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SHORT COMMUNICATION

SYNTHESES OF 7-METHYLTECTORIGENIN AND IRISOLIDONE

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Abstract—Syntheses of 7-methyltectorigenin and irisolidone using ethoxalyl chloride and ethyl orthoformate are described.

ISOLATION of 7-methyltectorigenin from *Dalbergia sisso* was reported by Seshadri *et al.*[1] who established the structure as 5,4'-dihydroxy-6,7-dimethyoxyisoflavone by partial synthesis from tectorigenin. In a direct synthesis of this compound by the ethoxalyl chloride method[2] a mixture of two isomers (m.p. 190–215°) was obtained, from which the carbethoxy derivative of 7-methyltectorigenin, being sparingly soluble in methanol, crystallized out first. It was purified by recrystallization from the same solvent. The other compound by virtue of its formation must be the carbethoxy derivative of the 8-isomer[3] and was purified by repeated crystallization from methanol or methanol–benzene. Both compounds were hydrolysed and decarboxylated to the corresponding isoflavones and were distinguished by complete methylation when only the former gave tri-*O*-methyltectorigenin.

Formation of a mixture of isomers in the cyclization reaction with ethoxalyl chloride is well established, but there is considerable variation in the relative yields of the isomers. For example, in the synthesis of caviunin[4] only the 6-isomer is formed. In the present synthesis, the the 6-isomer is the predominant product and there seems to be no difference in the isomer ratio when the cyclization reaction is carried out at room temperature instead of at 0°.

The starting material for the synthesis, 4,5-dimethoxyresorcinol was prepared by the method of Baker and Robinson.[5] It underwent Hoesch condensation with *p*-hydroxybenzyl cyanide exclusively in the free position *para* to the methoxy to give 4-hydroxybenzyl-2,6-dihydroxy-3,4-dimethoxyphenylketone. The course of the condensation reaction is in agreement with the observations of Baker[6] and Shriner.[7] The above ketone was cyclized with ethyl orthoformate to give 7-methyltectorigenin directly in good yield and the product crystallized out from the reaction mixture on keeping it overnight in a refrigerator.

1 A. BANERJI, V. V. S. MURTI, T. R. SESHADRI and R. S. THAKUR, *Indian J. Chem.* **1**, 25 (1963).
2 A. GHANIM, A. ZAMAN and A. R. KIDWAI, *Tetrahedron Letters* No. 3, 185 (1964).
3 W. BAKER, D. F. DOWNING, A. Y. FLOYD, B. GILBERT, W. D. OLLIS and R. C. RUSSELL, *Tetrahedron Letters* No. 5, 6 (1960).
4 S. F. DYKE, W. D. OLLIS and M. SAINSBURY, *J. Org. Chem.* **26**, 2453 (1961).
5 W. BAKER and R. ROBINSON, *J. Chem. Soc.* 152 (1929).
6 W. BAKER, R. NODZU and R. ROBINSON, *J. Chem. Soc.* 74 (1929).
7 R. L. SHRINER and R. W. STEPHENSON, *J. Am. Chem. Soc.* **64**, 2737 (1942).

The isoflavone irisolidone was isolated in minute amounts from *Iris nepalensis* and assigned the structure 5,7-dihydroxy-6,4′-dimethoxyisoflavone on the basis of degradations.[8] This structure was confirmed in the present synthesis of the compound from iretol and *p*-methoxybenzyl cyanide. 5,7-Dihydroxy-6,4′-dimethoxyisoflavone has been obtained earlier by the rearrangement of 5-hydroxy-8,4′-dimethoxy-7-benzyloxyisoflavone.[9]

EXPERIMENTAL

4-Hydroxybenzyl-2,6-Dihydroxy-3,4-Dimethoxyphenylketone(I)

4,5-Dimethoxyresorcinol (2 g) *p*-hydroxybenzyl cyanide (1·7 g) and anhydrous zinc chloride (1·2 g) were dissolved in 60 ml of dry ether. Dry HCl gas was passed through the solution for 5 hr at 0°, and the reaction mixture kept at 0° for 48 hr. The ketimine hydrochloride–zinc chloride complex was decomposed by boiling under reflux with water (100 ml, N_2 atmosphere) for 1 hr and on cooling, the ketone separated out. Crystallization from methanol or dilute ethanol gave (1·18 g) light yellow crystals, m.p. 199–200°. (Found: C, 62·61; H, 5·43. $C_{16}H_{16}O_6$ required: C, 63·15; H, 5·30%.)

Ethoxalylation of Ketone I

The above ketone (0·9 g) was dissolved in dry pyridine (25 cc) and freshly distilled ethoxalyl chloride (2 cc) added with shaking to the ice-cooled solution. After keeping at 0° for 3 days it was poured into water and extracted with $CHCl_3$. The extract was washed with dil H_2SO_4 and water, dried ($MgSO_4$) and evaporated. The residue (0·9 g) consisting of the isomeric mixture of the two carbethoxy isoflavones was taken up in methanol. The carbethoxy derivative of 7-methyltectorigenin (IIa) separated out on cooling (0·346 g), m.p. 235–236°. (Found: C, 62·27; H, 4·75. $C_{20}H_{18}O_8$ required: C, 62·17; H, 4·70%.) Concentration of the mother liquor gave a crude product, m.p. 192–225° (0·5 g). Repeated crystallization from methanol gave the carbethoxy derivative of 5,4′-dihydroxy-7,8-dimethoxyisoflavone (0·2 g) (IIb), m.p. 212–215°. (Found: C, 62·19, H, 4·81. $C_{20}H_{18}O_8$ required: C, 62·17; H, 4·70%).

5,4′-Dihydroxy-6,7-Dimethoxyisoflavone (7-Methyltectorigenin)

The carbethoxy isoflavone (IIa) (0·344 g) was refluxed in acetone (nitrogen atmosphere) for 4 hr with excess of 5% aqu. Na_2CO_3. Removal of acetone and subsequent acidification precipitated the acid, which crystallized from dilute methanol as light yellow solid (0·2 g), m.p. 297–298°. The acid was decarboxylated by heating in portions (25 mg) at 305° for 2–3 min. The product was taken up in ethyl acetate and the ethyl acetate solution washed with $NaHCO_3$ solution and water, dried and evaporated. The solid obtained on crystallization from methanol gave light yellow crystals of 7-methyltectorigenin (1·06 g), m.p. 231–233°, identical (m.m.p. and u.v. spectrum) with an authentic sample. (Found: C, 65·04; H, 4·71. Calc. for $C_{17}H_{14}O_6$: C, 64·96; H, 4·49%.) 7-Methyltectorigenin, obtained as above, on total methylation gave 5,6,7,4-tetramethoxyisoflavone, m.p. 180°, identical (m.m.p.) with an authentic sample. The synthetic 7-methyltectorigenin was also characterized as its diacetate, colourless crystals from methanol, m.p. and mixed m.p. 180–181°. (Found: C, 63·53; H, 4·47; Calc. for $C_{21}H_{18}O_8$: C, 63·31; H, 4·55%.)

Ethylorthoformate Method

The ketone I (550 mg) pyridine (4·4 ml), piperidine (0·3 ml) and freshly distilled ethyl orthoformate (3·5 ml) were refluxed for 8 hr. The reaction mixture was kept overnight at 0° when a crystalline solid separated out. This was filtered off and crystallization from methanol gave light yellow crystals, m.p. 230–235°. Mixed melting point with authentic 7-methyltectorigenin gave no depression.

5·4′-Dihydroxy-7,8-Dimethoxyisoflavone

The carbethoxyisoflavone (IIb) (0·2 g) was hydrolysed to give carboxyisoflavone, m.p. 270–271°. The carboxyisoflavone was decarboxylated in portions (25 mg) at 280° and the product crystallized from methanol as light yellow needles, m.p. 171–172°. (Found: C, 64·65; H, 4·61. $C_{17}H_{14}O_6$ required: C, 64·96; H, 4·49%).

4-Methoxybenzyl-2,4,6-Trihydroxy-3-Methoxyphenylketone(III)

Iretol (2 g), *p*-methoxybenzyl cyanide (1·9 g) and zinc chloride (1·2 g) in dry ether (60 ml) were treated with dry HCl gas as before and worked up in the usual manner to give a dark brown solid. This could not be crystallized directly and was purified by dissolving in ethyl acetate and adding *n*-hexane when the impurities separated

[8] LALIT PRAKASH, ASIF ZAMAN and A. R. KIDWAI, *J. Org. Chem.* **30**, 3561 (1965).
[9] L. FARKAS, J. VARADY and A. GOTTSEGEN, *Acta Chim. Acad. Sci. Hung.* **33**, 339 (1962).

out as dark brown oil. Evaporation of the solution and crystallization of the residue from benzene gave the ketone III (2·2 g), m.p. 123–125°. Alternatively the crude product was purified by passing through a column of magnesol using benzene–acetone (19:1) as eluent. λ_{max}^{EtOH} 236 and 283 nm λ_{max}^{Nujol} 3, 6·1 and 6·25 μ. (Found: C, 63·15; H, 5·30: Calc. for $C_{16}H_{16}O_6$: C, 62·76; H, 5·32%).

Ethoxalylation of Ketone III

Ethoxalyl chloride (4·2 ml) was added dropwise with shaking to a solution of the ketone III (2 g) in pyridine (40 ml), cooled in a freezing mixture. The residue was purified by chromatography over silica gel using benzene as solvent. Evaporation of benzene yielded a mixture of carbethoxyisoflavones (1·5 g) crystallized from methanol, m.p. 120–122°. This was dissolved in ethanol, streaked on formamide-impregnated Whatman No. 3 papers (56 cm × 15 cm), which were developed with benzene, acetic acid, formic acid and water (upper layer) (9:2:1:1). Fifty such chromatograms were prepared and the two bands, visible in u.v. light, were cut out.

2-*Carbethoxy*-5,7-*Dihydroxy*-6,4′-*Dimethoxyisoflavone*(*IVa*)

The higher R_f value bands were collected and extracted with dilute ethanol in a soxhlet. After removal of ethanol the residue was taken into ether. Evaporation of ether left a dark brown solid which was purified by chromatography on silica gel by elution with benzene and crystallized from ethyl acetate–hexane (0·16 g), m.p. 126–128°, λ_{max}^{EtOH} 237 and 293 nm, λ_{max}^{Nujol} 3, 5·8 and 6·05 μ. (Found: C, 62·17; H, 4·65. $C_{20}H_{18}O_8$ required: C, 62·17; H, 4·70%.)

5,7-*Dihydroxy*-6,4′-*Dimethoxyisoflavone* (*Irisolidone*)

The carbethoxyisoflavone (IVa) (0·15 g) on hydrolysis gave an oily residue of carboxyisoflavone (0·1 g) which crystallized from ethyl acetate–benzene as long yellow needles, m.p. 120–121°. Decarboxylation of this in portions (10 mg) at 260° for 3–4 min under N_2, and extraction of the crude product with ethyl acetate afforded a dark solid which was purified by chromatography over silica-gel (benzene–acetone, 20:1), m.p. 190–191°, from methanol, identical with irisolidone (m.m.p. and i.r. spectra). (Found: C, 64·78; H, 4·48. Calc. for $C_{17}H_{14}O_6$: C, 64·96; H, 4·48%).

2-*Carbethoxy*-5,7-*Dihydroxy*-8,4′-*Dimethoxyisoflavone*(*IVb*)

The bands having the lower R_f value were cut out and worked up as before. Crystallization from ethyl acetate–hexane gave bright yellow needles of carbethoxyisoflavone, IVb (0·2 g), m.p. 105–106, λ_{max}^{EtOH} 237 and 277 nm, $\lambda_{max}^{CHCl_3}$ 3, 5·8 and 6·05 μ. (Found: C, 61·64; H, 4·68. $C_{20}H_{18}O_8$ required: C, 62·17; H, 4·70%.)

5·7-*Dihydroxy*-8,4′-*Dimethoxyisoflavone*

The above carbethoxyisoflavone (IIIb) (0·2 g) was hydrolysed to give the carboxyisoflavone (0·15 g) as fine yellow needles from dil. EtOH m.p. 250–255°. The acid was decarboxylated in portions (10 mg) by heating 10° above its melting point (N_2 atmosphere), and the product was purified by passing it through a silica-gel column with benzene–acetone (19:1) and crystallizing it from benzene, m.p. 170–171°. λ_{max}^{EtOH} 266 nm (log ϵ 4·60); λ_{max}^{Nujol} 3·01, 6·03, 6·20 and 6·31 μ. (Found C, 64·76; H, 4·62. $C_{17}H_{14}O_6$ required: C, 64·96; H, 4·49%). 5,7-Dihydroxy-8,4′-dimethoxyisoflavone on acetylation yielded the *diacetate* as colourless needles from EtOH, m.p. 129–130°. (Found: C, 63·43; H, 4·50. $C_{21}H_{18}O_8$ required: C, 63·31; H, 4·55%.)

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