Tetrahedron Letters No.51, pp. 4519-4520, 1970. Pergamon Press. Printed in Great Britain.

NITRONE ISOMERIZATION IN THE 1,4-BENZODIAZEPINE SERIES

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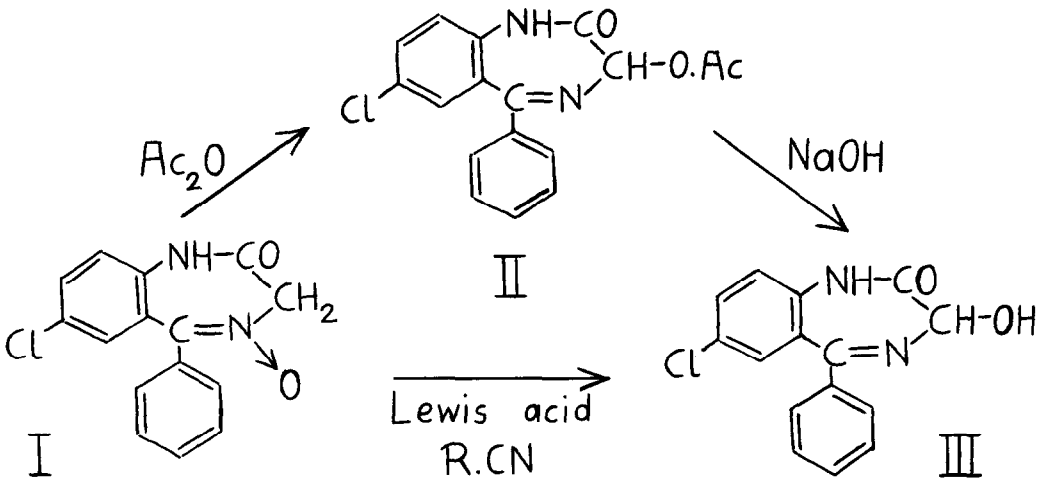
(Received in UK 17 August 1970; accepted for publication 8 October 1970)

During the past ten years derivatives of 1,4-Benzodiazepine have covered a large field in drug research (1). One of the results of these studies is the psychotherapeutic agent Oxazepam (III) which can be made from the isomeric nitrone[+] (I) by a two-step procedure (I → II → III, see 4):



Since isomerizations of heterocyclic N-oxides to the corresponding carbinolamines, oxazepines or oxaziridines by UV radiation (5, 6, 7) or chromate oxidation (8) are already known, it seemed to be possible

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+ Contrary to some statements in the literature (2) according to which the nitrone I can be gained only by ring closure of the ß-form of 2-Chloracetamido-5-chlorobenzophenone-oxime whilst the α-form, under similar conditions, yields the corresponding oxime-ether (3), we got I from the more easily obtainable α-oxime in about 80 % yield, by treating the α-oxime at 125° in DMF with the dried sodium salt of a cation exchanger.

to get III from I on a one-step way too. But all attempts to rearrange the nitrone I to III by UV radiation or oxidizing agents, were not successful.

Thereupon I was treated with $BF_3.O(C_2H_5)_2$ in an inert solvent (e.g. tetrahydrofuran) whereby the BF_3 adduct (m.p. 160 - 165°, dec.) was precipitated in an almost quantitative yield.

No conversion was achieved by heating the adduct in a number of usual solvents. However, an isomerization to III was readily obtained when a suspension of the adduct in acetonitrile or acrylonitrile was left to stand at room temperature. Further tests proved that the isomerization of I to III can be accomplished also by means of other Lewis acids, e.g. $AlCl_3$, and that it is not necessary to isolate the intermediarily formed adduct. The presence of a nitrile, however, is specific.

It can be assumed that this new possibility for the formation of carbinolimines from isomeric N-oxides is not restricted to benzodiazepines.

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