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ISOLATION OF SECOXYLOGANIN FROM *LONICERA JAPONICA* AND ITS CONVERSION INTO SECOLOGANIN[1]

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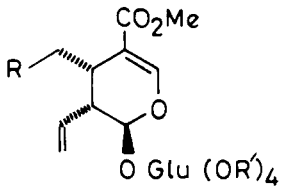
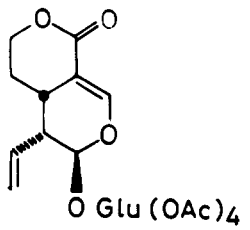
Secologanin [**1**] and secoxyloganin [**2**] are two secoiridoids that find extensive use in synthetic and biosynthetic studies of monoterpene indole alkaloids and related natural products (1). Although secologanin has been obtained in good yields from *Lonicera tartarica, Lonicera morrowii,* and *Symphoricarpus rivularis* (2), the presence of secoxyloganin has been detected only as a minor product in *Vinca rosea* (3), *Mentzelia lindleyi* (4), *Lonicera periclymenum* (5), and *Desfontainia spinosa* (6), and the compound used for synthetic studies has been obtained from secologanin by a three-step process (7). During our investigation on glycosides of *Lonicera japonica* Thunb. (Caprifoliaceae), we discovered that the fresh young shoots of this plant are a rich source of secoxyloganin. This paper details a simple procedure for the isolation of this compound in pure form and in good yield. Conversions of secoxyloganin tetraacetate [**3**] into secologanin tetraacetate [**4**] and sweroside tetraacetate [**5**] are also described.

The highlight of the present isolation procedure is the use of K_2CO_3-treated Si gel in the purification of this compound. Extensive damage took place when ordinary column grade Si gel was used for cc. Although the use of H_2O-deactivated Si gel prevented this damage, the pure compound could be obtained only when K_2CO_3-treated Si gel was used. The present isolation procedure has also the merit of avoiding the more sophisticated purification procedures used in the earlier isolation of this compound, hplc (5) and dccc (6). The pure compound, isolated in 0.47% yield, was fully characterized by the spectral data of the methyl ester **7**, the methyl ester tetraacetate **9**, and the permethylated derivative **8**.



1 R=CHO, R′=H
2 R=COOH, R′=H
3 R=COOH, R′=Ac
4 R=CHO, R′=Ac
6 R=CH_2OH, R′=Ac
7 R=COOMe, R′=H
8 R=COOMe, R′=Me
9 R=COOMe, R′=Ac



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In the second phase of our work, secoxyloganin tetraacetate [**3**] obtained from secoxyloganin (Ac_2O/C_5H_5N) was reduced to seco-alcohol [**6**] by the procedure of Ishizumi *et al.* (8). A slight modification of the reduction procedure (see Experimental) furnished sweroside tetraacetate [**5**]. Oxidation of **6** with CrO_3/C_5H_5N gave secologanin tetraacetate [**4**]. Secologanin has earlier been prepared from menthiafolin (9) and sweroside (10). The studies reported here provide yet another source of this valuable secoiridoid.

[1]C.D.R.I. Communication No. 4088.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on Toshniwal electrically heated apparatus and are uncorrected. The uv spectra were recorded on a Hitachi 320 automatic recording spectrophotometer while ir spectra were taken on a Perkin-Elmer Infracord-157 instrument. The ^{1}H-nmr spectra and ^{13}C-nmr spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer and CFT-20 (20 MHz) spectrometer with TMS as an internal standard. The eims and fdms spectra were taken on a JEOL JMS-D300 and JEOL JMS-OSIG2, respectively. Si gel (60–120 mesh) (Sisco Chemicals Lab) was equilibrated with H_2O (20 ml/100 g) for 1–2 h and stored in sealed bottles before use. When a basic Si gel is indicated, 60–120 mesh Si gel (Sisco Chemicals Lab) was equilibrated with a 25% aqueous solution of K_2CO_3 (20 ml/100 g) for 1–2 h and stored in sealed bottles before use. The solvent systems used were (A) EtOAc-MeOH (95:5) saturated with H_2O+HOAc (1 ml/100 ml) and (B) $CHCl_3$-MeOH-H_2O (65:35:20, lower phase).

PLANT MATERIAL.—The young shoots of *L. japonica* were collected from a house garden in Lucknow, India, in October 1984. A voucher specimen is deposited in the Medicinal Plant Herbarium of the Central Drug Research Institute, Lucknow (voucher no. 6012).

ISOLATION OF SECOXYLOGANIN [**2**].—The fresh plant material (680 g) was cut into small pieces and extracted with EtOH at room temperature. The EtOH extract was concentrated at 40–50° under vacuum, and the concentrate (62.0 g) was dissolved in H_2O (750 ml) and extracted with $CHCl_3$ (2.5 liters) and *n*-BuOH (3.6 liters). The *n*-BuOH extract was concentrated (18.58 g), dissolved in a minimum quantity of EtOH, and precipitated with Et_2O (1.8 liters). The supernatant was concentrated to give 5.83 g of secoxyloganin-rich material. The aqueous extract, which showed a major spot on tlc corresponding to secoxyloganin, was concentrated and then extracted with Et_2O-MeOH-HOAc (150:80:1) (3×750 ml). The extract was concentrated in vacuum to give 8.57 g of secoxyloganin-rich material. The two secoxyloganin-containing fractions were combined (14.40 g) and purified by cc, first on deactivated SiO_2 (eluent, solvent A) and then twice on deactivated basic SiO_2 gel (eluent, solvent B). The material so obtained was dissolved in H_2O and treated with ir 120 (H^+ form) to remove the potassium salts and concentrated to give 3.20 g of tlc pure secoxyloganin. The compound had ir, uv, and fdms data similar to those previously reported (5).

SECOXYLOGANIN METHYL ESTER [**7**].—A solution of **2** (50 mg) in MeOH (10 ml) was treated with an ethereal solution of CH_2N_2 (room temperature, 2h). The crude product (55 mg) was crystallized from $CHCl_3$, mp 132–134°. ^{1}H-nmr data were similar to those previously reported (5).

SECOXYLOGANIN TETRAACETATE [**3**].—A solution of **2** (25 mg), Ac_2O (0.5 ml), and C_5H_5N (1 ml) was left overnight at 15°. Usual aqueous work-up gave **3** as a white powder (30 mg), which exhibited ^{1}H-nmr values similar to those reported earlier (7).

TETRAMETHYL SECOXYLOGANIN METHYL ESTER [**8**].—Compound **2** (50 mg) was permethylated by the method of Hakomari (11), and the crude product was purified by cc to furnish 52 mg tetramethylsecoxyloganin methyl ester as a viscous mass, ^{1}H nmr (CCl_4) δ 7.29 (1H, d, J=2 Hz, H-3), 3.60 (s, OCH_3), 3.56 (s, OCH_3), 3.50 (s, OCH_3), 3.40 (s, OCH_3), 3.34 (s, OCH_3), 3.30 (s, OCH_3); eims *m/z* (rel. int.) $[M]^+$ 474 (0.18%), 456, 443, 410, 390, 365, 341, 330, 299, 279, $[M-$tetramethylglucose$-17]^+$ 256 (0.15%), $[$tetramethylglucose$-17]^+$ 219 (10%), 187, 165, 155, 149, 127, 111, and 101.

METHYL ESTER TETRAACETATE OF SECOXYLOGANIN [**9**].—A solution of **7** (50 mg), Ac_2O (1 ml), and C_5H_5N (2 ml) was left overnight at 15°. The crude product (62 mg), obtained after usual work-up, was crystallized from EtOH to furnish white needles, mp 140–141° [lit. (3) mp 140–145°]; other spectral data (uv, ir, ^{1}H nmr) similar to those previously reported (7).

SECO-ALCOHOL **6**.—A solution of $ClCOOC_2H_5$ (73 mg) in THF (1 ml) was added at −5° to a solution of **3** (100 mg) and Et_3N (47 mg) in THF (2 ml) in one batch, and the whole was stirred for 30 min at the same temperature. The white precipitate ($Et_3N^+HCl^-$) was filtered off and washed with THF (0.5 ml), and the combined filtrate and the washings were added over 15 min to a solution of $NaBH_4$ (71 mg) in MeOH (5 ml) at −5°. After the addition was complete, the reaction mixture was stirred for 30 min at the same temperature. It was then acidified with 10% H_3PO_4 and extracted with Et_2O (3×50 ml). The combined organic extracts were washed with 10% aqueous $NaHCO_3$ solution (10 ml) and H_2O (2×10 ml), dried (anhydrous Na_2SO_4), and concentrated to yield a white solid (76 mg) that was crystallized with hexane to give pure **6**. The product had mp and ^{1}H-nmr data identical to those previously reported (12).

SWEROSIDE TETRAACETATE [**5**].—A solution of $ClCOOC_2H_5$ (26 mg) in THF (2 ml) was added at −5° to a solution of **3** (80 mg) and Et_3N (30 mg) in THF (2 ml) in one batch, and the whole was stirred for 30 min at the same temperature. The white precipitate ($Et_3N^+HCl^-$) was filtered off and washed with THF (2 ml). The

combined filtrate and the washings were added dropwise to a solution of $NaBH_4$ (25 mg) in H_2O (2 ml) at 10–20° and stirred for 2 h at the same temperature. It was then acidified with 5% HCl (1 ml) and extracted with Et_2O (2×50 ml). The combined organic extracts were washed with 5% aqueous Na_2CO_3 (15 ml) and H_2O (5 ml), dried (anhydrous Na_2SO_4), and concentrated to yield a white solid (43 mg) that was crystallized from Et_2O, mp 164–165°; ^{1}H-nmr data similar to those previously reported (13).

SECOLOGANIN TETRAACETATE [**4**].—To a stirred and cooled (0°) solution of CrO_3 (66 mg), dry C_5H_5N (0.2 ml), and dry CH_2Cl_2 (1 ml) was added a solution of **6** (20 mg) in CH_2Cl_2 (1 ml) in one batch, and the whole was stirred for 3 h at 0 to 5°, when it was poured into a separatory funnel containing ice-cold aqueous 10% NaOH (5 ml) and extracted with CH_2Cl_2 (3×25 ml). The combined organic extracts were washed with H_2O (2×5 ml), 5% HCl (5 ml), and H_2O (2×5 ml), dried (anhydrous Na_2SO_4), and concentrated to furnish secologanin tetraacetate (9 mg) as a viscous mass; ^{1}H-nmr data similar to those previously reported (9).

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