RESEARCH ON UNSATURATED AZOLE DERIVATIVES.

X.* REACTIONS INVOLVING NUCLEOPHILIC ADDITION IN THE 2-ETHYNYLBENZIMIDAZOLE SERIES

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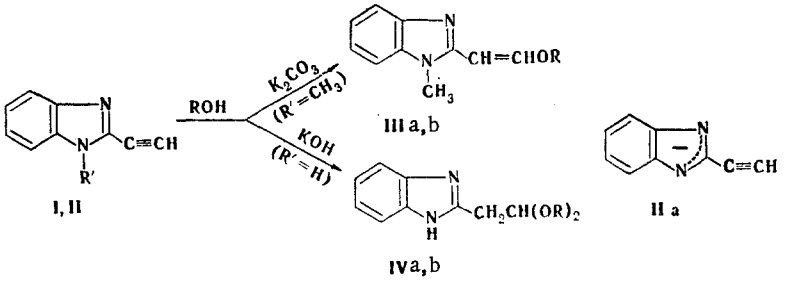
1-R-2-Ethynylbenzimidazoles (R = H, CH_3) add secondary amines, alcohols, and C—H acids via the Michael mechanism to give, respectively, enamines, 2-(β-alkoxy) (for R = CH_3) or 2-(β,β-dialkoxy) (for R = H) derivatives of benzimidazole and 1,2-substituted pyrido[1,2-a]benzimidazoles.

The effective stabilization of the anion of the α-C atom of the side chain of 2-substituted benzimidazoles, which is due to the high electrophilicity of the 2-benzimidazolyl grouping [2], promotes unusually easy addition of nucleophilic reagents to the C≡C bond of 1-methyl-2-ethynylbenzimidazole [3, 4]. In this connection, we felt it would be interesting to make a more detailed study of nucleophilic addition in the 2-benzimidazolylacetylene series.

A further study of the vinylation of 1-methyl-2-ethynylbenzimidazole by alcohols [3] showed that potassium carbonate can be used in place of potassium hydroxide as the catalyst in this reaction. On the other hand, 2-ethynylbenzimidazole (II) is not vinylated by alcohol in ether in the presence of potassium carbonate or potassium hydroxide. The presence of a strong base in this case evidently promotes the formation of N-anion IIa, and this leads to a considerable decrease in the electrophilicity of the alkynyl group and hinders the addition of alcohol. When II is refluxed in an alcohol solution of alkali, it does not undergo the cleavage observed for I (which gives 2-methylbenzimidazole [5]) but rather adds two molecules of alcohol to give 2-benzimidazolylacetaldehyde acetals (IVa, b); the yields of the latter are low because of side transformations.



I, II — IIIa,b — IVa,b — IIa

I $R'=CH_3$; II $R'=H$; III, IV a $R=CH_3$; b $R=C_2H_5$

This difference in the reactivities of 2-benzimidazolylacetylenes I and II is not observed in their reactions with amines. Thus vinylamines VIa-d are formed quite smoothly when I and II are refluxed with secondary amines Va-c in alcohol or tetrahydrofuran (THF). The structure of the latter is confirmed by the presence of absorption bands at 1640-1650 cm^{-1} (C=C) in the IR spectra. (See scheme at top of next page).

It is known that the nucleophilic cycloaddition of some C—H acids to 2-ethynylpyridine leads to the formation of quinolizidine derivatives [6]. We established that like 2-ethynyl-

*See [1] for communication IX.

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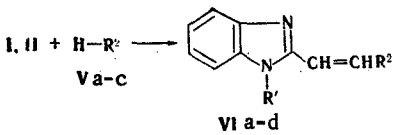
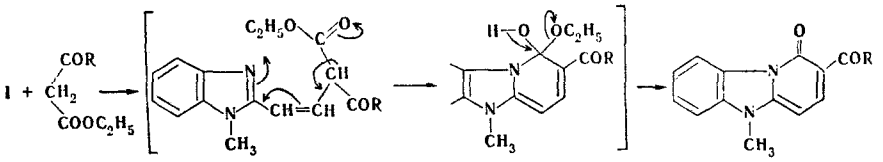


V a $R^2=NEt_2$; b R^2=N-piperidyl; c $R^2=NMe_2$; VI a $R^1=CH_3$; $R^2=NEt_2$; b $R^1=CH_3$; R^2=N-piperidyl; c $R^1=H$; $R^2=NMe_2$; d $R^1=H$; $R^2=NEt_2$

pyridine, I reacts with diethyl malonate (VIIa) and ethyl acetoacetate (VIIb) in the presence of sodium ethoxide to give 1-oxopyrido[1,2-a]benzimidazole derivatives (Xa, b).

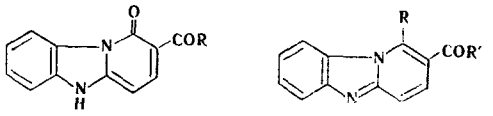


VII a-b VIII IX X a,b

a $R=OC_2H_5$; b $R=CH_3$

The reaction evidently commences with Michael addition of one molecule of the donor to the C≡C bond of acetylene I; as a result of condensation with splitting out of ethanol, addition product VIII is subsequently converted to cyclic amide X through intermediate cyclic hemiacetal IX. 2-Ethynylbenzimidazole II reacts with diethyl malonate (VIIa) in the same way as I to give a cyclic amide (XIa, R = OC_2H_5); however, excess sodium ethoxide and an increase in the heating time are required in this case. The IR spectrum of Xa, b and XIa contain characteristic absorption bands of a cyclic amide group (1650-1660 cm^{-1}).

The reaction of acetylene II with acetoacetic ester (VIIa) proceeds via a different pathway: a compound to which the 1-methyl-2-carbethoxypyrido[1,2-a]benzimidazole (XIIa) structure was assigned on the basis of the results of elementary analysis and the IR and PMR spectral data is formed instead of the expected cyclic amide XIb (R = CH_3) in this case:



XIa XII a-d

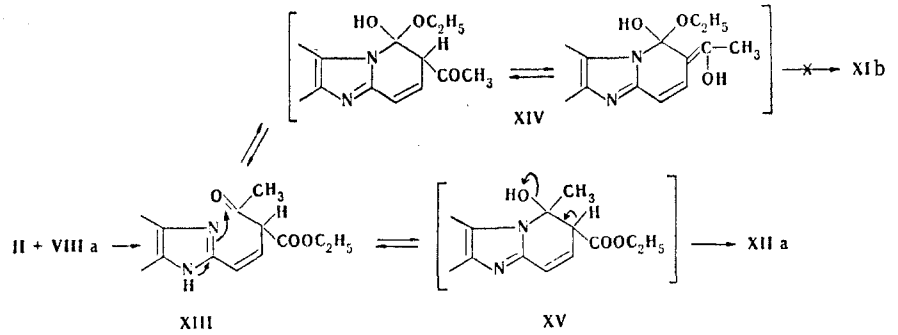
XI—XIIa R=CH_3, $R^1=OC_2H_5$; XII b R=CH_3, R^1=OH; c $R=R^1=CH_3$; d R=C_6H_5, $R^1=OC_2H_5$

The IR spectrum of XIIa contains the absorption band of an ester group (1720 cm^{-1}), and the PMR spectrum contains peaks (δ) at 4.2 and 1.1 ppm (CH_2CH_3, q and t), 3.17 ppm (s, CH_3), and 7.85 and 8.15 ppm (multiplet of aromatic protons of the annelated benzene and pyridine rings). Hydrolysis of ester XIIa in alcoholic alkali leads to the formation of acid XIIb.

We obtained unambiguous evidence for the possibility of cyclocondensation of C—H acids with acetylene II at the acyl group by reaction of II with acetylacetone (VIIc): 1-methyl-2-acetylpyrido[1,2-a]benzimidazole (XIIc) was obtained in high yield by refluxing these compounds with sodium ethoxide in alcohol. The IR spectrum of XIIc contains the absorption band of a ketone C=O group at 1645 cm^{-1}, the the PMR spectrum (δ, ppm) contains peaks at 2.5 ($COCH_3$) and 3.1 (CH_3) and two multiplets of aromatic protons (7.6 and 8.1).

Benzoylacetic ester (VIId) reacts with acetylene II in the same way as acetoacetic ester (VIIIa) to give 1-phenyl-2-carbethoxypyrido[1,2-a]benzimidazole (XIId). Thus, in contrast to methyl-substituted 2-ethynylbenzimidazole I, cyclocondensation of II with acylacetic esters VIIIa, b takes place at the acyl group, despite the fact that cyclization with the participation of the ester group is kinetically more favorable (the reaction of II with VIIa took 3-4 h, whereas the reaction of II with VIIb took 16 h). (See scheme at top of next page).

In contrast to IX, the presence of an acyl group that is capable of enolization in intermediate cyclic hemiacetal XIV hinders splitting out of an ethoxide ion and the formation of the expected amide XI (R = CH_3). In this case addition to the acyl group with subsequent splitting out of a hydroxide ion and the formation of an energically more favorable aromatic ring — pyrido[1,2-a]benzimidazole — under the conditions of thermodynamic control evidently becomes preferable.



EXPERIMENTAL

The IR spectra of solutions of the compounds in $CHCl_3$ were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in CF_3COOH were obtained with a Tesla BS-487-C spectrometer with hexamethyldisiloxane as the internal standard.

β-(1-Methyl-2-benzimidazolyl)alkoxyvinylbenzimidazoles (IIIa, b). A mixture of 0.31 g (2 mmole) of 1-methyl-2-ethynylbenzimidazole (I), 1.4 g (10 mmole) of finely ground potassium carbonate, and 5 ml of the corresponding alcohol was refluxed with vigorous stirring for 12-15 h; the end of the reaction was determined by means of thin-layer chromatography (TLC). The mixture was filtered, the filtrate was evaporated, and the residue was chromatographed on Al_2O_3 (elution with ether). Compounds IIIa, b were identical to the compounds described in [3] with respect to their IR spectra, R_f values in a thin layer of Al_2O_3, and the melting points of the picrates (170 and 159.5°C, respectively).

2-(β,β-Dialkoxyethyl)benzimidazoles (IVa, b, Table 1). A mixture of 0.43 g (3 mmole) of II, 0.8 g (15 mmole) of potassium hydroxide, and 5 ml of the corresponding alcohol was refluxed for 15 (for IVa) or 5 h (for IVb), after which the solvent was removed by distillation, and the residue was treated with water. The aqueous mixture was neutralized with acetic acid and extracted with chloroform. The extract was chromatographed on Al_2O_3 (elution with ether): impurities, which were readily soluble in ether, appeared in the first portions of the eluate, after which the pure reaction product was eluted.

2-(β-N-Dialkylaminovinyl)benzimidizoles (VIa-d, Table 1). A mixture of 2 mmole of 2-ethynylbenzimidazole (I, II), 2 mmole of the corresponding amine (Va-d), and 5 ml of alcohol was refluxed for 5 h. Vinylamine VIc was obtained by heating acetylene II with dimethylamine (Vc) in an ampul at 85-90°C. The solvent was removed by distillation, and the residue was chromatographed on Al_2O_3 (successive elution with chloroform and ether). Compounds VIc, d are stable in air for long periods, whereas VIc and particularly VIa undergo decomposition with resinification in the course of a week.

1-Oxo-2-R-5-methylpyrido[1,2-a]benzimidazoles (Xa, b, Table 1). A 4-mole sample of the corresponding C—H acid VIIa, b and 2 mmole of I were added to a solution of sodium ethoxide in 3 ml of alcohol (from 30 mg of Na), and the mixture was refluxed for 2-3 h. It was then cooled and diluted with 3 ml of ethanol containing 0.5 ml of glacial acetic acid, and the precipitate was removed by filtration.

1-Oxo-2-ethoxycarbonyl-5H-pyrido[1,2-a]benzimidazole (XI, Table 1). A 0.7-g (4 mmole) sample of VIId and 0.3 g (2 mmole) of II were added to a solution of sodium ethoxide [from 70 mg (0.003 g-atom) of Na] in 5 ml of alcohol, and the mixture was refluxed for 4 h. It was then cooled and treated with 3 ml of alcohol containing 0.2 ml of concentrated HCl, and the precipitate was removed by filtration.

1-Methyl-2-carbethoxypyrido[1,2-a]benzimidazole (XIIa, Table 1). A 1-ml (7-8 mmole) sample of acetoacetic ester (VIIb) and 0.3 g (2 mmole) of II were added to a solution of sodium ethoxide (from 50 mg of Na) in 5 ml of ethanol, and the mixture was refluxed for 16 h. It was then diluted with 30 ml of water containing 1 ml of acetic acid and allowed to stand for 2 h. The precipitate was removed by filtration, dried, and chromatographed on aluminum oxide (elution with chloroform). A sample for analysis was dried in vacuo over P_2O_5 at 50°C for 7 h.

1-Methyl-2-carboxypyrido[1,2-a]benzimidazole (XIIb, Table 1). A mixture of 0.5 g (2 mmole) of 1-methyl-2-carbethoxypyrido[1,2-a]benzimidazole (XIIa) and 5 ml of 5% alcoholic

TABLE 1. Yields and Constants of the Synthesized Compounds

Compound	mp, °C[a]	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IVa	118—119	3460	64,3	7,2	13,5	$C_{11}H_{14}N_2O_2$	64,1	6,8	13,6	50
IVb	136—137	3460	67,0	7,5	12,9	$C_{13}H_{18}N_2O_2$	66,6	7,7	11,9	43
VIa	204—206[b]	1640	52,6	4,8	18,4	$C_{14}H_{19}N_3 \cdot C_6H_3N_3O_7$	52,4	4,7	18,3	71
VIb	87—89	1640	72,1	8,2	16,4	$C_{15}H_{19}N_3 \cdot 0{,}5H_2O$	72,0	8.0	16,8	62
VIc	208—210	3480, 1650	64,8	7,6	20,1	$C_{11}H_{13}N_3 \cdot H_2O$	64,4	7,3	20,5	53
VId	185—187	1648, 3480	72,3	7,7	19,1	$C_{13}H_{13}N$	72,5	7,9	19,5	48
Xa	225—226	1685, 1730	67,0	5,0	10,4	$C_{15}H_{14}N_2O_3$	66,6	5,1	10,3	74
Xb	248—249	1660, 1675	69,6	5,1	11,6	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,6	62
XI	252[c]	1650, 1720 3150	65,6	4,6	10,8	$C_{14}H_{12}N_2O_3$	65,6	4,7	10,9	74
XIIa	105—108	1648, 1720	71,3	5,7	10,6	$C_{15}H_{14}N_2O_2$	70,9	5,5	11,0	78
XIIb	304 (dec.)	1650, 1720[d]	68,6	4,8	12,8	$C_{13}H_{10}N_2O_2$	69,0	4,4	12,4	100
XIIc	142—144	1640, 1695	74,6	5,0	12,7	$C_{14}H_{12}N_2O$	75,0	5,3	12,5	78
XIId	121—123	1640, 1730	76,0	5,4	8,9	$C_{20}H_{16}N_2O_2$	76,0	5,1	8,8	50

a) The following solvents were used for recrystallization: ethyl acetate—heptane (1:8) for IVa, ethyl acetate—hexane (1:5 and 1:2, respectively) for IVb and VIb, alcohol for VIa, ethyl acetate for VIc, d, 20% acetic acid for Xa, water—ethanol for Xb, dimethylformamide—water for XI, heptane for XIIa, c, d, and dimethylformamide for XIIb. b) This is the melting point of the picrate. c) The compound decomposes without melting. d) the IR spectrum of a suspension in mineral oil was recorded.

KOH solution was stirred at 45-50°C for 4 h, after which it was subjected to evaporation, and the residue was treated with water. The aqueous mixture was filtered, and the filtrate was neutralized with dilute HCl. After 1 h, the resulting precipitate was removed by filtration.

1-Methyl-2-acetylpyrido[1,2-a]benzimidazole (XIIc, Table 1). A 1-ml (10 mmole) sample of acetylacetone and 0.3 g (2 mmole) of 2-ethylbenzimidazole (II) were added to a solution of sodium ethoxide (from 50 mg of Na) in 5 ml of alcohol, and the mixture was refluxed for 14 h. Two-thirds of the volume of the liquid was then removed by distillation, and the concentrate was treated with water containing 1 ml of glacial acetic acid and extracted with chloroform. The combined extracts were dried with sodium sulfate and evaporated, and the residue was chromatographed on aluminum oxide (elution with chloroform). PMR spectrum: 2.5 ($COCH_3$), 3.1 (1-CH_3), and 7.6 and 8.1 ppm (m, aromatic H).

1-Phenyl-2-carbethoxypyrido[1,2-a]benzimidazole (XIId, Table 1). A 1.3-g (7 mmole) sample of benzoylacetic ester (IXc) and 0.3 g (2 mmole) of 2-ethynylbenzimidazole (II) were added to a solution of sodium ethoxide (from 50 mg of Na) in 15 ml of alcohol, and the mixture was refluxed for 12 h. It was then diluted with 50 ml of water containing 2 ml of glacial acetic acid and allowed to stand for 4 h. The liquid was decanted from the resulting oily precipitate, dried, and chromatographed on aluminum oxide [elution with chloroform—acetone (3:1)].

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