STUDIES IN THE FORMATION OF HETERO CYCLIC RINGS CONTAINING NITROGEN

Part IV. The Position of Chloro Group in the 1:2-Disubstituted Benzimazole from 4-Chloro-o-Phenylenediamine and Benzaldehyde

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By the condensation of 4-chloro-o-phenylenediamine (I) with more than three molar proportions of benzaldehyde in the absence of any solvent at 150-70°, Fischer and Limmer\(^1\) reported the formation of N:N'-dibenzylidene-4-chloro-o-phenylenediamine. They stated further that this dianil, by heating above its melting point, or by boiling in acids, was transformed into the corresponding benzimazole, 'p-chloro-ω-phenyl-N-benzyl benzimizazole'. Evidently, the position of the chloro group (5 or 6 position) in this benzimazole has been left unsolved.

The diamine is now condensed with two moles of benzaldehyde following the modified Hinsberg's procedure,\(^2\), \(^3\) when the 1:2-disubstituted benzimazole, 2-substituted benzimazole, and a benzodiazepine derivative have been isolated. The 1:2-disubstituted benzimazole obtained by us does not agree in its melting point and other properties with that reported by Fischer and Limmer. The product may be either 1-benzyl-2-phenyl-5-chloro benzimiazole (II), or 1-benzyl-2-phenyl-6-chloro benzimiazole (III). With a view to establishing the structure of this compound, syntheses of the two benzimiazoles (II) and (III) have been undertaken adopting a scheme similar to that made use of in the syntheses of the corresponding methyl benzimiazoles.\(^4\)
Starting from 4-chloro-2-nitro aniline (IV), the synthesis of 1-benzyl-2-phenyl-5-chloro benzimiazole (II) has been achieved as in the methyl series, through the intermediates, N-benzyl-4-chloro-2-nitro aniline (V), and N-benzyl-4-chloro-o-phenylenediamine (VI). Similarly, the 6-chloro isomer (III) has been synthesised from 5-chloro-2-nitro aniline (VII) through the corresponding benzyl derivative and diamine.

The 1:2-disubstituted benzimiazole obtained from benzaldehyde condensation has been found to be identical with 1-benzyl-2-phenyl-5-chloro-benzimiazole (II). It may be expected that in all the 1:2-disubstituted benzimiazoles formed from 4-chloro-o-phenylenediamine and aromatic aldehydes, the chloro group will be in position 5.

**Experimental**

All m.p.’s are uncorrected. The micro-analyses were carried out by one of the authors (C. V. R.). The experimental procedures are dealt with in a very brief manner, since the various details are exactly similar to those given for methyl series.

I. Condensation of 4-chloro-o-phenylenediamine with benzaldehyde

Condensation of 4-chloro-o-phenylenediamine (3.6 g.) with benzaldehyde (5.3 g.) in glacial acetic acid at room temperature for a period of one hour yielded 2:3:4-triphenyl-7-(or 8)-chloro benzodiazepine (0.65 g.), 1:2-disubstituted benzimiazole (6.5 g.), and 2-phenyl-5-(or 6)-chloro benzimiazole (0.7 g.). The diazepine derivative crystallised from alcohol in rectangular rods, m.p. 125° (Found: C, 79.2; H, 5.3; N, 7.4; C_{27}H_{19}N_{5}Cl requires C, 79.7; H, 4.7; N, 6.9%). The crude disubstituted benzimiazole was washed with hot dilute alcohol (1:1) and recrystallised from petroleum ether and alcohol to yield prismatic rods, m.p. 171° (Found C, 74.8; H, 5.1; N, 8.5; C_{26}H_{18}N_{5}Cl requires C, 75.3; H, 4.7; N, 8.8%) (cf. Fischer and Limmer, white needles from alcohol, volatilising at about 225°). 2-Phenyl-5-(or 6)-chloro benzimiazole came out as plates from alcohol, m.p. 210°, and was found to be identical with the product reported in literature.5-7
II. Synthesis of 1-benzyl-2-phenyl-5-chloro benzimidazole

(a) N-Benzyl-4-chloro-2-nitro aniline.—4-Chloro-2-nitro aniline (5.7 g.), prepared by the method of Crepaz, was benzylated with benzyl chloride (4 ml.), fused sodium acetate (3.0 g.), and iodine (0.07 g.) at 120° for twelve hours. The unreacted amine was separated by trituration with concentrated hydrochloric acid and the crude benzyl derivative (5.0 g.) thus obtained crystallised from petroleum ether in orange-red rhombic plates, m.p. 79° (Found: C, 59.9; H, 4.3; N, 11.2; C_{13}H_{11}N_{2}O_{2}Cl requires C, 59.4; H, 4.2; N, 10.7%). Feitelson, and co-workers reported the melting point of the compound as 68°.

(b) N\textsuperscript{1}-Benzyl-4-chloro-o-phenylenediamine.—N-Benzyl-4-chloro-2-nitro aniline (1.0 g.), on reduction with zinc and hydrochloric acid in alcoholic medium at 40–50°, yielded crude N\textsuperscript{1}-benzyl-4-chloro-o-phenylenediamine (0.8 g.) turning brown in air. The base was characterised as its hydrochloride, tiny rectangular rods from ethyl acetate, m.p. 163° (Found: C, 57.6; H, 5.5; N, 10.8; C_{15}H_{13}N_{2}Cl.HCl requires C, 58.0; H, 5.2; N, 10.4%).

(c) 1-Benzyl-2-phenyl-5-chloro benzimidazole.—N\textsuperscript{1}-Benzyl-4-chloro-o-phenylenediamine (0.47 g.) and benzaldehyde (0.21 g.) were condensed together in alcoholic medium containing nitrobenzene (5 ml.), and the crude benzimidazole (0.5 g.) was purified by repeated crystallisations from dilute alcohol, petroleum ether and finally from alcohol. The pure 1-benzyl-2-phenyl-5-chloro benzimidazole was obtained as prismatic rods from alcohol, m.p. 172° (Found: C, 75.0; H, 4.9; N, 8.7; C_{20}H_{18}N_{2}Cl requires C, 75.3; H, 4.7; N, 8.8%). The melting point was undepressed by the 1:2-disubstituted benzimidazole from the condensation of 4-chloro-o-phenylenediamine with benzaldehyde.

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

(a) N-Benzyl-5-chloro-2-nitro aniline.—5-Chloro-2-nitro aniline (5.7 g.), obtained by the hydrolysis of 5-chloro-2-nitro acetanilide\textsuperscript{10} using dilute hydrochloric acid (4:1), when benzylated following the procedure used in II (a), gave the crude benzyl derivative (5.0 g.). It crystallised from petroleum ether in bright yellow needles, m.p. 101 (Feitelson and co-workers; m.p. 100–101°).

(b) N\textsuperscript{2}-Benzyl-4-chloro-o-phenylenediamine.—Reduction of N-benzyl-5-chloro-2-nitro aniline (1.0 g.) as in II (b) resulted in N\textsuperscript{2}-benzyl-4-chloro-o-phenylenediamine (0.7 g.), a viscous pale brown oil. Its hydrochloride was
obtained as almost colourless leaflets from ethyl acetate, m.p. 175° (decomp.) (Found: C, 57.5; H, 5.7; N, 10.7; C\textsubscript{18}H\textsubscript{13}N\textsubscript{2}Cl\cdot HCl requires C, 58.0; H, 5.2; N, 10.4%).

(c) 1-Benzyl-2-phenyl-6-chloro benzimidazole.—Condensation of N\textsuperscript{2}-benzyl-4-chloro-o-phenylenediamine (0.47 g.) with benzaldehyde (0.21 g.) as in II (c) yielded the crude benzimidazole (0.4 g.), which on purification came out as bushy needles from alcohol, m.p. 160° (Found: C, 74.7; H, 5.1; N, 9.1; C\textsubscript{20}H\textsubscript{18}N\textsubscript{2}Cl requires C, 75.3; H, 4.7; N, 8.8%). The melting point was depressed by the 1:2-disubstituted benzimidazole obtained in I.

**SUMMARY**

5-Chloro and 6-chloro, 1-benzyl-2-phenyl-benzimidazoles have been synthesised starting from 4-chloro-2-nitro aniline and 5-chloro-2-nitro aniline respectively. The 1:2-disubstituted benzimidazole obtained by the condensation of 4-chloro-o-phenylenediamine with benzaldehyde has been found to be identical with the 5-chloro isomer.

**REFERENCES**

1. Fischer and Limmer  \[ J. Prakt. Chem., 1906, 74 (2), 58. \]
3. \[ Ibid., 1957, 45, 253. \]
4. \[ Ibid., 1956, 44, 331. \]
5. Fischer and Limmer  \[ J. Prakt. Chem., 1906, 74 (2), 67. \]