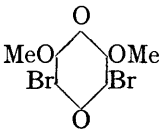
120. *Hexamethoxybenzene.*

By Sir Robert Robinson and C. Vasey.

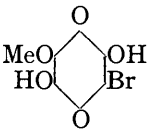
In the course of experiments on derivatives of pentahydroxybenzene, required for the synthesis of nobiletin (Tseng, J., 1938, 1003; Robinson and Tseng, *ibid.*, p. 1004), hexamethoxybenzene has been incidentally prepared by a simple method.

A few years ago Dr. H. Erdtman privately communicated the substance of an interesting synthesis of pentamethoxybenzene which he had devised (since published; Aulin and Erdtman, *Svensk Kem. Tidskr.*, 1937, **49**, 208). We employed the method for preparative purposes, but, as we did not know the full details, made some independent experiments.

According to Aulin and Erdtman, 2 : 6-dimethoxy-*p*-benzoquinone is brominated at 100° to 3 : 5-dibromo-2 : 6-dimethoxy-*p*-benzoquinone (I), whereas bromination in chloroform at the ordinary temperature affords the corresponding quinol.



(I.)



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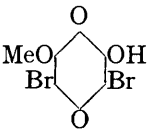
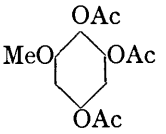
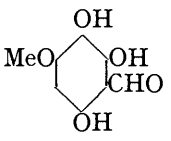


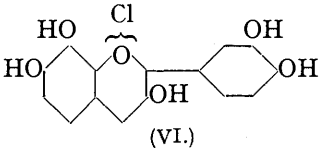
(III.)



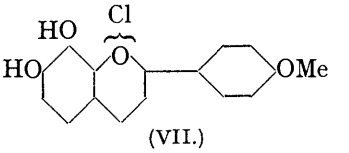
(IV.)

The Swedish authors hydrolysed (I) to (II) by means of aqueous methyl-alcoholic sodium hydroxide, and from (II) by reduction, acetylation, hydrolysis, and methylation, they obtained pentamethoxybenzene. To this we may add that hydrolysis of (I) by cold aqueous sodium hydroxide affords in the first instance 3 : 5-*dibromo*-6-*hydroxy*-2-*methoxy*-p-*benzoquinone* (III), which by reductive acetylation is converted into 2 : 3 : 5-*triacetoxyanisole* (IV). The corresponding trihydric phenol was not obtained analytically pure, but was converted into 2 : 3 : 6-trihydroxy-4-methoxybenzaldehyde (V) by the Gattermann synthesis. The constitution of this aldehyde is deduced from the colour reactions of the anthocyanidin obtained from it by coupling with ω : 4-dihydroxy-3 : 5-dimethoxyacetophenone (the intermediate for malvidin). Had the formyl group entered the other possible position, a synthesis of carajurin would have been feasible.

(V.)




(VI.)



(VII.)

As the above-mentioned colour reactions showed that the hydroxyl in position 2 of (V) took part in the benzopyrylium salt synthesis, the substance had reacted as a derivative of pyrogallolaldehyde. For comparison we prepared two flavylium salts from the latter aldehyde, namely, 3 : 7 : 8 : 3′ : 4′-*pentahydroxyflavylium chloride* (VI) and 7 : 8-*dihydroxy*-4′-*methoxyflavylium chloride* (VII). The action of methyl-alcoholic sodium methoxide on (I) gave *tetramethoxy*-p-*benzoquinone*, which was reduced and acetylated to *tetramethoxyquinol diacetate*. Hydrolysis and methylation yielded *hexamethoxybenzene*.

Experimental.

2 : 6-*Dibromo*-3 : 5-*dimethoxy*-p-*benzoquinone* (I).—A quantitative yield was obtained from dimethoxybenzoquinone (32 g.), bromine (24 c.c.), and chloroform (100 c.c.). The mixture was kept for a few hours and then distilled; the residue crystallised from acetic acid in red plates, m. p. 175°. Possibly the quinol derivative formed in the cold (cf. Aulin and Erdtmann, *loc. cit.*) is oxidised when the solvent is evaporated. Attempts to prepare a monobromo-derivative resulted in the formation of the dibromo-compound from half the dimethoxybenzoquinone employed.

3 : 5-*Dibromo*-6-*hydroxy*-2-*methoxy*-p-*benzoquinone* (III).—Finely powdered dibromodimeth-

oxybenzoquinone (20 g.) was shaken with cold aqueous 0·1N-sodium hydroxide (700 c.c.) for 10 minutes. The violet solution was filtered from unchanged material (4·6 g.) and acidified with hydrochloric acid. The red precipitate (10 g.) crystallised from dilute hydrochloric acid in red prisms, m. p. 183° (Found: C, 27·1; H, 1·4; OMe, 9·9; Br, 51·3. $C_7H_4O_4Br_2$ requires C, 27·0; H, 1·3; 1OMe, 9·9; Br, 51·3%). The substance is soluble in concentrated mineral acids to a salmon-coloured solution and in aqueous alkalis to violet solutions.

2 : 3 : 5-*Triacetoxyanisole* (IV).—Zinc dust (50 g.) was gradually added with shaking to a mixture of hydroxymethoxydibromobenzoquinone (27 g.), acetic acid (50 c.c.), and acetic anhydride (150 c.c.). After the addition of anhydrous sodium acetate (10 g.) the whole was refluxed for 7 hours and then decomposed with water (1 l.). A white mass of crystals (26 g.) separated and the *substance* crystallised from alcohol in needles, m. p. 105° (Found: C, 55·5; H, 4·9; OMe, 11·1. $C_{13}H_{14}O_7$ requires C, 55·4; H, 5·0; 1OMe, 11·0%). This substance is readily soluble in benzene, chloroform and hot alcohol, sparingly in light petroleum and cold alcohol. On boiling with aqueous sodium hydroxide in the air, the solution becomes green and then red; acidification then gives an orange-coloured solution indicating the presence of a quinone. The substance can be distilled under diminished pressure without decomposition.

The triacetate (10 g.) was refluxed with methyl alcohol (50 c.c.) and hydrochloric acid (2 c.c., *d* 1·165) for 1½ hours, and the solution concentrated at 40° under diminished pressure. The syrupy residue crystallised (m. p. 119—125°), but no method for further purification was found. This polyhydric phenol is freely soluble in alcohol, ether, acetone, acetic acid, ethyl acetate and water and sparingly soluble in hydrocarbons and chloroform.

2 : 3 : 6-*Trihydroxy*-4-*methoxybenzaldehyde* (V).—A rapid stream of hydrogen chloride was passed into a mixture of the above crude trihydroxyanisole (5 g.), zinc cyanide (6·4 g.), and ether (100 c.c.) while cooling in ice and then for ¾ hour at room temperature. The ether was decanted, and the aldimine hydrochloride boiled with water (60 c.c.) for 4 minutes. After cooling, the solid was collected, washed with water, and dried (3 g.). The *substance* crystallised from 30% acetic acid in yellow needles, decomp. 199—200° (Found: C, 52·3; H, 4·4. $C_8H_8O_5$ requires C, 52·2; H, 4·4%). It was freely soluble in alcohol, acetone and acetic acid, moderately readily soluble in ether, ethyl acetate and water, and sparingly soluble in hydrocarbons. It easily formed an orange 2 : 4-dinitrophenylhydrazone. In aerated aqueous sodium hydroxide a yellow solution was formed; this quickly became red, then green and finally colourless.

Condensation with ω : 4-dihydroxy-3 : 5-dimethoxyacetophenone was accomplished in the usual manner in ethyl acetate solution in the presence of hydrogen chloride. The deep bluish-red flavylium salt was purified by extraction with ethyl acetate from an acid solution and by solution in 1% hydrochloric acid after the addition of light petroleum. The salt is not extracted by the "cyanidin reagent" and it is completely extracted by the "delphinidin reagent" (cf. Robinson and Robinson, *Biochem. J.*, 1931, **25**, 1693). It gives a rich blue-violet solution in aqueous sodium carbonate and a greenish-blue solution in aqueous sodium hydroxide. The most significant property is that it is ferric negative and this shows that vicinal hydroxyl groups are not present.

3 : 7 : 8 : 3′ : 4′-*Pentahydroxyflavylium Chloride* (VI).—Dry hydrogen chloride was passed for 4 hours into a solution of pyrogallolaldehyde (Adams and Levine, *J. Amer. Chem. Soc.*, 1923, **45**, 2375) (2·5 g.) and ω : 3 : 4-triacetoxyacetophenone (3·9 g.) in the minimum quantity of ethyl acetate. After 12 hours, ether was added, and the red solid collected and boiled for 10 minutes with aqueous alcoholic hydrochloric acid. The *salt* was precipitated by the addition of concentrated hydrochloric acid and thrice crystallised from 2N-hydrochloric acid. It separated very slowly in long, red needles with a green reflex (Found in material dried over calcium chloride: C, 47·9; H, 4·3; Cl, 7·8. $C_{15}H_{11}O_6Cl,3H_2O$ requires C, 47·8; H, 4·5; Cl, 9·4%. Found in material dried at 110° in a high vacuum: C, 55·2; H, 3·5; Cl, 8·6. $C_{15}H_{11}O_6Cl$ requires C, 55·8; H, 3·4; Cl, 11·0%). It is evident that a part of the hydrogen chloride is replaced by water, an observation frequently made in other cases. The red solution in dilute hydrochloric acid becomes bluish-green on the addition of sodium carbonate and the colour fades. With sodium hydroxide the same coloration was followed by more rapid fading. The principal absorption band of a solution in 0·1N-hydrochloric acid occurs at 5180 A.

7 : 8-*Dihydroxy*-4′-*methoxyflavylium Chloride* (VII).—This was obtained like the foregoing salt from pyrogallolaldehyde and *p*-methoxyacetophenone. The *substance* crystallised from the reaction mixture and was recrystallised from much dilute hydrochloric acid, being obtained in reddish-violet, prismatic needles (Found in material dried at 100° in a high vacuum: C, 62·8; H, 4·3; Cl, 11·6. $C_{16}H_{13}O_4Cl$ requires C, 62·9; H, 4·3; Cl, 11·7%). The loss on drying corresponded to $1H_2O$. The colour reaction with aqueous sodium acetate is violet; with

sodium carbonate and sodium hydroxide, greenish-blue fading to red, and more rapidly in the latter case. The principle absorption band in 0·1N-hydrochloric acid solution occurs at 4620A.

Tetramethoxy-p-*benzoquinone.*—A solution of sodium methoxide (4 g. of sodium) in a little methyl alcohol was added to a suspension of 3 : 5-dibromo-2 : 6-dimethoxybenzoquinone (16 g.) in methyl alcohol (150 c.c.). After 3 hours, the mixture was heated on the steam-bath for ½ hour. The cooled solution was acidified with hydrochloric acid, and the solid collected; it crystallised from alcohol in orange needles, m. p. 130° (Found : C, 52·5; H, 5·4. $C_{10}H_{12}O_6$ requires C, 52·6; H, 5·3%). The *substance* is insoluble in cold aqueous sodium carbonate but slowly dissolves in 2N-sodium hydroxide to a violet solution. Acidification then affords a precipitate soluble in aqueous sodium carbonate, showing that hydrolysis has occurred.

1 : 2 : 4 : 5-*Tetramethoxy*-3 : 6-*diacetoxybenzene.*—A little more zinc dust than was necessary to decolorise the solution was added to a mixture of tetramethoxybenzoquinone (5 g.), sodium acetate (5 g.), acetic acid (10 c.c.), and acetic anhydride (30 c.c.). After refluxing for 7 hours, the product was added to water. The colourless solid that separated after some time crystallised from alcohol in white needles, m. p. 134° (Found : C, 53·7; H, 5·8. $C_{14}H_{18}O_8$ requires C, 53·5; H, 5·8%).

Hexamethoxybenzene.—A solution of tetramethoxydiacetoxybenzene (4 g.) in methyl alcohol (25 c.c.) and concentrated hydrochloric acid (1 c.c.) was refluxed for 1 hour in a coal-gas atmosphere. After cooling, sodium hydroxide (15 g.) in water (90 c.c.) was added and with vigorous stirring methyl sulphate (15 c.c.) was gradually introduced at about 90°. After 4 hours' stirring, more methyl sulphate (5 c.c.) and sodium hydroxide (15 g.), dissolved in a little water, were added. After a time the mixture was refluxed for ½ hour. The product was isolated by means of ether and purified by distillation under diminished pressure and crystallisation from light petroleum (b. p. 40—60°). The white needles, m. p. 81°, had b. p. *ca.* 278° (Found : C, 55·8; H, 7·0. $C_{12}H_{18}O_6$ requires C, 55·8; H, 7·0%). *Hexamethoxybenzene* is readily soluble in the common organic solvents and moderately readily soluble in water; it may be crystallised from hot water.

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