# Prenylated Dibenzoylmethane Derivatives from the Root of *Glycyrrhiza inflata* (Xinjiang Licorice)

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**Three dibenzoylmethanes were isolated from licorice of Xinjiang origin (botanically assigned to *Glycyrrhiza inflata*), and their structures were elucidated spectroscopically as 1-(2,4-dihydroxy-5-prenylphenyl)-3-(4-hydroxyphenyl)-1,3-propanedione (I), 1-(2,4-dihydroxy-5-prenylphenyl)-3-(4-hydroxy-3-prenylphenyl)-1,3-propanedione (II) and 1-(2,4-dihydroxy-5-prenylphenyl)-3-(2,2-dimethyl-2*H*-1-benzopyran-6-yl)-1,3-propanedione (III). The latter two constituents were new natural products, and were named glycyrdiones A and B, respectively.**

**Keywords** dibenzoylmethane; glycyrdione A; glycyrdione B; licorice; *Glycyrrhiza inflata*; Leguminosae

## Introduction

The dried roots of several *Glycyrrhiza species*[1] which contain glycyrrhizin, the main sweetening principle, are used medicinally as the crude drug licorice throughout the world. Since it was found that the flavonoid-rich fractions of licorice extract have an antigastric ulcer effect,[2] the phenolic constituents, though relatively minor, have drawn attention. In recent years there have been a growing number of reports on the biological activities, *i.e.*, antimicrobial,[3] enzyme inhibition[4] and anti-viral activities,[5] of licorice constituents, in which phenolics are designated as the active principles. These findings verify that the phenolics in licorice also constitute the indispensable part of the pharmacological efficacy of licorice. We have been engaged for years in a research program to identify the antimicrobial and antioxidant constituents in commercially available licorice of several origins.[3d,f] In a previous study on Xinjiang licorice (新疆甘草, shinkyo kanzo in Japanese; commercial name given to that collected in Xinjiang Province, China and botanically assigned *Glycyrrhiza inflata*),[6,7] bioassay-directed fractionation resulted in identification of the known chalcones licochalcones A and B as active principles.[3f] A subsequent re-examination of other chromatographic fractions revealed the presence of a number of unidentified minor constituents, which encouraged us to restart a chemical investigation of Xinjiang licorice. We report herein properties and structural assignment of three dibenzoylmethanes.

## Results

Chemical investigation of the root of commercially available Xinjiang licorice led to the isolation of three dibenzoylmethanes. The chloroform extract was chromatographed on a silica gel column using benzene with an increasing percentage of acetone for elution. Fractions were concentrated and monitored by thin-layer chromatography (TLC) on silica gel. Fractions showing similar TLC patterns were combined and further worked up by a combination of silica gel and Sephadex LH-20 column chromatography to yield compounds **1**—**3**.

Compounds **1**—**3** were isolated in pure crystal forms as yellow to pale yellow needles. Their molecular formulae were deduced to be $C_{20}H_{20}O_5$ for **1**, $C_{25}H_{28}O_5$ for **2** and $C_{25}H_{26}O_5$ for **3**, from the elementary analysis and mass spectrometry (MS), and were further confirmed by high-resolution mass spectrometry (HR-MS) (see Experimental). These compounds showed common characteristic chemical and physicochemical properties: a positive color reaction with Mg–HCl and $FeCl_3$, and emission of blue fluorescence on TLC after spraying with $H_2SO_4$ followed by heating when illuminated under ultraviolet (UV) rays. Their $\beta$-hydroxy chalcone nature was evident from both infrared (IR) and UV spectra, with and without a shift reagent (NaOMe).[8] These features closely resemble those of licodione, a dibenzoylmethane derivative isolated from *G. echinata callus*,[8] suggesting the presence of the same chromophoric unit in the molecules. The $^1$H-nuclear magnetic resonance ($^1$H-NMR) spectra of compounds **1**—**3** showed the presence of two characteristic isolated singlets resonating around $\delta$ 4.4—4.6 and $\delta$ 6.6—7.0, indicating that these compounds exist in an equilibrium mixture of diketonic and keto-enolic forms as observed with licodione.[8] (Fig. 1) The former upfield signals with integrations at 0.60—0.76H were attributed to methylene protons of the diketonic form, whereas the latter downfield signals with integrations at 0.62—0.70H were derived from vinyl methine protons of the keto-enolic form. The ratio of equilibrium mixtures was calculated at *ca.* 2 : 1 for **1**—**3** in excess of the keto-enolic form based upon the integration

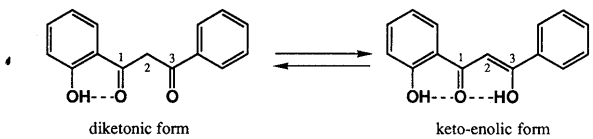


Fig. 1. Two Tautomeric Forms of Dibenzoylmethane

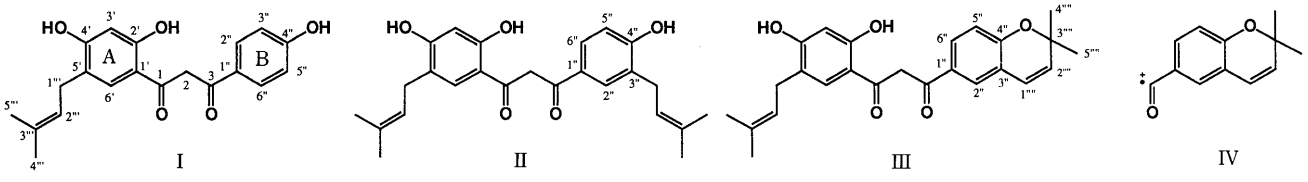

Table I. $^1$H-NMR Data for Keto-Enolic Tautomer of Dibenzoylmethane Derivatives Isolated from Xinjiang Licorice

| | I | II | III |
|---|---|---|---|
| 2 | 6.97 (0.65H, s) | 6.91 (0.62H, s) | 6.59 (0.70H, s) |
| 3′ | 6.40 (0.65H, s) | 6.39 (0.62H, s) | 6.39 (0.70H, s) |
| 6′ | 7.84 (0.65H, s) | 7.76 (0.62H, s) | 7.47 (0.70H, s) |
| 2″ | 7.95 (1.30H, d, $J$=9.0 Hz) | 7.77—7.84 | 7.57 (0.70H, d, $J$=2.3 Hz) |
| 3″ | 6.98 (1.30H,d, $J$=9.0 Hz) | — | — |
| 5″ | 6.98 (1.30H, d, $J$=9.0 Hz) | 6.97 (0.62H, d, $J$=8.5 Hz) | 6.84 (0.70H, d, $J$=8.6 Hz) |
| 6″ | 7.95 (1.30H, d, $J$=9.0 Hz) | 7.77—7.84 | 7.70 (0.70H, dd, $J$=8.6, 2.3 Hz) |
| 3-OH | 15.79 (0.65H, s) | 15.78 (0.62H, s) | 15.67 (0.70H, s) |
| 2′-OH | 12.28 (0.65H, br) | 12.28 (0.62H, br) | 12.39 (0.70H, s) |
| 4′-OH | *ca.* 9.4 | *ca.* 9.4 | 6.05 |
| 4″-OH | *ca.* 9.4 | *ca.* 9.4 | — |
| Prenyl | | | |
| 1‴ | 3.29 (1.30H, d, $J$=7.2 Hz) | 3.39 (1.24H, d, $J$=7.4 Hz) 3.28 (1.24H, d, $J$=7.2 Hz) | 3.34 (1.40H, d, $J$=7.2 Hz) |
| 2‴ | 5.33 (0.65H, m) | 5.35 (1.24H, m) | 5.31 (0.70H, m) |
| 4‴, 5‴ | 1.71, 1.73 (3.9H, s) | 1.61—1.76 | 1.6—1.8 |
| Chromene | | | |
| 1⁗ | — | — | 6.39 (0.70H, d, $J$=9.7 Hz) |
| 2⁗ | — | — | 5.69 (0.70H, d, $J$=9.7 Hz) |
| 4⁗, 5⁗ | — | — | 1.47 (4.2H, s) |

Spectra were measured in acetone-$d_6$ (I and II) or $CDCl_3$ (III) with TMS as internal standard.

Table II. $^1$H-NMR Data for Diketonic Tautomer of Dibenzoylmethane Derivatives Isolated from Xinjiang Licorice

| | I | II | III |
|---|---|---|---|
| 2 | 4.61 (0.70H, s) | 4.57 (0.76H, s) | 4.46 (0.60H, s) |
| 3′ | 6.37 (0.35H, s) | 6.37 (0.38H, s) | 6.35 (0.30H, s) |
| 6′ | 7.60 (0.35H, s) | 7.59 (0.38H, s) | 7.50 (0.30H, s) |
| 2″ | 7.97 (0.70H, d, $J$=9.1 Hz) | 7.77—7.84 | 7.68 (0.30H, d, $J$=2.3 Hz) |
| 3″ | 6.96 (0.70H, d, $J$=9.1 Hz) | — | — |
| 5″ | 6.96 (0.70H, d, $J$=9.1 Hz) | 6.96 (0.38H, d, $J$=8.5 Hz) | 6.81 (0.30H, d, $J$=8.6 Hz) |
| 6″ | 7.97 (0.70H, d, $J$=9.1 Hz) | 7.77—7.84 | 7.81 (0.30H, dd, $J$=8.6, 2.3 Hz) |
| 3-OH | — | — | — |
| 2′-OH | 12.37 (0.35H, s) | 12.37 (0.38H, s) | 12.23 (0.30H, s) |
| 4′-OH | *ca.* 9.4 | *ca.* 9.4 | 6.34 |
| 4″-OH | *ca.* 9.4 | *ca.* 9.4 | — |
| Prenyl | | | |
| 1‴ | 3.20 (0.70H, d, $J$=7.2 Hz) | 3.36 (0.76H, d, $J$=7.2 Hz) 3.20 (0.76H, d, $J$=7.4 Hz) | 3.28 (0.60H, d, $J$=7.2 Hz) |
| 2‴ | 5.25 (0.35H, m) | 5.35 (0.76 H, m) | 5.27 (0.30H, m) |
| 4‴, 5‴ | 1.61 (2.1H, s) | 1.61—1.76 | 1.6—1.8 |
| Chromene | | | |
| 1⁗ | — | — | 6.38 (0.30H, d, $J$=10.0 Hz) |
| 2⁗ | — | — | 5.68 (0.30H, d, $J$=10.0 Hz) |
| 4⁗, 5⁗ | — | — | 1.46 (1.8H, s) |

Spectra were measured in acetone-$d_6$ (I and II) or $CDCl_3$ (III) with TMS as internal standard.

Table III. $^{13}$C-NMR Data for Dibenzoylmethane Derivatives Isolated from Xinjiang Licorice

| | I | | II | | III | |
|---|---|---|---|---|---|---|
| | Enolic | Ketonic | Enolic | Ketonic | Enolic | Ketonic |
| 1 | 177.4 | 193.1 | 178.2 | 193.6 | 176.2 | 192.1 |
| 2 | 91.2 | 49.9 | 91.6 | 50.5 | 90.6 | 49.9 |
| 3 | 195.0 | 200.4 | 195.3 | 200.9 | 193.8 | 198.0 |
| 1′ | 112.6 | 114.1 | 113.0 | 114.4 | 112.8 | 114.2 |
| 2′ | 163.2 | 163.8 | 163.6 | 164.2 | 161.1 | 162.2 |
| 3′ | 103.8 | 103.2 | 104.3 | 103.6 | 104.3 | 103.8 |
| 4′ | 164.3 | 164.7 | 164.7 | 165.2 | 163.5 | 164.1 |
| 5′ | 121.8 | 121.5 | 122.2 | 121.9 | 118.9 | 119.4 |
| 6′ | 132.1 | 133.3 | 131.5 | 133.7 | 131.3 | 132.4 |
| 1″ | 125.8[a] | | 126.3[a] | | 125.0[a] | |
| 2″ | 129.8 | 131.3 | 127.8[a] | | 126.2 | 129.4 |
| 3″ | 116.5 | 116.2 | 130.0 | 129.7 | 121.1 | 120.9 |
| 4″ | 162.4 | 163.2 | 160.5 | 161.4 | 156.8 | 157.9 |
| 5″ | 116.5 | 116.2 | 116.5 | 116.1 | 116.6 | 116.4 |
| 6″ | 129.8 | 131.3 | 130.0 | 131.9 | 130.9 | 131.3 |
| Prenyl | | | | | | |
| 1‴ | 28.8 | 28.2 | 29.2 | 28.6 | 29.2 | 29.0 |
| | | | 29.6 | 29.3 | | |
| 2‴ | 124.0 | 123.0 | 123.6 | 123.3 | Nf | Nf |
| | | | 124.3 | 123.4 | | |
| 3‴ | 132.3 | 132.3 | 132.9 | 132.9 | 135.2 | 135.5 |
| | | | 133.7 | 133.5 | | |
| 4‴ | 25.9 | 25.7 | 26.3 | 26.2 | 25.8 | 25.7 |
| | | | 26.4 | 26.3 | | |
| 5‴ | 17.9 | 17.7 | 18.4 | 18.2 | 18.0 | 17.8 |
| Chromene | | | | | | |
| 1⁗ | | | | | 121.8 | 121.2 |
| 2⁗ | | | | | 128.0 | 127.5 |
| 3⁗ | | | | | 77.5 | 77.9 |
| 4⁗, 5⁗ | | | | | 28.3 | 28.5 |

Spectra were measured in acetone-$d_6$ (I and II) or $CDCl_3$ (III) with TMS as internal standard. Nf means that corresponding signals were not explicitly found. *a*) Signals were not observed in composite forms of two tautomers.

of the above signals, which was in good agreement with that of licodione.[8] In the $^{13}$C-NMR spectra, methylene carbons of the diketonic form appeared as triplets around $\delta$ 50, and vinyl carbons of the keto-enolic form were observed as doublets around $\delta$ 90.[9] Other resonances in the $^1$H- and $^{13}$C-NMR spectra of compounds **1**—**3** also appeared at the same ratio as pairs due to the existence of the two tautomeric structures. Results of the assignments are summarized in Tables I, II ($^1$H-NMR) and III ($^{13}$C-NMR). The presence of a $C_5$ unit was also indicated by the $^1$H- and $^{13}$C-NMR spectra; one prenyl for compound **1**, two prenyls for compound **2** and one prenyl and chromene for compound **3**. The position of $C_5$ attachments on the aromatic ring was easily deduced by comparing signal patterns and chemical shifts of aromatic protons with those of non-prenylated dibenzoylmethane licodione.[8] The structures for compounds **1**—**3** were finally elucidated as (I), (II) and (III) respectively. The structure (III) for compound **3** was further substantiated by the presence of the prominent (base peak) ion peak at 187 atomic mass units in the MS, which is attributed to the B ring benzoyl ion (IV) arising from fragmentation between 2-C and 3-C of a dibenzoylmethane.[8] Two of three dibenzoylmethanes, compounds **2** and **3**, isolated from *G. inflata*, are new natural products, and named glycyrdiones A and B, respectively,[10] while compound **1** was found to be identical to the one previously isolated as

a stress compound from *G. echinata callus*.[11]

## Discussion

Dibenzoylmethanes occur very rarely in nature, and have been isolated so far from the following genera; *Baccharis* (Compositae),[12] *Malus* (Rosaceae),[13] *Populus* (Salicaceae),[13] *Unona* (Anonaceae),[13] *Tinospora* (Menispermaceae),[14] *Dahlstedtia*,[15] *Galega*,[13] *Glycyrrhiza*,[8,11,13] *Milletia*,[13,16] *Pongamia*[13] and *Tephrosia*[17] (Leguminosae). As referred to in the introduction, plants belonging to the genus *Glycyrrhiza*, especially those of medicinal value, have long been the subject of extensive chemical investigation. Dibenzoylmethane occurs in only two species of the genus *Glycyrrhiza*, *G. echinata* and *G. inflata*. Both species are particularly noteworthy as abundant sources of such characteristic chalcones as licochalcones A, B and echinatin, which have an unusual substitution pattern of oxygen functional groups as compared to normal chalcones. A name "retrochalcone" is given to those chalcones presumed to have reversed A and B rings in terms of their biogenetic origins. Furuya *et al.* proved that the A ring of retrochalcone is derived from a phenylpropanoid precursor while its B ring is of the acetate-malonate origin in the tracer experiments using *G. echinata callus*.[18a,b] From this experimental evidence they designated licodione, a simple dibenzoylmethane which co-occurs with echinatin in *G. echinata callus*, as the biogenetic precursor of retrochalcone, assuming that it arises from either the direct oxidation of a chalcone isoliquiritigenin or 2,3-oxidation of 4′,7-dihydroxyflavone.[18c] More recently Grisebach *et al.* reported the enzymatic conversion of flavanone to flavone with a cell-free system prepared from parsley (*Petroselinum hortense*) cell cultures, and postulated the scheme for flavone biosynthesis as 2-hydroxylation of flavanone followed by its subsequent dehydration.[19] It is apparent that 2-hydroxyflavanone (a cyclic hemiketal form of dibenzoylmethane) is one of possible tautomeric forms of dibenzoylmethane, though its occurrence has not been confirmed in the equilibrium of licodione and its analogs.[8a,9] From this point of view, the *in vivo* formation of dibenzoylmethane will be best postulated as follows: a flavanone, the ultimate precursor, undergoes 2-hydroxylation followed by cleavage of the hemiketal ring to afford dibenzoylmethane. Several 2-hydroxyflavanones have been identified from natural sources in an isomerized form of co-occurring dibenzoylmethanes.[13] Thus, it is quite likely that 2-hydroxyflavanone serves as a common key intermediate in the biosynthesis of both flavone and dibenzoylmethane.

### Experimental

All melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Spectral data were obtained using the following apparatus: $^1$H- and $^{13}$C-NMR spectra with JEOL JNM GSX-400 ($^1$H, 400 MHz; $^{13}$C, 100 MHz), spectrometer with tetramethylsilane (TMS) as an internal standard; MS with a JEOL JMS-D300 mass spectrometer; IR spectra with a JASCO DS701G IR spectrometer; UV spectra with a Hitachi 340 UV spectrometer. Column chromatography was carried out with the following materials: Wakogel C-200 or Merck Kieselgel 60 (eluted with benzene–acetone, chloroform–acetone or hexane–ethyl acetate), Sephadex LH-20 (Pharmacia, column size: 3.6 × 30 cm; eluted with MeOH or MeOH–$CHCl_3$ = 2 : 1) and RP-8 reversed-phase silica gel (Merck, column size: 3.2 × 33 cm; eluted with MeOH–$H_2O$). TLC was conducted on a 0.25 mm pre-coated silica gel plate ($60GF_{254}$, Merck), and spots were detected by inspection under short (254 nm) or long (360 nm) wavelength UV lights, or by the colors developed with 10% $H_2SO_4$ spraying followed by heating on a hot plate.

**Plant Material** Licorice roots of Xinjiang origin (commercial name: shinkyo kanzo in Japanese; Xinjiang Gancao in Chinese) were obtained from Maruzen Kasei Co., Ltd., Onomichi, Japan.

**Extraction and Isolation** The crushed Xinjiang licorice roots (3 kg) were extracted with $CHCl_3$ at room temperature, and the extract was evaporated to dryness under reduced pressure to yield a semisolid residue (110 g). A portion of the residue (75 g) was dissolved in acetone and adsorbed on silica gel (75 g). The adsorbed material was transfered to a silica gel column (750 g; column size: 7 × 40 cm) packed in benzene. The column was eluted with a gradient solvent system of benzene–acetone (B–A), increasing the amount of acetone stepwise (98 : 2—84 : 16), to give a number of fractions, which were then combined into 13 fractions on the basis of their TLC patterns: (i) with 100% benzene, fr. I (1.4 g); (ii) with 98 : 2 B–A, fr. II (0.4 g); (iii) with 96 : 4 B–A, fr. III (3.3 g); (iv) with 94 : 6 B–A, fr. IV (3.5 g); (v) with 94 : 6 B–A, fr. V (9.9 g); (vi) with 94 : 6 B–A, fr. VI (1.7 g); (vii) with 92 : 8 B–A, fr. VII (16.6 g); (viii) with 90 : 10 B–A, fr. VIII (2.5 g); (ix) with 90 : 10 B–A, fr. IX (3.7 g); (x) with 88 : 12 B–A, fr. X (2.4 g); (xi) with 88 : 12 B–A, fr. XI (4.9 g); (xii) with 86 : 14 B–A, fr. XII (3.2 g); (xiii) with 84 : 16 B–A, fr. XIII (1.6 g). Fractions of 250 ml each were collected. Fr. III was chromatographed on silica gel (160 g; column size: 3.2 × 40 cm) on elution with B–A (98 : 2—92 : 8) to give 30 fractions. Fractions 13 and 14 (2.4 g) were successively chromatographed over Sephadex LH-20 (MeOH : $CHCl_3$ = 1 : 1) and silica gel (80 g; column size: 3.2 × 20 cm) to afford glycyrdione B (20 mg). Fr. V was chromatographed on silica gel (250 g; column size: 4.2 × 33 cm) and separated by elution with B–A (98 : 2—80 : 20) into 36 fractions. Combined fractions 15—17 (5.5 g) were rechromatographed on a column of silica gel (250 g; column size: 4.2 × 33 cm) on elution with hexane–ethyl acetate (19 : 1—1 : 1). Fractions 13—16 were combined and evaporated to dryness. To the residue was added a small amount of acetone, and the insoluble materials were removed by filtration. The filtrate was evaporated and recrystallized from benzene to afford glycyrdione A (220 mg). Fr. VI was subjected to silica gel column chromatography (210 g; column size: 4 × 40 cm) on elution with hexane–ethyl acetate (3 : 1). Fractions of 50 ml each were collected. Fractions 21—23 yielded 5′-prenyl-licodione (103 mg).

**5′-Prenyl-licodione (I)** Yellow needles from benzene, mp 138 °C. lit.[11] 130—135 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3360 (OH), 1610 (C=O), 1576, 1509, 1408, 1245, 1171. UV $\lambda_{max}^{MeOH}$ nm (log ε): 278sh (4.04), 288 (4.09), 340sh (4.03), 385 (4.36); $\lambda_{max}^{MeOH+MeONa}$ nm (log ε): 243 (3.91), 352 (4.55), 413 (3.89). $^1$H-NMR (acetone-$d_6$) δ: see Tables I and II. $^{13}$C-NMR (acetone-$d_6$) δ: see Table III. Electron impact (EI)-MS *m/z* (rel. int., %): 340 ($M^+$, 89), 205 (81), 121 (100). HR-MS Calcd for $C_{20}H_{20}O_5$: 340.1311. Found: 340.1365. *Anal.* Calcd for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found: C, 70.83; H, 5.91.

**Glycyrdione A (II)** Yellow needles from benzene, mp. 67 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3360, 1666, 1632, 1594, 1510, 1352, 1120. UV $\lambda_{max}^{MeOH}$ nm (log ε): 278 (4.02), 289 (4.08), 345sh (4.03), 386 (4.35); $\lambda_{max}^{MeOH+MeONa}$ nm (log ε): 250 (4.06), 358 (4.56), 410 (4.02). $^1$H-NMR (acetone-$d_6$) δ: see Tables I and II. $^{13}$C-NMR (acetone-$d_6$) δ: see Table III. EI-MS *m/z*: 408 ($M^+$, 11), 205 (17), 189 (100), 149 (12). HR-MS: Calcd for $C_{25}H_{28}O_5$: 408.1937. Found: 408.1990. *Anal.* Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.77; H, 6.89.

**Glycyrdione B (III)** Yellow needles from benzene, mp 132 °C. UV $\lambda_{max}^{MeOH}$ nm (log ε): 257 (4.22), 288 (4.05), 388 (4.42); $\lambda_{max}^{MeOH+MeONa}$ nm (log ε): 248 (4.24), 400 (4.54). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3360, 1613, 1580, 1488, 1407, 1278, 1253, 1126. $^1$H-NMR ($CDCl_3$) δ: see Tables I and II. $^{13}$C-NMR ($CDCl_3$) δ: see Table III. EI-MS *m/z* (rel. int., %): 406 ($M^+$, 14), 391 ($M^+ - 15$, 21), 373 (12), 213 (10), 187 (100). HR-MS: Calcd for $C_{25}H_{26}O_5$: 406.1779. Found: 406.1738. *Anal.* Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.45. Found: C, 74.09; H, 6.42.

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### References and Notes

1) The roots of *G. uralensis*, *G. glabra* var. *glandulifera* and *G. inflata* are currently of commercial value as either medicinals or sources of glycyrrhizin in Japan. What are called seihoku kanzo (xibei gancao in Chinese; 西北甘草) and tohoku kanzo (Dongbei gancao in Chinese; 東北甘草) in the crude drug market consist mostly of the

roots of *G. uralensis*, and have been used widely in traditional Chinese medicine (Kampo). The roots of *G. glabra* var. *glandulifera* and *G. inflata* are used mainly for the extraction of glycyrrhizin.
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