

STUDIES IN THE FORMATION OF HETEROCYCLIC RINGS CONTAINING NITROGEN

Part VI. Condensation of 4-Chloro-*o*-Phenylenediamine with Aromatic Aldehydes

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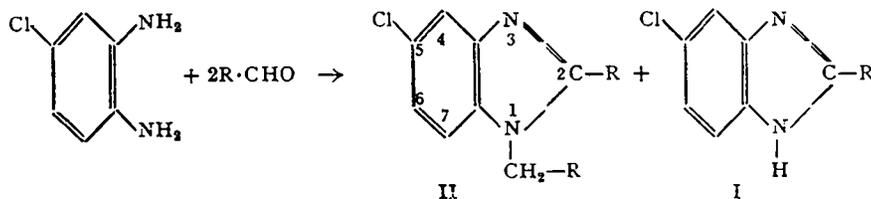
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THE condensation of 4-chloro-*o*-phenylenediamine with benzaldehyde and *p*-nitrobenzaldehyde under different conditions was studied by Fischer and Limmer¹ who reported the formation of dianils, which could be converted into the corresponding 1:2-disubstituted benzimidazoles. The position of the chloro group (5 or 6) in the benzimidazoles was not ascertained by these workers. In a recent publication,² the present authors established by unambiguous synthetic methods that the chloro group occupied position 5.

A systematic study of the condensation between 4-chloro-*o*-phenylenediamine and two moles of seventeen aromatic aldehydes (other than benzaldehyde²) containing alkyl, hydroxy, alkoxy, halo, nitro and amino substituents has been made in the present investigation with a view to finding out the influence of substituents in the aldehydes as well as of the chloro group of the diamine on the nature and relative yields of the reaction products. The condensations have been carried out following the modified Hinsberg's procedure,³ and the results obtained are summarised in Table I.

The reaction has been found to yield mono (I) and di (II) substituted benzimidazoles as in the other condensations.^{3,4} On account of the presence of low-melting resinous materials formed in the condensations, much difficulty has been encountered in processing the reaction products.



It was shown previously in the case of condensations with *o*-phenylenediamine³ and 4-methyl-*o*-phenylenediamine,⁴ that mono and di anils are possible intermediates in the formation of mono and disubstituted benzimidazoles. It was also shown that electron-releasing groups like hydroxy

TABLE I

Products of condensation of 4-chloro-o-phenylenediamine with R.CHO

No.	R-			% yield of (II)	% yield of (I)
1.	<i>p</i> -tolyl	2
2.	<i>o</i> -hydroxyphenyl	66	25
3.	<i>m</i> -hydroxyphenyl	95	..
4.	<i>p</i> -hydroxyphenyl	95	..
5.	<i>m</i> -methoxy- <i>p</i> -hydroxyphenyl	95	..
6.	3:4-methylenedioxyphenyl ¹	73	13
7.	<i>p</i> -methoxyphenyl	78	15
8.	<i>o</i> -chlorophenyl	45
9.	<i>p</i> -chlorophenyl	30	4
10.	2:4-dichlorophenyl	42
11.	<i>p</i> -bromophenyl	31	..
12.	<i>o</i> -nitrophenyl	50
13.	<i>m</i> -nitrophenyl	87	..
14.	<i>p</i> -nitrophenyl	68*	13
15.	2-hydroxy-5-nitrophenyl [†]
16.	<i>p</i> -dimethylaminophenyl	87	..
17.	1-naphthyl	88	..

* Compound reported in literature. † Dianil isolated in 95% yield.

and amino present in the aldehydes facilitate the exclusive formation of disubstituted benzimidazoles, while electron-withdrawing groups like halo and nitro favour the formation of considerable amounts of mono derivatives. The results presented in this paper further corroborate these views. The isolation of a stable dianil in the reaction with 5-nitrosalicylaldehyde which could be converted to the corresponding benzimidazole by refluxing

in acetic acid, lends support to the intermediary nature of dianils in the formation of disubstituted benziminazoles.

The influence of substituents in the aldehydes on the course of the reaction seems to be affected to a certain extent by the chloro group of the diamine. The condensation of the diamine with salicylaldehyde yielded, in addition to the 1:2-disubstituted benziminazole, a considerable amount of the mono derivative. *o*-Chloro- and *o*-nitro- benzaldehydes afforded exclusively monosubstituted benziminazoles in their reaction with this diamine whereas with other diamines^{3, 4} these aldehydes gave appreciable amounts of disubstituted benziminazoles also. These results indicate that the chloro group present in the diamine favours the formation of mono-substituted benziminazoles. *p*-Tolualdehyde gave a very small amount of the mono derivative and large amounts of high-melting products. Such high-melting and indefinite products have also been met with in the reactions of the diamine with halo and alkoxy aldehydes, on account of which the yields of benziminazoles have been rather low.

EXPERIMENTAL

All m.p.'s are uncorrected. The micro-analyses were carried out by one of the authors (C. V. R.). Unless otherwise mentioned, ethyl alcohol is the solvent used for recrystallisation.

General procedure for the condensations.—4-Chloro-*o*-phenylenediamine (one mole) and aromatic aldehyde (two moles) were dissolved separately in a 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 for one hour with occasional stirring. If any crystalline solid separated by this time, it was filtered and the clear filtrate was added to excess of crushed ice with vigorous stirring. The compound that separated was filtered, and the filtrate was made ammoniacal, when a small amount of another compound was obtained. The compounds thus isolated were purified and characterised.

2-(*p*-Methylphenyl)-5-(or 6)-chloro benziminazole was obtained by condensation with *p*-tolualdehyde, from the ammoniacal solution. It crystallised in prismatic rods, m.p. 228° (Found: C, 68.8; H, 5.0; N, 12.1; C₁₄H₁₁N₂Cl requires C, 69.3; H, 4.5; N, 11.5%).

1-(*o*-Hydroxybenzyl)-2-(*o*-hydroxyphenyl)-5-chloro benziminazole was obtained from the dilute acid solution of the salicylaldehyde condensation. The compound came out as needles from alcohol-acetone, m.p. 187° (Found:

C, 68.1; H, 4.8; N, 8.0; $C_{20}H_{15}N_2O_2Cl$ requires C, 68.5; H, 4.3; N, 8.0%).

2-(*o*-Hydroxyphenyl)-5-(or 6)-chloro benzimidazole was isolated from the ammoniacal solution of the above condensation. On purification, it came out as tiny rods, m.p. 273° (Found: C, 63.5; H, 3.9; N, 11.8; $C_{13}H_9N_2OCl$ requires C, 63.8; H, 3.7; N, 11.5%).

1-(*m*-Hydroxybenzyl)-2-(*m*-hydroxyphenyl)-5-chloro benzimidazole was obtained by condensation with *m*-hydroxybenzaldehyde mostly from the dilute acid solution and in small quantity from the ammoniacal solution. The product on recrystallisation gave tiny rectangular rods, m.p. 247° (Found: C, 68.0; H, 4.7; N, 8.4; $C_{20}H_{15}N_2O_2Cl$ requires C, 68.5; H, 4.3; N, 8.0%).

1-(*p*-Hydroxybenzyl)-2-(*p*-hydroxyphenyl)-5-chloro benzimidazole was isolated from *p*-hydroxybenzaldehyde condensation, as in the above case. It crystallised in rectangular rods, m.p. 230° (Found: C, 68.3; H, 4.0; N, 8.0; $C_{20}H_{15}N_2O_2Cl$ requires C, 68.5; H, 4.3; N, 8.0%).

1-(*m*-Methoxy-*p*-hydroxybenzyl)-2-(*m*-methoxy-*p*-hydroxyphenyl)-5-chloro-benzimidazole was prepared by condensation with vanillin and isolated as in the above two condensations. It was obtained as needles, m.p. 213° (Found: C, 64.0; H, 5.2; N, 7.0; $C_{22}H_{19}N_2O_4Cl$ requires C, 64.3; H, 4.6; N, 6.8%).

1-(3:4-Methylenedioxybenzyl)-2-(3:4-methylenedioxyphenyl)-5-chloro benzimidazole.—In the condensation with piperonal, a sticky solid separated from the dilute acid solution, which on crushing with a little methanol, yielded a granular solid. The solid crystallised in rectangular rods, m.p. 171° (Found: C, 65.6; H, 4.2; N, 7.0; $C_{22}H_{15}N_2O_4Cl$ requires C, 65.0; H, 3.7; N, 6.9%).

2-(3:4-Methylenedioxyphenyl)-5-(or 6)-chloro benzimidazole was isolated from the ammoniacal solution of the above condensation and was obtained as leaflets, m.p. 205° (Found: C, 61.5; H, 3.8; N, 9.8; $C_{14}H_9N_2O_2Cl$ requires C, 61.7; H, 3.3; N, 10.3%).

1-(*p*-Methoxybenzyl)-2-(*p*-methoxyphenyl)-5-chloro benzimidazole separated from the dilute acid solution of anisaldehyde condensation and was purified by recrystallisation, first from alcohol and then from petroleum ether, prismatic rods, m.p. 125° (Found: C, 69.2; H, 5.2; N, 8.0; $C_{22}H_{19}N_2O_2Cl$ requires C, 69.7; H, 5.0; N, 7.4%).

2-(*p*-Methoxyphenyl)-5-(or 6)-chloro benziminazole was obtained from the ammoniacal solution of the above condensation and on purification gave plates, m.p. 180° (Found: C, 64.7; H, 4.6; N, 10.9; $C_{14}H_{11}N_2OCl$ requires C, 65.0; H, 4.3; N, 10.8%).

2-(*o*-Chlorophenyl)-5-(or 6)-chloro benziminazole.—A sticky mass was obtained from the dilute acid solution of the condensation with *o*-chloro benzaldehyde, which on crushing with petroleum ether gave a granular solid. The solid crystallised in rectangular rods, m.p. 125° (Found: C, 59.0; H, 3.5; N, 10.6; $C_{13}H_8N_2Cl_2$ requires C, 59.3; H, 3.0; N, 10.6%).

1-(*p*-chlorobenzyl)-2-(*p*-chlorophenyl)-5-chloro benziminazole was obtained from the dilute acid solution of *p*-chlorobenzaldehyde condensation. The crude compound was purified by recrystallisation from alcohol and then from petroleum ether yielding needles, m.p. 150° (Found: C, 62.3; H, 3.7; N, 7.5; $C_{20}H_{13}N_2Cl_3$ requires C, 61.9; H, 3.4; N, 7.2%).

2-(*p*-chlorophenyl)-5-(or 6)-chloro benziminazole was isolated from the ammoniacal solution of the above condensation and on recrystallisation gave clusters of prismatic rods, m.p. 225° (Found: C, 58.8; H, 3.4; N, 10.5; $C_{13}H_8N_2Cl_2$ requires C, 59.3; H, 3.0; N, 10.6%).

2-(2:4-Dichlorophenyl)-5-(or 6)-chloro benziminazole separated from the glacial acetic acid solution in the condensation with 2:4-dichlorobenzaldehyde. The compound crystallised in tiny needles, m.p. 184° (Found: C, 52.1; H, 2.8; N, 9.5; $C_{13}H_7N_2Cl_3$ requires C, 52.4; H, 2.4; N, 9.4%).

1-(*p*-Bromobenzyl)-2-(*p*-bromophenyl)-5-chloro benziminazole.—In the *p*-bromobenzaldehyde condensation, a solid changing to a black resin separated out from the dilute acid solution. It was repeatedly crystallised from alcohol, and finally from petroleum ether yielding the pure benziminazole, prismatic rods, m.p. 155° (Found: C, 50.7; H, 3.2; N, 6.4; $C_{20}H_{13}N_2ClBr_2$ requires C, 50.4; H, 2.7; N, 5.9%).

2-(*o*-Nitrophenyl)-5-(or 6)-chloro benziminazole was obtained by the condensation with *o*-nitrobenzaldehyde, from the dilute acid solution. The compound was washed with a little benzene and recrystallised, shining yellow plates, m.p. 187° (Found: C, 56.5; H, 3.5; N, 15.5; $C_{13}H_8N_3O_2Cl$ requires C, 57.0; H, 2.9; N, 15.4%).

1-(*m*-Nitrobenzyl)-2-(*m*-nitrophenyl)-5-chloro benziminazole was isolated from the dilute acid solution in *m*-nitrobenzaldehyde condensation. It crystallised from benzene containing a small quantity of alcohol in

pale yellow needles, m.p. 193° (Found: C, 59.0; H, 3.5; N, 13.4; $C_{20}H_{13}N_4O_4Cl$ requires C, 58.8; H, 3.2; N, 13.7%).

2-(*p*-Nitrophenyl)-5-(or 6)-chloro benziminazole separated from the glacial acetic acid solution in the condensation with *p*-nitrobenzaldehyde. On purification, the compound came out as clusters of yellow needles, m.p. 257° (Found: C, 57.5; H, 3.3; N, 15.6; $C_{13}H_8N_3O_2Cl$ requires C, 57.0; H, 2.9; N, 15.4%).

1-(*p*-Nitrobenzyl)-2-(*p*-nitrophenyl)-5-chloro benziminazole was isolated from the dilute acid solution of the above condensation and on crystallisation yielded yellow prismatic rods, m.p. 227° (Fischer and Limmer¹ report m.p. 235°) (Found: C, 59.2; H, 3.7; N, 14.1; $C_{20}H_{13}N_4O_4Cl$ requires C, 58.8; H, 3.2; N, 13.7%).

N: *N'*-Di-(2-hydroxy-5-nitrobenzylidene)-4-chloro-*o*-phenylenediamine separated out from the glacial acetic acid solution in 5-nitrosalicylaldehyde condensation and crystallised from nitrobenzene in orange yellow needles, m.p. 260° (decomp.) (Found: C, 55.0; H, 3.2; N, 12.5; $C_{20}H_{13}N_4O_6Cl$ requires C, 54.5; H, 3.0; N, 12.7%).

1-(2-Hydroxy-5-nitrobenzyl)-2-(2-hydroxy-5-nitrophenyl)-5-chloro benziminazole, prepared by refluxing the above dianil in excess of acetic acid for twelve hours, crystallised from benzene in shining yellow prismatic rods, m.p. 314° (decomp.) (Found: C, 55.0; H, 3.5; N, 13.2; $C_{20}H_{13}N_4O_6Cl$ requires C, 54.5; H, 3.0; N, 12.7%).

1-(*p*-Dimethylaminobenzyl)-2-(*p*-dimethylaminophenyl)-5-chloro benziminazole.—The reaction between the diamine and *p*-dimethylaminobenzaldehyde was conducted at 100° as the reaction did not proceed satisfactorily at the laboratory temperature. The benziminazole was isolated partly from dilute acid solution and mostly from the ammoniacal solution. It crystallised from benzene-acetone in shining pale yellow prismatic rods, m.p. 239° (Found: C, 71.1; H, 5.8; N, 14.5; $C_{24}H_{25}N_4Cl$ requires C, 71.2; H, 6.2; N, 13.9%).

1-(1-Naphthyl methyl)-2-(1-naphthyl)-5-chloro benziminazole was obtained by the condensation with 1-naphthaldehyde, from the dilute acid solution. The compound was washed with a little acetone and recrystallised, rectangular rods, m.p. 199° (Found: C, 80.5; H, 5.0; N, 6.8; $C_{28}H_{19}N_2Cl$ requires C, 80.3; H, 4.5; N, 6.7%).

SUMMARY

The condensation of 4-chloro-*o*-phenylenediamine with two moles of seventeen aromatic aldehydes under acidic conditions has been found to yield mono and disubstituted benzimidazoles in varying proportions. The influence of substituents in the aldehydes on the mode of reaction and cyclisation has been found to be similar to that observed in the condensations with *o*-phenylenediamine.

REFERENCES

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