The Synthesis of Neobavaisoflavone and Related Compounds[1)]

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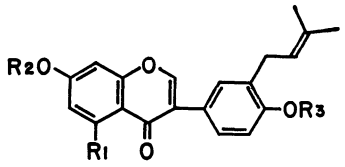
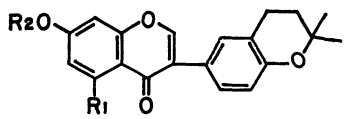
The condensation of 7-benzoyloxy-4′-hydroxyisoflavone with 2-methyl-3-buten-2-ol gave 7-benzoyloxy-4′-hydroxy-3′-(3-methyl-2-butenyl)isoflavone. The hydrolysis of the alkylated isoflavone with dilute alkali afforded neobavaisoflavone [7,4′-dihydroxy-3′-(3-methyl-2-butenyl)isoflavone], which was then converted into isoneobavaisoflavone on heating with formic acid. 7-Benzyloxy-4′-hydroxyisoflavone was condensed with 2-methyl-3-buten-2-ol to give a chroman derivative, which was then converted into isoneobavaisoflavone by hydrolysis. 3′-(3-Methyl-2-butenyl)-5,7,4′-trihydroxyisoflavone was also synthesized from 7-benzoyloxy-5,4′-dihydroxyisoflavone in a similar manner.

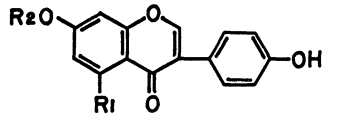
Neobavaisoflavone has recently been isolated from *Psoralea corylifolia* seeds (fruits).[2,3)] Its structure has been shown to be 7,4′-dihydroxy-3′-(3-methyl-2-butenyl)-isoflavone (**1**) on the basis of spectral and degradative evidence.[2,3)] In this paper, the unambiguous synthesis of **1** will be reported to confirm the proposed structure of the natural isoflavone. Also, the synthesis of 3′-(3-methyl-2-butenyl)-5,7,4′-trihydroxyisoflavone (**2**) is attempted as an example for the introduction of the 3-methyl-2-butenyl group into the B ring in phloroglucinol-type isoflavone.



(**1**) $R_1=R_2=R_3=H$
(**2**) $R_1=OH$, $R_2=R_3=H$
(**5**) $R_1=R_3=H$, $R_2=C_6H_5CO$
(**6**) $R_1=H$, $R_2=R_3=CH_3CO$
(**12**) $R_1=OH$, $R_2=C_6H_5CO$, $R_3=H$



(**7**) $R_1=R_2=H$
(**9**) $R_1=H$, $R_2=C_6H_5CH_2$
(**13**) $R_1=OH$, $R_2=C_6H_5CO$
(**14**) $R_1=OH$, $R_2=H$



(**3**) $R_1=R_2=H$
(**4**) $R_1=H$, $R_2=C_6H_5CO$
(**8**) $R_1=H$, $R_2=C_6H_5CH_2$
(**10**) $R_1=OH$, $R_2=H$
(**11**) $R_1=OH$, $R_2=C_6H_5CO$

The partial benzoylation of daidzein (**3**) in pyridine gave 7-benzoyloxy-4′-hydroxyisoflavone (**4**). In the UV spectrum of **4**, the absorption maximum did not show a bathochromic shift in the presence of sodium acetate. The condensation of **4** with 2-methyl-3-buten-2-ol in the presence of boron trifluoride etherate[4)] afforded 7-benzoyloxy-4′-hydroxy-3′-(3-methyl-2-butenyl) isoflavone (**5**). The mass spectrum of **5** gave a molecular ion at *m/e* 426 and a fragment ion at *m/e* 371 $[M-C_4H_7]^+$. The NMR spectrum exhibited the presence of one methylene group as a doublet centering at δ 3.36 ppm and one vinyl proton as a triplet centering at δ 5.34 ppm. The compound **5** was hydrolyzed with dilute alkali to yield the desired neobavaisoflavone [7,4′-dihydroxy-3′-(3-methyl-2-butenyl)isoflavone] (**1**) (mp 191—192 °C).[2,3)] The acetylation of **1** by the acetic anhydride–pyridine method gave the diacetate (**6**). The isoflavone (**1**) was also heated with formic acid to be cyclized into the corresponding chroman derivative (isoneobavaisoflavone) (**7**) (mp 243—244 °C).[2,3)] The properties of this synthetic isoflavone (**1**) were fully consistent with those of the natural neobavaisoflavone.

The partial benzylation of **3** in acetone–*N*,*N*-dimethylformamide also gave 7-benzyloxy-4′-hydroxyisoflavone (**8**), the UV spectrum of which, like that of **4**, did not exhibit the bathochromic shift upon the addition of sodium acetate. The condensation of **8** with 2-methyl-3-buten-2-ol, in contrast with that of **4**, yielded a chroman derivative (**9**) [MS, *m/e* 412 (M^+)] alone. The hydrogenolysis of **9** with palladium on charcoal in ethyl acetate–methanol gave the chroman (**7**), which was identical with isoneobavaisoflavone.

Furthermore, this condensation was also found to be useful for the introduction of the 3-methyl-2-butenyl group into the B ring of phloroglucinol-type isoflavones such as **11**. 7-Benzoyloxy-5,4′-dihydroxyisoflavone (**11**), derived from genistein (**10**), was converted into 7-benzoyloxy-5,4′-dihydroxy-3′-(3-methyl-2-butenyl)isoflavone (**12**) with 2-methyl-3-buten-2-ol, along with the formation of a slight amount of a cyclization product, whose structure was identified as **13** on the basis of the NMR spectrum. In this condensation, neither 6- nor 8-(3-methyl-2-butenyl)-5,7,4′-trihydroxyisoflavone was obtained. The hydrolysis of **12** and **13** gave 3′-(3-methyl-2-butenyl)-5,7,4′-trihydroxyisoflavone (**2**) and the chroman derivative (**14**) respectively. The latter compound (**14**) was easily obtained from **2** by the

above method.

The condensation described above seems to be a general method which can be used for the introduction of the 3-methyl-2-butenyl group into the B ring of isoflavones.

Experimental

All the melting points are uncorrected. The IR spectra were taken on a Hitachi 215 spectrophotometer, and the UV spectra on a Hitachi 124 spectrophotometer. The NMR spectra were measured with a JEOL PS-100 spectrometer (100 MHz), using tetramethylsilane as an internal standard (δ, ppm). The mass spectra were taken on a Hitachi RMS-4 mass spectrometer with a direct inlet system operating at 70 eV. Column chromatography was carried out on Kieselgel 60 (70-230 mesh) (Merck).

7-Benzoyloxy-4'-hydroxyisoflavone (4). To a solution of daidzein (**3**)[5] (1.0 g) in pyridine (50 ml) was added, drop by drop, a mixture of benzoyl chloride (0.8 ml) and dry ether (5 ml) with stirring and cooling in an ice bath; the mixture was then stirred with cooling for 5 h. The reaction mixture was diluted with cold water and acidified with 2 M-hydrochloric acid to give light yellow precipitates, which were collected and recrystallized from ethyl methyl ketone as light yellow needles (**4**) (640 mg): mp 234—235 °C; UV λ_{max} nm (log ε) (EtOH) 258 (3.86), (EtOH+AcONa) 258 (4.04). Found: C, 73.71; H, 3.84%. Calcd for $C_{22}H_{14}O_5$: C, 73.74; H, 3.94%.

7-Benzoyloxy-4'-hydroxy-3'-(3-methyl-2-butenyl)isoflavone (5). To a solution of **4** (1.0 g) and boron trifluoride etherate (1 ml) in dry dioxane (50 ml) was gradually added a solution of 2-methyl-3-buten-2-ol (0.4 ml) in dry dioxane (10 ml); the mixture was then heated with stirring at 60 °C for 5 h. The reaction mixrure was poured into cold water and extracted with ether. The ethereal solution was washed with 3% aqueous solution of sodium carbonate and dried. After the removal of the solvent, the residue was chromatographed over a silica-gel column with chloroform to give isoflavone (**5**), which was subsequently recrystallized from benzene–ethyl acetate as colorless prisms (105 mg): mp 152—153 °C; UV λ_{max} nm (log ε) (EtOH) 258 (4.51), (EtOH+AcONa) 258 (4.55); NMR (DMSO) δ 1.78 (6H, s, $CH_3\times2$), 3.36 (2H, d, J=7 Hz, $C\underline{H}_2CH$=), 5.34 (1H, t, J=7 Hz, $CH_2C\underline{H}$=), 7.26—8.28 (9H, m, $C_6\underline{H}_5CO$, 6-, 8-, 2'-, 6'-H), 7.99 (1H, s, 2-H), 8.40 (1H, d, J=9 Hz, 5-H); MS *m/e* 426 (M^+), 371, 322. Found: C, 76.00; H, 5.35%. Calcd for $C_{27}H_{22}O_5$: C, 76.04; H, 5.20%.

Neobavaisoflavone [7,4'-Dihydroxy-3'-(3-methyl-2-butenyl)isoflavone] (1). Compound **5** (74 mg) was hydrolyzed with 5% aqueous solution of sodium hydroxide (3 ml) in methanol (7 ml) at 50 °C for 5 min. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ether, and the ethereal solution was washed with water and dried. After the removal of the solvent, the residue was recrystallized from benzene–ethyl acetate to give the desired isoflavone (**1**) as colorless needles (33 mg): mp 191—192 °C (lit,[2,3] 195—196 °C); IR (KBr) 1625 cm^{-1}; UV λ_{max} nm (log ε) (MeOH) 248 (4.41), 258sh (4.37), 305sh (4.00), (MeOH+AcONa) 255 (4.55), 331 (4.11), (MeOH+NaOH) 255 (4.52), 331 (4.23); NMR (DMSO) δ 1.65 (6H, s, $CH_3\times2$), 3.20 (2H, d, J=7 Hz, $C\underline{H}_2CH$=), 5.25 (1H, t, J=7 Hz, $CH_2C\underline{H}$=), 6.78 (1H, d, J=9 Hz, 5'-H), 6.84 (1H, bs, 8-H), 6.90 (1H, q, J=9 and 2 Hz, 6-H), 7.16 (1H, q, J=9 and 2 Hz, 6'-H), 7.21 (1H, s, 2'-H), 7.95 (1H, d, J=9 Hz, 5-H), 8.23 (1H, s, 2-H), 9.48 (1H, s, 4'-OH), 10.84 (1H, s, 7-OH); MS *m/e* 322 (M^+, base), 307 (18), 293 (16), 267 (63), 237 (22), 137 (40), 131 (7). Found: C, 74.50; H, 5.70%. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63%.

Diacetate (6) of Neobavaisoflavone (1). After a mixture of **1** (20 mg), acetic anhydride (0.4 ml), and pyridine (0.2 ml) had been allowed to stand at room temperature for 24 h, cold water was added to the mixture. The resulting precipitates were recrystallized from benzene–ethyl acetate as colorless prisms (**6**) (20 mg): mp 115—116 °C (lit,[3] mp 120—121 °C); NMR ($CDCl_3$) δ 1.71 (6H, s, $CH_3\times2$), 2.32 and 2.36 (each 3H, s, CH_3CO), 3.28 (2H, d, J=7 Hz, $C\underline{H}_2CH$=), 5.23 (1H, t, J=7 Hz, $CH_2C\underline{H}$=), 7.06 (1H, d, J=9 Hz, 5'-H), 7.11—7.42 (4H, m, 6-, 8-, 2'-, 6'-H), 7.97 (1H, s, 2-H), 8.30 (1H, d, J=9 Hz, 5-H). Found: C, 71.04; H, 5.56%. Calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46%.

7-Benzyloxy-4'-hydroxyisoflavone (8). To a solution of daidzein (**3**) (800 mg) in acetone (10 ml) and *N,N*-dimethylformamide (10 ml) were addded benzyl chloride (0.5 ml), potassium iodide (600 mg), and 2% aqueous solution of potassium hydroxide (10.6 ml). The mixture was allowed to stand at room temperature for 24 h. The resulting precipitates were recrystallized from ethanol as colorless needles (**8**) (490 mg): mp 234.5—235.5 °C; UV λ_{max} nm (log ε) (EtOH) 262 (4.43), 306sh (4.01), (EtOH+AcONa) 262 (4.44), 306sh (4.02); NMR (DMSO) δ 5.22 (2H, s, $C_6H_5C\underline{H}_2$), 6.80 (2H, d, J=9 Hz, 3'-, 5'-H), 7.19 (1H, q, J=9 and 2 Hz, 6-H), 7.22 (1H, d, J=2 Hz, 8-H), 7.40 (2H, d, J=9 Hz, 2'-, 6'-H), 7.44 (5H, bs, $C_6\underline{H}_5CH_2$), 8.02 (1H, d, J=9 Hz, 5-H), 8.35 (1H, s, 2-H), 9.56 (1H, s, 4'-OH). Found: C, 76.52; H, 4.63%. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68%.

7-Benzyloxy-2',3'-dihydro-2',2'-dimethyl-3,6'-bi(4H-1-benzopyran)-4-one (9). To a solution of **8** (650 mg) and boron trifluoride etherate (0.6 ml) in dry dioxane (50 ml) was added a solution of 2-methyl-3-buten-2-ol (0.2 ml) in dioxane (10 ml), after which the mixture was heated with stirring at 60 °C for 5 h. The reaction mixture was then worked up in the same manner as in the preparation of **5**. The resulting product was chromatographed over a silica-gel column with benzene–ethyl acetate (10: 1) to give isoflavone (**9**), which was subsequently crystallized from carbon tetrachloride as colorless prisms (130 mg): mp 152—153 °C; NMR (DMSO) δ 1.28 (6H, s, $CH_3\times2$), 1.76 and 2.73 (each 2H, t, J=7 Hz, CH_2), 5.22 (2H, s, $C_6H_5C\underline{H}_2$), 6.72 (1H, d, J=9 Hz, 5'-H), 7.12 (1H, q, J=9 and 2 Hz, 6-H), 7.21 (1H, d, J=2 Hz, 8-H), 7.28 (1H, s, 2'-H), 7.32 (1H, d, J=9 Hz, 6'-H), 7.42 (5H, bs, $C_6\underline{H}_5CH_2$), 8.00 (1H, d, J=9 Hz, 5-H), 8.36 (1H, s, 2-H); MS m/*e* 412 (M^+), 397, 383, 357, 321. Found: C, 78.73; H, 6.02%. Calcd for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86%.

Isoneobavaisoflavone [2'3'-Dihydro-2',2'-dimethyl-7-hydroxy-3,6'-bi(4H-1-benzopyran)-4-one] (7). Compound (**9**) (100 mg) was hydrogenated over palladium on charcoal (10%; 50 mg) in ethyl acetate–methanol (20 ml, 1: 3) until the uptake of hydrogen ceased. The solvent was then removed under reduced pressure, and the residue was recrystallized from benzene–ethyl acetate to give colorless prisms (**7**) (50 mg): mp 243—244 °C (lit,[2] 232—233 °C); NMR (DMSO) δ 1.29 (6H, s, $CH_3\times2$), 1.78 and 2.76 (each 2H, t, J=7 Hz, CH_2), 6.70 (1H, d, J=9 Hz, 5'-H), 6.85 (1H, bs, 8-H), 6.92 (1H, q, J=9 and 2 Hz, 6-H), 7.24 (1H, q, J=9 and 2 Hz, 6'-H), 7.28 (1H, d, J=2 Hz, 2'-H), 7.94 (1H, d, J=9 Hz, 5-H), 8.26 (1H, s, 2-H), 10.86 (1H, bs, 7-OH); MS *m/e* 322 (M^+), 307, 293, 267. Found: C, 74.30; H, 5.80%. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63%.

Isoneobavaisoflavone (**7**) was also prepared from neobavaisoflavone with formic acid according to the procedure of Bajwa *et al.*;[3] it had a melting-point of 243—244 °C (no

depression in a mixed-melting-point determination with the isoflavone synthesized above).

7-Benzoyloxy-5,4'-dihydroxyisoflavone (11). To a solution of genistein (**10**)[6] (3.0 g) in pyridine (100 ml) was added, drop by drop, a mixture of benzoyl chloride (1.9 g) and ether (20 ml) with stirring and cooling in an ice bath, after which the mixture was stirred with cooling for 6 h. The reaction mixture was then worked up in the same manner as in the case of **4** to give isoflavone (**11**), which was recrystallized from ethyl acetate as colorless needles (2.4 g): mp 245—246 °C; UV λ_{max} nm (log ε) (EtOH) 259 (4.67), 305 (3.81), 332 (3.73), (EtOH+AcONa) 259 (4.69), 305 (4.05), 336 (3.94). Found: C, 70.69; H, 3.90%. Calcd for $C_{22}H_{14}O_6$: C, 70.58; H, 3.77%.

7-Benzoyloxy-5,4'-dihydroxy-3'-(3-methyl-2-butenyl)isoflavone (12) and 7-Benzoyloxy-2',3'-dihydro-2'2'-dimethyl-5-hydroxy-3,6'-bi(4H-1-benzopyran]-4-one (13). To a solution of **11** (2.0 g) and boron trifluoride etherate (2.5 g) in dioxane (150 ml) was gradually added a solution of 2-methyl-3-buten-2-ol (0.72 g) in dioxane (20 ml), after which the mixture was heated with stirring at 50—55 °C for 6 h. The reaction mixture was then poured into cold water to give light yellow precipitates. After the starting material **11** (0.8 g) had been removed from the collected precipitates by recrystallization from methanol, the resulting compounds soluble in methanol were chromatographed over a silica-gel column with chloroform–ethyl acetate (30: 1), giving an oil and a colorless solid. The solid was recrystallized from methanol as colorless needles (**12**) (330 mg): mp 118—119 °C; UV λ_{max} nm (log ε) (EtOH) 262 (4.64), 334sh (3.91), (EtOH+AcONa) 262 (4.64), 334sh (3.92); NMR ($CDCl_3$) δ 1.81 (6H, s, $CH_3\times2$), 3.42 (2H, d, J=7 Hz, $C\underline{H}_2CH$=), 5.34 (1H, t, J= 7Hz, $CH_2C\underline{H}$=), 5.50 (1H, bs, 4'-OH), 6.65—6.9 (3H, m, 6-, 8-, 5'-H), 7.16—7.36 (2H, bs, 2'-, 6'-H), 7.4—7.8 and 8.1—8.3 (5H, m, $C_6\underline{H}_5CO$), 7.91 (1H, s, 2-H), 12.92 (1H, s, 5-OH). Found: C, 73.22; H, 4.92%. Calcd for $C_{27}H_{22}O_6$: C, 73.29; H, 5.01%.

The oil was rechromatographed over a silica-gel column with chloroform–carbon tetrachloride (30: 1) to give colorless needles (**13**) (80 mg): mp 164—165 °C; NMR ($CDCl_3$) δ 1.36 (6H, s, $CH_3\times2$), 1.83 (2H, t, J=7 Hz, CH_2), 2.84 (2H, t, J=7 Hz, CH_2), 6.65—6.92 (3H, m, 6-, 8-, 5'-H), 7.13—7.35 (2H, m, 2'-, 6'-H), 7.4—7.8 and 8.16—8.24 (5H, m, $C_6\underline{H}_5CO$), 7.94 (1H, s, 2-H), 12.95 (1H, s, 5-OH). Found: C, 73.04; H, 5.05%. Calcd for $C_{27}H_{22}O_6$: C, 73.29; H, 5.01%.

3'-(3-Methyl-2-butenyl)-5,7,4'-trihydroxyisoflavone (2). Isoflavone (**12**) (350 mg) was hydrolyzed with 5% aqueous solution of sodium hydroxide (20 ml) in methanol (30 ml) at 60 °C for 15 min. After the reaction mixture had then been worked up in the same manner as in the case of **1**, the resulting compound was chromatographed over a silica-gel column with chloroform–acetone (30: 1) to give colorless needles (**2**) (210 mg) which were subsequently recrystallized from 1,2-dichloroethane: mp 171—172 °C; UV λ_{max} nm (log ε) (EtOH) 263 (4.54), 295 (4.06), 330 (3.72), (EtOH+AcONa) 273 (3.55), 331 (4.01); NMR (DMSO) δ 1.68 (6H, s, $CH_3\times2$), 3.24 (2H, d, J=7 Hz, $C\underline{H}_2CH$=), 5.28 (1H, t, J=7 Hz, $CH_2C\underline{H}$=), 6.21 (1H, d, J=2 Hz, 6-H), 6.37 (1H, d, J=2 Hz, 8-H), 6.83 (1H, d, J=9 Hz, 5'-H), 7.19 (1H, q, J=9 and 2 Hz, 6'-H), 7.24 (1H, bs, 2'-H), 8.31 (1H, s, 2-H), 9.57 (1H, s, 4'-OH), 10.95 (1H, s, 7-OH), 13.11 (1H, s, 5-OH); MS *m/e* 338 (M^+, base), 323 (23), 309 (20), 283 (93), 253 (40), 153 (65), 131 (18). Found: C, 71.24; H, 5.45%. Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36%.

5,7-Dihydroxy-2'3'-dihydro-2'2'-dimethyl-3,6'-bi(4H-1-benzopyran)-4-one (14). Compound (**13**) (60 mg) was hydrolyzed with 5% aqueous solution of sodium hydroxide (3 ml) in methanol (10 ml) under reflux for 15 min. The reaction mixture was then worked up in the same manner as in the case of **12** to give isoflavone (**14**), which was subsequently recrystallized from benzene–ethyl acetate as colorless needles (31 mg): mp 214—215 °C; NMR (DMSO) δ 1.30 (6H, s, $CH_3\times2$), 1.77 (2H, t, J=7 Hz, CH_2), 2.75 (2H, t, J=7 Hz, CH_2), 6.19 (1H, d, J=2 Hz, 6-H), 6.36 (1H, d, J=2 Hz, 8-H), 6.73 (1H, d, J=9 Hz, 5'-H), 7.13—7.40 (2H, m, 2'-, 6'-H), 8.32 (1H, d, 2-H), 10.90 (1H, s, 7-OH), 12.97 (1H, s, 5-OH); MS *m/e* 338 (M^+), 323, 309, 283. Found: C, 71.26; H, 5.43%. Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36%.

Compound **14** was also obtained from **2** by the same method as in the case of **7**.

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