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new one step synthesis of xanthones

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Xanthones and their derivatives have been prepared by condensation of \( \rho \)-hydroxybenzoic acid derivatives with noxydric, dihydric and trihydric phenols in the presence of a condensing agent such as acetic anhydride, Lewis catalysts, a mixture of phosphorus oxychloride and zinc chloride or PPA. In continuation of work on the thesis of benzo-\( \gamma \)-pyrone, a new synthesis of xanthone derivatives is now reported. Smooth condensation of the \( \rho \)-yl or a methyl ester of an \( \rho \)-hydroxy-aromatic acid and a phenol is achieved by heating the mixture under reflux in benzyl ether, without addition of a condensing agent.

Phenols, such as phloroglucinol, orcinol, pyrogallol, \( \alpha \)-naphthol and \( \beta \)-naphthol, when condensed with ethyl salicylate, give directly the corresponding xanthone derivatives. Whereas phenols like resorcinol, 2-methy1resorcinol and catechol, give the corresponding hydroxyxanthones as well as the intermediate isophenone derivatives, less reactive phenols such as resol and 3,4-\( \alpha \)-xylanol give only the corresponding isophenone derivatives, which are dehydrated to the corresponding methyl or dimethyl xanthones by concentrated sulfuric acid (85 per cent). In the case of resorcinol, a mixture of 1-hydroxy- and 3-hydroxyxanthone was obtained, which 3-hydroxyxanthone was preponderant. With orcinol, hydroxy-3-methyl- and 3-hydroxy-1-methylxanthone were obtained, the former as the major product.

These results indicate that \( \gamma \)-substitution in the resorcinol nucleus took place in both cases, which is rather difficult without a condensing agent. A similar observation was made during the condensation of resorcinol with diethyl benzylmalonate.2

A mixture of an ethyl ester of an \( \rho \)-hydroxybenzoic acid and a phenol (1:1mol) is dissolved in the minimum quantity of hot biphenyl ether and is heated under reflux for 1 to 25h, depending upon the reactivity of the phenol. The cooled reaction mixture is diluted with light petroleum or steam distilled and the separated crude product was washed successively with cold sodium hydrogen carbonate to remove any hydrolysed acid and water. The product, a hydroxybenzophenone or a xanthone derivative is suitably purified by passage through a column of alumina (if necessary), followed by crystallisation from an appropriate solvent. Yields vary from 30–65 per cent. All the compounds gave satisfactory elemental analyses and were characterised by the preparation of their methyl ether or acetyl derivatives and by measurements of their infrared and n.m.r. spectra.

Received 7 October 1977

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Studies in the Synthesis of Xanthone Derivatives. Part-I

Synthesis of Furanoxanthones

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Manuscript received 29 May 1978, accepted 30 August 1978

2-MethyIresorcinol, on thermal condensation with ethyl cyclohexanone-2-carboxylate in diphenyl ether gave 6-hydroxy-5-methyl-1,2,3,4-tetrahydroxanthone, which on allylation, Claisen migration, cyclisation with conc. sulphuric acid followed by dehydrogenation with palladised charcoal, gave 4,5'-dimethylfurano(3',2'-2,3)xanthone (III). (III), was also synthesised from 3-hydroxy-4-methylxanthone by similar series of reactions. 5'-Methylfurano(3',2'-2,3)xanthone (V) was synthesised, starting from resorcinol and ethyl cyclohexanone-2-carboxylate and also from 3-hydroxyxanthone. The structures of intermediate dihydrofuranoxanthones were confirmed by NMR spectra.

The synthesis of linear or angular type of Furanoxanthones have been reported by many workers1-6. The synthesis of angular furano compounds is simple, while a linear isomer needs a blocking group8 like an acetyl or a methyl group in order that the Claisen migration of an allyloxy derivative produces an appropriate intermediate for the synthesis of a linear furano compound. Rajagopal and co-workers4 have used this procedure for the synthesis of linear furanoxanthones.

In general, two approaches have been used for the building up of a furan ring especially for α-methyl furano derivatives. The one based on Scheinmann and Suschitzky's work9, gives dihydrofurano compounds, which were dehydrogenated by treatment with N-bromosuccinimide in presence of benzoil peroxide followed by dehydrobromination with pyridine. The second route is an adaptation of the method of Admas and Rindfusz7 involving addition of bromine to α-acetoxy-allyl derivatives followed by cyclisation and dehydrobromination by alcoholic alkali. Rajagopal and co-workers adopted second route for the synthesis of 4,5'-dimethylfurano(2',3'-3,4)xanthone (V), which was also synthesised from 3-hydroxyxanthone by carrying out allylation, Claisen migration and cyclisation with conc. sulphuric acid, followed by dehydrogenation with palladised charcoal. The structure of (V) was confirmed by NMR. The mixed m. p. of the compounds prepared by the above procedures remained unpressed.

Similarly, resorcinol was condensed with ethyl cyclohexanone-2-carboxylate in diphenyl ether to give 6-hydroxy-1,2,3,4-tetrahydroxanthone (Id). (Id), on allylation followed by Claisen migration gave 5'-methylfurano(3',2'-2,3)xanthone (IV), which was also synthesised from 3-hydroxyxanthone by carrying out allylation, Claisen migration and cyclisation with conc. sulphuric acid, followed by dehydrogenation with palladised charcoal. The structure of (V) was confirmed by NMR. The mixed m. p. of the compounds prepared by the above procedures remained unpressed.

Condensation of 2-methyIresorcinol with ethyl cyclohexanone-2-carboxylate in boiling diphenyl ether, according to Desai, Trivedi and Sethna8 gave 6-hydroxy-5-methyl-1,2,3,4-tetrahydroxanthone (Ia). This on allylation followed by Claisen migration gave 3-allyl-6-hydroxy-5-methyl-1,2,3,4-tetrahydroxanthone (Ic). Cyclisation of (Ic) by trituration with conc. sulphuric acid afforded 5,5'-dimethylfurano(3',2'-2,3)xanthone (III). (III), was also synthesised by carrying out allylation of 3-hydroxyxanthone followed by Claisen migration give (Vib). (Vib), was cyclised with conc. sulphuric acid to yield dihydrofuranoxanthone (VII). The structure of (VII) was confirmed by NMR spectrum (CDCl3) : 61.65, 3H doublet, J=7Hz, CH3 group at C5'-CH3 ; 2.47. 3H singlet, -CH3 group at C4'-CH3 ; 2.9-3.7, 2H multiples at C4'-Ha ; 5.15, 1H quartet, J=7Hz, at C5'-H f 7.3-7.8, 3H multiple!, at C5-H, C6-H and C7-H (aromatic) ; 8.0, 1H singlet, at Cx-H ; 8.35, 1H* doublet, J=9Hz, at C8-H. This on dehydrogenation with DDQ in dry benzene gave (III). The mixed m. p. of the compounds prepared by the above procedures remained unpressed.

In the present work, o-hydroxy-allylxanthones were converted into dihydrofuranoxanthones using conc. sulphuric acid, according to Shaikh and Trivedi10. This method is very convenient and gives quantitative yields of dihydrofuranoxanthones, which on dehydrogenation with DDQ in benzene or with palladised charcoal in diphenyl ether gave the corresponding α-methylfuranoxanthones.

In conclusion, the synthesis of furanoxanthones has been successfully achieved by the use of allylation, Claisen migration and cyclisation with conc. sulphuric acid.
group at C5'-CH₃; 6.84, 1H singlet, at C4'-H; 7.45-7.8, 4H multiplet, at C5-H, C6-H and C7-H (aromatic); 8.32, 1H doublet, J=9Hz, at Cl-H; 8.5, 1H doublet, J=9Hz, at C8-H. The mixed m.p. of the compounds (V), obtained by both the procedures, remained undepressed.

Condenser to facilitate the removal of alcohol formed. After cooling, the separated product was filtered and washed several times with petroleum ether. It crystallised from dimethyl formamide, m.p. 270°. Yield 2g (Found : C, 72.90; H, 6.08. C₁₁H₁₄O₂ requires C, 73.05; H, 6.08%).

6-Allyloxy-5-methyl-1,2,3,4-tetrahydroxanthone (Ib):
A mixture of 6-hydroxy-5-methyl-1,2,3,4-tetrahydroxanthone (2g), allylbromide (1g) and anhydrous potassium carbonate (8 g) was refluxed in dry acetone (200 ml) in water bath for 10 hr. The reaction mixture was poured into water. The separated product was filtered, washed with very dilute sodium hydroxide solution to remove unreacted compound, the product crystallised from benzene-petroleum ether, m.p. 110°. Yield 1.5g (Found : C, 75.68; H, 6.34. C₁₁H₁₄O₂ requires C, 75.53; H, 6.66%).

7-Allyl-6-hydroxy-5-methyl-1,2,3,4-tetrahydroxanthone (Ic):
6-Allyloxy-5-methyl-1,2,3,4-tetrahydroxanthone (2g) was refluxed with dimethylaniline (10 ml) for 8 hr. After cooling, the reaction mixture was poured into cone hydrochloric acid (50 ml) containing pieces of ice, the separated product was filtered and dissolved in sodium hydroxide solution. The solution was filtered. The filtrate on acidification with cone hydrochloric acid gave the product, which was crystallised from alcohol. M.p. 221°, yield 1.5 g (Found : C, 75.26; H, 6.20. C₁₇H₁₉O₂ requires C, 75.53; H, 6.66%). IR spectrum : 1625 cm⁻¹ (β-pyronyl>C=O group) and a broad band at 3500 cm⁻¹ (aromatic-OH group).

5,5',-Dimethyl-1,2,3,4,4',5'-hexahydrofurano(2',3'-6,7) xanthone (II):
7-Allyl-6-hydroxy-5-methyl-1,2,3,4-tetrahydroxanthone (1g) was triturated with cone sulphuric acid (5 ml) in a water bath for 15 minutes. The contents were poured into crushed ice, the separated product was filtered and washed with dilute sodium hydroxide solution to remove uncyclised compound. It crystallised from alcohol, m.p. 210°, yield 0.8. (Found : C, 75.18; H, 6.35. C₁₁H₁₄O₂ requires C, 75.53; H, 6.66%). IR spectrum : 1635 cm⁻¹ (β-pyronyl>C=O group).

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4,5'-Dimethylfurano (3',2'-2,3)xanthone (III) :

A mixture of 5, 5'-dimethyl-1,2,3,4,4',5'-hexahydrofurano (2',3'-6,7)xanthone (0.5 g) pallidised charcoal (10%, 0.3 g) and diphenyl ether (5 ml) was refluxed for 10 hr. The reaction mixture was filtered and washed several times with petroleum ether. It crystallised from acetic acid, m.p. 242°. Yield 0.25 g. (Found : C, 77.00 ; H, 4.34. C17H12O3 requires C, 77.27 ; H, 4.55%). IR spectrum 1640 cm⁻¹ (ν-pyronyl C=O group), 825 cm⁻¹ (furan ring).

5, 5'-Dimethyl(2',3'-2,3)xanthone (IV) :

A mixture of 5'-methyl-1,2,3,4,4',5'-hexanhydrofurano (3',2'-2,3)xanthone (0.6 g) and DDQ (0.535 g) was refluxed in sodium dried benzene (30 ml) in a water bath for 15 minutes. The reaction mixture was worked up as described above. The product crystallised from benzene-petroleum ether, m.p. 278°, yield 2 g. (Found : C, 77.13 ; H, 5.14. C18H16O3 requires C, 76.67 ; H, 5.26%). IR spectrum 1635 cm⁻¹ (ν-pyronyl C=O group) and a broad band at 3200 cm⁻¹ (aromatic -OH group).

5'-Allyl-6-hydroxy-1,2,3,4-tetrahydroxanthone (V) :

A mixture of 6-hydroxy-1,2,3,4-tetrahydroxanthone (2 g), allylbromide (1 g) and anhydrous potassium carbonate (8 g) was refluxed in dry acetone (200 ml) in a water bath for 10 hr. The reaction mixture was worked up as described above, the product crystallised from petroleum ether, m.p. 172°, yield 1.5 g. (Found : C, 75.00 ; H, 6.25%).

2-Allyl-3-hydroxy-4-methylxanthone (VI) :

A mixture of 3-hydroxy-4-methylxanthone (2.5 g), allylbromide (2 g) and anhydrous potassium carbonate (12 g) was refluxed in dry acetone (300 ml) in a water bath for 11 hr. The reaction mixture was worked up as described above. The product crystallised from benzene-petroleum ether, m.p. 149° (lit8., m.p. 144°). Yield 3 g. (Found : C, 75.23 ; H, 5.02. C14H11O3 requires C, 76.67 ; H, 5.26%).

3'-Allyloxy-4-methylxanthone (VII) :

A mixture of 3,4-dihydroxy-4-methylxanthone (2.5 g) in dimethyl aniline was refluxed for 4 hr. The reaction mixture was worked up as described above. The product crystallised from alcohol, m.p. 165°. Yield 2.5 g (lit8., m.p. 165°). (Found : C, 76.47 ; H, 5.56. C13H15O3 requires C, 76.67 ; H, 5.26%). IR spectrum 1635 cm⁻¹ (ν-pyronyl C=O group) and a broad band at 3200 cm⁻¹ (aromatic -OH group).

4,5'-Dimethyl-4'-S'-dihydrofurano (3',2'-2,3)xanthone (VIII) :

A mixture of 4,5'-dimethyl-4'-S'-dihydrofurano (3',2'-2,3) xanthone (0.6 g) and DDQ (0.535 g) was refluxed in sodium dried benzene (30 ml) in a water bath for 6 hr. The separated product was filtered off and the filtrate on evaporation gave solid, denser to facilitate the removal of alcohol formed. After cooling, the separated product was filtered and washed several times with petroleum ether. It crystallised from alcohol, m.p. 278°, yield 2.0 g. (Found : C, 72.38 ; H, 5.79. C14H11O3 requires C, 72.21 ; H, 5.55%).

6-Hydroxy-1,2,3,4-tetrahydroxanthone (ID) :

A mixture of resorcinol (3 g) and ethyl cyclohexanone-2-carboxylate (4 ml) was refluxed with diphenyl ether (10 ml) for 3 hr. with a short condenser to facilitate the removal of alcohol formed. After cooling, the separated product was filtered and washed several times with petroleum ether. It crystallised from alcohol. M.P. 278°, yield 2.0 g. (Found : C, 72.38 ; H, 5.79. C14H11O3 requires C, 72.21 ; H, 5.55%).
3-Allyloxyxanthone (VIc):

A mixture of 3-hydroxyxanthone (2 g), allyl bromide (1.6 g) and anhydrous potassium carbonate (8 g) was refluxed in dry acetone (200 ml.) in a water bath for 14 hr. The reaction mixture was worked up as described above. The product crystallised from benzene-petroleum ether, m.p. 136° (lit., m.p. 137°), yield 2.4 g. (Found: C, 75.69; H, 4.53. C₁₆H₁₂O₃ requires C, 76.19; H, 4.76%).

4-Allyl-3-hydroxyxanthone (VId):

3-Allyloxyxanthone (2 g) was refluxed with dimethylaniline (10 ml) for 5 hr. The reaction mixture was worked up as described before. The product crystallised from alcohol, m.p. 240° (lit., m.p. 253°), yield 1.8 g. (Found: C, 75.78; H, 4.76. C₁₆H₁₂O₃ requires C, 76.19; H, 4.76%). IR spectrum: 1632 cm⁻¹ (α-pyronyl>C=O group), and a broad band at 3150 cm⁻¹ (aromatic -OH group).

4', 5'-Dihydro-5'-methylfurano (2',3'-3,4)xanthone (VIII):

4'-Allyl-3-hydroxyxanthone (1 g) was triturated with sulphuric acid (85%, 6 ml) in a water bath for 15 minutes. The reaction mixture was worked up as described above. It crystallised from alcohol and benzene-petroleum ether, m.p. 181° (lit., m.p. 180°), yield 0.8 g. (Found: C, 76.40; H, 4.66. C₁₆H₁₁O₃ requires C, 76.19; H, 4.76%). NMR (CDCl₃): 5.15 (3H, d, J=7Hz, C₅'-CH₃), 2.80-3.62 (2H, m, C₄'-H₃), 5.15 (1H, q, J = 7Hz, C₅'-H), 6.7 (1H, d, J=9Hz, C₂-H), 7.2-7.7 (3H, m, C₆-H and C₇-H), 8.06 (1H, d, J=9Hz, C₈-H), 8.25 (1H, d, J=9Hz, C₉-H).

5'-Methylfurano (2',3'-3,4)xanthone (V):

A mixture of 4',5'-dihydro-5'-methylfurano (2',3'-3,4)xanthone (0.5 g), palladised charcoal (10%, 0.3 g) and diphenyl ether (4 ml) was refluxed for 12 hr. The reaction mixture was worked up as described before. The product chromatographed on alumina. Elution with benzene-petroleum ether (3 : 7) gave the product, which crystallised from alcohol, m.p. 172°, (lit., m.p. 170°), yield 0.3 g. Mixed m.p. with the compound obtained as above was not depressed. (Found: C, 76.37; H, 4.87. C₁₆H₁₅O₃ requires C, 76.19; H, 4.76%).

Acknowledgement

The authors thank Dr. Sukh Dev, Director, Malti Ghem. Research Centre, Nandesari, Baroda and Dr. Y. A. Shaikh, Department of Medicinal Chemistry, Purdue University, U.S.A. for NMR spectra, Prof. E. Gellert, University of Wollongong, Australia for IR spectra and Prof. S. M. Sethna, Pro-Vice Chancellor of M. S. University of Baroda for his keen interest in the work. We are also thankful to Dr. S. S. Lele and Shri S. S. Madhav Rao for micro analysis of the compound.

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