Acid-catalysed Cyclisation of o-Nitrophenylhydrazines to *N*-Aminobenzimidazoles

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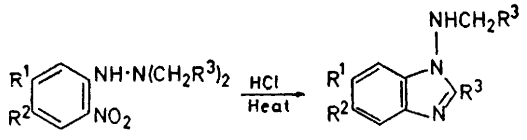
Summary *N*-(*o*-Nitroanilino)-substituted aliphatic amines undergo cyclisation to *N*-aminobenzimidazoles in good yield in hot mineral acid.

MANY reports of the base-catalysed cyclisation of *o*-nitrophenylhydrazines and related systems illustrate this reaction as a route to benzotriazoles.[1] We now report a novel acid-catalysed cyclisation of the *o*-nitrophenyl hydrazines† (**1**) under mild conditions resulting in *N*-aminobenzimidazoles (**2**). Thus, treatment of (**1f**) with constant boiling hydrochloric acid under reflux gives the ring-chlorinated tricyclic derivative (**2g**) in 63% yield. The position of the chlorine is confirmed because the same product is formed when starting with (**1g**). The suggested structure is supported by analytical and spectral data as well as synthesis. In particular, the coupling between the NH and the adjacent CH_2 (or Me) group is clearly seen in the n.m.r. spectra in carbon tetrachloride or deuteriochloroform, and is removed when deuterium oxide is added, thus eliminating the alternative structure (**3**). The benzimidazole (**2b**) was unambiguously synthesised by the interaction of 6-chloro-1-formamidobenzimidazole[2] successively with sodium hydride and methyl iodide in tetrahydrofuran followed by basic hydrolysis of this methylated product.

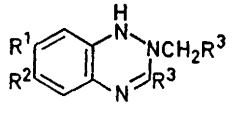


(1) (2)

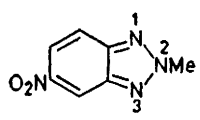
	R^1	R^2	R^3	R^3–R^3	(2) (Yield, %)
a	H	H	H	—	**b**(60)
b	Cl	H	H	—	**b**(68)
c	H	NO_2	H	—	**c**(42)
d	H	CF_3	H	—	**d**(50)
e	H	CO_2Et	H	—	**l**(79)
f	H	H	—	$[CH_2]_3$	**g**(63)
g	Cl	H	—	$[CH_2]_3$	**g**(23)
h	H	NO_2	—	$[CH_2]_3$	**h**(6), (50)[a]
i	Cl	H	—	CH_2OCH_2	**i**(36)
j	Cl	H	—	$[CH_2]_4$	**j**(46)
k	H	NO_2	—	$[CH_2]_4$	**k**(10)[a]
l	H	CO_2H	H	—	—

[a] Using polyphosphoric acid.

The cyclisation can be accomplished without concomitant ring chlorination by use of hydrobromic or trifluoroacetic acid instead of hydrochloric acid. A variety of *N*-aminobenzimidazoles (**2**) has been made by this method (Table) usually in good yield from *o*-nitrophenylamino-substituted dialkylamines or cyclic amines. Anomalous results were observed with the 2,4-dinitrophenylhydrazines (**1c**, **h**, and

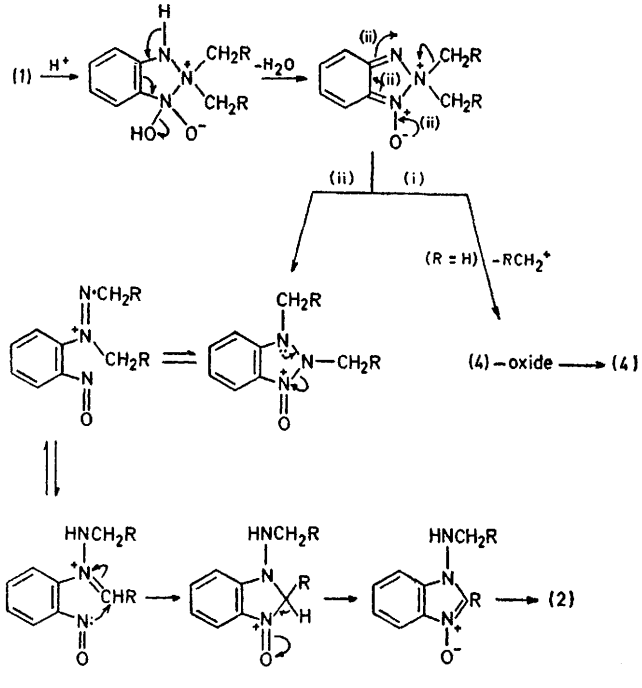


(3)



(4)

k). Thus the dimethylhydrazine (**1c**) gave a mixture of the triazole (**4**) and its 3-oxide while the other analogues (**1h** and **1k**) gave only low yields of the corresponding aminobenzimidazoles (**2h** and **2k**) under these conditions. However, use of polyphosphoric acid at 78° instead of hydrochloric acid allowed the isolation of the appropriate benzimidazole (**2**) even in these cases in good yield except for the



SCHEME

† The preparation of these compounds will be described elsewhere.

dimethyl derivative (**1c**) which still gave some triazole (**4**; 21%) and its *N*-oxide (12%).

The reaction is mechanistically related to several acid-catalysed cyclisations reported by us resulting in benzimidazoles[3] and is rationalised in the Scheme. The rearrangement step is best viewed as a 1,5-sigmatropic shift (ii) analogous to that observed recently with 2,2-dialkylisobenzimidazoles which transform on heating to give 1,2-dialkylbenzimidazoles.[4] The indispensable presence of the NH group is demonstrated by the fact that no cyclisation occurred when it was replaced by CH_2, CO, or SO_2. Also when the piperidino-group (**1f**) was exchanged for a cyclohexyl moiety the compound was unchanged on acid treatment. The introduction of halogen in the aromatic ring during the rearrangement is characteristic of an *N*-oxide intermediate and we have observed similar examples during hydrochloric acid-catalysed cyclisations involving benzimidazole *N*-oxides.[5]

We thank S.R.C. for a Research Studentship to D.W.S.L.

(*Received, 22nd November* 1972; *Com.* 1955.)

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