RESEARCH ON UNSATURATED AZOLE DERIVATIVES.

VII.* NEW SYNTHESES IN THE 2-VINYLBENZIMIDAZOLE SERIES

I. I. Popov, V. N. Narezhnaya, and A. A. Zubenko

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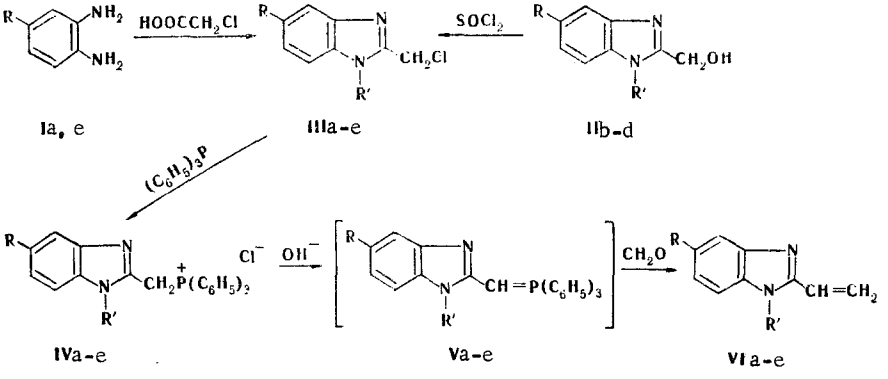
2-Vinylbenzimidazole and substituted (at the nitrogen atom and in the aromatic ring) homologs of 2-vinylbenzimidazoles were synthesized from the readily accessible 2-chloromethylbenzimidazoles and formalin by means of the Wittig reaction in a two-phase aqueous system.

Communications regarding the synthesis of 2-vinylbenzimidazole and polymeric materials based on it appeared quite some time ago [2, 3]; however, until recently there was no reliable method for the synthesis of this monomer in the literature [4]. This has stimulated the search for new methods for its preparation [5-7].

The direct condensation of o-phenylenediamine with acrylic acid leads to the formation of 2,3,4,5-tetrahydro-1H-1,5-benzo-2-diazepinone in 4 N hydrochloric acid [8] and 4,8-dioxo-1,2,3,4,7,8-hexahydro-6H-(1,4)-diazepino[3,2,1-i,j]quinoline in polyphosphoric acid [9]. Attempts to dehydrate 2-α- and 2-β-hydroxyethylbenzimidazoles by means of anhydrides of phosphoric and acetic acids were unsuccessful, and dehydrohalogenation of 2-α- and 2-β-chloro- or -bromoethylbenzimidazoles by the action of aqueous alkali with heating leads to the formation of a polymer [8]. It was recently shown that monomeric 2-vinylbenzimidazole can be obtained by spontaneous dehydrohalogenation of 2-β-bromoethylbenzimidazole in the solid state [5] or by dehydrobromination by means of a milder base (triethylamine) [6].

Conditions that exclude the possibility of polymerization of the thermally labile monomers at the instant of their formation are necessary for the successful synthesis of 2-vinylbenzimidazoles. We have found a general preparative method for the preparation of 2-vinylbenzimidazoles, under conditions that exclude heating of the reaction mixture, from the readily accessible 2-chloromethylbenzimidazoles by the Wittig reaction via the scheme



Ia, e — IIIa-e — IIb-d

IVa-e — Va-e — VIa-e

I a, III-VI a R=R′=H; II-VI b R=H, R′=CH3; c R=R′=CH3; d R=OCH3, R′=CH3; I e III-VI e R=NO2, R′=CH3

The reaction of 2-chloromethylbenzimidazoles IIIa-e with triphenylphosphine in dioxane gives phosphonium salts IVa-e in good yields. It is more convenient to use alcohol as the solvent in the preparation of phosphonium salt IVd, since starting IIId is only slightly soluble in dioxane. Compounds IVa-e were found to be rather strong conjugate acids due to the influence of the strong inductive effect of the 2-benzimidazolyl group [13]. Thus phos-

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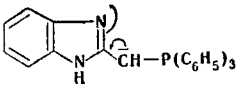
phonium salts IVa-d react with sodium carbonate, and IVe even reacts with sodium bicarbonate in water. However, according to our data, in the case of IVa expected ylide Va is not formed; instead, a mixture of products of hydrolysis of Va — triphenylphosphine oxide and 2-methylbenzimidazole — is formed. This is apparently explained by the instability of phosphorane Va, which readily undergoes alkaline hydrolysis under the reaction conditions. Let us note that 2-methylbenzimidazole and only a small amount of 2-vinylbenzimidazole were obtained as the principal products when phosphonium salt IVa was treated with sodium ethoxide in alcohol with the subsequent addition of an alcohol solution of formaldehyde (see [14]).

It would seem that the high electrophilicity of the 2-benzimidazolyl fragment [13] should ensure the sufficient stability of phosphoranes Va-e and particularly ylide Va, the stabilization of which may promote the effective participation of the heterocyclic ring in the distribution of the charge of ylide form Va:



Va

In fact, Va and Ve were found to be the most stable of the ylides obtained. The stability of Va and Ve is apparently due to the effect of the nitro group of the heteroaromatic ring. The formation of phosphoranes Va, e can be recorded by means of chromatography in a thin layer of aluminum oxide; however, they cannot be isolated in pure form because they readily undergo hydrolysis. We noted that phosphorane Va can be stored in the chloroform extract for some time without visible changes and that its hydrolysis is complete in 2-3 h. This made it possible to develop a convenient method for the preparation of 2-vinylbenzimidazoles VIa-e in a two-phase aqueous system without isolation of phosphoranes Va-e from the reaction mixture. For this, phosphonium salts IVa-e were dissolved in chloroform, and aqueous solutions of sodium carbonate and formalin were added to it simultaneously. 2-Vinylbenzimidazoles VIa-c and VIe were obtained in high yields by this method. Since phosphonium salt IVd is insoluble in chloroform, the reaction was carried out in an aqueous alcohol medium; this leads to a decrease in the yield of monomer VId.

In contrast to the rather stable 2-vinylbenzimidazoles VIa, e, vinyl derivatives VIb-d are extremely thermally labile and readily undergo polymerization at the instant of isolation from the reaction mixture; VIb is stable only in the form of the monohydrate. When it is dried in vacuo over phosphorus pentoxide or in air at 50-60°C, it forms a transparent plastic polymer that solidifies with time. On prolonged storage VIb undergoes cleavage to give 1,2-dimethylbenzimidazole (compare this with the thermal cleavage of 2-propenylbenzimidazole [15]).

The UV spectra of VIa-d contain three absorption maxima at 215-225 nm ($\pi\rightarrow\pi^*$ transition of the vinyl group), 240-245 nm ($\pi\rightarrow\pi^*$ transition of the annelated benzene ring), and 290-315 nm (long-wave absorption of a benzimidazole ring conjugated with a vinyl group). 2-Vinylbenzimidazoles VIb-d are readily quaternized when they are refluxed with methyl iodide in alcohol to give quaternary salts VIIb-d; Under these conditions, nitro derivative VIe does not react with methyl iodide, apparently because of a considerable decrease in the basicity of the ring nitrogen atom under the influence of the nitro group. A hypsochromic shift and a decrease in the intensities of the $\pi\rightarrow\pi^*$ transition of the vinyl group and the long-wave absorption of the benzimidazole ring as compared with the starting VIb-d are observed in the UV spectra of quaternary salts VIIb-d; the changes in the $\pi\rightarrow\pi^*$ transition of the benzene ring are insignificant. The IR spectra of 2-vinylbenzimidazoles VIa-e contain absorption bands at 960 and 980 cm^{-1} (monosubstituted ethylenes) and at 1590-1595 and 1630-1640 cm^{-1} (stretching vibrations of C=C and C=N bonds of the heteroaromatic ring and the vinyl group), and the spectrum of VIe also contains absorption bands of a nitro group at 1530 (ν_{as}) and 1340 (ν_s) cm^{-1}.

EXPERIMENTAL

The IR spectra of solutions of the compounds in $CHCl_3$ were recorded with a UR-20 spectrometer. The UV spectra of methanol solutions of the compounds ($3\cdot10^{-6}$ g concentrations) were recorded with a Specord Spectrophotometer.

1-Methyl-2-hydroxymethylbenzimidazole (IIb). A mixture of 31.5 g (0.21 mole) of 2-hydroxymethylbenzimidazole, 30 ml of alcohol, 12 g (0.3 mole) of sodium hydroxide, and 75

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Crystallization solvent	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIc	150	Water	67,8	6,9	16,0	$C_{10}H_{12}N_2O$	68,2	6,8	15,9	48
IId	191	Water	62,9	6,7	14,6	$C_{10}H_{12}N_2O_2$	62,5	6,2	14,6	53
IIIc	107	Heptane	61,7	5,6	14,8	$C_{10}H_{11}ClN_2$[a]	61,7	5,6	14,4	77
IIId	150	Hexane	56,8	5,4	13,7	$C_{10}H_{11}ClN_2O$[a]	57,0	5,2	13,3	86
VIa	186—187	Ethyl acetate	75,4	5,9	19,8	$C_9H_8N_2$	75,0	5,5	19,5	85
VIb	61[c]	Hexane	67,8	6,9	15,8	$C_{10}H_{10}N_2 \cdot H_2O$	68,2	6,8	15,9	86
VIc	77	Hexane	77,0	6,4	16,0	$C_{11}H_{12}N_2$	76,8	6,8	16,3	88
VId	80	Hexane	70,4	6,6	14,9	$C_{11}H_{12}N_2O$	70,2	6,4	14,9	50
VIe	170	Ethyl acetate	59,0	4,0	20,3	$C_{10}H_9N_3O_2$	59,1	4,4	20,7	90

[a]Chlorine content in IIIc, d: found: 18.0 and 16.8%; calculated: 18.3 and 16.9%, respectively. [b]According to [4], mp 187-189°C. [c]Melting point of the monohydrate.

ml of water was stirred vigorously until the solid material dissolved, after which the mixture was cooled with ice water, and 29 ml (0.3 mole) of dimethyl sulfate was added dropwise in the course of 40-50 min at no higher than 5°C (otherwise a large amount of oily impurities is formed). The mixture was stirred for another 30 min, and the precipitate was removed by filtration to give 19.4 g (57%) of a product with mp 128-130°C (from water) (mp 125-130°C [12]).

5-Nitro-1-methyl-2-chloromethylbenzimidazole (IIIe). A mixture of 16.7 g (0.1 mole) of 4-nitro-2-amino-N-methylaniline and 14.2 g (0.15 mole) of chloroacetic acid was refluxed for 3 h in 150 ml of 4 N HCl, after which it was cooled and neutralized with sodium acetate solution, and the precipitate was removed by filtration to give 17 g (75%) of a product with mp 191-192°C (from ethanol) [11].

1-Methyl-5-R-2-hydroxymethylbenzimidazoles (IIc-d). A mixture of 0.1 mole of the corresponding 2-nitro-4-R-methylaniline and 60 ml of concentrated HCl was heated on a boiling-water bath, and a solution of 60 g (0.3 mole) of stannous chloride in 90 ml of HCl was added with stirring. The mixture was stirred for 30 min, 11.4 g (0.15 mole) of glycolic acid was added gradually, and the mixture was refluxed for 2 h and allowed to stand overnight. The precipitate was removed by filtration and suspended in a small amount of warm water. The suspension was treated with dilute alkali, the mixture was cooled, and the product was extracted with chloroform.

1-Methyl-5-R-2-chloromethylbenzimidazoles (IIIc, d). A 0.1-mole sample of the corresponding IIc, d was heated in 40 ml of dry dioxane until it dissolved, after which the solution was cooled with ice water, and 14.2 ml (0.2 mole) of thionyl chloride was added in portions to the cooled (with ice water) solution. The mixture was then refluxed for 1 h, cooled, and poured into 70 ml of water. The aqueous mixture was neutralized with sodium bicarbonate, and the precipitate was removed by filtration.

2-Benzimidazolylmethyltriphenylphosphonium Chlorides (IVa-e). A solution of the corresponding 2-chloromethylbenzimidazole (IIIa-e) and 15.8 g (0.06 mole) of triphenylphosphine in 60 ml of dioxane was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration. Compound IVa, with mp 289°C (from ethanol—dimethylformamide), was obtained in 81% yield; IVb, with mp 259°C (from water), was obtained in 87% yield; IVc, with mp 145°C (from alcohol—ether), was obtained in 94% yield; and IVe, with mp 235°C (from ethyl acetate), was obtained in 86% yield. For the preparation of IVd, a solution of 1.1 g (0.005 mole) of IIId and 1.31 g (0.005 mole) of triphenylphosphine in 10 ml of alcohol was refluxed for 5 h, after which half the solvent was removed by distillation, the concentrate was cooled, and IVd was precipitated by the addition of ether to give 1.5 g (62%) of a product with mp 200°C (from dioxane).

Phosphonium salts IVa-e were used without additional purification in the synthesis of the 2-vinylbenzimidazoles.

2-Vinylbenzimidazoles (VIa-e). A 2-ml sample of 40% aqueous formaldehyde and 8 ml of a saturated aqueous solution of sodium carbonate were added to a solution of 0.01 mole of phosphonium salt IVa-e in 15 ml of chloroform, and the mixture was stirred for 1 h. The chloroform layer was separated and extracted with dilute HCl, and the HCl extract was

neutralized with ammonia. The precipitated VIa, e were removed by filtration, while VIb and VIc, which separated in the form of oils, were extracted with ether. The extract was then dried over anhydrous sodium sulfate, the solvent was removed by evaporation, and the residue was chromatographed on aluminum oxide. In the preparation of VId, 4 ml of formalin and 12 ml of a saturated solution of sodium carbonate were added to a solution of 0.01 mole of phosphonium salt IVd in 200 ml of water, and the mixture was stirred for 1 h. It was then worked up as described for VIb, c.

2-Vinylbenzimidazole Methiodides (VIIb-d). Methiodides VIIb-d were obtained by refluxing VIb-d with methyl iodide in alcohol for 8-10 h and were crystallized from alcohol–ether. The yields and melting points were as follows: 80% VIIb, mp 219°C; 92% VIIc, mp 172°C; 94% VIId, mp 190°C. The results of elementary analysis of VIIb-d were in agreement with the calculated values; the halogen content was determined by potentiometric titration.

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PYRROLO[1,2-a]BENZIMIDAZOLES IN THE HETARYLATION REACTION

T. V. Stupnikova, A. K. Sheinkman, V. I. Zherebchenko, and G. P. Kutrov

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The direct incorporation of isoquinoline, benzimidazole, and acridine residues in pyrrolo[1,2-a]benzimidazole and its derivatives was accomplished by the reaction of N-heteroaromatic compounds with pyrrolo[1,2-a]benzimidazole and its analogs in the presence of acylating agents.

The increased electron density in the pyrrole ring [1, 2] is responsible for the ease of electrophilic substitution reactions in pyrrolo[1,2-a]benzimidazoles (I). In the case of protonation [1, 2], acylation [3], nitration, diazo coupling, and nitrosation [4] it has been shown that the 1 position is the most reactive position in the benzimidazole (I) molecule; if the 1 position is occupied, the 3 position is then the most reactive. It seemed possible to us to accomplish the direct introduction of N-heterocyclic residues in such compounds under the influence of N-acyl heteroaromatic cations in situ under the conditions of the hetarylation reaction [5]. In fact, in the case of the reaction of I with isoquinoline and benzoyl chloride we obtained both the previously described benzoyl derivative and

Kiev State University, Kiev 252000. Donetsk State University, Donetsk 340055. Dnepropetrovsk Construction-Engineering Institute, Dnepropetrovsk 320092.

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