A New and Simple Synthesis of Benzimidazole *N*-Oxides

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Summary *o*-Nitro-*NN*-dialkylanilines give the corresponding benzimidazole *N*-oxides by the action of hot aqueous acid.

CONVERSION of benzimidazoles into their *N*-oxides cannot be carried out by direct oxidation. In fact, such *N*-oxides are deoxygenated under oxidising conditions.[1,2a] The most general indirect synthesis of these *N*-oxides involves reduction of *N*-acyl-*o*-nitroanilines,[2] while another[3] requires acid-catalysed condensation of an *o*-nitrosoaniline (prepared by photolysis of *N*-nitro-phenyl derivatives of α-amino-acids) with an aldehyde. Certain *N*-nitrophenyl derivatives of α-amino-acids (which under photolytic conditions give both *o*-nitrosoanilines and aldehydes) photolyse in acid solution to give benzimidazole *N*-oxides directly.[3]

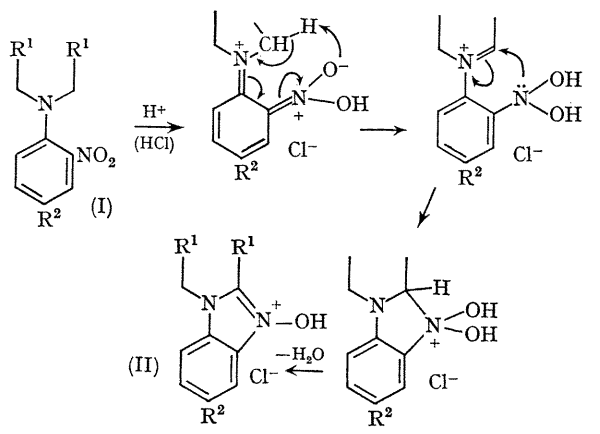
We now report a new synthesis of this system. We have recently shown that *o*-nitro-*NN*-dialkylanilines cyclise under thermal,[4] reductive[5] or acid-catalysed conditions[6] to give benzimidazoles, by a mechanism possibly involving a benzimidazole *N*-oxide intermediate. This is supported by isolation of the acetylated products expected of such an *N*-oxide in the presence of acetic anhydride.[6] We now find that the action of hot aqueous acid (*e.g.* hydrochloric acid) on the *o*-nitro-*NN*-dialkylanilines (I) yields the benzimidazole *N*-oxides (II), often in practicable yields (see Table), according to the mechanism in the scheme by analogy with our previous work. The products are isolated as hydrochlorides after evaporating the solvent and removal of starting material and by-products with ether or chloroform, followed by crystallisation of the residue from methanol–ether. No attempt has been made to optimise conditions but it is evident that yields and reaction rates may be increased by varying the reaction temperature (see expts. e, g, j, k, l) within a range compatible with the stability of

TABLE

Benzimidazole-N-*oxide hydrochlorides* (II) *prepared by cyclisation of* o-*nitrodialkylanilines of type* (I) *with hot hydrochloric acid*

Expt.	(II) R¹	(II) R²	Reaction Temp.	Reaction time (hr.)	M.p. (d)	Unreacted (I) (%)	Yield (%) A	Yield (%) B
a	$-[CH_2]_2-$	H	110°	20	224°	19	51	63
b	"	CO_2H	110	2	255—260	24	61	80
c	"	CF_3†	110	1	196—198	63	33	90
d	"	NO_2	110	20	212	47	32	60
e	$-[CH_2]_3-$	H	110	20	—	89	0	0
e_1	"	H	160	7	202—204	10	61	67
f	"	NO_2	110	20	228	80	20	100
g	$-CH_2OCH_2-$	H	110	20	201	68	26	81
g_1	"	H	150	12	—	66	30	90
h	"	NO_2	110	20	216	87	13	99
j_1	$-[CH_2]_4-$	H	110	1	212	—	12	—
j_2	"	H	110	2	—	—	16	—
j_3	"	H	110	4	—	—	25	—
j_4	"	H	110	8	—	—	38	—
j_5	"	H	110	20	—	15	61	72
j_6	"	H	110	40	—	—	74	—
k	"	NO_2	110	20	206	80	16	100
k_1	"	NO_2	150	12	—	19	76	94
l	Me	H	110	20	240	75	8	32
l_1	"	H	150	12	—	10	47	52

A—percentage yield calculated on the total amount of starting material.
B—percentage yield calculated on consumed starting material.
† Traces of the carboxylic acid (IIb) were also isolated.



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the *N*-oxide. The cyclisation to the *N*-oxide is accompanied to a small extent by elimination and migration of the nitro-group by a mechanism which is under investigation. Thus in most cases the corresponding *N*-phenyl- and *N*-*p*-nitrophenyl amines together with some starting compound were found among the reaction products.

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