

PARTIAL METHYL ETHERS OF POLYHYDROXY COUMARINS

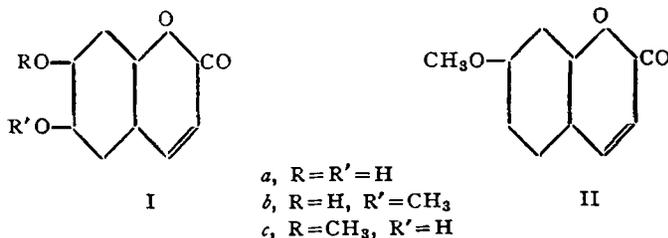
Part I. Partial Methylation of 5 : 7-Dihydroxy-4-Methyl Coumarin

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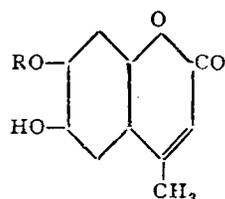
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THE possibility of obtaining partial methyl ethers of polyhydroxy coumarins by direct methylation would at first sight seem to be slender. No position of the coumarin structure seems to offer protection to a hydroxyl group just like the 5-position in chromones and flavones by a process of chelation. However, some instances are met with in the literature where coumarins have been successfully subjected to partial methylation. For example, Tiemann and Will¹ obtained a monomethyl ether by methylating æsculetin (I *a*) with methyl iodide and methyl alcoholic potash. Its constitution was not settled by them but the substance was different from scopoletin, a naturally occurring monomethyl ether of æsculetin. Moore² showed that scopoletin was the 6-methyl ether (I *b*) of æsculetin and hence Tiemann and Will's synthetic product should be the 7-methyl ether (I *c*). Its constitution was further established by Bargellini and Monti³ who showed its identity with the nuclear oxidation product of umbelliferone methyl ether (II).



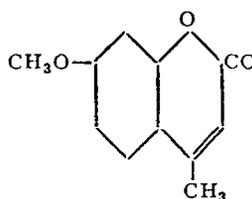
The partial methylation of 4-methyl æsculetin (III *a*) was carried out by Bargellini and Martegiani⁴ using methyl iodide and methyl alcoholic potash at 100°. The constitution of the resulting monomethyl ether, m.p. 173-5°, was not settled and it was considered to be either the 6- or 7-monomethyl ether of 4-methyl æsculetin. No derivatives were described. Their product was probably impure because more recently Velluz and Amiard⁵ carried out the partial methylation of 4-methyl æsculetin using dimethyl sulphate and aqueous sodium carbonate at 60° and obtained a monomethyl ether melting at 208-09°. They considered it to be 7-methoxy-6-hydroxy-4-methyl

coumarin (III *b*). The constitution should be considered to be correct based on the analogy of the methylation of æsculetin. It has been confirmed recently by Sawhney, Seshadri and Thiruvengadam⁶ when this monomethyl ether was shown to be identical with the nuclear oxidation product of 4-methyl umbelliferone methyl ether (IV). It is therefore conclusively proved that the hydroxyl in the 7-position is markedly more easily methylated as compared to the 6-hydroxyl group.



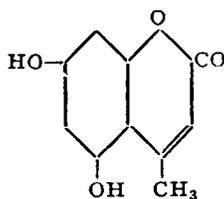
a, R = H
b, R = CH₃

III

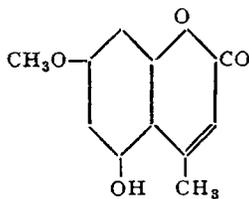


IV

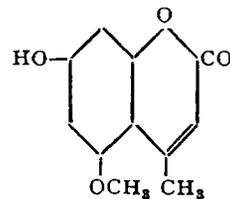
A similar report has been made by Schmid⁷ of having carried out the partial methylation of 5:7-dihydroxy-4-methyl coumarin (V) with diazomethane in methyl alcoholic solution and of having obtained a monomethyl ether. Using the analogy of æsculetin and 4-methyl æsculetin in which the 7-hydroxyl has greater reactivity (Merz and Hagemann⁸) he considered it to be 7-monomethyl ether (VI). His experiments prove the possibility of monomethylation of 5:7-dihydroxy-4-methyl coumarin but do not definitely establish the position of the methoxyl group.



V



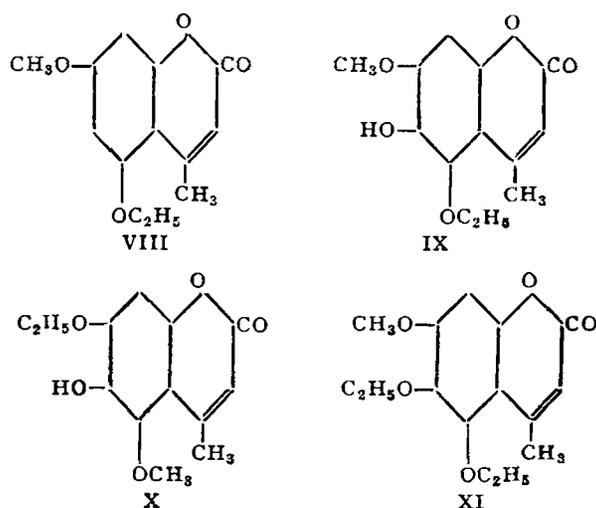
VI



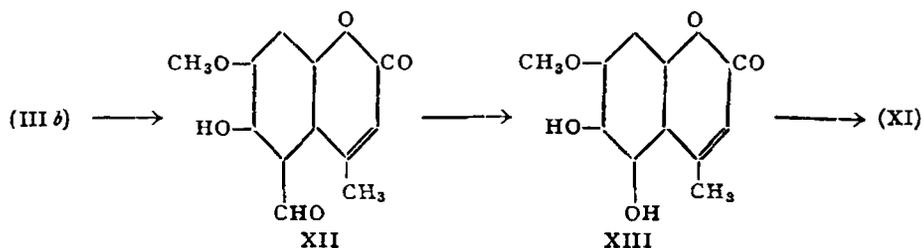
VII

Partial methylation of 5:7-dihydroxy-4-methyl coumarin has now been carried out using dimethyl sulphate and aqueous sodium carbonate and the result is in agreement with that of Schmid.⁷ The constitution of the partial methylation product has now been established in the following manner. The monomethyl ether of 5:7-dihydroxy-4-methyl coumarin is ethylated and this methyl ethyl ether is subjected to nuclear oxidation by means of alkaline persulphate. As reported earlier⁶ the oxidation of the *cis*-acid is not so satisfactory and preliminary conversion to the *trans*-acid is necessary for good yield. After nuclear oxidation, reconversion to the coumarin is effected in the presence of mercuric chloride as catalyst. The product

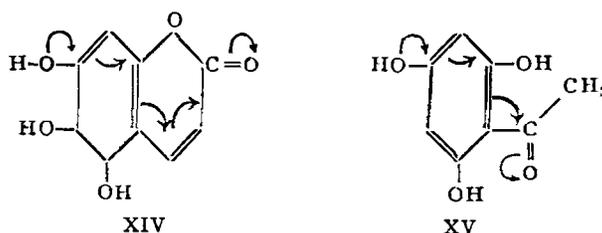
may have either of the constitutions (IX) or (X) depending on whether the monomethyl ether has the formula (VI) or (VII). This point has been settled by ethylating the oxidation product whereby is obtained a substance identical with 7-methoxy-5:6-diethoxy-4-methyl coumarin (XI). This result conclusively proves the constitution of the methyl ethyl ether as (VIII) and the original monomethyl ether as (VI). It is therefore established that partial methylation of 5:7-dihydroxy-4-methyl coumarin has taken place in the 7-position.



For the above comparison synthesis of 7-methoxy-5:6-diethoxy-4-methyl coumarin (XI) has been made from 7-methoxy-6-hydroxy-4-methyl coumarin (III *b*) as follows. It is condensed with hexamine whereby the ortho-aldehyde (XII) is obtained. Subsequent Dakin's reaction yields 7-methoxy-5:6-dihydroxy-4-methyl coumarin (XIII). The constitution of this substance is proved by complete methylation whereby the trimethyl ether is formed and found to be identical with 5:6:7-trimethoxy-4-methyl coumarin obtained by the methylation of 4-methyl fraxinol.⁶ When the dihydroxy compound (XIII) is ethylated with excess of diethyl sulphate it yields 7-methoxy-5:6-diethoxy-4-methyl coumarin (XI).



In seeking for an explanation of the success of partial methylation in the abovementioned cases of dihydroxy coumarins, as already mentioned, there is no possibility of partial protection. Obviously the factor involved is the higher reactivity of the 7-hydroxyl as compared with the others. This seems to be due to the effect of electromeric polarisation of the carbonyl group which is transmitted to the 7-position (*para*-position) effectively by the presence of conjugation. The 6-hydroxyl is not influenced in this way (XIV). Though the electromeric effect could be transmitted also to the 5-position (*ortho*-position) it cannot be obviously as strong as to the 7-position. There is analogy for this in the greater reactivity of the *para*-hydroxyl group in phloroacetophenone⁹ (XV). In this connection may be mentioned the success of partial monomethylation in hydroxy isoflavones and flavanones involving the selective activation of the 7-hydroxyl group.¹⁰



EXPERIMENTAL

7-Methoxy-6-hydroxy-4-methyl-coumarin-5-aldehyde (XII)

To an intimate mixture of 7-methoxy-6-hydroxy-4-methyl coumarin^{5,6} (3 g.) and hexamine (6 g.) was added glacial acetic acid (25 c.c.) and the mixture heated in a boiling water-bath for 6 hours. The deep orange solution was hydrolysed by adding a boiling solution of hydrochloric acid (20 c.c. of concentrated hydrochloric acid and 20 c.c. of water). The mixture was left overnight and then distilled under reduced pressure. The residual pasty mass was diluted with water and repeatedly extracted with ether and the ether solution dried over calcium chloride. The aldehyde obtained by evaporating the ether solution was crystallised from ethyl alcohol when it came out as yellow rectangular prisms melting at 214–6°. Yield, 1.5 g. With alcoholic ferric chloride it gave a pale green colour changing to pinkish green (Found: C, 61.3; H, 4.5; C₁₂H₁₀O₅ requires C, 61.6 and H, 4.3%).

7-Methoxy-5:6-dihydroxy-4-methyl coumarin (XIII)

The above hydroxy-aldehyde (1 g.) was dissolved in pyridine (10 c.c.) and sodium hydroxide solution (5 c.c., 1 N) was added. It was cooled in ice and hydrogen peroxide (1.5 c.c., 20%) was slowly added with shaking. After one hour it was acidified with cold dilute hydrochloric acid, filtered

and the filtrate repeatedly extracted with ether. The ethereal layer was successively washed with dilute hydrochloric acid and water and dried over anhydrous sodium sulphate. It was evaporated and the residue crystallised from methyl alcohol when it came out as colourless rectangular plates and prisms melting at 237–8°. Yield, 0.6 g. It gives a violet colour with ferric chloride (Found: C, 59.3; H, 4.6; $C_{11}H_{10}O_5$ requires C, 59.5 and H, 4.5%).

5:6:7-Trimethoxy-4-methyl coumarin

The above methoxy dihydroxy coumarin (0.5 g.) was refluxed in dry acetone (50 c.c.) with dimethyl sulphate (1 g.) and anhydrous potassium carbonate (3 g.) for 6 hours. The solution was filtered and the filtrate evaporated. The residue on crystallisation from ethyl acetate came out as thick rhombic plates melting at 113–4°. Mixed melting point with an authentic sample prepared by the methylation of 4-methyl fraxinol⁶ was undepressed.

7-Methoxy-5-hydroxy-4-methyl coumarin (VI)

5:7-Dihydroxy-4-methyl coumarin (5 g.) was dissolved in aqueous sodium carbonate (50 c.c., 10%). To this solution dimethyl sulphate (5 g.) was added and the mixture slowly heated with shaking in the course of half an hour to 60°. Shaking was continued for further half an hour without external heating and then the mixture allowed to stand for three hours at room temperature. The solid that separated out was collected and dissolved in aqueous sodium hydroxide (50 c.c., 5%). The alkaline solution was acidified and filtered. The residue was collected and crystallised from alcohol when it came out as colourless prismatic needles melting at 256–7°. Yield, 2.5 g. Schmid⁷ reported 251–2° as its melting point.

On methylation with dimethyl sulphate and potassium carbonate in dry acetone it gave 5:7-dimethoxy-4-methyl coumarin, m.p. 172–3°, identical with an authentic sample.

Its acetate was prepared using acetic anhydride and pyridine. On crystallisation from alcohol it was obtained as colourless rectangular plates melting at 189–90°. Schmid⁷ gave 191° as the melting point for this compound.

7-Methoxy-5-ethoxy-4-methyl coumarin (VIII)

The above partial methylation product (3 g.) was ethylated by refluxing in dry acetone solution (200 c.c.) with diethyl sulphate (6 g.) and anhydrous potassium carbonate (15 g.) for 10 hours. The solution was filtered and the residue washed with hot acetone. The filtrate was evaporated and the product crystallised from methyl alcohol when it came out as colourless

elongated rectangular plates melting at 188–9°. Yield, 2.7 g. (Found: C, 67.0; H, 5.7; $C_{13}H_{14}O_4$ requires C, 66.7 and H, 6.0%).

7-Methoxy-5-ethoxy-6-hydroxy-4-methyl coumarin (IX)

(a) *Direct oxidation of 7-methoxy-5-ethoxy-4-methyl coumarin.*—Methoxy-ethoxy coumarin from the previous experiment (2 g.) was dissolved in aqueous sodium hydroxide (50 c.c., 10%) by heating and also adding pyridine (10 c.c.). A saturated solution of potassium persulphate (5 g.) was added drop by drop to the above solution, cooled in ice-water and with constant stirring, during 5 hours. The solution was allowed to stand for 24 hours, and just acidified (congo-red) when the original substance separated out (0.5 g.). It was filtered and the filtrate was twice extracted with ether to remove the last traces of the unchanged substance. The aqueous layer was treated with sodium bisulphite (1 g.) and concentrated hydrochloric acid (20 c.c.) and heated at 70–80° for half an hour. The solution was cooled, filtered and the filtrate extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate and evaporated. The residue crystallised from methyl alcohol to give colourless stout prisms, m.p. 201–2°. Yield, 0.2 g. (Found: C, 62.5; H, 5.4; $C_{13}H_{14}O_5$ requires C, 62.4 and H, 5.6%).

(b) *Oxidation through the coumaric acid.*—7-Methoxy-5-ethoxy-4-methyl coumarin (2 g.) was dissolved in pyridine (20 c.c.), aqueous sodium hydroxide (50 c.c., 10%) and yellow mercuric oxide (1 g.) added to it. This was shaken vigorously for 2 hours, filtered and the filtrate directly treated with a saturated solution of potassium persulphate (5 g.), added dropwise and with constant mechanical stirring and cooling in ice-water for 6 hours. After 24 hours the solution was saturated with hydrogen sulphide and then acidified with concentrated hydrochloric acid (congo-red). The solid that separated out was filtered and the filtrate extracted with ether, to remove the original compound. Concentrated hydrochloric acid (30 c.c.) and sodium bisulphite (1 g.) were added to the aqueous solution and heated at 70–80° for half an hour. It was cooled and shaken with mercuric chloride (0.5 g.) for 15 minutes. The mixture was filtered and the filtrate extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate and then evaporated. The residue was crystallised from alcohol and then from ethyl acetate when it came out as colourless prisms melting at 201–2°. Yield, 0.35 g. Mixed melting point with the sample described in the above experiment was undepressed.

7-Methoxy-5:6-diethoxy-4-methyl coumarin (XI)

(a) *From 7-methoxy-5:6-dihydroxy-4-methyl coumarin.*—7-Methoxy-5:6-dihydroxy-4-methyl coumarin (1.0 g.) was dissolved in dry acetone (100 c.c.)

diethyl sulphate (2 g.) and anhydrous potassium carbonate (10 g.) added and the solution refluxed for 10 hours. It was filtered and the filtrate evaporated. The residue was crystallised from methyl alcohol when it came out as long flat needles melting at 168–9° (Found: C, 64.7; H, 6.5; $C_{15}H_{18}O_5$ requires C, 64.7 and H, 6.5%).

(b) *From 7-methoxy-5-ethoxy-6-hydroxy-4-methyl coumarin.*—7-Methoxy-5-ethoxy-6-hydroxy-4-methyl coumarin (0.4 g.) was ethylated with diethyl sulphate (0.5 g.) and the product worked up as in the above experiment. It crystallised from methyl alcohol as colourless long flat needles melting at 168–9°. Mixed melting point with the sample described in experiment (a) above was undepressed.

SUMMARY

Earlier investigations have shown that partial methylation of the 7-position of 6:7-dihydroxy coumarin is definitely possible. Claims were made by Schmid that in 5:7-dihydroxy-4-methyl coumarin also partial methylation takes place in the 7-position. But no proof was provided. This has now been given by the ethylation of the partial methyl ether and subjecting it to nuclear oxidation and final ethylation. The product is found to be 7-methoxy-5:6-diethoxy-4-methyl coumarin which has also been made by an independent and unambiguous method for purposes of comparison. The constitution of the partial methyl ether is thus established as 7-methoxy-5-hydroxy-4-methyl coumarin.

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