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A POSSIBLE ZWITTERION INTERMEDIATE IN THE REACTION OF 3-METHOXY-1-METHYLBENZIMIDAZOLIUM IODIDE WITH VARIOUS NUCLEOPHILES

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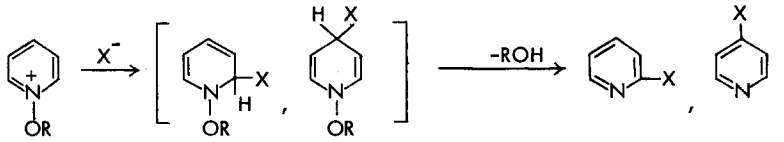
The reactions of N-alkoxyquaternary salts (I) of pyridine and its congeners with cyanide ion (1), Grignard reagents (2), and some reagents bearing an active methylene group (3) have been reported to produce α- or α- and γ-substituted derivatives (III).

Evidence has been presented (4) that the reaction with cyanide ion is initiated by nucleophilic attack at the α- or γ-position of I to give the N-alkoxydihydropyridine type intermediate (II, X=CN) which loses alcohol to afford III (X=CN). The other nucleophilic substitutions are believed to proceed analogously.



I II III

As a part of our study on benzimidazole N-oxides (5), the reactions of 3-methoxy-1-methylbenzimidazolium iodide (IV) with various nucleophiles were investigated in comparison with those of I. The salt IV, prepared as already described (6), underwent reaction with a number of nucleophiles under mild conditions, giving the 2-substituted 1-methylbenzimidazoles (V) in good yield (see the accompanying Table).

TABLE

Reaction of 3-Methoxy-1-methylbenzimidazolium Iodide (IV)

Reagent	Solvent	Reaction temp.	Product*[1] (X in V)	Yield (%)
KCN	H_2O	room temp.	CN (6)	quant.
NaOH	"	"	OH (7)	"
CH_3MgI	$(C_2H_5)_2O$	ca. 35°	CH_3 (8)	85
$NaHSO_3$	H_2O	room temp.	SO_3H (6)	quant.
CH_3ONa	CH_3OH	"	OCH_3 (6)	95
$(CH_3)_2CHONa$	$(CH_3)_2CHOH$	ca. 95°	$OCH(CH_3)_2$	70
$NH_2NH_2 \cdot H_2O$	H_2O	room temp.	$NHNH_2$ (6)	50
NH_3	"	"	NH_2 (9)	quant.
CH_3NH_2	CH_3OH	"	$NHCH_3$*[2]	"
$(CH_3)_2NH$	"	"	$N(CH_3)_2$ (7)	85
$C_6H_5NH_2$	none	ca. 95°	NHC_6H_5*[2]	85
$CH_2(CN)CO_2CH_3$	"	120°	$CH(CN)CO_2CH_3$ (6)	50
$CH_2(CN)_2$	"	ca. 95°	$CH(CN)_2$*[3]	75
$NaBH_4$	C_2H_5OH	room temp.	H (10)	quant.

*1 Satisfactory analyses were obtained for all compounds described and each of known compounds was identified with an authentic sample.
*2 Each compound was identified with a sample prepared from 2-chloro-1-methylbenzimidazole and the appropriate amine.
*3 The structure was established by hydrolysis to 1,2-dimethylbenzimidazole.

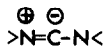
In contrast to those in I, the reaction in this series covers a wide scope and distinct differences between the two series were noted in the reaction with alkali or aniline: IV was converted to V (X=OH or NHC_6H_5), whereas I has been reported to decompose into pyridine and an aldehyde or pyridine N-oxide and N-alkylaniline, respectively (11).

Recently, Olofson et al. (12) have shown that the deuterium exchange rate of the 2-hydrogen of N,N'-dimethylimidazolium salt is 30,000 times that of the 3- or 5-hydrogen of N,N'-dimethylpyrazolium salt. In the former a much greater percentage of

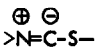
the positive charge is localized at the two α-positions to the forming carbanion, while in the latter one of two positively charged nitrogens is α to the forming carbanion. Similar great difference in lability between the 2-hydrogen of IV and the 2- or 4-hydrogen of I can be expected.

The n.m.r. study showed that deuterium exchange of the 2-hydrogen of IV in deuterium oxide occurred even at room temperature in the absence of any catalyst, whereas no such deuterium exchange in I was observed under the same conditions. The extraordinary low τ value (-1.00 in $CDCl_3$) of the 2-hydrogen of IV also indicates that this hydrogen is unusually deschielded and is therefore unusually acidic.

Breslow's studies on the mechanism of thiamine action and subsequent papers (13) have demonstrated remarkable facility with which zwitterions of type VI and VII can be formed.



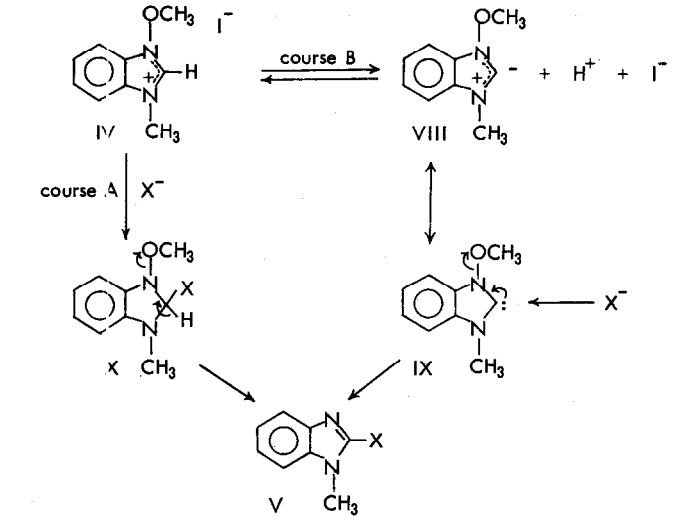
VI

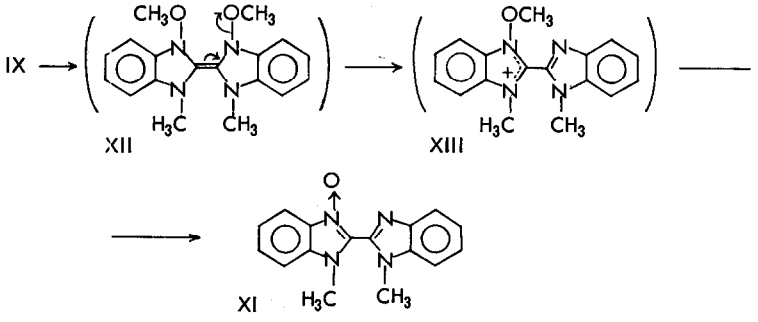


VII

From these facts, the nucleophilic substitution in IV may proceed via the following course (B) rather than a course (A) similar to that in I. Loss of the 2-proton of IV accelerated by the reagent used would produce a zwitterion intermediate (VIII), whose carbene-type resonance hybride (IX) undergoes nucleophilic attack at the 2-position with concerted departure of the methoxy group yielding the product V.

Further evidence for the formation of the zwitterion-carbene type intermediate was obtained by refluxing a solution of IV in anhydrous acetonitril in the presence of triethylamine which gave 1,1'-dimethyl-2,2'-bibenzimidazole 3-oxide (XI) (6) in 64% yield. The formation of XI can be rationalized by the sequence IX ⟶ (XII) ⟶ (XIII) ⟶ XI.





A similar dimerization reaction which gives 1,1',3,3'-tetraphenyl-2,2'-bibenzimidazolidine from the corresponding zwitterion has been shown recently (14, 15). Removal of one of the methoxy groups of XII followed by the double bond shift leads to the quaternary salt XIII, the decomposition of which into the N-oxide XI is parallels to the known reaction in N-alkoxypyridinium salt (11).

The zwitterions of type VI and VII have been shown to react as nucleophilic carbenes (13), however their electrophilic reactions are little known. In the present series, the detachable methoxy group would enhance the electrophilic character of VIII.

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