SYNTHESIS OF N-GLYCOSIDES OF BENZIMIDAZOLE AND ITS DERIVATIVES

A. T. Ayupova, Ch. Sh. Kadyrov, L. V. Molchanov, and S. S. Khalikov

UDC 547.785.5'963.32:543.422.25

N-Benzimidazolylglucopyranosides were synthesized by condensation of N-trimethylsilyl derivatives of benzimidazole and its 2,5,6-trisubstituted derivatives with acetobromoglucose with subsequent removal of the protective groups. The β configuration of the glycoside center was proved on the basis of PMR spectral data.

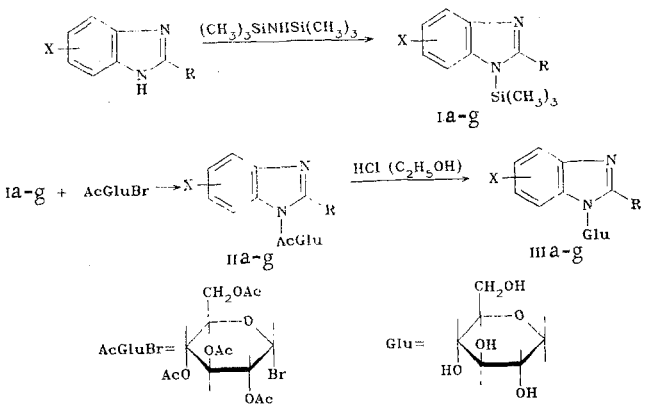
A structural analog of purine, viz., benzimidazole, and a number of its derivatives have pesticide activity [1]. The products of their glycosylation can be regarded as anomalous nucleosides that may be of interest as biologically active compounds. In addition, the possibility of suppressing the growth of malignant tumors and effects on the growth of viruses are associated with analogs of nucleosides [2].

The principal methods for the construction of a glycoside bond in nucleosides involve the condensation of acylhalogenoses with silver, mercury, or trimethylsilyl derivatives of heterocyclic bases [3-5].

We used silyl condensation to obtain N-nucleosides of 2,5,6-trisubstituted benzimidazoles. A method for the preparation of ribofuranosides of benzimidazole, 2-chlorobenzimidazole, and 5,6-dimethylbenzimidazole, as well as glucopyranosylbenzimidazoles, has been described in the literature [4, 6, 7].

We synthesized previously undescribed glucopyranosides of 2,5,6-trisubstituted benzimidazoles by condensation of their N-trimethysilyl derivatives with α-acetobromoglucose and subsequent deacylation with ethanol saturated with dry hydrogen chloride. Trimethylsilyl derivatives Ia-g were similarly obtained [8] by heating 2,5,6-trisubstituted benzimidazoles with excess hexamethyldisiloxane (HMDS) with a reflux condenser without access to moisture for 10-15 h.

Removal of the excess HMDS at atmospheric pressure in all cases left residues of colorless crystalline silyl derivatives Ia-g, which were used without additional purification for the subsequent chemical transformations:



I—III a–d R=H; I—III e–g R=CH_3; I—III a X=H; b X=5(6)-Cl; c X=5(6)-CH_3; d X=5,6-di-CH_3; e X=H; f X=5(6)-CH_3O; g X=5(6)-Cl

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 812-814, June, 1984. Original article submitted May 12, 1983.

 0009-3122/84/2006-0662$08.50

TABLE 1. Constants of the Synthesized II and III

Compound	mp, °C (solvent)	R_f	m/z	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
IIa	152—153[a] (ethanol)	0,50	448, 331, 118	56,2	5,3	6,5	$C_{21}H_{24}N_2O_9$	56,1	5,4	6,3	39
IIb	83—85 (ethyl acetate)	0,35	482, 331, 152	52,4	4,7	4,9	$C_{21}H_{23}ClN_2O_9$	52,2	4,8	5,8	38
IIc	147—148[b] (chloroform)	0,40	462, 331, 132	56,9	5,5	5,9	$C_{22}H_{26}N_2O_9$	57,1	5,6	6,1	45
IId	259—260 (benzene)	0,33	476, 331, 146	58,1	5,7	5,2	$C_{23}H_{28}N_2O_9$	57,9	5,9	5,9	47
IIe	178—179 (ethanol)	0,43	462, 331, 132	57,2	5,4	6,7	$C_{22}H_{26}N_2O_9$	57,2	5,6	6,1	42
IIf	140—142 (ethanol)	0,38	492, 331, 162	56,3	5,4	5,5	$C_{23}H_{28}N_2O_{10}$	56,1	5,7	5,7	52
IIg	85—86 (ethanol)	0,32	496, 331, 166	53,2	4,9	4,3	$C_{22}H_{25}ClN_2O_9$	53,2	5,0	5,6	52
IIIa	216[c] (benzene)	0,44		55,9	5,6	9,8	$C_{13}H_{16}N_2O_5$	55,7	5,7	10,0	50
IIIb	162—164 (ethanol)	0,59		49,7	4,6	7,9	$C_{13}H_{15}ClN_2O_5$	49,6	4,8	8,9	43
IIIc	209—210[d] (petroleum ether)	0,53		57,2	6,0	9,7	$C_{14}H_{18}N_2O_5$	57,1	6,1	9,5	57
IIId	305—306 (water)	0,57		58,6	6,3	9,3	$C_{15}H_{20}N_2O_5$	58,4	6,5	9,1	39
IIIe	224—226 (ethanol)	0,65		57,2	5,9	9,7	$C_{14}H_{18}N_2O_5$	57,1	6,1	9,5	49
IIIf	279—280 (benzene)	0,46		55,6	5,9	8,0	$C_{15}H_{20}N_2O_5$	55,5	6,1	8,6	46
IIIg	190—193 (petroleum ether)	0,56		51,4	5,1	7,9	$C_{14}H_{17}ClN_2O_5$	51,2	5,2	8,8	53

[a]According to the data in [7], this compound had mp 152-153°C. [b]According to the data in [7], this compound had mp 175°C. [c]According to the data in [7], this compound had mp 216°C. [d]According to the data in [7], this compound had mp 275°C.

The structures of II and III and the β configuration of the glycoside center were proved on the basis of data from the PMR and mass spectra and the results of elementary analysis (Table 1). A doublet at δ 4.65 ppm with J = 8.4 Hz, which is related to the anomeric proton and constitutes evidence that the residue is connected to the aglycone by a β-glycoside bond [9, 10], is clearly seen in the PMR spectra of II and III in deuteropyridine. Signals of protons of acetyl groups of the hydrocarbon part of the molecule at δ 1.52, 1.75, 1.92, and 2.00 ppm are visible in the spectra of acetates II. Molecular-ion peaks (M^+) and peaks of ion fragments are present in the mass spectra of II (Table 1).

An investigation of the effect of the synthesized glucopyranosides of 2,5,6-trisubstituted benzimidazoles on *Verticillum dahliae* Kleb, *Fusarium oxysporium*, *Phizoctonia solani*, and *Thielaviopsis basicola* showed that these compounds have only a slight fungicidal effect.

EXPERIMENTAL

The mass spectra were recorded with an MKh-1303 mass spectrometer at an ionizing voltage of 30 eV at 150-210°C with direct introduction of the samples into the ion source. The PMR spectra of solutions in deuteropyridine were recorded with a Jeol C-60HL/60 spectrometer with HMDS as the internal standard. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in a chloroform—acetone—methanol system (1:1:0.1) with development with iodine vapors.

1-Trimethylsilyl-5(6)-chloro-2-methylbenzimidazole (Ig). A 3.33-g (0.02 mole) sample of 5(6)-chloro-2-methylbenzimidazole was refluxed with stirring in 10 ml of freshly distilled HMDS by means of a reflux condenser for 15 h without access to moisture, after which the excess HMDS was removed by distillation at atmospheric pressure, and the colorless crystalline mass of crude product that formed after cooling was used for the subsequent transformations. Compounds Ia-f were similarly obtained.

1-(2',3',4',6'-Tetra-O-acetyl)-β-D-glucopyranosyl-5(6)-chloro-2-methylbenzimidazole (IIg). A mixture of 4.77 g (0.02 mole) of Ig and 8.22 g (0.02 mole) of finely ground α-acetobromoglucose [11] was heated at 150-160°C on an oil bath for 2 h, during which the mixture melted and darkened. The dark mass was cooled and treated with chloroform (200 ml) until it had dissolved completely. The solution was filtered, and the filtrate was washed with a saturated solution of sodium bicarbonate (four 100-ml portions) and cold water (four 100-ml portions). The chloroform layer was dried over sodium sulfate and concentrated *in vacuo* to a syrup. The syrup was dissolved in anhydrous methanol (100 ml), and the solution was decolorized with activated charcoal. The filtrate was concentrated to 15-20 ml and treated with petroleum ether (50 ml, bp 40-60°C). The solution was maintained at 5-10°C for 18-24 h to crystallize the product. Workup gave 4.9 g (52.3%) of a product with mp 85-86°C (ethanol).

Compounds IIa-f were similarly obtained (Table 1).

1-β-D-Glucopyranosyl-5(6)-chloro-2-methylbenzimidazole (IIIg). A 4.96-g (0.01 mole) sample of IIg was dissolved in 250 ml of ethanol saturated with dry hydrogen chloride, and the solution was allowed to stand at 25°C for 24 h until the acetyl groups had been split out completely (according to TLC). After complete deacylation, the alcohol was removed by vacuum distillation to dryness, and the residue was again dissolved in absolute ethanol. The reaction product was precipitated by means of ethyl acetate to give 2 g (53%) of a product with mp 190-193°C (petroleum ether).

LITERATURE CITED

1. N. N. Mel'nikov, in: The Chemistry and Technology of Pesticides [in Russian], Khimiya, Moscow (1974), p. 632.
2. E. Gale, in: The Strategy of Chemotherapy [Russian translation], Inostr. Lit., Moscow (1960), p. 246.
3. B. N. Stepanenko, E. M. Kuz'mina, and Z. S. Dubinkina, Usp. Khim., 42, 1121 (1973).
4. E. Ya. Lukevits, A. E. Zabolotskaya, and I. I. Solomennikov, Usp. Khim., 18, 370 (1974).
5. Z. A. Shabarova and A. A. Bogdanova, in: The Chemistry of Nucleic Acids and Their Components [in Russian], Khimiya, Moscow (1978), p. 411.
6. H. Bräuniger and A. Koine, Arch. Pharm., 296, 668 (1963).
7. L. B. Townsend and G. R. Revankar, Chem. Rev., 70, 389 (1970).
8. I. V. Alekseeva, A. S. Shalomai, V. L. Mikitruk, and V. P. Chernetskii, Khim. Geterotsikl. Soedin., No. 9, 1260 (1977).
9. R. U. Lemieux and J. D. Stevens, Can. J. Chem., 44, 249 (1966).
10. F. F. Blanko, I. A. Korbukh, M. N. Preobrazhenskaya, and H. Dorn, Khim. Geterotsikl. Soedin., No. 11, 1512 (1981).
11. N. K. Kochetkov (editor), Methods in the Chemistry of Carbohydrates [in Russian], Mir, Moscow (1967), p. 123.