SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XXXIX. A Note on the Synthesis of Isogenistein and 8-Methyl Isogenistein

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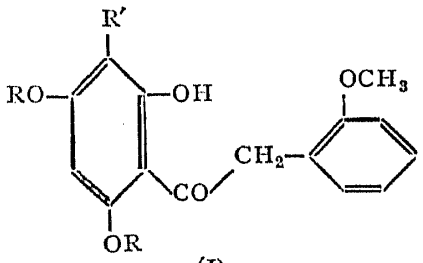
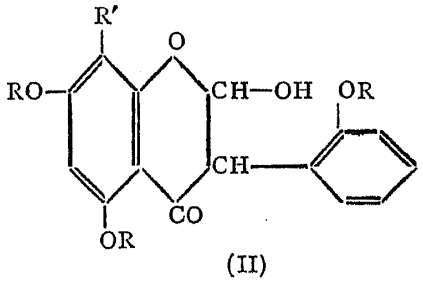
In an earlier paper on the Synthesis of Isogenistein, Seshadri and Varadarajan[1] observed that the condensation of 2-hydroxy-4:6:2′-trimethoxy phenyl benzyl ketone (I *b*) with ethyl formate gave rise to a product having a melting point of 180–81°. The analytical results agreed with the molecular formula $C_{18}H_{18}O_6$ and there was no loss on drying *in vacuo* at 110° for 6 hours. Since it did not give a green or blue colour with nitric acid (a reaction considered to be characteristic of isoflavanone derivatives), it was reported to be a hydrate of 5:7:2′-trimethoxy isoflavone, the molecule



(I)

(*a*) R=R′=H
(*b*) R=CH_3; R′=H
(*c*) R=H; R′=CH_3
(*d*) R=R =CH_3



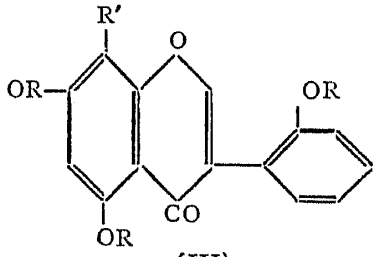
(II)

(*a*) R=CH_3; R′=H
(*b*) R=R′CH_3

of water being unusuallly strongly held. Prof. W. Baker in a private communication, however, suggested that this compound may be 2-hydroxy-5:7:2′-trimethoxy isoflavanone (II *a*), since 5:7:2′-trimethoxy-isoflavone (III *a*) obtained by him by the exthoxalyl chloride method[2] had a melting point 138–39°. Later Karmarkar *et al.*[3] reported that by the ethyl formate sodium method itself they obtained the above trimethoxy isoflavone (III *a*) melting at 138°. The condensation has now therefore been repeated a number of times; the product has invariably been found to melt at 180–81°. The same compound is also obtained by using methyl-formate in the place of ethyl formate. Whalley[4] has also reported a higher melting compound, m.p. 196° (decomp.), using methyl formate for the condensation. Since

Narasimhachari *et al.*[5] have found that with methyl formate 2-hydroxy isoflavanones are generally formed, it should be concluded that in this particular case ethyl formate has also behaved similarly and yielded 2-hydroxy-5:7:2′-trimethoxy-isoflavanone (II *a*). Dehydration of (II *a*) could be effected by using sodium acetate and acetic anhydride and also by 16% alcoholic sulphuric acid.[5] The dehydrated product is found to melt at 140–41° and the analytical values agree with the requirements of the anhydrous trimethoxy isoflavone (III *a*), $C_{18}H_{16}O_5$. When the above 2-hydroxy isoflavanone (II *a*) was boiled with animal charcoal in alcoholic solution, the dehydration was only partial; the resulting mixture could however be easily separated by fractional crystallisation. Whalley[4] has carried out the dehydration of (II *a*) using hot acetic acid and has reported 140° as the melting point of the dehydrated product.

Seshadri and Varadarajan[1] carried out the demethylation of 2-hydroxy-5:7:2′-trimethoxy isoflavanone (II *a*) using aluminium chloride in benzene and also hydriodic acid in acetic anhydride and reported that the isogenistein obtained thereby melted at 222–23° with sintering at 183°. Baker *et al.*[2] in their earlier note recorded 187° as the melting point for the Isogenistein (III *b*). Subsequently Karmarkar *et al.*[3] who used aluminium bromide in benzene for the demethylation of (III *a*) gave the same melting point (187°) for (III *b*). We have now demethylated our new sample of trimethoxy isoflavone (III *a*) (melting point 140–41°) using anhydrous aluminium chloride in benzene. After the first crystallisation from dilute alcohol the product melts at 187° but further crystallisation yields a sample which sinters at 183° and melts at 222–23°. More recently Baker *et al.*[6] have suggested that the isoflavone (III *b*) is dimorphic corresponding to the two melting points.



(III)

(*a*) R=CH_3; R′=H
(*b*) R=R′=H
(*c*) R=R=CH_3
(*d*) R=H; R′=CH_3

In connection with the above work another difference in the findings of different workers may be mentioned. Samples of 2:4:6-trihydroxy-2′-methoxy phenyl benzyl ketone (I *a*) obtained by Seshadri and Varadarajan[1]

and by Whalley[4] are monohydrates whereas Baker *et al.*[6] and Karmarkar *et al.*[3] have obtained it in the anhydrous form.

Investigations similar to above have now been made on the condensation of ethyl formate with 2-hydroxy-3-methyl-4 : 6 : 2′-trimethoxy phenyl bnzyl ketone (I *d*), reported earlier.[7] The product has been found definitely to be 2-hydroxy-5 : 7 : 2′-trimethoxy-8-methyl isoflavanone (II *b*); it undergoes dehydration when boiled with sodium acetate and acetic anhydride yielding 5 : 7 : 2′-trimethoxy 8-methyl isoflavone (III *c*). Whalley[4] has also reported similar results. However, Karmarkar *et al.*[3] under the same conditions have obtained 5 : 7 : 2′-trimethoxy-8-methyl isoflavone (III *c*) directly.

In the present work the above ketone (I *d*) has been made from C-methyl phloroglucinol[8] and *ortho* methoxy benzyl cyanide[1] and subsequent partial methylation of the trihydroxy ketone intermediate. Its condensation with methyl formate gave the same 2-hydroxy-isoflavanone (II *b*) as obtained from ethyl formate.[7] (II *b*) was dehydrated using sodium acetate and acetic anhydride and the dehydrated product (III *c*) was demethylated to 8-methyl isogenistein (III *d*) using anhydrous aluminium chloride in benzene following the method of Seshadri and Varadarajan.[7] However, Whalley[9] has reported that the demethylation of 8-methyl isogenistein trimethyl ether (III *c*) using aluminium chloride and benzene produces a mixture of 6 and 8-methyl isogenistein. But the exact conditions under which the change was brought about are not yet available. It has been conclusively established in several cases that anhydrous aluminium chloride in benzene does not cause any isomerisation of pyrone derivatives during demethylation (see Mukerji *et al.*[10]; Seshadri and Varadarajan[11]). In the present work also a single product was obtained and no isomeric change has been detected.

A careful research of the past literature has revealed that in the synthesis of a few complex isoflavones using sodium and ethyl formate the corresponding 2-hydroxy isoflavanones have been met with as intermediate stages. Wolfrom *et al.*[12] using osajetin and tetrahydro osajetin dimethyl ether and Harper[13] using derritol and elliptol methyl ethers have recorded this observation. However, the synthesis of isogenistein and 8-methyl isogenistein are the first two instances of the simple type of isoflavones wherein the exclusive formation of stable-2-hydroxy isoflavanones has been observed.

Experimental

2-*Hydroxy*-5 : 7 : 2′-*trimethoxy isoflavanone* (*II a*)

(i) *Preparation using methyl formate.*—A suspension of 2-hydroxy-4 : 6 : 2′-trimethoxy phenyl benzyl ketone[1] (I *b*) (1 g.) in freshly distilled methyl

formate (20 c.c.) was treated with powdered sodium (0·7 g.) at 0° and the mixture left in the refrigerator for 48 hours. Ice and hydrochloric acid were then added and the excess of methyl formate was allowed to evaporate slowly by gently warming the mixture in a hot water-bath. The precipitate was collected and crystallised from alcohol when 2-hydroxy-5:7:2′-trimethoxy isoflavanone came out as colourless rectangular rods melting at 180–81°. Yield 0·8 g. A mixed melting point with the product obtained by the ethyl formate condensation[1] was undepressed.

(ii) *Dehydration of (II a) to 5:7:2′-trimethoxy isoflavone (III a).*—(*a*) The above 2-hydroxy isoflavanone (II *a*) (1 g.) was refluxed with acetic anhydride (15 c.c.) and sodium acetate (5 g.) at 140–50° for 2 hours. The mixture was poured into ice and the solid product crystallised from dilute alcohol when 5:7:2′-trimethoxy isoflavone separated as colourless needles melting at 140–41°. Yield 0·4 g. (Found: C, 69·2; H, 5·2. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

(*b*) The above 2-hydroxy isoflavanone (II *a*) (0·5 g.) was dehydrated using 16% alcoholic sulphuric acid.[5] The product crystallised from dilute alcohol as colourless needles melting at 140–41°. Yield 0·35 g. A mixed melting point with the sample obtained in (*a*) was undepressed.

(*c*) 2-Hydroxy isoflavanone (II *a*) (0·5 g.) was taken in boiling alcohol (50 c.c.) and refluxed with animal charcoal (1 g.) for 30 minutes. The hot solution was filtered and allowed to cool. The crystalline mass, which separated out was filtered and was found to be the original 2-hydroxy isoflavanone (II *a*) (m.p. 180–81°). The mother liquor on concentration gave another crystalline solid which was identical in every respect with 5:7:2′-trimethoxy isoflavone obtained by methods (*a*) and (*b*).

5:7:2′-Trihydroxy isoflavone (Isogenistein) (III b)

Demethylation of 5:7:2′-trimethoxy isoflavone (III *a*) was carried out using anhydrous aluminium chloride in benzene in the same way as reported by Seshadri and Varadarajan.[1] But unlike the 2-hydroxy isoflavanone, 5:7:2′-trimethoxy isoflavone was easily soluble in benzene. The demethylated product crystallised from dilute alcohol as short yellow needles melting at 187°. On further crystallisation the substance sintered at 183° and melted completely at 222–23°.

5:7:2′-Triacetoxy isoflavone

The above trihydroxy isoflavone (III *b*) (0·15 g.) was acetylated by boiling with acetic anhydride and pyridine. The triacetate crystallised from alcohol as thin colourless plates melting at 135–37°. Baker *et al.*[6] have

reported 132–34° as the melting point of the acetate whereas Karmarkar *et al.*[3] have recorded 154°. (Found in a sample dried at 110° *in vacuo* for 5 hours: C, 63·6; H, 4·5. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·1%).

2 : 4 : 6-*Trihydroxy*-3-*methyl*-2′-*methoxy phenyl benzyl ketone* (*I c*)

To a solution of C-methyl phloroglucinol (7 g.) and *o*-methoxy phenyl acetonitrile[1] (9 g.) in dry ether (200 c.c.) was added powdered fused zinc chloride (2 g.). The mixture was cooled in an ice-bath and dry hydrogen chloride was passed in for 5 hours. The mixture was then left in the ice-chest for 12 hours, when the ketimine hydrochloride separated as a dark red oil. The ethereal layer was decanted and the residue washed with dry ether. Water (150 c.c.) was added to the residue and the mixture heated on a boiling water-bath under reflux for 2 hours. On cooling in the refrigerator a pale yellow solid separated. It was filtered and crystallised first from water, twice from ethyl acetate and finally from petroleum-ether when small yellowish white needles melting at 198–200° were obtained. Yield 5 g. (Found: C, 66·4; H, 5·5. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%).

2-*Hydroxy*-3-*methyl*-4 : 6 : 2′-*trimethoxy-phenyl-benzyl ketone* (*I d*)

The above ketone (I *c*) (2 g.) in dry acetone (150 c.c.) was refluxed with dimethyl sulphate (1·3 c.c.; 2 moles) and freshly ignited potassium carbonate (3 g.) for 4 hours. The potassium salts were filtered off and washed with acetone. The residue left after distilling off acetone crystallised from alcohol as thick colourless rectangular rods melting at 146–48°. Yield 1·8 g. A mixed melting point with an authentic sample of 2-hydroxy-3-methyl-4 : 6 : 2′-trimethoxy-phenyl-benzyl ketone described earlier[7] was not depressed.

2-*Hydroxy*-5 : 7 : 2′-*trimethoxy*-8-*methyl isoflavanone* (*II b*)

The above ketone (I *d*) (1 g.) was condensed with sodium (1 g.) and methyl formate (25 c.c.) at 0°. After keeping for 48 hours at the same temperature, ice and hydrochloric acid were added and the excess of methyl formate was removed under reduced pressure. The precipitate was collected and crystallised from alcohol when thick colourless prisms separated out and melted at 178–79°. A mixed melting point with the product obtained by the ethyl formate condensation[7] was undepressed.

5 : 7 : 2′-*Trimethoxy*-8-*methyl isoflavone* (*III c*)

The above 2-hydroxy isoflavanone (II *b*) (1 g.) was refluxed with fused sodium acetate (4 g.) and acetic anhydride (15 c.c.) for 2 hours at 140–50°. The mixture was treated with ice and the solid product filtered. It crystallised from dilute alcohol as colourless needles (m.p. 184–86°). Admixture

of this substance with the corresponding 2-hydroxy isoflavanone (II *b*) depressed the melting point to 160° (Found: C, 69·7; H, 5·3; $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%).

5:7:2′-*Trihydroxy*-8-*methyl isoflavone* (8-*Methyl isogenistein*) (*III d*)

The above trimethyl ether (III *c*) (0·5 g.) was demethylated using anhydrous aluminium chloride in benzene following the procedure described earlier.[7] The demethylated product when crystallised from dilute alcohol twice, separated as colourless tablets melting at 230–32°. A mixed melting point with the sample described earlier[7] was not depressed.

SUMMARY

It is established that the condensation of 2-hydroxy-4:6:2′-trimethoxy phenyl benzyl ketone and its 3-methyl derivative with ethyl formate as well as with methyl formate produces the corresponding 2-hydroxy isoflavanones. These undergo dehydration to the trimethyl ether of isogenistein and 8-methyl isogenistein respectively. Demethylation of the above ethers can be conveniently effected by aluminium chloride in benzene solution. The 2-hydroxy isoflavanones also yield the same products by undergoing dehydration along with demethylation.

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