STUDIES IN THE FORMATION OF HETEROCYCLIC RINGS CONTAINING NITROGEN

Part II. The Position of Methyl Group in the 1: 2-Disubstituted Benziminazole from 4-Methyl-o-phenylenediamine and Benzaldehyde

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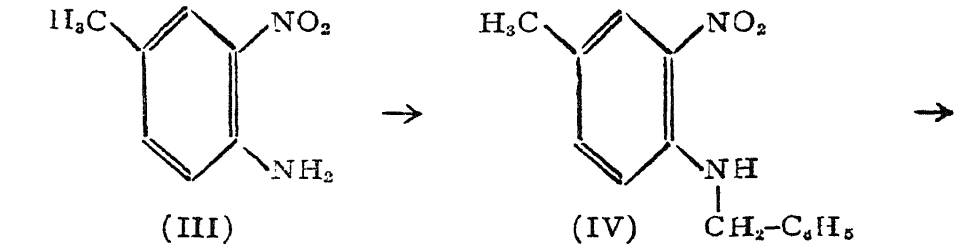
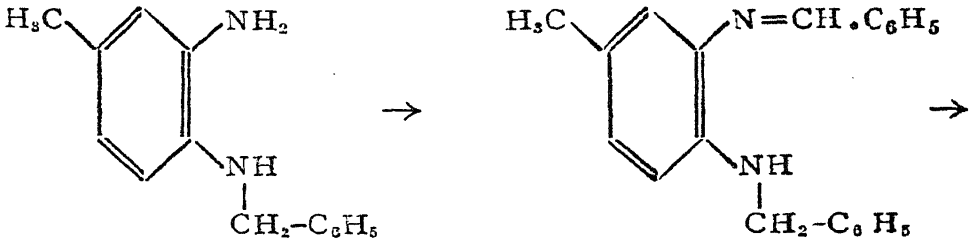
BY the condensation of 4-methyl-*o*-phenylenediamine with benzaldehyde, Ladenburg[1] obtained a product, which was proved by Hinsberg[2] to be a 1:2-disubstituted benziminazole. Hinsberg prepared a number of compounds having similar structure by extending the reaction to other aldehydes, but in all these cases, he represented the aromatic part of the ring as $C_7H_6\langle$, leaving the position of the methyl group uncertain. Later, Pinnow and Wiskott[3] condensed 4-nitro-*o*-phenylenediamine with benzaldehyde and pointed out that two isomeric forms of the disubstituted benziminazole ($-NO_2$ in 5 or 6 position) were possible. They, however, obtained only one product, and did not succeed in their attempts to fix the position of the nitro group in it.

In our systematic investigation of the reaction between 4-methyl-*o*-phenylenediamine and aromatic aldehydes, we were confronted with the assignment of position to the methyl group. As a typical case, the product obtained by condensation with benzaldehyde was studied in detail. When the condensation of the diamine with benzaldehyde was carried out according to the modified Hinsberg's procedure,[4] in addition to the 1:2-disubstituted benziminazole, the 2-monosubstituted benziminazole and a benzodiazacycloheptatriene derivative also could be isolated. The disubstituted compound was found to be identical with that reported by Ladenburg, and it may be either 1-benzyl-2-phenyl-5-methyl benziminazole (I), or 1-benzyl-2-phenyl-6-methyl benziminazole (II). It was felt that the only way of proving its structure would be to prepare the two benziminazoles (I) and (II) by unambiguous methods and compare the condensation product with them.

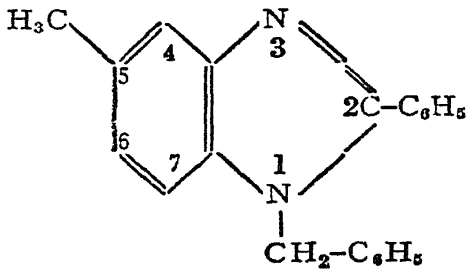
Synthesis of 1-benzyl-2-phenyl-5-methyl benziminazole has been achieved starting from 3-nitro-*p*-toluidine (III), prepared by well-known procedures.[5] It has been benzylated adopting the procedure used for the benzylation of



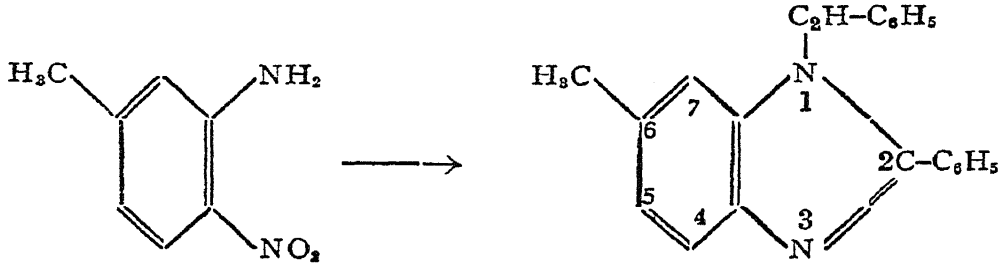
(III) (IV)



(V) (VI)



(I)



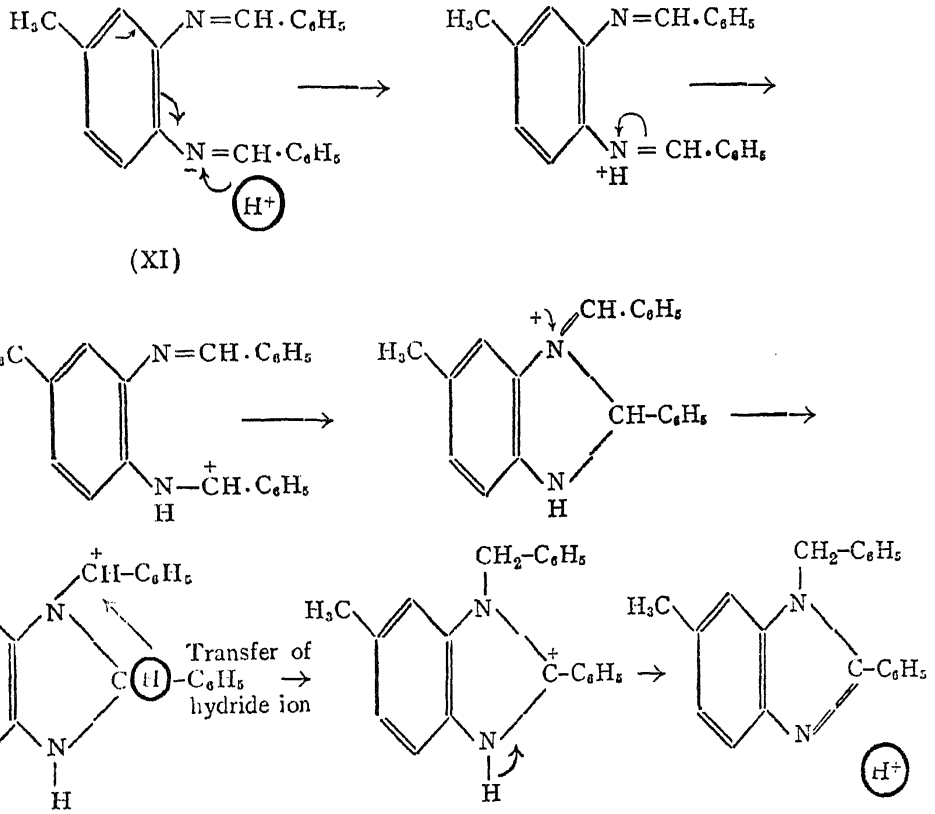
(VII) (II)

nitranilines,[6] when N-benzyl-3-nitro-*p*-toluidine (IV) is obtained. Reduction of this nitro compound with zinc dust and hydrochloric acid has given rise to 4N-benzyl-3 : 4-tolylenediamine (V), which on condensation with benzaldehyde in alcoholic medium yielded 3N-benzylidene-4N-benzyl-3 : 4-tolylenediamine (VI). By the oxidative cyclisation of this anil (VI) by refluxing in alcohol in the presence of air, or by the direct condensation of the amine (V) with benzaldehyde in alcoholic medium containing nitrobenzene,[7] 1-benzyl-2-phenyl-5-methyl benziminazole (I) has been obtained. Adopting similar procedure, 1-benzyl-2-phenyl-6-methyl benziminazole (II) has been synthesised from 4-nitro-*m*-toluidine[5,8] (VII), through the corresponding benzyl derivative (VIII), diamine (IX) and anil (X).

The two benziminazoles thus synthesised differed markedly in crystalline and also in melting point. The 1 : 2-disubstituted benziminazole

obtained by the condensation of 4-methyl-*o*-phenylenediamine with benzaldehyde was found to be identical with 1-benzyl-2-phenyl-6-methyl benziminazole.

The formation of the 6-methyl isomer instead of the 5-methyl derivative could be explained on the basis of the influence of the methyl group in the aromatic ring of the intermediate dianil (XI). It could reasonably be assumed that the anil para to the methyl becomes active and promotes cyclisation by the transfer of a hydride ion to the carbon atom in the other anil. Such hydride ion migrations seem to be fairly frequent in organic reactions as reviewed recently by Braude.[9] The mechanism of this cyclisation may be represented by the following stages which are initiated by a proton, supplied by the condensing agent, attaching itself to the negatively charged nitrogen para to the methyl group.



(XI)

In general, it may be expected that in all the 1:2-disubstituted benziminazoles formed from 4-methyl-*o*-phenylenediamine and aromatic aldehydes, the methyl group will be in position 6.

Experimental

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

Except the 1 : 2-disubstituted benziminazole now proved to be 1-benzyl-2-phenyl-6-methyl benziminazole and 2-phenyl-5-(or 6-) methyl benziminazole, all other compounds recorded below have not so far been reported in literature.

Condensation of 4-methyl-o-phenylenediamine with benzaldehyde

4-Methyl-*o*-phenylenediamine (1·5 g.) was dissolved in a little more than minimum quantity of glacial acetic acid and benzaldehyde (2·7 g.) added with thorough shaking. The reaction was allowed to proceed at room temperature for one hour with occasional stirring, and by the end of this time a crystalline solid A (0·4 g.) separated out. The mixture was filtered and the clear acetic acid solution poured into a large excess of crushed ice with vigorous stirring and left overnight. A granular solid B (3·0 g.) was obtained and the filtrate on making ammoniacal, gave another product C (0·5 g.).

Solid A, on recrystallisation from a mixture of alcohol and acetone, gave colourless needles, m.p. 160°, and analysed for 2 : 3 : 4-triphenyl-7-(or 8-) methyl benzodiazacycloheptatriene (Found: C, 87·5; H, 6·1; N, 7·6; $C_{28}H_{22}N_2$ requires C, 87·1; H, 5·7; N, 7·3%). Substance B, obtained as colourless prismatic rods, m.p. 195° on recrystallisation from alcohol and benzene, was found to be the 1 : 2-disubstituted benziminazole. The compound C crystallised from alcohol in colourless needles, m.p. 249°, and could be identified as 2-phenyl-5-(or 6-) methyl benziminazole.

1-*Benzyl-2-phenyl-5-methyl benziminazole* (*I*)

(*a*) *N-benzyl-3-nitro*-p-*toluidine* (*IV*).—3-Nitro-*p*-toluidine (III; 15 g.), fused sodium acetate (9 g.), iodine (0·2 g.) and freshly distilled benzyl chloride (13 g.) were thoroughly mixed and heated on a boiling water-bath for twelve hours. The resulting product, while hot, was poured into excess of ice water (200 ml.) and the solid that separated was filtered. The unreacted benzyl chloride was removed by pressing the solid with filter-paper and washing with cold petroleum ether (b.p. 60–80°). The remaining solid was washed with dilute sulphuric acid (1 : 2) to remove the unconverted amine, with water until free from acid, and dried (yield 12 g.). Recrystallisation from petroleum ether gave shining orange-red prismatic rods, m. p. 95 (Found: C, 68·9; H, 5·9; N, 11·3; $C_{14}H_{14}N_2O_2$ requires C, 69·4; H, 5·8; N, 11·6%).

(*b*) 4*N-benzyl*-3 : 4-*tolylenediamine* (*V*).—To N-benzyl-3-nitro-*p*-toluidine (IV; 4 g.) in hot alcohol (50 ml.) was added zinc dust (6 g.). The mixture was kept on a water-bath at 40–50°, and the addition of concentrated hydro-

chloric acid was regulated so that a slow evolution of hydrogen could be maintained (6 hours). The solution was filtered, concentrated to a small volume and poured into excess of water (300 ml.). Concentrated ammonia was added to the clear solution until the precipitated zinc hydroxide re-dissolved, and the ammoniacal solution was extracted with ether. The ethereal extracts, after drying, were evaporated, yielding crude 4N-benzyl-3:4-tolylenediamine (2·4 g.) as a viscous oil turning brown in air. The hydrochloride was obtained by passing dry hydrogen chloride into its dry ethereal solution and repeatedly washing the product with ether and hot petroleum ether. Recrystallisation from ethylacetate-petroleum ether mixture yielded colourless rectangular rods, m.p. 122° (Found: C, 67·1; H, 7·2; N, 11·0; $C_{14}H_{16}N_2$. HCl requires C, 67·6; H, 6·8; N, 11·3%).

(*c*) *3N-benzylidene-4N-benzyl-3:4-tolylenediamine* (*VI*).—4N-Benzyl-3:4-tolylenediamine (V; 0·6 g.) in alcohol (4 ml.) and benzaldehyde (0·3 g.; 1 mole) were heated on a boiling water-bath for fifteen minutes, when a light yellow crystalline solid separated. The mixture was cooled, filtered, and the residue washed with alcohol (yield 0·7 g.); light yellow rectangular rods, m.p. 162° (Found: C, 84·4; H, 6·6; N, 9·0; $C_{21}H_{20}N_2$ requires C, 84·0; H, 6·7; N, 9·3%). Recrystallisation was not carried out since it showed a tendency to undergo oxidative cyclisation resulting in the corresponding benziminazole.

(*d*) 1-*Benzyl-2-phenyl-5-methyl benziminazole* (*I*).—

(i) *By the oxidative cyclisation of the anil* (*VI*).—The anil (0·5 g.) was suspended in alcohol (50 ml.) and refluxed for eight hours passing a slow stream of air. The resulting solution was concentrated to one-third of the original volume, cooled and filtered. The residue was found to be mostly the unchanged anil. The filtrate was evaporated and the residue (0·25 g.) thus obtained, on recrystallisation from dilute alcohol and benzene, gave colourless hexagonal prisms of (I), m.p. 157° (Found: C, 84·7; H, 6·4; N, 9·5; $C_{21}H_{18}N_2$ requires C, 84·6; H, 6·1; N, 9·4%).

(ii) *By the condensation of the diamine* (*V*) *with benzaldehyde.*—To the diamine (1 g.) in alcohol (5 ml.) were added benzaldehyde (0·5 g.; 1 mole) and nitrobenzene (10 ml.), and refluxed for one hour. The solution remaining after evaporation of alcohol was steam distilled to remove nitrobenzene, and the residue (1·2 g.) on recrystallisation from alcohol and benzene gave (I) identical in all respects with the product reported in (*d*)-*i*, and different from the condensation product B of 4-methyl-*o*-phenylenediamine with benzaldehyde.

1-*Benzyl*-2-*phenyl*-6-*methyl benziminazole* (*II*)

(*a*) *N-benzyl*-4-*nitro*-m-*toluidine* (*VIII*).—4-Nitro-*m*-toluidine (VII; 15 g.) when benzylated following the procedure used for 3-nitro-*p*-toluidine, gave the crude benzyl derivative (10·5 g.). It crystallised from petroleum ether in orange rhombic plates, m.p. 103° (Found: C, 69·6; H, 5·7; N, 11·4; $C_{14}H_{14}N_2O_2$ requires C, 69·4; H, 5·8; N, 11·6%).

(*b*) 3*N-benzyl*-3 : 4-*tolylenediamine* (*IX*).—Reduction of (VIII), (4 g.) when carried out in a manner similar to that of (IV), resulted in 3N-benzyl-3 : 4-tolylenediamine (2·4 g.), colourless solid, m.p. 52°, rapidly turning dark brown in air. The hydrochloride of (IX) was obtained as transparent rectangular rods from a mixture of acetone and ether, m.p. 192° (decomp.) (Found: C, 67·7; H, 6·9; N, 11·2; $C_{14}H_{16}N_2$.HCl requires C, 67·6; H, 6·8; N, 11·3%).

(*c*) 4N-*benzylidene*-3*N-benzyl*-3 : 4-*tolylenediamine* (*X*).—Condensation of (IX) (0·6 g.) with benzaldehyde (0·3 g.) in alcoholic solution for a period of thirty to forty minutes yielded 4N-benzylidene-3N-benzyl-3 : 4-tolylenediamine (0·7 g.), yellow thick rectangular plates, m.p. 166° (Found: C, 84·4 ; H, 7·1; N, 9·2; $C_{21}H_{20}N_2$ requires C, 84·0; H, 6·7; N, 9·3%).

(*d*) 1-*Benzyl*-2-*phenyl*-6-*methyl benziminazole* (*II*)

(i) *By the oxidative cyclisation of the anil* (*X*).—The anil (0·5 g.) on oxidative cyclisation in alcoholic medium gave a compound (0·3 g.) which on recrystallisation from benzene gave colourless glistening prismatic rods, m.p. 197° (Found: C, 84·6; H, 6·4; N, 9·4; $C_{21}H_{18}N_2$ requires C, 84·6; H, 6·1; N, 9·4%).

(ii) *By the condensation of the diamine* (*IX*) *with benzaldehyde*.—The diamine (1 g.) was condensed with benzaldehyde (0·5 g.) in alcohol solution containing nitrobenzene, as in the preparation of benziminazole (I). The crude product (1·3 g.) on purification gave a crystalline compound identical with (II) reported in (*d*)-*i*, and with the condensation product B of 4-methyl-*o*-phenylenediamine with benzaldehyde, mixed m.p. undepressed.

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SUMMARY

1-Benzyl-2-phenyl-5-methyl- and 1-benzyl-2-phenyl-6-methylbenziminazoles have been synthesised starting from 3-nitro-*p*-toluidine and 4-nitro-*m*-toluidine respectively. The 1 : 2-disubstituted benziminazole obtained

by the condensation of 4-methyl-*o*-phenylenediamine with benzaldehyde has been shown to be identical with the 6-methyl benziminazole.

References

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