The Pigments of " Dragon's Blood " Resin. Part VI. 3 : 5-Dihydroxydiphenyl Ether.*

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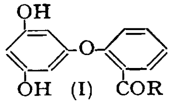
A synthesis of 3 : 5-dihydroxydiphenyl ether and a new route to 5-bromoresorcinol are described.

THE cyclisation of the diphenyl ether (I; R = CH_2·COPh), prepared from, *e.g.*, (I; R = OH) or (I; R = Me), should lead to a model compound of the dracorubin type, but the exploratory experiments now described have led us to abandon this route, mainly because of the difficulties of obtaining the requisite hydroxydiphenyl ethers. In the course of this work a synthesis has been developed of 5-bromoresorcinol from 3 : 5-dihydroxybenzoic acid in place of 1 : 3 : 5-trinitrobenzene which was employed by Hodgson and Wignall (*J.*, 1926, 2826).


(I)

3 : 5-Dihydroxybenzoic acid was converted into 3 : 5-dimethoxybenzoic acid and thence by way of the acid chloride into the corresponding amide which was subjected to the Hofmann degradation to yield 3 : 5-dimethoxyaniline. Replacement of the amino-group according to standard procedure, followed by demethylation of the product, furnished 5-bromoresorcinol.

EXPERIMENTAL

5-Bromoresorcinol (With J. YATES).—A solution of 3 : 5-dimethoxybenzoyl chloride (Brown, Cartwright, Robertson, and Whalley, *J.*, 1949, 859) (from 10 g. of the acid) in ether (50 ml.) was slowly added to well-stirred ammonia solution (200 ml.; *d* 0·88) containing crushed ice (100 g.), and ½ hr. later the resulting 3 : 5-dimethoxybenzamide was collected and crystallised from aqueous methanol, forming prisms (9·3 g.), m. p. 143° (cf. Suter and Weston, *J. Amer. Chem. Soc.*, 1939, **61**, 234, who report m. p. 146°).

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* Part V, *J.*, 1954, 3137.

Powdered 3 : 5-dimethoxybenzamide (5·4 g.) was added to a stirred solution of sodium hypobromite (from 1·8 ml. of bromine, 7·2 g. of sodium hydroxide, and 60 ml. of water) at 0°, and an hour later the mixture was heated on the steam-bath for 1 hr. Isolated with ether, the resulting 3 : 5-dimethoxyaniline was obtained as a low-melting solid (3·9 g.), b. p. 120°/0·2 mm. The acetate separated from aqueous alcohol in plates, m. p. 156° (Found : N, 7·2. Calc. for $C_{10}H_{13}O_3N$: N, 7·2%) (cf. Oakeshott and Plant, *J.*, 1927, 489).

Prepared in the usual manner from this amine (8 g.), 48% hydrobromic acid (50 ml.), and sodium nitrite (3·9 g.) dissolved in water (10 ml.), a solution of the diazonium salt was added to a mixture of cuprous bromide (4 g.) and 48% hydrobromic acid (10 ml.) at 50°, and the mixture kept at this temperature for ½ hr. 1-*Bromo*-3 : 5-*dimethoxybenzene* was isolated with ether and purified by distillation in a vacuum and then crystallisation from light petroleum (b. p. 40—60°), forming prisms (5·5 g.), m. p. 66° [Found : Br, 37·7; OMe, 26·6. $C_6H_3Br(OMe)_2$ requires Br, 36·9; OMe, 28·6%].

A solution of 1-bromo-3 : 5-dimethoxybenzene (4·5 g.) in a mixture of hydriodic acid (50 ml.; *d* 1·7) and acetic acid (from 33 ml. of the anhydride) was boiled for ½ hr. and then treated with aqueous sodium hydrogen sulphite (500 ml.). Extraction of this with ether gave 5-bromoresorcinol which was purified by distillation (b. p. 137—140°/0·25 mm.), and crystallised from light petroleum (b. p. 60—80°), forming prisms (2·7 g.), m. p. 87° (Found : Br, 40·8. Calc. for $C_6H_5O_2Br$: Br, 42·3%).

Prepared from 5-bromoresorcinol (10 g.), benzyl bromide (13·8 ml.), and potassium carbonate (30 g.) in boiling acetone (150 ml.) during 12 hr., followed by the removal of unchanged benzyl bromide with steam, 1 : 3-*dibenzyloxy*-5-*bromobenzene* formed prisms (15 g.), m. p. 66°, from light petroleum (b. p. 40—60°) or aqueous methanol (Found : C, 64·3; H, 4·6; Br, 22·5. $C_{20}H_{17}O_2Br$ requires C, 65·0; H, 4·6; Br, 21·7%).

Methyl 2 : 4-*Dibenzyloxy*-6-*hydroxybenzoate*.—A solution of methyl 2 : 4 : 6-trihydroxybenzoate (Herzig, Wenzel, and Tolk, *Monatsh.*, 1902, **23**, 86) (5 g.), potassium carbonate (20 g.), and benzyl chloride (6·6 ml., 2·2 mol.) in boiling acetone (200 ml.) was refluxed for 20 hr.; a solution of the product in ether was shaken with 2N-aqueous sodium hydroxide, giving the sodium derivative of methyl 2 : 4-dibenzyloxy-6-hydroxybenzoate (3 g.). This was collected, washed with ether, and decomposed with an excess of 2N-hydrochloric acid to give *methyl* 2 : 4-*dibenzyloxy*-6-*hydroxybenzoate* which separated from dilute methanol in needles, m. p. 117° (Found : C, 71·8; H, 5·5. $C_{22}H_{20}O_5$ requires C, 72·5; H, 5·5%). This ester, which is moderately soluble in methanol or benzene and sparingly soluble in light petroleum (b. p. 60—80°), has an intense reddish brown ferric reaction in alcohol. Concentration of the ethereal liquors remaining after isolation of the sodium salt furnished a small amount of a *substance*, forming needles, m. p. 110°, from methanol, with an intense reddish brown ferric reaction (Found : C, 76·5; H, 5·9. $C_{29}H_{26}O_5$ requires C, 76·6; H, 5·8%). This is probably a *C*-benzyl derivative of methyl 2 : 4-dibenzyloxy-6-hydroxybenzoate.

OO-*Dibenzylphloroglucinol*.—Prepared by the simultaneous hydrolysis and decarboxylation of methyl 2 : 4-dibenzyloxy-6-hydroxybenzoate (6 g.) in boiling 2N-aqueous sodium hydroxide (200 ml.) during 2 hr., OO-*dibenzylphloroglucinol* separated from benzene–light petroleum (b. p. 60—80°) in needles (4·5 g.), m. p. 94° (Found : C, 78·5; H, 6·0. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%). Methylation of this by the methyl sulphate–potassium carbonate method furnished a quantitative yield of *OO*-dibenzyl-*O*-methylphloroglucinol, b. p. 179°/0·005 mm., debenzylated quantitatively by hydrogenolysis to *O*-methylphloroglucinol, m. p. and mixed m. p. 76°.

3 : 5-*Dihydroxydiphenyl Ether*.—(*a*) A stirred mixture of the potassium salt of *OO*-dimethylphloroglucinol (7·7 g.), bromobenzene (6·3 g.), and copper bronze was kept at 220—230° for 2½ hr., the excess of bromobenzene was removed with steam, and the residual liquor acidified and extracted with ether. Evaporation of the extracts which had been washed with 2N-aqueous sodium hydroxide, left 3 : 5-*dimethoxydiphenyl ether*, which was purified by distillation and then crystallisation from light petroleum (b. p. 40—60°), forming plates (4—5 g.), b. p. 135—140°/0·5 mm., m. p. 62·5° [Found : C, 73·0; H, 6·0; OMe, 27·3. $C_{12}H_8O(OMe)_2$ requires C, 73·0; H, 6·1; OMe, 27·0%]. This ether (1·2 g.) was obtained from potassium phenoxide (2·2 g.), 1-bromo-3 : 5-dimethoxybenzene (5 g.) and copper bronze (0·1 g.) by the same method.

The demethylation of 3 : 5-dimethoxydiphenyl ether (5 g.) with boiling hydriodic acid (50 ml.; *d* 1·7) containing acetic acid (from 35 ml. of anhydride) for 1 hr. gave an alkali-soluble fraction from which light petroleum (b. p. 40—60°) extracted a little phenol. Subsequent extraction with hot benzene gave 3 : 5-*dihydroxydiphenyl ether* in needles (0·6 g.), m. p. 70° (Found : C, 71·6; H, 5·0. $C_{12}H_{10}O_3$ requires C, 71·3; H, 5·0%). The *di*-p-*nitrobenzoate* separated from alcohol in pale yellow needles, m. p. 138° (Found : N, 5·5. $C_{26}H_{16}O_9N_2$ requires N, 5·6%).

Aluminium chloride or bromide in warm benzene or potassium hydroxide in hot ethylene glycol was less effective for this demethylation.

(*b*) An intimate mixture of potassium phenoxide (1·5 g.), 1 : 3-dibenzyloxy-5-bromobenzene (3·7 g.), and copper bronze (0·1 g.) was maintained at 200° for 3 hr., diluted with water (50 ml.), and extracted with ether (100 ml.). After being washed with 2N-aqueous sodium hydroxide (3 × 30 ml.), evaporation of this extract left 3 : *5-dibenzyloxydiphenyl ether*, forming rosettes of needles (1 g.), m. p. 72°, from light petroleum (b. p. 40—60°) (Found : C, 81·6; H, 5·8. $C_{26}H_{22}O_3$ requires C, 81·7; H, 5·8%). Hydrogenolysis of this ether (1 g.) dissolved in methanol (100 ml.) furnished 3 : 5-dihydroxydiphenyl ether (0·25 g.), m. p. 70°, identical with the specimen prepared by method (*a*).

(*c*) Prepared by the interaction of the potassium salt of *OO*-dimethylphloroglucinol (6 g.), *p*-fluoronitrobenzene (8 g.), and copper bronze (0·1 g.) at 160—170° for 1 hr., 3 : *5-dimethoxy-4'-nitrodiphenyl ether* separated from alcohol or light petroleum (60—80°) in rhombs (8·3 g.), m. p. 118° [Found : C, 61·4; H, 4·9; N, 5·1; OMe, 22·0. $C_{12}H_7O_3N(OMe)_2$ requires C, 61·1; H, 4·8; N, 5·1; OMe, 22·5%]. Catalytic reduction of this ether (1·4 g.) in methanol (125 ml.) with a palladium–charcoal catalyst gave *4'-amino-*3 : *5-dimethoxydiphenyl ether*, as pale buff rhombs (1·1 g.), m. p. 95° [from light petroleum (b. p. 80—100°)] [Found : C, 68·4; H, 6·1; N, 5·8; OMe, 25·3. $C_{12}H_9ON(OMe)_2$ requires C, 68·6; H, 6·2; N, 5·7; OMe, 25·3%]. The *acetate* separated from aqueous methanol in plates, m. p. 106° [Found : N, 4·9; OMe, 21·8. $C_{14}H_{11}O_2N(OMe)_2$ requires N, 4·9; OMe, 21·3%].

A solution of the diazonium salt from this amine (2·45 g.) was slowly mixed with cold 50% hypophosphorous acid (30 ml.), and 12 hr. later the product was isolated with ether and purified with steam, yielding 3 : 5-dimethoxydiphenyl ether (1·3 g.).

(*d*) Prepared from the potassium salt of *OO*-dibenzylphloroglucinol (1·25 g.), *p*-fluoronitrobenzene (1·8 g.), and copper bronze (0·1 g.) at 150° for 2½ hr. with removal of excess of nitro-compound with steam, 3 : *5-dibenzyloxy-4'-nitrodiphenyl ether* separated from alcohol in needles (1·2 g.), m. p. 97° (Found : C, 73·1; H, 4·9; N, 3·1. $C_{26}H_{21}O_5N$ requires C, 73·1; H, 5·0; N, 3·3%). The attempted preparation of this ether from *p*-nitrophenol and 1 : 3-dibenzyloxy-5-bromobenzene was unsuccessful.

Hydrogenolysis of 3 : 5-dibenzyloxy-4'-nitrodiphenyl ether (2 g.) in methanol (125 ml.) gave 4'-amino-3 : 5-dihydroxydiphenyl ether which separated from ethyl acetate in rhombs (0·8 g.), m. p. 182°, and was characterised as the *triacetate*, prisms, m. p. 142° (from benzene) (Found : N, 4·1. $C_{18}H_{17}O_6N$ requires N, 4·1%).

4'-Amino-3 : 5-dihydroxydiphenyl ether (3 g.), dissolved in 2N-hydrochloric acid (30 ml.), was diazotised at 0° with a solution of sodium nitrite (1 g.) in a little water, and the mixture treated with 50% hypophosphorous acid (20 ml.), added during ½ hr. The mixture was kept for 24 hr. at 0°, and 3 : 5-dihydroxydiphenyl ether (0·2 g.), m. p. and mixed m. p. 70°, then isolated with ether.

3 : *5-Dibenzyloxy-2'-carboxydiphenyl ether.*—This was prepared in low yield by the interaction of the potassium salt of *OO*-dibenzylphloroglucinol (5 g.), ethyl *o*-fluorobenzoate (5·6 g.), and copper bronze (0·1 g.) at 180° for 1 hr., followed by hydrolysis with 10% aqueous alcoholic sodium hydroxide (100 ml.) of the resulting crude ester. The *acid* separated from aqueous methanol or benzene in prisms (1 g.), m. p. 142° (Found : C, 74·8; H, 5·2. $C_{27}H_{22}O_5$ requires C, 76·0; H, 5·2%).

*2'-Carboxy-*3 : *5-dimethoxydiphenyl Ether* (With V. VENKATESWARLU).—Prepared by the interaction of the potassium salt of *OO*-dimethylphloroglucinol (6 g.), copper bronze (0·1 g.), and ethyl *o*-fluorobenzoate (8 g.), by the standard method, *2'-ethoxycarbonyl-*3 : *5-dimethoxydiphenyl ether* (6 g.) was purified by distillation (b. p. 185°/0·5 mm.) and then by crystallisation from aqueous ethanol, forming plates, m. p. 49° (Found : C, 67·6; H, 5·8. $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%). Hydrolysis of this with warm 10% alcoholic sodium hydroxide furnished *2'-carboxy-*3 : *5-dimethoxydiphenyl ether* which separated from aqueous methanol in plates, or from water or benzene in prisms (yield 90%), m. p. 138° [Found : C, 65·3; H, 5·3; OMe, 22·7. $C_{13}H_8O_3(OMe)_2$ requires C, 65·7; H, 5·2; OMe, 22·6%].

Attempts to prepare 2-chlorocarbonyl-3 : 5-dimethoxydiphenyl ether, under a variety of conditions gave only a low yield of the requisite derivative together with much 1 : *3-dimethoxyxanthone* which separated from alcohol in almost colourless plates, m. p. 169—170° [Found : C, 70·2; H, 4·7; OMe, 24·0. $C_{13}H_6O_2(OMe)_2$ requires C, 70·3; H, 4·7; OMe, 24·2%], identical with a specimen (1·2 g.) prepared by the cyclisation of 2'-carboxy-3 : 5-dimethoxydiphenyl ether (2 g.) with concentrated sulphuric acid during 24 hr. Demethylation of this xanthone with boiling hydriodic acid–acetic acid gave 1 : 3-dihydroxyxanthone which separated from aqueous alcohol in yellow plates, m. p. 258—260° (Found : C, 68·5; H, 3·3. Calc. for $C_{13}H_8O_4$: C, 68·4; H, 3·5%) (cf. Nishikawa and Robinson, *J.*, 1922, **121**, 839, who record m. p. 251°).

5-O-*Benzyl*-3-O-*methylphloroglucinol* (With V. VENKATESWARLU).—A solution of methyl 2 : 6-dihydroxy-4-methoxybenzoate (50 g.) in boiling acetone (250 ml.), containing benzyl bromide (42 g.) and potassium carbonate (60 g.), was refluxed for 10 hr. On isolation the resulting *methyl* 2-*benzyloxy*-6-*hydroxy*-4-*methoxybenzoate* formed plates (55 g.), m. p. 82°, from methanol (Found : C, 67·1; H, 5·9. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). Simultaneous hydrolysis and decarboxylation of this ester (50 g.) with a boiling solution of potassium hydroxide (50 g.) in water (250 ml.) for 1 hr. furnished 5-O-*benzyl*-3-O-*methylphloroglucinol* (yield, 90%), b. p. 172°/3 mm. (Found : C, 73·5; H, 5·4. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%).

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