4. J. Catalan, J. L. G. de Paz, and M. Yanez, J. Mol. Struct., 107, 257 (1984).
5. J. Catalan, P. Perez, and M. Yanez, Tetrahedron, 38, 3693 (1982).
6. M. J. S. Dewar and W. Thiel, J. Am. Chem. Soc., 99, 4899 (1977).
7. M. J. S. Dewar and W. Thiel, J. Am. Chem. Soc., 99, 4907 (1977).
8. S. Olivella, F. Urpi, and J. Vilarrasa, J. Comput. Chem., 5, 230 (1984).
9. P. Tomasik and C. D. Johnson, Adv. Heterocycl. Chem., 20, 1 (1976).

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

23.* SYNTHESES BASED ON 2-(2-HYDROXYETHYLAMINO)BENZIMIDAZOLES

V. A. Anisimova and M. V. Levchenko

UDC 547.785.5.04':542.
944'945.24'951.1'958.1

The possibility of annelation of the imidazoline ring on the basis of 2(2-hydroxyethylamino)-benzimidazoles was studied. It was shown that the action of hydrobromic, sulfuric, nitrosylsulfuric, and polyphosphoric acids, acetic anhydride, and phosphorus oxychloride on them does not lead to 2,3-dihydroimidazo[1,2-*a*]-benzimidazoles. In the case of $POCl_3$ the products were 2-(2-chloroethylamino)benzimidazoles, treatment of which with alcoholic alkali led primarily to nucleophilic substitution of the chlorine atom by a methoxy group. Three-ring imidazolines are formed in 12-15% yields in this case. It was established that the reaction proceeds through the intermediate formation of aziridine derivatives.

The ease of replacement of the sulfo group in benzimidazole-2-sulfonic acids by various amines, including the β-hydroxyethylamino group, was demonstrated in [2]. Considering the fact that derivatives of nitrogen heterocycles that have this sort of group in the α position relative to the nitrogen atom of the heteroatom are convenient synthones in the synthesis of condensed imidazoline systems with a common nitrogen atom, we investigated the possibility of the use of 2-(2-hydroxyethylamino)benzimidazoles I for the synthesis of 2,3-dihydroimidazo[1,2-*a*]benzimidazole derivatives VII.

Attempts to bring about the cyclization of amino alcohols I directly to VII by the action of HBr, H_2SO_4, and nitrosylsulfuric and polyphosphoric acids were unsuccessful (see [3-6]). Sulfonation of the OH group to give acids II occurs as a result of the action of H_2SO_4. Treatment with nitrosylsulfuric acid leads to nitrosoamino sulfonic acid III, which remains unchanged when it is treated with alkali. Acetic anhydride also proved to be an unsuitable reagent for the transition to VII: Its action on amino alcohols Ia,b leads only to acetylation of the amino and hydroxy groups. Bands that characterize the absorption of the NH and OH groups in starting Ib vanish in the IR spectrum of the resulting diacetate IVb, and bands at 1685 and 1735 cm^{-1}, which should be ascribed to the carbonyl absorption of acetamido and acetoxy groups respectively, appear. The same bands are also present in the spectrum of IVa, which was similarly obtained. Two partially overlapped singlets of methyl protons of two acetyl groups at 1.82 and 1.77 ppm are observed in the PMR spectrum of a solution of IVb in $CDCl_3$; the ring $N-CH_3$ group gives a singlet at 3.6 ppm, and the ethylene protons appear in the form of two symmetrical doublets at 4.18 and 4.0 ppm.

Refluxing amino alcohols I in phosphorus oxychloride leads to chlorination of the hydroxy group and the formation of 2-(2-chloroethylamino)benzimidazole hydrochlorides V. The

*See [1] for communication 22.

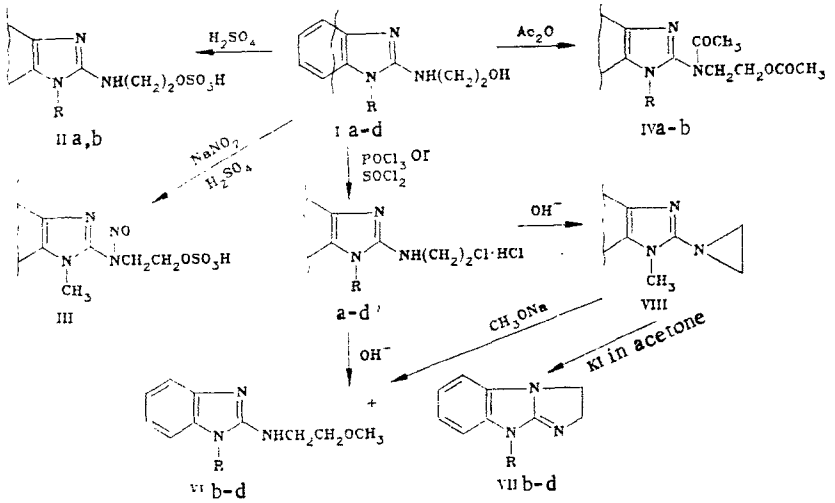
Scientific-Research Institute of Physical and Organic Chemistry, M. A. Suslov Rostov State University, Rostov-on-Don 344090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 59-63, January, 1987. Original article submitted July 16, 1985.

 0009-3122/87/2301-0048$12.50

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
Ic	167	64,4	7,2	—	20,6	$C_{11}H_{15}N_3O$	64,4	7,4	—	20,5	97,5
Id	182	71,7	6,3	—	15,9	$C_{16}H_{17}N_3O$	71,9	6,4	—	15,7	98,5
III	271 (dec.)	40,3	4,2	—	19,0	$C_{10}H_{12}N_4O_5S$	40,0	4,0	—	18,7	73,3
IVa	174	59,6	5,8	—	15,9	$C_{13}H_{15}N_3O_3$	59,8	5,8	—	16,1	96
IVb	105	60,9	6,4	—	15,3	$C_{14}H_{17}N_3O_3$	61,1	6,2	—	15,3	88
Va	147—148	46,7	5,0	30,1	18,3	$C_9H_{10}ClN_3 \cdot HCl$	46,6	4,8	30,5	18,1	95
Vb	198—199	48,6	5,2	28,6	17,2	$C_{10}H_{12}ClN_3 \cdot HCl$	48,8	5,3	28,8	17,1	94—96
Vc	199—200	50,7	5,9	27,0	16,3	$C_{11}H_{14}ClN_3 \cdot HCl$	50,8	5,8	27,3	16,1	100
Vd	214	59,5	5,3	22,2	13,1	$C_{16}H_{16}ClN_3 \cdot HCl$	59,7	5,3	22,0	13,0	97—100
VIb	72—73	64,2	7,5	—	20,6	$C_{11}H_{15}N_3O$	64,4	7,4	—	20,5	88
VIa	131—132	65,9	8,0	—	19,4	$C_{12}H_{17}N_3O$	65,7	7,8	—	19,2	85
VId	135—136	72,7	6,9	—	14,7	$C_{17}H_{19}N_3O$	72,6	6,8	—	14,9	86
VIII	65—66	69,2	6,2	—	24,5	$C_{10}H_{11}N_3$	69,3	6,4	—	24,3	68

same salts are readily formed by the action of thionyl chloride in dry chloroform or benzene on I. In contrast to the analogous derivatives in series of other nitrogen heterocycles [7, 8], they cannot be converted to 2,3-dihydroimidazo[1,2-α]benzimidazoles VII in good yields by means of alkaline reagents. Thus refluxing Vb-d with a methanol solution of NaOH leads primarily to nucleophilic substitution of the chlorine atom by a methoxy group to give VIb-d (85-88% yields), whereas 2,3-dihydro derivatives VIIb-d were obtained in low yields (12-15%) in this case. The yields of VII increase slightly when methanol is replaced by ethanol. In the case of chloro amine Va the reaction is accompanied by the formation of a dark-colored dye, the structure of which was not established. In the PMR spectra of VI the protons of the OCH_3 group absorb at 3.35 ppm; the protons of the ethylene bridge give a singlet signal at 3.55-3.65 ppm, and the broad signal (1 proton unit) at 4.63 ppm should be ascribed to the absorption of the proton of an NH group. In the IR spectra absorption of the NH group is observed at 3435-3448 cm^{-1}.



I—VII a R=H, b R=CH_3, c R=C_2H_5, d R=$CH_2C_6H_5$

Chromatographic monitoring of the course of the reaction V → VI + VII revealed that it proceeds through the intermediate formation of 2-aziridinylbenzimidazoles, which, under the reaction conditions, are rapidly converted to VI and VII under the influence of nucleophiles. When we carried out this reaction under milder conditions, we were able to isolate aziridine VIII in individual form. Its IR spectrum does not contain the absorption band of an NH group that is observed in the spectrum of the starting chloro amine base at 3445 cm^{-1}. The PMR spectrum contains a singlet signal (4 proton units) at 2.35 ppm, which can be assigned to the absorption of the protons of the ethylene bridge of the aziridine ring; a signal of protons of the N–CH_3 group is found at 3.62 ppm, and a multiplet of benzene ring protons is observed at 7.1-7.5 ppm.

Aziridine VIII is quite labile: treatment of it with an ether solution of HCl in the cold gives starting Vb; methoxy derivative VIb was obtained by the action of sodium methoxide. The conversion of VIII to the isomeric 9-methyl-2,3-dihydroimidazo[1,2-*a*]benzimidazole (VIIb) takes place readily in acetone containing KI. The mechanism of this sort of isomerization in the quinazoline and quinoxaline series was described in [9, 10].

Thus we have shown that the methods that are usually employed in series of other nitrogen heterocycles for annelation of the imidazoline ring on the basis of hydroxyethylamino and chloroethylamino derivatives are not suitable for the preparative synthesis of 2,3-dihydroimidazo[1,2-*a*]benzimidazoles. We were able to obtain the latter in virtually quantitative yields from chloro amines V only in the absence of reagents that promote ionization of the amino group and serve as nucleophiles, viz., by thermal intramolecular cyclization of bases V [11].

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform or suspensions in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in deuterochloroform were recorded with a Tesla BS-487 C spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The course of the reactions and the purity of the compounds obtained were monitored by thin-layer chromatography (TLC) on aluminum oxide with elution by chloroform or benzene and development with iodine vapors in a moist chamber. Information regarding the synthesized compounds is presented in Table 1.

1-Ethyl- and 1-Benzyl-2-(2-hydroxyethylamino)-benzimidazoles (Ic,d). These compounds were synthesized by the method [2] described for Ia,b by fusion of the corresponding 1-ethyl- and 1-benzylbenzimidazole-2-sulfonic acids [12] with monoethanolamine (1 h, 155°C). Absorption bands of NH groups at 3430-3460 cm^{-1} and broad absorption bands of associated OH groups at 3200-3350 cm^{-1} are observed in the IR spectra ($CHCl_3$) of amino alcohols Ia-d.

2-N-(1-Methyl-2-benzimidazolyl)aminoethyl-1-hydrosulfate (IIb). A 0.95 g (5 mmole) sample of amino alcohol Ib was added cautiously with stirring to 5 ml of concentrated H_2SO_4, and the resulting solution was allowed to stand at 20°C. After a few hours, the mixture was poured over 10 g of crushed ice, and the aqueous mixture was neutralized with NH_4OH or NaOH solution and evaporated to dryness. The residue was extracted several times with boiling dimethylformamide (DMF), and the solvent was evaporated from the extract. The oily residue was triturated with acetone, and the crystals of acid IIb were removed by filtration, washed with acetone, and dried in a desiccator over P_2O_5. The crystals were purified by crystallization from a small volume of water containing a few drops of alcohol. The yield was 1.3 g (85%). Acid IIb is very hygroscopic and deliquesces in air. When it was dried in a dry box at 115-120°C, it lost part of its water and was converted initially to an oil and then again crystallized to give a snow-white dihydrate with mp 170°C. Found, %: N 13.4. $C_{10}H_{13}N_3O_4S \cdot 2H_2O$. Calculated, %: N 13.7. The very same acid was also obtained when the process was carried out at 150-160°C. It remained unchanged when it was treated with alkalis.

2-N-(2-Benzimidazolyl)aminoethyl-1-hydrosulfate (IIa). This compound was obtained in 87% yield by the method described above for hydrosulfate IIb. The snow-white very hygroscopic crystals had mp 153°C (after drying at 110-120°C). Found, %: $C_9H_{11}N_3O_4S \cdot 3H_2O$. Calculated, %: N 13.5.

2-N-(1-Methyl-2-benzimidazolyl)-N-nitrosoamino-ethyl-1-hydrosulfate (III). A 0.21 g (3 mmole) sample of $NaNO_2$ was added in small portions with stirring to a cooled (to 0-3°C) solution of 0.3 g (1.5 mmole) of amino alcohol Ib in 2 ml of concentrated H_2SO_4, and the mixture was maintained at this temperature for 1 h and then at 20°C for 1 h. The solution was then poured over ice, and the aqueous mixture was made strongly alkaline by the addition of 40% NaOH solution. The mixture was heated at 80°C for 5 min, after which it was cooled and neutralized with CH_3COOH. The resulting precipitate of inorganic salts was separated, the mother liquor was evaporated to dryness, and the residue was treated with several portions of boiling acetone. The acetone solution was evaporated, and the residue was crystallized from a small amount of water to give 0.33 g of light-yellow fine crystals.

2-(N-Acetyl-2-acetoxyethylamino)benzimidazole (IVa). A solution of 0.9 g (5 mmole) of Ia in 5 ml of acetic anhydride was refluxed for 2 h, after which it was cooled and poured into 20 ml of water. After decomposition of the excess anhydride, the mixture was neutralized with $NaHCO_3$ and extracted with chloroform (three 15-ml portions). Evaporation of the

solvent from the extract and recrystallization of the residue from ethyl acetate gave 1.1 g of snow-white crystals.

2-(N-Acetyl-2-acetoxyethylamino)-1-methylbenzimidazole (IVb). This compound was obtained by a procedure similar to that used to prepare diacetate IVa by refluxing a solution of 0.75 g (4 mmole) of amino alcohol Ib in 5 ml of acetic anhydride. The oil that was liberated after neutralization of the reaction mixture was extracted with chloroform (three 10-ml portions), the chloroform extract was evaporated to a small volume, and this small volume was purified chromatographically to remove resinous impurities with a column (2.5 × 5.0 cm) packed with Al_2O_3 by elution with $CHCl_3$. Recrystallization of the product from isooctane gave 0.97 g of diacetate IVb in the form of snow-white needles. In the presence of sodium acetate the reaction is complete in 30 min.

1-R-2-(2-Chloroethylamino)benzimidazole Hydrochlorides Va-d. A) A solution of 5 mmole of amino alcohol Ib,d in 7-10 ml of $POCl_3$ was refluxed for 2-3 h, after which the excess phosphorus oxychloride was removed by distillation at reduced pressure, and the residue was triturated with 5 ml of acetone until crystallization of the salt was complete. The precipitate was removed by filtration, washed with ether, and crystallized from alcohol (Vd) or alcohol with ether (Vb).

B) A mixture of 25 mmole of amino alcohol Ia-d, 20-30 ml of dry chloroform or benzene, and 3.3 ml (a 30% excess) of $SOCl_2$ was refluxed until the reaction was complete (2-2.5 h for Ia, 1 h for Ib,d, and 15 min for Ic), after which the mixture was cooled, and the resulting precipitate of hydrochloride Va-d was removed by filtration, washed with the solvent in which the process was carried out until the odor of $SOCl_2$ vanished, and air dried. The salts obtained were quite pure and could be used without additional purification for the subsequent syntheses. Where necessary, hydrochloride Va was crystallized from acetone, and salt Vc was purified by reprecipitation from solution in alcohol by the addition of ether.

1-R-2-(2-Methoxyethylamino)benzimidazoles VIb-d. Samples (5 mmole) of salts Vb-d were refluxed in 15-20 ml of a 10% solution of NaOH in methanol for 1-2 h, after which the mixture was cooled, the NaCl was separated, and the methanol was evaporated. The residue was purified initially with a chromatographic column packed with Al_2O_3 (elution with benzene), with collection of the fraction with R_f 0.6 ($CHCl_3$), and then by crystallization of VIb from petroleum ether and VIc,d from ethyl acetate.

9-R-2,3-Dihydroimidazo[1,2-α]benzimidazoles VIIb-d. After separation of methoxy derivatives VIb-d by means of column chromatography (see the preceding method), VIIb-d, which were identical to the compounds described in [1], were eluted from the column by means of acetone or alcohol. The yields were 12-15%.

2-Aziridinyl-1-methylbenzimidazole (VIII). A 2.5 g (10 mmole) sample of hydrochloride Vb was added to a solution of 0.8 g (20 mmole) of NaOH in 20 ml of methanol, after which the mixture was stirred until the starting salt had dissolved completely, and the resulting solution was allowed to stand at 20°C. The next day, the precipitated NaCl was removed by filtration, the methanol was evaporated from the filtrate, and the residue was purified chromatographically with a long narrow column (1.3 × 30 cm) packed with activity IV Al_2O_3 (elution with benzene) with collection of the fraction with R_f ~ 0.75. Evaporation of the eluate gave 1.1 g of snow-white crystals of aziridine VIII.

1-Methyl-2,3-dihydroimidazo[1,2-α]benzimidazole (VIIb). A 0.63 g (3.75 mmole) sample of KI was added to a solution of 0.52 g (3 mmole) of aziridine VIII in 20 ml of anhydrous acetone, and the mixture was refluxed until the reaction was complete (~5 h). The mixture was then cooled, the KI was removed by filtration, and the filtrate was evaporated. The residue was dissolved in 3 ml of $CHCl_3$, and the solution was passed through a layer of Al_2O_3 (elution with $CHCl_3$). The oil (R_f 0.5) that remained after the $CHCl_3$ was evaporated was triturated with petroleum ether to give 0.48 g (92%) of snow-white crystals with mp 68°C. No melting-point depression was observed for a mixture of this product with a genuine sample of VIIb [1].

LITERATURE CITED

1. V. A. Anisimova, M. V. Levchenko, and A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 7, 918 (1986).
2. A. M. Simonov and V. N. Komissarov, Khim. Geterotsikl. Soedin., No. 6, 826 (1975).

3. P. Baviani, F. Rose, A. Vartanian, and C. Warolin, French Patent Application No. 2473522; Ref. Zh. Khim., 160124P (1982).
4. J. L. H. Van Gelder, A. H. M. Raeymaekers, L. F. C. Roevens, and W. J. Van Laerhoven, U.S. Patent No. 3983133 (1976); Ref. Zh. Khim., 110173P (1977).
5. K. Körmendy and F. Ruff, Acta Chim. Hung., 112, No. 1, 65 (1983).
6. H.-L. Pan and T. L. Fletcher, J. Heterocycl. Chem., 9, 859 (1972).
7. W. L. Mosby, Heterocyclic Systems with Bridgehead Nitrogen Atoms, Part 1, Interscience (1961), pp. 183, 467.
8. Chau-der Li, Men Hui Lee, and A. C. Santorelli, J. Med. Chem., 22, 1030 (1979).
9. F. Claudi, P. Franchetti, M. Grifantini, and S. Martelli, J. Org. Chem., 39, 3508 (1974).
10. H. W. Heine and A. C. Brooker, J. Org. Chem., 27, 2943 (1962).
11. V. A. Anisimova, M. V. Levchenko, Yu. V. Koshchienko, and A. F. Pozharskii, USSR Inventor's Certificate No. 952847; Byull. Izobret., No. 31, 126 (1982).
12. A. V. El'tsov, K. M. Krivozheiko, and M. B. Kolesova, Zh. Org. Khim., 3, 1518 (1967).

MECHANISM OF THE CATALYTIC OXIDATION OF NITROGEN-CONTAINING METHYL-SUBSTITUTED HETEROCYCLES TO HETARYL ALDEHYDES

L. Ya. Leitis, R. A. Skolmeistere, and M. V. Shimanskaya

UDC 542.943.7:547.821.2

An interrelationship between the electronic structures of methyl derivatives of nitrogen-containing heterocyclic compounds and the character of the interaction with the catalyst, the mechanism of heterogeneous-catalytic oxidation, and the selectivity of the process was established.

The heterogeneous-catalytic oxidation of methyl-substituted heterocycles by air oxygen is one of the most promising methods for the preparation of oxygen-containing derivatives such as aldehydes.

The high reactivities of heterocyclic compounds necessitate the purposeful selection of catalysts that ensure the selective oxidation of the methyl group without destroying the ring. In this paper we present several principles of the reaction mechanism that may serve as a basis for the creation of optimal catalytic systems. As model catalysts we used vanadium-containing systems of the oxide and phosphate type, which have shown their worth in the partial oxidation of nitrogen-containing methyl-substituted heterocycles [1].

A comparison of the rates of partial oxidation of methyl derivatives of pyridine, quinoline, and pyrazine in the presence of vanadyl phosphate with their electronic structures showed that an important factor for the oxidation of these compounds to hetaryl aldehydes is the magnitude of the positive charge on the ring carbon atom bonded to the methyl group to be oxidized [$q_{C(CH_3)}$] [2]. The investigated methyl-substituted heterocycles can be arbitrarily divided into two groups that differ with respect to the character of the interaction with the catalyst and the mechanism of oxidation. One group is made up of compounds with higher $q_{C(CH_3)}$ values (0.05-0.2 according to the MO LCAO CNDO/2 method) that contain oxidizable methyl groups in the 2 and 4 positions of the ring. 3-Methyl derivatives with positive charges $q_{C(CH_3)} < 0.05$ are included in the other group. Under comparable conditions, substantial differences in the selectivity with respect to hetaryl aldehydes are observed for compounds of both groups. In the first case the selectivity is no lower than 40% (44-100%), and in the second case the selectivity is no less than 3-10%.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 64-67, January, 1987. Original article submitted June 16, 1986.

 0009-3122/87/2301-0052$12.50