

## II. CHEMISTRY

### Organic Chemistry

#### CONSTITUTIONS OF LAXANTHONES-II : SYNTHETIC STUDIES

D. K. BHARDWAJ, M. S. BISHT and R. K. JAIN

*Department of Chemistry, University of Delhi, Delhi 110 007*

*(Received 6 December 1979)*

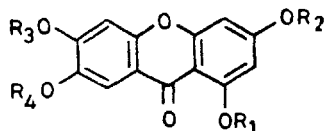
Among 1, 3, 6, 7-tetraoxygenated xanthenes isolated from *Lawsonia inermis*, the isomeric laxanthone-II and isolaxanthone-II were proposed their constitutions as 1-hydroxy-3, 6-diacetoxy-7-methoxyxanthone (I) and 1-hydroxy-3, 6-diacetoxy-7-methoxyxanthone (II) respectively, based on spectral data and characterisations of their derivatives. Laxanthone-II and isolaxanthone-II on deacetylations followed by ethylations of the resulting products, gave diethyl ethers which were characterised as 1-hydroxy-3, 6-diethoxy-7-methoxyxanthone (IV) and 1-hydroxy-3, 7-diethoxy-6-methoxyxanthone (V) respectively, by comparisons with three possible isomeric 1-hydroxy-3, 6, 7-diethoxymonomethoxyxanthenes (III, IV, V). This paper reports the syntheses of the isomeric xanthenes (III, IV, V) needed for these comparisons and thereby confirms the constitutions proposed for laxanthone-II and isolaxanthone-II.

**Key words:** Laxanthenes-II; Synthetic Studies

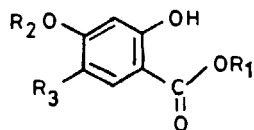
#### INTRODUCTION

CHEMICAL examination of *Lawsonia inermis* led to the isolations (Bhardwaj *et al.*, 1977 & 1978a; and Jain 1977) of a number of 1, 3, 6, 7-tetraoxygenated xanthenes; laxanthone-I (VI), laxanthone-II (I) and isolaxanthone-II (II). During the course of our work on the constitutions of the two isomeric laxanthenes, these were deacetylated followed by the ethylations of the resulting trihydroxymonomethoxyxanthenes to obtain their corresponding diethyl ethers which were characterised by their comparisons with the three possible isomeric xanthenes (III, IV and V). This paper describes the syntheses of these xanthenes (III, IV and V).

Isomeric 1-hydroxy-3, 6, 7-diethoxymonomethoxyxanthenes (III, IV and V) needed for the present work were synthesised by the condensations of the suitably substituted 2-hydroxybenzoic acids (XV, XVII and XX) with phloroglucinol followed by the selective alkylations of the resulting 1, 3-dihydroxyxanthenes. For this purpose, the three 2-hydroxybenzoic acids (XV, XVII and XX) having substituents as present in the A ring of the isomeric xanthenes were also made. Ethylation of  $\beta$ -resorcylic acid (X) (Clarke, 1930) followed by the hydrolysis of the resulting ester (XI) yielded 2-hydroxy-4-ethoxybenzoic acid (XII) which on nuclear hydroxylation under alkaline conditions as done in the similar cases (Bhardwaj, 1978b; and Rajagopalan, 1949) gave 2, 5-dihydroxy-4-ethoxybenzoic acid (XIII). Ethylation of XIII yielded the ethyl ester (XIV) which was hydrolysed to obtain the required 2-hydroxy-4, 5-diethoxybenzoic acid (XV). Similarly, methylation and then hydrolysis of XIII gave 2-hydroxy-4-ethoxy-5-methoxybenzoic acid (XVII) through its



- I,  $R_1 = H$ ;  $R_2 = R_3 = COCH_3$ ;  $R_4 = CH_3$ .  
 II,  $R_1 = H$ ;  $R_2 = R_4 = COCH_3$ ;  $R_3 = CH_3$ .  
 III,  $R_1 = H$ ;  $R_2 = CH_3$ ;  $R_3 = R_4 = C_2H_5$ .  
 IV,  $R_1 = H$ ;  $R_2 = R_3 = C_2H_5$ ;  $R_4 = CH_3$ .  
 V,  $R_1 = H$ ;  $R_2 = R_4 = C_2H_5$ ;  $R_3 = CH_3$ .  
 VI,  $R_1 = R_2 = H$ ;  $R_3 = R_4 = CH_3$ .  
 VII,  $R_1 = R_2 = H$ ;  $R_3 = C_2H_5$ ;  $R_4 = CH_3$ .  
 VIII,  $R_1 = R_2 = H$ ;  $R_3 = R_4 = C_2H_5$ .  
 IX,  $R_1 = R_2 = H$ ;  $R_3 = CH_3$ ;  $R_4 = C_2H_5$ .



- X,  $R_1 = R_2 = R_3 = H$ .  
 XI,  $R_1 = R_2 = C_2H_5$ ;  $R_3 = H$ .  
 XII,  $R_1 = R_3 = H$ ;  $R_2 = C_2H_5$ .  
 XIII,  $R_1 = H$ ;  $R_2 = C_2H_5$ ;  $R_3 = OH$ .  
 XIV,  $R_1 = R_2 = C_2H_5$ ;  $R_3 = OC_2H_5$ .  
 XV,  $R_1 = H$ ;  $R_2 = C_2H_5$ ;  $R_3 = OC_2H_5$ .  
 XVI,  $R_1 = CH_3$ ;  $R_2 = C_2H_5$ ;  $R_3 = OCH_3$ .  
 XVII,  $R_1 = H$ ;  $R_2 = C_2H_5$ ;  $R_3 = OCH_3$ .  
 XVIII,  $R_1 = H$ ;  $R_2 = CH_3$ ;  $R_3 = OH$ .  
 XIX,  $R_1 = C_2H_5$ ;  $R_2 = CH_3$ ;  $R_3 = OC_2H_5$ .  
 XX,  $R_1 = H$ ;  $R_2 = CH_3$ ;  $R_3 = OC_2H_5$ .

methyl ester (XVI). The third acid, 2-hydroxy-4-methoxy-5-ethoxybenzoic acid (XX) was made by hydrolysing the ethyl ester (XIX) obtained by the ethylation of 2, 5-dihydroxy-4-methoxybenzoic acid (XVIII) (Rajagopalan, 1949). Condensations of 2-hydroxybenzoic acids (XV, XVII and XX) with phloroglucinol gave 1, 3-dihydroxyxanthenes, (VIII), (VII) and (IX) respectively. Selective methylation of VIII gave its 3-methyl ether (III) whereas selective ethylations VII and IX gave their corresponding 3-ethyl ethers (IV and V). The diethyl ethers of the hydrolysis products of laxanthone-II and isolaxanthone-II were identical only with IV and V

respectively, but not with the other isomers. Hence, the methoxyl functions were fixed at C<sub>7</sub> and C<sub>6</sub> in laxanthone-II and isolaxanthone-II, respectively. *A priori*, the constitutions I and II assigned to laxanthone-II and isolaxanthone-II respectively were confirmed unequivocally.

#### EXPERIMENTAL

##### 2, 5-Dihydroxy-4-ethoxybenzoic acid (XIII):

$\beta$ -Resorcylic acid (X) (Clarke, 1930) (30 g) on refluxing with diethyl sulphate (65 ml) and anhydrous potassium carbonate (120g) in acetone (500 ml) gave ethyl 2-hydroxy-4-ethoxybenzoate (XI) which crystallised from methanol as colourless needles (26 g), m.p. 52° [lit. (Heilbron, 1965) m.p. 53–54°]. The ester (XI) (20 g) was hydrolysed by refluxing with aqueous sodium hydroxide (150 ml, 10%) for 1 hr. 2-Hydroxy-4-ethoxybenzoic acid (XII) thus obtained, crystallised from methanol as colourless needles (16 g) m.p. 154° [lit. (Kuhn, 1950), m.p. 148–50°]. To the solution of the acid (XII) (15 g) in aqueous sodium hydroxide (120 ml, 10%) cooled at 10°, aqueous potassium persulphate (25 g/300 ml) was added dropwise during a period of 4 hrs with stirring. It was kept for 24 hrs at room temperature, neutralised to congo-red with hydrochloric acid and then extracted repeatedly with ether to remove the unchanged acid (XII). The remaining aqueous solution was treated with sodium sulphite (12 g) and hydrochloric acid (75 ml), heated at 80° for 30 minutes and then cooled. 2, 5-Dihydroxy-4-ethoxybenzoic acid (XIII) thus obtained, was filtered out and crystallised from methanol as creamish coloured needles (5 g), m.p. 212° (Found : C, 54.7; H, 5.4. C<sub>9</sub>H<sub>10</sub>O<sub>5</sub> requires C, 54.54; H, 5.09%). It gave brown ferric reaction.

##### 2-Hydroxy-4, 5-diethoxybenzoic acid (XV):

A solution of the above acid (XIII) (5 g) in acetone (120 ml) was treated with diethyl sulphate (7.5 ml) and anhydrous potassium carbonate (20 g) and then refluxed for 6 hrs. Ethyl 2-hydroxy-4, 5-diethoxybenzoate (XIV) (4.5 g) thus obtained, was purified and directly hydrolysed by heating with aqueous sodium hydroxide (50 ml, 10%) to obtain 2-hydroxy-4, 5-diethoxybenzoic acid (XV) which was filtered, washed and dried. It crystallised from ethanol as light yellow prisms (3.5 g), m.p. 179° (Found : C, 58.7; H, 6.5. C<sub>11</sub>H<sub>14</sub>O<sub>5</sub> requires C, 58.4; H 6.24%). It gave brown ferric reaction.

##### 1, 3-Dihydroxy-6, 7-diethoxyxanthone (VIII):

A mixture of anhydrous phloroglucinol (1.5 g), 2-hydroxy-4, 5-diethoxybenzoic acid (XV) (2.0 g), fused zinc chloride (6.0 g) and freshly distilled phosphorus oxychloride (20 ml) was heated in an oil-bath at 70–75° for 3 hrs, cooled, treated with ice and left overnight. The reaction product was filtered, washed first with aqueous sodium bicarbonate (10%) to remove the unchanged acid (XV), then with dilute hydrochloric acid and finally with water. It crystallised from methanol-acetone mixture to give 1, 3-dihydroxy-6, 7-diethoxyxanthone (VIII) as light yellow needles (0.8 g), m.p. 234–35° (Found : C, 64.8; H, 5.4. C<sub>17</sub>H<sub>16</sub>O<sub>6</sub> requires C, 64.55; H, 5.10%). It gave green ferric reaction.

*1-Hydroxy-3-methoxy-6, 7-diethoxyxanthone (III):*

A solution of the above dihydroxydiethoxyxanthone (VIII) (0.5 g) in acetone (50 ml) was treated with dimethyl sulphate (0.18 ml) and anhydrous potassium carbonate (2 g). The resulting reaction mixture was refluxed for 8 hrs and worked up as usual. It crystallised from methanol to give 1-hydroxy-3-methoxy-6, 7-diethoxyxanthone (III) as pale yellow needles (0.4 g), m.p. 176° (Found: C, 65.1; H, 5.4.  $C_{18}H_{18}O_6$  requires C, 65.44; H, 5.49%). It gave olive-green ferric reaction.

*Ethyl 2-hydroxy-4-methoxy-5-ethoxybenzoate (XIX):*

A solution of 2, 5-dihydroxy-4-methoxybenzoic acid (XVIII) (4 g) in acetone (100 ml) was treated with diethyl sulphate (6.3 ml) and ignited potassium carbonate (20 g) and then heated under reflux for 6 hrs. The reaction product which was worked up as usual, crystallised from aqueous methanol to give ethyl 2-hydroxy-4-methoxy-5-ethoxybenzoate (XIX) as colourless needles (3.6 g), m.p. 75° (Found: C, 59.7; H, 7.0.  $C_{12}H_{16}O_5$  requires C, 59.99; H, 6.71%). It gave green ferric reaction.

*2-Hydroxy-4-methoxy-5-ethoxybenzoic acid (XX):*

A mixture of the above ester (XIX) (3.5 g) and aqueous sodium hydroxide (40 ml; 10%) was heated under reflux for an hour. The reaction product which was worked up as usual, crystallised from methanol to give 2-hydroxy-4-methoxy-5-ethoxybenzoic acid (XX) as light yellow prisms (2.6 g), m.p. 187° (Found: C, 56.3; H, 6.0.  $C_{10}H_{12}O_5$  requires C, 56.6; H, 5.7%). It gave brown ferric reaction.

*1, 3-Dihydroxy-6-methoxy-7-ethoxyxanthone (IX):*

A mixture of anhydrous phloroglucinol (1.1 g) and the above acid (XX) (1.5 g), fused zinc chloride (4.5 g) and freshly distilled phosphorus oxychloride (15 ml) was heated in an oil-bath at 70–75° for 3 hrs. The reaction mixture was cooled, treated with ice and left overnight. The solid was filtered, washed with aqueous sodium bicarbonate (10%) to remove the unchanged acid (XX), then with dilute hydrochloric acid and finally with water. It crystallised from methanol-acetone to give 1, 3-dihydroxy-6-methoxy-7-ethoxyxanthone (IX) as light-yellow needles (0.65g), m.p. 291–92° (Found: C, 63.6; H, 5.1.  $C_{16}H_{14}O_6$  requires C, 63.57; H, 4.67%). It gave green ferric reaction.

*1-Hydroxy-3, 7-diethoxy-6-methoxyxanthone (V):*

A solution of the above xanthone (IX) (0.5 g) in acetone (50 ml) was treated with anhydrous potassium carbonate (2.0 g) and diethyl sulphate (0.35 ml) and then refluxed on a water-bath for 6 hrs. The reaction product which was worked up as usual, crystallised from methanol to give 1-hydroxy-3, 7-diethoxy-6-methoxyxanthone (V) as pale yellow needles (0.4 g), m.p. 161–62°, (Found: C, 65.7; H, 5.8.  $C_{18}H_{18}O_6$  requires C, 65.44; H, 5.49%). It gave olive-green ferric reaction.

On direct comparison, the synthetic xanthone (V) agreed with the diethyl ether of the hydrolysis product of iso-laxanthone-II.

*Methyl 2-hydroxy-4-ethoxy-5-methoxybenzoate (XVI):*

A solution of 2, 5-dihydroxy-4-ethoxybenzoic acid (XIII) (5 g) in acetone (150 ml) was treated with dimethyl sulphate (5 ml) and anhydrous potassium carbonate (20 g) and then refluxed on a water-bath for 8 hrs. The reaction product which was worked up as usual, crystallised from aqueous methanol to give methyl 2-hydroxy-4-ethoxy-5-methoxybenzoate (XVI) as colourless prisms (4.5 g), m.p. 120° (Found: C, 58.3; H, 6.6.  $C_{11}H_{14}O_5$  requires C, 58.40; H, 6.24%). It gave brown ferric reaction.

*2-Hydroxy-4-ethoxy-5-methoxybenzoic acid (XVII):*

The above ester (XVI) (2 g) was heated under reflux with aqueous sodium hydroxide (30 ml, 10%) for one hour. The clear alkaline solution when cooled and acidified with hydrochloric acid, gave 2-hydroxy-4-ethoxy-5-methoxybenzoic acid (XVII). It crystallised from ethanol as colourless needles (1.5 g), m.p. 181–82° (Found: C, 57.0; H, 6.0.  $C_{10}H_{12}O_5$  requires C, 56.6; H, 5.7%). It gave green ferric reaction.

*1, 3-Dihydroxy-6-ethoxy-7-methoxyxanthone (VII):*

A mixture of phloroglucinol (1.1 g), 2-hydroxy-4-ethoxy-5-methoxybenzoic acid (XVII) (1.3 g), fused zinc chloride (4.5 g) and freshly distilled phosphorus oxychloride (15 ml) was heated in an oil-bath at 70–75° for 3 hrs. The resulting reaction mixture was cooled, treated with ice and left overnight. The solid was filtered, washed first with aqueous sodium bicarbonate (10%) to remove the unreacted acid (XVII), then with dilute hydrochloric acid and finally with water. It crystallised from methanol-acetone as pale yellow needles (0.45 g), m.p. 275–77° (Found: C, 63.2; H, 5.1.  $C_{16}H_{14}O_6$  requires C, 63.57; H, 4.67%). It gave green ferric reaction.

*1-Hydroxy-3, 6-diethoxy-7-methoxyxanthone (IV):*

A solution of the above xanthone (VII) (0.4 g) in acetone (50 ml) was treated with diethyl sulphate (0.15 ml) and anhydrous potassium carbonate (2 g) and then refluxed on a water-bath for 8 hrs. The reaction product which was worked out as usual crystallised from methanol as light yellow needles (0.3 g), m.p. 186° (Found: C, 65.2; H, 5.5.  $C_{18}H_{18}O_6$  requires C, 65.44; H, 5.49%). It gave olive-green ferric reaction. On direct comparison, the synthetic xanthone (IV) agreed with the diethyl ether of the hydrolysis product of laxanthone-II.

#### ACKNOWLEDGEMENTS

The authors are grateful to the Council of Scientific and Industrial Research and University Grants Commission, New Delhi for the grants and to the Head of the Chemistry Department, University of Delhi, for providing research facilities.

## REFERENCES

- Bhardwaj, D. K., Seshadri, T. R., and Singh, R. (1977) Xanthones from *Lawsonia inermis*. *Phytochem.*, **16**, 1616.
- Bhardwaj, D. K., Jain, R. K., Jain, S. C., and Mehta, C. K. (1978a) 1-Hydroxy-3, 7-dimethoxy-6-acetoxyxanthone, a new xanthone from *Lawsonia inermis*. *Phytochem.*, **17**, 1440.
- Bhardwaj, D. K., Jain, S. C., and Singh, R. (1978b) A convenient synthesis of athryriol. *Indian J. Chem.*, **16B**, 150.
- Clarke, H. T. (1930) *Organic Synthesis*. Chapman and Hall, London, **10**, 94.
- Heilbron, I. (1965) *Dictionary of Organic Compounds*. Eyre and Spottiswoode, London, **2**, 1055.
- Jain, S. C. (1977) A chemical study of some naturally occurring polyphenolics, *Ph.D. Thesis*, University of Delhi.
- Kuhn, R., Zilliken, F., and Trischmann, H. (1950) Synthesis of methyl 2-hydroxy-4-aminobenzoate, conversions by reduction and its effect on *Tuber bacillus*. *Ber.dt. Chem. Ges.*, **83**, 304.
- Rajagopalan, S., Seshadri, T. R., and Varadarajan, S. (1949) A new synthesis of asaronic acid, aldehyde and their derivatives. *Proc. Indian Acad. Sci.*, **30A**, 265.