SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XXVI. A Synthesis of 8-Methyl Isogenistein

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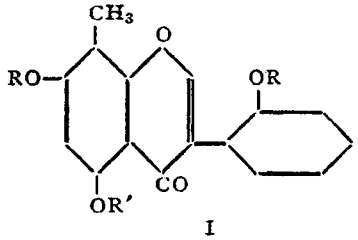
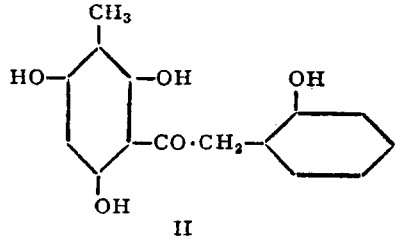
AMONG the crystalline products from soya beans Okano and Beppu[1] reported the isolation of the glycoside, 8-methyl isogenistin (sugar position unsettled) and its aglucone, 8-methyl isogenistein. The analytical values of the aglucone corresponded to the formula $C_{16}H_{12}O_5$. It was found to yield a dimethyl ether (I *b*), a trimethyl ether (I *c*) and a triacetate. On heating with alkali, it gave a tetrahydroxy ketone which was considered to have the structure, 2:4:6:2′-tetrahydroxy-3-methyl phenyl benzyl ketone (II) since it yielded C-methyl phloroglucinol (III *a*) and *o*-hydroxy phenyl acetic acid (IV *a*) on further degradation. The parent aglucone should therefore be 6- or 8-methyl-5:7:2′-trihydroxy isoflavone (I *a*). The location of the methyl group was determined by degradation of the trimethyl ether (I *c*) with alkali, when C-methyl phloroglucinol α-dimethyl ether (III *b*) and *o*-methoxy phenyl acetic acid (IV *b*) were obtained as the products. Hence Okano and

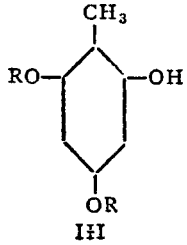


I

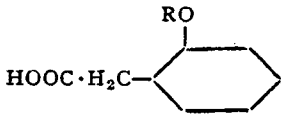
a, R=R′=H
b, R=CH3, R′=H
c, R=R′=CH3



II



III

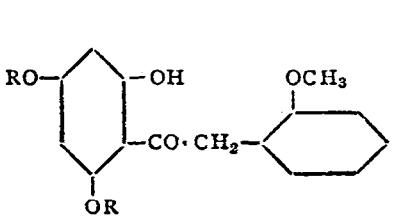


IV

a, R=H
b, R=CH3

Beppu[1] assigned the structure of 8-methyl-5: 7: 2′-trihydroxy isoflavone (8-methyl isogenistein) (I *a*) to the natural compound.

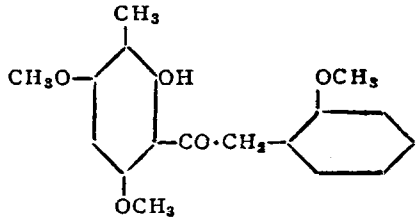
A synthesis of a compound of this structure (I *a*) has now been carried out along the lines of the synthesis of 8-methyl genistein, described in an earlier paper.[2] For this purpose, 2: 4: 6-trihydroxy-2′-methoxy phenyl benzyl ketone (V *a*) described in Part XXIV[3] is heated with excess of methyl iodide and potassium carbonate in acetone solution. The product is fractionally crystallised from alcohol. The less soluble fraction is 2-hydroxy-3-methyl-4: 6: 2′-trimethoxy phenyl benzyl ketone (VI). It does not give any blue or green colour with concentrated nitric acid[4] but gives a wine red ferric reaction. These properties are in agreement with this C-methyl formula. The more soluble fraction is identical with 2-hydroxy-4: 6: 2′-trimethoxy phenyl benzyl ketone (V *b*) described in an earlier publication.[3]



V

a, R=H

b, R=CH₃



VI

Condensation of 2-hydroxy-3-methyl-4: 6: 2′-trimethoxy phenyl benzyl ketone (VI) with ethyl formate and sodium[5] gives a good yield of 5: 7: 2′-trimethoxy-8-methyl isoflavone (I *c*).* This compound is found to melt at 178–79° and seems to be quite different from the trimethyl ether of the natural compound, whose melting point was reported as 152–53° by Okano and Beppu.[1] In this case also, as with 5: 7: 2′-trimethoxy isoflavone,[3] considerable difficulties exist in demethylation. When a mixture of acetic anhydride and hydriodic acid is employed for this purpose, a resinous product is obtained from which a small quantity of crystalline material melting at 230–32° could be isolated. The demethylation is more conveniently effected by aluminium chloride in benzene solution.[6] The product melts at 230–32° and is identical with the compound obtained by the demethylation of (I *c*) with hydriodic acid. Okano and Beppu[1] reported the melting point of the natural compound to be 300–02°. They have also mentioned that it gave a violet red colour with alcoholic ferric chloride. The deep green

* This compound has subsequently been found to be 2-hydroxy-5: 7: 2′-trimethoxy-8-methyl isoflavanone and has been converted into 5: 7: 2′-trimethoxy-8-methyl isoflavone, m.p. 183–84°.

colour given in this reaction by the synthetic substance in the present work is similar to the one given by the isomeric 8-methyl genistein[2] and is more in agreement with expectations for this structure than the violet red colour exhibited by the natural compound.

There is also considerable difference in the melting points of the acetates of the synthetic product and the natural compound of Okano and Beppu.[1] The latter has been reported to melt at 188° while the triacetate obtained in the present work becomes glassy at about 110°. and melts at 120° completely showing that it is hydrated. These differences clearly establish that the natural compound cannot have the structure assigned to it by Okano and Beppu and similar to other compounds occurring along with it, it should a'so have a more complex structure (see Parts XXIII[2] and XXIV[3]).

EXPERIMENTAL

2-Hydroxy-3-methyl-4: 6: 2'-trimethoxy phenyl benzyl ketone (VI)

To a solution of 2: 4: 6-trihydroxy-2'-methoxy phenyl benzyl ketone (V *a*)[3] (5 g.) in acetone (150 c.c.), methyl iodide (10 c.c.) and potassium carbonate (20 g.) were added and the mixture refluxed for 4 hours. The potassium salts were filtered off and washed with acetone. After distilling off the solvent, water was added to the residue to dissolve potassium iodide. The precipitate was filtered and crystallised from alcohol four times when 2-hydroxy-3-methyl-4: 6: 2'-trimethoxy phenyl benzyl ketone was obtained in the form of thick colourless rectangular rods melting at 146–48°. Yield 0·65 g. It gave a wine red colour with alcoholic ferric chloride and was insoluble in aqueous sodium hydroxide (10%). It did not give a blue or green colour with concentrated nitric acid (Found: C, 68·0; H, 6·1; $C_{18}H_{20}O_5$ requires C, 68·4; H, 6·3%).

The alcoholic mother liquors on concentration yielded 2-hydroxy-4: 6: 2'-trimethoxy phenyl benzyl ketone (V *b*) which when recrystallised twice from alcohol separated as sheaves of colourless thin plates melting at 116–18° alone or when mixed with an authentic sample of the ketone described earlier.[3] Yield 3·0 g.

*5: 7: 2'-Trimethoxy-8-methyl isoflavone (I c)**

The above ketone (VI) (1 g.) was condensed with sodium (1 g.) and ethyl formate (25 c.c.) at 0°. After 48 hours in the refrigerator, ice and hydrochloric acid were added and the unreacted ester evaporated off. The precipitate was collected and crystallised from alcohol twice. 5: 7: 2'-Trimethoxy-8-methyl isoflavone separated as thick colourless prisms melting

* Please see footnote on an earlier page.

at 178–79°. Yield 0·75 g. (Found: C, 65·9; H, 5·7; $C_{19}H_{18}O_5$, H_2O requires C, 66·3; H, 5·8%). The water of crystallisation was not lost even on drying at 120° for 4 hours under reduced pressure.

5:7:2′-*Trihydroxy-8-methyl isoflavone* (8-*Methyl isogenistein*) (*I a*)

(i) The above trimethyl ether (0·5 g.) was suspended in benzene (200 c.c.) and well powdered anhydrous aluminium chloride (2·0 g.) was added and the mixture refluxed for 2 hours. Benzene was then distilled off and the residual aluminium chloride complex decomposed with ice and hydrochloric acid (10 c.c.). After 4 hours, the yellow precipitate of the trihydroxy isoflavone was collected and purified by dissolution in dilute sodium carbonate solution. The colourless precipitate obtained on acidification of the carbonate solution was crystallised twice from alcohol, when 8-methyl isogenistein separated as colourless tablets melting at 230–32° (decomp.). Yield 0·2 g. It gave a permanent deep green colour with alcoholic ferric chloride. (Found in a sample dried *in vacuo* at 120° for 6 hours: C, 67·8; H, 4·6; $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%).

(ii) 5:7:2′-Trimethoxy-8-methyl isoflavone (0·9 g.) was dissolved in acetic anhydride (25 c.c.) and hydriodic acid (37 c.c., d., 1·7) was added carefully and the mixture refluxed for 2 hours at 140°, cooled and diluted with a saturated solution of sodium bisulphite (150 c.c.). The solution was neutralised by adding sodium bicarbonate. After 12 hours, the dark precipitate was collected, treated with dilute sodium carbonate solution and filtered. The filtrate on neutralisation gave the trihydroxy isoflavone, which when crystallised twice from dilute alcohol came out as colourless tablets melting at 230–32°. A mixed melting point with the sample obtained in (i) above was not depressed. Yield 90 mg.

5:7:2′-*Triacetoxy-8-methyl isoflavone*

The above trihydroxy isoflavone (0·2 g.) was acetylated with acetic anhydride and pyridine. The triacetate was crystallised thrice from alcohol. It was obtained as long colourless irregular prisms. It sintered at 110° and became glassy and melted at 118–20°. The melting point did not rise on further crystallisation (Found: C, 63·2; H, 4·9; $C_{22}H_{18}O_8$, $\frac{1}{2}H_2O$ requires C, 63·0; H, 4·5%).

The above acetate (0·15 g.) was deacetylated with a mixture of alcohol (7 c.c.) and concentrated hydrochloric acid (7 c.c.) by heating in a water-bath for 30 minutes. The solution was concentrated to 10 c.c., diluted with water and left overnight in the refrigerator. The precipitate was collected and crystallised from dilute alcohol. It melted at 230–32° and was identical with 5:7:2′-trihydroxy-8-methyl isoflavone.

SUMMARY

One of the crystalline compounds occurring in soya beans has been considered by Okano and Beppu to be 8-methyl isogenistein and this structure was based on the alkali degradation of the compound and its trimethyl ether. A compound of this structure is now synthesised starting from 2:4:6-trihydroxy-2'-methoxy phenyl benzyl ketone, along the lines of synthesis of 8-methyl genistein described in Part XXII. Here also the products are found to be different from those reported by Okano and Beppu and the natural compound should therefore have a more complex structure.

REFERENCES

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3. ———— .. *Ibid.*, 1953, **37A**, 514.
4. Rao and Seshadri .. *Ibid.*, 1949, **30A**, 30.
5. Venkataraman *et al.* .. *J.C.S.*, 1934, 513 and 1770.
6. Seshadri *et al.* .. *Proc. Ind. Acad. Sci.*, 1947, **24A**, 213; 1947, **25A**, 432; 1949, **29A**, 72; 1952, **35A**, 34, 82 and 202.