19. M. I. S. Dewar, Faraday Discussions of the Chemical Society, No. 62, 197 (1977).
20. T. V. Stupnikova, B. P. Zemskii, Yu. B. Vysotskii, R. S. Sagitullin, and Kh. Ya. Lopatinskaya, Khim. Geterotsikl. Soedin., No. 7, 959 (1980).
21. M. M. Mestechkin, Yu. B. Vysotskii, L. S. Gutyrya, and G. E. Vaiman, Teor. Éksp. Khim., 11, 362 (1975).
22. V. É. Umanskii and A. V. Luzanov, Problems of Computer Mathematics and Technology [in Russian], Naukova Dumka, Kiev (1976), p. 74.
23. Q. N. Porter and J. Baldes, Mass Spectrometry of Heterocyclic Compounds, Interscience, New York–London (1977).
24. R. Johnston, Handbook of Mass Spectrometry for Organic Chemists [Russian translation], Mir, Moscow (1975).
25. M. M. Mestechkin, The Density-Matrix Method in Molecular Theory [in Russian], Naukova Dumka, Kiev (1977).
26. V. I. Khvostenko, The Mass Spectrometry of Negative Ions in Organic Chemistry [in Russian], Nauka, Moscow (1981).
27. A. L. Buchachenko and A. M. Vasserman, Stable Radicals [in Russian], Khimiya, Moscow (1973).

FREE-RADICAL HYDROXYMETHYLATION OF BENZIMIDAZOLE

B. I. Khristich, E. B. Tsupak, and O. I. Kononogova

UDC 547.785.5:542.953.2'97

Several benzimidazole derivatives were subjected to free-radical hydroxymethylation. Benzimidazole displays lower activity than quinoline in the first stage of the transformation, viz., in the addition of the hydroxymethyl radical. The yields of hydroxymethylation products are also determined by the ability of the intermediate benzimidazolium cation radicals to undergo oxidation and are increased in the presence of a catalyst, viz., silver ions.

Benzimidazole, like other heteroaromatic compounds, undergoes free-radical substitution in the imidazole ring [1]. It therefore seemed of interest to realize its hydroxymethylation by a method that gives excellent results in the 2-methylquinoline series: 4-Hydroxymethylquinaldine is formed in 86% yield when quinaldine is refluxed with ammonium persulfate in aqueous methanol in the presence of sulfuric acid (method A) [2].

In the present research we have shown that this reaction with 1-methyl- and 1-phenylbenzimidazoles (Ia, c) gives 2-hydroxymethyl derivatives (IIa, c) in considerably lower yields, viz., 28 and 8%, respectively. However, the yield of carbinol IIa increases to 43% when the temperature is raised to 100°C (in an ampul) (method B).

The previously observed [3] decrease in the yields of homolytic substitution products in the benzimidazole series as compared with pyridine and quinoline can be explained either by the lower susceptibility of the benzimidazolium cation to attack of the radical or by the relative difficulty of the second step in the process, viz., oxidative dehydrogenation.

Considering the correlation of the relative rates of homolytic alkylation [4] and acylation [5] with the chemical shifts of the protons in the substitutable positions of the pyridine ring it may be assumed that the lower yields in the benzimidazole series are due to the difficulty involved in the first step of the process, since the chemical shifts of the 2-H protons in the 1-methyl- and 1-phenylbenzimidazolium cations (8.50 and 8.66 ppm, respectively) are lower than the chemical shift of the 4-H proton in the quinaldinium cation (8.99 ppm).

However, 1-methyl-5-nitrobenzimidazole (If), which in an acidic medium has a chemical shift of the 2-H proton that is almost the same (8.94 ppm) as that of the quinaldinium cation, undergoes virtually no hydroxymethylation under these conditions. Similar results were ob-

Rostov State University, Rostov-on-Don 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1679-1681, December, 1982. Original article submitted December 7, 1981; revision submitted June 17, 1982.

0009-3122/82/1812-1299$07.50

TABLE 1. Yields of 1-R-5-R'-2-Hydroxymethylbenzimidazoles (IIa-g)

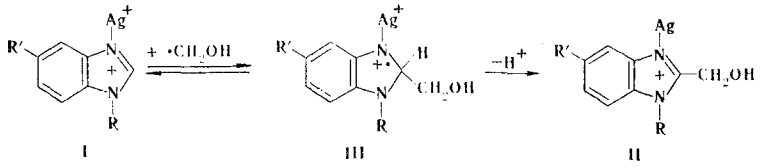
Compound	R	R′	δ,* ppm	Yield, %		
				A	B	C
IIa	CH_3	H	8,50	28	43	45
IIb	$CH_2C_6H_5$	H	8,45	—	8	33
IIc	C_6H_5	H	8,66	8	13	18
IId	p-$CH_3OC_6H_4$	H	8,66	—	—	8
IIe	p-$C_6H_5C_6H_4$	H	8,66	—	—	7
IIf	CH_3	NO_2	8,94	—	9	15
IIg	CH_3	OCH_3	8,46	—	5	21

*The chemical shift of the 2-H proton of the cations of starting Ia-g.

tained with other substituted benzimidazoles (Table 1). These data indicate the extremely important role of the second step of the transformation. In fact, the minimal yields were obtained with compounds in which the substituents promote delocalization of the unpaired electron.

The latter fact compelled us to use a catalyst in the hydroxymethylation, viz., silver ions, which, due to coordination with the pyridine nitrogen atom, should facilitate intramolecular oxidation of cation radical III.

$$2Ag^+ + S_2O_8^{2-} \longrightarrow 2Ag^{2+} + 2SO_4^{2-}$$



In fact, the yields of carbinols are increased appreciably in this case, and this makes it possible to use the reaction for preparative purposes.

However, even in the presence of the catalyst the yields of 2-hydroxymethylbenzimidazoles (IIa-g) are still considerably lower than in the quinoline series. This indicates the lower susceptibility of the benzimidazole ring to nucleophilic attack by hydroxymethyl radicals.

The IR spectra of solutions of the 2-hydroxymethylbenzimidazoles in chloroform contain a broad band of a hydroxy group at 2800-3500 cm^{-1}. In the case of IIa, b the spectra were found to be identical to the spectra of genuine samples.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in trifluoroacetic acid were recorded with a Tesla BS-467 spectrometer with hexamethyldisiloxane as the internal standard.

(2,4-Dinitrophenyl)(4-biphenylyl)amine. A mixture of 33.8 g (0.28 mole) of p-aminobiphenyl, 40.4 g (0.20 mole) of 2,4-dinitrochlorobenzene, 40.8 g (0.30 mole) of crystalline sodium acetate, and 300 ml of ethanol was refluxed for 2.5 h. The orange crystals that formed when the mixture was cooled were removed by filtration and washed with ethanol and several times with water to give 56.3 g (84%) of a product with mp 130-131°C (from petroleum ether–benzene). Found: C 64.5; H 4.0; N 12.4%. $C_{18}H_{13}N_3O_4$. Calculated: C 64.5; H 3.9; N 12.5%.

5-Amino-1-(p-biphenylyl)benzimidazole. A 10.05-g (0.03 mole) sample of (2,4-dinitrophenyl)(4-biphenylyl)amine was added to a solution of 26 g (0.15 mole) of sodium dithionite in a mixture of 70 ml of water, 40 ml of concentrated ammonium hydroxide, and 90 ml of ethanol, and the mixture was stirred until the exothermic reaction ceased. It was then refluxed until the starting substance had dissolved completely. The solution was cooled and diluted with cold water, and the aqueous mixture was placed in an ice bath. The precipitated crystals of the triamine were removed by filtration, washed with cold water, and squeezed thoroughly on a filter. The crude triamine was mixed with 50 ml of 99% formic acid, 10 ml of con-

TABLE 2. 1-R-5-R'-2-Hydroxymethylbenzimidazoles (IIa-g)

Compound	mp,* °C	Found, %			Empirical formula	Calc., %		
		C	H	N		C	H	N
IIa	125—130 [6]	—	—	—	$C_9H_{10}N_2O$	—	—	—
IIb	185—187 [7]	—	—	—	$C_{15}H_{14}N_2O$	—	—	—
IIc	101	75,0	5,7	12,3	$C_{14}H_{12}N_2O$	75,0	5,4	12,5
IId	110—111	70,3	5,3	11,0	$C_{15}H_{14}N_2O_2$	70,8	5,6	11,0
IIe	184—185	79,8	5,8	9,6	$C_{20}H_{16}N_2O$	80,0	5,4	9,3
IIf	167—168	52,5	4,2	19,9	$C_9H_9N_3O_3$	52,2	4,4	10,3
IIg	183	62,0	6,6	—	$C_{10}H_{12}N_2O_2$	62,5	6,3	—

*The compounds were recrystallized: IIa, f from water, IIb from alcohol, and the remaining compounds from benzene.

centrated HCl was added, and the mixture was refluxed for 4 h. The resulting clear solution was evaporated to dryness on a steam bath, the residue was dissolved in the minimum amount of 10% HCl, and the solution was refluxed for 1 h. The crystalline precipitate that formed when the solution was cooled was removed by filtration, squeezed on a filter, and triturated with concentrated ammonium hydroxide. 5-Amino-1-(p-biphenylyl)benzimidazole was removed by filtration, washed with water, and dried to give 6.3 g (74%) of colorless prisms (from ethanol) with mp 171-173°C. Found: C 80.3; H 5.2; N 14.6%. $C_{19}H_{15}N_3$. Calculated: C 80.0; H 5.3; N 14.7%.

1-(p-Biphenyl)benzimidazole (Ie). A 4.3-g (15 mmole) sample of 5-amino-1-(p-biphenylyl)-benzimidazole was dissolved by heating in a mixture of 23 ml of concentrated HCl and 20 ml of water, the solution was cooled to 0°C, and a solution of 1.2 g (17 mmole) of sodium nitrite in 5 ml of water was added dropwise. A solution of 9.5 g (90 mmole) of sodium hypophosphite in 20 ml of water was then added slowly at 0-5°C, and the mixture was allowed to stand in a refrigerator overnight. The oil that separated after neutralization with ammonium hydroxide was purified by chromatography with a column filled with aluminum oxide by elution with benzene to give 2.2 g (54%) of colorless crystals with mp 164-165°C (from benzene–petroleum ether). Found: C 84.1; H 5.5; N 10.5%. $C_{19}H_{14}N_2$. Calculated: C 84.4; H 5.2; N 10.4%.

1-R-5-R'-2-Hydroxymethylbenzimidazoles (IIa-g, Tables 1 and 2). A) A 2.3-g (10 mmole) sample of ammonium persulfate was added to a solution of 5.0 mmole of 1-methyl- or 1-phenylbenzimidazole (Ia or Ic) in a mixture of 7 ml of methanol, 3.5 ml of water, and 0.28 ml (5.2 mmole) of concentrated H_2SO_4, after which the methanol was removed by distillation, and the residual sulfuric acid solution was made strongly alkaline with ammonium hydroxide. The oil that separated was extracted with chloroform, and the extract was concentrated and separated with a chromatographic column filled with aluminum oxide by elution with chloroform.

B) A mixture of 5.0 mmole of benzimidazole (Ia-c, f, g), 7 ml of methanol, 3.5 ml of water, 0.28 ml (5.2 mmole) of concentrated H_2SO_4, and 2.3 g (10 mmole) of ammonium persulfate was heated at 40-50°C in a sealed ampul with periodic shaking until the ammonium persulfate had dissolved completely. The ampul was then heated on a boiling-water bath for 7 h. The substances were isolated as in method A.

C) A 0.17-g (1.0 mmole) sample of silver nitrate was added to a solution of 5.0 mmole of benzimidazole (Ia-g) in a mixture of 7 ml of methanol, 3.5 ml of water, and 0.28 ml (5.2 mmole) of concentrated H_2SO_4, and the mixture was refluxed for 3 h. It was then cooled, and the silver was precipitated with a small amount of HCl. The mixture was then worked up as described in method A. In the hydroxymethylation of Ie 10.5 ml of methanol was used because of the low solubility of this compound.

LITERATURE CITED

1. F. Bertini, R. Galli, F. Minisci, and O. Porta, Chem. Ind. (Milan), 54, 223 (1972).
2. W. Buratti, G. P. Gardini, F. Minisci, F. Bertini, R. Galli, and M. Perchinunno, Tetrahedron, 27, 3655 (1971).
3. A. Arnone, M. Cecere, R. Galli, F. Minisci, P. Perchinunno, O. Porta, and G. Gardini, Gazz. Chim. Ital., 103, 13 (1973).
4. F. Minisci, R. Mondelli, G. P. Gardini, and O. Porta, Tetrahedron, 28, 2403 (1972).
5. T. Caronna, G. Fronza, F. Minisci, and O. Porta, J. Chem. Soc., Perkin Trans. II, No. 10, 1477 (1972).

6. F. Minisci and O. Porta, Zh. Vses. Khim. Ova., 24, 134 (1979).
7. N. P. Bednyagina and I. Ya. Postovskii, Zh. Obshch. Khim., 30, 3193 (1960).
8. D. D. Dalgatov and A. M. Simonov, Zh. Obshch. Khim., 33, 1007 (1963).

REACTION OF 3,4-DICYANO-5-AMINOPYRAZOLE WITH ETHYL ORTHOFORMATE

Yu. N. Bulychev, I. A. Korbukh, and M. N. Preobrazhenskaya

UDC 547.711.1'859.07:543.422.51

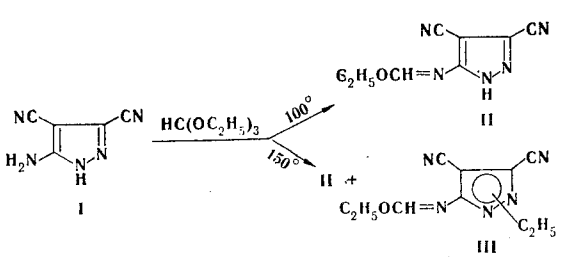
The condensation of 3,4-dicyano-5-aminopyrazole with ethyl orthoformate was studied. Under severe conditions (150°C) the principal reaction product is N-ethyl-3,4-dicyano-5-ethoxymethylaminopyrazole. Alkylation of the pyrazole ring does not occur at 100°C, but 3,4-dicyano-5-ethoxymethyleneaminopyrazole is formed. Isomeric 1- and 2-ethyl-4-aminopyrazolo[2,4-d]pyrimidine-3-carboxylic acid methyl imino esters were obtained by the action of a methanol solution of ammonia on the principal reaction product. This constitutes evidence that N-ethyl-3,4-dicyano-5-ethoxymethyleneaminopyrazole is a mixture of 1- and 2-ethyl-3,4-dicyano-5-ethoxymethyleneaminopyrazoles.

The reaction of aminoimidazoles or aminopyrazoles that contain a nitrile group in the ortho position with carboxylic acid ortho esters with subsequent cyclization under the influence of various agents is a widely used method for the synthesis of purines or pyrazolo[3,4-d]pyrimidines [1]. It is customary to assume that ethoxymethyleneamino derivatives of the corresponding azoles are formed in the reaction with ethyl orthoformate. However, neither the structure of the intermediate ethoxymethyleneamino derivatives nor the reaction itself have been studied. The aim of the present research was to study the reaction of 3,4-dicyano-5-aminopyrazole (I) with ethyl orthoformate, to identify the products of this reaction, and to synthesize substitued pyrazolo[3,4-d]pyrimidines from them.

The preparation of 5-ethoxymethyleneamino derivatives by refluxing 3,4-dicyano-5-aminopyrazole (I) and its 1- or 2-methyl derivative in ethyl orthoformate has been previously described [2-5]; the products were subsequently converted to the corresponding pyrazolo[3,4-d]-pyrimidines by the action of a methanol solution of ammonia.

We have established that not only the formation of an ethoxymethyleneamino group but also alkylation of the pyrazole ring occur when 3,4-dicyano-5-aminopyrazole (I) is refluxed in ethyl orthoformate at 150-160°C. In contrast to other authors, we isolated N-ethyl-3,4-dicyano-5-ethoxymethyleneaminopyrazole (III) as the principal products in 68% yield under these conditions and 3,4-dicyano-5-ethoxymethyleneaminopyrazole (II) in only 16% yield.

The formation of alkyl derivatives in the reaction of substituted pyrazoles with ethyl orthoformate has not been heretofore described, although there have been reports of the alkylation of some secondary amines by carboxylic acid ortho esters (for example, see [6]).



The formation of N-alkyl derivative III can be avoided by condensation of pyrazole I with ethyl orthoformate under mild conditions. 3,4-Dicyano-5-ethoxymethyleneaminopyrazole (II) was obtained in 80% yield by heating I with this ester at 100-110°C for 3 h. According

All-Union Oncological Science Center, Academy of Medical Sciences of the USSR, Moscow 115478. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1682-1685, December, 1982. Original article submitted May 4, 1982.

 0009-3122/82/1812-1302$07.50