

STUDIES IN THE FORMATION OF HETEROCYCLIC RINGS CONTAINING NITROGEN

Part III. Condensation of 4-Methyl-*o*-Phenylenediamine with Aromatic Aldehydes

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THE reaction between 4-methyl-*o*-phenylenediamine and aromatic aldehydes was studied for the first time by Ladenburg¹ making use of benzaldehyde, anisaldehyde, and salicylaldehyde under different sets of conditions. The compound obtained from benzaldehyde was proved by Hinsberg² to be 1:2-disubstituted benziminazole, and that from anisaldehyde to possess analogous structure. However, Ladenburg (*loc. cit.*) could not prepare a similar compound when salicylaldehyde was used. He described in this case, the formation of two different compounds, one from one mole of the amine and three moles of aldehyde, and the other from two moles of amine and three moles of aldehyde, but could not assign definite structures to them. Hinsberg³ through an extensive study of the reaction making use of aliphatic aldehydes reported the formation of 1:2-disubstituted benziminazoles from one mole of the amine and two moles of aldehyde occasionally accompanied by 2-mono-substituted benziminazoles. However, these workers left the position of the methyl group in the 1:2-disubstituted benziminazoles (5- or 6- position) uncertain. In a recent communication,⁴ the present authors provided evidence to show that in these benziminazoles the methyl group occupied position 6 and not 5.

The condensation between 4-methyl-*o*-phenylenediamine and seventeen aromatic aldehydes has been studied making use of the modified Hinsberg's procedure,⁵ and the results obtained are summarised in Table I. In a large measure, these results are in close agreement with those from simple *o*-phenylenediamine⁵ and support the step-wise mechanism proposed earlier. In that communication it was shown that nucleophilic substituents in the aldehydes facilitate the exclusive formation of 1:2-disubstituted benziminazoles, while electrophilic groups favour the formation of monosubstituted compounds. The results presented in this paper further corroborate this view. Benzodiazepine derivatives could be isolated in condensations with benzaldehyde and *m*-nitrobenzaldehyde, and also with anisaldehyde. Monosub-

stituted benzimidazoles could not, however, be obtained in the condensations with anisaldehyde, piperonal, and *p*-nitrobenzaldehyde. 5-Nitrosalicylaldehyde afforded a stable dianil under normal experimental conditions, and the corresponding benzimidazole could be obtained only after refluxing it for twelve hours in acetic acid.

TABLE I

No.	Aldehyde condensed	Percentage yield of		
		1:2-Disubstituted benzimidazole	2-Substituted benzimidazole	Benzo-diazepine derivative
1.	benzaldehyde	75*	18*	4*
2.	salicylaldehyde	95
3.	<i>m</i> -hydroxybenzaldehyde	95
4.	<i>p</i> -hydroxybenzaldehyde	82
5.	vanillin	70
6.	anisaldehyde	70*	..	4
7.	piperonal	95
8.	<i>o</i> -chlorobenzaldehyde	70	25*	..
9.	<i>p</i> -chlorobenzaldehyde	70	20	..
10.	2:4-dichlorobenzaldehyde	40	..
11.	3:4-dichlorobenzaldehyde	55	20	..
12.	<i>o</i> -nitrobenzaldehyde	50	38	..
13.	<i>m</i> -nitrobenzaldehyde	65	19	10
14.	<i>p</i> -nitrobenzaldehyde	82
15.	5-nitrosalicylaldehyde†
16.	<i>p</i> -dimethylaminobenzaldehyde	83
17.	1-naphthaldehyde	80	8	..

* Compounds already known in literature; † dianil was isolated in 95% yield.

EXPERIMENTAL

All m.p.'s are uncorrected. The microanalyses were carried out by one of the authors (C. V. R.). The percentage of nitrogen alone is recorded here since it is significant for deciding between the possible structures and not those of carbon and hydrogen.

General procedure for the condensation of 4-methyl-o-phenylenediamine with aromatic aldehydes

4-Methyl-*o*-phenylenediamine (one mole) and aromatic aldehyde (two moles) were dissolved separately in slight excess of glacial acetic acid, and mixed together in a conical flask, when evolution of heat was noticed. The

reaction was allowed to proceed at room temperature for one hour with occasional stirring. If any crystalline solid separated by this time, it was found to be generally a benzodiazepine derivative. This was separated by filtration, and the filtrate added to excess of crushed ice with vigorous stirring. The product obtained, if any, at this stage was found to be the 1:2-disubstituted benziminazole. The filtrate from this compound gave another substance on making it ammoniacal, which was either di- or mono-substituted benziminazole.

The condensation of 4-methyl-*o*-phenylenediamine with benzaldehyde has already been reported in our previous communication.⁴

1. 1-(*o*-Hydroxybenzyl)-2-(*o*-hydroxyphenyl)-6-methyl benziminazole.—4-Methyl-*o*-phenylenediamine was condensed with salicylaldehyde, and the acid solution was added to excess of crushed ice. The compound that separated was crystallised from alcohol, rectangular rods, m.p. 187° (Found: N, 8.2; C₂₁H₁₈N₂O₂ requires N, 8.5%). The acid filtrate, on making ammoniacal, yielded a small amount of the same substance.

2. 1-(*m*-Hydroxybenzyl)-2-(*m*-hydroxyphenyl)-6-methyl benziminazole.—The diamine was condensed with *m*-hydroxybenzaldehyde, and as no substance separated by the addition of the acid solution to crushed ice, the solution was made ammoniacal. The product obtained was the disubstituted benziminazole, which came out from alcohol in cubes, m.p. 245° (Found: N, 8.9; C₂₁H₁₈N₂O₂ requires N, 8.5%).

3. 1-(*p*-Hydroxybenzyl)-2-(*p*-hydroxyphenyl)-6-methyl benziminazole.—The diamine was condensed with *p*-hydroxybenzaldehyde, and the disubstituted benziminazole could be isolated from the ammoniacal solution as in 2 above. The product crystallised in needles from benzene, m.p. 185° (Found: N, 8.2; C₂₁H₁₈N₂O₂ requires N, 8.5%).

4. 1-(*m*-Methoxy-*p*-hydroxybenzyl)-2-(*m*-methoxy-*p*-hydroxyphenyl)-6-methylbenziminazole.—The diamine was condensed with vanillin, and the disubstituted benziminazole could be isolated by making the dilute acid solution ammoniacal, just as in 2 and 3. It was purified by crystallisation from ethyl acetate, thin rectangular plates, m.p. 217° (Found: N, 7.6; C₂₃H₂₂N₂O₄ requires N, 7.2%).

5. 2:3:4-Tri-(*p*-methoxyphenyl)-7-(or 8)-methyl benzodiazepine.—The diamine was condensed with anisaldehyde, and the solid that separated from glacial acetic acid solution was filtered. It crystallised from alcohol in prismatic rods, m.p. 136° (Found: N, 5.9; C₃₁H₂₈N₂O₃ requires N, 5.9%).

6. 1-(*p*-Methoxybenzyl)-2-(*p*-methoxyphenyl)-6-methyl benziminazole.—The filtrate obtained after the separation of the diazepine derivative in the above condensation, was added to excess of crushed ice. The compound that separated was crystallised from alcohol, rectangular rods, m.p. 152°, and was found to be identical with that reported by Ladenburg.¹

7. 1-(3:4-Methylenedioxybenzyl)-2-(3:4-methylenedioxyphenyl)-6-methyl-benziminazole.—The diamine was condensed with piperonal, and the acid solution was added to excess of crushed ice. The compound that separated was crystallised from petroleum ether (b.p. 60–80°), prismatic rods, m.p. 155° (Found: N, 7.4; C₂₃H₁₈N₂O₄ requires N, 7.3%). The filtrate, on making ammoniacal, gave a small amount of the same compound.

8. 1-(*o*-Chlorobenzyl)-2-(*o*-chlorophenyl)-6-methyl benziminazole.—The diamine was condensed with *o*-chlorobenzaldehyde, and the acid solution was added to excess of crushed ice. The compound that separated was crystallised from petroleum ether, bundles of prismatic rods, m.p. 144°, (Found: N, 7.9; C₂₁H₁₆N₂Cl₂ requires N, 7.6%).

9. 2-(*o*-Chlorophenyl)-5-(or 6)-methyl benziminazole.—The filtrate obtained after the separation of the disubstituted benziminazole from the above condensation was made ammoniacal when the monosubstituted benziminazole separated. It crystallised from ethyl acetate in plates, m.p. 160°, and was identical with the one reported by Fischer.⁶

10. 1-(*p*-Chlorobenzyl)-2-(*p*-chlorophenyl)-6-methyl benziminazole.—4-Methyl-*o*-phenylenediamine was condensed with *p*-chlorobenzaldehyde, and the acid solution was added to crushed ice. The compound that separated was crystallised from alcohol, rectangular rods, m.p. 166° (Found; N, 7.6; C₂₁H₁₆N₂Cl₂ requires N, 7.6%).

11. 2-(*p*-Chlorophenyl)-5-(or 6)-methyl benziminazole.—The filtrate obtained after the separation of the disubstituted benziminazole from the above condensation, was made ammoniacal, when the monosubstituted compound was obtained. It could be purified by recrystallisation from alcohol, rectangular plates, m.p. 221° (Found: N, 11.9; C₁₄H₁₁N₂Cl requires N, 11.5%).

12. 2-(2:4-Dichlorophenyl)-5-(or 6)-methyl benziminazole.—The diamine was condensed with 2:4-dichlorobenzaldehyde, and the acid solution was added to excess of crushed ice. A low-melting solid was found to separate out, which on treatment with a small quantity of benzene or ethyl acetate, yielded a granular substance. The granular solid, on purification, gave the pure benziminazole needles from alcohol, m.p. 165° (Found: N, 10.5%;

$C_{14}H_{10}N_2Cl_2$ requires N, 10.1%). A small amount of the same compound was isolated by making the acid filtrate ammoniacal.

13. 1-(3:4-Dichlorobenzyl)-2-(3:4-dichlorophenyl)-6-methyl benzimidazole.—The diamine was condensed with 3:4-dichlorobenzaldehyde and the acetic acid solution was added to crushed ice, when a sticky mass, which appeared to be a mixture, separated. The mass was treated with a little methanol, when a granular solid separated out. The granular solid, on recrystallisation from alcohol, yielded the pure disubstituted benzimidazole, bushy needles, m.p. 144° (Found: N, 6.3; $C_{21}H_{14}N_2Cl_4$ requires N, 6.4%).

14. 2-(3:4-Dichlorophenyl)-5-(or 6)-methyl benzimidazole.—The methanolic filtrate obtained after the separation of the disubstituted benzimidazole given above, on concentration, gave a resinous mass. It was repeatedly crystallised from alcohol and finally from ethyl acetate to yield the pure monosubstituted compound, rectangular rods, m.p. > 300° (Found: N, 10.2; $C_{14}H_{10}N_2Cl_2$ requires N, 10.1%).

15. 1-(*o*-Nitrobenzyl)-2-(*o*-nitrophenyl)-6-methyl benzimidazole.—4-Methyl-*o*-phenylenediamine was condensed with *o*-nitrobenzaldehyde, and the acid solution was added to excess of crushed ice. A resinous mass separated out, which on repeated crystallisation from alcohol, gave the pure benzimidazole, yellow microcrystalline solid, m.p. 135° (Found: N, 14.5; $C_{21}H_{16}N_4O_4$ requires N, 14.4%).

16. 2-(*o*-Nitrophenyl)-5-(or 6)-methyl benzimidazole.—The acid filtrate from above was made ammoniacal when the monosubstituted benzimidazole separated out. It was crystallised from alcohol, yellow rectangular plates, m.p. 214° (Found: N, 16.6; $C_{14}H_{11}N_3O_2$ requires N, 16.6%).

17. 2:3:4-Tri-(*m*-nitrophenyl)-7-(or 8)-methyl benzodiazepine.—The diamine was condensed with *m*-nitrobenzaldehyde, and the compound that separated from glacial acetic acid solution was filtered. It was crystallised from benzene, orange-red plates, m.p. 170° (Found: N, 13.5; $C_{28}H_{19}N_5O_6$ requires N, 13.4%).

18. 1-(*m*-Nitrobenzyl)-2-(*m*-nitrophenyl)-6-methyl benzimidazole.—The acid filtrate obtained after the separation of the diazepine derivative from the above condensation, was added to excess of crushed ice. The compound that separated was crystallised from alcohol, tiny yellow rods, m.p. 157° (Found: N, 14.5; $C_{21}H_{16}N_4O_4$ requires N, 14.4%).

19. 2-(*m*-Nitrophenyl)-5-(or 6)-methyl benzimidazole.—The dilute acid filtrate obtained after the separation of the disubstituted benzimidazole in *m*-nitrobenzaldehyde condensation, was made ammoniacal, when an yellow

solid was obtained. It crystallised from alcohol in yellow clusters of needles m.p. 195° (Found: N, 16.3; $C_{14}H_{11}N_3O_2$ requires N, 16.6%).

20. 1-(*p*-Nitrobenzyl)-2-(*p*-nitrophenyl)-6-methyl benziminazole.—The diamine was condensed with *p*-nitrobenzaldehyde, and the acid solution was added to crushed ice, when a yellow substance separated. It was crystallised from alcohol, yellow needles, m.p. 193° (Found: N, 14.7; $C_{21}H_{16}N_4O_4$ requires N, 14.4%).

21. Bis-(5-nitrosalicylidene)-tolylene-3:4-diamine.—A solution of 5-nitrosalicylaldehyde in glacial acetic acid was added to a similar solution of 4-methyl-*o*-phenylenediamine, when an orange-yellow solid immediately separated. It was sparingly soluble in the common organic solvents, and could be crystallised from hot nitrobenzene in orange needles, m.p. 215° (Found: N, 13.4; $C_{21}H_{16}N_4O_6$ requires N, 13.3%).

22. 1-(2-Hydroxy-5-nitrobenzyl)-2-(2-hydroxy-5-nitrophenyl)-6-methyl benziminazole.—The above dianil was refluxed in glacial acetic acid for a period of twelve hours. The solution was diluted, filtered, and the filtrate was made ammoniacal. A yellow compound that separated, on crystallisation from benzene, yielded the pure benziminazole, yellow microcrystalline solid, m.p. 286° (decomp.) (Found: N, 13.3; $C_{21}H_{16}N_4O_6$ requires N, 13.3%).

23. 1-(*p*-Dimethylaminobenzyl)-2-(*p*-dimethylaminophenyl)-6-methyl benziminazole.—The diamine was condensed with *p*-dimethylaminobenzaldehyde at 100° for one hour, since the reaction did not proceed at room temperature. The acid solution, on addition to crushed ice, did not give any precipitate, and therefore it was made ammoniacal. The compound that separated was crystallised from benzene, prismatic rods, m.p. 248° (Found: N, 15.1; $C_{25}H_{28}N_4$ requires N, 14.6%).

24. 1-(1-Naphthyl methyl)-2-(1-naphthyl)-6-methyl benziminazole.—4-Methyl-*o*-phenylenediamine was condensed with 1-naphthaldehyde by the general method, and the acetic acid solution was added to excess of crushed ice. The compound that separated was crystallised from benzene-petroleum ether, prismatic rods, m.p. 172°, (Found: N, 6.7; $C_{29}H_{22}N_2$ requires N, 7.0%).

25. 2-(1-Naphthyl)-5-(or 6)-methyl benziminazole.—The filtrate obtained after the separation of the disubstituted benziminazole from the above condensation was made ammoniacal, and the compound that separated was recrystallised from alcohol, prismatic rods, m.p. 233° (Found: N, 10.6; $C_{18}H_{14}N_2$ requires N, 10.9%).

SUMMARY

The reaction between 4-methyl-*o*-phenylene diamine and seventeen aromatic aldehydes has been investigated, and twenty-three new compounds obtained have been characterised. The results are in close agreement with those from *o*-phenylenediamine and aromatic aldehydes, and corroborate the inferences drawn regarding the influence of substituents in the aldehydes on the mode of the reaction and cyclisation.

REFERENCES

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