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CHEMISTRY OF THE PODOCARPACEAE—X[1]

SYNTHESIS OF PODOSPICATIN AND ITS TRIMETHYL ETHER

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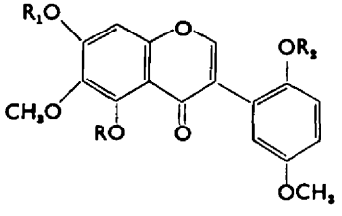
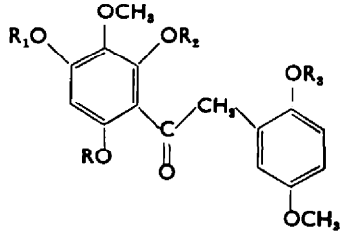
Abstract—Podospicatin (I) and its trimethyl ether(II) have been synthesized by separate standard procedures respectively, involving in the former a rearrangement with alkali.

EVIDENCE was adduced[2] for the constitution of podospicatin as I. Its synthesis and that of its trimethyl ether is now reported.

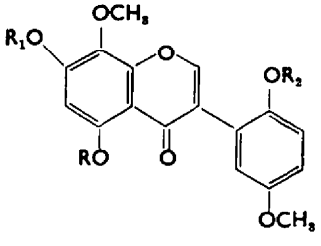
2,5-Dimethoxyresorcinol[3] was condensed with 2-benzyloxy-5-methoxyphenylacetonitrile in a Hoesch reaction to give 2-benzyloxy-5-methoxybenzyl-2,4-dihydroxy-3,6-dimethoxyphenyl ketone (III) which on cyclization with ethyl orthoformate[4] gave 2′-benzyloxy-7-hydroxy-5,8,5′-trimethoxyisoflavone (IV).



I R = R_1 = R_2 = H
II R = R_1 = R_2 = CH_3
VIII R = H; R_1 = R_2 = CH_2Ph
X R = H; R_1 = R_2 = CH_3
XI R = R_1 = H; R_2 = CH_3



III R = CH_3; R_1 = R_3 = H; R_2 = CH_2Ph
IX R = H; R_1 = R_3 = R_5 = CH_3



IV R = CH_3; R_1 = H; R_2 = CH_2Ph
V R = R_1 = H; R_2 = CH_2Ph
VI R = H; R_1 = R_2 = CH_2Ph
VII R = R_1 = R_2 = CH_2Ph

[1] Part IX, *Tetrahedron* To be submitted for publication.
[2] L. H. Briggs and T. P. Cebalo, *Tetrahedron* **6**, 145 (1959).
[3] T. S. Gardner, E. Wenis and J. Lee, *J. Org. Chem.* **15**, 841 (1950).
[4] S. A. Kagal, S. S. Karmarkar and K. Venkataraman, *Proc. Indian Acad. Sci.* **44A**, 36 (1956).

Selective demethylation of IV with anhydrous aluminium chloride in nitrobenzene[5] yielded 2′-benzyloxy-5,7-dihydroxy-8,5′-dimethoxyisoflavone (V), which on reaction with two moles of benzyl chloride gave a mixture of the two isoflavones, 7,2′-dibenzyloxy-5-hydroxy-8,5′-dimethoxyisoflavone (VI) and 5,7,2′-tribenzyloxy-8,5′ dimethoxyisoflavone (VII). The isoflavone (VI) on isomerization with potassium ethylate by Seshadri's method[6] afforded 7,2′-dibenzyloxy-5-hydroxy-6,5′-dimethoxyisoflavone (VIII), identical with podospicatin 6,2′-dibenzyl ether obtained directly from podospicatin. Finally, debenzylation of VIII with acetic acid–hydrochloric acid gave 5,7,2′-trihydroxy-6,5′-dimethoxyisoflavone (I), m.p. 211–212°, identified with podospicatin by mixed m.p. and IR spectra.

For the synthesis of podospicatin trimethyl ether antiarol[7] and 2,5-dimethoxyphenylacetic acid[8] were condensed with boron trifluoride[9] to give the known ketone,[10] 6-hydroxy-2,3,4-trimethoxyphenyl-2,5-dimethoxybenzyl ketone (IX). Condensation of IX with ethyl orthoformate then gave 5,6,7,2′,5′-pentamethoxyisoflavone (II) identical in all respects with that obtained from methylation of the natural product.

The m.p. of 5-hydroxy-6,7,5′,2′-tetramethoxyisoflavone was previously reported[2] as 120–121·5°. Repetition of the methylation of podospicatin with two moles of dimethyl sulphate gave a product with the same m.p. as that previously reported. Selective dealkylation of podospicatin trimethyl ether with aluminium chloride in nitrobenzene, however, gave a product m.p. 148–150,* which by its mode of formation and analysis must be podospicatin 7,2′-dimethyl ether.

Of the isoflavonoids described only I, IV, and V dissolve in 2N sodium hydroxide solution, II, IV and X dissolve in concentrated hydrochloric acid with a yellow colour, I, V, VI, VIII and X give an orange-red colour with uranyl nitrate[11] and I, V, VI, VIII and IX give a characteristic deep green colour with ferric chloride solution.

EXPERIMENTAL

Analysis were by Dr A. D. Campbell and associates, University of Otago, New Zealand. IR spectra were measured (KBr) in an Infracord instrument and UV spectra were measured in alcoholic solution using a Perkin Elmer 137 instrument. Light petroleum was of b.p. 40–60°.

2-Benzyloxy-5-methoxyacetophenone

A mixture of 2-hydroxy-5-methoxyacetophenone[12] (270 g), benzyl chloride (275 g) and sodium hydroxide (1650 ml; 15% solution) was refluxed for 5 hr. Extraction with ether yielded *2-benzyloxy-5-methoxyacetophenone* as an oil (218·1 g), b.p. 154–158°/0·1 mm (Found: C, 75·0; H, 6·3; $C_{16}H_{16}O_3$ requires: C, 75·0; H, 6·3%).

* We are indebted to Professor L. Farkas for pointing out the discrepancy in the melting point of our original material with that of his own preparation, m.p. 152–153°.

[5] R. N. Iyer, K. H. Shah and K. Venkataraman, *Curr. Sci., India* **18,** 404 (1949); *Proc. Indian Acad. Sci.* **33A,** 116 (1951).

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2-Benzyloxy-5-methoxyphenylacetic acid

This was prepared by a modified Willgerodt reaction as described by Schwenk *et al.*[13] A mixture of 2-benzyloxy-5-methoxyacetophenone (218 g), morpholine (77 g) and sulphur (27 g) was refluxed for 8 hr, KOH (3200 ml; 10% solution) was then added and refluxing continued for a further 12 hr. Only a very small amount of oil was formed on acidifying the basic solution decanted from the gummy material which separated. To the gummy material was added ethanol (750 ml), NaOH (150 g) and water (500 ml) and the solution refluxed for 24 hr. After distillation of ethanol and acidification of the residue, ether extraction yielded *2-benzyloxyl-5-methoxyphenylacetic acid* (187 g), crystallizing from chloroform-light petroleum as long rectangular plates, m.p. 112–113·5° (Found: C, 70·2; H, 6·0; O, 23·5; $C_{16}H_{16}O_4$ requires: C, 70·6; H, 5·9; O, 23·5%).

2-Benzyloxy-5-methoxyphenylacetamide

Thionyl chloride (30 ml) was added to a solution of 2-benzyloxy-5-methoxyphenylacetic acid (60 g) in anhydrous benzene (250 ml) and the mixture refluxed for 2 hr. After removal of the benzene and thionyl chloride *in vacuo* ether (500 ml) was added to the residue and the mixture saturated with ammonia. The solid produced, after filtering and washing with water, was dissolved in ethyl acetate, washed with $KHCO_3$aq and water, and the solution dried and concentrated.

Crystallization of the residue from ethanol yielded *2-benzyloxy-5-methoxyphenylacetamide* as colourless needles (44 g), m.p. 133–135° (Found: C, 80·0; H, 6·5; N, 5·2; $C_{16}H_{17}NO_3$ requires: C, 70·8; H, 6·3; N, 5·2%).

2-Benzyloxy-5-methoxyphenylacetonitrile

This was prepared by dehydration of the corresponding amide following the method of Stephens *et al.*[14] To 2-benzyloxy-5-methoxyphenylacetamide (10·8 g) dissolved in pyridine (50 ml) benzenesulphonyl chloride (12 ml) was added dropwise with constant agitation over a period of 10 min when the temp rose to 45°. After standing for a further 15 min the reaction mixture was poured into water. Ether extraction of the resultant oil yielded *2-benzyloxy-5-methoxyphenylacetonitrile* (8 g) which crystallized from ether–light petroleum as thick rods, m.p. 57–59° (Found: C, 76·4; H, 6·1; N, 5·6; $C_{16}N_{15}NO_2$ requires: C, 75·9; H, 6·0; N, 5·5%).

2-Benzyloxy-5-methoxybenzyl-2,4-dihydroxy-3,6-dimethoxyphenyl ketone (III)

A mixture of 2,5-dimethoxyresorcinol[8] (5·43 g), 2-benzyloxy-5-methoxyphenylacetonitrile (8·5 g) and freshly fused $ZnCl_2$ (3 g) in anhydrous ether (150 ml), cooled in an ice bath, was saturated with dry HCl, allowed to stand in a refrigerator for 24 hr and then resaturated with HCl for 30 min. After allowing to stand for a further 24 hr the reaction mixture was poured into anhydrous ether (600 ml) and the oily ketimine hydrochloride which separated washed thoroughly with a further quantity of anhydrous ether. The ketimine was dissolved in water (600 ml) and heated on a steam bath for 4 hr.

The resulting *ketone* (III; 3·5 g) crystallized from aqueous ethanol as colourless rhombs, m.p. 147–148°. (Found: C, 68·05; H, 5·5; O, 26·7; $C_{24}H_{24}O_7$ requires: C, 67·9; H, 5·7; O, 26·4%).

2′-Benzyloxy-7-hydroxy-5,8,5′-trimethoxyisoflavone (IV)

A mixture of the ketone (III; 3·5 g), freshly distilled ethyl orthoformate (10 ml), piperidine (1·5 ml) and pyridine (20 ml) was refluxed for 4½ hr. The cooled reaction mixture was poured into ice-cold HClaq and the precipitate filtered and washed thoroughly with water. The *isoflavone* (IV) crystallized from ethanol as colourless rhombs (1·9 g), m.p. 202–204°. (Found: C, 68·8; H, 5·1; $C_{25}H_{22}O_7$ requires: C, 69·1; H, 5·1%). λ_{max} 250 sh, 260, 298 mμ (log ε 4·56, 4·22, 3·78); ν_{max} 3077 (OH), 1645 cm^{-1} (CO).

2′-Benzyloxy-5,7-dihydroxy-8,5′-dimethoxyisoflavone (V)

To the isoflavone (IV; 100 mg) in nitrobenzene (1·3 ml), anhydrous $AlCl_3$ (35 mg) dissolved in nitrobenzene (0·4 ml) was added, and the mixture maintained at ca. 100° for 1 hr. The cooled mixture

[13] E. Schwenck and E. Bloch, *J. Amer. Chem. Soc.* **64**, 3051 (1942).

[14] C. R. Stephens, E. J. Bianco and F. J. Pilgrim, *J. Amer. Chem. Soc.* **77**, 1701 (1955).

was poured into dil. HCl (17·5 ml) and steam distilled to remove nitrobenzene. The resulting *isoflavone* (V), after washing with water, crystallized from aqueous ethanol as yellow needles (79 mg), m.p. 163–165°. (Found: C, 68·5; H, 4·9; $C_{24}H_{20}O_7$ requires: C, 68·6; H, 4·8%). λ_{max} 264, 292 mμ (log ε 4·37, 3·93); ν_{max} 3333, 3226 (OH) and 1658 cm^{-1} (CO).

7,2′-Dibenzyloxy-5-hydroxy-8,5′-dimethoxyisoflavone (VI) and
5,7,2′-tribenzyloxy-8,5′-dimethoxyisoflavone (VII)

A mixture of the above isoflavone (V; 130 mg), benzyl chloride (0·04 ml), anhydrous potassium carbonate (1 g), sodium iodide (40 mg) and acetone (8 ml) was refluxed for 2½ hr. The acetone was then distilled off, water (10 ml) added and the resulting mixture steam distilled to remove excess benzyl chloride.

Although extraction with ether yielded a gum which, when crystallized from ethanol gave needles (120 mg) of indefinite m.p., further treatment of the product with boiling ether (15 ml) gave a soluble fraction (68 mg) and an insoluble residue (26 mg).

The soluble fraction crystallized from ethanol as needles, m.p. 127–129°, and proved to be the *dibenzyl ether* (VI) (Found: C, 73·0; H, 5·1; $C_{31}H_{26}O_7$ requires: C, 72·9; H, 5·1%). λ_{max} 264, 293 mμ (log ε 4·26, 3·78); ν_{max} 1653 cm^{-1} (CO).

The insoluble fraction after repeated crystallization from ethanol, formed needles, m.p. 158–159°, corresponding to the *tribenzyl ether* (VII) (Found: C, 75·2; H, 5·55; $C_{37}H_{32}O_7$ requires: C, 75·5; H, 5·5%). λ_{max} 255, 260, 295 mμ (log ε 4·27, 4·27, 3·76); ν_{max} 1645 cm^{-1} (CO).

7,2′-Dibenzyloxy-5-hydroxy-6,5′-dimethoxyisoflavone (VIII)

(i) A mixture of podospicatin (263 mg), benzyl chloride (202 mg), K_2CO_3 (750 mg), NaI (200 mg) and acetone (20 ml) was refluxed for 7 hr. The potassium salts were filtered off, washed with hot acetone and the combined filtrates concentrated. After steam distillation to remove the excess benzyl chloride repeated crystallization of the solid residue from ethanol afforded the *dibenzyl ether* (VIII) as needles (135 mg), m.p. 152–154° (Found: C, 73·1; H, 5·3; $C_{31}H_{26}O_7$ requires: C, 72·9; H, 5·1%). λ_{max} 264, 298 mμ (log ε 4·32, 4·10); ν_{max} 3333 (OH) and 1639 cm^{-1} (CO).

(ii) 7,2′-Dibenzyloxy-5-hydroxy-8,5′-dimethoxyisoflavone (17 mg) was refluxed with potassium ethylate [EtOK (0·2 g) in abs. EtOH (10 ml)] for 12 min. Acidification to Congo red and dilution with water yielded a gum which partly solidified on standing. Extraction with ether yielded a solid which on repeated crystallization from ethanol gave needles (12 mg), m.p. 151–153°, undepressed on admixture with the above product. The IR spectra were also identical.

5,7,2′-Trihydroxy-6,5′-dimethoxyisoflavone (*Podospicatin*) (I)

A solution of the dibenzyl ether (VIII; 30 mg) in glacial acetic acid (1·5 ml) and conc HCl (0·7 ml) was heated on a steam bath for 1½ hr, cooled and poured into water. The product (14 mg), after repeated crystallization from 60% acetic acid afforded needles, m.p. and mixed m.p. with podospicatin 211–212°. The IR spectra were also identical.

6-Hydroxy-2,3,4-trimethoxyphenyl-2,5-dimethoxybenzyl ketone (IX)

2,5-Dimethoxyphenylacetic acid[6] (3·2 g) was dissolved in ice-cold, ethanol-free, chloroform (30 ml) and the solution saturated with BF_3. A red oily complex separated. To this was added antiarol[7] (1·6 g) and BF_3 again bubbled through the reaction mixture for a further 20 min. This was then allowed to stand overnight in the refrigerator and then poured into water. The resultant oil yielded to ether, after extraction with 10% $KHCO_3$aq, a solid product (1·2 g). Repeated crystallization from ethanol gave the ketone (IX) as needles, m.p. 101–103°, undepressed on admixture with an authentic sample obtained by degradation of podospicatin trimethyl ether.[10] The IR spectra were also identical.

5,6,7,3′,5′-Pentamethoxyisoflavone (II)

A mixture of the above ketone (IX; 0·2 g), ethyl orthoformate (1 ml), piperidine (4 drops) and pyridine (4 ml) was heated under reflux for 4½ hr. The solution turned from green to a light red. After cooling, the reaction mixture was poured into ice-cold HCl yielding a gum (130 mg) which solidified on standing. Repeated crystallization from ethanol afforded the pentamethoxyflavone

(II) as prisms, m.p. and mixed m.p. with podospicatin trimethyl ether 158–160°. The IR spectra were also identical.

5-Hydroxy-6,7,2',5'-tetramethoxyisoflavone (X)

To the isoflavone (II; 41 mg) in nitrobenzene (0·4 ml), anhydrous $AlCl_3$ (16 mg in 0·2 ml of nitrobenzene) was added and the reaction mixture maintained at 100–105° for 1 hr. The cooled solution was poured into dil. HCl and steam distilled to remove nitrobenzene. The resulting isoflavone (X; 30 mg), after washing with water, crystallized from 60% acetic acid as needles, m.p. 148–150° (Found: 63·8; H, 5·3; OMe, 34·1; $C_{19}H_{18}O_7$ requires: C, 63·7; H, 5·1; 4 OMe, 34·6%). λ_{max} 263, 298 mμ (log ε 4·26, 4·05); ν_{max} 1667 cm^{-1} (CO).

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