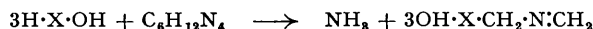


346. *A Method for Preparing Secondary Amines and Schiff's Bases from Phenols and Hexamine.*

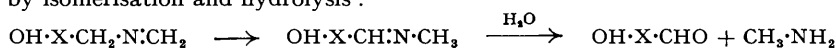
By J. C. DUFF and (MISS) V. I. FURNESS.

Phenols heated with hexamine and boric acid in 2-ethoxyethanol form secondary amines of the type $\text{OH}\cdot\text{X}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CH}_2\cdot\text{X}\cdot\text{OH}$ ($\text{H}\cdot\text{X}\cdot\text{OH}$ = the phenol). Dehydrogenation of these amines by heating them with hexamine in acetic acid produces Schiff's bases of the type $\text{OH}\cdot\text{X}\cdot\text{CH}\cdot\text{N}\cdot\text{CH}_2\cdot\text{X}\cdot\text{OH}$ which can be hydrolysed to phenolic aldehydes. These reactions are regarded as explaining the mechanism of the general method for preparing *o*-hydroxy-aldehydes described by Duff (*J.*, 1941, 547). New secondary amines and Schiff's bases from eleven phenolic compounds are described.

A GENERAL method for preparing *o*-hydroxy-aldehydes from phenols and hexamine has been described by one of the authors (Duff, *J.*, 1941, 547). The reaction conditions in the anhydrous medium, glyceroboric acid, prevented identification of the intermediate compounds which yielded aldehydes on hydrolysis. It was recorded that the stages of the reaction might be



followed by isomerisation and hydrolysis:



This suggestion of isomerisation was based on the explanation given by Sommelet (*Compt. rend.*, 1913, 157, 854) for the formation of benzaldehyde in a reaction between benzyl chloride and hexamine. Angyal and Rassack (*J.*, 1949, 2700) have recently examined the Sommelet

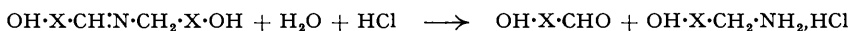
reaction and in the light of their results the present authors decided to investigate the reactions between phenols and hexamine under new conditions.

In their investigation Angyal and Rassack, while emphasising a dehydrogenation mechanism, limited their experimental evidence to reactions in aqueous conditions. For this reason they ascribe the dehydrogenation function of hexamine to its hydrolysis products, with special reference to the hydrolysis fragment, $\text{CH}_2\cdot\text{NH}$. In one example they heated dibenzylamine in acetic acid with hexamine and aqueous formaldehyde solution and obtained benzaldehyde. As this reaction had a bearing on our investigation we have re-examined it and find it proceeds more readily when the dibenzylamine is heated with hexamine in glacial acetic acid. Subsequent hydrolysis gave benzaldehyde and benzylamine at once. The ease with which this reaction proceeds led us to the view that phenolic aldehydes might arise from the hydrolysis of phenolic Schiff's bases which had been formed from phenolic secondary amines by the dehydrogenating action of hexamine.

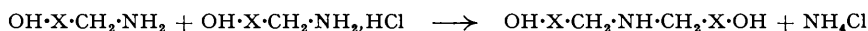
Few phenolic secondary amines of the form $\text{OH}\cdot\text{X}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CH}_2\cdot\text{X}\cdot\text{OH}$ ($\text{H}\cdot\text{X}\cdot\text{OH} = \text{a phenol}$) have been previously recorded. Zinke *et al.* (*Monatsh.*, 1948, **78**, 311; 1949, **80**, 148) described the preparation of secondary amines of this type by heating hexamine with a phenol at 130° . They applied this reaction successfully only to 2:4-dimethyl- and 2:4-dichlorophenol. From the other two phenols they tested, 3:4-dimethyl- and *p-tert.*-butyl-phenol, the resulting amines were complex, the molecules containing at least four phenol nuclei linked by $-\text{CH}_2\cdot\text{NH}\cdot\text{CH}_2-$ bridges. They did not try the further action of hexamine on the secondary amines. Hultsch (*Chem. Ber.*, 1949, **82**, 16) described the preparation of secondary amines from 2:4-dimethyl- and 2-methyl-4-*tert.*-butyl-phenol by heating them with hexamine and water. This method involves separation of the secondary amine from resinous products. He also described the formation of the secondary amines mixed with tertiary amines when the phenol is heated with hexamine until the temperature was 180° . Hultsch did not describe the further action of hexamine on the secondary amines.

Duff and Bills (*J.*, 1934, 1307) obtained a Schiff's base directly from β -naphthol and hexamine in acetic acid and by hydrolysis of the base separated 2-hydroxy-1-naphthaldehyde and 2-hydroxy-1-naphthylmethylamine. The secondary amine which probably gave rise to the Schiff's base was not observed. Acetic acid was found to be an unsuitable medium for obtaining Schiff's bases from other phenols. Since boric acid had proved useful in glycerol for preparing phenolic aldehydes the present authors decided to use boric acid in other non-aqueous media and found a suitable solvent in 2-ethoxyethanol. Boric anhydride was also tried in many experiments but only in the reaction involving *m*-xylenol did it offer advantages over boric acid. Metaboric acid proved unsuitable owing to its low solubility. In the absence of boric acid the reactions between phenols and hexamine were too complex. In the presence of boric acid the reactions proceeded on simpler lines.

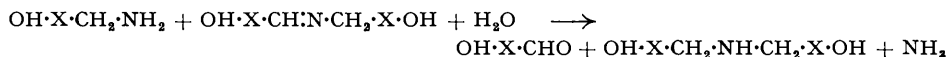
Eleven phenols ($\text{H}\cdot\text{X}\cdot\text{OH}$) were used in this investigation and from each a secondary amine $\text{OH}\cdot\text{X}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CH}_2\cdot\text{X}\cdot\text{OH}$ and a Schiff's base $\text{OH}\cdot\text{X}\cdot\text{CH}\cdot\text{N}\cdot\text{CH}_2\cdot\text{X}\cdot\text{OH}$ were obtained. All the amines are new and were obtained crystalline. They are not hydrolysed on boiling in alcohol with hydrochloric acid. When heated in acetic acid with hexamine they yielded yellow Schiff's bases. When the Schiff's bases were hydrolysed in alcohol with hydrochloric acid it was expected the results would be in accordance with the equation



However this only applied to the Schiff's bases from β -naphthol and 4-chloro-3:5-dimethylphenol. All the other Schiff's bases on hydrolysis yielded a phenolic aldehyde and, in place of the expected primary amine, the original secondary amine and ammonium chloride. This may have occurred either by the reaction



or by reaction of the primary amine with the Schiff's base:



The identity of the secondary amine formed in each case was established by analysis and by reconversion into the Schiff's base and thence into the aldehyde by hydrolysis. All the Schiff's bases yielded the phenolic aldehydes which were produced by the glyceroboric acid method (Duff, *loc. cit.*) except in the case of the Schiff's base derived from 4-chloro-3-methylphenol.

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The aldehyde which was obtained in this case was the new aldehyde, 4-chloro-2-formyl-3-methylphenol (I), thus indicating that the Schiff's base which yielded it had the structure (II).



The aldehyde formed from 4-chloro-3-methylphenol in the glyceroboric acid reaction is the other *o*-aldehyde. The identity of the 2-aldehyde was established by oxidation of the methyl ether to a chloro-methoxyphthalic acid which yielded a phthalein with phenol. In all cases where an *o*-hydroxy-aldehyde was separated by steam-distillation the residual liquors were tested for the presence of *p*-hydroxy-aldehydes with negative results. The only *p*-hydroxy-aldehyde obtained came from α -naphthol which yielded 4-hydroxy-1-naphthaldehyde from hydrolysis of the Schiff's base, together with some of the secondary amine and ammonium chloride.

EXPERIMENTAL.

All m. p.s are uncorrected.

Preparation of Secondary Amines.—The phenol (10 g.) and boric acid (4 g.) were dissolved in boiling 2-ethoxyethanol (40 ml.). Hexamine (5 g.) was then added and the solution boiled under reflux for 2 hours and cooled. The method of extraction varied with the nature of the phenol:

(a) *From phenol and cresols.* The reaction mixture was filtered and poured into 150 ml. of water. The resultant oil was washed with water by decantation and left overnight with water. It was then separated and stirred with cold alcohol, and the residual solid was recrystallised from aqueous alcohol.

Phenol yielded *di-o-hydroxybenzylamine* (2.5 g.) as a micro-crystalline white powder, m. p. 190—200° (decomp.) [Found: C, 73.4; H, 6.2; N, 6.0%; *M* (Rast), 240. $C_{14}H_{15}O_2N$ requires C, 73.4; H, 6.5; N, 6.1%; *M*, 229]. Crystals of a *hydrochloride* were obtained from a solution of the base in warm concentrated hydrochloric acid (Found: HCl, 13.8. $C_{14}H_{16}O_2N.HCl$ requires HCl, 13.75%).

o-Cresol yielded *di-(2-hydroxy-3-methylbenzyl)amine* (5.1 g.), m. p. 150—155° (decomp.) [Found: C, 74.9; H, 7.4; N, 5.2%; *M* (Rast), 265. $C_{16}H_{19}O_2N$ requires C, 74.7; H, 7.4; N, 5.4%; *M*, 257].

m-Cresol yielded *di-(2-hydroxy-4-methylbenzyl)amine* (7.5 g.), m. p. 150—157° (decomp.) [Found: C, 74.1; H, 7.4; N, 5.3%; *M* (Rast), 270].

p-Cresol yielded *di-(2-hydroxy-5-methylbenzyl)amine* (7.7 g.), m. p. (anhyd.) 168—170° (decomp.) [Found: C, 69.2; H, 7.2; N, 5.1; H_2O , 6.8%; *M* (Rast), 275. $C_{16}H_{19}O_2N.H_2O$ requires C, 69.8; H, 7.6; N, 5.1; H_2O , 6.6%; *M*, 275]. Crystals of a *hydrochloride* were obtained by passing hydrogen chloride through a solution of the base in alcohol (Found: HCl, 12.4%).

(b) *From p-chlorophenol and 4-chloro-3-methylphenol.* The reaction mixture was poured into 150 ml. of water. The oil which separated was washed with water by decantation and then stirred with ether. The residual solid was recrystallised from alcohol.

p-Chlorophenol yielded *di-(2-hydroxy-5-chlorobenzyl)amine* (2.8 g.), m. p. 155—160° (decomp.) [Found: C, 56.1; H, 4.2; N, 4.9%; *M* (Rast), 295. $C_{14}H_{13}O_2NCl_2$ requires C, 56.3; H, 4.3; N, 4.7%; *M*, 298]. Crystals of a *hydrochloride* were obtained by passing hydrogen chloride through a solution of the base in alcohol and hydrochloric acid (Found: HCl, 11.0. $C_{14}H_{13}O_2NCl_2.HCl$ requires HCl, 10.9%).

4-Chloro-3-methylphenol yielded *di-(2-hydroxy-5-chloro-6-methylbenzyl)amine* (5.5 g.), m. p. 185—190° (decomp.) [Found: C, 58.8; H, 5.1; N, 4.35%; *M* (Rast), 340. $C_{16}H_{17}O_2NCl_2$ requires C, 58.9; H, 5.2; N, 4.3%; *M*, 326]. Crystals of a *hydrochloride* were obtained on addition of concentrated hydrochloric acid to a solution of the base in hot acetic acid (Found: HCl, 9.9. $C_{16}H_{17}O_2NCl_2.HCl$ requires HCl, 10.0%).

(c) *From β -naphthol, 4-chloro-3:5-dimethylphenol, and 4-hydroxydiphenyl.* The reaction mixture was poured into 150 ml. of water and set aside overnight. The solid was collected. The β -naphthol compound was washed with boiling alcohol and recrystallised from aqueous acetone; the 4-chloro-3:5-dimethylphenol compound was washed with water and recrystallised from aqueous alcohol; the 4-hydroxydiphenyl compound was washed with warm acetone and recrystallised from alcohol. The following were prepared.

Di-(2-hydroxy-1-naphthylmethyl)amine (6.1 g.), m. p. 170—178° (decomp.) [Found: C, 80.2; H, 6.1; N, 4.0%; *M* (Rast), 325. $C_{22}H_{19}O_2N$ requires C, 80.2; H, 5.8; N, 4.2%; *M*, 329]; *hydrochloride* formed by hydrochloric acid in warm 2-ethoxyethanol (Found: HCl, 10.2. $C_{22}H_{19}O_2N.HCl$ requires HCl, 10.0%).

Di-(3-chloro-6-hydroxy-2:4-dimethylbenzyl)amine (6.8 g.), m. p. 219° (decomp.) [Found: C, 61.2; H, 6.2; N, 3.95%; *M* (Rast), 335. $C_{18}H_{21}O_2NCl_2$ requires C, 61.0; H, 5.95; N, 3.95%; *M*, 354]; *hydrochloride*, obtained in acetic acid (Found: HCl, 9.3. $C_{18}H_{21}O_2NCl_2.HCl$ requires HCl, 9.3%).

Di-(2-hydroxy-5-phenylbenzyl)amine (5 g.), m. p. 195—200° (decomp.) [Found: C, 82.3; H, 6.05; N, 3.5%; *M* (Rast), 370. $C_{26}H_{23}O_2N$ requires C, 81.9; H, 6.05; N, 3.7%; *M*, 381]; *hydrochloride*, obtained in acetic acid (Found: HCl, 8.6. $C_{26}H_{23}O_2N.HCl$ requires HCl, 8.7%).

(d) *From m-5-xylene.* Boric anhydride (2 g.) was used in place of boric acid, and a smaller amount of hexamine (2.5 g.) and a larger amount of solvent (50 ml.) were added. The cooled reaction mixture

was poured into water (150 ml.), and the solid which precipitated was collected and washed with alcohol. The amine could only be obtained pure as the hydrochloride. This separated from a solution of the base in warm 2-ethoxyethanol and concentrated hydrochloric acid on cooling. *Di-(2-hydroxy-4:6-dimethylbenzyl)amine hydrochloride* (4.5 g.) had m. p. 215—220° (decomp.) [Found: C, 66.7; H, 7.5; N, 4.0; HCl, 11.4%; *M* (Rast), 310. $C_{18}H_{23}O_2N.HCl$ requires C, 67.1; H, 7.4; N, 4.4; HCl, 11.4%; *M*, 321.5].

(e) From α -naphthol. 2-Methoxyethyl acetate (50 ml.) was used in place of 2-ethoxyethanol. Recrystallisation from aqueous alcohol yielded *di-(4-hydroxy-1-naphthylmethyl)amine* (4.7 g.), a pale yellow powder, m. p. 205° (decomp.) [Found: C, 80.2; H, 5.5; N, 4.1%; *M* (Rast), 335. $C_{22}H_{19}O_2N$ requires C, 80.2; H, 5.8; N, 4.2%; *M*, 329]; the hydrochloride was obtained in glacial acetic acid (Found: HCl, 10.1. $C_{22}H_{19}O_2N.HCl$ requires HCl, 10.0%).

Preparation of Schiff's Bases.—The secondary amine (5 g.) and hexamine (5 g.) were heated in acetic acid (15 ml.) on a boiling water-bath for the periods stated below. The solutions were then strongly coloured, and in most cases showed a marked green fluorescence when cold. The solution was filtered and poured into sufficient water to give complete precipitation (15—30 ml.). The solid was collected immediately and washed with water, except for the compounds from phenol, *m*-5-xylene, and α -naphthol which were washed with dilute hydrochloric acid. The Schiff's bases from phenol, the cresols, and *m*-xylene were too soluble and too readily hydrolysed to be recrystallised. The other bases were recrystallised from the aqueous alcohol. The following were prepared.

2-Hydroxy-N-2'-hydroxybenzylidenebenzylamine (1.2 g.), a bright yellow powder (after 16 hours' heating) (Found: C, 73.5; H, 5.9; N, 6.4. $C_{14}H_{13}O_2N$ requires C, 74.0; H, 5.7; N, 6.2%); *2-hydroxy-N-(2-hydroxy-3-methylbenzylidene)-3-methylbenzylamine* (3.8 g.), an orange powder (after 9 hours' heating) (Found: C, 75.5; H, 6.4; N, 5.45. $C_{16}H_{17}O_2N$ requires C, 75.3; H, 6.7; N, 5.5%); *2-hydroxy-N-(2-hydroxy-4-methylbenzylidene)-4-methylbenzylamine* (2.7 g.), a bright yellow powder (after 9 hours' heating) (Found: C, 75.4; H, 6.8; N, 5.6%); *2-hydroxy-N-(2-hydroxy-5-methylbenzylidene)-5-methylbenzylamine* (3.5 g.), a bright yellow powder (after 9 hours' heating) (Found: C, 75.9; H, 7.0; N, 5.5%); *5-chloro-2-hydroxy-N-(5-chloro-2-hydroxybenzylidene)benzylamine* (4.2 g.), a yellow powder (after 6 hours' heating) (Found: C, 57.0; H, 4.1; N, 4.5. $C_{14}H_{11}O_2NCl_2$ requires C, 56.8; H, 3.7; N, 4.7%); *3-chloro-6-hydroxy-N-(3-chloro-6-hydroxy-2-methylbenzylidene)-2-methylbenzylamine* (3.7 g.), a bright yellow powder (after 6 hours' heating) (Found: C, 59.5; H, 4.8; N, 4.4. $C_{16}H_{15}O_2NCl_2$ requires C, 59.3; H, 4.65; N, 4.35%); *2-hydroxy-1-naphthyl-N-(2-hydroxy-1-naphthylmethylene)methylamine* (4.5 g.) (after 2 hours' heating) (Found: N, 4.3. Calc. for $C_{22}H_{17}O_2N$: N, 4.3%); *3-chloro-N-(3-chloro-6-hydroxy-2:4-dimethylbenzylidene)-6-hydroxy-2:4-dimethylbenzylamine* (3.7 g.), an orange-yellow powder (after 6 hours' heating) (Found: C, 61.2; H, 5.7; N, 4.3. $C_{18}H_{16}O_2NCl_2$ requires C, 61.3; H, 5.4; N, 4.0%); *2-hydroxy-N-(2-hydroxy-5-phenylbenzylidene)-5-phenylbenzylamine* (4.9 g.), a bright yellow powder (after 6 hours' heating) (Found: C, 82.3; H, 5.7; N, 3.5. $C_{26}H_{21}O_2N$ requires C, 82.3; H, 5.55; N, 3.7%); (from the hydrochloride of the secondary amine) *2-hydroxy-N-(2-hydroxy-4:6-dimethylbenzylidene)-4:6-dimethylbenzylamine* (2.0 g.), a bright yellow powder (after 2 hours' heating) (Found: C, 75.5; H, 7.5; N, 5.5. $C_{18}H_{21}O_2N$ requires C, 76.3; H, 7.4; N, 4.95%); and *4-hydroxy-N-(4-hydroxy-1-naphthylmethylene)-1-naphthylmethylamine* (4.3 g.), a yellow powder (after 2 hours' heating) (Found: C, 80.4; H, 5.3; N, 4.2. $C_{22}H_{17}O_2N$ requires C, 80.7; H, 5.2; N, 4.3%).

Hydrolysis of Schiff's Bases.—The Schiff's base (2 g.) was heated with 20 ml. of a mixture of equal volumes of alcohol and hydrochloric acid (*d* 1.17). When the mixture had reached the b. p. it was filtered and the filtrate was steam-distilled until no more aldehyde was obtained. For the α -naphthol compound, the solution was extracted with ether instead of being distilled. In most cases some solid amine hydrochloride separated from the still residue on concentration and cooling. With *o*- and *m*-cresol, there was no separation owing to the high solubility of the hydrochlorides, and the free bases were obtained by neutralising the solution. The amine in each case was filtered off and examined and the filtrate tested for aldehydes and ammonium chloride. The following aldehydes were obtained, together with secondary amine and ammonium chloride.

Salicylaldehyde (0.6 g.) (phenylhydrazone, m. p. 142°); 2-hydroxy-3-methylbenzaldehyde (0.3 g.) (phenylhydrazone, m. p. 92°); 2-hydroxy-4-methylbenzaldehyde (0.6 g.), m. p. and mixed m. p. 59°; 2-hydroxy-5-methylbenzaldehyde (0.45 g.), m. p. and mixed m. p. 56°; 5-chloro-2-hydroxybenzaldehyde (0.5 g.), m. p. and mixed m. p. 99.5°; 4-chloro-2-formyl-3-methylphenol (0.6 g.), m. p. 100.5° (Found: C, 55.7; H, 4.4. $C_8H_7O_2Cl$ requires C, 56.3; H, 4.1%) [methylation with methyl sulphate and then oxidation with potassium permanganate afforded a dibasic acid (Found: equiv., 119. Calc. for $C_9H_7O_2Cl$: equiv., 116) which gave a phtalein reaction with phenol, thus confirming that the aldehyde group was *ortho* to the methyl group]; 2-hydroxy-1-naphthaldehyde (0.7 g.), m. p. and mixed m. p. 82° [with 2-hydroxy-1-naphthylmethylamine hydrochloride (Duff, *J.*, 1934, 1307)]; 4-chloro-2-formyl-3:5-dimethylphenol (0.4 g.), m. p. and mixed m. p. 95° [with 3-chloro-6-hydroxy-2:4-dimethylbenzylamine hydrochloride, a microcrystalline white powder (Found: C, 48.9; H, 5.8; N, 6.6; HCl, 16.3. $C_9H_{12}ONCl.HCl$ requires C, 48.7; H, 5.8; N, 6.3; HCl, 16.4%); 3-formyl-4-hydroxydiphenyl (0.3 g.), m. p. and mixed m. p. 102°; 4-formyl-3:5-dimethylphenol (0.15 g.), m. p. and mixed m. p. 49°; and 4-hydroxy-1-naphthaldehyde (0.1 g.), m. p. 180°.

Reaction with Dibenzylamine.—Dibenzylamine (5 g.) and hexamine (1 g.) were heated in glacial acetic acid (10 ml.) for 5 minutes at the b. p. The solution became deep yellow. Dilute hydrochloric acid was added and the mixture was steam-distilled. Benzaldehyde (1.2 g.) was obtained. The residue was treated with toluene-*p*-sulphonyl chloride and yielded toluene-*p*-sulphonbenzylamide, m. p. and mixed m. p. 115°