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RESEARCH ON BENZIMIDAZOLE DERIVATIVES

XLI.* SYNTHESIS OF 2-METHYLPYRROLO[1,2-a]BENZIMIDAZOLE DERIVATIVES

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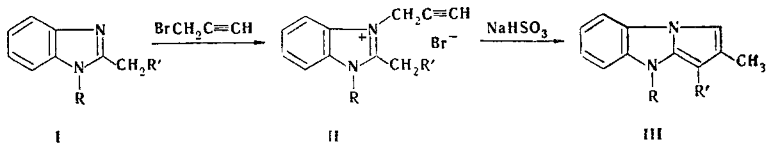
It is shown that 1,2-dialkylbenzimidazoles react with propargyl bromide to give 1,2-dialkyl-3-(2-propynyl)benzimidazolium hydrobromides, the cyclization of which leads to 2-methylpyrrolo[1,2-a]benzimidazole derivatives.

1,2-Dialkylbenzimidazoles (Ia-e) react with propargyl bromide in refluxing ethanol or n-butanol to give 1,2-dialkyl-3-(2-propynyl)benzimidazolium bromides (IIa-e) in good yields. Pyrrolo[1,2-a]benzimidazole derivatives (IIIa-e) are formed in low yields (3-5%) when salts II are refluxed in aqueous sodium carbonate or bicarbonate solutions [2]. The yields of derivatives III can be raised (to 30-40%) by refluxing salts II in an aqueous sodium bicarbonate solution in the presence of sodium hydrosulfite, which prevents oxidation of the intermediately formed methylene bases (see [3]).

The use of a suspension of potassium hydroxide in absolute tetrahydrofuran (THF) at room temperature for the cyclization of salts II led to pyrrolo[1,2-a]benzimidazoles IIId, e in good yields only in the case of IId, e ($R' = C_6H_5$); resinification of the reaction mixture occurs when $R' = H$, CH_3.



I—III a $R=CH_3$, $R'=H$; b $R=C_2H_5$, $R'=H$; c $R=R'=CH_3$; d $R=CH_3$, $R'=C_6H_5$; e $R=C_2H_5$, $R'=C_6H_5$

Considerable amounts (up to 25%) of 1,2-dialkylbenzimidazoles Ia-e, which are formed as a result of alkaline cleavage of starting quaternary salts II (see [4]), are formed during the cyclization.

The mechanism of the conversion of salts IIa-e to derivatives IIIa-e is evidently analogous to the mechanism of the cyclization of 1-alkyl-2-imino-3-(2-propynyl)benzimidazolines to imidazo[1,2-a]benzimidazole derivatives [5], which includes rearrangement of the propargyl group to an allenic group.

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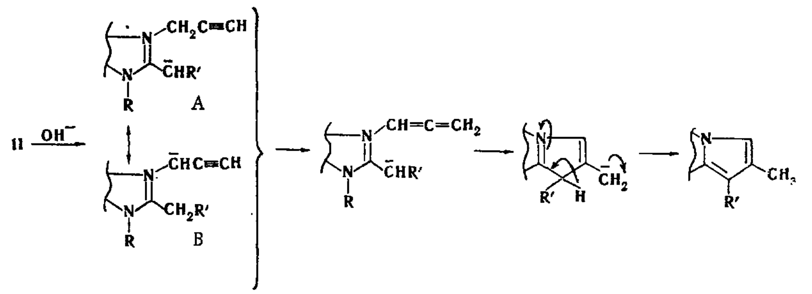
*See [1] for communication XL.

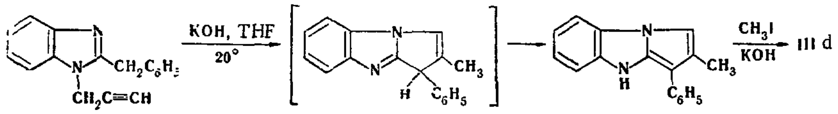
Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 972-975, July, 1976. Original article submitted June 30, 1975.



The high yields of IIId, e (when R' = C_6H_5) are explained by the effect of the phenyl group, which promotes stabilization of anion A, as a consequence of which its concentration in the reaction mixture increases, and this leads to an increase in the cyclization rate and the yield. On the other hand, when R' = H or CH_3, the concentration of anion A is low because of its low stability, and this promotes the occurrence of side transformations.

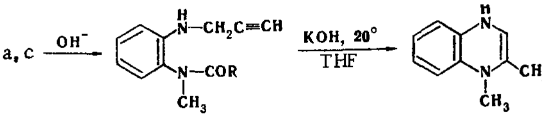
We were unable to isolate intermediates in the cyclization.

Treatment of 1-(2-propynyl)-2-benzylbenzimidazole (IV) [6] with a suspension of potassium hydroxide in THF at 20° gives pyrrolo[1,2-a]benzimidazole (V), the IR spectrum of which contains a band at 3455 cm^{-1} (=NH). Methylation of V with methyl iodide in alcoholic potassium hydroxide solution gives IIId.



IV V

Treatment of salts IIa with aqueous potassium or sodium hydroxide solutions leads, as one should have expected [7], to products of opening of the imidazole ring – N-substituted o-phenylenediamines (VI) – which undergo successive hydrolysis and cyclization to 1,2-dimethyl-1,4-dihydroquinoxaline (VII) in THF solution in the presence of potassium hydroxide.



VI a,b VII

VI a R=CH_3; b R=C_2H_5

EXPERIMENTAL

The IR spectra of mineral oil suspensions of IIa-d and VIa, b and a chloroform solution of V were recorded with a UR-20 spectrometer.

1,2-Dialkyl-3-(2-propynyl)benzimidazolium Hydrobromides (IIa-d; Table 1). A solution of 0.01 mole of the appropriate 1,2-dialkylbenzimidazole (Ia-d) in 5 ml of ethanol was refluxed on a water bath for 1 h, after which it was cooled, and the precipitated hydrobromide was removed by filtration and washed successively with ethanol and ether to give colorless crystals that were quite soluble in water and alcohol. IR spectrum: $\nu(\equiv C-H)$ 3200 cm^{-1}.

1,9-Dialkyl-2-methylpyrrolo[1,2-a]benzimidazoles (IIIa-e; Table 1). A solution of 0.01 mole of the appropriate hydrobromide IIa-e, 1.7 g (0.02 mole) of sodium bicarbonate, and 0.5 g of sodium hydrosulfite in 7 ml of water was refluxed for 4 h, after which it was cooled, and the reaction product was extracted with ether. The ether was removed by distillation, and the residue was chromatographed with a column filled with Al_2O_3 (elution with ether).

9H-1-Phenyl-2-methylpyrrolo[1,2-a]benzimidazole (V). A 1.23-g (5 mmole) sample of 2-benzyl-1-(2-propynyl)benzimidazole (IV) [6] was added to a suspension of 3 g of potassium hydroxide in 5 ml of absolute THF, and the mixture was allowed to stand at room temperature overnight. It was then diluted with water and extracted with chloroform. Workup of the extract gave 1 g (81%) of light-yellow prisms with mp 64-65° (from aqueous ethanol). Found: C 82.5; H 6.0; N 11.3%. $C_{17}H_{14}N_2$. Calculated: C 82.9; H 5.7; N 11.4%. IR spectrum: $\nu(=N-H)$ 3455 cm^{-1}. The picrate was obtained as yellow prisms with mp 251-253° (from ethanol).

TABLE 1. 1,2-Dialkyl-3-(2-propynyl)benzimidazolium Hydrobromides and 2-Methylpyrrolo[1,2-a]benzimidazoles

Compound	R	R′	mp, °C*	Empirical formula	Found, %				Calc., %				Yield, %
					C	H	Br	N	C	H	Br	N	
IIa	CH_3	H	241—243	$C_{12}H_{12}N_2 \cdot HBr$	54,3	5,1	29.8	10,9	54.4	4,9	30,2	10,6	92
IIb	CH_3	CH_3	246	$C_{13}H_{14}N_2 \cdot HBr$	55,7	5,3	28,3	9.6	55,9	5,4	28,7	10,0	91
IIc	C_2H_5	H	196—198	$C_{13}H_{14}N_2 \cdot HBr$	55,5	5,8	30,1	10,3	55,9	5,4	28,7	10,0	92
IId	CH_3	C_6H_5	244—245	$C_{18}H_{16}N_2 \cdot HBr$	63.5	4,8	23,6	7,8	63.3	5,0	23,5	8,2	96
IIe	C_2H_5	C_6H_5	203—204	$C_{19}H_{15}N_2 \cdot HBr$	64,0	5,8	22,1	8,3	64,2	5,4	22.5	8,0	95
IIIa	CH_3	H	88—89 †[3]	$C_{12}H_{12}N_2$	—	—	—	—	—	—	—	—	32
IIIb	CH_3	CH_3	99—100 †[3]	$C_{13}H_{14}N_2$	—	—	—	—	—	—	—	—	30
IIIc	C_2H_5	H	178—179 †[8]	$C_{13}H_{14}N_2 \cdot C_6H_3N_3O_7$	—	—	—	—	—	—	—	—	41
IIId	CH_3	C_6H_5	151—152 †[9]	$C_{18}H_{16}N_2 \cdot C_6H_3N_3O_7$	—	—	—	—	—	—	—	—	76
IIIe	C_2H_5	C_6H_5	132—133 †[5]	$C_{19}H_{18}N_2 \cdot C_6H_3N_3O_7$	—	—	—	—	—	—	—	—	73

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*Compounds IIa-e were purified for analysis by crystallization from ethanol.

†With decomposition.

1-Phenyl-2,9-dimethylpyrrolo[1,2-a]benzimidazole (IIId). A) A solution of 0.47 g (4 mmole) of methyl iodide in 1 ml of ethanol was added dropwise to a solution of 1 g (4 mmole) of V and 0.3 g (4 mmole) of potassium hydroxide in 5 ml of ethanol, and the mixture was stirred for 1 h. It was then diluted with 30 ml of water and extracted with ether. Removal of the ether from the extract by distillation gave 0.7 g (68%) of IIId.

B) A 1-g sample of hydrobromide IId was added to a suspension of 5 g of potassium hydroxide in 4 ml of absolute THF, and the mixture was allowed to stand at 20° for 4 h. Water (20 ml) was added, and the reaction product was extracted with chloroform. Workup of the extract gave IIId in 76% yield.

The picrates of the compounds obtained by methods A and B were identical and had mp 151-152°.

N-Methyl-N′-acetyl-N′-(2-propynyl)-o-phenylenediamine (VIa). A 2.65-g (0.01 mole) sample of hydrobromide IIa was treated with 10 ml of 40% aqueous sodium hydroxide solution, the mixture was triturated thoroughly, and the solid material was removed by filtration to give 1.9 g (94%) of colorless needes, with mp 121-123° (from ethanol), that were quite soluble in acetone, chloroform, and alcohol. Found: C 71.6; H 7.1; N 14.1%. $C_{12}H_{14}N_2O$. Calculated: C 71.3; H 6.9; N 13.8%. The IR spectrum contained the following bands: $\nu(C=O)$ 1650; $\nu(N-H)$ 3375; and $\nu(\equiv C-H)$ 3200 cm^{-1}.

N-Methyl-N′-propionyl-N′-(2-propynyl)-o-phenylenediamine (VIb). This compound, with mp 104-105° (from ethanol), was obtained as colorless needles in 91% yield from hydrobromide IIc by the method used to prepare VIa. Found: C 72.0; H 7.6; N 13.2%. $C_{13}H_{16}N_2O$. Calculated: C 72.2; H 7.4; N 13.0%. IR spectrum: $\nu(C=O)$ 1650; $\nu(N-H)$ 3372; and $\nu(\equiv C-H)$ 3200 cm^{-1}.

1,2-Dimethyl-1,4-dihydroquinoxaline (VII). A 1-g sample of potassium hydroxide was added to a solution of 0.01 mole of VIa or VIb in 5 ml of absolute THF, after which the mixture was allowed to stand at room temperature for 4 h. Water (20 ml) was added, and the reaction product was removed by filtration to give 1.16 g (73%) of light-yellow plates with mp 161-162° (from aqueous ethanol). Found: C 75.4; H 7.2; N 17.4%. $C_{10}H_{12}N_2$. Calculated: C 75.0; H 7.5; N 17.5%.

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