CONSTITUTION OF DALBERGIN

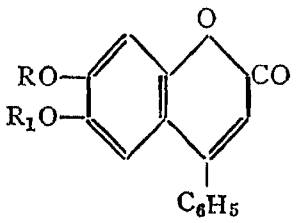
Part III. Synthesis of Dalbergin, Iso-Dalbergin and Their Ethers

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

(Department of Chemistry, University of Delhi, Delhi)

Received November 15, 1956

In Part II[1] it was shown that dalbergin is a monomethyl ether of 4-phenyl aesculetin. The position of the methoxy group has now been established by the synthesis of 7-methoxy-6-ethoxy-4-phenyl coumarin (I) and 7-ethoxy-6-methoxy-4-phenyl coumarin (II); the former agreed in every respect with 0-ethyl dalbergin and hence the constitution of dalbergin should be that of 4-phenyl aesculetin-7-methyl ether (III).



I, $R=CH_3$, $R_1=C_2H_5$
II, $R=C_2H_5$, $R_1=CH_3$
III, $R=CH_3$, $R_1=H$
IV, $R=R_1=H$
V, $R=H$, $R_1=CH_3$

For the preparation of the above-mentioned mixed ethers nuclear oxidation with alkaline persulphate has been employed. 4-Phenyl-7-methoxy coumarin yields the 6-hydroxy compound (III) which is ethylated to form the 6-ethoxy compound (I). Using 7-ethoxy-4-phenyl coumarin instead and finally methylating the nuclear oxidation product, the isomeric-7-ethoxy-6-methoxy-4-phenyl coumarin (II) has been prepared. In the course of these preparations, the intermediate 7-methoxy-6-hydroxy-4-phenyl coumarin (III) has been found to be identical with dalbergin. Another method of synthesis involves partial methylation of 4-phenyl aesculetin (IV) using dimethyl sulphate and sodium bicarbonate. That such partial methylation is possible in the 7-position has already been shown in connection with 4-methyl aesculetin[2] and 4-methyl-5:7-dihydroxy coumarin.[3] Partial ethylation is also successful and provides an alternative method for the preparation of 7-0-ethyl-4-phenyl aesculetin and the mixed ether (II).

6-Methoxy-7-hydroxy-4-phenyl coumarin (iso-dalbergin) (V) would be analogous to scopoletin and may be expected to occur in nature. Its synthesis has been carried out through the intermediate 6-hydroxy-7-benzyloxy compound, which has been prepared by two methods: (1) nuclear oxidation of 7-benzyloxy-4-phenyl coumarin, and (2) partial benzylation of

4-phenyl aesculetin (IV). Further stages involve methylation of 7-benzyloxy-6-hydroxy-4-phenyl coumarin and subsequent debenzylation. The identity of iso-dalbergin has been confirmed by its ethylation to yield the mixed ether (II).

The earlier method for the preparation of 4-phenyl aesculetin[1] (IV) employed hydroxy quinol acetate and the Pechmann condensation with benzoyl acetic ester. As an alternative method the nuclear oxidation of 4-phenyl umbelliferone has been explored. The method is successful though the yield is not good.

EXPERIMENTAL

0-*Ethyl dalbergin* was prepared by ethylation of dalbergin[1] with diethyl sulphate and potassium carbonate in acetone solution. It crystallised from methyl alcohol as colourless long rhombohedral plates, m.p. 163–64° (Found: C, 72·8; H, 5·4; $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%.)

4-*Phenyl*-6-*hydroxy*-7-*methoxy coumarin* (*Dalbergin*) (*III*)

(*a*) *Partial methylation of* 4-*phenyl aesculetin* (*IV*).—4-Phenyl aesculetin[1] (2 g.) was refluxed in dry acetone (300 c.c.) with dimethyl sulphate (0·75 c.c.) and sodium hydrogen carbonate (4 g.) for 24 hours, the acetone solution filtered, and the inorganic salts washed with hot acetone (50 c.c.). The solvent was distilled off and the residue treated with water. The solid crystallised first from methanol and finally from ethyl acetate as colourless rhombohedral prisms (1·5 g.), m.p. 210–11°, undepressed by an authentic sample of dalbergin.[4] Its colour reactions were the same as those of natural dalbergin. The acetate, methyl ether and ethyl ether of the above 4-phenyl-6-hydroxy-7-methoxy coumarin melted at 158-59°, 144–45° and 163–64° respectively and agreed in all respects with acetyl dalbergin,[4] 0-methyl dalbergin[1, 4] and 0-ethyl dalbergin respectively.

(*b*) *Nuclear oxidation of* 4-*phenyl*-7-*methoxy coumarin*.—4-Phenyl-7-methoxy coumarin is conveniently prepared by the methylation of 4-phenyl umbelliferone[5] using the dimethyl sulphate-potassium carbonate-acetone method, m.p. 116–18°. It (5 g.) was refluxed with aqueous sodium hydroxide (5 g. in 100 c.c. water) for two hours. The solution was cooled (15–20°), stirred and treated dropwise with potassium persulphate (9 g. in 200 c.c. water) during two hours. After twenty-four hours at room temperature the deep brown solution was acidified to congo-red and the unchanged product filtered off, ether extration removing 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 was filtered and crystallised from methyl alcohol (2·7 g.); m.p. 210–11°, undepressed by an authentic sample of dalbergin.[4]

4-*Phenyl-7-ethoxy coumarin.*—4-Phenyl-7-hydroxy coumarin[5] (10 g.) was refluxed with diethyl sulphte (9 c.c., excess), potassium carbonate (20 g.) and acetone (150 c.c.) for six hours. The product crystallised from methyl alcohol yielding colourless rectangular plates (9·0 g.), m.p. 104–05° (Found: C, 76·1; H, 5·3; $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%).

4-*Phenyl-6-hydroxy-7-ethoxy coumarin.*—It was prepared by the nuclear oxidation of the above 4-phenyl-7-ethoxy coumarin (5 g.) in aqueous sodium hydroxide (5 g. in 100 c.c. water) with potassium persulphate (9 g.) as in the earlier case. It crystallised from ethyl acetate-petroleum ether mixture as pale yellow rectangular tablets (1·2 g.), m.p. 156–57.° (Found: C, 71·6; H, 5·1; $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%.) The acetate prepared with acetic anhydride and pyridine crystallised from benzene petroleum ether mixture as colourless lance-shaped crystals, m.p. 108–09°.

4-*Phenyl-6-methoxy-7-ethoxy coumarin* (II).—The above 6-hydroxy compound (0·5 g.) was refluxed in dry acetone (75 c.c.) with dimethyl sulphate (0·5 c.c.) and potassium carbonate (2 g.) for six hours. The product crystallised from methyl alcohol as colourless prismatic needles (0·4 g.), m.p. 106–08°. (Found: C, 72·7; H, 5·7; $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%.)

4-*Phenyl-7-benzyloxy coumarin.*—4-Phenyl-7-hydroxy coumarin[5] (12 g.) in acetone (200 c.c.) was refluxed with anhydrous sodium iodide (10 g.), benzyl chloride (7 c.c.) and potassium carbonate (15 g.) for eight hours, the acetone solution filtered and the inorganic salts washed with more of hot acetone. The solvent was distilled off and the excess of benzyl chloride removed by steam distillation. The benzyl ether crystallised from ethyl acetate and light petroleum mixture as colourless needles and narrow rectangular plates (8 g.), m.p. 91–92°. (Found: C, 80·6; H, 5·2; $C_{22}H_{16}O_3$ requires C, 80·5; H, 4·9%.)

4-*Phenyl-6-hydroxy-7-benzyloxy coumarin*

(*a*) *Nuclear oxidation of* 4-*phenyl-7-benzyloxy coumarin.*—4-Phenyl-7-benzyloxy coumarin (5 g.) was oxidised with potassium persulphate (9 g.) in sodium hydroxide solution (100 c.c., 5%) as in the earlier cases. The product crystallised from benzene yielding colourless prismatic needles (0·7 g.), m.p. 213–14°. (Found: C, 76·2; H, 4·8; $C_{22}H_{16}O_4$ requires C, 76·7; H, 4·7%.) The acetate prepared with acetic anhydride and pyridine

crystallised from methyl alcohol as colourless thick rectangular, plates m.p. 159–60°.

(*b*) *Partial benzylation of 4-phenyl aesculetin.*—4-Phenyl aesculetin[1] (3 g.) in acetone (150 c.c.) was refluxed with sodium iodide (4 g.), benzyl chloride (0·9 c.c.) and sodium bicarbonate (4 g.), for twenty-four hours. Acetone was distilled off and the residue treated with water; the solid product crystallised first from ethyl alcohol and finally from ethyl acetate (1·5 g.); m.p. 213–14°. Mixed m.p. with the product obtained in (*a*) was undepressed.

4-Phenyl-6-methoxy-7-benzyloxy coumarin was prepared by refluxing the above 6-hydroxy-coumarin (1 g.) in acetone (150 c.c.) with dimethyl sulphate (0·4 c.c.) and potassium carbonate (1 g.). The product crystallised from ethyl alcohol as colourless long prisms (1 g.), m.p. 196–98°. (Found: C, 76·9; H, 5·6; $C_{23}H_{18}O_4$ requires C, 77·1; H, 5·1%.)

4-Phenyl-6-methoxy-7-hydroxy coumarin (*Iso-dalbergin*).—The foregoing compound (0·5 g.) was dissolved in glacial acetic acid (15 c.c.), concentrated hydrochloric acid (15 c.c.) added, and the solution heated on a steam-bath for one hour. Acetic acid, benzyl chloride and hydrochloric acid were completely distilled off under reduced pressure and the residue washed with a small amount of petroleum ether to remove the last traces of benzyl chloride. Crystallisation from ethyl acetate-petroleum ether mixture yielded colourless shining very thin rectangualr plates (0·25 g.), m.p. 195–96°. (Found: C, 72·0; H, 4·8; $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%.) The acetate prepared with acetic anhydride and pyridine crystallised from ethyl alcohol yielding colourless short prismatic meedles, m.p. 171–72°. The ethyl ether prepared by ethylation of the above coumarin with ethyl sulphate and potassium carbonate in acetone medium crystallised from methyl alcohol, m.p. 106–08° undepressed by the sample of 4-phenyl-6-methoxy-7-ethoxy coumarin reported earlier.

4-Phenyl-6: 7-dihydroxy coumarin (*Nor-dalbergin*) (*IV*).—4-Phenyl-7-hydroxy coumarin[5] (5 g.) was dissolved in aqueous sodium hydroxide (5 g. in 100 c.c. water) and oxidised with potassium persulphate (9 g. in 200 c.c. water). The product crystallised from methyl alcohol as colourless small rectangular tablets and tiny prisms (0·8 g.), m.p. 268–69°, undepressed by an authentic sample of nor-dalbergin.[1, 4] The acetate and the methyl ether melted at 157–58° and 144–45° respectively and agreed in all respects with acetyl nor-dalbergin[1, 4] and methyl dalbergin[1, 4] respectively.

ACKNOWLEDGEMENT

We convey our thanks to the Council of Scientific and Industrial Research, India, for a research grant.

SUMMARY

The position of the methoxyl group in dalbergin has been established by synthesis using two methods: (1) partial methylation of 4-phenyl-aesculetin and (2) nuclear oxidation of 4-phenyl umbelliferone methyl ether. By similar methods the 7-benzyl ether of 4-phenyl aesculetin and from it by methylation and debenzylation iso-dalbergin has been prepared. The ethyl ethers of dalbergin and iso-dalbergin have also been obtained.

REFERENCES

1. Ahluwalia and Seshadri .. *J.C.S.*, under publication.
2. Velluz and Amiard .. *Bull. Soc. Chim.*, France, 1948, 1109.
3. Sawhney and Seshadri .. *Proc. Ind. Acad. Sci.*, 1953, **37 A**, 592.
4. Ahluwalia and Seshadri .. *J. Sci. Ind. Res.*, 1956, **15 B**, 66.
5. Pechmann and Duisberg .. *Ber.*, 1883, **16**, 2126.