RESEARCH ON UNSATURATED AZOLE DERIVATIVES

III.* ELECTROPHILIC SUBSTITUTION REACTIONS IN THE 2-ETHYNYLBENZIMIDAZOLE SERIES

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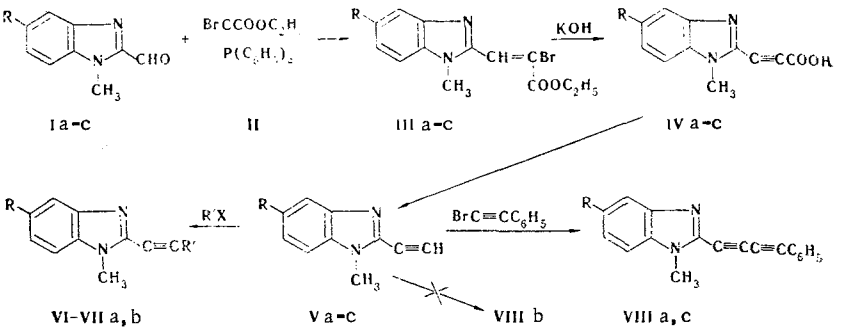
UDC 547.785.5:542.953

2-Alkynylbenzimidazoles were obtained by alkylation of 2-benzimidazolylacetylenes with alkyl halides in liquid ammonia in the presence of sodium metal. The strong −I effect of the 2-benzimidazolyl group hindered attack of electrophilic reagents in alkylation and hydration reactions of 2-benzimidazolylacetylenes. Condensation of 2-ethynylbenzimidazoles with bromophenylacetylene under the conditions of the Cadiot−Chodkiewicz reaction gives unsymmetrical diynes.

Little study has been devoted to ethynyl derivatives in the condensed azole series. Only the synthesis of 2-ethynylbenzoxazole by reaction of 2-chlorobenzoxazole with sodium acetylide in liquid ammonia [2] and the synthesis of a number of substituted 2-ethynylbenzimidazoles (Va, c) by means of the Wittig reaction [1, 2] have been described. Continuing these investigation, we subjected substituted 2-formylbenzimidazoles (Ia-c) to reaction with carbethoxybromomethylenetriphenylphosphorane (II). This reaction proceeds most smoothyl in methanol, but the yields of esters (III) formed in this case are somewhat lower (see [1]). Treatment of IIIa-c with alcoholic alkali, which was carried out as previously described [1], gives 2-benzimidazolylpropiolic acids (IVa-c), the decarboxylation of which gives 2-benzimidazolylacetylenes (Va-c).



a R=H; b R=OCH$_3$; c R=CH$_3$; VI R′=CH$_3$; VII R′=C$_2$H$_5$

A disadvantage of this as yet unique method for the preparation of 2-ethynyl-substituted benzimidazoles is the multistep character of the process. Attempts to use 2-acetylbenzimidazoles for this purpose as in the case of 2- and 4-acetylquinolines and 2- and 4-acetylpyridines [4] were unsuccessful. Halogen is eliminated to give 1-methylbenzimidazole in the reaction of 1-methyl-2-iodobenzimidazole with sodium acetylide in liquid ammonia. Attempts to use the condensation of o-phenylenediamine with propiolic acid

* See [1] for communication II.

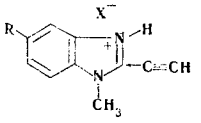
Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1544-1546, November, 1974. Original article submitted July 13, 1973.

(compare this with the condensation of o-aminophenol [2]) for the synthesis of 2-ethynylbenzimidazoles were also unsuccessful. The utilization of 2-vinylbenzimidazoles for this purpose is restricted by the fact that they are difficult to obtain [4].

The 2-ethynylbenzimidazoles (Va-c) that we obtained are quite stable crystalline compounds. In contrast to ethynylquinolines and ethynylpyridines [5], they remain practically unchanged on long storage but are rapidly polymerized at temperatures close to their melting points to give a dark-violet brittle mass. Compounds Va-c react with ammoniacal solutions of silver oxide and cuprous oxide to give the corresponding acetylides [3], which do not explode on impact but burn with fulmination in a burner flame.

A bathochromic shift of the maximum of the long-wave absorption (~20 nm) relative to benzimidazole is observed in the UV spectra of 2-ethynylbenzimidazoles; this is evidence for the presence of conjugation of the heterocyclic ring with the acetylene group. It might have been assumed that the extremely high electrophilicity of the 2-benzimidazolyl group [6] would have a substantial effect on the reactivity of 2-benzimidazolylacetylenes. In fact, the shift of the electron density of the acetylene group under the influence of the strong −I effect of benzimidazole hinders attack of electrophilic reagents. Thus sodium 2-benzimidazolylacetylides, in contrast to acetylenes of the aliphatic series [7], react with difficulty with ethyl bromide and do not react with propargyl bromide in liquid ammonia. Alkylation proceeds successfully only with methyl iodide.

The substituents in the benzene ring of 2-ethynylbenzimidazole have a definite effect on electrophilic substitution. Thus Va and Vc react with bromophenylacetylene in n-butylamine solution to give unsymmetrical diacetylenes (VIIIa,c), while Vb does not undergo this reaction under similar conditions; however, raising the temperature and increasing the reaction time promote the occurrence of side transformations to give resinous substances. We were also unable to obtain 2-acetylbenzimidazoles by hydration of 2-benzimidazolylacetylenes (Va-c), inasmuch as the formation of the cation of IX under the conditions of the Kucherov reaction promotes an increase in the −I effect of the 2-benzimidazolyl radical, and this evidently hinders electrophilic addition (see [8, 9]).



EXPERIMENTAL

The IR spectra of chloroform solutions or mineral-oil pastes of the compounds were recorded with a UR-20 spectrometer.

Ethyl β-(5-R-1-Methyl-2-benzimidazolyl)-α-bromoacrylates (IIIa-c, Table 1). A 1-mmole sample of the appropriate 2-formylbenzimidazole and 1 mmole of carbethoxybromomethylenetriphenylphosphorane (II) were dissolved in 5 ml of methanol. The solution was held at room temperature for 1 h, after which it was refluxed for 5 min and cooled. The resulting precipitate was removed by filtration and crystallized from alcohol.

2-Benzimidazolylacetylenes (Va-c). These compounds were obtained from IIIa-c by the method in [1].

1-(5-R-1-Methyl-2-benzimidazolyl)-2-R'-acetylenes (VIa,b and VIIa,b, Table 2). A 0.1-g (4 mmole) sample of sodium metal was added to 30 ml of liquid ammonia at −60°, after which 4 mmole of V was added. A solution of 4 mmole of alkyl halide in 3 ml of dry ether was then added dropwise with stirring. The solution was gradually decolorized and became clear. It was stirred until the ammonia had evaporated completely, and the residue was decomposed with water. The liberated oil was extracted with chloroform. The solvent was removed by distillation, and the residue was chromatographed on aluminum oxide with elution by ether or chloroform.

4-Phenyl-1-(1-methyl-2-benzimidazolyl)-1,3-butadiyne (VIIIa). A solution of 0.4 ml (2.35 mmole) of bromophenylacetylene in 0.5 ml of methanol was added dropwise with stirring to a mixture of 0.31 g (2 mmole) of Va, 1 ml of n-butylamine, 0.024 g of hydroxylamine hydrochloride, and 0.006 g of cuprous chloride in 2 ml of methanol at 40° in a nitrogen atmosphere. The mixture was stirred at 40° for 8 h, after which water was added, and the liberated oil was extracted with chloroform. The chloroform extract was washed with water to remove n-butylamine and dried with potassium carbonate. The solvent was removed by distillation, and the residue was chromatographed on aluminum oxide with elution by chloroform to give

TABLE 1. Ethyl β-5-R-1-Methyl-2-benzimidazolyl-α-bromoacrylates

Compound	R	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	Br	N	C	H	Br	N	
IIIa	H	150	$C_{13}H_{13}BrN_2O_2$	50,3	4,0	25,5	19,3	50.5	4,2	25,9	19,1	55
IIIb	OCH_3	154*	$C_{14}H_{15}BrN_2O_3$	50,2	4,4	23,7	8,5	50,0	4.4	23,3	8,2	52
IIIc	CH_3	174*	$C_{14}H_{15}BrN_2O_2$	52,3	4,6	24,9	8,9	52,0	4,6	24,8	8,9	59

*These compounds melted with decomposition.

TABLE 2. 1-(5-R-1-Methyl-2-benzimidazolyl)-2-R'-acetylenes

Compound	R	R'	mp,* °C	Empirical formula	Found, %			Calc., %			$\nu_{C\equiv C}$, cm^{-1}	Yield, %
					C	H	N	C	H	N		
VIa	H	CH_3	104	$C_{11}H_{10}N_2$	77,8	6,0	16,2	77,6	5,9	16.5	2250	70
VIb	OCH_3	CH_3	139—140	$C_{12}H_{12}N_2O$	72,3	6,1	14,3	72,0	6,0	14,0	2255	72
VIIa	H	C_2H_5	55	$C_{12}H_{12}N_2$	78,0	6,7	15,5	78,3	6,5	15,2	2250	50
VIIb	OCH_3	C_2H_5	98	$C_{13}H_{14}N_2O$	73,1	6,6	13,3	72,9	6,5	13,1	2248	55

*Compounds VIa and VIIa were recrystallized from petroleum ether–benzene, and VIb and VIIb were recrystallized from aqueous alcohol.

0.35 g (70%) of colorless plates with mp 192° (from alcohol). The product was soluble in acetone, benzene, and dioxane. IR spectrum ($CHCl_3$): 2228, 2150 cm^{-1} (C≡C). Found, %: C 84.0; H 4.6; N 11.2. $C_{18}H_{12}N_2$. Calculated, %: C 84.3; H 4.7; N 10.9.

4-Phenyl-1-(1,5-dimethyl-2-benzimidazolyl)-1,3-butadiyne (VIIIc). This compound, with mp 160° (from petroleum ether–chloroform), was similarly obtained in 30% yield. The product was soluble in benzene and ether. IR spectrum ($CHCl_3$): 2225, 2155 cm^{-1} (C≡C). Found, %: C 84.2; H 5.4; N 10.7. $C_{19}H_{14}N_2$. Calculated, %: C 84.4; H 5.2; N 10.4.

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