—	—	95
Xb	C_2H_5	236[7]	$C_{12}H_{13}N_3 \cdot C_6H_3N_3O_7$	—	—	—	—	—	—	—	—	93
Xc	$CH_2C_6H_5$	111—112[8]	$C_{17}H_{15}N_3$	—	—	—	—	—	—	—	—	94
XIa	C_2H_5	289—291	$C_{12}H_{14}BrN_3 \cdot HBr$	40,1	4,0	44,1	11,5	39,9	4,2	44,3	11,6	83
XIb	i-C_3H_7	236—237	$C_{13}H_{16}BrN_3 \cdot HBr$	41,4	4,2	42,4	11,5	41,6	4,5	42,7	11,2	78
XIc	$CH_2C_6H_5$	278—280	$C_{17}H_{16}BrN_3 \cdot HBr$	48,0	3,7	38,2	9,8	48,2	4,0	37,8	9,9	85
XIIa	C_2H_5	57—59	$C_{12}H_{14}BrN_3$	51,0	5,1	28,3	15,3	51,4	5,0	28,5	15,0	96
XIIb	i-C_3H_7	oil	$C_{13}H_{16}BrN_3$	53,3	5,2	27,4	14,1	53,1	5,4	27,2	14,3	97
XIIc	$CH_2C_6H_5$	103—105	$C_{17}H_{16}BrN_3$	59,4	4,4	23,1	12,5	59,6	4,7	23,4	12,3	95

*The compounds were purified for analysis by crystallization: XIIa-c from heptane, and XIa-c from ethanol.

with a column filled with Al_2O_3 [elution with chloroform—ethanol (5:1)] to give colorless oils that were soluble in organic solvents but insoluble in water.

Oxidative Dimerization of 1-Alkyl-3-(2'-propynyl)-2-iminobenzimidazolines (IIIa,b and Vb). A) A mixture of 0.55 g (3 mmole) of IIIa and 0.3 g (3 mmole) of cuprous chloride was shaken with 10 ml of pyridine and 2 ml of methanol in an oxygen atmosphere for 2 h. During the reaction, the solution turned red-brown. The mixture was poured into 150 ml of water, the aqueous mixture was made alkaline with 10 ml of ammonia, and the precipitate was removed by filtration. The yield of the diyne copper salt (VIIa) with mp 360°, which was a brown amorphous powder, was 1.2 g (81%). Found: C 53.2; H 3.8; N 17.4%. $C_{22}H_{18}N_6Cu_2$. Calculated: C 53.5; H 4.1; N 17.1%.

B) Copper salt VIIb was similarly obtained in 76% yield from IIIb. The brown amorphous powder had mp 280°. Found: C 55.2; H 4.7; Cu 24.0; N 15.8%. $C_{24}H_{22}Cu_2N_6$. Calculated: C 55.3; H 4.3; Cu 24.3; N 16.1%.

C) Diyne VIII was similarly obtained from Vb in 80% yield. The turquoise prisms had mp 217-219° (from aqueous dioxane). Found: N 17.4%. $C_{28}H_{28}N_6O_2$. Calculated: N 17.5%.

1-Benzyl-2-imino-3-propadienylbenzimidazoline (IXc). A solution of 0.52 g (2 mmole) of IIIc in 1 ml of THF was added at 0° to a suspension of 0.56 g (0.01 mole) of thoroughly calcined and powdered potassium hydroxide in 10 ml of absolute THF, and the mixture was stirred at 0° for 2 h. Water (20 ml) was then added, the aqueous mixture was extracted with ether, the ether was removed by distillation, and the residue was crystallized from aqueous ethanol to give 0.6 g (81%) of yellowish prisms with mp 102-104° that were soluble in acetone, chloroform, and ether but insoluble in water. Found: C 77.9; H 6.2; N 15.9%. $C_{17}H_{15}N_3$. Calculated: C 78.2; H 5.8; N 16.1%.

9-Alkyl-2-methylimidazo[1,2-a]benzimidazoles (Xa-c, Table 2). A) A 0.01-mole sample of the appropriate imine (IIIa-c) was added to a solution of sodium ethoxide, obtained from 0.46 g (0.02 g-atom) of sodium metal and 5 ml of absolute ethanol, and the mixture was refluxed on a water bath for 1 h. It was then cooled, 15 ml of water was added, and the mixture was extracted with chloroform. The reaction product was purified by chromatography with a column filled with Al_2O_3 (with elution by ether).

B) A 2-mole sample of IIIa-c was added to a suspension of 0.28 g (5 mmole) of potassium hydroxide (previously thoroughly calcined and powdered) in 5 ml of absolute THF, and the mixture was allowed to stand at room temperature for 24 h, after which 20 ml of water was added, and the mixture was extracted with chloroform. The products were obtained in 90-92% yields.

C) Compounds Xa-c can be obtained from salts IIa-c by the method described in A or B. The yields were 85-88%.

D) Compounds Xb,c were obtained by method B from XIa,c or XIIa,c, whereas Xc can be obtained from XIV or XV under the same conditions. The yields were 85-90%.

1-Alkyl-3-(β-bromoallyl)-2-iminobenzimidazoline Hydrobromides (XIa-c, Table 2). These compounds were obtained from the appropriate 2-aminobenzimidazoles I and 2,3-dibromo-1-propene, as in the preparation of II. The products were colorless crystals that were soluble in water and alcohol.

1-Alkyl-3-(β-bromoallyl)-2-iminobenzimidazolines (XIIa-c, Table 2). These compounds were obtained from XIa-c by the method used to prepare III. The products were colorless prisms (XIIb was an oil) that were soluble in organic solvents and turned red on storage.

1-Benzyl-2-imino-3-(β-ethoxyallyl)benzimidazoline (XIII). A) A 0.68-g sample (2 mmole) of XIIc was added to a solution of 0.17 g (3 mmole) of potassium hydroxide in 3 ml of ethanol, and the mixture was allowed to stand overnight. Water (20 ml) was then added, and the mixture was extracted with chloroform. Workup of the chloroform extract gave 0.55 g (90%) of colorless needles with mp 96-98° (from heptane) that were soluble in chloroform, acetone, and ether but insoluble in water. Found: C 74.1; H 6.6; N 13.8%. $C_{19}H_{21}N_3O$. Calculated: C 74.4; H 6.8; N 13.7%.

B) This compound was similarly obtained from XV in 93% yield.

1-Benzyl-2-imino-3-(α-bromoallyl)benzimidazoline Hydrobromide (XIV). This compound, with mp 266-267° (from ethanol), was obtained in 87% yield from Ic and 1,3-dibromo-1-propene, as described for II. The colorless needles were quite soluble in water. Found: C 48.0; H 3.7; Br 38.2; N 9.8%. $C_{17}H_{17}Br_2N_3$. Calculated: C 48.2; H 4.0; Br 37.8; N 9.9%.

1-Benzyl-2-imino-3-(α-bromoallyl)benzimidazoline (XV). This compound was obtained in 94% yield from XIV by the method described for III. The yellowish prisms has mp 119-120° (from heptane). Found: C 59.4; H 4.4; Br 23.1; N 12.5%. $C_{17}H_{16}BrN_3$. Calculated: C 59.6; H 4.7; Br 23.4; N 12.3%.

LITERATURE CITED

1. P. V. Tkachenko, I. I. Popov, and A. M. Simonov, Khim. Geterotsikl. Soedin., 1540 (1974).
2. J. Jwai and T. Hiraoka, Chem. Pharm. Bull., 11, 1564 (1963).
3. S. Kano, J. Pharm. Soc. Japan, 92, 927 (1972).
4. A. M. Simonov, A. A. Belous, V. A. Anisimova, and S. V. Ivanovskaya, Khim.-Farmats. Zh., 7 (1969).
5. A. J. Hubert and H. Reimlinger, J. Chem. Soc., C, 606 (1968).
6. A. M. Simonov and V. A. Anisimova, Khim. Geterotsikl. Soedin., 838 (1970).
7. P. M. Kochergin and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 1, 133 (1967).
8. A. M. Simonov, V. A. Anisimova, and T. A. Borisova, Khim. Geterotsikl. Soedin., 111 (1973).