Synthesis of Alpinum Isoflavone, Osajin, and Warangalone

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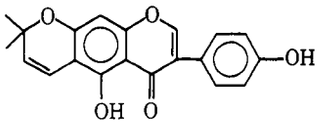
Genistein (5) when heated with prenyl bromide in the presence of methanolic methoxide yields 7,4′-di-*O*-prenyl- (6), 6,8-diprenyl- (7), and 6-prenyl- (8) genisteins separable by column chromatography. Structures of these compounds have been established by their nmr spectra and those of their derivatives. Oxidative cyclization of 8 with DDQ affords natural alpinum isoflavone (1) and a similar reaction of 7 gives a mixture of natural osajin (2) and warangalone (3) which have been separated by column chromatography and identified by mass spectra.

Four isopentenylated derivatives of genistein are known to occur in nature. Among these, alpinum isoflavone[2] (1) is the monoisopentenylated genistein and has a linear 2,2-dimethylpyran ring condensed with the ring A. The other three compounds are diisopentenylated derivatives. Thus osajin[3] (2) has a prenyl unit in the 6 position and an angular 2,2-dimethylpyran ring condensed with the ring A, whereas warangalone[4] (3, also called scandenone[5]) and chandalone[4] (4) have a linearly condensed 2,2-dimethylpyran ring besides a prenyl unit. Their structures have been given mainly on the basis of their degradations and spectral data and by synthesis of their 4′-methyl ethers.[6] However, none of them has been synthesised as such. This has now been accomplished in all cases except chandalone.



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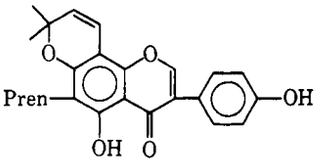

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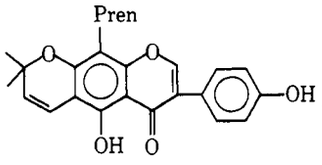

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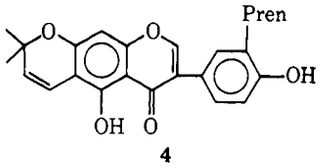
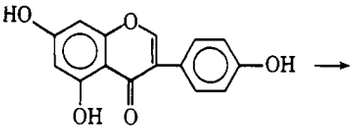


4

Pren = $-CH_2CH{=}CMe_2$

Genistein[7] (5) has been treated with prenyl bromide in the presence of methanolic methoxide, when a mixture of several products resulted as shown by tlc. However column chromatography yielded only three pure products. The first eluate gave an oily liquid which could not be crystallized but was homogeneous as shown by tlc and identical with the product obtained by reaction of genistein with 2 mol of prenyl bromide in the presence of K_2CO_3 and acetone. Its nmr spectrum in $CDCl_3$ suggested it to be 7,4′-di-*O*-prenylgenistein (6). Thus there are two singlets at δ 1.77 and 1.82 of two *gem*-dimethyl groups, one multiplet centered at δ 4.63 of four methylenoxy protons, another multiplet centered at δ 5.53 of two methine protons, and two doublets (J = 2 Hz) at δ 6.68 and 6.42 of two aromatic protons in the 6 and 8 positions, besides other signals of rings B and C.



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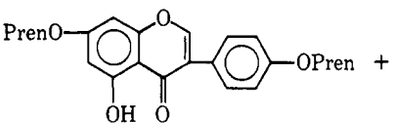

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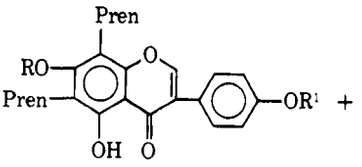
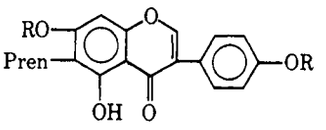


7, R = R′ = H
9, R = R′ = Me
10, R = H; R′ = Me

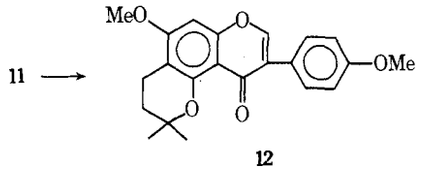


8, R = H
11, R = Me

The second eluate was identified as 6,8-diprenylgenistein (7) as follows. Elemental analysis revealed the presence of two prenyl residues. All the three hydroxyls were indicated to be free by the formation of its triacetate [nmr ($CDCl_3$) δ 2.31, 2.37, and 2.43 (3 s, 3 $-OCOCH_3$] and dimethyl ether (9) showing positive ferric reaction and nmr singlets at δ 3.78 and 3.83 of two methoxy groups. Both the prenyl units are therefore attached to the nucleus, which was further confirmed and found to be in the condensed benzene ring by its nmr spectrum and that of its acetate and dimethyl ether (see Experimental Section). Thus there were no aromatic protons of ring A but at the same time there were signals of all the four aromatic protons of ring B. The structure 7 was further established by comparing its dimethyl ether (9) with an authentic sample prepared from 6,8-diprenylbiochanin A[5] (10) by methylation with diazomethane.

The third prenylation product analyzed for a monoprenyl derivative of genistein. Since it formed a triacetate (nmr 3 s at δ 2.35, 2.38, and 2.45 of three acetoxy groups), it was inferred that all three hydroxyls were free. The prenyl unit was indicated in the condensed benzene ring by its nmr spectrum and that of its triacetate (see Experi-

mental Section). Thus it showed only one singlet of one aromatic proton of ring A and two pairs of doublets of four aromatic protons of ring B, besides signals of other protons. Hence the third prenylation product could be either 6- or 8-prenylgenistein. The former location of the prenyl unit (see structure 8) was established in two ways. (1) When it was methylated with 2 mol of dimethyl sulfate in the presence of K_2CO_3 and acetone, it formed a 7,4′-dimethyl ether which was found identical in melting point, mixture melting point, and tlc with authentic 5-hydroxy-7,4′-dimethoxy-6-prenylisoflavone.[5] (2) The dimethyl ether (11) on treatment with formic acid gave a cyclic product (12) as shown by its negative ferric reaction and its nmr spectrum. Thus the nmr spectrum in CCl_4 shows two triplets of two methylene groups at δ 1.75 and 2.60 (J = 6.5 Hz) besides other expected signals (see Experimental Section). Had it been a 8-C-prenyl derivative, cyclization would not have taken place.



12

8 ⟶ 1

7 ⟶ 2 + 3

Although products with C-prenyl and O-prenyl units in the ring A have only been isolated in the above experiment, the side phenyl might also have been affected and one of the products could be the 6,3′-diprenyl derivative. However, its isolation was not successful and thus synthesis of chandalone could not be achieved.

The above synthetic 6-C-prenylgenistein (8) has been oxidatively cyclized with DDQ in benzene medium, when it gave alpinum isoflavone (1) whose properties (melting point, tlc behavior, ir, nmr, and mass spectra) were identical with those described for the natural sample.

Similar oxidative cyclization of 6,8-diprenylgenistein (7) yielded two products separable by column chromatography. The first product had properties identical in all respects with those given for natural warangalone[4] (3). The linear nature of the pyran part was established by its mass spectrum, which showed a fragment of mass ion m/e 349 [$(M - 55)^+$], characteristic of o-prenyl phenols,[8] besides other fragments (see Experimental Section). The second product had properties identical in all respects with those reported for natural osajin[3] (2). The angular nature of the pyran part was established by its mass spectrum which did not show a $(M - 55)^+$ mass ion fragment, but instead showed a $(M - 56)^+$ mass ion (m/e 348) characteristic of o-prenyl phenols[8] besides other fragments (see Experimental Section).

Experimental Section[9]

Prenylation of Genistein (5). To a solution of genistein[7] (5, 4 g) in anhydrous methanol (150 ml) was added a methanolic solution in sodium methoxide (7 g of Na/100 ml) in methanol. The solution was cooled, treated with prenyl bromide (8 ml), and refluxed for 3 hr. After removal of the solvent *in vacuo*, the reaction mixture was treated with crushed ice and acidified with dilute HCl. The solid product was collected and examined on tlc using solvent A, which showed the presence of a number of compounds. It was subjected to column chromatography over silica gel and the column was eluted successively with (1) benzene–light petroleum (1:1), (2) benzene–light petroleum (95:5), and (3) benzene–ethyl acetate (75:25), giving fractions A–C.

Fraction A yielded 7,4′-di-O-prenylgenistein (6) as a thick oil (0.3 g): reddish-brown ferric reaction; R_f 0.70 (solvent B); nmr δ 1.77, 1.82 [2 s, 12, $(CH_3)_2C=$], 4.63 (m, 4, $-OCH_2$), 5.53 (m, 2, $-CH=$), 6.38, 6.42 (2 d, J = 2 Hz, two aromatic meta-coupled H in positions 6 and 8), 6.95 (d, J = 9 Hz, 2, 2 aromatic H in positions 3′ and 5′), 7.47 (d, J = 9 Hz, 2 H, 2 aromatic H in positions 2′ and 6′), and 7.73 (s, 1 H in position 2). It was found identical in tlc with the product obtained by reaction of genistein with 2 mol of prenyl bromide in the presence of K_2CO_3 and acetone.

Fraction B crystallized from ethyl acetate–light petroleum mixture, affording 5,7,4′-trihydroxy-6,8-diprenylisoflavone (7) as white, rhombic plates: mp 140°; intense green ferric reaction; R_f 0.66 (solvent B); nmr δ 1.87, 1.98 [2 broad s, 12, $(CH_3)_2C=$], 3.55, 3.68 (2 d, 4, J = 3 Hz, $ArCH_2$), 5.42 (m, 2, $-CH=$), 6.95 (d, J = 9 Hz, 2 H in positions 3′ and 5′), 7.50 (d, J = 9 Hz, 2 H in positions 2′ and 6′), and 8.08 (s, 1 H in position 2).

Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.9; H, 6.5. Found: C, 74.4; H, 6.9.

The acetate prepared by acetic anhydride–pyridine method cyrstallized from ethyl acetate–light petroleum mixture as colorless needles: mp 190°; no ferric reaction; R_f 0.80 (solvent C); nmr δ 1.69, 1.79 [2 broad s, 12, $(CH_3)_2C=$], 2.31, 2.37, and 2.43 (3 s, 9, $-OCOCH_3$), 3.25, 3.46 (2 d, J = 10 Hz, 4, $ArCH_2$), 5.11 (m, 2, $-CH=$), 7.19 (d, J = 9 Hz, 2 H in positions 3′ and 5′), 7.55 (d, J = 9 Hz, 2 H in positions 2′ and 6′), and 7.97 (s, 1 H in position 2).

Anal. Calcd for $C_{31}H_{32}O_8$: C, 69.9; H, 6.1. Found: C, 69.8; H, 5.8.

Fraction C crystallized from benzene, yielding 5,7,4′-trihydroxy-6-C-prenylisoflavone (8) as colorless needles (0.3 g): mp 221°; intense geeen ferric reaction; R_f 0.52 (solvent B); nmr (CD_3COCD_3) δ 1.68, 1.80 [2 s, 6, $(CH_3)_2C=$], 3.34 (d, J = 7 Hz, 2, $ArCH_2$), 5.27 (m, 1, $-CH=$), 6.44 (s, 1 H in position 8), 6.85 (d, J = 9 Hz, 2 H in positions 3′ and 5′), 7.40 (d, J = 9 Hz, 2 H in positions 2′ and 6′), and 7.95 (s, 1 H in position 2).

Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.0; H, 5.4. Found: C, 71.5; H, 5.8.

The acetate prepated by the acetic anhydride–pyridine method crystallized from ethyl acetate–light petroleum mixture as colorless needles: mp 160°; no ferric reaction; R_f 0.60 (solvent D); nmr δ 1.74, 1.82 [2 s, 6, $(CH_3)_2C=$], 2.35, 2.38, and 2.45 (3 s, 9, $-OCOCH_3$), 3.39 (d, J = 7 Hz, 2, $ArCH_2$), 5.08 (m, 1, $-CH=$), 7.01 (d, J = 10 Hz, 2 H in positions 3′ and 5′), 7.33 (s, 1 H in position 8), 7.56 (d, J = 10 Hz, 2 H in positions 2′ and 6′), and 7.97 (s, 1 H in position 2).

Anal. Calcd for $C_{26}H_{24}O_8$: C, 67.3; H, 5.2. Found: C, 67.8; H, 5.1.

5-Hydroxy-7,4′-dimethoxy-6,8-diprenylisoflavone (9). Method I. 5,7,4′-Trihydroxy-6,8-diprenylisoflavone (7, 100 mg) was refluxed with dimethyl sulfate (2 mol, 0.5 ml), K_2CO_3 (0.5 g), and acetone (15 ml) for 4 hr. The product (9) crystallized from methanol as long, hexagonal plates: mp and mmp with the sample prepared below 86°; green ferric reaction; R_f 0.67 (solvent A); nmr (CCl_4) δ 1.70, 1.80 [2 s, 12, $(CH_3)_2C=$], 3.40 (m, 4, $ArCH_2$), 3.78, 3.83 (2 s, 6, $-OCH_3$), 5.20 (m, 2, $-CH=$), 6.87 (d, J = 9 Hz, 2 H in positions 3′ and 5′), 7.44 (d, J = 9 Hz,. 2 H in positions 2′ and 6′), and 7.94 (s, 1 H in position 2).

Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.6; H, 7.0. Found: C, 75.0; H, 6.9.

Method II. 5,7-Dihydroxy-4′-methoxy-6,8-diprenylisoflavone (10, 10 mg) was dissolved in dry ether (5 ml) and treated with freshly prepared diazomethane in ether, until the color of the solution remained yellow. After the solution was kept overnight in ice, ether was distilled off and the residue was crystallized from methanol, when 9 was obtained as long, hexagonal plates, mp 86°.

5-Hydroxy-7,4′-dimethoxy-6-C-prenylisoflavone (11). 5,7,4′-Trihydroxy-6-C-prenylisoflavone (8, 50 mg) on methylation with 2 mol of dimethyl sulfate gave 11 (30 mg), which crystallized from benzene–light petroleum mixture as light yellow flakes: mp 123° (lit.[6] mp 122–123°); intense green ferric reaction; R_f 0.50 (solvent A); identical in melting point and tlc behavior with an authentic sample.

Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.1; H, 6.1. Found: C, 71.8; H, 6.2.

Formic acid cyclization of 11 yielded 7,4′-dimethoxy-6″,6″-dimethyl-4″,5″-dihydropyrano[2″,3″:5,6]isoflavone (12): mp 160° (lit.[6] mp 159–160°); no ferric reaction; R_f 0.50 (solvent B); nmr (CCl_4) δ 1.40 [s, 6, $(CH_3)_2C<$], 1.75, 2.60 (2 t, J = 6.5 Hz, 4, $-CH_2$), 3.78, 3.83 (2 s, 6, $-OCH_3$), 6.20 (s, 1 H in position 8), 6.82 (d, J = 9 Hz, 2 H in positions 3′ and 5′), 7.40 (d, J = 9 Hz, 2 H in positions 2′ and 6′), and 7.62 (s, 1 H in position 2).

Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.1; H, 6.1. Found: C, 72.0; H, 6.0.

5,4′-Dihydroxy-6″,6″-dimethylpyrano[2″,3″:7,6]isoflavone

(Alpinum Isoflavone, 1). To a solution of 8 (250 mg) in dry, freshly distilled benzene (15 ml) was added DDQ (180 mg) and the resulting red solution was refluxed for 30 min, when the colorless hydroquinone separated out. The solid was filtered while hot and the residue was washed with hot, dry benzene. Removal of benzene gave a residue which was purified by column chromatography over silica gel. Elution with chloroform–ethyl acetate (9:1) and crystallization from the same solvent mixture gave 1 (160 mg) as colorless plates: mp 216° (lit.[2] mp 216°); intense green ferric reaction; R_f 0.56 (solvent B); nmr δ 1.48 [s, 6, $(CH_3)_2C<$], 5.64, 6.78 (2 d, J = 10 Hz, 2, 2 olefinic H of pyran ring), 6.36 (s, 1 H in position 8), 6.87 (d, J = 9 Hz, 2 H in positions 3′ and 5′), 7.38 (d, J = 9 Hz, 2 H in positions 2′ and 6′), and 7.85 (s, 1 H in position 2); mass spectrum m/e 336, 321, 295, 203, and 118.

Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.4; H, 4.8. Found: C, 70.9; H, 5.2.

The above data are completely identical with those reported[2] for natural alpinum isoflavone. This was confirmed by comparing the ir spectrum in detail with one, kindly supplied by Professor Scheinmann, for a natural sample. They were completely identical.

Further, the acetate prepared by the acetic anhydride–pyridine method has the same properties as reported for the natural sample. Thus it crystallized from ethyl acetate–light petroleum mixture as colorless needles: mp 219°; R_f 0.42 (solvent B); nmr δ 1.50 [s, 6, $(CH_3)_2C<$], 2.30, 2.44 (2 s, 6, $-OCOCH_3$), 5.73, 6.52 (2 d, J = 10 Hz, 1 H, 2 olefinic H of pyran ring), 7.50 (d, J = 9 Hz, 2 H in positions 2′ and 6′), and 7.80 (s, 1 H in position 2).

Anal. Calcd for $C_{24}H_{20}O_7$: C, 68.6; H, 4.8. Found: C, 68.1; H, 5.3.

5,4′-Dihydroxy-8-prenyl-6″,6″-dimethylpyrano[2″,3″:7,6]-isoflavone (Warangalone, 3) and 5,4′-Dihydroxy-6-*C*-prenyl-6″,6″-dimethylpyrano[2″,3″:7,8]isoflavone (Osajin, 2). 5,7,4′-Trihydroxy-6,8-diprenylisoflavone (**7**, 0.5 g) on similar treatment with DDQ gave a residue (0.3 g) which proved to be a mixture on tlc. It was purified by column chromatography over silica gel. Elution with benzene–chloroform (94:6) gave the first few fractions as a single entity which crystallized from methanol as cream needles (100 mg): mp 160–163° (lit.[4] mp 163–165°); intense green ferric reaction; R_f 0.56 (solvent B); mass spectrum m/e 404, 389, 351, 349, 231, 181, 121, 118, and 55; ir ν_{max} 3600, 3300, 1660, 1625, and 1595 cm^{-1}.

Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.2; H, 6.0. Found: C, 73.9; H, 6.4.

These data agree with those described for natural warangalone[4] (**3**), although direct comparison could not be made because of nonavailability of the sample.

The later fractions eluted by benzene–chloroform (9:1) were found by tlc to be a mixture of compounds. They were separated by fractional crystallization from light petroleum (bp 60–80°) when **2** was obtained as pale yellow crystals (50 mg): mp 190–192° (lit.[3] mp 190–192.5°); intense green ferric reaction; R_f 0.52 (solvent B); ir ν_{max} 3390, 1645, 1615, 1580 cm^{-1}; mass spectrum m/e 404, 389, 351, 348, 333, 231, 181, 121, and 56.

Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.2; H, 6.0. Found: C, 73.9 H, 5.6.

These data were found identical with those described for natural osajin.[3] However, direct comparison could not be made because of nonavailability of the sample.

Acknowledgments. The authors thank Professor T. R. Seshadri for kindly supplying samples of 6,8-diprenylbiochanin A and 5-hydroxy-7,4′-dimethoxy-6-*C*-prenylisoflavone. Their thanks are also due to Dr. F. Scheinmann for supplying the ir spectrum of alpinum isoflavone.

Registry No.—**1**, 34086-50-5; **1** acetate, 51472-54-9; **2**, 482-53-1; **3**, 4449-55-2; **5**, 446-72-0; **6**, 51225-25-3; **7**, 51225-28-6; **7** acetate, 51225-26-4; **8**, 51225-30-0; **8** acetate, 51225-29-7; **9**, 51225-27-5; **10**, 27762-81-8; **11**, 27762-83-0; **12**, 27762-86-3.

References and Notes

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(9) All melting points were taken on a Büchi melting point apparatus and are uncorrected. Tlc was carried out on silica gel plates using one of the following solvent systems: (A) benzene; (B) benzene–ethyl acetate (75:25); (C) toluene–ethyl formate–formic acid (5:4:1); and (D) benzene–ethyl acetate (1:1). Spraying reagent was either 10% aqueous H_2SO_4 or 10% alcoholic $FeCl_3$. Column chromatography was carried out using silica gel supplied by NCL Poona. Ir spectra were measured in Nujol mulls using a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were determined in $CDCl_3$ unless otherwise stated, using a 60-MHz spectrophotometer. Chemical shifts are mentioned in parts per million ppm downfield from TMS used as internal standard. Mass spectra were taken with a MS-72 spectrometer, 70 eV ionizing voltage, 900 × 10 trap current, and 2 kV accelerating voltage.

A New Method for the Synthesis of Enones. Total Synthesis of (±)-Mayurone and (±)-Thujopsadiene

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When a β-carboxy ketone is treated with lead tetraacetate, oxidative decarboxylation occurs, and the corresponding α,β-unsaturated ketone is produced in high yield. By use of this method, both *cis*- and *trans*-methyloctalones **10** and **8** are prepared. In addition, the method can be used to synthesize cross-conjugated dienones such as **6**, and phenols such as tetrahydro-β-naphthol (**17**) from the corresponding β-carboxy-α',β'-unsaturated ketones. Use of the method in natural product synthesis is illustrated in a total synthesis of (±)-mayurone (**18**). Mayurone is then further transformed into thujopsadiene (**20**) and thujopsene (**19**).

The oxidative decarboxylation of carboxylic acids is a well-known reaction.[1] It has, however, received little synthetic attention owing probably to the fact that a multiplicity of products usually result. Experimentally, the best method for effecting the reaction is due to Kochi,[2] who showed that good yields of olefins can be obtained by employing lead tetraacetate (LTA) as the oxidant in the presence of cupric ion. In the case of primary carboxylic acids. good yields of terminal olefins result. The reaction presumably proceeds *via* the following pathway.

$$RCH_2CH_2COOH \xrightarrow{LTA} RCH_2CH_2C(=O)Pb(OAc)_3 \xrightarrow{-CO_2}$$

$$RCH_2CH_2\cdot \xrightarrow{Cu^{2+}} RCH_2CH_2^+ \xrightarrow{-H^+} RCH{=}CH_2$$