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HETEROCYCLIC COMPOUNDS. PART XXXI. THE SYNTHESIS OF PARTIALLY METHYLATED ETHERS OF POLYHYDROXY COUMARINS

By R. D. Desai and (Miss) J. V. Parghi

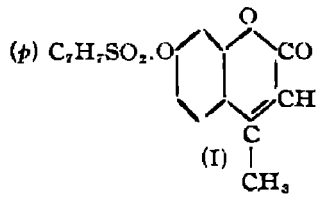
Partial tosylation of 4-methyl-5 :7-dihydroxycoumarin furnished 4-methyl-5-hydroxy-7-coumarinyl-*p*-toluenesulphonate which could be methylated to 4-methyl-5-methoxy-7-coumarinyl-*p*-toluenesulphonate. Its detosylation afforded 4-methyl-5-methoxy-7-hydroxycoumarin. Partial tosylation of 4-methyl-7 :8-dihydroxycoumarin provided 4-methyl-8-hydroxy-7-coumarinyl-*p*-toluenesulphonate; its methylation and subsequent detosylation yielded 4-methyl-7-hydroxy-8-methoxycoumarin, while the partial methylation of 4-methyl-7 :8-dihydroxycoumarin furnished the isomeric 4-methyl-7-methoxy-8-hydroxycoumarin. 5-Hydroxy-6-methoxy-4 :7-dimethylcoumarin was prepared by the alkaline persulphate oxidation of 5-*O*-mesyl derivative of 5-hydroxy-4 :7-dimethylcoumarin, followed by its methylation and subsequent demesylation. 4-Methyl-5 :7-dihydroxy-6-methoxycoumarin was prepared by the alkaline persulphate oxidation of di-*O*-mesyl derivative of 4-methyl-5 :7-dihydroxycoumarin, its methylation and subsequent demesylation.

4-Methyl-5 : 7-dihydroxycoumarin was partially methylated by Schmidt (*Helv. Chim. Acta*, 1947, **30**, 1661) as well as by Sawhney and Seshadri (*Proc. Ind. Acad. Sci.*, 1953, **37A**, 592) with the formation of 4-methyl-5-hydroxy-7-methoxycoumarin (m.p. 256-57°). We have found that partial tosylation of 4-methyl-5 : 7-dihydroxycoumarin furnishes 4-methyl-5-hydroxy-7-coumarinyl *p*-toluenesulphonate (I) which on methylation and subsequent detosylation of the methyl ether affords the isomeric 4-methyl-5-methoxy-7-hydroxycoumarin, m.p. 197°. Velluz and Amiard (*Bull. soc. chim.*, 1948, 1109) obtained 7-methoxy-6-hydroxy-4-methylcoumarin by the partial methylation of 6 : 7-dihydroxy-4-methylcoumarin. The synthesis of the isomeric 7-hydroxy-6 methoxy-4-methylcoumarin or 4-methylscopoletin from 6 : 7-dihydroxy-4 methylcoumarin by partial tosylation, methylation and detosylation has already been described in the previous paper (this *Journal*, 1956, **33**, 483).

The partial methylation of 4-methyl-7 : 8-dihydroxycoumarin does not seem to have been studied. On partial methylation with dimethyl sulphate and potassium carbonate in dry acetone, it afforded 4-methyl-7-methoxy-8-hydroxycoumarin (m.p. 145°), providing a yellow non-fluorescent solution in dilute alkali. The isomeric 4-methyl-7-hydroxy-8-methoxycoumarin, (m.p. 157°) which gave a blue fluorescent solution in dilute alkali, was prepared by the partial tosylation of 4-methyldaphnetin, which yielded 4-methyl-8-hydroxy-7-coumarinyl-*p*-toluenesulphonate (II), followed by its methylation and subsequent detosylation. Thus, in the case of dihydroxycoumarins, whenever there is one hydroxyl-group in 7-position and the other hydroxyl group in any other position (5, 6 or 8), methylation and tosylation affect preferentially position- 7 only. Our preliminary experiments on partial mesylation of polyhydroxy coumarins show similarity between tosylation and mesylation, but these experiments will form the subject of a further communication.

Miss Bhavsar and Desai (this *Journal*, 1954, 31, 141) have prepared 5-hydroxy-6-methoxy-4 : 7-dimethylcoumarin (III) by the oxidation of 4 : 7-dimethyl-5-coumarinyl-*p*-toluenesulphonate with alkaline potassium persulphate, its methylation and subsequent detosylation. We have found that (III) can be prepared in an improved yield by the oxidation of 4 : 7-dimethyl-5-coumarinyl-methanesulphonate (IV) with alkaline potassium persulphate to 4 : 7 - dimethyl - 6-hydroxy - 5-coumarinyl - methanesulphonate (V), its methylation to 4 : 7 - dimethyl - 6-methoxy - 5-coumarinyl-methanesulphonate (VI) and subsequent demesylation.

Miss Bhavsar and Desai (*loc. cit.*) failed to oxidise 4-methyl-5 : 7-coumarinyl di-*p*-toluenesulphonate. This is due to the steric hindrance offered by the bulky tosyl groups, as we have now succeeded in oxidising 4-methyl-5:7 coumarinyl-dimethanesulphonate (VII) by alkaline potassium persulphate to 4 - methyl-6 - hydroxy - 5 : 7-coumarinyl-dimethanesulphonate (VIII) which on methylation and subsequent demesylation furnishes 4-methyl-5 : 7-dihydroxy-6-methoxycoumarin (IX).



(I)

EXPERIMENTAL

Monotosylation of 4-Methyl-5 : 7-dihydroxycoumarin and Formation of 4-Methyl-5-hydroxy-7-coumarinyl-p-toluenesulphonate (I)

A mixture of 4-methyl-5:7-dihydroxycoumarin (2 g.), *p*-toluenesulphonyl chloride (2 g.), acetone (50 c. c.) and anhydrous potassium carbonate (6 g.) in a round-bottomed flask was refluxed for 12 hours. After removal of the acetone, the solid was treated with 5% NaOH solution. The monotosylated derivative went in solution while the ditosylated product remained insoluble. On acidification with HCl (c nc.), monotosyl derivative (1.3 g.) was recovered. It crystallised from alcohol in white needles, m.p. 240°. It dissolved in alkali with a yellow colour and showed no fluorescence. (Found : S, 9.1. $C_{17}H_{14}O_6S$ requires S, 9.2 per cent).

4-Methyl-5-methoxy-7-coumarinyl-p-toluenesulphonate was obtained by refluxing the mixture of (I, 0.5 g.), anhydrous potassium carbonate (4 g.), dimethyl sulphate (2 g.) and anhydrous acetone (50 c. c.) for 12 hours. The residue left after removal of the acetone was treated with water. The insoluble product crystallised from alcohol in white plates, m.p. 188°. Its reddish brown solution in H_2SO_4 (conc.) showed a green fluorescence. (Found : S, 8.6. $C_{18}H_{16}O_6S$ requires S, 8.8 per cent).

4-Methyl-5-methoxy-7-hydroxycoumarin was prepared by pouring a solution of the preceding coumarin (0.5 g.) in H_2SO_4 (conc., 10 c.c.) in ice-cold water after 12 hours

and crystallised from ethyl acetate in white needles, m.p. 197°. It dissolved in alkali solution with a blue fluorescence. (Found : C, 64.3 ; H, 4.7. $C_{11}H_{10}O_4$ requires C, 64.1 ; H, 4.9 per cent).

Partial Methylation of 4-Methyl-7 : 8-dihydroxycoumarin and Formation of 4-Methyl-7-methoxy-8-hydroxycoumarin

A mixture of 4-methyl-7 : 8-dihydroxycoumarin (2 g.), dimethyl sulphate (1 c.c.), anhydrous potassium carbonate (3 g.) and acetone (30 c.c.) was refluxed on a water-bath for 12 hours. After removal of the acetone, the residue was treated with 5% NaOH solution. Acidification of the alkaline solution with concentrated hydrochloric acid gave a solid which crystallised from alcohol in white needles, m.p. 145°, depressed to 130° by admixture with a specimen of 4-methyl-7-hydroxy-8-methoxycoumarin, m.p. 157°, described hereunder. (Found : C, 64.0 ; H, 4.7. $C_{11}H_{10}O_4$ requires C, 64.1 ; H, 4.9 per cent). It dissolved in alkali solution with a yellow colour and no fluorescence, while its alcoholic solution developed a green coloration with ferric chloride.

4-Methyl-8-hydroxy-7-coumarinyl-p-toluenesulphonate (II) was prepared by refluxing a mixture of 4-methyl-7 : 8-dihydroxycoumarin (2 g.), *p*-toluenesulphonyl chloride (2 g.), anhydrous potassium carbonate (3 g.) and acetone for 12 hours, and worked up as usual. The monotosylated derivative (1.4 g.) crystallised from alcohol in white needles, m.p. 222°. It dissolved in alkali solution with a yellow colour and no fluorescence. Its alcoholic solution developed a green coloration with ferric chloride. (Found: S, 9.3. $C_{17}H_{14}O_6S$ requires S, 9.2 per cent).

4-Methyl-8-methoxy-7-coumarinyl-p-toluenesulphonate was prepared by heating a mixture of (II, 1 g.), dimethyl sulphate (5 c.c.), anhydrous potassium carbonate (10 g.) and acetone (75 c.c.) for 24 hours, and worked up as usual. It crystallised from alcohol in white needles, m.p. 148°. Its alcoholic solution showed no coloration with ferric chloride. (Found : S, 8.6. $C_{18}H_{16}O_6S$ requires S, 8.8 per cent).

4-Methyl-7-hydroxy-8-methoxycoumarin was obtained by pouring a solution of the preceding coumarin (0.5 g.) in H_2SO_4 (conc., 10 c.c.) in ice-cold water after 12 hours and crystallised from alcohol in white needles, m.p. 157°. It dissolved in alkali solution with a blue fluorescence, while its alcoholic solution gave no coloration with ferric chloride. (Found : C, 64.2 ; H, 4.6. $C_{11}H_{10}O_4$ requires C, 64.1 ; H, 4.9 per cent).

4 : 7-Dimethyl-5-coumarinyl-methanesulphonate (IV) was prepared by heating a mixture of 4:7-dimethyl-5-hydroxycoumarin (3.8 g.), methanesulphonyl chloride (2.5 g.), anhydrous potassium carbonate (10 g.) and acetone (50 c.c.) for 12 hours, and worked up as usual. It crystallised from alcohol in white thin needles, m.p. 198°. (Found : S, 11.8. $C_{12}H_{12}O_5S$ requires S, 11.9 per cent).

Oxidation of (IV) to *4 : 7-Dimethyl-6-hydroxy-5-coumarinyl-methanesulphonate* (V).—The oxidation of the solution of (IV, 2 g.) in pyridine (50 c.c.) was carried out by the gradual addition of the solution of KOH (4 g.) in water (40 c.c.) and potassium persulphate (4 g.) in water (100 c.c.), as described by Miss Bhavsar and Desai (*loc cit.*), in the case of the *-O*-tosyl analogue. The solid (0.4 g.) crystallised from alcohol in white

needles, m.p. 205°, and dissolved in alkali solution with a yellow colour and no fluorescence. (Found : S, 11.2. $C_{12}H_{12}O_6S$ requires S, 11.3 per cent).

4 : 7-*Dimethyl*-6-*methoxy*-5-*coumarinyl*-*methanesulphonate* (VI) was obtained by methylation of (V) with dimethyl sulphate in presence of anhydrous potassium carbonate and acetone as usual. It crystallised from alcohol in white needles, m. p. 202°. It was insoluble in dilute sodium hydroxide solution. (Found : S, 10.8. $C_{13}H_{14}O_6S$ requires S, 10.7 per cent).

4 : 7-*Dimethyl*-5-*hydroxy*-6-*methoxycoumarin* (III) was obtained by pouring the solution of (VI, 0.2 g.) in H_2SO_4 (conc., 5 c. c.) after 12 hours in ice-cold water and crystallised from ethyl acetate in white plates, m.p. 206°, undepressed by a sample prepared by Miss Bhavsar and Desai (*loc. cit.*).

4-*Methyl*-5 : 7-*coumarinyl*-*dimethanesulphonate* (VII) was prepared by refluxing a mixture of 4-methyl-5 : 7-dihydroxycoumarin (1.9 g.), methanesulphonyl chloride (2.5 g.), sodium bicarbonate (4 g.) and acetone (75 c.c.) for 6 hours, and purified as usual. It crystallised from alcohol in white needles, m.p. 173°. (Found : S, 18.5. $C_{12}H_{12}O_8S_2$ requires S, 18.4 per cent).

4-*Methyl*-6-*hydroxy*-5 : 7-*coumarinyl*-*dimethanesulphonate* (VIII) was prepared by the oxidation of (VII, 3.5 g.), dissolved in pyridine (50 c.c.), with a solution of KOH (9 g.) in water (90 c.c.) and potassium persulphate (8 g.) in water (200 c.c.). After working up the solution as usual, the solid (0.5 g.) crystallised from alcohol in white plates, m.p. 210°. It dissolved in alkali with a deep yellow colour. (Found : S, 17.4. $C_{12}H_{12}O_9S_2$ requires S, 17.5 per cent).

4-*Methyl*-6-*methoxy*-5 : 7-*coumarinyl*-*dimethanesulphonate* was obtained by methylation of (VIII) with dimethyl sulphate in presence of anhydrous potassium carbonate and acetone. It crystallised from dilute alcohol in white needles, m.p. 134°. (Found : S, 16.7. $C_{13}H_{14}O_9S_2$ requires S, 16.9 per cent).

4-*Methyl*-5 : 7-*dihydroxy*-6-*methoxycoumarin* (IX) was obtained by pouring a solution of the preceding coumarin (0.3) in H_2SO_4 (conc., 10 c.c.) after 12 hours in ice-cold water. It crystallised from alcohol in white needles, m.p. 230°. It was soluble in alkali solution with a deep yellow colour, and its alcoholic solution gave no coloration with ferric chloride. (Found : C, 59.2, H, 4.3. $C_{10}H_{10}O_5$ requires C, 59.5 ; H, 4.5 per cent).

4-*Methyl*-5 : 6 : 7-*trihydroxycoumarin* was obtained by pouring the solution of (VIII, 0.2 g.) in H_2SO_4 (conc., 5 c.c.) in ice-cold water after 12 hours. It crystallised from alcohol in white needles, m.p. 277°, undepressed by a sample prepared independently by Miss Bhavsar and Desai (*Ind. J. Phar.*, 1951, **13**, 200), Parikh and Sethna (this *Journal*, 1950, **27**, 369) and Sawhney, Seshadri and Thiruvengadam (*Proc. Ind. Acad. Sci.*, 1951, **33A**, 11).

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DEPARTMENT OF CHEMISTRY,
L. D. ARTS COLLEGE & M. G.
SCIENCE INSTITUTE,
AHMEDABAD-9.

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