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AURONES AND AURONE GLUCOSIDES—XI

SYNTHESIS OF HISPIDOL AND ITS GLUCOSIDES

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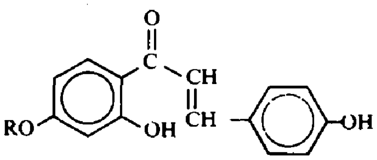
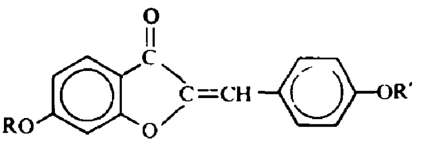
Abstract—The synthesis of 6,4'-dihydroxy-aurone, a component of soy-bean seedlings, as well as that of, 6,4'-dihydroxy-aurone-6-β-D-glucoside, -4'-β-D-glucoside and -6-4'-di-β-D-glucoside is reported.

AN INVESTIGATION on the flavonoid constituents of soy-bean (*Soya hispida*) by paper chromatography has been recently published by Wong.[1]

In addition to some isoflavones and isoflavon-glucosides isolated earlier from this source (daidzein,[2] daidzin,[2] genistein[3] and genistin[2]), isoliquiritigenin (Ia) and 6,4'-dihydroxyaurone (IIa) have been detected as new components. The latter (IIa) has been found for the first time in plant material and hence the name hispidol has been proposed.



Ia: R = H
Ib: R = glucosil



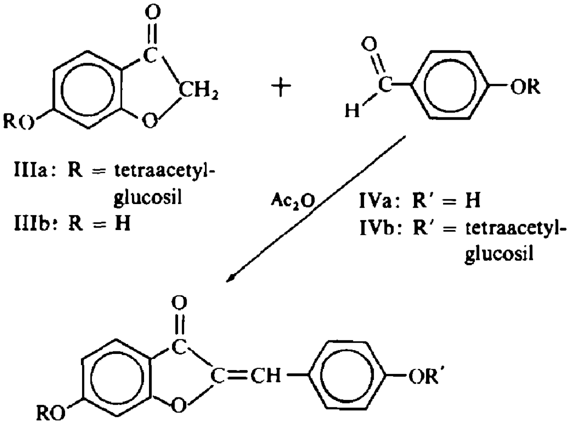
IIa: R = R' = H
IIb: R = glucosil; R' = H
IIc: R = H; R' = glucosil
IId: R = R' = glucosil

In order to demonstrate the biogenetic relationship between chalcone and aurone constituents, Wong incubated synthetic isoliquiritigenin-4'-β-D-glucoside (Ib) with an extract of soy-bean seedlings and isolated from this material (two-dimensional paper chromatography) a new substance, which on grounds of its UV spectrum was considered to be hispidol-6-glucoside (IIb). This assumption was further supported by the oxidation of isoliquiritigenin-4'-glucoside to a yellow crystalline product, isolated by chromatography and characterized but with a m.p. of 191–192°.

A method of general applicability for the synthesis of aurones and aurone glycosides,[4] has been applied successfully to prove the structure of a number of natural aurone glucosides.[4–9] In this paper, the synthesis of hispidol glucosides and a convenient new way for the preparation of the aglycone is reported.

In order to prepare hispidol-6-β-D-glucoside (IIb) by an unambiguous synthesis, 6-hydroxycoumarane-3-one-β-D-glucoside tetraacetate[10] (IIIa) was condensed with *p*-hydroxybenzaldehyde (IVa) in acetic anhydride to yield 6,4'-dihydroxy-aurone-6-β-D-glucoside pentaacetate (Vb). Catalytic saponification according to Zemplén[11] afforded pure hispidol-6-β-D-glucoside (IIb), having identical UV and IR spectra with the specimen prepared by Wong,* but melting some 20° higher, i.e. at 211–212°. Some impurities revealed in Wong's specimen by TLC may explain its lower m.p.

6,4'-Dihydroxy-aurone (hispidol; IIa), described by Geissman and Harborne,[12] was prepared by the condensation of 6-hydroxycoumaran-3-one[13] (IIIb) and *p*-hydroxybenzaldehyde (IVa) in acetic anhydride. Subsequent deacetylation[11] of the product (6,4'-diacetoxy-aurone, Va) gave rise to hispidol (IIa) identical in every respect with the natural product.



IIIa: R = tetraacetylglucosil
IIIb: R = H

IVa: R' = H
IVb: R' = tetraacetylglucosil

Va: R = R' = Ac
Vb: R = tetraacetylglucosil; R' = Ac
Vc: R = Ac; R' = tetraacetylglucosil
Vd: R = R' = tetraacetylglucosil)

The aforementioned discrepancies in the m.p. of the 6-glucoside of hispidol prompted us to prepare the 4'-glucoside (IIc) and the 6,4'-diglucoside (IId) of the same aglycone. Thus condensation of 6-hydroxycoumaran-3-one (IIIa)[13] with *p*-hydroxybenzaldehyde-glucoside tetraacetate[14] (IVb) afforded Vc, and that of 6-hydroxycoumaran-3-one-6-glucoside tetraacetate (IIIa) and IVb gave Vd. The methyl–ethers of IIb and IIc were also prepared, both by condensation of the corresponding methylated components and methylation of IIb and IIc. Saponification of the aurone acetates was accomplished in each case by the method of Zemplén.[11]

EXPERIMENTAL

6,4'-Dihydroxyaurone-6-β-D-glucoside pentaacetate (*hispidol-6-glucoside acetate* (Vb). Compound IIIa[10] (1·2 g) and IVa (0·3 g) was refluxed for 4 hr in Ac_2O (20 ml). The reaction mixture was poured into water, the product separated and crystallized from MeOH—$CHCl_3$, giving Vb (0·9 g), as pale yellow needles;

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* We are indebted to Dr. E. Wong (New Zealand) for a specimen of hispidol-6-glucoside.

m.p. 189–190°; $[\alpha]_D^{20} = -27{\cdot}0°$ ($c = 2$; in $CHCl_3$). (Found: C, 59·29; H, 4·75; $C_{31}H_{30}O_{14}$ (626·6) requires: C, 59·42; H, 4·82%).

6,4'-Dihydroxyaurone-6-β-D-glucoside (*hispidol-6-glucoside*) (IIb). Compound Vb (0·2 g) was deacetylated in MeOH (10 ml) with N MeONa (0·5 ml). The pH of the reaction mixture was adjusted to 6 with AcOH, it was evaporated to dryness in vacuum, giving a dark red oil. This was crystallized from MeOH—H_2O, giving IIb, as yellow cubes (0·13 g), m.p. 211–212°. UV (EtOH): 226, 254, 390 mμ (log ε 3·91, 4·11, 4·44); (lit.[1] UV (EtOH): 255, 397 mμ). (Found: C, 55·84; H, 5·67; $C_{21}H_{20}O_9{\cdot}2\,H_2O$ (452·4) requires: C, 55·75; H, 5·37%).

Hydrolysis of synthetic hispidol-6-glucoside. Compound IIb (0·1003 g) was refluxed with dil HCl (15 ml H_2O, 3 ml HCl) for 4 hr. The aglycone, which separated, yielded 0·0598 g (97%), m.p. 286–288°. In admixture with IIa no m.p. depression was observed. The glucose content of the filtrate based on optical rotation was 0·0381 g (87%).

6,4'-Diacetoxyaurone (*hispidol diacetate*; Va). Compound IIIb[13] (1·5 g) and IVa (1·22 g) was refluxed in Ac_2O (30 ml) for 4 hr. The reaction mixture was poured into water, when a sticky oil separated. This was crystallized from MeOH—AcOH, giving Va (1·2 g), as pale yellow needles of m.p. 162–163°. (Found: C, 67·49; H, 4·38. $C_{19}H_{14}O_6$ (338·3) requires: C, 67·45; H, 4·17%).

6,4'-Dihydroxyaurone (*hispidol*; IIa). Compound Va (0·85 g) afforded on deacetylation IIa (0·5 g), as small needles of m.p. 288° (dec) Lit.[12]: 288°). UV (EtOH): 235, 254, 388 mμ (log ε 4·02, 4·14, 4·48 (Lit.[12]: 234, 254, 388 mμ (log ε 4·01, 4·09, 4·44). (Found: C, 70·62; H, 3·95; $C_{15}H_{10}O_4$ (254·2) requires: C, 70·85; H, 3·97%).

6,4'-Dihydroxyaurone-4'-β-D-glucoside pentaacetate (*hispidol-4'-glucoside acetate*); Vc. Compound IIIb[13] (0·8 g) and IVb[14] (2·3 g) was refluxed in Ac_2O (30 ml) for 4 hr. The reaction mixture solidified on pouring into water. Crystallization of the crude product from MeOH—$CHCl_3$, gave Vc, as pale yellow needles (2·6 g), m.p. 218–219°; $[\alpha]_D^{20} = -32{\cdot}2°$ ($c = 2$, in $CHCl_3$). (Found: C, 59·47; H, 4·85; $C_{31}H_{30}O_{14}$ (626·6) requires: C, 59·42; H, 4·82%).

6,4'-Dihydroxyaurone-4'-β-D-glucoside (*hispidol-4'-glucoside*; IIc). Deacetylation of Vc (2·0 g) yielded after recrystallization from MeOH, IIc (1·3 g), as yellow needles, m.p. 211–211·5°. UV (EtOH): 232, 245, 352 mμ (log ε 4·32, 4·34, 4·73). (Found: C, 60·79; H, 5·06. $C_{21}H_{20}O_9$ (416·4) requires: C, 60·57; H, 4·85%).

Hydrolysis of hispidol-4'-glucoside. Compound IIc (0·1080 g) was hydrolysed as described above to give 0·0592 g (90%) of the aglycone, m.p. 286–288°; on admixture with IIa no m.p. depression was observed. The glucose content, calculated from the optical rotation of the filtrate, was 0·0414 g (88%).

6,4'-Dihydroxyaurone-6,4'-di-β-D-glucoside octaacetate (*hispidol-6,4'-diglucoside acetate*; Vd). Compound IIIa[10] (1·2 g) and IVb[14] (1·1 g) was refluxed for 4 hr in Ac_2O (30 ml). The reaction mixture was poured into water, the oily ppt solidified after standing. Recrystallization from MeOH afforded Vd (1·1 g) as small yellow needles, m.p. 172–173°; $[\alpha]_D^{20} = -42{\cdot}0°$ ($C = 2$, in $CHCl_3$). (Found: C, 56·24; H, 5·02. $C_{43}H_{46}O_{22}$ (914·9) requires: C, 56·46; H, 5·07%).

6,4'-Dihydroxyaurone-6,4'-di-β-D-glucoside (*hispidol-6,4'-diglucoside*; IId). Deacetylation of Vd gave IId (0·35 g), as yellow needles, m.p. 243–244°. UV (EtOH): 254, 344, 370 mμ (log ε 4·13, 4·38, 4·32). (Found: C, 55·89; H, 5·44. $C_{27}H_{30}O_{14}$ (578·5) requires: C, 56·05; H, 5·23%).

Hydrolysis of hispidol-6,4'-diglucoside. Compound IId (0·1194 g) was hydrolysed as described above. The aglycone yielded 0·0411 g (79%), m.p. 286–288°. On admixture with IIa no m.p. depression was observed. The glucose content form optical rotation of the filtrate was 0·0620 g (84%).

6-Hydroxy-4'-methoxyaurone-6-β-D-glucoside tetraacetate. Compound IIIa[10] (1·2 g) and *p*-anisaldehyde (0·34 g) was refluxed in Ac_2O (30 ml) 4 hr. The reaction mixture was poured into water. The oil, which separated, crystallized slowly on standing. Recrystallization of the crude product from MeOH—$CHCl_3$, gave 6-hydroxy-4'-methoxy-aurone-6-β-D-glucoside tetraacetate (0·5 g), as pale yellow needles, m.p. 202–203°, $[\alpha]_D^{20} = -40{\cdot}0°$ ($c = 1$, in $CHCl_3$). (Found: C, 59·99; H, 5·19; MeO, 5·33. $C_{30}H_{30}O_{13}$ (598·6) requires: C, 60·19; H, 5·05; MeO, 5·18%).

6-Hydroxy-4'-methoxyaurone-6-β-D-glucoside. Deacetylation of 6-hydroxy-4'-methoxyaurone-6-β-D-glucoside tetraacetate (0·8 g) gave a crude product, which crystallized from MeOH (0·3 g), m.p. 198°. (Found: C, 61·40; H, 4·90; MeO, 7·45. $C_{22}H_{22}O_9$ (430·4) requires: C, 61·39; H, 5·14; MeO, 7·21%). Methylation of IIb (0·2 g) with MeI (K_2CO_3, MeOH) afforded the same 6-hydroxy-4'-methoxyaurone-6-β-D-glucoside.

Hydrolysis of 6-hydroxy-4'-methoxyaurone-6-β-D-glucoside. 6-Hydroxy-4'-methoxyaurone-6-β-D-glucoside (0·0983 g) was hydrolysed as described above. The aglycone weighed 0·0572 g (93%), m.p. 265°. On admixture with 6-hydroxy-4′-methoxyaurone no m.p. depression was observed. The glucose content, from optical rotation of the filtrate was 0·0380 g (92%).

4′-Hydroxy-6-methoxyaurone-4′-β-D-glucoside tetraacetate. 6-Methoxycoumaran-3-one[15] (1·64 g) and IVb[14] (4·52 g) was refluxed in Ac_2O (30 ml) for 4 hr. After pouring the reaction mixture into water the product soon solidified. Recrystallization from $CHCl_3$—MeOH gave pale yellow needles (2·1 g), m.p. 165–166°, $[\alpha]^{20}_{D} = -24{\cdot}5^\circ$ ($c = 1$, in $CHCl_3$). (Found: C, 59·89; H, 5·20; MeO, 4·94. $C_{30}H_{30}O_{13}$ (598·6) requires: C, 60·19; H, 5·05; MeO, 5·18%).

4′-Hydroxy-6-methoxyaurone-4′-β-D-glucoside. Deacylation of 4′-hydroxy-6-methoxyaurone-4′-β-D-glucoside tetraacetate (0·5 g) gave a crude glucoside, which crystallized from MeOH, as pale yellow needles, m.p. 241–242°. (Found: C, 61·20; H, 5·04; MeO, 6·88. $C_{22}H_{22}O_9$ (430·4) requires: C, 61·39; H, 5·14; MeO, 7·21%).

Methylation of IIc (0·2 g) with MeI (K_2CO_3, MeOH) afforded the same 4′-hydroxy-6-methoxyaurone-4′-β-D-glucoside.

Hydrolysis of 4′-hydroxy-6-methoxyaurone-β-D-glucoside. 4′-Hydroxy-6-methoxyaurone-4′-β-D-glucoside (0·1060 g) was hydrolysed as described above. The aglycone yielded 0·0662 g (98%), m.p. 216°. A mixed m.p. with authentic 4′-hydroxy-6-methoxyaurone was not depressed. The glucose content from optical rotation of the filtrate was 0·0428 g (95%).

6-Acetoxy-4′-methoxyaurone. Compound IIIb[13] (1·5 g) and *p*-anisaldehyde (1·36 g) was refluxed in Ac_2O (20 ml) for 4 hr. The reaction mixture was poured into water and the resulting amorphous product was recrystallized several times from MeOH—AcOH, to give 6-acetoxy-4′-methoxyaurone, as pale yellow needles (0·5 g), m.p. 176–177°. (Found: C, 69·60; H, 4·34; MeO, 9·65. $C_{18}H_{14}O_5$ (310·3) requires: C, 69·67; H, 4·55; MeO, 10·00%).

6-Hydroxy-4′-methoxyaurone. Deacylation of 6-acetoxy-4′-methoxyaurone (0·6 g) yielded 6-hydroxy-4′-methoxyaurone (0·4 g), as yellow crystals, m.p. 265°. (lit.[12] 259°). (Found: C, 71·44; H, 4·51; MeO, 11·32. $C_{16}H_{12}O_4$ (268·3) requires: C, 71·64; H, 4·50; MeO, 11·57%).

4′-Acetoxy-6-methoxyaurone. 6-Methoxycoumaran-3-one[15] (1·64 g) and IVa (1·22 g) was refluxed in Ac_2O (20 ml) for 4 hr. The reaction mixture after being poured into water, afforded 4′-acetoxy-6-methoxyaurone, as a rapidly solidifying oil. The yellow needles (0·75 g) melted after recrystallization from MeOH—$CHCl_3$ at 170–171°. (Found: C, 70·00; H, 4·30; MeO, 9·82. $C_{18}H_{14}O_5$ (310·3) requires: C, 69·67; H, 4·55; MeO, 10·00%).

4′-Hydroxy-6-methoxyaurone. Deacetylation of 4′-acetoxy-6-methoxyaurone (0·6 g) gave 4′-hydroxy-6-methoxyaurone (0·4 g), as yellow needles, m.p. 216° (MeOH). (Found: C, 71·39; H, 4·31; MeO, 11·32. $C_{16}H_{22}O_4$ (268·3) requires: C, 71·64; H, 4·50; MeO, 11·57%).

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