RESEARCH ON UNSATURATED AZOLE DERIVATIVES.

VIII.* NEW SYNTHESES IN THE 2-ETHYNYLBENZIMIDAZOLE SERIES

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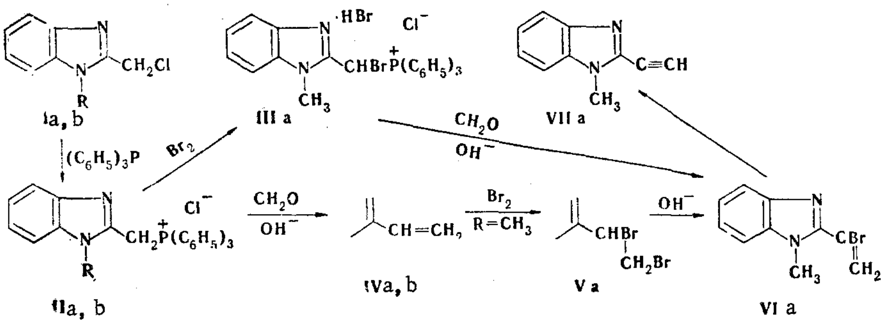
2-Ethynylbenzimidazole was synthesized via the Wittig reaction, and a new synthesis of 1-methyl-2-ethynylbenzimidazole was developed.

Ethynyl derivatives of benzimidazole may be of interest as monomers for the synthesis of polymeric materials with semiconductor properties (see [2]). A previously proposed method for the preparation of 1-methyl-2-ethynylbenzimidazole [3, 4], which is based on the reaction of 1-methyl-2-formyl-2-ethynylbenzimidazole with carbalkoxybromomethylenetriphenylphosphorane, is quite simple in a preparative respect but is also a multistep method and involves the application of starting compounds that are difficult to obtain. The use of the more accessible 2-chloromethylbenzimidazole [1] in place of 2-formylbenzimidazole [3, 4] makes it possible to simplify the synthesis. On the basis of this compound we developed two methods for the synthesis of 1-methyl-2-(α-bromovinyl)benzimidazole (VIa), which was subsequently converted to 1-methyl-2-ethynylbenzimidazole (VIIa).



I-VIIa $R=CH_3$; b $R=H$

1-Methyl-2-vinylbenzimidazole (IVb) [1], which is obtained from phosphonium salt IIe by the action of formaldehyde and sodium carbonate, reacts smoothly with bromine in chloroform to give dibromo derivative Va, which was converted to 1-methyl-2-(α-bromovinyl)benzimidazole (VIa) by the action of potassium carbonate in alcohol. It is more convenient to obtain VIa by bromination of phosphonium salt IIa and treatment of product IIIa with aqueous sodium carbonate solution and formalin. Despite the fact that three steps are combined in this process, bromovinyl compound VIa can be obtained in high yield. Compound VIa was converted to the previously described [5] benzimidazole VIIa in satisfactory yield by the action of potassium hydroxide in tetrahydrofuran (THF).

We found that it was not possible to subject 2-vinylbenzimidazole IVb [1] or phosphonium salt IIIb [1] to similar transformations, since the bromination of these compounds is complicated by the formation of difficult-to-separate mixtures of products. We accomplished the synthesis of 2-ethynylbenzimidazole VIIb from 2-formylbenzimidazole VIII by the Wittig reaction via the scheme

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*See [1] for communication VII.

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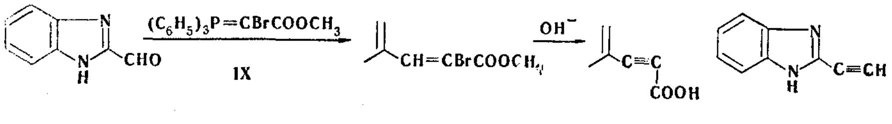
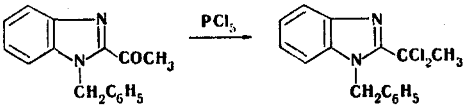


VIII X XI VII b

It is known [6, 7] that the polymeric structure of 2-formylbenzimidazole is the reason for its reduced reactivity as compared with its N-methyl derivative. According to our data, VIII does not react with phosphorane IX in benzene, alcohol, or chloroform at the boiling point. This reaction was accomplished in dimethylformamide (DMF) at 115-120°C in the presence of a catalytic amount of benzoic acid (see [8]). The complete and rapid depolymerization of aldehyde VIII evidently occurs under these conditions (see [7]), since the reaction is complete in 5-10 min. The resulting ester X was converted by the action of alcoholic alkali to 2-benzimidazolylpropiolic acid XI, which is stable only in the crystal hydrate form. When it is dried in air or in vacuo over P_2O_5, it undergoes decarboxylation to give 2-ethynylbenzimidazole VIIa; the latter is obtained in higher yield when a suspension of the acid in alcohol is heated. The structure of 2-ethynylbenzimidazole was confirmed by the IR spectroscopic data and also by its alkylation to the known 1-methyl-2-ethynylbenzimidazole [7].

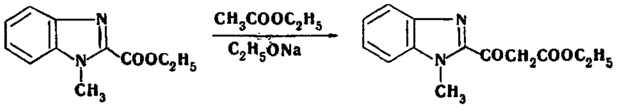
Attempts to accomplish the synthesis of 1-methyl-2-ethynylbenzimidazole from 1-methyl-2-chlorobenzimidazole and 1-methylbenzimidazole-2-sulfonic acid were unsuccessful. In contrast to 2-chlorobenzoxazole [9] and 2-chlorobenzothiazole [10], 1-methyl-2-chlorobenzimidazole does not react with sodium acetylide in liquid ammonia, and when the experiment is carried out in DMF or dimethyl sulfoxide (DMSO), one observes pronounced resinification of the reaction mixture, from which only traces of acetylene VIIa can be isolated. The reaction of sodium acetylide with sodium 1-methylbenzimidazole-2-sulfonate proceeds similarly.

It would seem that the synthesis of 2-ethynylbenzimidazoles could be easily accomplished from the accessible 2-acetylbenzimidazoles. According to our data, 2-acetylbenzimidazoles do not react with phosphorus pentachloride when the reagents are refluxed in benzene. Fusion of XII with PCl_5 at 110-115°C leads to 1-benzyl-2-(α,α-dichloroethyl)benzimidazole (XIII) in very low yield; however, we were unable to bring about its dehydrochlorination with potassium hydroxide or sodium amide.



XII XIII

Keto ester XV, which we synthesized by condensation of ethyl 1-methylbenzimidazole-2-carboxylate (XIV) with ethyl acetate in the presence of sodium ethoxide, also does not react with phosphorus pentachloride in refluxing benzene, and fusion of XIV with PCl_5 leads to resinification.



XIV XV

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectometer.

1-Methyl-2-(α,β-dibromoethyl)benzimidazole (Va). A solution of 1.6 g (10 mmole) of bromine in 5 ml of chloroform was added dropwise with stirring and cooling to a solution of 1.6 g (10 mmole) of 1-methyl-2-vinylbenzimidazole (IVa) [1] in 10 ml of chloroform, and the mixture was stirred for 1 h. The solvent was then removed by evaporation, and the residue was chromatographed on Al_2O_3 in ether to give 2.4 g (75%) of a product with mp 106-108°C (from alcohol). Found: C 38.0; H 3.1; Br 50.7; N 8.9%. $C_{10}H_{10}Br_2N_2$. Calculated: C 37.7; H 3.1; Br 50.3; N 8.8%.

1-Methyl-2-(α-bromovinyl)benzimidazole (VIa). A) A 5-g sample of finely ground potassium carbonate was added to a solution of 3.2 g (0.01 mole) of 1-methyl-2-(α,β-dibromoethyl)-benzimidazole (Va) in 20 ml of ethanol, and the mixture was stirred vigorously at 60°C for

2 h. It was then filtered, the filtrate was evaporated, and the residue was chromatographed on Al_2O_3 in ether to give 1.9 g (80%) of a product with mp 72°C (from hexane).

B) A solution of 1.6 g (0.01 mole) of bromine in 5 ml of chloroform was added dropwise with stirring to a solution of 4.5 g (0.01 mole) of 1-methyl-2-benzimidazolylmethyltriphenylphosphonium chloride (IIa) [1] in 15 ml of chloroform, and the mixture was stirred for 15 min. A total of 3 ml of 40% aqueous formaldehyde and 12 ml of a saturated solution of sodium carbonate were added, and the mixture was stirred vigorously for 1 h. It was then acidified to pH 1-2 with 15% hydrochloric acid, and the aqueous layer was separated, washed with chloroform (three 7-ml portions), neutralized with sodium bicarbonate, and extracted with chloroform. The solvent was removed by evaporation, and the residue was chromatographed on aluminum oxide in ether to give 2 g (85%) of needles (from hexane) with mp 72°C. No melting-point depressions were observed for mixtures of this product with sample obtained by methods A and B. Found: 50.8; H 3.5; Br 34.2; N 12.0%. $C_{10}H_9BrN_2$. Calculated: C 50.6; H 3.8; Br 33.8; N 11.8%.

1-Methyl-2-ethynylbenzimidazole (VIIa). A) A solution of 4.8 g (0.02 mole) of 1-methyl-2-(α-bromovinyl)benzimidazole (VIb) in 10 ml of THF was added dropwise with stirring in a nitrogen atmosphere to a suspension of 5 g of calcined potassium hydroxide in 15 ml of dry THF while maintaining the temperature of the reaction mixture from −13 to 16°C. The mixture was then stirred at this temperature for 3 h [the end of the reaction was determined by thin-layer chromatography (TLC)], after which it was decomposed with 30 ml of water, and the aqueous mixture was extracted with chloroform. The solvent was removed by evaporation, and the residue was chromatographed on Al_2O_3 in benzene to give 1.2-1.4 g (38-45%) of product.

B) A solution of 0.9 g (7 mmole) of dimethyl sulfate in 2 ml of alcohol was added dropwise with cooling (0-5°C) and stirring to a solution of 0.7 g (5 mmole) of 2-ethynylbenzimidazole (VIIb) in 10 ml of a 10% alcohol solution of potassium hydroxide, and the mixture was stirred at 0°C for 2 h. It was then decomposed with water, and the aqueous mixture was extracted with chloroform. The extract was dried, the solvent was removed by evaporation, and the residue was chromatographed on Al_2O_3 in benzene to give 0.2 g (25%) of product.

The compounds obtained by methods A and B have identical R_f values in a thin layer of aluminum oxide, melt at 100°C (from petroleum ether), and do not depress the melting point of VIIa obtained by the method in [3].

Methyl α-Bromo-β-(2-benzimidazolyl)acrylate (X). A mixture of 14.6 g (0.1 mole) of 2-formylbenzimidazole (VIII), 41 g (0.1 mole) of carbomethoxybromomethylenetriphenylphosphorane (IX), 0.5 g of benzoic acid, and 70 ml of DMF was heated rapidly to 120-125°C, and the resulting clear solution was allowed to cool in the air. A strong stream of hydrogen chloride was passed through the cold solution for 1 min, after which 300 ml of benzene was added. After 1 h, the reaction product was removed by filtration, washed with benzene, dried, and treated with 100 ml of water. It was then neutralized with sodium bicarbonate, and the solid material was removed by filtration to give 17.3 g (62%) of a product with mp 165°C (from ethyl acetate). Found: C 46.7; H 3.6; Br 28.2; N 10.3%. $C_{11}H_9BrN_2O_2$. Calculated: C 47.0; H 3.2; Br 28.5; N 9.97%.

2-Ethynylbenzimidazole (VIIb). A mixture of 28.1 g (0.1 mole) of ester X and 250 ml of a 15% alcohol solution of potassium hydroxide was maintained at room temperature for 24 h, after which the solvent was removed by distillation at room temperature, and the residue was treated with 200 ml of water. The aqueous mixture was filtered, and the filtrate was acidified to pH 2-3 with 10% hydrochloric acid. The precipitated acid XI was removed by filtration, washed thoroughly with water, and added to 200 ml of alcohol. The mixture was heated until CO_2 evolution ceased (5-10 min), after which the alcohol was removed by distillation, and the residue was chromatographed on Al_2O_3 in acetone to give 11.1 g (80% based on ester X) of a product with mp 184°C (from ethyl acetate). IR spectrum (mineral oil): 3290 (≡C—H) and 3100-3280 cm^{-1} (associated N—H). Found: C 75.9; H 4.5; N 19.6%. $C_9H_6N_2$. Calculated: C 76.0; H 4.2; N 19.7%.

1-Benzyl-2-acetylbenzimidazole (XII). A mixture of 8.6 g (0.06 mole) of 2-acetylbenzimidazole [11], 9 ml (0.07 mole) of benzyl chloride, 5.5 g (0.01 mole) of potassium hydroxide, and 45 ml of ethanol was heated to 60-65°C and stirred for 5 h. The hot reaction mixture was filtered, the solvent was removed from the filtrate by distillation, and the residue was vacuum distilled at 190-200°C (2 mm) to give 8.4 g (56%) of a product with mp 100°C (from hexane—chloroform). IR spectrum ($CHCl_3$): 1690 cm^{-1} (C=O). Found: C 76.4; H 5.7; N 11.4%. $C_{16}H_{14}N_2O$. Calculated: C 76.8; H 5.6; N 11.2%.

1-Benzyl-2-(α,α-dichloroethyl)benzimidazole (XIII). A mixture of 5 g (0.02 mole) of ketone XII and 5 g (0.22 mole) of PCl_5 was heated to 110-115°C and stirred at this temperature for 2 h. It was then cooled and treated with 15 ml of chloroform and 15 ml of water, and the aqueous layer was separated and made slightly alkaline with sodium bicarbonate. The resulting oil was extracted with chloroform, the solvent was removed by distillation, and the residue was treated with 2-3 ml of ethanol. The resulting white crystals, which were only slightly soluble in alcohol, were removed by filtration to give 0.6 g (10%) of a product with mp 87°C (from water—dioxane). Found: C 62.5; H 4.5; Cl 23.0; N 9.2%. $C_{16}H_{14}Cl_2N_2$. Calculated: 62.8; H 4.6; Cl 23.3; N 9.2%.

Ethyl 1-Methylbenzimidazole-2-carboxylate (XIV). A solution of 2.2 ml (0.02 mole) of dimethyl sulfate in 3 ml of absolute alcohol was added dropwise with stirring and cooling to a solution of 3.8 g (0.02 mole) of ethyl benzimidazole-2-carboxylate [12] in 15 ml of absolute alcohol containing sodium ethoxide (from 60 mg of Na), and the mixture was stirred for 1 h. It was then filtered, and the filtrate was evaporated. The residue was chromatographed on Al_2O_3 in chloroform to give 2.5 g (60%) of a colorless oil. The picrate had mp 194°C (from alcohol—DMF). Found: C 47.5; H 3.5; N 16.4%. $C_{11}N_{12}N_2O_2 \cdot C_6H_3N_3O_7$. Calculated: C 47.2; H 3.5; N 16.2%.

Ethyl β-Oxo-β-(1-methyl-2-benzimidazolyl)propionate (XV). A 3.5-ml (0.035 mole) sample of dry ethyl acetate and 2.4 g (0.035 mole) of sodium ethoxide were added to a solution of 2.1 g (0.01 mole) of vacuum dried (at 80°C) ester XIV in 40 ml of absolute benzene, and the mixture was refluxed for 8 h. The solvent was then removed by distillation, the residue was treated with 20 ml of water containing 2 ml of acetic acid, and the aqueous mixture was extracted with chloroform. The extract was dried with sodium sulfate, the solvent was removed by evaporation, and the residue was chromatographed on aluminum oxide in chloroform to give 1.8 g (75%) of a product with mp 60-61°C (from hexane). IR spectrum ($CHCl_3$): 1730 ($COOC_2H_5$) and 1690 cm^{-1} ($COCH_2$). Found: C 63.8; H 6.0; N 11.4%. $C_{13}H_{14}N_2O_3$. Calculated: C 63.4; H 5.7; N 11.4%.

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