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THE MECHANISM OF INDAZOLE FORMATION BY THE POLYPHOSPHORIC ACID CATALYSED CYCLISATION OF m- and p-NITROPHENYLHYDRAZONES

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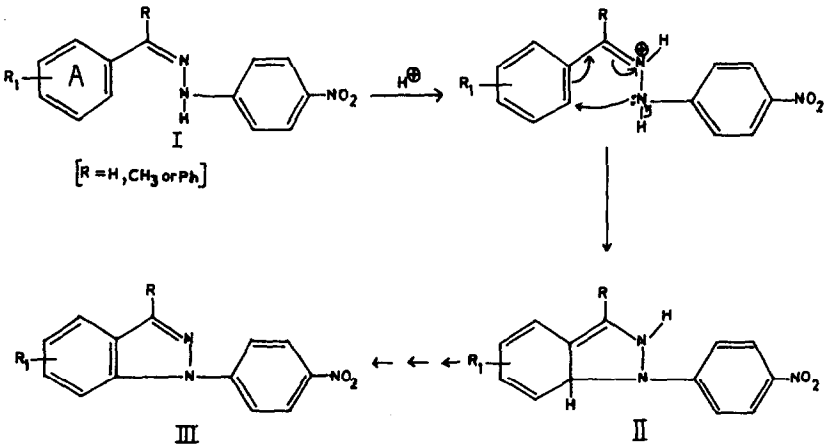
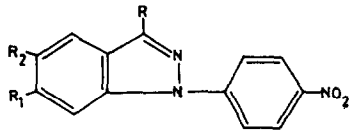
Indazoles are formed (1,2,3) when the p-nitrophenylhydrazones of several acetophenones (1,2), benzaldehydes (2), benzophenones (2) and acetylated aromatic hydrocarbons (3) are treated with polyphosphoric acid (PPA) at an elevated temperature. The cyclisation step of this reaction has been postulated (1,2) to involve, after protonation of N_2, nucleophilic attack by the N_1 atom of the hydrazone group on the ortho-position of the aromatic ring of the ketonic or aldehydic moiety, as shown in I⟶II. However, this



postulation is invalidated by the following observations.

(i) With electron-releasing groups substituted ortho- and para- in ring A of (I), which would tend to prevent nucleophilic attack as shown, poor to reasonable yields of indazoles are obtained, whereas a nitro-substituent in this ring, which should facilitate the nucleophilic attack, completely inhibits the reaction (2).

(ii) The indazoles derived from the p-nitrophenylhydrazones of 3,4-dimethoxyacetophenone, 3,4-dimethoxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde were shown to be exclusively the 5,6-disubstituted compounds (IV, R = CH_3, $R_1 = R_2 = OCH_3$; R = H, $R_1 = R_2 = OCH_3$; R = H, R_1 = OH, $R_2 = OCH_3$ respectively) and not the corresponding 6,7-disubstituted isomers



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which would have resulted from the alternative direction of cyclisation (2), and which would have been expected, at least as the major isomeric products, on the basis of the proposed (1,2) cyclisation mechanism.

(iii) From the cyclisation of the p-nitrophenylhydrazones of acetyl derivatives of aromatic hydrocarbons, it was found (3) that where two directions of ring closure were possible, the pyrazole nucleus is produced by ring formation between the N_1 atom of the hydrazone and the ortho-carbon atom on the parent aromatic nucleus having greatest nucleophilicity (i.e. the position most susceptible to electrophilic attack). Similarly, in the case of 2-benzoylthiophene p-nitrophenylhydrazone, cyclisation occurs on the thiophene nucleus (3).

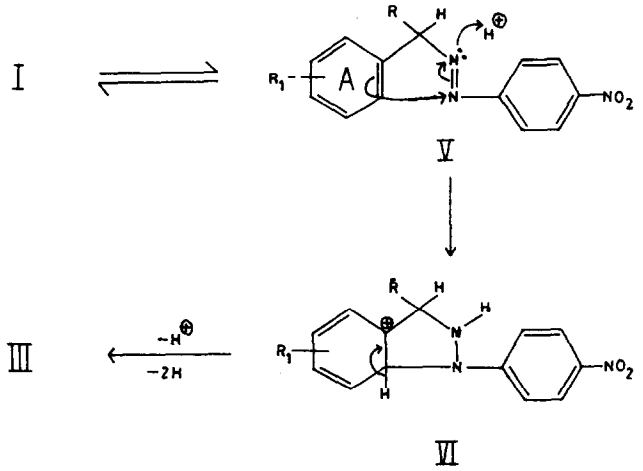
(iv) 2-Chloro- and 2,4-dimethoxyacetophenone p-nitrophenylhydrazones afford 4-chloro- and 4,6-dimethoxy-3-methyl-1-p-nitrophenylindazoles respectively(2). If the cyclisation stage involved nucleophilic attack by N_1, elimination of the 2-chloro- and 2-methoxy-substituents as their anions rather than elimination of hydride ion from C_6 would be expected (4), and would have led to the formation of 3-methyl-1-p-nitrophenylindazole and 6-methoxy-3-methyl-1-p-nitrophenylindazole respectively.

(v) The presence of a para- or meta-nitro- substituent on the hydrazine moiety, which will lessen the electron density at N_1 by comparison with the

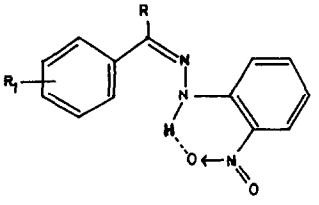
unsubstituted phenylhydrazones (5), appears to be essential for indazole formation since the corresponding acetophenone phenylhydrazones undergo Fischer indolisation on treatment with PPA (2). Some acetophenone m-nitrophenylhydrazones give, in fact, a mixture of the indazole together with the corresponding 4- and 6- nitroindoles when treated with PPA (2).

This mechanistic postulation (1,2) also fails to account for the observations that indazole formation only occurs using a PPA catalyst (neither indazoles or indoles are formed with hydrochloric or sulphuric acids as catalysts) (1,2) and that indazoles are not formed from the corresponding o-nitrophenylhydrazones (2).

The above observations (i - v) are fully consistent with the following mechanism for indazole formation from p- or m- nitrophenylhydrazones, in which the cyclisation stage involves an ELECTROPHILIC attack on the ortho-position of the aromatic ring A, probably initiated by protonation of N_2 of the hydrazine moiety, which is in the form of its azo-tautomer as shown below in (V). The oxidation of (VI) to (III) must be effected by the C = N and/or nitro



groups of other hydrazone molecules (1). In neutral solvents or in acidic media such as concentrated sulphuric acid or boron trifluoride/ether/acetic acid there is no evidence for the formation of the azo-tautomer from a phenylhydrazone (6). In this case, however, formation of the azo-tautomer intermediate might be possible through the effect of the nitro-substituent or by a specific effect of the PPA. In the case of m-nitrophenylhydrazones, the increased basicity of the hydrazine moiety (5) would allow a competing equilibrium between the hydrazone (I) and its enehydrazine tautomer to become established which would ultimately lead to some indole formation (7). The ortho-nitro-substituent on the phenylhydrazine moiety could prevent indazole formation by intra-molecular hydrogen bond formation as shown in (VII) which would inhibit the formation of the necessary intermediate azo-tautomer.



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