

# SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

## Part VI. Synthesis of Halo and Nitro Derivatives of Dihydroxy Xanthenes

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THE insecticidal properties of xanthenes and their derivatives were reported by a number of workers<sup>1-5</sup> but little work seems to have been done on the physiological activity of hydroxy and methoxy xanthenes. With a view to correlating the chemical constitution and insecticidal activity in the xanthenes, halo and nitro derivatives of 3:6- and 1:6-dihydroxy xanthenes and their methyl ethers have been made and tested as potential insecticides.

The important methods used in the past for the synthesis of xanthenes are (a) the condensation of *o*-hydroxy benzoic acids with phenols,<sup>6</sup> (b) the ring closure of *o*-aryloxy benzoic acids<sup>7</sup> and (c) the condensation of *o*-hydroxy-aryl nitriles with phenols.<sup>8</sup> The first of these three methods has been studied very extensively using different catalysts and reaction conditions as well as different derivatives of the starting components.<sup>9-18</sup> One of such modifications is due to Shah and co-workers<sup>16-18</sup> who made use of the mixture of phosphorous oxychloride and fused zinc chloride to effect a smooth condensation of *o*-hydroxy benzoic acids and reactive phenols. It is reported to give good yields of relatively pure hydroxy xanthenes under mild conditions, and has been adopted in the present investigation. It leads to the formation of either the intermediate hydroxy benzophenones or directly the xanthenes, depending on the nature of the phenolic acid and phenol made use of.

Following this method, chloro and nitro resorcylic acids have been condensed with resorcinol, chloro resorcinol and orcinol, and the results obtained are summarised in Table I.

Direct isolation of xanthenes in the condensations with orcinol confirms the earlier observation of Shah and co-workers that xanthenes were formed in these cases owing to the greater reactivity of  $\gamma$ -position and the instantaneous cyclisation of the intermediate benzophenones.

Along with the above syntheses a number of halo and nitro derivatives of 3:6-dihydroxy xanthone have been prepared by direct halogenation and

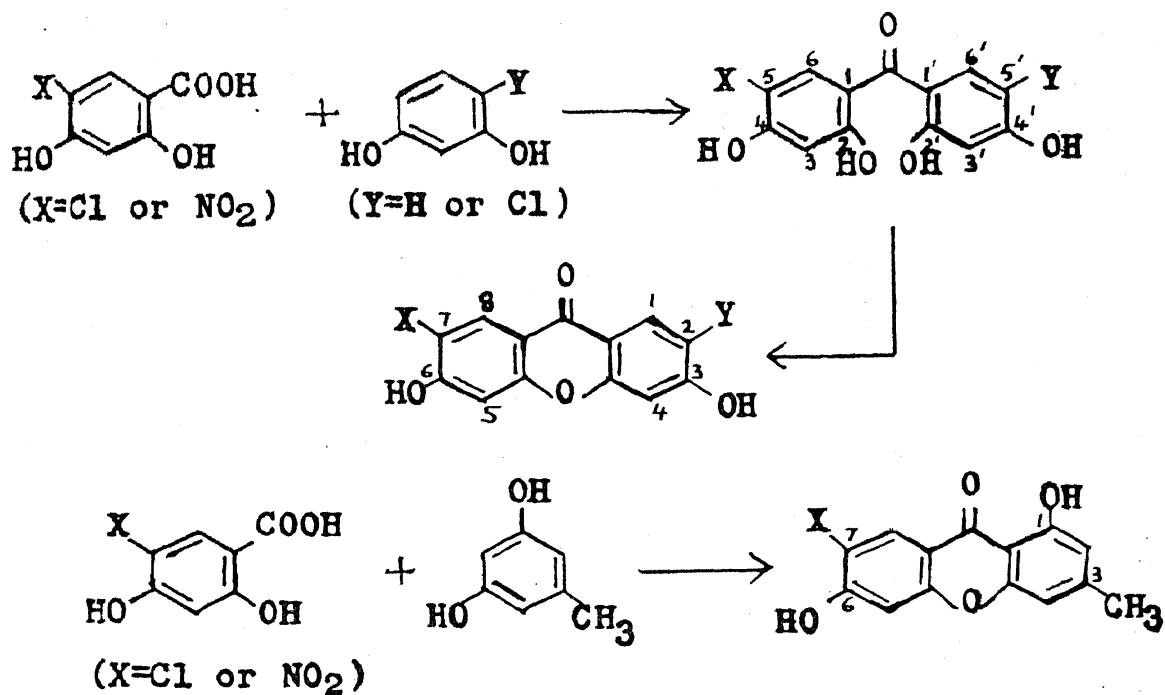


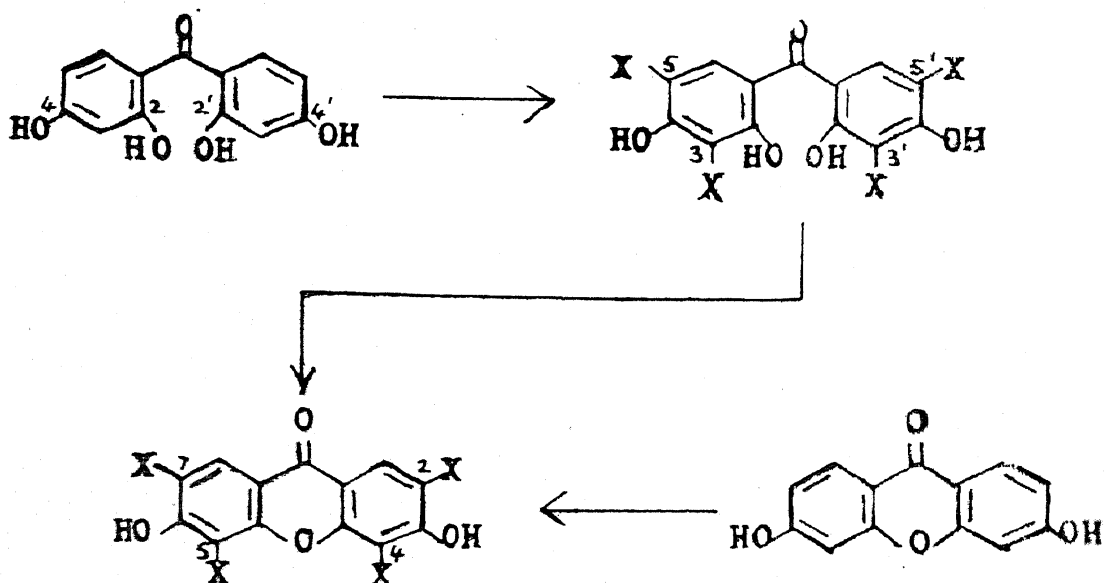
TABLE I

Products of condensation of chloro and nitro resorcylic acids with resorcinol, chloro resorcinol and orcinol

Sl. No.	Hydroxy acid	Phenol condensed	Primary product obtained	Xanthone obtained by cyclisation
1.	5-Chloro- $\beta$ -resorcylic acid	Resorcinol	5-Chloro-2:2':4:4'-tetrahydroxy benzophenone	2-Chloro-3:6-dihydroxy xanthone
2.	do.	4-Chloro-resorcinol	5:5'-Dichloro-2:2':4:4'-tetrahydroxy benzophenone	2:7-Dichloro-3:6-dihydroxy xanthone
3.	do.	Orcinol	7-Chloro-3-methyl-1:6-dihydroxy xanthone	..
4.	5-Nitro- $\beta$ -resorcylic acid	Resorcinol	5-Nitro-2:2':4:4'-tetrahydroxy benzophenone	Could not be cyclised
5.	do.	Orcinol	7-Nitro-3-methyl-1:6-dihydroxy xanthone	..

nitration of the xanthone as well as by substitution in the intermediate benzophenone and subsequent cyclisation. 2:2':4:4'-Tetrahydroxy benzophenone yields, by chlorination, bromination and nitration with excess of the appropriate reagent, the corresponding 3:3':5:5'-tetra-substituted products. Bromination under controlled conditions, however, gave the 5:5'-dibromobenzophenone. The tetrachloro, tetrabromo and dibromo benzophenones could be cyclised to 2:4:5:7-tetrachloro-, 2:4:5:7-tetrabromo and 2:7-dibromo-3:6-dihydroxy xanthenes, respectively. Attempts to cyclise the nitro benzophenone however have been unsuccessful.

Chlorination, bromination and nitration of 3:6-dihydroxy xanthone resulted in the formation of the corresponding 2:4:5:7-tetra-substituted derivatives, the chloro and bromo compounds being identical with those obtained by the cyclisation of the respective tetrachloro- and bromo-benzophenones. The tetrabromo xanthone was found to be identical with the one reported by Meyer and Conzetti.<sup>19</sup>



Since the methyl ethers are known to possess better insecticidal activity compared to the free hydroxy xanthenes, the various hydroxy xanthenes prepared have been converted into their methyl ethers.

All the hydroxy xanthenes and their methyl ethers have been tested against fish following the procedure of Krishnaswamy and Seshadri,<sup>20</sup> taking the turning time as criterion.

Halo and nitro derivatives of 3:6-dihydroxy xanthone are feebly toxic, whereas the derivatives of 1:6-dihydroxy-3-methyl xanthone are comparatively more toxic. This may be attributed to the ability of these compounds to form chelated metal complexes owing to the hydroxyl in one position being ortho to the carbonyl group. The methyl ethers have been found to be more active than the corresponding hydroxy xanthenes. Details of the results of the toxicity experiments will be published elsewhere.

### EXPERIMENTAL

#### I. 2-Chloro-3:6-Dihydroxy Xanthone

(a) 5-Chloro-2:2':4:4'-tetrahydroxy benzophenone.—A mixture of 5-chloro- $\beta$ -resorcylic acid<sup>21</sup> (1 g.), resorcinol (1.25 g.) fused zinc chloride (3 g.) and phosphorous oxychloride (5 ml.) was heated at 70–80° for one hour, and then cooled and poured on crushed ice. The product (0.7 g.) that separated was filtered, and recrystallised from boiling water, prismatic rods, m.p. 190° C. (Found: C, 55.6; H, 3.6;  $C_{13}H_9O_5Cl$  requires C, 55.7; H, 3.2%).

(b) 2-Chloro-3:6-dihydroxy xanthone.—The chlorobenzophenone (0.5 g.) from (a) was heated in a sealed tube with water (20 ml.) at 200–220° for two hours and a half. On cooling, 2-chloro-3:6-dihydroxy xanthone (0.4 g.) separated out. It was filtered, washed and recrystallised from dilute alcohol, micro-needles, m.p. 338° C. (Found: C, 59.1; H, 2.8;  $C_{13}H_7O_4Cl$  requires C, 59.5; H, 2.7%). It did not give any colouration with ferric chloride and gave a bluish-violet fluorescence in alkaline solution.

The methyl ether was prepared by refluxing the xanthone in acetone solution with dimethyl sulphate and anhydrous potassium carbonate for sixteen hours. It crystallised from dilute alcohol as needles, m.p. 210° C. (Found: C, 62.2; H, 4.1;  $C_{15}H_{11}O_4Cl$  requires C, 62.1; H, 3.7%).

#### II. 2:7-Dichloro-3:6-Dihydroxy Xanthone

(a) 5:5'-Dichloro-2:2':4:4'-tetra hydroxy benzophenone.—Condensation of 5-chloro resorcylic acid (1 g.) and 4-chloro resorcinol (1.2 g.) as in I (a) yielded a crystalline substance (0.65 g.), prismatic rods from dilute alcohol, m.p. 207° C. (Found: C, 49.7; H, 2.9;  $C_{13}H_8O_5Cl_2$  requires C, 49.5; H, 2.5%).

(b) 2:7-Dichloro-3:6-dihydroxy xanthone.—Cyclisation of the above benzophenone (0.5 g.) in a sealed tube as in I (b) gave clusters of needles

from alcohol, m.p. 310° C. (Found C, 52.1; H, 2.4;  $C_{13}H_6O_4Cl_2$  requires C, 52.5; H, 2.0%). Its methyl ether crystallised in needles from dilute alcohol, m.p. 237° C. (Found: C, 55.4; H, 3.3;  $C_{15}H_{10}O_4Cl_2$  requires C, 55.4; H, 3.1%).

### III. 2:7-Dibromo-3:6-Dihydroxy Xanthone

(a) 5:5'-Dibromo-2:2':4:4'-tetrahydroxy benzophenone.—To a solution of 2:2':4:4'-tetrahydroxy benzophenone<sup>16</sup> (0.7 g.) in acetic acid (7 ml.) was added drop by drop a solution of bromine (0.8 g.) in acetic acid (8 ml.), and the reaction mixture was kept aside for one hour. The product (0.5 g.) that separated was filtered and recrystallised from alcohol, rectangular rods, m.p. 211° C. (Found: C, 38.2; H, 2.1;  $C_{13}H_8O_5Br_2$  requires C, 38.6; H, 1.9%).

(b) 2:7-Dibromo-3:6-dihydroxy xanthone.—The dibromobenzophenone (0.4 g.) on cyclisation in a sealed tube in aqueous solution at 200–220° C. gave a product (0.35 g.). Crystallisation from alcohol-acetone gave a microcrystalline solid, m.p. 330° C. (Found: C, 40.4; H, 1.9.  $C_{13}H_6O_4Br_2$  requires C, 40.4; H, 1.6%). Methylation of the product gave the corresponding methyl ether, needles from benzene, m.p. 260°. (Found: C, 44.0; H, 2.6;  $C_{15}H_{10}O_4Br_2$  requires C, 43.5; H, 2.4%).

### IV. 5-Nitro-2:2':4:4'-Tetrahydroxy Benzophenone

5-Nitro- $\beta$ -resorcylic acid (2.0 g.) was condensed with resorcinol (2.0 g.) as previously described. The product obtained by pouring the reaction mixture in ice-water was suspended in a saturated solution of sodium bicarbonate. The insoluble material was filtered, washed with a little ice-water, and recrystallised from acetic acid, plates, m.p. 178° C. (Found: C, 53.8; H, 3.0; N, 5.4;  $C_{13}H_9O_7N$  requires C, 53.6; H, 3.1; N, 5.6%).

### V. 2:4:5:7-Tetrachloro-3:6-Dihydroxy Xanthone

A. Chlorination of the xanthone.—To 3:6-dihydroxy xanthone<sup>16</sup> (0.2 g.) in acetic acid (25 ml.) was added with thorough shaking a solution of sulphuryl chloride (0.7 g.) in acetic acid (10 ml.). The reaction mixture was heated at 60–70° for two hours and then gradually raised to 100° C. The product (0.15 g.) was crystallised from dilute alcohol, needles, m.p. 318° C. (Found: C, 42.3; H, 1.6;  $C_{13}H_4O_4Cl_4$  requires C, 42.6; H, 1.1%).

B. Chlorination of benzophenone and cyclisation: (a) 3:5:3':5'-Tetrachloro-2:2':4:4'-tetrahydroxy benzophenone.—2:2':4:4'-Tetrahydroxy-

benzophenone (1.2 g.) was dissolved in acetic acid (14 ml.) and to this a solution of chlorine (0.7 g.) in acetic acid (7 ml.) was added drop by drop and the reaction mixture kept aside for one hour. The product (0.5 g.) obtained by diluting the reaction mixture with water was recrystallised from alcohol, needles, m.p. 238° C. (Found: C, 40.1; H, 1.8;  $C_{13}H_6O_5Cl_4$  requires C, 40.6; H, 1.5%).

(b) 2:4:5:7-Tetrachloro-3:6-dihydroxy xanthone.—Cyclisation of the above benzophenone (0.4 g.) as in previous cases gave the xanthone (0.35 g.), needles from alcohol, m.p. and mixed m.p. with the product obtained in V (A) 317° C. On methylation, it gave a methyl ether which crystallised in needles from alcohol, m.p. 241° C. (Found: C, 45.9; H, 2.3;  $C_{15}H_8O_4Cl_4$  requires C, 45.7; H, 2.0%).

#### VI. 2:4:5:7-Tetrabromo-3:6-Dihydroxy Xanthone

(a) 3:5:3':5'-Tetrabromo-2:2':4:4'-tetrahydroxy benzophenone.—To a solution of 2:2':4:4'-tetrahydroxy benzophenone (0.5 g.) in acetic acid (7 ml.) was added drop by drop a similar solution of bromine (1.2 g.). The compound that separated after leaving the reaction mixture for one hour at room temperature was filtered and recrystallised from alcohol, rectangular rods, m.p. 254° C. (Found: C, 27.9; H, 1.2;  $C_{13}H_6O_5Br_4$  requires C, 27.8; H, 1.1%).

(b) 2:4:5:7-Tetrabromo-3:6-dihydroxy xanthone.—The above benzophenone (0.4 g.), on cyclisation in aqueous solution in a sealed tube, gave the tetrabromo xanthone, micro-needles from alcohol, m.p. and mixed m.p. with the compound obtained by the bromination of 3:6-dihydroxy xanthone.<sup>19</sup> 281° C. Its methyl ether was obtained as needles from benzene, m.p. 230° C. (Found: C, 31.5; H, 1.5;  $C_{15}H_8O_4Br_4$  requires C, 31.4; H, 1.3%).

#### VII. 2:4:5:7-Tetranitro-3:6-Dihydroxy Xanthone

3:6-Dihydroxy xanthone (0.25 g.) was added to nitric acid (*d.* 1.4; 5 ml.) and the mixture was heated on a steam-bath for three hours. The solid that separated was filtered, washed and recrystallised from dilute alcohol, plates, m.p. 240° C. (Found: C, 38.4; H, 1.3; N, 13.5;  $C_{13}H_4O_{12}N_4$  requires C, 38.2; H, 1.0; N, 13.5%).

#### VIII. 3:5:3':5'-Tetranitro-2:2':4:4'-Tetrahydroxy Benzophenone

To a solution of 2:2':4:4'-tetrahydroxy benzophenone (0.5 g.) in acetic acid (10 ml.) was added dropwise a mixture of nitric acid (*d.* 1.4; 2 ml.) and acetic acid (10 ml.) at room temperature. The reaction mixture

was heated to 60–70° and poured on crushed ice. The product that separated was filtered and purified from methyl alcohol, needles, m.p. 178° C. (Found: C, 36.2; H, 1.7;  $C_{13}H_6O_{13}N_4$  requires C, 36.5; H, 1.5%).

*IX. 7-Chloro-1:6-Dihydroxy-3-Methyl Xanthone*

The condensation of 5-chloro- $\beta$ -resorcylic acid with orcinol (1.0 g.) yielded a product that crystallised from dilute alcohol as micro-crystalline solid, m.p. 287° C. (Found: C, 61.2; H, 3.4;  $C_{14}H_9O_4Cl$  requires C, 60.8; H, 3.2%). The substance gave a dark green colour with ferric chloride and greenish fluorescence in alcohol. Its methyl ether crystallised from alcohol in needles, m.p. 230° C. (Found: C, 62.1; H, 4.2;  $C_{15}H_{11}O_4Cl$  requires C, 62.0; H, 3.8%).

*X. 7-Nitro-1:6-Dihydroxy-3-Methyl Xanthone*

5-Nitro- $\beta$ -resorcylic acid (1.0 g.) on condensation with orcinol (1.0 g.) gave transparent plates from alcohol, m.p. 190° C. (Found: C, 57.9; H, 3.6;  $C_{14}H_9O_6N$  requires C, 58.4; H, 3.1%). It gave dark green colour with ferric chloride and green fluorescence in alcohol.

#### SUMMARY

The condensation of resorcinol and 4-chloro resorcinol with chloro- and nitro-substituted  $\beta$ -resorcylic acids, has yielded the corresponding tetrahydroxy benzophenones, which with the exception of those containing nitro groups, could be cyclised to the respective 3:6-dihydroxy xanthenes. In the case of condensations with orcinol, however, 1:6-dihydroxy xanthenes could be directly isolated. A number of halo and nitro derivatives of 3:6-dihydroxy xanthone have also been prepared by direct halogenation and nitration of the xanthone, as well as by substitution in the intermediate benzophenone and subsequent cyclisation.

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