SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XXIII. A New Synthesis of 8-Methyl Genistein

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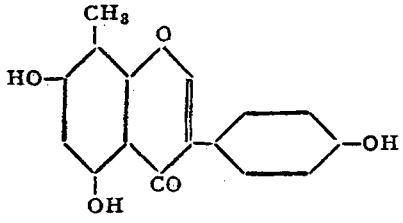
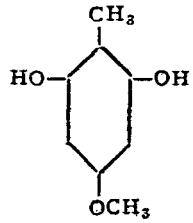
Received November 5, 1952

OKANO and BEPPU[1] isolated four crystalline substances from soya beans and considered them to be isoflavones. To one of these, they assigned the constitution of 8-methyl genistein (I) on the basis of degradation studies. Later Shriner and Hull[2] reported a synthesis of a compound of this structure starting from C-methyl phloroglucinol α-methyl ether (II) and *p*-methoxy phenyl acetonitrile. They found that the melting points of the synthetic isoflavone and its triacetate were in agreement with those reported for the natural substance and its acetate.



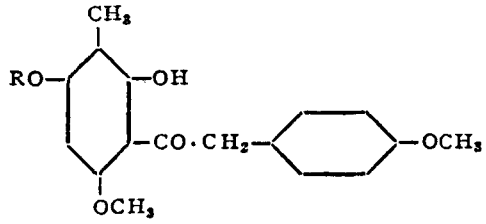
I



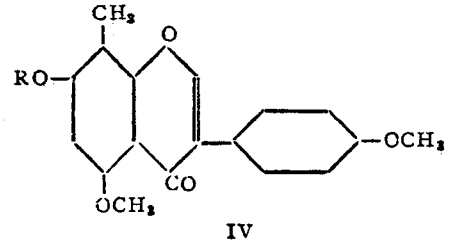
II

In an earlier publication[3] was described a synthesis of 8-methyl genistein, in which nuclear methylation of 2:4:6-trihydroxy-4'-methoxy phenyl benzyl ketone was used as a step. However the products of this synthesis were quite different from the natural compound and its derivatives and from the synthetic substance reported by Shriner and Hull.[2] In view of these discrepancies, it was thought necessary to re-examine the synthesis of 8-methyl genistein of Shriner and Hull.[2] For this purpose, the α-monomethyl ether of C-methyl phloroglucinol (II) has been made by the action of dry hydrogen chloride on an absolute methyl alcoholic solution of C-methyl phloroglucinol according to the method of Weidel[4] as modified by Curd and Robertson.[5] It is condensed with *p*-methoxy phenyl acetonitrile[3] under the conditions of Hoesch reaction. The product could be separated into two fractions: (i) soluble in aqueous sodium carbonate and (ii) soluble in aqueous sodium hydroxide. Fraction (i) gives a crystalline solid melting at 87–88°, with a negative ferric reaction and is identical with *p*-methoxy phenyl acetic acid.

Fraction (ii) yields 2: 4-dihydroxy-3-methyl-6: 4'-dimethoxy phenyl benzyl ketone (III *a*). It gives a positive reaction with ferric chloride and is found to melt at 162–64°. Shriner and Hull[2] reported that their compound of this structure melted at 125–27°. These authors did not note *p*-methoxy phenyl acetic acid as one of the products of the reaction and it is possible that their ketone sample had a lower melting point due to admixture with the acid.



III

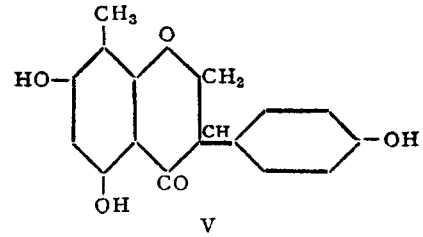


IV

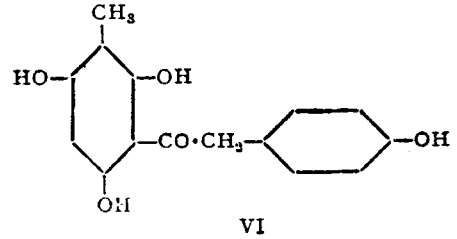
a, R = H
b, R = CH_3

On methylation with methyl iodide and potassium carbonate in acetone solution, (III *a*) yields 2-hydroxy-3-methyl-4 : 6 : 4'-trimethoxy phenyl benzyl ketone (III *b*), in every way identical with the product described in our earlier paper.[3] This establishes the authenticity of the ketone (III *b*) and it also proves that the synthesis of 8-methyl genistein (I) described in Part XXII[3] is quite unambiguous and there is really no discrepancy between that synthesis and the method of Shriner and Hull.[2]

To settle the question more definitely, 2: 4-dihydroxy-3-methyl-6: 4'-dimethoxy phenyl benzyl ketone (III *a*) has now been condensed with ethyl formate in presence of sodium.[6] The product is soluble in aqueous sodium hydroxide and does not give any colour with ferric chloride. It should therefore be 8-methyl-5: 4'-dimethoxy-7-hydroxy isoflavone (IV *a*). It melts at 287–90°. Shriner and Hull[2] however recorded that their substance melted at 268–72°. No compound having this melting point could be isolated in the present work. On methylation, the above dimethyl ether (IV *a*) yields 8-methyl-5: 7: 4'-trimethoxy isoflavone (IV *b*) identical with the product described in Part XXII.[3] Thus the two methods give rise to the same compounds and there is total agreement. There is therefore no



V



VI

doubt regarding the authenticity of 8-methyl genistein (I) obtained synthetically.[3] The earlier results of Shriner and Hull[2] are therefore difficult to explain.

These experiments also conclusively prove that the natural isoflavone isolated by Okano and Beppu[1] cannot have the constitution 8-methyl genistein (I). The degradation reactions carried out by Okano and Beppu[1] with the natural compound can be equally well explained if it was an isoflavanone, *i.e.*, if it had the structure of 8-methyl-5:7:4′-trihydroxy isoflavanone (V) since a compound of this structure can also give rise to 2:4:6:4′-tetrahydroxy-3-methyl phenyl benzyl ketone (VI). Complex isoflavanone derivatives, *e.g.*, rotenone and its allies, have long been known to occur in nature.

The existence of simpler isoflavanones has been shown by the recent study of padmakastein, isolated by Narasimhachari and Seshadri.[7] A synthesis of the tetrahydroxy ketone (VI) should throw some light on the structure of the natural compound from soya beans. This has now been attempted by the demethylation of 2:4:6-trihydroxy-3-methyl-4′-methoxy phenyl benzyl ketone[3] with aluminium chloride in benzene solution. Due to the very poor solubility of this ketone in benzene, demethylation does not take place. However, the required tetrahydroxy compound (VI) could be obtained by employing the easily soluble methyl ether (III *b*) for this demethylation. The product is readily soluble in sodium carbonate and melts at 235–37°. Okano and Beppu[1] stated that their tetrahydroxy ketone melted at 190°. It is possible therefore that the natural compound isolated by them is not an isoflavone or isoflavanone but has a different structure.

EXPERIMENTAL

2:4-Dihydroxy-3-methyl-6:4′-dimethoxy phenyl benzyl ketone (III a)

To a solution of C-methyl phloroglucinol α-monomethyl ether (II)[5] (3·8 g.) and *p*-methoxy phenyl acetonitrile[3] (5·5 g.) in dry ether (150 c.c.) was added powdered fused zinc chloride (1·5 g.). The mixture was cooled in an ice-bath and dry hydrogen chloride was passed in for 5 hours. It was then left in the ice-chest for 15 hours. Dry ether (100 c.c.) was then added to precipitate the ketimine hydrochloride completely. An oil mixed with some crystals separated. The ether portion was decanted off and the ketimine hydrochloride washed with dry ether twice. Water (150 c.c.) was added and the mixture heated under reflux in a boiling water-bath for 1·5 hours. On cooling, a red oil separated. It did not solidify on keeping at 0° for a number of hours. The mixture was extracted with ether and the ether solution washed first with aqueous sodium carbonate thrice. The carbonate solution was acidified, extracted with ether and ether distilled.

The residue crystallised from 75% alcohol (charcoal) and melted at 87–88°. It dissolved in aqueous sodium bicarbonate and did not give any colour with ferric chloride. A mixture of the substance with an authentic sample of *p*-methoxy phenyl acetic acid also melted at 87–88°.

The original ether solution remaining after extraction with sodium carbonate was then extracted with aqueous sodium hydroxide (10%) thrice. The combined deep red alkaline extract was cooled to 0° and acidified with hydrochloric acid. The reddish sticky solid that was precipitated was filtered and washed with water. On macerating with cold alcohol, the coloured impurities dissolved. The colourless solid was filtered, washed with a small quantity of cold alcohol and crystallised from dilute alcohol when 2:4-dihydroxy-3-methyl-6:4′-dimethoxy phenyl benzyl ketone separated as fine feathery colourless needles and long rectangular rods melting at 162–64°. Shriner and Hull[2] gave the melting point as 125–27°. It was easily soluble in alcohol and it gave a pinkish brown ferric reaction in alcoholic solution. A solution of the substance in aqueous sodium hydroxide was colourless (Found: C, 67·9; H, 6·2; $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%).

2-Hydroxy-3-methyl-4:6:4′-trimethoxy phenyl benzyl ketone (III b)

A solution of the above dihydroxy ketone (III *a*) (0·2 *g.*) in acetone (75 c.c.) was treated with methyl iodide (1·0 c.c.) and potassium carbonate (2 g.) and the mixture refluxed for two hours. The solution was filtered and the solid residue washed with acetone. The oil left on distilling off the solvent was treated with water (100 c.c.) and the solid so obtained was filtered after two hours. It crystallised from alcohol as colourless rectangular rods melting at 114–15° and a mixture of the substance with 2-hydroxy-3-methyl-4:6:4′-trimethoxy phenyl benzyl ketone[3] had the same melting point. Yield 0·2 g.

5:4′-Dimethoxy-7-hydroxy-8-methyl isoflavone (IV a)

A suspension of 2:4-dihydroxy-3-methyl-6:4′-dimethoxy phenyl benzyl ketone (0·6 g.) in freshly distilled ethyl formate (15 c.c.), cooled to 0° was gradually added with stirring to powdered sodium (0·5 g.). The mixture was stirred for one hour and left in the ice-chest for 48 hours. Pieces of ice and hydrochloric acid (15 c.c.) were then added and the mixture stirred well and left overnight. Unreacted ethyl formate was evaporated under reduced pressure and the dark solid was filtered after cooling. It was macerated with cold alcohol and filtered and the residue crystallised from boiling alcohol. 5 : 4′-Dimethoxy-7-hydroxy-8-methyl isoflavone (IV *a*) was obtained in the form of colourless rhombic prisms melting at 287–90°

(decomp.). Shriner and Hull[2] have reported the melting point of this substance to be 268–72°. Yield 0·15 g. It was sparingly soluble in alcohol and easily soluble in acetone. It did not give any colour with alcoholic ferric chloride and was soluble in aqueous sodium hydroxide (Found: C, 68·8; H, 5·0; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

Methylation

The above compound (0·1 g.) in acetone (100 c.c.) was heated under reflux with methyl iodide (0·3 c.c.) and potassium carbonate (1 g.) for 3 hours. The potassium salts were filtered off and washed with acetone. The solvent was distilled off from the combined filtrate and water (60 c.c.) added to the residue. The precipitate was collected and crystallised from alcohol. It separated as colourless thick prisms melting at 181–83° and the mixed melting point with a sample of 8-methyl-5:7:4′-trimethoxy isoflavone[3] was not depressed.

2:4:6:4′-*Tetrahydroxy-3-methyl phenyl benzyl ketone* (*VI*)

To a solution of 2-hydroxy-3-methyl-4:6:4′-trimethoxy phenyl benzyl ketone (III *b*)[3] (0·4 g.) in dry benzene (30 c.c.), well powdered anhydrous aluminium chloride (1·6 g.) was added and the mixture refluxed on a water-bath for 2 hours. Benzene was then distilled off and the aluminium chloride complex decomposed by the addition of ice and hydrochloric acid. The tetrahydroxy ketone that separated was filtered and purified by dissolving in aqueous sodium carbonate (10%). Yield 0·2 g. When crystallised from dilute alcohol twice, it was obtained as pale yellow rectangular rods and prisms melting at 235–37°. It gave a deep pink colour with alcoholic ferric chloride and a solution of the substance in aqueous sodium carbonate was pale yellow (Found: C, 66·1; H, 5·4; $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%).

SUMMARY

In view of the discrepancies between the products of the synthesis of 8-methyl genistein described in Part XXII and those of Shriner and Hull, the method of these authors has been re-examined. 2:4-Dihydroxy-3-methyl-6:4′-dimethoxy phenyl benzyl ketone and 5:4′-dimethoxy-7-hydroxy-8-methyl isoflavone prepared now are found to have melting points much higher than those reported by Shriner and Hull. However, on methylation, they yield their respective monomethyl ethers which are identical with those described in Part XXII. There is thus complete agreement between the two syntheses.

The natural compound of Okano and Beppu cannot be 8-methyl genistein. However the degradation reactions could be explained on the

basis of an isoflavanone structure. In order to make sure of the primary degradation product, *viz.*, 2:4:6:4′-tetrahydroxy-3-methyl phenyl benzyl ketone, it has now been synthetically obtained from its trimethyl ether by demethylation with aluminium chloride. But the synthetic product is found to be different from the tetrahydroxy ketone of Okano and Beppu and therefore the natural compound may not be a simple isoflavone or isoflavanone but may have a different structure.

References

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7. Narasimhachari and Seshadri .. *Proc. Ind. Acad. Sci.*, 1952, **35 A**, 202.