831. *The Scope of the Knoevenagel Synthesis of Aromatic Secondary Amines.*

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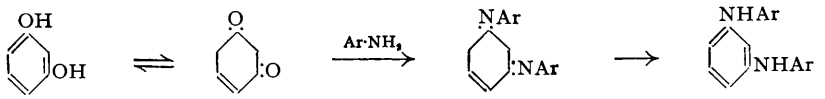
Knoevenagel's method for preparing aromatic secondary amines by iodine-catalysed condensation of hydroxy-compounds with aromatic amines has been extended, as regards the phenolic component, to several polyhydric benzene and naphthalene derivatives and to 6-bromo-2-naphthol, and, as regards the amino-component, to a series of substituted anilines and to 2-aminopyridine. Attempts to synthesise *N-cyclo*alkyl-β-naphthylamines resulted chiefly in di-β-naphthylamine, in contrast to statements in the literature.

The varied synthetical use in our Laboratory of aromatic secondary and tertiary amines warranted a broad investigation into methods for their preparation. Knoevenagel (*J. prakt. Chem.*, 1914, **89**, 1) found that α- and β-naphthol reacted readily with aniline and its homologues in the presence of small amounts of iodine, to yield α-aryl-α- and -β-naphthylamines. It has now been found that resorcinol and aniline or *p*-toluidine similarly give good yields of 1 : 3-dianilino- and 1 : 3-di-*p*-toluidino-benzene. *o*- and *p*-Diphenols were less reactive, as quinol and *p*-toluidine gave a mixture of much 5-hydroxy-4′-methyldiphenyl-

amine and a little 1 : 4-di-*p*-toluidinobenzene (the yield of the latter was raised slightly by prolonged heating), and catechol gave only small amounts of diamine. Quinol also gave predominantly a hydroxy-diphenylamine with, *e.g.*, *m*-toluidine, 2 : 4-dimethylaniline, and *p*-anisidine.

The present procedure for the preparation of hydroxydiarylamines and 1 : 3- and 1 : 4-diarylaminobenzenes is far more convenient than those which involve the use of dehydrating agents (Calm, *Ber.*, 1883, **16**, 2794, 2805; Philip and Calm, *Ber.*, 1884, **17**, 2431; Hatschek and Zega, *J. prakt. Chem.*, 1886, **33**, 209, 230; Philip, *ibid.*, 1886, **34**, 70) or mineral acids (Bradfield, Cooper, and Orton, *J.*, 1927, 2856). The difference in the reactivity of the three dihydric phenols suggests that the Knoevenagel amination process involves the formation of *N*-arylketimines with rearrangement to arylamines. For resorcinol the sequence of reaction would be :



From that viewpoint, phloroglucinol, a substance with pronounced ketonic properties, should be highly reactive; as thus expected, it gave, even on brief heating, the 1 : 3 : 5-trisarylaminobenzenes listed in Table 1.

Knoevenagel (*loc. cit.*) readily obtained 2 : 3- and 2 : 7-dianilinonaphthalene from aniline and 2 : 3- and 2 : 7-dihydroxynaphthalene respectively. This observation has now been extended to several other arylamines and to 1 : 6- and 2 : 6-dihydroxynaphthalene (for the new products see Table 2). Whereas both 1-chloro-2-naphthol and 2-chloro-1-naphthol were completely dehalogenated on condensation with aniline in the presence of iodine (Knoevenagel, *loc. cit.*), the bromine atom in 6-bromo-2-naphthol has now been found to resist the action of aniline and *p*-toluidine, 6-bromo-*N*-phenyl- and -*p*-tolyl-2-naphthylamine being readily obtained. An attempt to prepare *N-cyclo*hexyl-β-naphthylamine from β-naphthylamine and *cyclo*hexanol in the presence of iodine yielded only di-β-naphthylamine (by the action of iodine on β-naphthylamine alone; cf. Knoevenagel, *loc. cit.*, and Butterworth and Hey, *J.*, 1940, 388). Di-β-naphthylamine was also obtained as sole secondary amine when β-naphthylamine was heated with *cyclo*hexyl bromide, 3-methyl*cyclo*hexyl bromide, or *cyclo*heptyl bromide; Loevenich, Utsch, Moldrickx, and Schaefer (*Ber.*, 1929, **62**, 3097) held that in those reactions *N-cyclo*hexyl-, *N*-3-methyl-*cyclo*hexyl-, and *N-cyclo*heptyl-β-naphthylamine were formed, but from the melting points it seems that their products were di-β-naphthylamine in different degrees of purity.

The Knoevenagel synthesis of secondary amines could be extended to the heterocyclic group : 2-aminopyridine readily gave 2-α- and 2-β-naphthylaminopyridine (of interest as intermediates for the synthesis of antihistamines) which had hitherto been prepared less conveniently (Fischer, *Ber.*, 1902, **35**, 3674).

Experimental

Condensation of 2-Aminopyridine with Naphthols.—A mixture of β-naphthol (10 g.), redistilled 2-aminopyridine (10 g.), and iodine (0·2 g.) was refluxed for 24 hours; the mixture was taken up in benzene, and the benzene solution washed with aqueous sodium hydroxide, then with water, and dried (Na_2SO_4); removal of the solvent and vacuum-fractionation of the residue gave 2-β-naphthylaminopyridine (75%), b. p. *ca.* 245—250°/15 mm., prisms, m. p. 135° (from benzene–*cyclo*hexane) (lit., 133°). Similarly, α-naphthol gave 2-α-naphthylaminopyridine (60%), prisms, m. p. 116° (from benzene–*cyclo*hexane) (lit., 115°).

Attempted Synthesis of N-cyclo*Hexyl-β-naphthylamine.*—(*a*) A mixture of *cyclo*hexyl bromide (25 g.) and β-naphthylamine (40 g.) was refluxed for 2 hours; the product, which contained much *cyclo*hexene, was washed with dilute aqueous ammonia and taken up in benzene; vacuum-fractionation yielded di-β-naphthylamine (8 g.), leaflets (from ethanol), m. p. 172° alone or mixed with an authentic sample (Knoevenagel, *loc. cit.*). Similar results were recorded when *cyclo*hexyl bromide was replaced by 3-methyl*cyclo*hexyl or *cyclo*heptyl bromide, or simply 48% hydrobromic acid (10 c.c.). (*b*) *cyclo*Hexanol (20 g.), β-naphthylamine (40 g.), and iodine (0·2 g.) were heated for 10 hours at 230—240° (cf. Knoevenagel's preparation of *N-iso*amylaniline, *loc. cit.*); di-β-naphthylamine, m. p. 172°, was the only product isolated.

6-Bromo-N-phenyl-2-naphthylamine.—6-Bromo-2-naphthol (7 g.), aniline (20 g.), and iodine (0·1 g.) were gently refluxed for 20 hours with removal of the water formed. The mixture was treated with dilute hydrochloric acid, and the solid product washed with cold methanol and recrystallised from ethanol, to give the secondary amine as prisms (10 g.), m. p. 126° (Found : C, 64·2; H, 4·1. $C_{16}H_{12}NBr$ requires C, 64·4; H, 4·4%); the picrate formed, from ethanol, brown-violet needles, m. p. 125°.

6-Bromo-N-p-tolyl-2-naphthylamine crystallised from ethanol as leaflets, m. p. 157° (Found : C, 65·3; H, 4·6. $C_{17}H_{14}NBr$ requires C, 65·4; H, 4·5%), giving a brown-violet picrate.

Condensation of Resorcinol with Arylamines.—Resorcinol (25 g.), *p*-toluidine (60 g.), and iodine (1 g.) were refluxed for 3 days. Working up in the usual way gave 1 : 3-di-*p*-toluidinobenzene (20 g.), crystallising from ethanol as prisms, m. p. 139°; the same reaction with aniline gave 1 : 3-dianilinobenzene, m. p. 96°, in lower yield (15 g.).

Condensation of Quinol with the Toluidines.—(*a*) Quinol (10 g.), *p*-toluidine (25 g.), and iodine (0·5 g.) were refluxed for 3 days, and the mixture worked up in the usual way; vacuum-fractionation yielded 4-hydroxy-4′-methyldiphenylamine (9 g.), b. p. 238—240°/15 mm., prisms, m. p. 119° (from ligroin, b. p. 80—100°) (Hatschek and Zega, *loc. cit.*), and 1 : 4-di-*p*-toluidinobenzene (2·5 g.), m. p. 182° (from ethanol). (*b*) Similarly *m*-toluidine gave *4-hydroxy-3′-methyldiphenylamine* (11 g.), b. p. 232—234°/15 mm., needles, m. p. 61—62° (from ligroin) (Found : C, 78·2; H, 6·6. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·5%); the portion of b. p. >260°/15 mm. yielded, on crystallisation from ethanol, 1 : 3-*di*-m-*toluidinobenzene* (2 g.), leaflets, m. p. 112° (Found : C, 83·1; H, 7·2. $C_{20}H_{20}N_2$ requires C, 83·3; H, 6·9%).

Condensation of Quinol with 2 : 4-Dimethylaniline.—Quinol (10 g.), 2 : 4-dimethylaniline (25 g.), and iodine (0·25 g.) were refluxed for 48 hours, to yield *4-hydroxy-2′ : 4′-dimethyldiphenylamine* (10 g.), b. p. 235—238°/14 mm., prisms, m. p. 85—86° (from ligroin, b. p. 80—100°) (Found : C, 78·7; H, 7·1. $C_{14}H_{15}ON$ requires C, 78·9; H, 7·0%), and 1 : 3-*di*-(2 : 4-*dimethylanilino*)*benzene* (2 g.), b. p. >280°/15 mm., needles (from ethanol), m. p. 120° (Found : C, 83·2; H, 7·8. $C_{22}H_{24}N_2$ requires C, 83·5; H, 7·6%).

Condensation of Quinol with p-*Anisidine.*—Quinol (10 g.), *p*-anisidine (25 g.), and iodine (0·25 g.) yielded, after 48 hours, *4-hydroxy-4′-methoxydiphenylamine* (10 g.), b. p. 245—248°/14 mm., leaflets (from ligroin, b. p. as above), m. p. 93° (Found : C, 72·4; H, 6·0. $C_{13}H_{13}O_2N$

TABLE 1. 1 : 3 : 5-*Trisarylaminobenzenes.*

Aryl group	M. p.	Formula	Found, % C	Found, % H	Required, % C	Required, % H
Ph [a]	196°	$C_{24}H_{21}N_3$	—	—	—	—
o-C_6H_4Me	157	$C_{27}H_{27}N_3$	82·2	7·2	82·4	6·9
m-C_6H_4Me	133	$C_{27}H_{27}N_3$	82·5	6·8	82·4	6·9
p-C_6H_4Cl	226	$C_{24}H_{18}N_3Cl_3$	63·0	4·2	63·4	4·0
2 : 3 : 1-C_6H_3ClMe	164	$C_{27}H_{24}N_3Cl_3$	65·1	5·0	65·3	4·8
2 : 4 : 1-$C_6H_3Me_2$	150	$C_{30}H_{33}N_3$	82·5	7·5	82·8	7·6
p-$CMe_2Et{\cdot}C_6H_4$	159	$C_{39}H_{51}N_3$	83·1	9·2	83·4	9·1
o-$MeO{\cdot}C_6H_4$	139	$C_{27}H_{27}O_3N_3$	73·3	6·3	73·5	6·1
p-$MeO{\cdot}C_6H_4$	167	$C_{27}H_{27}O_3N_3$	73·6	6·2	73·5	6·1
o-C_6H_4Ph	173	$C_{42}H_{33}N_3$	86·7	5·5	87·0	5·7
p-C_6H_4Ph [b]	252	$C_{42}H_{33}N_3$	87·2	5·5	87·0	5·7
α-$C_{10}H_7$	227	$C_{36}H_{27}N_3$	86·0	5·6	86·2	5·4

[a] Minunni (*Gazzetta*, 1890, **20**, 237) gave m. p. 193°. [b] Recrystallised from benzene; almost insoluble in ethanol.

TABLE 2. *Bisarylaminonaphthalenes.*

Substituents	M. p.	Formula	Found, % C	Found, % H	Required, % C	Required, % H
1 : 6-Dianilino	164°	$C_{22}H_{18}N_2$	85·0	6·0	85·2	5·8
1 : 6-Di-*p*-toluidino	146	$C_{24}H_{22}N_2$	85·1	6·3	85·2	6·5
1 : 6-Di-(2 : 4-dimethylanilino)	103	$C_{26}H_{26}N_2$	85·0	7·4	85·2	7·1
1 : 6-Di-*p*-methoxyanilino	183	$C_{24}H_{22}O_2N_2$	77·5	6·1	77·8	5·9
2 : 7- ,,	176	$C_{24}H_{22}O_2N_2$	77·6	6·2	77·8	5·9
2 : 7-Di-*p*-hydroxyanilino [a]	243—245 [b]	$C_{22}H_{18}O_2N_2$	76·9	5·4	77·2	5·2
2 : 7-Di-β-naphthylamino	253—255 [b]	$C_{30}H_{22}N_2$	89·0	5·4	88·7	5·4
2 : 6-Di-*p*-toluidino	193	$C_{24}H_{22}N_2$	85·2	6·6	85·2	6·5
2 : 6-Di-*o*-toluidino	183	$C_{24}H_{22}N_2$	85·0	6·5	85·2	6·5
2 : 6-Di-α-naphthylamino	212 [b]	$C_{30}H_{22}N_2$	88·9	5·2	88·7	5·4

[a] All substances were recrystallised from ethanol–benzene, except this which was recrystallised from aqueous ethanol. [b] With decomp.

requires C, 72·6; H, 6·0%), and 1 : 3-*di*-p-*anisidinobenzene* (12 g.), leaflets (from benzene), m. p. 189° (Found : C, 74·8; H, 6·2. $C_{20}H_{20}O_2N_2$ requires C, 75·0; H, 6·3%).

Condensation of Phloroglucinol and Dihydroxynaphthalenes with Arylamines.—(*a*) Phloroglucinol (1 mol.), the arylamine (4—5 mols.), and iodine (2%) were heated at 190—200° for 6 hours with removal of water; the warm product was treated with methanol, and the solid obtained washed thoroughly with the same solvent and recrystallised from ethanol or benzene. The 1 : 3 : 5-*trisarylaminobenzenes* (Table I) thus obtained in almost theoretical yield were needles or leaflets. (*b*) In the case of dihydroxynaphthalenes, purification of the *products* (Table 2) in most instances required vacuum-distillation before crystallisation.

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