200. Verproside, a New Iridoid Glucoside from *Veronica officinalis* L. *(Scrophulariaceae)*[1])

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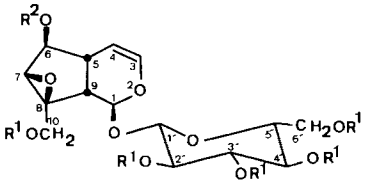
Summary

A new iridoid glucoside, verproside (**2**), has been isolated from *Veronica officinalis* L. and its structure has been established to be 6-*O*-protocatechuoylcatalpol.

Introduction. – During our investigations on iridoid glucosides from *Veronica officinalis* L., we isolated aucubin, catalpol (**1**), mussaenoside, ladroside [2] and three new catalpol esters, veronicoside (benzoylcatalpol) [3], minecoside (isoferuloylcatalpol) and verminoside (caffeoylcatalpol) [4]. This paper describes the isolation and structure determination of the fourth new catalpol ester, named verproside.



1 catalpol; $R^1 = R^2 = H$

2 verproside; $R^1 = H$, R^2 = protocatechuoyl (= 3,4-dihydroxybenzoyl)

3 verproside heptaacetate; $R^1 = Ac$, R^2 = diacetylprotocatechuoyl (= 3,4-diacetoxybenzoyl)

Results and discussion. – Verproside (**2**) is a white amorphous substance, $[\alpha]_D^{20} = -164.80°$ ($c = 0.86$, CH_3OH) with a molecular formula $C_{22}H_{26}O_{13}$. The IR. of **2** and its heptaacetate **3** shows the characteristic iridoid (1655 cm^{-1}) and ester (1715 cm^{-1}) bands, and in the UV. maxima appear at 216, 224, 263 and 295 nm.

In the ^{1}H-NMR. spectrum (100 MHz, CD_3OD) of verproside (**2**) the signals of three aromatic protons appear in the ratio 1:2 at 6.74–6.86 and 7.40–7.52 ppm corresponding to the protons of the protocatechuoyl moiety. The two doublets at 5.16 and 6.35 ppm are assignable to H–C(1) and H–C(3), and the two proton broad multiplet at 2.54–2.70 ppm to H–C(5) and H–C(9). The singlet at 3.74 ppm can be attributed to the proton at C(7). The signals of the 2 protons at C(10) appear as an *AB*-system at 3.84 and 4.18 ppm ($J = 13.0$ Hz).

[1]) Presented in part by *O. St.* and *F. Ü. A.-Y.* at the 27th Scientific Meeting of the 'Gesellschaft für Arzneipflanzenforschung', Budapest, Hungary, July 16–22, 1979; s. also [1].

[2]) Part of the thesis of *F. Ü. A.-Y.*, ETH Zürich, Nr. 6377, Zürich 1979.

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Verproside was acetylated with acetic anhydride/pyridine at room temperature. After purification by column chromatography recrystallization gave the hepta-acetate **3** as white clusters of needles, m.p. 116.8–117.4°, $[\alpha]_D^{20} = -93.5°$ ($c = 0.50$, $CHCl_3$).

The ^{1}H-NMR. of **3** exhibits the signals due to the five acetyl groups attached to the aliphatic part at 1.94–2.16 ppm, while the signals of the two acetyl groups of the protocatechuoyl moiety appear at 2.26–2.37 ppm. The aromatic region shows the signals of three protons at 7.24–8.06. The chemical shifts of the two diastereotopic protons at C(10) at 4.00 and 5.05 ppm with $J = 13.0$ Hz are comparable with other C(6)-acylated derivatives [3] [4].

The ^{1}H-NMR. spectrum of **3** suggested the position of esterification with protocatechuic acid to be at HO–C(6) of catalpol [3] [4]. The presence of the protocatechuoyloxy group at C(6) has also been confirmed by the ^{13}C-NMR. of **2** and the MS. of **3** (s. below).

The MS. of verproside heptaacetate (**3**) shows, besides the molecular ion (M^+) at *m/z* 792, the fragments resulting after the cleavage at the O–C(1′) bond; further fragments of acetylated glucose as well as of catalpol aglucone appear at *m/z* 445, 207, 135, and 107. The fragments at *m/z* 237, 221, 179, 137, 109, and 77 result from the acetylated protocatechuic acid. Thus, the MS. is an additional proof for the esterification at HO–C(6) of the iridoid skeleton.

Comparison of the ^{13}C-NMR. of verproside (**2**) with that of catalpol (**1**) verifies the position of esterification. Both spectra show identical shifts for the glucose C-atoms; therefore, the ester linkage in **2** is either at HO–C(6) or at HO–C(10). As the chemical shift of C(10) is about the same in **1** and **2**, the linkage to the protocatechuoyloxy group has to be at C(6), and the expected downfield shift (*ca.* 2 ppm) for the signal of the α-C-atom C(6) and the upfield shift (*ca.* 2 ppm) for the ones of the two β-C-atoms C(5) and C(7) of **2** are observed. Similar shifts were also observed for the other three catalpol esters with the acyloxy group at C(6) [3] [4][3]).

Finally, alkaline hydrolysis of **2** afforded catalpol (**1**) and protocatechuic acid identified by standard procedures. According to the above mentioned data, the structure of verproside (**2**) is established to be 6-*O*-protochatechuoylcatalpol.

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Table. *^{13}C-NMR. spectral data of* **1**–**3**

C-Atom	1	2	3	C-Atom	1	2	3
C(1)	95.33	95.07	94.35	C(1′)	99.74	99.55	96.65
C(3)	141.78	142.18	141.29	C(2′)	74.82	74.54	70.65
C(4)	104.03	102.91	101.94	C(3′)	78.54	78.04	72.52
C(5)	39.10	36.54	35.10	C(4′)	71.74	71.32	68.22
C(6)	79.58	81.26	80.40	C(5′)	77.70	77.30	72.22
C(7)	62.55	60.22	58.66	C(6′)	62.90	62.68	62.43
C(8)	66.23	66.75	62.66	C(1″)		121.83	127.91
C(9)	43.60	42.92	41.97	C(2″)		117.58	125.29
C(10)	61.60	61.08	61.12	C(3″)		145.81	142.17
				C(4″)		151.66	146.53
				C(5″)		115.97	123.75
				C(6″)		123.98	128.33
				*C*O		167.86	164.85–170.52
				*C*H$_3$CO			20.55

[3]) For a detailed account on the effect of acylation on ^{13}C-NMR. spectra of iridoid glycosides, see [5].

Experimental Part

General procedures. S. [3] [4].

Isolation and purification. The fraction 4 of the second counter-current distribution [3], which contained mainly minecoside, verminoside and verproside, was chromatographed on silicagel 60 (70–230 mesh, *Merck*) with CH_2Cl_2/MeOH/H_2O 80:20:2. On further chromatography (semi-preparative HPLC. using reversed phase C_{18} column and MeOH/H_2O 2:3) of the appropriate fractions pure *verproside* (**2**) was obtained as a white amorphous substance, $[\alpha]_D^{20} = -164.80°$ ($c = 0.86$, CH_3OH). – UV. (CH_3OH): 295 (3.87), 263 (4.09), 224 (4.07) and 216 (4.09). – IR. (KBr): 3400 (OH), ~1720 (C=O, ester), 1655 (C=C). – ^{1}H-NMR. (CD_3OD): 2.54–2.70 (*m*, 2 H, H–C(5), H–C(9)); 3.74 (*s*, 1 H, H–C(7)); 3.84, 4.18 (*A B*, $J = 13$, 2 H, 2 H–C(10)); 4.74–5.22 (H–C(1), H–C(4), and H–C(6), partly covered); 6.35 (*d*, $J = 6$, 1 H, H–C(3)); 6.74–6.86 (1 arom. H); 7.40–7.52 (2 arom. H).

Synthesis of verproside heptaacetate (**3**). Compound **2** was acetylated with acetic anhydride/pyridine for 1 h at room temp., and the product was recrystallized from abs. EtOH to give **3** as white clusters of needles, m.p. 116.8–117.4°, $[\alpha]_D^{20} = -93.5°$ ($c = 0.50$, $CHCl_3$). – UV. (EtOH): 205 (4.39) and 236 (4.15). – IR. (KBr): 1755 (C=O), 1655 (C=C). – ^{1}H-NMR. ($CDCl_3$): 1.94–2.16 (5 CH_3COOC (aliph.)); 2.26–2.37 (2 CH_3COOC (arom.)); 2.62–2.80 (*m*, 2 H, H–C(5), H–C(9)); 3.58–3.78 (*m*, 1 H, H–C(5′)); 3.72 (*s*, 1 H, H–C(7)); 4.00, 5.05 (*AB*, $J = 13$, 2 H, 2 H–C(10)); 4.80–5.24 (3 H, H–C(1), H–C(4), and H–C(6) partly covered by the signals of glucose protons); 6.31 (*d*, $J = 6$, 1 H, H–C(3)); 7.24–7.36 (1 arom. H); 7.86–8.06 (2 arom. H).– MS.: 43 (100.0), 45 (9.6), 55 (4.0), 60 (9.6), 63 (1.9), 73 (4.0), 77 (2.9), 81 (9.6), 85 (3.2), 91 (2.8), 97 (9.0), 103 (5.0), 107 (2.3), 109 (35.3), 115 (9.6), 119 (2.4), 127 (11.6), 131 (2.5), 135 (5.1), 137 (14.3), 145 (7.7), 149 (5.9), 154 (10.9), 157 (4.6), 164 (2.8), 169 (73.8), 179 (10.9), 187 (1.9), 196 (2.4), 207 (1.0), 211 (2.7), 221 (3.1), 229 (2.6), 237 (0.5), 271 (4.1), 289 (0.8), 331 (35.3), 445 (4.0), 481 (0.3), 492 (0.4), 4.96 (0.4), 547 (0.6), 554 (0.6), 792 (M^+ 0.6).

Hydrolysis of **2**. A solution of **2** in methanolic 0.1N NaOH was kept overnight and then neutralized with 0.1N HCl. After column chromatography over silicagel with CH_2Cl_2/MeOH/H_2O 4:1:0.1, protocatechuic acid and catalpol were identified by comparison with authentic samples on TLC.and analytical HPLC. [6].

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