CONSTITUTION OF DALBERGIN

Part V. A Further Study of 4-Phenyl Coumarins

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In earlier publications[1, 2] two important characteristics of 4-phenyl coumarins were recorded: (i) They give marked colour reactions[2] with magnesium and hydrochloric acid in alcoholic solution. In most cases there is an intermediate emerald green stage but finally it becomes deep red. The final colour has now been studied in two typical cases, 6 : 7-dihydroxy- and 7 : 8-dihydroxy-4-phenyl coumarins. The products have the characteristic properties of the flavylium salts and after purification by methods familiarly used in the flavylium series, the 4-phenyl-6 : 7-dihydroxy-pyrylium chloride gave a reddish brown ferric reaction whereas the 7 : 8-dihydroxy compound gave a deep blue colour. Similar differences were noticed in the 2-phenyl pyrylium salts also.[3] (ii) They exhibit marked stability to boiling alkali[1] but undergo conversion into the corresponding coumarilic acids[4] when mercuric oxide is added to the boiling alkaline solution.

In order to collect more information about this group of compounds tri-substituted 4-phenyl coumarins have now been prepared. They are most conveniently obtained by adopting the method of *para*-nuclear oxidation. 4-Phenyl-5 : 7-dimethoxy coumarin on oxidation with alkaline persulphate gave the 6-hydroxy product. For purposes of comparison it has also been synthesised using 2 : 6-dimethoxy quinol and benzoyl acetic ester. 4-Phenyl-7 : 8-dimethoxy coumarin on similar oxidation gave the corresponding 6-hydroxy product. The hydroxy compounds gave on methylation 5 : 6 : 7-trimethoxy and 6 : 7 : 8-trimethoxy 4-phenyl coumarins and on demethylation 5 : 6 : 7-trihydroxy and 6 : 7 : 8-trihydroxy 4-phenyl coumarins. All these compounds exhibit bright colour reactions with magnesium and hydrochloric acid. In the course of the present study, calophyllolide,[5] which is an important naturally occurring 4-phenyl coumarin, was found to give a feeble pink colour. This peculiarity may be due to the presence of an acyl group in the molecule having an adverse effect. This surmise is supported by the further observation that 7-hydroxy-8-acetyl 4-phenyl coumarin[6] gives no colour and its methyl ether a feeable colour like calophyllolide. The trimethoxy compounds yielded the corresponding *o*-methoxy cinnamic acids

by the combined action of alcoholic potash and methyl sulphate. As in simpler cases these coumarins were also stable to the action of hot potash and were recovered unchanged on acidification, but in the presence of mercuric oxide they yielded the corresponding coumarilic acids in about 45–50% yield. It is significant that the alternative method of preparing the coumarilic acids by using bromine and subsequently potash does not work satisfactorily in all cases. Though it proceeded smoothly in the case of 6: 7: 8-trimethoxy-4-phenyl coumarin, it was complicated by nuclear bromination when 5: 6: 7-trimethoxy-4-phenyl coumarin was employed. It appeared that the presence of a methoxy group in the 5-position encourages nuclear bromination. This has been confirmed by doing parallel experiments with the simpler 4-phenyl-5: 7-dimethoxy coumarin where also nuclear bromination complicated the reaction. Hence it could be concluded that the mercuric oxide-alkali method is the most suitable general process for all the phenyl coumarins.

Experimental

Procedure for colour reaction

A solution of 50–100 mg. of the 4-phenyl coumarin in alcoholic hydrochloric acid was treated with magnesium powder (2–3 g.) added slowly with occasional cooling and shaking. The reaction mixture was allowed to remain for 5–10 minutes when it attained a deep red colour. It was diluted with water and extracted with isoamyl alcohol (5 c.c.). The isoamyl alcoholic solution was diluted with a large excess of petroleum ether (150 c.c.) and the pyrylium salt extracted with hydrochloric acid (1: 1; 10 c.c.). The acidic solution was re-extracted with isoamyl alcohol (5 c.c.). and ferric reaction performed after adding excess of sodium acetate following the procedure of Robinson and Robinson.[7]

Preparation of trimethoxy and trihydroxy coumarins

4-Phenyl-6-hydroxy-7: 8-dimethoxy coumarin.—4-Phenyl-7: 8-dimethoxy coumarin[1] (5 g.) was refluxed with aqueous sodium hydroxide (5 g. in 100 c.c. water) till there was complete solution (2 hours). The solution was cooled (15–20°), stirred and treated dropwise with potassium persulphate (9 g. in 200 c.c. water) during 2 hours. After 24 hours at room temperature, the deep brown solution was acidified with dilute hydrochloric acid (Congo-red) and the unchanged product filtered off; further ether extraction removed the last traces of it. The clear brown solution was heated in a boiling water-bath with sodium sulphite (5 g.) and concentrated hydrochloric acid (100 c.c.) for half-an-hour. After cooling the solid product (2·5 g.) was filtered and crystallised from methyl alcohol yielding colourless micacious plates,

m.p. 212–13° (Found: C, 68·5; H, 4·7; $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). With magnesium and hydrochloric acid it gave a pink colour changing to green and finally to reddish brown.

The acetate prepared by boiling with acetic anhydride and pyridine crystallised from methanol as colourless stout rhombohedral prisms, m.p. 136–37°.

4-*Phenyl*-6: 7: 8-*trimethoxy coumarin* was prepared by refluxing the above 6-hydroxy coumarin (1 g.) in acetone (75 c.c.) with dimethyl sulphate (0·5 c.c.) and potassium carbonate (2 g.) for 4 hours. The product (0·9 g.) crystallised from methyl alcohol as colourless stout polygonal prisms, m.p. 109–10° (Found: C, 69·1; H, 5·1; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). With magnesium and hydrochloric acid it gave a pink red colour which changed to green and finally deep red on standing.

4-*Phenyl*-6: 7: 8-*trihydroxy coumarin*.—4-Phenyl-6-hydroxy-7: 8-dimethoxy coumarin (1 g.) was heated with hydriodic acid (10 c.c.) in acetic anhydride (10 c.c.) for 2 hours at 140–45°. After working up in the usual way, the product crystallised from methanol as very pale yellow tiny prisms and needles, m.p. 238–39° (Found: C, 66·2; H, 3·9; $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%). It gave a deep blue colour with alcoholic ferric chloride and with magnesium and hydrochloric acid a pink colour which changed to green and finally red.

The triacetate was prepared by heating the above product with acetic anhydride and a drop of pyridine. It crystallised from methanol as colourless needles and elongated rectangular plates, m.p. 187–88°.

4-*Phenyl*-6-*hydroxy*-5: 7-*dimethoxy coumarin*

(*a*) *Nuclear oxidation of* 4-*phenyl*-5: 7-*dimethoxy coumarin*.—4-Phenyl-5: 7-dimethoxy coumarin required for this was prepared by methylation of 4-phenyl-5: 7-dihydroxy coumarin[8] with dimethyl sulphate and potassium carbonate in acetone medium. On crystallisation from methyl alcohol it melted at 166–67°, the same as reported earlier[9] for the sample prepared by the cyclisation of O-dimethyl-phlorobenzophenone.

(*a*) 4-Phenyl-5: 7-dimethoxy coumarin (5 g.) was oxidised with potassium persulphate (9 g.) in sodium hydroxide solution (5 g. in 100 c.c. water) as in the earlier case. The product (1·5 g.) crystallised from methanol as colourless thin rhombohedral plates, m.p. 185–86° (Found: C, 68·6; H, 4·8; $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). With magnesium and hydrochloric acid it gave a light pink colour.

(*b*) 2: 6-Dimethoxy quinol[10] (2·5 g.) was made into a paste with benzoyl acetic ester (3 c.c.), the solution cooled in ice and concentrated sulphuric acid (10 c.c.) added gradually (1 hour) with stirring at 0°. The deep red viscous solution thus obtained was kept in a refrigerator for 24 hours and then poured into water (100 c.c.) with stirring. The pale yellow precipitate (0·5 g.) was filtered and crystallised from methanol, m.p. 185–86°, undepressed by admixture with the product obtained in experiment (*a*).

The acetate crystallised from ethyl acetate as colourless stout rectangular prisms, m.p. 153–54°.

4-*Phenyl*-5: 6: 7-*trimethoxy coumarin* was prepared by methylation of the above 6-hydroxy-coumarin (1 g.) in acetone solution. The product (1 g.) separated as colourless stout rhombic prisms from methanol, m.p. 140–41° (Found: C, 69·0; H, 5·3; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). With magnesium and hydrochloric acid it gave a pink colour which changed to green and finally deep red.

4-*Phenyl*-5: 6: 7-*trihydroxy coumarin* was prepared by demethylation of 4-phenyl-6-hydroxy-5: 7-dimethoxy coumarin with hydriodic acid in acetic anhydride medium. The product crystallised from methanol as pale yellow shining small plates, m.p. 236–37° (Found: C, 66·9; H, 3·9; $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%).

The triacetate crystallised from alcohol as colourless large rectangular plates, m.p. 184–85°.

Conversion into coumarilic acids

3-*Phenyl*-4: 6-*dimethoxy coumarone*-2-*carboxylic acid.*—4-Phenyl-5: 7-dimethoxy coumarin (2 g.) was dissolved in hot aqueous potassium hydroxide (30 c.c., 20%). The solution was diluted with water (70 c.c.) and refluxed with freshly prepared yellow mercuric oxide (15 g.) for 20 hours. The mixture was filtered, the filtrate saturated with hydrogen sulphide to remove all combined mercury as mercuric sulphide and filtered again and acidified. The acid product was purified (sodium-hydrogen carbonate) and crystallised from ethyl alcohol; colourless large rectangular plates and tablets (0·9 g.), m.p. 218–19° (Found: C, 67·8; H, 5·1; $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%). It gave a red colour with alcoholic ferric chloride.

3-*Phenyl*-4: 6-*dimethoxy coumarone*

(i) *Mercuric chloride method.*—The above acid (0·5 g.) and mercuric chloride (1 g.) were refluxed with aqueous alcohol (75 c.c., 50%) for 10 hours. The solution was acidified with hydrochloric acid to make the strength 1%.

Alcohol was distilled off under reduced pressure and the solution extracted with ether. The ether solution was washed with aqueous sodium hydrogen carbonate and the solvent distilled. The residue (0·4 g.) crystallised from methanol as colourless micacious rectangular plates, m.p. 89–90°. Mixed m.p. with an authentic sample prepared as given in (ii) was undepressed (Found: C, 75·3; H, 5·4; $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

(ii) *Copper-quinoline method.*—3-Phenyl-4: 6-dimethoxy coumarone-2-carboxylic acid (0·5 g.) was heated at 220° in quinoline (10 c.c.) with copper powder (0·4 g.) until the evolution of carbon dioxide ceased (30 min.). The cooled mixture was poured into ether, the solution filtered and washed with dilute hydrochloric acid to remove quinoline and then with aqueous sodium hydrogen carbonate and the solvent distilled off. The viscous residue (0·3 g.) crystallised from methanol, m.p. 89–90°.

2: 4: 6-*Trimethoxy-β-phenyl cinnamic acid* was prepared from 4-phenyl-5: 7-dimethoxy coumarin by the action of dimethyl sulphate and methanolic potash as was done with O-methyldalbergin.[1] It crystallised from methanol as colourless stout rectangular prisms, m.p. 201–03° (Found: C, 68·5; H, 6·1; $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%).

3-*Phenyl*-4: 5: 6-*trimethoxy coumarone*-2-*carboxylic acid* was prepared from 4-phenyl-5: 6: 7-trimethoxy coumarin, mercuric oxide and aqueous sodium hydroxide (20 hours refluxing) as in earlier cases. It crystallised from methanol as colourless small prisms, m.p. 202–03°. Yield 42% (Found: C, 65·9; H, 5·1; $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). Decarboxylation of the acid either with mercuric chloride or copper and quinoline gave a low melting product (neutral) which could not be crystallised.

2: 4: 5: 6-*Tetramethoxy-β-phenyl cinnamic acid* prepared from 4-phenyl-5: 6: 7-trimethoxy coumarin by the usual method crystallised from methanol as colourless shining stout prisms, m.p. 170–71° (Found: 65·7; H, 6·1; $C_{19}H_{20}O_6$ requires C, 66·2; H, 5·9%).

3-*Phenyl*-5: 6: 7-*trimethoxy coumarone*-2-*carboxylic acid*

(i) *Action of mercuric oxide and alkali on* 4-*phenyl*-6: 7: 8-*trimethoxy coumarin.*—The reaction was carried out as in earlier cases. The product crystallised from methanol as colourless rectangular prisms, m.p. 192–93° (Found: C, 65·2; H, 4·7; $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). Yield 45%. Mixed m.p. with an authentic sample prepared by method (ii) was undepressed.

(ii) 3-*Bromo*-4-*phenyl*-6 : 7 : 8-*trimethoxy coumarin*.—To a hot solution of 4-phenyl-6 : 7 : 8-trimethoxy coumarin (3·1 g.) in glacial acetic acid (20 c.c.) was added a solution of bromine in glacial acetic acid (18 c.c., 10%) with shaking (10 min.). Bromine was taken up immediately and on cooling a colourless product (2·8 g.) separated out. It crystallised from glacial acetic acid as colourless large rectangular prisms, m.p. 152–53° (Found: C, 54·9; H, 3·7; $C_{18}H_{15}O_5$ Br requires C, 55·2; H, 3·8%).

Action of alkali on the bromo coumarin.—The above bromo compound (2 g.) was refluxed with aqueous sodium hydroxide (100 c.c.; 10%) for 4 hours. The solution was cooled, the insoluble portion filtered off, and the filtrate acidified with dilute hydrochloric acid. The product was filtered and purified by means of sodium hydrogen carbonate. It crystallised from methanol, m.p. 192–93°.

Decarboxylation of the above acid either with mercuric chloride or with copper and quinoline gave an oily liquid product (neutral) which could not be crystallised.

2 : 3 : 4 : 5-*Tetramethoxy-β-phenyl cinnamic acid* prepared from 4-phenyl-6 : 7 : 8-trimethoxy coumarin as in earlier cases crystallised from methanol as colourless small tiny rectangular prisms, m.p. 116–17° (Found: C, 65·8; H, 5·7; $C_{19}H_{20}O_6$ requires C, 66·2; H, 5·9%).

Summary

The two important characteristics of 4-phenyl coumarin derivatives, *i.e.*, the colour reaction with magnesium and hydrochloric acid and the transformation with alkali and mercuric oxide into coumarilic acids are shown to be characteristics of the group by the study of more members. The coloured product is somewhat similar to flavylium salts. Calophyllolide does not give marked colour reaction probably due to the presence of acyl group. Mercuric oxide-alkali method is specially convenient for the preparation of 3-phenyl coumarilic acids since the alternative bromination method does not work satisfactorily with 5-substituted coumarins.

References

1. Ahluwalia, V. K. and Seshadri T. R. .. *J. Chem. Soc.*, 1957, 970.
2. ——, Mehta, A. C. and Seshadri, T. R. *Proc. Ind. Acad. Sci.*, 1957, **45 A**, 293.
3. Ponniah, L. and Seshadri, T. R. .. *Ibid.*, 1953, **38 A**, 77.
4. Ahluwalia, V. K. Mehta, A. C. and Seshadri T. R. *Tetrahedron*, 1958, **4**, 271.

5. Potier, A. O., Buzas A. and Lederer, E. *Bull. Soc. Chim., France*, 1951, 577.
6. Limaye, D. B. and Joshi, M. C. .. *Rasayanam*, 1941, 226.
7. Robinson, G. M. and Robinson, R. .. *Biochem. J.*, 1931, 1687.
8. Kostanecki, V. and Weber, C. .. *Ber.*, 1893, **26**, 2906.
9. Pollak, V. .. *Monatsh.* **18**, 743.
10. Baker, W. .. *Jour. Chem. Soc.*, 1941, 663.