A NEW SYNTHESIS OF DALBERGIN AND METHYL DALBERGIN AND A SYNTHESIS OF ALLO-DALBERGIN

By V. K. Ahluwalia, A. C. Mehta and T. R. Seshadri, F.A.Sc.

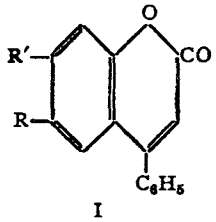
(Department of Chemistry, University of Delhi, Delhi)

Received March 18, 1957

In an earlier paper,[1] 4-phenyl coumarins occurring in nature were considered to be related to benzophenone derivatives. This was supported by the ready oxidation of the former into the latter. The oxidation of methyl dalbergin (I *a*) producing 2-hydroxy-4: 5-dimethoxy benzophenone (II *a*) has already been described.[1] Under the same conditions, 4-phenyl-7-methoxy coumarin (I *b*) yields 2-hydroxy-4-methoxy benzophenone (II *b*). The reverse change of a benzophenone into a 4-phenyl coumarin has been used in the past in two cases. Limaye and Ramkrishna[2] boiled 2: 4-dihydroxy benzophenone with acetic anhydride and sodium acetate and obtained 4-phenyl umbelliferone acetate. Similarly using 2: 6-dihydroxy benzophenone, Seshadri and Varadarajan[3] prepared 4-phenyl-5-hydroxy coumarin and its derivatives. This method has now been applied for the synthesis of dalbergin (I *c*) and methyl dalbergin (I *a*) using 2: 5-dihydroxy-4-methoxy benzophenone (II *c*) and 2-hydroxy-4: 5-dimethoxy benzophenone (II *a*) respectively. In exploratory experiments for working out the best conditions of the reaction 2-hydroxy-4-methoxy benzophenone (II *b*) was employed for conversion into 4-phenyl-7-methoxy coumarin (I *b*). The yields by this method at their best are not satisfactory as compared with the application of the Pechmann's reaction using benzoyl acetic ester.[1, 4, 5]

However, the benzophenone method is convenient for the preparation of 4-phenyl-5-methoxy-6-hydroxy coumarin, which can be called allo-dalbergin. As already mentioned Seshadri and Varadarajan[3] prepared 4-phenyl-5-hydroxy and 4-phenyl-5-methoxy coumarins by this method. The alternative method of preparing these compounds using β-resorcylic ester and benzoyl acetic ester along with aluminium chloride in nitrobenzene medium did not work satisfactorily. 4-Phenyl-5-methoxy coumarin undergoes nuclear oxidation to yield allo-dalbergin whose methyl ether and acetate have also been prepared.

Ahluwalia, Mehta and Seshadri[5] reported that partial methylation of nor-dalbergin (4-phenyl-6: 7-dihydroxy coumarin) was successful in

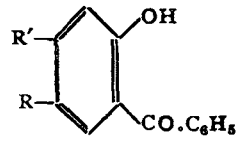


I

(*a*) R = R′ = OCH_3

(*b*) R = H; R′ = OCH_3

(*c*) R = OH; R′ = OCH_3



II

providing a convenient synthesis of dalbergin (I *c*). It has now been found that the method of partial demethylation can also be successfully employed. When methyl dalbergin (I *a*) is heated at 100° with hydrobromic acid in acetic acid, a mixture of dalbergin and nor-dalbergin is formed. But by using hydriodic acid at 115–20° for half an hour a better yield of dalbergin is obtained. The separation of the mixture could be effected by taking advantage of the property of nor-dalbergin to form a water-soluble complex with borax.

One of the extraordinary properties of dalbergin and methyl dalbergin has been the bright colour reactions they give with magnesium and alcoholic hydrochloric acid. In this respect there is resemblance to the flavonoids. A study has been made here of the behaviour of a number of 4-phenyl coumarins in this reaction. As will be seen from the results presented below, most of the 4-phenyl coumarins give the colour reaction, but it is most prominent with 6:7-disubstituted compounds and least with 5- and 5:7-substituted coumarins. The methyl ethers yield brighter colours as compared with hydroxy compounds.

The 3-phenyl coumarin derivatives do not give this colour reaction. The following methoxy and hydroxy-3-phenyl coumarins have been examined in this connection: 7-methoxy, 7-hydroxy, 7:8-dimethoxy, 7:8-dihydroxy, 6:7-dimethoxy and 6:7-dihydroxy. It would appear that there is something specific in regard to the substitution in the 4-position. Hence, in order to examine if a methyl group in this position will serve the same purpose as a phenyl group, a number of 4-methyl coumarins have been tested. Their reactions are positive though the colours are less intense as compared with the 4-phenyl coumarins. The same effect of position of the methoxy and hydroxy substituents is found here too.

In order to examine the combined effect of 3-phenyl along with the 4-methyl substituent the following 3-phenyl-4-methyl coumarins have been examined and they do not give any colour: 7-hydroxy, 6-methoxy, 6-hydroxy and 5-hydroxy.

The colour reaction with magnesium and alcoholic hydrochloric acid (known as the anthocyanin colour reaction) has been largely used in the field of flavonoids; generally a deep red or pink colour is observed. The flavanone, plathymenin was recorded by King *et al.*[5a] to give rise to pink and intense blue colour in this reaction. It has not been used before in the case of coumarins. From what has been recorded in the previous paragraphs, it would appear that this colour reaction is capable of being used for distinguishing between differently substituted coumarins.

Experimental

4-Phenyl-7-methoxy coumarin.—2-Hydroxy-4-methoxy benzophenone, (10 g.),[4,6,7] fused sodium acetate (5 g.) and acetic anhydride (11 c.c.) were heated in an oil-bath (165–70°) for 24 hrs., adding 2·5 c.c. of acetic anhydride after every six hours. The mixture was poured into water and the product (2 g.) crystallised from alcohol, m.p. 116–17°, undepressed by the sample prepared by using the Pechmann's reaction.[4]

Permanganate oxidation of 4-phenyl-7-methoxy coumarin.—4-Phenyl-7-methoxy coumarin in acetone was oxidised with potassium permanganate added in small quantities. When the product was worked up following the procedure described in a recent paper[1] it gave benzoic acid, oxalic acid and 2-hydroxy-4-methoxy benzophenone.

4-Phenyl-6-hydroxy-7-methoxy coumarin (dalbergin).—2: 5-Dihydroxy-4-methoxy benzophenone[7] (10 g.) gave acetyl dalbergin (3 g.) which crystallised from alcohol, m.p. 157–58°, undepressed by the acetate obtained from natural dalbergin.[8] On deacetylation it yielded dalbergin, m.p. 209–10°, undepressed by the natural sample.[8]

4-Phenyl-6: 7-dimethoxy coumarin (methyl dalbergin).—2-Hydroxy-4: 5-dimethoxy benzophenone[7,9] (10 g.) gave on cyclisation in a similar way methyl dalbergin (2 g.), m.p. and mixed m.p. with the natural sample[8] 144–45°.

Partial demethylation of methyl dalbergin:

(*a*) *With hydrobromic acid.*—Methyl dalbergin (2 g.) in glacial acetic acid (20 c.c.) was heated on a boiling water-bath with hydrobromic acid (66%; 20 c.c.) for 1 hr. The solution was poured into ice and the solid product filtered. It was digested with a warm (60–70°) solution of borax (5 g. in 30 c.c. water). The insoluble portion (0·6 g.) crystallised from methanol, m.p. 209–10°; mixed m.p. with natural dalbergin[8] was undepressed. The borax solution was treated with dilute sulphuric acid and the product (0·5 g.) obtained crystallised from alcohol, m.p. 267–68°; mixed m.p. with an authentic sample of nor-dalbergin[8] was undepressed.

(*b*) *With hydriodic acid.*—Methyl dalbergin (2 g.) in acetic anhydride (20 c.c.) was heated with hydriodic acid (20 c.c.) at 115–20° for half an hour. The solution was poured into saturated aqueous sodium bisulphite and the solid product filtered. It was separated into dalbergin (1·0 g.) and nor-dalbergin (0·6 g.) as in the above case.

4-Phenyl-5-methoxy-6-hydroxy coumarin (*Allo-dalbergin*).—It was prepared by the nuclear oxidation of 4-phenyl-5-methoxy coumarin[3] (2·7 g.) in aqueous sodium hydroxide (3 g. in 60 c.c. water) with potassium persulphate (4·8 g. in 100 c.c. water) following the procedure described in a recent paper.[5] It (1·5 g.) crystallised from benzene as colourless stout rectangular tablets, m.p. 178–79° (Found: C, 71·1; H, 4·8; $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

The acetate (acetic anhydride and pyridine method) crystallised from methanol as colourless stout prisms, m.p. 114–16°. The methyl ether was prepared by means of methyl sulphate and anhydrous potassium carbonate in acetone solution. It crystallised from methanol as colourless thick rhombohedral plates, m.p. 134–36°.

Colour reactions:

Procedure.—A solution of about 5–10 mg. of the coumarin was dissolved in alcohol (5 c.c.) and an equal volume of concentrated hydrochloric acid added. The solution was treated with magnesium powder in small lots a number of times.

4-Phenyl coumarins.—(1) 4-Phenyl-7-hydroxy coumarin—pink red changing to green and finally fading to dirty yellow on standing. (2) 4-Phenyl-7-methoxy coumarin—red quickly changing to green and red on standing. (3) 4-Phenyl-7: 8-dihydroxy coumarin—pink changing to deep red. (4) 4-Phenyl-7: 8-dimethoxy coumarin—red changing to brown and again deep red; slowly fades to brown yellow on further addition of magnesium and hydrochloric acid. (5) 4-Phenyl-6: 7-dihydroxy coumarin (nor-dalbergin)—pink red changing to green and finally deep red on standing. (6) 4-Phenyl-6: 7-dimethoxy coumarin (methyl-dalbergin)—same as (5). (7) 4-Phenyl-6-hydroxy-7-methoxy coumarin (dalbergin)—same as (5). (8) 4-Phenyl-6-methoxy-7-hydroxy coumarin (iso-dalbergin)—pink red changing to green and finally pink. (9) 4-Phenyl-5-methoxy coumarin—red, fades slowly. (10) 4-Phenyl-5-hydroxy coumarin—orange yellow; fades slowly. (11) 4-Phenyl-5-methoxy-6-hydroxy coumarin (allo-dalbergin)—red; fades quickly. (12) 4-Phenyl-5: 6-dimethoxy coumarin—deep red changing to brown

red and finally fades. (13) 4-Phenyl-5: 7-dimethoxy coumarin—red fading slowly to yellow. (14) 4-Phenyl-5: 7-dihydroxy coumarin—orange, fades slowly.

4-*Methyl coumarins.*—(1) 4-Methyl-7-hydroxy coumarin—pink with slight green tinge changing finally to pink. (2) 4-Methyl-7-methoxy coumarin—pink changing to blue and finally to red. (3) 4-Methyl-6: 7-dihydroxy coumarin—red changing to pink and finally red. (4) 4-Methyl-6: 7-dimethoxy coumarin—pink changing to blue and finally deep red. (5) 4-Methyl-5: 7-dihydroxy coumarin—no colour. (6) 4-Methyl-5: 7-dimethoxy coumarin—no colour. (7) 4-Methyl-5: 6-dihydroxy coumarin—no colour. (8) 4-Methyl-5: 6-dimethoxy coumarin-red colour.

SUMMARY

Though the benzophenone method of synthesis is not quite advantageous for dalbergin and methyl dalbergin, it is more convenient for the preparation of allo-dalbergin (4-phenyl-5-methoxy-6-hydroxy coumarin) and its methyl ether. These compounds and other 4-phenyl coumarins give markedly coloured solutions when treated with alcohol, hydrochloric acid and magnesium; a number of 4-methyl coumarin derivatives also give similar colour reactions. On the other hand 3-phenyl and 3-phenyl-4-methyl coumarin derivatives do not respond to this test which may therefore be of diagnostic value.

ACKNOWLEDGEMENT

Our thanks are due to the Council of Scientific & Industrial Research for a research grant.

REFERENCES

1. Ahluwalia and Seshadri .. *J.C.S.*, 1957, 970.
2. Limaye and Ramkrishna .. *Rasayanam*, 1937, **1**, 80.
3. Seshadri and Varadarajan .. *Proc. Ind. Acad. Sci.*, 1952, **35 A**, 80.
4. Kostanecki and Tambor .. *Ber.*, 1895, **28**, 2305.
5. Ahluwalia, Mehta and Seshadri *Proc. Ind. Acad. Sci.*, 1957, **45 A**, 15.

5*a*. King, King and Neill .. *J.C.S.*, 1953, 1055.

6. Kauffmann *et al.* .. *Ber.*, 1910, **43**, 1208.
7. Laumas, Neelakantan and Seshadri Unpublished work.
8. Ahluwalia, Sawhney and Seshadri *Jour. Sci. Ind. Res.*, 1956, **15 B**, 66.
9. Bargellini and Martegiani .. *Atti. R. Acad. Lincei.*, 1911, **20**, 183.