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SYNTHESIS OF ALPINUM ISOFLAVONE, DERRONE AND RELATED PYRANOISOFLAVONES*

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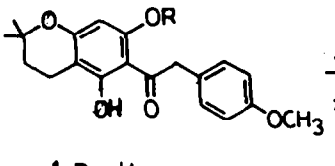
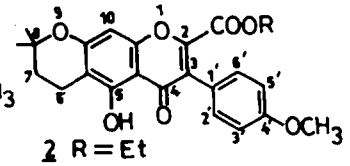
Abstract - Reaction of phenacylchroman 1 with ethoxyalyl chloride in pyridine followed by hydrolysis of the resulting esters 2 and 3 and decarboxylation of the acids 4 and 5, gave dihydro-4'-O-methyl alpinum isoflavone 6 and 4'-O-methylderrone 7 respectively. Similarly 8 gave 11 which was selectively demthylated to 7. DDQ dehydrogenation of 6, 7 and 11 gave 14, 15 and 17. Demethylation of 6 and 7 followed by dehydrogenation gave alpinum isofavone 18 and derrone 19.

Alpinum isoflavone 18, a linear pyranoisoflavone was isolated from Laburnum alpinum[1], Calopogonium mucunoides[2], Erythrina variegata[3] and Millettia thonningii[4]. Its angular isomer derrone 19 and dimethyl ether 16 occur in Derris robusta which also contains 15[5-7]. In addition to 18, Calopogonium mucunoides[8] contains 14 and 15. The present paper deals with the synthesis of these isoflavones. Further this is the first reported synthesis of alpinum isoflavone and derrone by a common procedure.

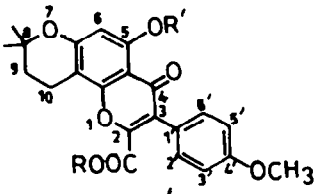
Seshadri et al[9] synthesised 4'-O-methyl alpinum isoflavone by prenylation of 5,7-dihydroxy-4'-methoxy isoflavone followed by acid-catalysed cyclisation. Scheinmann and coworkers[1] obtained 4'-O-methyl derrone by reacting the same isoflavone with 3-methyl-but-2-enal. Ollis et al[10] used ethoxalyl chloride in pyridine for reaction with desoxy benzoins in the synthesis of some simple isoflavones. The reaction involves C-ethoxalylation of the reactive methylene group of the desoxybenzoin followed by cyclisation and concomittant dehydration to give the carbethoxyisoflavone. This is hydrolysed to the acid which on decarboxylation gives the isoflavone. The yields are quite high for the first two steps and satisfactory for decarboxylation. The reagent has the further advantage that it can be used with both mono- and poly-hydroxy derivatives. Alpinum isoflavone and derrone have each a chelated hydroxyl and the appropriately substituted phenacylchroman (dihydropyranodesoxybenzoin) 1 could possibly yield both the isomeric carbethoxydihydropyrano isoflavones on reaction with ethoxalyl chloride in pyridine. Hydrolysis, decarboxylation and dehydrogenation would then result in the formation of alpinum isoflavone 18 and derrone 19 respectively. With this in view the present work was undertaken. Further the reaction of phenacyl chromans with ethoxalyl chloride has not been studied so far.



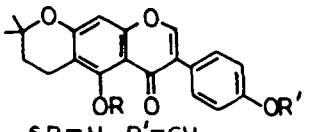
1 R = H
8 R = CH_3



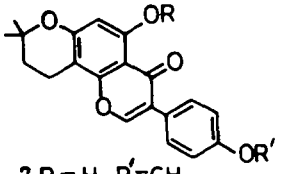
2 R = Et
4 R = H



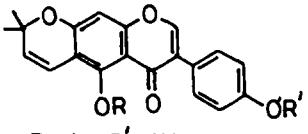
3 R = Et, R′ = H
5 R = R′ = H
9 R = Et, R′ = CH_3
10 R = H, R′ = CH_3



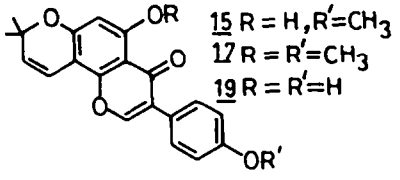
6 R = H, R′ = CH_3
12 R = R′ = H



7 R = H, R′ = CH_3
11 R = R′ = CH_3
13 R = R′ = H



14 R = H, R′ = CH_3
16 R = R′ = CH_3
18 R = R′ = H



15 R = H, R′ = CH_3
17 R = R′ = CH_3
19 R = R′ = H

RESULTS AND DISCUSSION

Phenacyl chroman 1[11] has two hydroxyl groups ortho to the phenacyl moiety and hence on reaction with ethoxalyl chloride in pyridine can be expected to give a mixture of two isomeric products 2 and 3. TLC of the crude product showed the presence of two components and these were separated on a silica gel column. Their IR spectra showed absorption for the ester group at 1745 cm^{-1}. The methylene and methyl protons appeared as a quartet at δ 4.18 and a triplet at δ 1.06-1.08 in their PMR spectra. Hydrolysis of the esters gave the acids 4 and 5 which on thermal decarboxylation yielded 6 and 7 respectively.

The identity of products 6 and 7 was established as follows. Phenacyl-chroman 8[11] on similar reaction with ethoxyalyl chloride in pyridine gave the ester which after hydrolysis and decarboxylation to 11, followed by selective demethylation gave a product identical with 7. The other isomer from 1 was therefore assigned the linear structure 6. It then follows that the ester and acid corresponding to 6 have the structures 2 and 4 and those corresponding to 7 are 3 and 5. A characteristic difference in the chemical shifts of the 5-hydroxyl proton could be discerned in the PMR spectra of the linear and angular isoflavones and their carbethoxy derivatives. Thus the proton showed signals at δ 13.22 and 12.62 in 6 and 7 while in 2 and 3 the signal appeared at δ 12.86 and 12.26, there being a difference of 0.60 ppm between the two protons in each case. This characteristic difference can plausibly serve to distinguish the linear compound from its angular isomer.

Dihydropyranoisoflavones 6, 7, 11, 12 and 13 were dehydrogenated to the pyranoderivative 14, 15, 17, 18 and 19 with DDQ in benzene. Methylation of 14 with dimethyl sulphate yielded 16.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 237 spectrometer and PMR spectra in $CDCl_3$ on a Varian XL-100 spectrometer (100 MHz) using TMS as internal standard.

Reaction of phenacylchroman 1 with ethoxalyl chloride and pyridine.

Formation of 2-carbethoxy isoflavones 2 and 3. To a cooled solution of 1 (2.5 g) in dry pyridine (25 ml), freshly distilled ethoxalyl chloride (4.5 ml) was added with stirring and the mixture was kept at 0° for 2 days. It was then poured into cold water, extracted with chloroform and the organic layer washed with dilute HCl, water and dried ($MgSO_4$). Removal of solvent gave a residue which showed two spots on TLC. The residue was chromatographed over silica gel and eluted with hexane-chlorform (i) 90:10 and (ii) 80:20 to give fractions A and B.

2-Carbethoxy-5-hydroxy-3-(4'-methoxy)phenyl-8,8-dimethyl-6,7-dihydro-4H,8H-benzo[1,2b:5,4b']dipyran-4-one (2)

Fraction A on removal of solvent gave residue which crystallised from the same solvent to give 2 (950 mg), m.p. 141-42°; IR : 3200, 1745, 1660, 1610 cm^{-1}; PMR : δ1.06(t,3H,$-CO_2CH_2CH_3$, J=7Hz), 1.38(s,6H,$(CH_3)_2C<$), 1.85(t,2H, 6-CH_2, J=7Hz), 2.74(t,2H,7-CH_2,J=7Hz), 3.86(s,3H,$C_{4'}$-OCH_3), 4.18(q,2H,$-CO_2CH_2CH_3$,J=7Hz), 6.43(s,1H,C_{10}-H), 6.98(d,2H,$C_{3'}$-H and $C_{5'}$-H,J=8Hz), 7.24(d,2H,$C_{2'}$-H and $C_{6'}$-H, J=8Hz), 12.86(s,1H,C_5-OH), (Found : C, 68.3 ; H, 5.9. $C_{24}H_{24}O_7$ requires C,67.9; H,5.7%).

2-Carbethoxy-5-hydroxy-3(4'-methoxy)phenyl-8,8-dimethyl-9,10-dihydro-4H,8H-benzo[1,2b:5,6b']dipyran-4-one (3)

Removal of solvent from fraction B gave a solid which crystallised from the same solvent to give 3 (970 mg), m.p. 192-93°, IR : 3210, 1740, 1660 and 1615 cm^{-1}; PMR : δ 1.08 (t,3H,$-CO_2CH_2CH_3$,J=7Hz), 1.40(s,6H,$(CH_3)_2C<$), 1.88(t, 2H,10-CH_2,J=7Hz), 2.86(t,2H,9-CH_2,J=7Hz), 3.86(s,3H,$C_{4'}$-OCH_3), 4.20(q,2H, $-CO_2CH_2CH_3$,J=7Hz),6.32(s,1H,C_6-H), 6.98(d,2H,$C_{3'}$-H and $C_{5'}$-H,J=8Hz), 7.24(d, 2H,$C_{2'}$-H and $C_{6'}$-H,J=8Hz), 12.26(s,1H,C_5-OH). (Found : C,68.2; H,5.8. $C_{24}H_{24}O_7$ requires C, 67.9; H,5.7%).

Hydrolysis of carbethoxy isoflavones 2 and 3.

Formation of isoflavone 2-carboxylic acids 4 and 5 . The ester 2 or 3 (700 mg) was dissolved in acetone (30 ml) and refluxed with aqueous sodium carbonate solution (5%, 15 ml) for 4 h. Evaporation of solvent and acidification with HCl (1:1) afforded 4 or 5.

5-Hydroxy-3-(4'-methoxy)phenyl-8,8-dimethyl-6,7-dihydro-4H,8H-benzo[1,2b:5,4-b']dipyran-4-one-2-carboxylic acid (4). It crystallised from methanol (595 mg), m.p. 233-35°. (Found : C, 67.0 ; H, 5.3. $C_{22}H_{20}O_7$ requires C, 66.7 ; H, 5.1%).

5-Hydroxy-3-(4'-methoxy)phenyl-8,8-dimethyl-9,10-dihydro-4H,8H-benzo-[1,2b:5,6b']dipyran-4-one-2-carboxylic acid (5). The product crystallised from methanol (610 mg), m.p. 248-50°. (Found : C, 67.1; H, 5.3. $C_{22}H_{20}O_7$ requires : C, 66.7; H, 5.1%).

Decarboxylation of isoflavone carboxylic acids 4 and 5.

Formation of dihydropyranoisoflavones 6 and 7. The acid 4 or 5 (500 mg) was heated to a temperature of about 10° above its melting point until the evolution of carbondioxide ceased. The crude melt was washed with dilute sodium bicarbonate solution, filtered and washed with water to give 6 or 7.

5-Hydroxy-3-(4'-methoxy)phenyl-8,8-dimethyl-6,7-dihydro-4H,8H-benzo-[1,2b:5,4b']dipyran-4-one (6). It crystallised from benzene (320 mg), m.p. 177-79°. IR : 1665, 1610, 1580, 1520 cm^{-1}; PMR : δ 1.38(s,3H,$(CH_3)_2$-C<), 1.84(t,2H,7-CH_2, J=7Hz), 2.76(t,2H,6-CH_2,J=7Hz), 3.86(s,3H,$C_{4'}$-OCH_3),6.36(s, 1H,C_{10}-H),6.94(d,2H,$C_{3'}$-H and $C_{5'}$-H,J=8Hz), 7.42(d,2H,$C_{2'}$-H and $C_{6'}$-H,J=8Hz), 7.82(s,1H,C_2-H), 13.22(s,1H,C_5-OH). (Found : C, 71.5;H, 5.8. $C_{21}H_{20}O_5$ requires : C, 71.6; H, 5.7%).

5-Hydroxy-3-(4'-methoxy)phenyl-8,8-dimethyl-9,10-dihydro-4H,8H-benzo-[1,2b:5,6b']dipyran-4-one (7). It crystallised from benzene (340 mg), m.p. 172-74°. IR: 1660, 1615, 1575, 1520 cm^{-1}; PMR: δ1.38(s,6H,$(CH_3)_2$-C<), 1.86(t,2H,9-CH_2,J=7Hz), 2.80(t,2H,10-CH_2,J=7Hz), 3.86(s,3H,$C_{4'}$-OCH_3),6.30(s, 1H,C_6-H), 7.00(d,2H,$C_{3'}$-H and $C_{5'}$-H,J=8Hz), 7.48(d,2H,$C_{2'}$-H and $C_{6'}$-H,J=8Hz), 7.94(s,1H,C_2-H), 12.62(s,1H,C_5-OH). (Found : C,71.5; H, 5.4. $C_{21}H_{20}O_5$ requires C, 71.6 ; H, 5.7%).

Ethoxalylation of phenacylchroman 8

Formation of 2-carbethoxy-3(4'-methoxy)phenyl-5-methoxy-8,8-dimethyl-9,10-dihydro-4H,8H-benzo[1,2b:5,6b']dipyran-4-one (9). Phenacylchroman 8 (1.5 g) was dissolved in pyridine (18ml) and to the cooled solution, ethoxalyl chloride (3 ml) was added with stirring. After keeping at 0° for 2 days, it was poured into water, extracted with chloroform and worked up. The product crystallised from methanol (1.17 g), m.p. 207-08°; IR : 1750, 1650, 1620, 1580, 1375 cm^{-1}. PMR : δ1.06(t, 3H, $-CO_2CH_2CH_3$, J=7Hz), 1.40(s,6H,$(CH_3)_2C<$), 1.88(t,2H, 9-CH_2, J=7Hz), 2.88(t,2H,10-CH_2,J=7Hz), 3.86(s,3H,C_4,-OCH_3), 3.90(s,3H,C_8-OCH_3), 4.18(q,2H,$-CO_2CH_2CH_3$,J=7Hz), 6.32(s,1H,C_6-H), 6.94(d,2H,C_3,-H and C_5,-H, J=8Hz), 7.22(d,2H,C_2,-H and C_6,-H,J=8Hz). (Found : C,68.2; H, 6.2. $C_{25}H_{26}O_7$ requires C, 68.5 ; H, 5.9%).

Hydrolysis of carbethoxyisoflavone 9

Formation of 3-(4'-methoxy)phenyl-5-methoxy-8,8-dimethyl-9,10-dihydro-4H,8H-benzo[1,2b:5,6b']dipyran-4-one-2-carboxylic acid (10). The ester 9 (800 mg) in acetone (40 ml), was refluxed with aqueous sodium carbonate solution (5%, 20 ml) for 4 h and worked up. The product crystallised from methanol (660 mg), m.p. 222-23°. (Found : C, 67.7 ; H, 5.5. $C_{23}H_{22}O_7$ requires C, 67.4; H, 5.4%).

Decarboxylation of isoflavone carboxylic acid 10.

Synthesis of 3-(4'-methoxy)phenyl-5-methoxy-8,8-dimethyl-9,10-dihydro-4H,8H-benzo[1,2b:5,6b']dipyran-4-one (11). Acid 10 (500 mg) was heated to 10° above its melting point till evolution of carbon dioxide ceased and the residual product was worked up to give 11 which crystallised from benzene (325mg), m.p. 206-07°; IR : 1655 cm^{-1}. PMR : δ1.40(s,6H,$(CH_3)_2C<$), 1.88(t,2H,9-CH_2, J=7Hz), 2.80(t, 2H,10-CH_2,J=7Hz), 3.86(s,3H,C_4,-OCH_3), 3.94(s,3H,C_8-OCH_3), 6.32(s,1H,C_6-H), 6.96(d,2H,C_3,-H and C_5,-H,J=8Hz),7.52(d,2H,C_2,-H and C_6,-H, J=8Hz), 7.82(s,1H,C_2-H). (Found : C, 72.0; H, 6.4. $C_{22}H_{22}O_5$ requires C,72.1; H, 6.0%).

Selective demethylation of 11

Formation of 7. A mixture of 11 (50 mg), anhydrous aluminium chloride (150 mg) and acetonitrile (15 ml) was refluxed for 3 h and the solvent was removed. The residue was heated on a water bath with dilute HCl for 0.5 h, cooled and the solid filtered off, washed with water and dried. It crystallised from benzene to give a product (30 mg) m.p. 172-74°, which was identical with the angular isomer 7 obtained from phenacylchroman 1 (m.m.p., co-TLC and superimposable IR).

Demethylation of dihydropyranoisoflavones 6 and 7. Synthesis of 12 and 13. To a solution of 6 or 7 (120 mg), HBr (48%, 4 ml) was added dropwise and the mixture was heated on a water bath for 6 h after which it was cooled, poured into water and the resulting solid was filtered.

5-Hydroxy-3(4'-hydroxy)phenyl-8,8-dimethyl-6,7-dihydro-4H,8H-benzo-[1,2b:5,4b']dipyran-4-one (Dihydroalpinum isoflavone) (12). The product crystallised from methanol, (75 mg), m.p. 130-32° (Found : C, 71.3 ; H, 5.5. $C_{20}H_{18}O_5$ requires : C, 71.0 ; H, 5.2%).

5-Hydroxy-3(4'-hydroxy)phenyl-8,8-dimethyl-9,10-dihydro-4H,8H-benzo-[1,2b:5,6b']dipyran-4-one (Dihydroderrone) (13). It crystallised from methanol (70 mg), m.p. 138-40° (Found : C, 70.8; H, 5.3. $C_{20}H_{18}O_5$ requires C, 71.0 ; H, 5.2%).

Dehydrogenation of dihydropyranoisoflavones 6, 7, 11, 12 and 13. Synthesis of pyranoisoflavones 14, 15, 17, 18 and 19. To a solution of 6, 7 or 11 (150 mg) in dry benzene (40 ml). DDQ (325 mg) was added and the mixture refluxed for 30 h,cooled and the hydroquinone was filtered off. Removal of solvent gave the product 14, 15 or 17. In a similar way 12 or 13 (60 mg) in dry benzene (20 ml) was refluxed with DDQ (130 mg) for 30 h and worked up to give 18 or 19.

5-Hydroxy-3(4'-methoxy)phenyl-8,8-dimethyl-4H,8H-benzo[1,2b:5,4b']dipyran-4-one (4'-O-methylalpinumisoflavone) (14). The product crystallised from acetone-hexane (95 mg), m.p. 135-37° (lit.[1] 136-37°). IR : 1655, 1615 cm^{-1}; PMR : δ 1.44 (s,6H,$(CH_3)_2C<$), 3.86(s,3H,C_4,-OCH_3), 5.65(d,1H, C_7-H,J=10Hz), 6.75(d,1H,C_6-H,J=10Hz), 6.36(s, 1H, C_{10}-H),7.00(d,2H,C_3,-H and C_5,-H,J=8Hz), 7.48(d,2H,C_2,-H and C_6,-H,J=8Hz), 7.85(s,1H,C_2-H), 13.16(s,1H,C_8-OH). (Found : C, 72.2; H, 5.0. Calc. for $C_{21}H_{18}O_5$: C, 72.0 ; H, 5.1%).

5-Hydroxy-3(4'-methoxy)phenyl-8,8-dimethyl-4H,8H-benzo[1,2b:5,6b']dipyran-4-one (4'-O-Methylderrone)(15) The compound crystallised from aqueous ethanol (100 mg), m.p. 170-71° (lit[1] 168-70°). IR : 1650, 1620 cm^{-1}. PMR : δ 1.48(s,6H, $(CH_3)_2C<$), 3.86(s,3H,C_4,-OCH_3), 5.60(d,1H,C_9-H,J=10Hz), 6.70(d,1H,C_{10}-H,J=10Hz), 7.00(d,2H,C_3,-H and C_5,-H,J=8Hz), 7.48(d,2H,C_2,-H and C_6,-H,J=8Hz), 7.92(s,1H, C_2-H), 12.94(s,1H,C_5-OH). (Found : C, 72.3; H, 5.3. Calc. for $C_{21}H_{18}O_5$: C, 72.0; H, 5.1%).

3(4'-methoxy)phenyl-5-methoxy-8,8-dimethyl-4H,8H-benzo[1,2b:5,6b']dipyran-4-one (17). It crystallised from benzene (95 mg), m.p. 122-23° (lit.[1] 120-22°). IR : 1640, 1600 cm^{-1}. (Found : C, 72.7 ; H, 5.3. Calc. for $C_{22}H_{20}O_5$: C, 72.5; H, 5.4%).

5-Hydroxy-3(4'-hydroxy)phenyl-8,8-dimethyl-4H,8H-benzo[1,2b:5,4b']dipyran-4-one (Alpinum isoflavone) (18). It crystallised from acetone-hexane (35 mg), m.p. 212-14° (lit.[1] 213-14°) ; IR : 3400, 1650 cm^{-1}. PMR : δ 1.46(s,6H, $(CH_3)_2C<$), 5.60(d, 1H,C_7-H,J=10 Hz), 6.31(s,1H, C_{10}-H), 6.74(d,1H,C_6-H,J=10Hz), 6.78(d,2H,C_3,-H and C_5,-H,J=8Hz), 7.33(d,2H,C_2,-H and C_6,-H,J=8Hz), 7.80(s,1H, C_2-H), 13.18(s,1H,C_5-OH). (Found : C, 71.2 ; H, 4.4. Calc. for $C_{20}H_{16}O_5$: C, 71.4 ; H, 4.7%).

5-Hydroxy-3(4'-hydroxy)phenyl-8,8-dimethyl-4H,8H-benzo[1,2b:5,6b']dipyran-4-one (Derrone) (19). It crystallised from benzene-ethyl acetate (37 mg), m.p. 217-18° (lit.[5] 216-18°). IR : 3390, 1655 cm^{-1}. PMR : δ 1.46(s,6H,$(CH_3)_2C<$), 5.56(d,1H,C_9-H,J=10Hz), 6.26(s,1H,C_6-H), 6.65(d,1H,C_{10}-H, J=10Hz), 6.78(d,2H, C_3,-H and C_5,-H,J=8Hz), 7.29(d,2H,C_2,-H and C_6,-H, J=8Hz), 7.76(s,1H,C_2-H), 13.77(s,1H,C_5-OH). (Found : C, 71.6 ; H, 4.5. Calc. for $C_{20}H_{16}O_5$: C, 71.4 ; H, 4.7%).

Methylation of 14 (30 mg) in acetone (5 ml) with dimethyl sulphate (0.2 ml) and K_2CO_3 (100 mg) afforded alpinum isoflavone dimethyl ether, 16, m.p. 119-21° (lit.[5] m.p. 119-20).

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