## 282. *Reactions between Hexamethylenetetramine and Phenolic Compounds. Part II. Formation of Phenolic Aldehydes. Distinctive Behaviour of* p-*Nitrophenol.*

By J. C. Duff and E. J. Bills.

Part I (J., 1932, 1987) described the preparation of 3- and 5-aldehydosalicylic acids from an aqueous solution of salicylic acid and hexamethylenetetramine. The reactions of α- and β-naphthols with the latter compound have now been studied. In aqueous-alcoholic solutions the products were the same as those obtained when using formaldehyde in place of hexamethylenetetramine; β-naphthol yielded 1 : 1′-methylene-2 : 2′-dinaphthol, whilst α-naphthol yielded a complex amorphous compound apparently identical with that obtained by Breslauer and Pictet (*Ber.*, 1907, **40**, 3786) using formaldehyde.

It was found, however, that if the reaction was effected by heating in acetic acid solution, β-naphthol yielded a yellow crystalline Schiff's base, 2 : 2′-*dihydroxy*-1-*naphthylidene*-1′-*naphthylmethylamine* (I), readily hydrolysed by acids into the aldehyde and amine, thereby affording a new and more convenient method for preparing these two compounds.

(I.) $OH{\cdot}C_{10}H_6{\cdot}CH{:}N{\cdot}CH_2{\cdot}C_{10}H_6{\cdot}OH$ $(C_{10}H_7{\cdot}O{\cdot}CH_2)_2NH$ (II.)

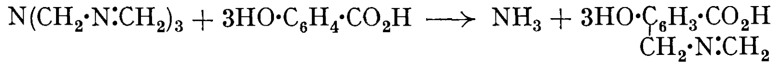
The formation of (I) may be represented by the equation

$$N_4(CH_2)_6 + 4C_{10}H_7{\cdot}OH \longrightarrow 2(I) + 2CH_3{\cdot}NH_2.$$

Betti (*Gazzetta*, 1904, **34**, 212) obtained a crystalline compound, $N(CH_2{\cdot}C_{10}H_6{\cdot}OH)_3$, from β-naphthol, formaldehyde, and alcoholic ammonia.

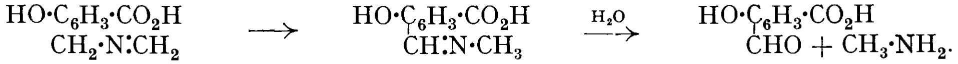
α-Naphthol and hexamethylenetetramine when heated in a mixture of alcohol and acetic acid yielded a yellow compound, s-*di-α-naphthoxydimethylamine* (II), which differed from (I) in not dissolving in aqueous sodium hydroxide and in undergoing hydrolysis to formaldehyde, ammonia, and a resinous product. Our results therefore differ from those of Marotta and Alessandrini * (*Gazzetta*, **1931**, **61**, 977), who state that similar compounds result from both naphthols, through condensation of 3 mols. of naphthol with 1 mol. of trimethanolamine; their method of preparation, however, involved aqueous dilution, and their compounds resinified easily. They also state that phenol under similar conditions yields a compound corresponding to union of 2 mols. with 1 mol. of trimethanolamine, but we find that the product varies in composition according to the time of heating.

We heated salicylic acid and hexamethylenetetramine together in acetic acid solution; no compound separated from the resulting yellow solution, even on addition of water, but subsequent hydrolysis with hydrochloric acid yielded 3- and 5-aldehydosalicylic acids. This method of preparation is more rapid than that described in Part I (*loc. cit.*), but again we were unable to separate the intermediate compound which yields the aldehydes on hydrolysis. As salicylic acid does not yield a derivative corresponding to the β-naphthol derivative (I), the most probable reaction appears to be



$$N(CH_2{\cdot}N{:}CH_2)_3 + 3HO{\cdot}C_6H_4{\cdot}CO_2H \longrightarrow NH_3 + 3HO{\cdot}\underset{CH_2{\cdot}N{:}CH_2}{C_6H_3}{\cdot}CO_2H$$

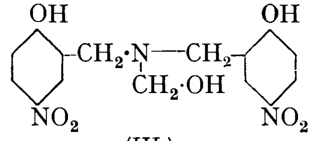
followed by isomerisation and hydrolysis :



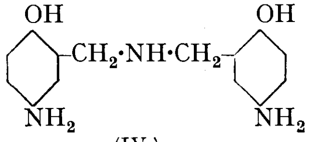
$$\underset{CH_2{\cdot}N{:}CH_2}{HO{\cdot}C_6H_3{\cdot}CO_2H} \longrightarrow HO{\cdot}\underset{CH{:}N{\cdot}CH_3}{C_6H_3}{\cdot}CO_2H \xrightarrow{H_2O} HO{\cdot}\underset{CHO}{C_6H_3}{\cdot}CO_2H + CH_3{\cdot}NH_2.$$

This would also apply to the formation of the aldehydes by the method in Part I (*loc. cit.*).

We were unable to obtain any definite compound from interaction between 2-hydroxy-3-naphthoic acid and hexamethylenetetramine either in aqueous or in acetic acid solution. *m*- and *p*-Hydroxybenzoic acids also failed to yield any derivatives under similar conditions. The behaviour of nitrophenols has also been examined. Neither in aqueous nor in acetic acid solution could any definite compound be obtained from *o*- and *m*-nitro- or from dinitrophenols. *p*-Nitrophenol and hexamethylenetetramine when heated in acetic acid gave only resinous products, but from cold aqueous-alcoholic solution there was obtained an addition *compound*, $C_6H_{12}N_4,2HO{\cdot}C_6H_4{\cdot}NO_2$. Prolonged heating of *p*-nitrophenol in aqueous hexamethylenetetramine solution at 100° yielded a yellow compound, N-*hydroxymethylbis-5-nitro-2-hydroxybenzylamine* (III), very stable in hot aqueous sodium hydroxide and dilute mineral acid solutions. It forms a red *disodium* derivative, and also *salts* with mineral acids. On oxidation (III) yields 5-nitrosalicylic acid and ammonia, and on reduction it affords the *hydrochloride* of bis-5-amino-2-hydroxybenzylamine (IV). It is not attacked by nitrous acid and forms only a *dibenzoyl* derivative. The foregoing reaction confirm the constitution of (III). Its formation apparently is due to the hydrolysis of hexamethylenetetramine to trimethanolamine, which condenses with *p*-nitrophenol. Both ammonia and formaldehyde were evolved in the course of the preparation.



(III.)



(IV.)

## EXPERIMENTAL.

*3- and 5-Aldehydosalicylic Acids.*—Salicylic acid (10 g.) and hexamethylenetetramine (10 g.) were dissolved in anhydrous acetic acid (40 c.c.) and heated for 6 hours in boiling water.

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* The nitrogen contents of these authors' compounds are all appreciably higher than required by their suggested formulæ.

The hot solution was mixed with 80 c.c. of boiling water and 50 c.c. of concentrated hydrochloric acid and cooled after 10 minutes. The pale yellow crystalline product was separated by the method described in Part I (*loc. cit.*), and 3- and 5-aldehydosalicylic acids (1·1 and 2 g. respectively) and unchanged salicylic acid were isolated.

*Compound* (I).—When β-naphthol (10 g.) and the above quantities of hexamethylenetetramine and acetic acid were similarly heated for 1 hour, this *compound* separated in almost quantitative yield as a microcrystalline powder. It was collected and well washed with alcohol (Found : C, 81·0; H, 5·2; N, 4·5. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2; N, 4·3%). Its *hydrochloride* formed pale yellow crystals from alcohol (Found: HCl, 9·8. $C_{22}H_{17}O_2N,HCl$ requires HCl, 10·0%). (I) forms a yellow crystalline sodium derivative from 10% aqueous sodium hydroxide, but this is hydrolysed in water, and the original material is regenerated on addition of dilute acetic acid.

*Hydrolysis.* A solution of the Schiff's base (7 g.) in boiling alcohol (70 c.c.) was mixed with concentrated hydrochloric acid (10 c.c.) and 15 c.c. of hot water and refluxed for $1\frac{1}{2}$ hours on the water-bath. The colourless needles which separated on cooling were recrystallised from 300 c.c. of alcohol; yield 3 g. The substance was the hydrochloride of 2-hydroxy-1-naphthylmethylamine (Found : N, 6·7; HCl, 17·6. Calc. for $C_{11}H_{11}ON,HCl$ : N, 6·7; HCl, 17·4%). The reactions and m. p.'s of the salt and of the free base were identical with those described by Betti (*Gazzetta*, 1906, **36**, 388).

The mother-liquor from the hydrolysis was mixed with 2 vols. of water, and the resulting precipitate was crystallised from 40 c.c. of 70% acetic acid, yielding 3·2 g. of 2-hydroxy-1-naphthaldehyde (Found : C, 76·5; H, 4·8. Calc. for $C_{11}H_8O_2$ : C, 76·7; H, 4·6%), identified by its reactions, and mixed m. p. (82°) with a specimen prepared by the Reimer–Tiemann process.

*Compound* (II).—α-Naphthol (4 g.) in alcohol (40 c.c.) was mixed with a hot solution of hexamethylenetetramine (3 g.) in acetic acid (40 c.c.), and the solution heated with constant shaking for 20 minutes on a boiling water-bath, filtered at once, and the *compound* (II) washed with alcohol, being obtained as a microcrystalline yellow powder (Found : C, 79·7; H, 5·6; N, 4·5. $C_{22}H_{19}O_2N$ requires C, 80·2; H, 5·8; N, 4·3%). It gave a blue colour in concentrated sulphuric acid. Pale yellow crystals of a *hydrochloride* were obtained from acetic acid solution (Found : HCl, 9·9. $C_{22}H_{19}O_2N,HCl$ requires HCl, 10·0%). (II) did not dissolve in hot aqueous sodium hydroxide, and when heated with dilute sulphuric acid yielded only formaldehyde and a resinous product which dissolved to a green solution in aqueous sodium hydroxide.

*Hexamethylenetetramine-di-*p*-nitrophenol*, m. p. 128°, separated in colourless leaflets when solutions of *p*-nitrophenol (10 g. in 50 c.c. alcohol) and hexamethylenetetramine (10 g. in 40 c.c. water) were mixed at 15° [Found : $C_6H_{12}N_4$, 33·8; *p*-nitrophenol (by $TiCl_3$), 66·0.

$$C_6H_{12}N_4,2HO{\cdot}C_6H_4{\cdot}NO_2$$

requires $C_6H_{12}N_4$, 33·5; $HO{\cdot}C_6H_4{\cdot}NO_2$, 66·5%). On boiling in aqueous solution it yielded ammonia and formaldehyde.

*Compound* (III).—*p*-Nitrophenol (10 g.) was dissolved in a hot solution of hexamethylenetetramine (10 g. in 100 c.c. water), and the solution heated at 100° for 12 hours. The *compound* separated as a yellow sandy powder and was obtained pure after digestion with boiling alcohol (yield 5 g.), m. p. 255° (decomp.) (Found : C, 51·8; H, 4·2; N, 12·1; $NO_2$, 26·4. $C_{15}H_{15}O_7N_3$ requires C, 51·6; H, 4·3; N, 12·0; $NO_2$, 26·4%). It is insoluble in water and in organic solvents, but dissolves in hot 10% aqueous sodium hydroxide, the cooled solution depositing the *disodium* derivative as trihydrate, red crystals (Found : Na, 10·5; N, 9·3; $NO_2$, 20·7; $H_2O$, 12·1. $C_{15}H_{13}O_7N_3Na_2,3H_2O$ requires Na, 10·5; N, 9·4; $NO_2$, 20·6; $H_2O$, 12·1%); this derivative is hydrolysed in water and addition of dilute acid regenerates (III) quantitatively. The *hydrochloride* of (III) forms small colourless crystals (Found : HCl, 9·4. $C_{15}H_{15}O_7N_3,HCl$ requires HCl, 9·5%). A *sulphate* and a *phosphate* were obtained in colourless crystals (Found : $H_2SO_4$, 21·7. $C_{15}H_{15}O_7N_3,H_2SO_4$ requires $H_2SO_4$, 21·9%. Found : $H_3PO_4$, 21·9. $C_{15}H_{15}O_7N_3,H_3PO_4$ requires $H_3PO_4$, 21·9%). All three salts are hydrolysed in water. The *dibenzoyl* derivative of (III) crystallised from benzene–alcohol in colourless crystals, m. p. 181° (Found : N, 7·3. $C_{29}H_{23}O_9N_3$ requires N, 7·5%); it could not be hydrolysed on boiling with 60% phosphoric acid.

*Oxidation of* (III).—A solution of (III) (2·5 g.) and potassium hydroxide (2 g.) in 50 c.c. of water was heated at 100° while potassium permanganate (3 g.) was added in small portions during 1 hour. On filtering, acidifying the filtrate with dilute hydrochloric acid, and crystallising the precipitate from acetic acid, 5-nitrosalicylic acid (1 g.) was obtained (identified by equiv., properties, and mixed m. p. 228°).

*Reduction of* (III).—5 G. of (III) in 150 c.c. of concentrated hydrochloric acid were reduced by adding 30 g. of tin and heating at 100° for 3 hours. After removal of tin by hydrogen sulphide, evaporation of the filtrate yielded colourless crystals of the *hydrochloride* of (IV)

(Found : HCl, 29·4; N, 11·2. $C_{14}H_{17}O_2N_3,3HCl$ requires HCl, 29·1; N, 11·5%). The salt was very soluble in water and showed the usual reactions of an aminophenol salt. The free base was precipitated by sodium carbonate but was not obtained crystalline. During the reduction, formaldehyde was evolved, and this accounts for the difference in the structures of (IV) and (III).

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