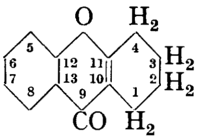
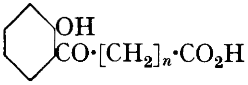
64. *Reactions of* 1 : 2 : 3 : 4-*Tetrahydroxanthone.*

By H. I. Hall and S. G. P. Plant.

1 : 2 : 3 : 4-Tetrahydroxanthone (I ; named in this paper " tetrahydroxanthone ") has been prepared by the condensation of phenol with ethyl *cyclo*hexanone-2-carboxylate in the presence of phosphoric oxide (Simonis reaction) ; it has previously been obtained by Sen (*J. Indian Chem. Soc.*, 1929, **6**, 925) by an unambiguous method. It was unaffected by nitric acid in acetic acid, but, when dissolved in nitric acid (*d* 1·5) at 0°, was transformed solely into 7-*nitrotetrahydroxanthone*, the structure of which was established by conversion through the *amine* into 7-*chlorotetrahydroxanthone* ; the latter was synthesised from *p*-chlorophenol by the Simonis reaction.

(I.)





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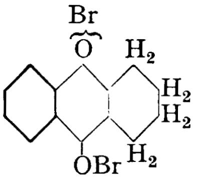


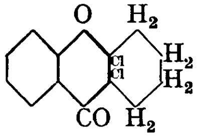
(III.)

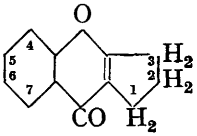
On fission with boiling aqueous-alcoholic potassium hydroxide tetrahydroxanthone gave *cyclo*hexanone, salicylic acid, and ε-o-*hydroxybenzoylhexoic acid* (II ; $n = 5$), but no phenol, a result which confirms the structure assigned to it. A very small quantity of a neutral *substance*, m. p. 130°, was obtained from the reaction mixture. This appears to be a secondary product derived from the intermolecular condensation of *cyclo*hexanone, since the same compound was obtained under similar conditions from 7-methyltetrahydroxanthone.

When tetrahydroxanthone was treated with bromine in acetic acid or carbon disulphide solution, an additive product, which liberated iodine from aqueous potassium iodide and was apparently the compound (III) (compare Baker and Robinson, J., 1925, **127**, 1424), separated, but when the acetic acid solution was boiled, a complex reaction ensued with the evolution of much hydrogen bromide. From the product a small quantity of a *dibromo*-compound which may be 5 : 7-dibromotetrahydroxanthone was isolated. It has not been possible definitely to confirm its identity, since the compound did not undergo smooth degradation with alkali and attempts to apply the Simonis reaction to 2 : 4-dibromophenol have been unsuccessful.

Tetrahydroxanthone combined additively with chlorine in carbon tetrachloride, and the product, since it was stable in the presence of aqueous potassium iodide, was apparently 10 : 11-*dichlorohexahydroxanthone* (IV). The absence of nuclear substitution

(IV.)





(V.)

was confirmed by the fact that with boiling aqueous-alcoholic alkali the compound yielded *cyclo*hexanone, salicylic acid, and the acid (II; $n = 5$). Further confirmation was obtained by the preparation of 7-methyltetrahydroxanthone from *p*-cresol by the Simonis reaction and its conversion into a similar *dichloride* under analogous conditions. The latter was also degraded with alkali, *cyclo*hexanone and 5-methylsalicylic acid being obtained.

The condensation of phenol with ethyl *cyclo*pentanone-2-carboxylate in the presence of phosphoric oxide has yielded 2 : 3-*dihydropentachromone* (V), which, with fuming nitric acid, has given its 6-*nitro*-derivative. The compound (V), on degradation with alkali, gave δ-*o*-hydroxybenzoylvaleric acid (II; $n = 4$) as the sole product.

There has been much published work in recent years (see *Ann. Reports*, 1931, **28**, 155; Robertson and collaborators, J., 1932, 1180, 1681; Chakravarti, *J. Indian Chem. Soc.*, 1931, **8**, 619; 1932, **9**, 25, 31, 389) on the course of the condensation between phenols and β-ketonic esters in the presence of phosphoric oxide, and it has been established that in many cases the product is not the chromone but the isomeric coumarin. The applications of the Simonis reaction now described are interesting from this point of view. In addition to those mentioned, 7-*bromotetrahydroxanthone* has been prepared from *p*-bromophenol. The structures of 7-methyl-, 7-chloro-, and 7-bromo-tetrahydroxanthone have been established by degradation with alkali, in each case *cyclo*hexanone together with the corresponding derivatives of salicylic acid and of ε-*o*-hydroxybenzoylhexoic acid being obtained.

EXPERIMENTAL.

Tetrahydroxanthone.—P_2O_5 (60 g.) was added to a solution of PhOH (40 g.) in ethyl *cyclo*hexanone-2-carboxylate (40 g.), and, after a few min., a vigorous reaction with considerable frothing took place. When cold, the residue was treated with ice, NaOH (60 g. in H_2O), and Et_2O, and stirred mechanically until two clear layers remained. The ethereal solution was shaken with NaOH aq., dried with $CaCl_2$, and evaporated. The residue, when distilled, gave tetrahydroxanthone (b. p. 195—212°/9 mm.), colourless plates (5·5 g.), m. p. 104°, from petroleum (b. p. 60—80°) (Found : C, 78·2; H, 6·2. Calc. : C, 78·0; H, 6·0%).

Nitration of Tetrahydroxanthone.—A solution of tetrahydroxanthone (0·5 g.) in HNO_3 (10 c.c., *d* 1·5) at 0° was kept in ice for 1 hr. and then poured on ice-water. The ppt. melted at 171—191°, and, on crystn. twice from EtOH, gave 7-*nitrotetrahydroxanthone* in pale yellow needles, m. p. 203° (Found : C, 63·9; H, 4·7. $C_{13}H_{11}O_4N$ requires C, 63·7; H, 4·5%).

The latter compound (2 g.) in the min. quantity of AcOH at 40° was treated gradually with Zn dust (8 g.), and, after the mixture had been made alkaline with NaOH aq., the product was extracted with Et_2O. When the extract had been dried (K_2CO_3) and evaporated, the residue was dissolved in dil. HCl, the solution filtered, and 7-*aminotetrahydroxanthone*, yellow needles, m. p. 179° (after crystn. twice from EtOH), was recovered by pptn. with alkali (Found : C, 72·8; H, 6·1. $C_{13}H_{13}O_2N$ requires C, 72·6; H, 6·0%). A cold solution of this amine (0·86 g.) in dil. HCl was diazotised and slowly added with shaking to cuprous chloride (0·7 g.) in a little conc. HCl. After a short time the product was extracted with Et_2O, purified by boiling in EtOH with charcoal, and recovered from the EtOH by pptn. with H_2O; 7-*chlorotetrahydroxanthone*, colourless needles, m. p. 151—153°, from EtOH, identical (mixed m. p.) with a synthetical specimen, was obtained (Found : C, 66·1; H, 4·6. $C_{13}H_{11}O_2Cl$ requires C, 66·5; H, 4·7%).

Degradation of Tetrahydroxanthone with Alkali.—A mixture of tetrahydroxanthone (3 g.), KOH aq. (10 c.c. of 30%), and EtOH (20 c.c.) was refluxed for 1 hr. and then steam-distilled. The distillate (100 c.c.) was treated with $NHPh{\cdot}NH_2$ (2 c.c.) and shaken; *cyclo*hexanone-phenylhydrazone separated and was converted, after the addition of conc. H_2SO_4 (12 c.c.), into tetrahydrocarbazole (1·1 g.; identified by mixed m. p.) by boiling. The solution remaining from the steam distillation was filtered from a small quantity of neutral solid, acidified with conc. H_2SO_4, and then made alkaline with Na_2CO_3 aq. When steam-distilled, the absence of PhOH in the distillate was demonstrated with $FeCl_3$ aq., and the residual solution was again acidified with conc. H_2SO_4. The ppt. was extracted with Et_2O and dried with Na_2SO_4; the residue, after evaporation, was dissolved in MeOH, the solution saturated with dry HCl and refluxed for 5 hr. The esters obtained by dilution with H_2O were taken up in Et_2O, shaken with Na_2CO_3 aq., and recovered by evaporation. After steam distillation, the volatile ester was hydrolysed with KOH aq. and yielded salicylic acid (0·85 g.) (mixed m. p.). The non-volatile ester, on hydrolysis, gave ε-o-*hydroxybenzoylhexoic acid* (1·3 g.), colourless plates, m. p. 97—99°, from petroleum (b. p. 60—80°) (Found : C, 66·3; H, 7·0. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). The acid gave a purple colour with $FeCl_3$ aq., and its methyl ester separated from MeOH in colourless plates, m. p. 40—42°.

7-*Chloro- and* 7-*Bromo-tetrahydroxanthone.*—A mixture of ethyl *cyclo*hexanone-2-carboxylate (40 g.), *p*-chlorophenol (54 g.), and P_2O_5 (60 g.) was heated on the steam-bath for 20 min., allowed to cool, and mechanically stirred with ice, NaOH (60 g. in H_2O), and Et_2O until completely dissolved. After the ethereal solution had been shaken with NaOH aq., dried, and evaporated, the semi-solid residue gave 7-chlorotetrahydroxanthone (6·0 g.) in colourless needles, m. p. 154°, on crystn. from EtOH. This compound (4·5 g.), when degraded with aq.-alc. KOH, gave *cyclo*hexanone (estimated as 1·5 g. of tetrahydrocarbazole), 5-chloro-2-hydroxybenzoic acid (1·0 g. Found : C, 48·8; H, 2·9. Calc. : C, 48·7; H, 2·9%), m. p. 172° (after crystn. from EtOH aq.), and ε-5-*chloro*-2-*hydroxybenzoylhexoic acid* (1·0 g.), colourless plates, m. p. 122°, from EtOH (Found : C, 57·7; H, 5·7. $C_{13}H_{15}O_4Cl$ requires C, 57·7; H, 5·5%).

7-*Bromotetrahydroxanthone*, prepared like the 7-chloro-compound, separated from EtOH or petroleum in colourless needles, m. p. 151° (Found : Br, 28·2. $C_{13}H_{11}O_2Br$ requires Br, 28·7%), and, on degradation (3 g.) with aq.-alc. KOH, yielded *cyclo*hexanone (0·7 g. tetrahydrocarbazole), 5-bromo-2-hydroxybenzoic acid (0·7 g.), m. p. 163—165° (identified by mixed m. p. with a specimen prepared as described by Hewitt, Kenner, and Silk, J., **1904**, **85**, 1228), and ε-5-*bromo*-2-*hydroxybenzoylhexoic acid* (1·1 g.), colourless plates, m. p. 120°, from EtOH (Found : C, 49·8; H, 4·9. $C_{13}H_{15}O_4Br$ requires C, 49·5; H, 4·8%).

Bromination of Tetrahydroxanthone.—When tetrahydroxanthone in AcOH was treated at room temp. with an equimolecular quantity of Br, the dibromide (III), yellow prisms, m. p. 115°, after rapid crystn. from AcOH, separated as a red oil which soon solidified. It instantaneously liberated I from KI aq., and gave tetrahydroxanthone on treatment with NaOH aq. or NH_3 aq. The same compound separated when tetrahydroxanthone was treated with Br in CS_2.

When a solution of tetrahydroxanthone (16 g.) in warm AcOH was treated with Br (14 g. in AcOH) and then boiled for ½ hr., the deep red colour changed rapidly to yellow and HBr was freely evolved. After cooling, the solution was poured on excess of ice–NH_3 aq., and the product extracted with Et_2O. When the extract had been dried ($CaCl_2$) and evaporated, the residue gave ? : ?-*dibromotetrahydroxanthone* (1·2 g.) in colourless prisms, m. p. 147°, on crystn. from EtOH and then petroleum (b. p. 60—80°) (Found : C, 43·3, 43·5; H, 2·6, 2·8; Br, 45·0. $C_{13}H_{10}O_2Br_2$ requires C, 43·6; H, 2·8; Br, 44·7%). The m. p. was greatly depressed by admixture with 7-bromotetrahydroxanthone.

Chlorination of Tetrahydroxanthone.—When a solution of tetrahydroxanthone (8 g.) in CCl_4 (60 c.c.) at 20° was treated with Cl (2·84 g. in 45 c.c. CCl_4) a slight turbidity developed, but no definite product separated. The CCl_4 was distilled off completely on the steam-bath, only a trace of HCl being evolved, and the oily residue, when rubbed with EtOH, gave 10 : 11-*dichlorohexahydroxanthone*, colourless plates (3·9 g.), m. p. 64—65°, from EtOH (Found : C, 57·7, 57·2; H, 4·5, 4·4; Cl, 26·4. $C_{13}H_{12}O_2Cl_2$ requires C, 57·6; H, 4·4; Cl, 26·2%). This compound (4·9 g.), which did not liberate I from KI aq., on degradation with aq.-alc. KOH, gave *cyclo*hexanone (0·5 g. tetrahydrocarbazole), salicylic acid (0·5 g.), and a little ε-*o*-hydroxybenzoylhexoic acid (m. p. 97—99°, after being twice crystallised from petroleum).

Chlorination of 7-*Methyltetrahydroxanthone.*—Prepared like tetrahydroxanthone, *p*-cresol being used, 7-methyltetrahydroxanthone was collected at 220—240°/24 mm. and separated from petroleum (b. p. 60—80°) in colourless needles, m. p. 102—103° (Found : C, 78·5; H, 6·9. Calc. : C, 78·5; H 6·5%) (Sen, *loc. cit.*, gives m. p. 113°). On degradation (4 g.) with aq.-alc. KOH, it gave *cyclo*hexanone (1·1 g. tetrahydrocarbazole), 5-methylsalicylic acid (0·9 g.), m. p. 151° (Found : C, 62·9; H, 5·3. Calc. : C, 63·2; H, 5·3%), and ε-2-*hydroxy*-5-*methyl*-

benzoylhexoic acid (1·4 g.; intense violet colour with $FeCl_3$ aq.), colourless needles, m. p. 87°, from petroleum (b. p. 60—80°) (Found: C, 67·5; H, 7·4. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%), but no *p*-cresol.

When the 7-methyl compound was chlorinated (7 g.) as for tetrahydroxanthone, 10 : 11-*dichloro-7-methylhexahydroxanthone* (4·5 g.), colourless plates, m. p. 110—111°, from EtOH, was obtained (Found: C, 58·6, 58·5; H, 4·9, 4·9. $C_{14}H_{14}O_2Cl_2$ requires C, 58·9; H, 4·9%). This compound did not liberate I from KI aq., and, on degradation (3·5 g.) with aq.-alc. KOH, it gave *cyclo*hexanone (0·25 g. tetrahydrocarbazole) and 5-methylsalicylic acid (0·45 g.).

2 : 3-*Dihydropentachromone*.—Prepared like tetrahydroxanthone, ethyl *cyclo*pentanone-2-carboxylate being used, 2 : 3-*dihydropentachromone* was collected at 185—195°/20 mm., and obtained from petroleum (b. p. 60—80°) in colourless plates, m. p. 120—121° (Found: C, 77·6; H, 5·5. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%). On degradation with aq.-alc. KOH this compound (4 g.) yielded no *cyclo*pentanone, phenol, or salicylic acid, the sole product being δ-*o*-hydroxybenzoylvaleric acid (3·3 g.), colourless plates, m. p. 93—94°, from benzene–petroleum, identical (mixed m. p.) with the compound described by Paterson and Plant (J., 1925, **127**, 1797).

6-*Nitro*-2 : 3-*dihydropentachromone*, prepared like 7-nitrotetrahydroxanthone, separated from EtOH in almost colourless needles, m. p. 184° (Found: C, 62·6; H, 4·1. $C_{12}H_9O_4N$ requires C, 62·3; H, 3·9%), and, on reduction as before, yielded 6-*amino*-2 : 3-*dihydropentachromone*, pale yellow needles, m. p. 240°, from EtOH (Found: N, 7·2. $C_{12}H_{11}O_2N$ requires N, 7·0%).

THE DYSON PERRINS LABORATORY, OXFORD.

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