SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part LVIII. Syntheses of 5 : 7–Dimethoxy–6–hydroxy Isoflavone and Muningin

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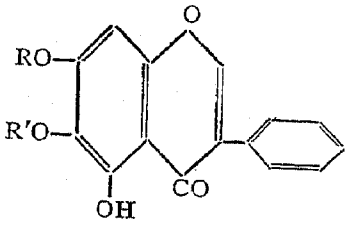
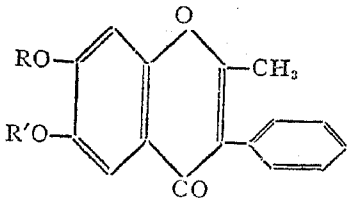
It has been reported earlier that 7-methyl ethers of polyhydroxy isoflavones could be prepared both by partial demethylation[1–3] as well as partial methylation.[1,4] A method which has been successfully employed in the preparation of 5-methyl ethers depends on the partial benzylation of the other reactive hydroxyls, methylation of the 5-hydroxy group and final debenzylation.[2] Recently benzoylation[5] has also been employed in connection with a synthesis of muningin. It has, however, been observed in this laboratory that a more convenient method is to effect partial acetylation of the reactive hydroxyls, methylation in the 5-position and final deacetylation.[6]

Among naturally occurring flavonoids, muningin (XI) is unique in having a methoxy group in the 5-position and having at the same time more reactive hydroxy groups free in other positions. Further, it is a 5: 7-dimethoxy compound and hence a combination of methods was needed for its synthesis and for the synthesis of analogous compounds. As the first step the preparation of the 7-methyl ether (III) of 5: 6: 7-trihydroxy isoflavone (I) was attempted. It was observed that partial demethylation of 5: 6: 7-trimethoxy isoflavone with hydriodic acid did not proceed as smoothly as with members of the 5: 7-dimethoxy type and the yield of the required product was low. As an alternative, partial methylation of 5: 6: 7-trihydroxy isoflavone (I) was attempted using the acetone, potassium carbonate method and 1 mole of dimethyl sulphate. The major product was 6: 7-dimethoxy-5-hydroxy isoflavone (II) and the monomethyl ether (III) could not be successfully obtained. Even in the simpler case of 2-methyl-6: 7-dihydroxy isoflavone (IV) partial methylation could not be effected by this method and only dimethyl ether (V) could be obtained. Obviously the difference in the reactivity of the 6 and 7-hydroxyl groups is not appreciable enough for this method.

On the other hand by avoiding potassium carbonate and using sodium bicarbonate instead, and carrying out the methylation over a longer period,

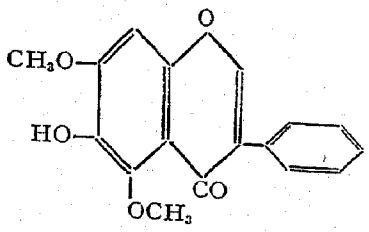


I, R, R′=H
II, R, R′=CH_3
III, R=CH_3, R′=H

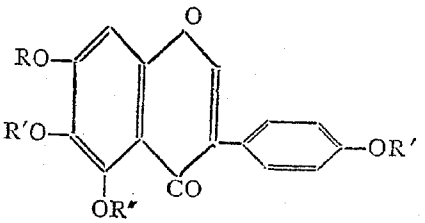


IV, R, R′=H
V, R, R′=CH_3
VI, R=CH_3, R′=H

the 7-monomethyl ether (VI) could be obtained without serious difficulty. The bicarbonate method was used earlier[7] for a similar case in the coumarin series, that is, partial benzylation of 6:7-dihydroxy coumarin. Extending the method, 7-methoxy-5:6-dihydroxy isoflavone (III) could be conveniently prepared, and when it was subjected to partial acetylation of the 6-hydroxy group, methylation of 5-hydroxyl and final deacetylation it yielded 5:7-dimethoxy-6-hydroxy isoflavone (VII) whose properties were the same as those described earlier[8] except the ferric reaction. Following the same procedure and starting from 5:6:7:4′-tetrahydroxy isoflavone (VIII) the 7-methyl ether (IX), and its diacetate (X) were obtained and final methylation and hydrolysis gave muningin (XI) (see also ref. 5 and 6).



VII



VIII, R, R′, R″ = H
IX, R = CH_3, R′ and R″ = H
X, R = CH_3; R′ = $COCH_3$, R″ = H
XI, R, R″ = CH_3, R′ = H

EXPERIMENTAL

5:6:7-trimethoxy and 5:6:7:4′-tetramethoxy isoflavones were prepared from the appropriate phenyl benzyl ketones by ring closure using ethyl formate. Yields upto 20% were reported earlier in the isoflavone condensation of 2-hydroxy-4:5:6:4′-tetramethoxy phenyl benzyl ketone by Krishnamurthy and Seshadri[9] and King *et al.*[10]; it has now been found that if the reaction mixture is kept for 96 hours instead of the usual 24 hours the yields are as good as 55%. 5:6:7-Trihydroxy isoflavone and 5:6:7:4′-tetrahydroxy isoflavone were obtained in very good yield by demethylation with hydriodic acid.

7-Methoxy-5 : 6-dihydroxy isoflavone (III)

5 : 6 : 7-Trihydroxy isoflavone (2 g.) was dissolved in acetone (100 c.c.), methyl sulphate (0·7 c.c.; 1 mole) and sodium bicarbonate (5 g.) were added and the mixture refluxed for 24 hours. Acetone was distilled off and the residue treated carefully with dilute hydrochloric acid till all the bicarbonate was decomposed. After filtering, washing and drying, the product crystallised from alcohol as fine silky needles melting at 222–24°. A mixed melting point with an authentic sample prepared by Aghoramurthy, Venkatasubramanian and Seshadri[11] was undepressed. Yield 0·7 g.

7-Methoxy-6-acetoxy-5-hydroxy isoflavone

The above methyl ether (1 g.) was dissolved in pyridine (8 c.c.) and acetic anhydride (0·5 c.c.; 1·5 moles) added. The solution was stirred well for 7 minutes. During this process a solid started separating out. Pieces of ice and water were added and the product was filtered, washed well and dried. It crystallised from ethyl acetate as colourless rectangular plates melting at 184–85°. Yield 0·8 g. It gave a red colour with alcoholic ferric chloride (Found: C, 66·5; H, 4·6; $C_{18}H_{14}O_6$ requires C, 66·3; H, 4·3%).

5 : 7-Dimethoxy-6-acetoxy isoflavone

The above partial acetate (0·5 g.) was methylated in acetone solution using methyl sulphate (0·4 c.c., excess) and potassium carbonate (2 g.) for 40 hours. The product crystallised from alcohol as colourless thick rectangular tablets melting at 205–07°. Yield 0·3 g. (Found: C, 67·7; H, 5·1; $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·7%).

5 : 7-Dimethoxy-6-hydroxy isoflavone (VII)

The above acetate of the dimethyl ether (0·2 g.) was placed in a small test-tube immersed in freezing mixture. Ice cold sulphuric acid (2 c.c.) was added dropwise during the course of about five minutes, and the tube was then transferred to another beaker containing ice and water. It was stirred and kept at this temperature for 10 minutes. Addition of ice caused the separation of the deacetylated product as a colourless solid which crystallised from dilute alcohol as colourless thick rectangular tablets and prisms melting at 184–86°. It was freely soluble in dilute alkali but gave no colour with ferric chloride (Found: C, 68·1; H, 5·2; $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%).

7-Methoxy-5 : 6 : 4′-trihydroxy isoflavone (IX)

5 : 6 : 7 : 4′-Tetrahydroxy isoflavone (2 g.) in acetone solution was methylated with methyl sulphate (0·7 c.c.; 1 mole) and sodium bicarbonate

(5 g.). The product crystallised from acetic acid as small prisms melting at 263–65° (decomposition) with shrinking at 258°. Venkataraman *et al.*[5] reported the same melting point. Yield 0·6 g. (Found: C, 64·0; H, 4·3; $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%).

7-Methoxy-6: 4'-diacetoxy-5-hydroxy isoflavone (X)

The above mono-methyl ether (0·5 g.) was partially acetylated with acetic anhydride (0·4 c.c.; 2·5 moles) in pyridine (5 c.c.) solution as before. The product crystallised from ethyl acetate as colourless stout rectangular prisms melting at 206–08°. It gave a red colour with ferric chloride; yield 0·4 g. (Found: C, 62·5; H, 4·5; $C_{20}H_{16}O_8$ requires C, 62·5; H, 4·2%).

5: 7-Dimethoxy-6: 4'-dihydroxy isoflavone (muningin) (XI)

The above compound (0·5 g.) in acetone solution was refluxed with dimethyl sulphate (0·5 c.c.; excess) and potassium carbonate (4 g.) for 40 hours. The product separated from alcohol as colourless needles melting at 230–32° agreeing with the melting point recorded for muningin acetate by King *et al.*[10]

The above acetate (0·2 g.) was deacetylated using cold concentrated sulphuric acid. The product gave all the reactions for muningin as described by King *et al.*[10] It crystallised from dioxane as colourless rectangular tablets melting with decomposition at 285°. Mixed melting point with the natural sample was undepressed (Found: C, 64·5; H, 4·8; $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%).

SUMMARY

Of the two methods of obtaining 7-methyl ethers of 5: 6: 7-hydroxy isoflavones partial methylation employing sodium bicarbonate is more convenient. Thus 7-methoxy-5: 6-dihydroxy and 7-methoxy-5: 6: 4'-trihydroxy isoflavones have been prepared. These could be partially acetylated, methylated in the 5-position and finally deacetylated to yield 5: 7-dimethoxy-6-hydroxy isoflavone and muningin respectively.

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