

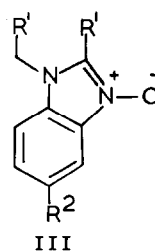
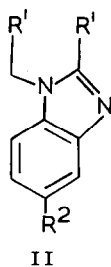
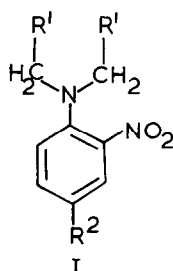
Thermal and Photolytic Cyclisation, Rearrangement,  
and Denitration Reactions of o-Nitro-t-Anilines

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o-Nitro-t-Anilines (I) are known to cyclise to the corresponding benzimidazoles (II) under a wide variety of conditions. As early as 1897

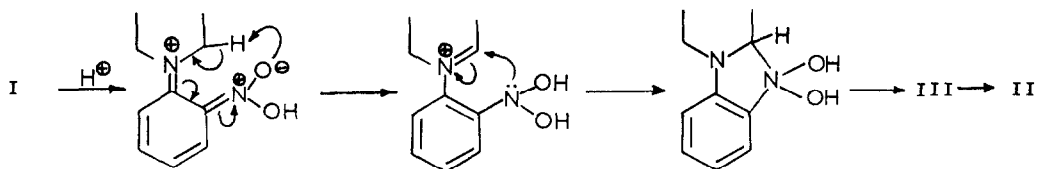


|                | a | b                               | c                               | d                               | e                               | f                               | g                                | h                               |
|----------------|---|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|----------------------------------|---------------------------------|
| R <sup>1</sup> | H | (CH <sub>2</sub> ) <sub>2</sub> | (CH <sub>2</sub> ) <sub>3</sub> | (CH <sub>2</sub> ) <sub>4</sub> | (CH <sub>2</sub> ) <sub>2</sub> | (CH <sub>2</sub> ) <sub>4</sub> | CH <sub>2</sub> OCH <sub>2</sub> | (CH <sub>2</sub> ) <sub>2</sub> |
| R <sup>2</sup> | H | H                               | H                               | H                               | Cl                              | Cl                              | H                                | NO <sub>2</sub>                 |

Pinnow demonstrated that during the reduction of o-nitrodimethylaniline (Ia) with tin and hydrochloric acid, some 1-methylbenzimidazole was produced<sup>1</sup>.

Since that time the cyclisation of a variety of o-nitro-t-anilines has been accomplished with other transition metal reducing agents<sup>2</sup>, sodium sulphite<sup>3</sup>, triethylphosphite<sup>4</sup>, heat<sup>5</sup>, lithium piperidide<sup>6</sup>, lithium aluminium hydride<sup>7</sup> and ultra violet irradiation of 2,4-dinitrophenyl derivatives of aziridines<sup>8</sup>.

In several of the above methods, the mechanism we have postulated<sup>2,4,5</sup> requires the intermediate formation of a benzimidazole-N-oxide (III); (see scheme 1) and in order to confirm our proposed pathway we have endeavoured to terminate the reaction at the N-oxide stage. Recently we observed that



Scheme I

the action of hot aqueous mineral acid gave the N-oxides (III) in good yields together with minor products arising from loss or rearrangement of the ortho nitro-group<sup>9</sup>.

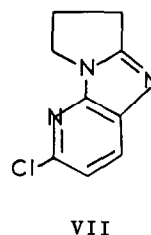
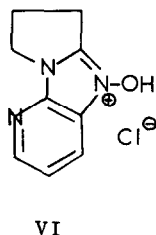
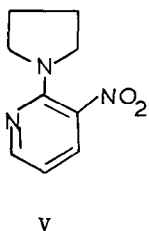
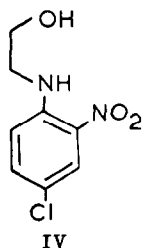
We now wish to report the acid catalysed photo-cyclisation of o-nitro-anilines to give either benzimidazoles (II) or benzimidazole-N-oxides (III) (see Table). The cyclisation is generally free from side reactions and

TABLE

Benzimidazoles (II) and benzimidazole-N-oxides (III) prepared by cyclisation of o-nitro compounds (I or V) by photolysis in aqueous methanolic hydrochloric acid<sup>10</sup>.

| I/V | Reaction Time (hr.) | Product (Yield, %) | m. p. °C         | Unreacted I (%) | Remarks                        |
|-----|---------------------|--------------------|------------------|-----------------|--------------------------------|
| Ib  | 48                  | IIIb (78)          | 145 <sup>o</sup> | 4               | 1. H <sub>2</sub> O            |
| Ic  | 66                  | IIC (83)           | 102              | 11              |                                |
| Id  | 24                  | IId (81)           | 125              | 2               |                                |
| Ie  | 54                  | IIIe (13)          | 125              | 86              | 1. H <sub>2</sub> O            |
| If  | 65                  | IIIf (79)          | 129              | 10              | 2. H <sub>2</sub> O            |
| Ig  | 80                  | IIIg (55)          | 130              | 23              | 2. H <sub>2</sub> O + IV (17%) |
| V   | 40                  | VI (78)            | 182              | 2               | 1. H <sub>2</sub> O + VII (7%) |

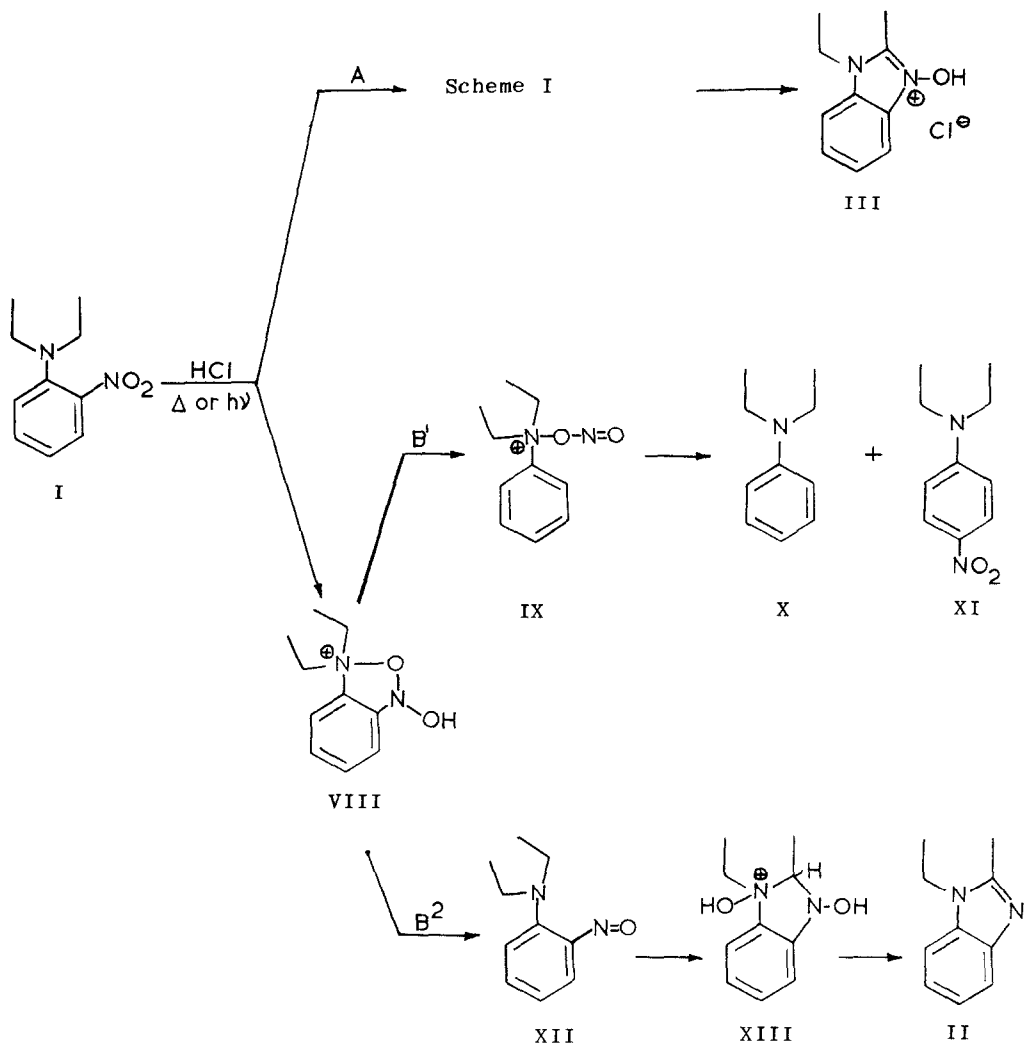
proceeds extremely slowly in the absence of acid. In the case of the morpholine compound (Ig) ring-opening and nuclear chlorination occur to produce (IV). Application of this cyclisation to other aromatic systems has so far only been carried out with the pyridine analogue (V) which gave a



high yield of the corresponding N-oxide (VI) together with the chlorinated product (VII).

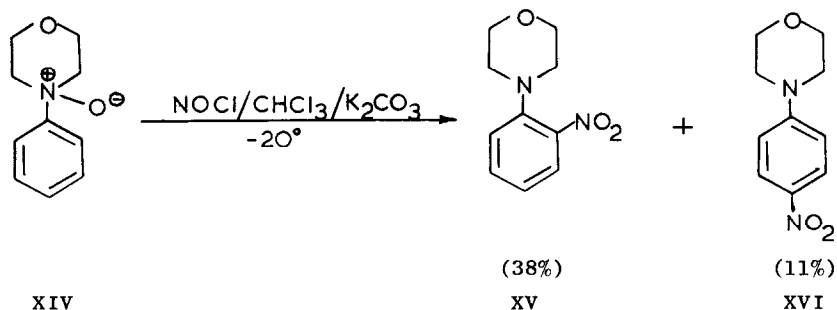
Since the benzimidazole-N-oxides (IIIc and d) are photo-stable under the reaction conditions, they are thus not the precursors of the benzimidazoles (IIc and IID). Furthermore, the reactions yield either the benzimidazole (II) or its N-oxide (III), apparently dependent upon a combination of steric (cf. Ib with Ic and Id) and electronic (cf. Id with If) factors.

We propose the following scheme as a plausible mechanism for the thermal and photochemical acid-catalysed reaction (Scheme 2). The thermal or photochemical reaction to yield the N-oxide hydrochloride (route A) proceeds according to Scheme 1). The by-products (X and XI) isolated in the thermal reaction can then be considered to arise from the reduced furoxan intermediate (VIII). This rearranges thermally (route B<sup>1</sup>) to the N-nitrite (IX) which, in a manner analogous to the nitramine rearrangement gives the p-nitro-compound (XI), or loses its nitro group to give the denitrated compound (X). The furoxan intermediate may also be invoked to explain the photochemical formation of the benzimidazole (route B<sup>2</sup>) by way of the o-nitroso-N-oxide (XII) and the unstable N-oxide (XIII) which by loss of water and oxygen yields the aromatic system (II). The cyclisation (XII→XIII) has several analogies in our work<sup>2b</sup>. Evidence for the proposed



reaction path is as follows:

1. A variety of *o*-substituted nitrobenzenes undergo oxygen transfer to yield an *o*-substituted nitrosobenzene and several mechanisms have in fact been proposed involving intermediates analogous to VIII<sup>11</sup>.
2. The action of the nitrosyl chloride on the N-oxide (XIV) gave predominantly the *o*-nitrated compound (XV) and the *p*-isomer (XVI). Phenyl morpholine itself under the same conditions gave mostly the *p*-isomer.



3. The *p*-nitro *t*-anilines are stable to hot acid, showing the necessity for an ortho-*t*-amine to bring about rearrangement.
4. The rearrangement of the nitro-group appears to be intramolecular since a mixture of *o*-nitrophenyl pyrrolidine (Ib; 5 gram) and phenyl morpholine (1 gram) gave only *p*-nitrophenylpyrrolidine and no crossed product. Similarly another mixture of *o*-nitrophenyl morpholine (Ig; 5 gram) and phenyl pyrrolidine (1 gram) gave *p*-nitrophenyl morpholine but no *p*-nitrophenyl pyrrolidine.

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