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FLAVONOIDS FROM *TEPHROSIA*—XI[1]

THE STRUCTURE OF GLABRATEPHRIN

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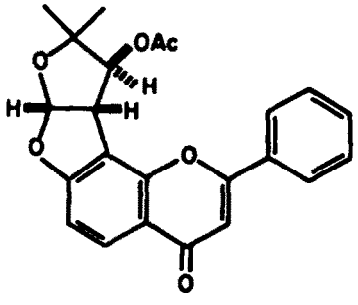
Abstract—Physico-chemical techniques and X-ray crystallography established the structure of glabratephrin, a flavone isolated from *Tephrosia semiglabra* Sond., as (4'-acetoxy-5',5'-dimethyltetrahydrofuran-2'-one)-3'-spiro-9-(8,9-dihydro-2-phenyl-4H-furo[2,3-h]benzo[3,4-b]pyran-4-one).

In a recent communication we reported on the structural elucidation of semiglabrin (1), a new flavone isolated from *Tephrosia semiglabra* Sond.[2] In the course of the investigation we isolated a minor component for which the trivial name glabratephrin was proposed.[2] We now wish to describe the structural assignment and relative stereochemistry of this compound.



(1)

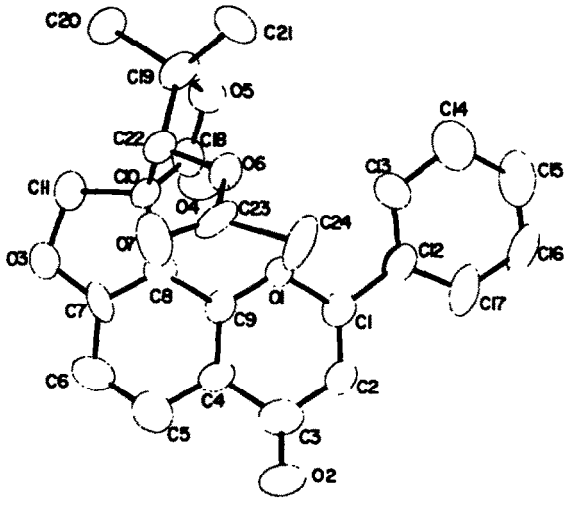


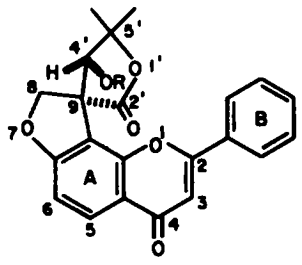
Fig. 1. An ORTEP drawing of glabratephrin.

Chemical derivatization together with physico-chemical techniques provided insight in the different fragments which constituted the glabratephrin molecule. Single crystal X-ray crystallography verified the proposed structure 2 for glabratephrin and established the relative stereochemistry as shown in 2 and in Fig. 1.

Glabratephrin (2), $[\alpha]_D^{24} - 214.9°$ (*c*, 0.98 in $CHCl_3$) analyzed for $C_{24}H_{20}O_7$. The UV absorption λ_{max} 218, 247, 256 and 309 nm ($\log \epsilon$ 4.22, 4.23, 4.23 and 4.30 respectively) was characteristic of a 7-oxygenated flavone chromophore such as occurs in semiglabrin (1).[2] The IR spectrum exhibited absorption at 1760 (lactone CO), 1740 (acetate CO) and 1640 (γ-pyrone CO) cm^{-1}. Absorption in the OH region was absent.

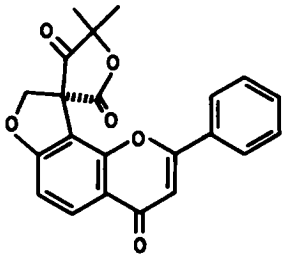
The 100 MHz ^1H NMR spectrum of glabratephrin had the following characteristics. The two high-field singlets at δ 1.59 (3H) and δ 1.49 (3H) were assigned to the *gem*-Me_2 group adjacent to an oxygen function. The protons of the secondary OAc group appeared as a singlet at δ 1.52 (3H). In the aromatic region a pair of doublets (J = 8.5 Hz) was discernible at δ 6.96 (1H) and δ 8.19 (1H) and were ascribed to the two *ortho*-coupled protons at C_6 and C_5, respectively. The presence of the C_5 proton signal at low field (δ 8.19), due to the deshielding effect of the *peri* CO group, confirmed the angular structure as indicated in (2) for glabratephrin. The multiplets centred at δ 7.89 (2H) and δ 7.53 (3H) were assigned to the B-ring protons. The singlet at δ 6.77 (1H) was characteristic of the C_3 proton of a flavone.[3-5] The $C_{4'}$ methine proton appeared as a singlet at δ 5.41. The singlet at δ 4.98 (2H), due to the C_8 methylene protons, changed to a double doublet (J = 8.5 Hz) upon addition of 30 μl 0.1 M Eu(fod)$_3$ (in $CDCl_3$) to the sample.

Chemical evidence for the presence of an OAc ester group in glabratephrin was provided by mild alkaline hydrolysis to give glabratephrinol (3), $C_{22}H_{18}O_6$. In the NMR spectrum the $C_{4'}$ proton now appeared at δ 4.49 as



(2) R = Ac

(3) R = H



(4)

a doublet (J = 4.0 Hz) due to spin–spin coupling with the OH proton at δ 5.50 (1H, d, J = 4.0 Hz). The latter signal disappeared upon addition of D_2O to the sample while the doublet at δ 4.49 changed to a singlet. The C_8 methylene protons appeared as an AB system (J = 8.5 Hz) at δ 4.94 (1H) and δ 4.84 (1H). Absorption bands at 1740 cm^{-1} and 1635 cm^{-1} in the IR spectrum were assigned to the lactone CO and the flavone CO group, respectively.

The secondary nature of the OH group in glabratephrinol (3), inferred from NMR data was confirmed by oxidation with Jones reagent to give glabratephrinone (4), $C_{22}H_{16}O_6$. The IR spectrum showed strong absorption in the CO region at 1800, 1755 and 1645 cm^{-1}. The NMR spectrum of (4) was similar to that of glabratephrin (2) except for the appearance of the C_8 methylene protons as a pair of doublets (J = 8.5 Hz) at δ 5.02 (1H) and δ 4.89 (1H).

Glabratephrin is a further representative of the new types of flavonoids isolated from *Tephrosia* species.[1,2] These compounds illustrate the novel pattern in which an isoprenoid unit can be incorporated in a heterocyclic system.

Crystallography

Cell dimensions were determined from least-squares refinement of 25 reflections and a unique set of data was then collected on a Philips PW 1100 diffractometer using a conventional $\omega/2\theta$ scan within the limit $2\theta < 40°$ yielding 1164 reflections; of these 992 with $F > 2\sigma_F$ were considered "observed" and used in the structure solution and refinement. No absorption correction was applied.

Crystal data $C_{24}H_{20}O_7$, M = 420.42, orthorhombic, space group $P2_12_12_1$; a = 19.952(10), b = 14.666(9), c = 7.094(6) Å, $D_c = 1.345\ gcm^{-3}$ (Z = 4), V = 2076 Å^3. Monchromatic Mo(K_α) radiation (λ = 0.7107 Å). Neutral atom scattering factors.[6,7]

The structure was solved by direct methods using the MULTAN program[8] and refined[9] by full-matrix least-squares methods with anisotropic thermal parameters. Satisfactory positions for the hydrogen atoms could not be found from difference syntheses and none were included in the final refinement. The final conventional R index was 8.9% for the 992 reflections.

The results are given in the Tables and in the Fig. The structure is illustrated in the Fig. showing the nomenclature used in the Tables. There are no hydrogen bonds or intermolecular contacts less than 3.3 Å.

Table 1. Atomic fractional cell co-ordinates (x, y, z) (x10^4) and thermal parameters of the form T = $\exp[-2\pi^2(U_{11}h^2a^{*2} + \cdots 2U_{23}klb^*c^*)]$ (10^3) with least squares standard deviations in the final digit in parentheses

ATOM	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	4228(5)	1573(8)	9576(19)	34(7)	29(7)	47(9)	1(6)	5(7)	1(7)
O(2)	6099(7)	554(10)	10651(26)	51(9)	77(11)	94(13)	22(9)	13(10)	-2(11)
O(3)	4932(6)	4585(9)	10004(23)	52(8)	39(9)	81(14)	-9(7)	-11(10)	-4(10)
O(4)	3383(7)	3046(11)	12133(21)	84(11)	91(11)	46(9)	23(10)	-1(9)	-11(10)
O(5)	2805(6)	3323(8)	9491(18)	42(7)	57(9)	41(8)	5(7)	7(8)	-4(8)
O(6)	3796(6)	2664(8)	6529(16)	50(8)	32(7)	22(7)	4(6)	3(7)	-6(6)
O(7)	4718(7)	3131(9)	5093(23)	60(9)	50(8)	79(12)	-19(8)	25(10)	-13(10)
C(1)	4354(10)	650(12)	9655(29)	59(14)	41(13)	25(12)	1(11)	-3(12)	14(11)
C(2)	4971(10)	304(13)	10028(34)	52(14)	37(12)	65(18)	5(11)	8(15)	-3(14)
C(3)	5535(11)	863(15)	10394(32)	53(15)	78(16)	28(13)	16(14)	17(13)	-9(14)
C(4)	5391(10)	1874(13)	10159(34)	51(12)	44(13)	64(17)	13(11)	-23(14)	-2(14)
C(5)	5933(11)	2507(17)	10476(32)	59(14)	74(16)	54(17)	-5(14)	11(14)	0(16)
C(6)	5786(10)	3435(16)	10465(34)	43(14)	76(17)	49(15)	0(12)	-7(13)	-23(15)
C(7)	5116(10)	3686(14)	10093(33)	53(13)	51(14)	44(15)	-29(13)	-10(13)	9(14)
C(8)	4624(9)	3071(13)	9786(28)	41(11)	43(11)	28(12)	6(11)	3(11)	-13(12)
C(9)	4743(8)	2149(11)	9827(25)	45(11)	36(10)	21(11)	-1(9)	15(10)	13(10)
C(10)	3985(9)	3613(12)	9341(31)	43(11)	31(11)	68(15)	4(10)	-11(13)	9(12)
C(11)	4189(9)	4608(12)	9898(32)	59(12)	35(11)	59(16)	0(10)	1(14)	-17(13)
C(12)	3755(10)	103(12)	9136(28)	60(13)	33(11)	39(12)	1(10)	21(11)	14(10)
C(13)	3170(9)	547(14)	8460(29)	44(12)	59(14)	36(13)	-6(12)	-3(11)	2(13)
C(14)	2594(13)	19(21)	7853(29)	82(18)	87(17)	35(13)	-15(15)	5(13)	-11(14)
C(15)	2646(14)	-928(16)	8077(34)	103(21)	54(16)	57(17)	-33(15)	12(16)	12(14)
C(16)	3211(13)	-1363(14)	8720(40)	94(20)	27(12)	94(21)	-1(13)	35(19)	-5(14)
C(17)	3765(12)	-837(13)	9191(34)	94(16)	35(12)	71(17)	-10(12)	31(15)	-11(13)
C(18)	3373(9)	3289(13)	10490(27)	63(12)	46(12)	29(11)	-5(11)	0(11)	-2(11)
C(19)	2922(10)	3700(13)	7598(25)	59(12)	47(12)	20(10)	14(11)	9(11)	5(11)
C(20)	2759(10)	4779(12)	7598(32)	56(13)	36(12)	72(16)	21(10)	-4(14)	-18(13)
C(21)	2505(10)	3189(15)	6214(30)	46(13)	69(14)	58(14)	-1(12)	-21(12)	-20(13)
C(22)	3713(9)	3563(12)	7322(29)	44(11)	33(11)	44(13)	8(10)	-1(12)	0(12)
C(23)	4338(10)	2549(12)	5418(29)	62(13)	36(11)	57(14)	24(10)	0(12)	11(13)
C(24)	4333(11)	1561(12)	4683(33)	93(16)	22(10)	59(15)	10(11)	21(15)	-15(13)

Table 2. Non-hydrogen interatomic distances and angles (Å, degrees); least squares estimated standard deviations in the final digit are given in parentheses

C(1)-O(1)	1.38(2)	C(13)-C(14)	1.45(3)
C(1)-C(2)	1.36(3)	C(14)-C(15)	1.40(4)
C(2)-C(3)	1.42(3)	C(15)-C(16)	1.37(4)
C(3)-O(2)	1.23(3)	C(16)-C(17)	1.39(3)
C(3)-C(4)	1.52(3)	C(17)-C(12)	1.38(3)
C(4)-C(9)	1.38(3)	C(10)-C(18)	1.54(3)
C(4)-C(5)	1.44(3)	C(10)-C(22)	1.53(3)
C(5)-C(6)	1.39(3)	C(18)-O(4)	1.22(2)
C(6)-C(7)	1.41(3)	C(18)-O(5)	1.34(2)
C(7)-C(8)	1.35(3)	C(19)-O(5)	1.47(2)
C(7)-O(3)	1.37(2)	C(19)-C(20)	1.62(3)
C(8)-C(9)	1.37(2)	C(19)-C(21)	1.49(3)
C(8)-C(10)	1.54(3)	C(19)-C(22)	1.60(3)
C(9)-O(1)	1.34(2)	C(22)-O(6)	1.44(2)
C(10)-C(11)	1.57(3)	C(23)-O(6)	1.35(2)
C(11)-O(3)	1.48(2)	C(23)-C(24)	1.54(3)
C(1)-C(12)	1.49(3)	C(23)-O(7)	1.17(2)
C(12)-C(13)	1.42(3)		
C(9)-O(1)-C(1)	118(1)	C(11)-C(10)-C(22)	112(2)
O(1)-C(1)-C(2)	123(2)	C(18)-C(10)-C(22)	101(1)
O(1)-C(1)-C(12)	112(2)	C(10)-C(18)-O(4)	126(2)
C(12)-C(1)-C(2)	125(2)	C(10)-C(18)-O(5)	112(2)
C(1)-C(2)-C(3)	123(2)	O(4)-C(18)-O(5)	122(2)
C(2)- C(3)- C(4)	113(2)	C(18)-O(5)-C(19)	111(1)
C(2)-C(3)-O(2)	123(2)	O(5)-C(19)-C(20)	110(2)
O(2)-C(3)-C(4)	123(2)	O(5)-C(19)-C(21)	109(2)
C(3)-C(4)-C(9)	119(2)	O(5)-C(19)-C(22)	103(2)
C(3)-C(4)-C(5)	118(2)	C(20)-C(19)-C(21)	112(2)
C(9)-C(4)-C(5)	123(2)	C(20)-C(19)-C(22)	109(2)
C(4)-C(5)-C(6)	118(2)	C(21)-C(19)-C(22)	114(2)
C(5)-C(6)-C(7)	117(2)	C(10)-C(22)-C(19)	103(1)
C(6)-C(7)-C(8)	123(2)	C(10)-C(22)-O(6)	112(1)
C(6)-C(7)-O(3)	121(2)	O(6)-C(22)-C(19)	106(1)
O(3)-C(7)-C(8)	116(2)	C(22)-O(6)-C(23)	116(1)
C(7)-C(8)-C(9)	122(2)	O(6)-C(23)-C(24)	108(2)
C(7)-C(8)-C(10)	107(2)	O(6)-C(23)-O(7)	123(2)
C(9)-C(8)-C(10)	131(2)	C(24)-C(23)-O(7)	129(2)
C(8)-C(9)-O(1)	119(2)	C(1)-C(12)-C(13)	120(2)
C(8)-C(9)-C(4)	117(2)	C(1)-C(12)-C(17)	121(2)
O(1)-C(9)-C(4)	124(2)	C(17)-C(12)-C(13)	119(2)
C(7)-O(3)-C(11)	107(1)	C(12)-C(13)-C(14)	120(2)
O(3)-C(11)-C(10)	105(1)	C(13)-C(14)-C(15)	116(2)
C(8)-C(10)-C(11)	102(1)	C(14)-C(15)-C(16)	124(2)
C(8)-C(10)-C(18)	113(2)	C(15)-C(16)-C(17)	118(2)
C(8)-C(10)-C(22)	117(2)	C(16)-C(17)-C(12)	122(2)
C(11)-C(10)-C(18)	111(2)		

EXPERIMENTAL

M.ps were determined with a Kofler hot-stage apparatus and are uncorrected. The IR spectra were determined on a Unicam SP-200 spectrophotometer using KBr. UV spectra refer to solutions in MeOH and were recorded on a Unicam SP-800 spectrophotometer. NMR spectra were recorded on a Varian HA-100 instrument with TMS as internal standard (δ 0.00) in $CDCl_3$. Mass spectra were recorded on an AEI M.S. 9 spectrometer with direct insertion technique. Optical rotations were measured with a Perkin–Elmer 411 polarimeter.

Extraction and isolation. The sun-dried and ground plant material (1.26 kg) was extracted with CH_2Cl_2 for 24 h in a Soxhlet apparatus. The CH_2Cl_2 extract was fractionated according to the procedure previously described (cf. Ref. 2) to give glabratephrin (2; 230 mg).

Glabratephrin (2) crystallized from benzene–n-hexane, m.p. 227–228°. It had $[\alpha]_D^{25}$ −214.9° (*c* 0.98 in $CHCl_3$); λ_{max} 218, 247, 256 and 309 nm (log ε 4.22, 4.23, 4.23 and 4.27 respectively); ν_{max} 1760 (CO), 1740 (acetate CO), 1640 (flavone CO) cm^{-1} (Found: C, 68.60; H, 4.89. $C_{24}H_{20}O_7$ requires: C, 68.57; H, 4.80%).

Glabratephrinol (3)

A soln of 2 (100 mg) in 0.2 N methanolic KOH (20 ml) was stirred at room temp. for 20 min. The soln was diluted with H_2O; acidified (6 N HCl) and extracted with CH_2Cl_2 to give a colourless oil. Crystallization from $CHCl_3$–n-hexane gave 3 (80 mg).

m.p. 223–225°; $[\alpha]_D^{24} - 61.6°$ (*c*, 0.80 in $CHCl_3$); λ_{max} 214, 247, 257 and 311 nm (log ϵ 4.55, 4.40, 4.43 and 4.43 respectively); ν_{max} 1740 (CO) and 1635 (flavone CO) cm^{-1}; M^+, 378; NMR: δ 1.54 and 1.72 (each: s, 3H; *gem*-Me_2), 4.49 (d, 1H, J = 4.0 Hz, C_4–H), 4.94 and 4.84 (each: d, 1H, J = 8.5 Hz; C_8–H), 5.50 (d, 1H, J = 4.0 Hz, disappears on addition of D_2O, C_4–OH), 6.24 (s, 1H, C_3–H), 6.88 (d, 1H, J = 8.5 Hz, C_6–H), 7.56 (d, 1H, J = 8.5 Hz, C_5–H) and 7.6–7.1 (m, 5H) (Found: C, 69.66; H, 4.71. $C_{22}H_{18}O_6$ requires: C, 69.84; H, 4.79%).

Oxidation of glabratephrinol (3). A soln of 3 (100 mg) in the minimum volume of acetone was titrated with chromic acid (1 ml) (from 3 g CrO_3, 30 ml H_2O and 3 ml H_2SO_4) over a period of 30 min. The mixture was diluted with water and extracted with CH_2Cl_2 to give 4 (68 mg), m.p. 239–241° (from acetone–n-hexane); λ_{max} 220, 249, 255 (sh) and 307 nm (log ϵ 4.34, 4.28, 4.28 and 4.30, respectively); ν_{max} 1800 (CO), 1755 (CO) and 1645 (CO) cm^{-1}; M^+, 376; NMR: δ 1.41 and 1.58 (each: s, 3H; *gem*-Me_2), 4.89 and 5.02 (each: d, 1H, J = 8.5 Hz; C_8–H), 6.63 (s, 1H, C_3–H), 7.02 (d, 1H, J = 8.5 Hz, C_6–H), 7.52 (m, 3H) and 7.74 (m, 2H) (B-ring H), and 8.20 (d, 1H, J = 8.5 Hz, C_5–H) (Found: C, 70.27; H, 4.20. $C_{22}H_{16}O_6$ requires: C, 70.21; H, 4.29%).

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