55. ortho-*Hydroxylation of Phenols. Part III.* Derivatives of Pyrogallol.*

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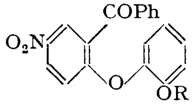
By the method developed earlier,* hydroxylation of 2-(2''-hydroxyaryloxy)-5-nitrobenzophenones, *e.g.*, (I; R = H), affords 2-(2'' : 6''-dihydroxyaryloxy)-5-nitrobenzophenones, *e.g.*, (II; R = H). When heated with piperidine the latter compounds undergo rearrangement with cyclisation to xanthen derivatives which are conveniently isolated as fluorones, *e.g.*, (V; X = H). This process is blocked by the presence of methyl (but not by bromo-)substituents in the 3'' : 5''-positions, allowing normal scission to 4 : 6-dimethylpyrogallol. It is also prevented by methylation (or toluene-sulphonation) of the hydroxyl groups, the ethers being cleaved to partial methyl ethers of pyrogallol.

These observations have been combined in a synthesis of 1 : 2 : 3 : 4-tetramethoxybenzene, representing three consecutive hydroxylations of phenol.

The process used for hydroxylating phenols to the corresponding catechols * affords intermediates of type (I; R = H or Me). These should be capable of renewed hydroxylation to (II; R = H or Me) thereby providing a useful method of converting phenols ultimately into simple derivatives of pyrogallol. To test this expectation a solution of the guaiacol derivative (I; R = Me) in concentrated sulphuric acid was successively treated with acetic acid and hydrogen peroxide. The hydroxylation product (II; R = Me) was not obtained crystalline and similar reluctance to crystallise was later found to be general in partial methyl ethers of the class. Nevertheless, scission of the crude product with piperidine yielded pyrogallol 1-methyl ether which was characterised as the diacetate and dibenzoate, the erroneous description of the latter ester (Herzig and Klimosch, *Monatsh.*, 1909, **30**, 539) being incidentally corrected. Moreover, methylation of (II; R = Me) afforded the crystalline 2-(2'' : 6''-dimethoxyphenoxy)-5-nitrobenzophenone which, on scission with piperidine, yielded pyrogallol 1 : 3-dimethyl ether.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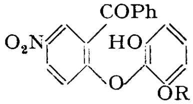
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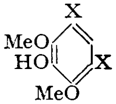
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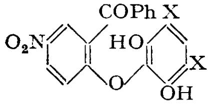
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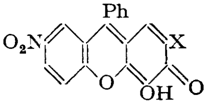
(V)

The catechol derivative (I; R = H) was smoothly hydroxylated to the pyrogallol derivative (II; R = H), the structure of which was confirmed by methylation to the 2'' : 6''-dimethoxy-compound. Scission of (II; R = H) with piperidine, however, could not be achieved since here dehydration intervened, leading ultimately to a highly coloured crystalline product which is considered to be the fluorone derivative (V; X = H). This interpretation is consistent with related observations outlined below. It assumes in (II; R = H) migration of the benzoylated nitrophenyl radical to an adjacent oxygen atom—a process known to occur in alkaline media (Part II)—and subsequent cyclisation involving the reactive *p*-position of a phenolic ion. Attempts to block the latter phase by bromination were unsuccessful. Bromination of (II; R = H) yielded a dibromo-derivative which is formulated as (IV; X = Br) since by methylation with diazomethane followed by scission with piperidine it afforded a dibromopyrogallol dimethyl ether (III; X = Br). On treatment with piperidine (IV; X = Br) yielded a monobromo-dehydration product (V; X = Br), one bromine atom having been eliminated during cyclisation.

The compounds just described form a series ultimately derived from phenol as parent substance and a similar series of products was obtained starting from *p*-cresol. Here also, following the second hydroxylation step, the product of attempted scission was of the

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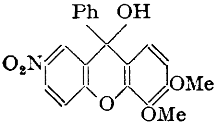
* Part II, preceding paper.

fluorone type and bromination of the appropriate intermediate was again ineffective in preventing cyclisation. In this series the orientation of the bromo-substituents in the methyl homologues of (III; X = Br), (IV; X = Br), and (V; X = Br) is unequivocally determined since the bromine atoms occupy the only free positions of the original tolyl nucleus. By successive hydroxylation and treatment with piperidine, homologues of (V; X = H) were likewise produced from 2-(2″-hydroxy-3″-methylphenoxy)- and 2-(2″-hydroxy-4″ : 5″-dimethylphenoxy)-5-nitrobenzophenone, compounds which are derived from *o*-cresol and 3 : 4-dimethylphenol respectively (Part II). A more interesting case is provided in 3 : 5-dimethylphenol as starting compound since in the intermediate (IV; X = Me), produced at the second hydroxylation stage, fluorone formation is blocked by the methyl substituents. In this case normal scission with piperidine occurred and 4 : 6-dimethylpyrogallol (as III; X = Me; HO for each MeO) was isolated.

Closer examination of the process by which the fluorone (V; X = H) is produced from (IV; X = H) revealed that dehydration occurs only or mainly during removal of excess of piperidine by treatment with acid. When the amine was removed from the reaction mixture by water in presence of benzene a tar was precipitated, which yielded the fluorone when treated with acid and reacted with diazomethane in ether–methanol forming 3 : 4-dimethoxy-7-nitro-9-phenylxanthhydrol (VI). Incomplete removal of piperidine before methylation led to another product—apparently containing piperidine—but it also yielded the xanthhydrol (VI) on treatment with sulphuric acid. Oxidation of the xanthhydrol (VI) by hydrogen peroxide in sulphuric–acetic acid gave an uncrystallisable gum. This, however, on methylation afforded crystalline 2-(2″ : 3″ : 6″-trimethoxyphenoxy)-5-nitrobenzophenone (VII) which by scission with piperidine and renewed methylation yielded 1 : 2 : 3 : 4-tetramethoxybenzene (VIII), identical with a sample supplied by Professor W. Baker, F.R.S., whom we warmly thank.



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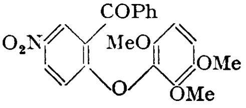

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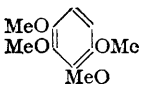

(VIII)

These results accordingly show that, although compounds of type (I; R = H) may be hydroxylated to those of type (II; R = H), the latter in general are rearranged and cyclised by piperidine rather than cleaved to pyrogallols. On the other hand the mono- and the di-methyl ethers derived from type (II; R = H) undergo normal scission. Similarly cleavage of the ditoluene-*p*-sulphonate of (II; R = H) yielded a compound which was characterised by further acylation to pyrogallol tritoluene-*p*-sulphonate and is regarded as pyrogallol 1 : 3-ditoluene-*p*-sulphonate. Preliminary tests showed, however, that neither acetylation nor benzoylation of (II; R = H) effectively suppressed fluorone formation in subsequent reaction with piperidine.

EXPERIMENTAL

Pyrogallol Methyl Ethers.—To a cold solution of 2-(2″-methoxyphenoxy)-5-nitrobenzophenone (0·5 g.) in concentrated sulphuric acid (1 c.c.), acetic acid (8 c.c.) and then dropwise 30% hydrogen peroxide (0·5 c.c.) were added. When the original red colour had faded to amber, the mixture was poured on crushed ice, yielding an uncrystallisable flocculent yellow precipitate (II; R = Me). This was heated under reflux with piperidine (½ hour), cooled, diluted with benzene, and repeatedly extracted with water. From the aqueous extract after acidification, pyrogallol 1-methyl ether was recovered in chloroform : it distilled *in vacuo* as an oil which afforded the diacetate, m. p. 91—92° (Herzig and Pollak, *Monatsh.*, 1904, **25**, 508, give m. p. 91—93°), and the *dibenzoate*, m. p. 83° (from ethanol) (Found : C, 72·5; H, 4·6. $C_{21}H_{16}O_5$ requires C, 72·4; H, 4·6%). The dibenzoate, prepared from authentic pyrogallol 1-methyl ether (Hilleman, *Ber.*, 1938, **71**, 34) and benzoyl chloride in pyridine, had m. p. and mixed m. p. 83° whereas Herzig and Klimosch (*loc. cit.*) erroneously record m. p. 156—158° for the compound prepared in an ambiguous way.

With methyl sulphate in alkali, (II; R = Me) afforded 2-(2″ : 6″-*dimethoxyphenoxy*)-5-

nitrobenzophenone as cubes, m. p. 170°, from ethanol (Found: C, 66·5; H, 4·7. $C_{21}H_{17}O_6N$ requires C, 66·5; H, 4·5%). This compound was cleaved by hot piperidine and, from the acid-washed benzene solution of the products, pyrogallol 1 : 3-dimethyl ether was extracted by alkali, recovered in ether, distilled, and identified as the benzoate, m. p. 115° (Hofmann, *Ber.*, 1879, **12**, 1373, records m. p. 118°).

2-(2″ : 6″-*Dihydroxyphenoxy*)-5-*nitrobenzophenone* (II; R = H).—The red solution obtained by warming 2-(2″-hydroxyphenoxy)-5-nitrobenzophenone (0·5 g.) in concentrated sulphuric acid (0·5 c.c.) was cooled and acetic acid (8 c.c.) and then, dropwise with shaking, 30% hydrogen peroxide (0·5 c.c.) were added. When the colour became amber (10 min.) the mixture was poured on ice and afforded 2-(2″ : 6″-*dihydroxyphenoxy*)-5-*nitrobenzophenone* as yellow crystals, m. p. 180° (decomp.), from methanol (Found: C, 65·1; H, 3·85. $C_{19}H_{13}O_6N$ requires C, 65·0; H, 3·7%). It reacted (*a*) with ethereal diazomethane forming the dimethyl ether, m. p. and mixed m. p. 170°; (*b*) with toluene-*p*-sulphonyl chloride in pyridine (15 min. at 100°), forming the *ditoluene*-p-*sulphonate*, colourless prisms of m. p. 144° (from ethanol) (Found: C, 60·0; H, 4·0. $C_{33}H_{25}O_{10}NS_2$ requires C, 60·1; H, 3·8%), and (*c*) with bromine in chloroform, affording the 3″ : 5″-*dibromo*-derivative (IV; X = X = Br), pale yellow needles of m. p. 206° (from benzene) (Found: C, 44·9; H, 2·3. $C_{19}H_{11}O_6NBr_2$ requires C, 44·8; H, 2·2%).

4-*Hydroxy*-7-*nitro*-9-*phenylfluorone* (V; X = H).—The maroon-coloured precipitate, obtained by boiling (II; R = H) with piperidine (2 min.) and pouring the cooled solution into dilute sulphuric acid, was dried and warmed with anisole. After being decanted from tar the anisole solution deposited the *fluorone* as stout black needles, m. p. 320° (decomp.) (Found: C, 68·2; H, 3·4. $C_{19}H_{11}O_5N$ requires C, 68·5; H, 3·3%).

3-*Bromo*-4-*hydroxy*-7-*nitro*-9-*phenylfluorone* (V; X = Br), black needles, m. p. 324° (decomp.) (from anisole), was similarly prepared from (IV; X = Br) (Found: C, 55·5; H, 2·7. $C_{19}H_{10}O_5NBr$ requires C, 55·4; H, 2·45%).

Toluene-p-*sulphonates of Pyrogallol*.—The ditoluene-*p*-sulphonate of (II; R = H) was heated (1 hour) with piperidine, and an acid-washed benzene solution of the products was shaken with dilute sodium hydroxide. The sodium salt thereby precipitated was treated with acid in presence of chloroform from which *pyrogallol* 1 : 3-*ditoluene*-p-*sulphonate* was recovered as prisms, m. p. 126° (methanol) (Found: C, 55·1; H, 4·1. $C_{20}H_{18}O_7S_2$ requires C, 55·3; H, 4·2%). With toluene-*p*-sulphonyl chloride in pyridine (15 min. at 100°) this formed the *tritoluene*-p-*sulphonate*, prisms, m. p. 139° (from ethanol), identical with a sample prepared directly from pyrogallol (Found: C, 54·9; H, 4·05. $C_{27}H_{24}O_9S_3$ requires C, 55·1; H, 4·1%).

4 : 6-*Dibromopyrogallol* 1 : 3-*Dimethyl Ether*.—2-(3″ : 5″-*Dibromo*-2″ : 6″-*dimethoxyphenoxy*)-5-*nitrobenzophenone*, colourless needles, m. p. 139° (from ethanol) (Found: C, 47·05; H, 2·7. $C_{21}H_{15}O_6NBr_2$ requires C, 46·95; H, 2·8%), was formed from (IV; X = Br) and ethereal diazomethane. Treated with piperidine as described for the unbrominated compound, it yielded 4 : 6-*dibromopyrogallol* 1 : 3-*dimethyl ether* as needles, m. p. 132°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 31·0; H, 2·7. $C_8H_8O_3Br_2$ requires C, 30·8; H, 2·6%).

2-(2″ : 6″-*Dihydroxy*-4″-*methylphenoxy*)-5-*nitrobenzophenone*, obtained by hydroxylating 2-(2″-hydroxy-4″-methylphenoxy)-5-nitrobenzophenone, formed yellow prisms, m. p. 166° (decomp.), from chloroform (Found: C, 65·9; H, 4·3. $C_{20}H_{15}O_6N$ requires C, 65·5; H, 4·1%). It afforded (*a*) with methyl sulphate in alkali 2-(2″ : 6″-*dimethoxy*-4″-*methylphenoxy*)-5-*nitrobenzophenone*, colourless prisms, m. p. 200—201° (from ethanol) (Found: C, 66·9; H, 4·7. $C_{22}H_{19}O_6N$ requires C, 67·15; H, 4·9%), likewise produced from the pink uncrystallisable solid obtained by hydroxylating 2-(2″-methoxy-4″-methylphenoxy)-5-nitrobenzophenone; (*b*) with bromine in chloroform, the 3″ : 5″-*dibromo*-derivative, yellow cubes, m. p. 204° (from ethanol) (Found: C, 46·0; H, 2·5. $C_{20}H_{13}O_6NBr_2$ requires C, 45·9; H, 2·5%); and (*c*) with hot piperidine and subsequent treatment with acid, 4-*hydroxy*-1-*methyl*-7-*nitro*-9-*phenylfluorone*, m. p. 277° (decomp.) (from anisole) (Found: C, 69·0; H, 3·6. $C_{20}H_{13}O_5N$ requires C, 69·2; H, 3·8%). When the 3″ : 5″-dibromo-compound (cf. *b*) was used in reaction (*c*), 3-*bromo*-4-*hydroxy*-1-*methyl*-7-*nitro*-9-*phenylfluorone* was produced and had m. p. 300° (decomp.) (Found: C, 56·5; H, 3·0. $C_{20}H_{12}O_5NBr$ requires C, 56·4; H, 2·8%).

4 : 6-*Dibromo*-5-*methylpyrogallol* 1 : 3-*dimethyl ether* was obtained as colourless needles, m. p. 130° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 33·1; H, 3·0. $C_9H_{10}O_3Br_2$ requires C, 33·2; H, 3·1%), by the action of piperidine on 2-(3″ : 5″-*dibromo*-2″ : 6″-*dimethoxy*-4″-*methylphenoxy*)-5-*nitrobenzophenone*, m. p. 144° (from ethanol) (Found: C, 48·2; H, 2·9. $C_{22}H_{17}O_6NBr$ requires C, 47·9; H, 3·1%), which in turn was prepared by direct bromination or by (diazomethane) methylation of the brominated 2″ : 6″-dihydroxy-compound.

4-*Hydroxy*-2-*methyl*-7-*nitro*-9-*phenylfluorone*, m. p. 295° (decomp.) (from anisole) (Found: C, 69·5; H, 3·9. $C_{20}H_{13}O_5N$ requires C, 69·2; H, 3·8%), was formed when the crude hydroxylation product (m. p. 106°) from 2-(2″-hydroxy-3″-methylphenoxy)-5-nitrobenzophenone was heated with piperidine and the cooled solution was poured into dilute sulphuric acid.

4-*Hydroxy*-1 : 2-*dimethyl*-7-*nitro*-9-*phenylxanthhydrol*, yellowish prisms, m. p. 221° (from aqueous acetic acid) (Found: C, 69·1; H, 4·9. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7%), was formed when the red solution of 2-(2″-hydroxy-4″ : 5″-dimethylphenoxy)-5-nitrobenzophenone in concentrated sulphuric acid was poured on ice.

2-(2″ : 6″-*Dihydroxy*-3″ : 4″-*dimethylphenoxy*)-5-*nitrobenzophenone* was obtained from the sulphuric acid solution of the foregoing experiment by the addition of acetic acid, an intense blue colour being developed; this faded to amber on subsequent addition of hydrogen peroxide, whereupon the whole was poured on ice. It formed yellow prisms, m. p. 175° (decomp.), from benzene–light petroleum (b. p. 60—80°) (Found: C, 66·6; H, 4·5. $C_{21}H_{17}O_6N$ requires C, 66·5; H, 4·5%), and, by heating with piperidine followed by treatment with cold dilute sulphuric acid, afforded 4-*hydroxy*-1 : 2-*dimethyl*-7-*nitro*-9-*phenylfluorone* as glistening black needles, m. p. 300° (decomp.), from anisole (Found: C, 69·7; H, 4·4. $C_{21}H_{15}O_5N$ requires C, 69·8; H, 4·2%).

2-(2″-*Hydroxy*-6″-*methoxy*-3″ : 4″-*dimethylphenoxy*-5-*nitrobenzophenone*, which crystallised, with difficulty, as orange-yellow prisms, m. p. 149°, from methanol (Found: C, 67·35; H, 5·0. $C_{22}H_{19}O_6N$ requires C, 67·15; H, 4·9%), was prepared by adding hydrogen peroxide to the blue-green solution of 2-(2″-methoxy-4″ : 5″-dimethylphenoxy)-5-nitrobenzophenone (0·5 g.) in sulphuric–acetic acid (0·5 : 8 c.c.) and, after 5 min., pouring the filtered solution on ice.

2-(2″ : 6″-*Dihydroxy*-3″ : 5″-*dimethylphenoxy*)-5-*nitrobenzophenone* (IV; X = X = Me), colourless needles, m. p. 196° (from ethanol) (Found: C, 66·5; H, 4·5. $C_{21}H_{17}O_6N$ requires C, 66·5; H, 4·5%), was prepared by adding hydrogen peroxide to the purple solution of 2-(2″-hydroxy-3″ : 5″-dimethylphenoxy)-5-nitrobenzophenone in sulphuric–acetic acid and pouring the resultant mixture on ice.

4 : 6-*Dimethylpyrogallol*, prepared from the foregoing compound as described for pyrogallol 1-methyl ether, was sublimed at 80°/3 mm. and formed colourless needles, m. p. 123°, from benzene (Found: C, 62·5; H, 6·7. $C_8H_{10}O_3$ requires C, 62·4; H, 6·5%).

3 : 4-*Dimethoxy*-7-*nitro*-9-*phenylxanthhydrol* (VI).—The solution obtained by heating (IV; X = H) with piperidine for 2 min., cooling, and diluting with benzene, was washed with water (*a*) exhaustively, whereupon a tar separated, or (*b*) until the tar just began to form. In the former case the tar, separated by decantation and dried *in vacuo*, was treated with ethereal diazomethane and after some hours the *xanthhydrol* (VI) was recovered from the resultant yellow solution. It formed colourless needles, m. p. 184°, from benzene (charcoal)–light petroleum (b. p. 60—80°) (Found: C, 66·3; H, 4·7. $C_{21}H_{17}O_6N$ requires C, 66·5; H, 4·5%), and in acetic acid, saturated with hydrogen chloride, gave with ferric chloride red plates of the chloride-ferrichloride, or afforded with perchloric acid in acetic acid red needles of the perchlorate.

In case (*b*), evaporation of the dried benzene solution and subsequent methylation gave yellow prisms, m. p. 227°, which have not yet been identified (Found: C, 67·3; H, 6·45; N, 6·3. $C_{21}H_{17}O_6N,C_5H_{11}N$ requires C, 67·3; H, 6·1; N, 6·0). The *substance* yielded the xanthhydrol (VI) when its solution in concentrated sulphuric acid was poured on ice but could not be prepared by heating (VI) with piperidine or from the fluorone (V; X = H) by similar treatment followed by methylation.

1 : 2 : 3 : 4-*Tetramethoxybenzene*.—The flocculent precipitate, produced by adding hydrogen peroxide (0·2 c.c.) to a solution of (VI) (0·2 g.) in concentrated sulphuric–acetic acid (0·25 : 3·5 c.c.) and pouring the whole on ice, could not be crystallised but with methyl sulphate in alkali gave 2-(2″ : 3″ : 6″-*trimethoxyphenoxy*)-5-*nitrobenzophenone* as pale yellow prisms, m. p. 134° (from methanol) (Found: C, 64·4; H, 4·9. $C_{22}H_{19}O_7N$ requires C, 64·5; H, 4·7%). This compound was heated (1 hour) with piperidine, benzene was added, and the solution was successively extracted with dilute sulphuric acid and alkali. To the alkaline extract methyl sulphate was added with shaking and, after brief heating, tetramethoxybenzene was recovered in chloroform as colourless prisms, (micro-)m. p. 85° and mixed m. p. 85—86° with an authentic sample (Found: C, 60·5; H, 6·95. Calc. for $C_{10}H_{14}O_4$: C, 60·0; H, 7·1%). Baker. Jukes, and Subrahmanyam (*J.*, 1934, 1683) record m. p. 89°.

7-*Nitro*-9-*phenylfluorone*.—When 2-(3″-*methoxyphenoxy*)-5-*nitrobenzophenone*, prisms, m. p. 100° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 68·7; H, 4·6. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%), was heated for 2½ hours with constant-boiling hydrobromic acid in acetic acid, and the cooled solution was poured into water, 7-*nitro*-9-*phenylfluorone* was obtained as orange needles, m. p. 308° (from benzene) (Found : C, 71·9; H, 3·9. $C_{19}H_{11}O_4N$ requires C, 71·9; H, 3·5%).

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