

STUDIES IN THE FORMATION OF HETEROCYCLIC RINGS CONTAINING NITROGEN

Part V. The Position of Nitro Group in the 1:2-Disubstituted Benzimidazole from 4-Nitro-*o*-Phenylenediamine and Benzaldehyde

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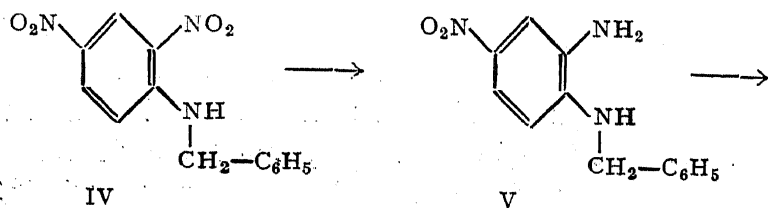
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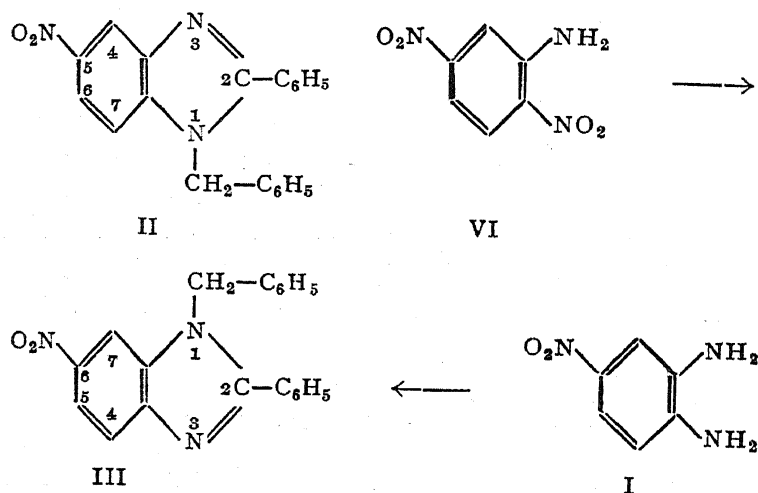
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PINNOW AND WISKOTT¹ carried out the condensation of 4-nitro-*o*-phenylenediamine hydrochloride with benzaldehyde, and reported the formation of α -phenyl nitro benzimidazole [*i.e.*, 2-phenyl-5-(or 6-)-nitro benzimidazole], and *N*-benzyl- α -phenyl nitro benzimidazole (*i.e.*, the 1:2-disubstituted benzimidazole). They stated that the disubstituted benzimidazole can exist in two isomeric forms, 1-benzyl-2-phenyl-5-nitro benzimidazole and 1-benzyl-2-phenyl-6-nitro benzimidazole. However, they did not succeed in their attempts to fix the position of nitro group in it.

By the condensation of 4-nitro-*o*-phenylenediamine (I) with two moles of benzaldehyde following the modified Hinsberg's procedure,² using hot acetic acid due to the very low solubility of the diamine in the cold solvent, both the 2-substituted and 1:2-disubstituted benzimidazoles could be isolated. Unlike in the condensations of the aldehyde with *o*-phenylenediamine,² 4-methyl-*o*-phenylenediamine,³ and 4-chloro-*o*-phenylenediamine,⁴ no benzodiazepine derivative could be isolated in this condensation. The separation of the mono- and disubstituted benzimidazoles could be conveniently effected by making use of the selective solubility of the monosubstituted benzimidazole in aqueous potash.¹ The compounds thus obtained have been found to be identical with the respective products reported by Pinnow and Wiskott. The position (5 or 6) of the nitro group in the 1:2-disubstituted benzimidazole has been established, as in the case of methyl³ and chloro⁴ benzimidazoles, by synthesising the 5- and 6-nitro benzimidazoles (II) and (III) separately by unambiguous methods, and comparing them with the condensation product.





1-Benzyl-2-phenyl-5-nitro benzimidazole (II) has been synthesised starting from N-benzyl-2:4-dinitro aniline (IV) in two steps. By the selective reduction of the ortho nitro group in N-benzyl-2:4-dinitro aniline (IV) making use of ammonium sulphide, N¹-benzyl-4-nitro-*o*-phenylenediamine (V) could be obtained. This diamine (V), on condensation with equimolecular proportion of benzaldehyde in alcoholic nitrobenzene medium, yielded 1-benzyl-2-phenyl-5-nitro benzimidazole (II). The synthesis of the 6-nitro benzimidazole (III) has been achieved starting from 2:5-dinitro aniline (VI) in three steps, by benzylation, selective reduction, and benzaldehyde condensation.

The 1:2-disubstituted benzimidazole obtained by the condensation of 4-nitro-*o*-phenylenediamine with benzaldehyde has been found to be identical with 1-benzyl-2-phenyl-6-nitro benzimidazole (III). In general, it may be expected that all the 1:2-disubstituted benzimidazoles from 4-nitro-*o*-phenylenediamine and aromatic aldehydes, will have the nitro group in position 6.

EXPERIMENTAL

All m.p.'s are uncorrected. The micro-analyses were carried out by one of the authors (C. V. R.).

I. Condensation of 4-nitro-*o*-phenylenediamine with benzaldehyde

The diamine (0.51 g.) was dissolved in minimum quantity of almost boiling glacial acetic acid, and benzaldehyde (0.7 g.) was added to it with thorough shaking. The reaction was allowed to proceed for a period of one hour with occasional stirring. The solution was slowly added to excess of crushed ice, and the solid (0.95 g.) that separated was filtered and washed. The crude reaction product thus obtained was triturated with 5% potassium

hydroxide solution. The alkali solution was filtered, and the residue (0.65 g.) was washed with water until free from alkali and dried. The dry substance was purified by recrystallisation, first from alcohol, and then from a mixture of acetone and petroleum ether, yielding the pure disubstituted benzimidazole as light yellow prismatic rods, m.p. 187° (cf. Pinnow and Wiskott, m.p. $187-88^{\circ}$). The alkaline filtrate was acidified with acetic acid when 2-phenyl-5-(or 6)-nitro benzimidazole (0.3 g.) separated out. It was filtered, washed, and on recrystallisation from alcohol, yielded an almost colourless compound, m.p. 203° .^{1, 5}

II. Synthesis of 1-benzyl-2-phenyl-5-nitro benzimidazole

(a) *N*¹-Benzyl-4-nitro-*o*-phenylenediamine.—*N*-Benzyl-2:4-dinitro aniline (27 g.), obtained by the method of Cullinane *et al.*,⁶ was reduced by means of ammonium sulphide adopting the procedure used for the reduction of 2:4-dinitroaniline.⁷ The crude reduction product (15 g.), on recrystallisation from alcohol, yielded pure *N*¹-benzyl-4-nitro-*o*-phenylenediamine, dark-red rectangular rods, m.p. 148° (Found: C, 63.6; H, 5.2; N, 17.2; $C_{13}H_{13}N_3O_2$ requires C, 64.2; H, 5.4; N, 17.3%).

(b) 1-Benzyl-2-phenyl-5-nitro benzimidazole.—*N*¹-Benzyl-4-nitro-*o*-phenylenediamine (4.0 g.) was dissolved in alcohol (50 ml.), and benzaldehyde (1.8 g.) was added followed by nitrobenzene (25 ml.). The mixture was refluxed on a boiling water-bath for one hour. The solution remaining after the evaporation of alcohol was steam-distilled to remove nitrobenzene, and the residue (4.5 g.) was crystallised repeatedly from alcohol, and finally from a mixture of acetone and petroleum ether. The pure 1-benzyl-2-phenyl-5-nitro benzimidazole came out as shining pale yellow rectangular rods, m.p. 160° (Found: C, 73.1; H, 4.4; N, 12.8; $C_{20}H_{15}N_3O_2$ requires C, 73.0; H, 4.6; N, 12.8%). The melting point was depressed by the 1:2-disubstituted benzimidazole obtained in I.

III. Synthesis of 1-benzyl-2-phenyl-6-nitro benzimidazole

(a) *N*-Benzyl-2:5-dinitro aniline.—2:5-Dinitro aniline (1.2 g.), obtained from the products of nitration of *m*-nitro acetanilide,^{8, 9} fused sodium acetate (0.6 g.), and benzyl chloride (1.6 g.) were taken in a round-bottomed flask fitted with a reflux condenser and a calcium chloride guard tube. A speck of iodine was added, and the mixture was heated at 200° on an oil-bath for a period of twelve hours. The resulting mass was poured into ice-water, stirred well, and the product that separated was filtered. The excess benzyl chloride was removed by pressing the product in folds of filter-paper, and

washing with cold petroleum ether. The remaining solid was washed with dilute sulphuric acid (1:1) to remove the unconverted amine, then with water until free from acid, and dried. The crude benzyl derivative (0.6 g.) thus obtained crystallised from benzene in orange-red prisms, m.p. 166° (Found: C, 57.0; H, 4.1; N, 14.9; $C_{13}H_{11}N_3O_4$ requires C, 57.1; H, 4.0; N, 15.4%).

(b) *N*²-Benzyl-4-nitro-*o*-phenylenediamine.—N-Benzyl-2:5-dinitro aniline (0.5 g.) was reduced as in II (a), and the reduction product was isolated by diluting the reaction mixture and acidifying it carefully with acetic acid keeping the solution stirred. The crude diamine separated out as a red solid (0.3 g.). Due to the small quantity of the crude diamine available at hand, almost all of it was made use of for the next step. Attempts to prepare a crystalline hydrochloride from 50 mg. of the diamine were unsuccessful.

(c) 1-Benzyl-2-phenyl-6-nitro benziminazole.—N²-Benzyl-4-nitro-*o*-phenylenediamine (0.24 g.) was condensed with benzaldehyde (0.11 ml.) in alcoholic solution containing nitrobenzene as in II (b). The crude product (0.25 g.), on purification from alcohol and then from a mixture of acetone and petroleum ether, yielded pure 6-nitro benziminazole as light yellow prismatic rods, m.p. 187° (Found: C, 72.8; H, 4.9; N, 12.9; $C_{20}H_{15}N_3O_2$ requires C, 73.0; H, 4.6; N, 12.8%). The melting point was undepressed by the 1:2-disubstituted benziminazole obtained by the condensation from 4-nitro-*o*-phenylenediamine and benzaldehyde.

SUMMARY

1-Benzyl-2-phenyl-5-nitro benziminazole and 1-benzyl-2-phenyl-6-nitro benziminazole have been synthesised starting from N-benzyl-2:4-dinitro aniline and 2:5-dinitro aniline respectively. The 1:2-disubstituted benziminazole obtained by the condensation of 4-nitro-*o*-phenylenediamine with benzaldehyde has been found to be identical with the 6-nitro benziminazole.

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