

# Glycyrrhetic Acid Derivatives with Modified Ring A

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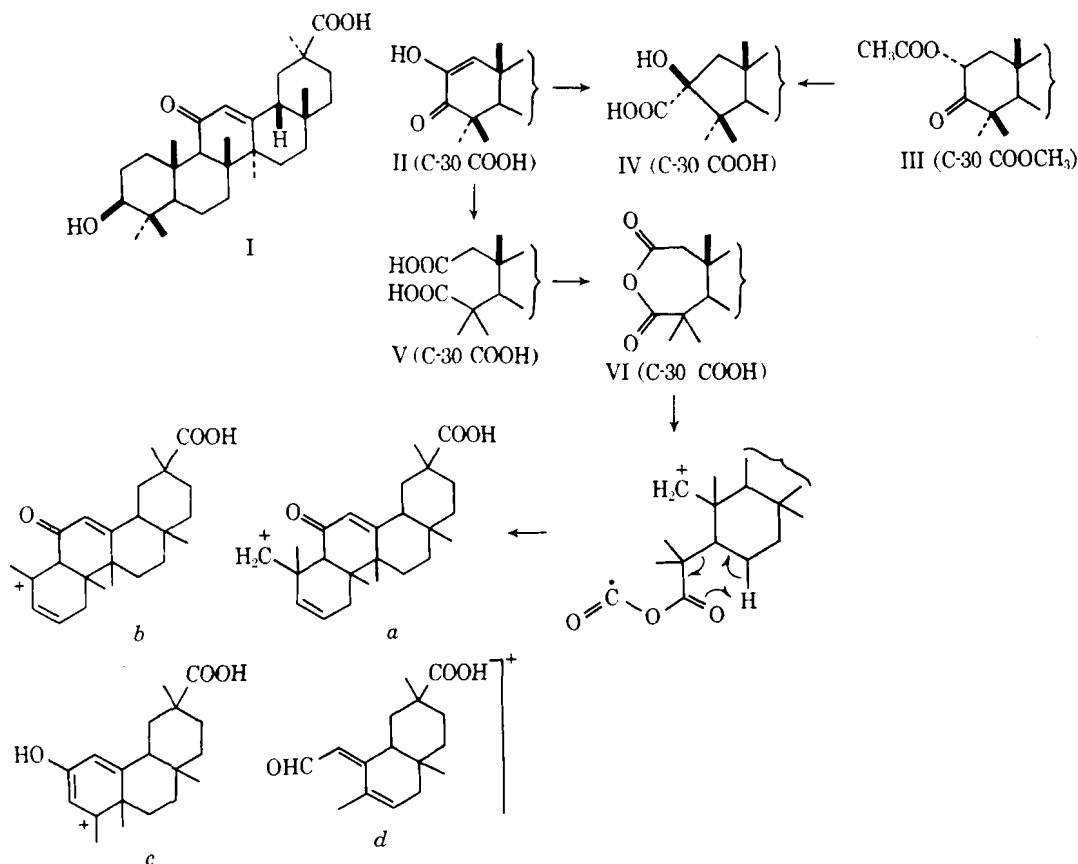
**Abstract** □ Ring A in glycyrrhetic acid (a therapeutically useful triterpenoid) was modified by contraction to an A-norhydroxy-acid derivative and by cleavage to a *seco*-A-2,3-dicarboxylic acid variant.

**Keyphrases** □ Glycyrrhetic acid derivatives—modification of ring A □ Triterpenoid aglycones—modification of ring A in glycyrrhetic acid

Glycyrrhetic acid (I), the principal triterpenoid aglycone obtained by acid hydrolysis of licorice (*Glycyrrhiza glabra* L.) root saponins, is perhaps the only triterpenoid with an established therapeutic utility (as an anti-inflammatory agent). Of the numerous studies made to modify this compound's structure, with the object of modifying its activity, very few have been concerned with ring A of the pentacyclic system. During studies in this area, the dicarboxylic and tricarboxylic acids were obtained by ring A contraction and cleavage, respectively, and are described (Scheme I). The first resulted by benzylic acid rearrangement of the diosphenol system in 2-hydroxy-18 $\beta$ -oleana-1,12-dien-3,11-dion-30-oic acid (II) (1) through reaction with boiling alcoholic potassium hydroxide and by a similar treatment of methyl 2 $\alpha$ -acetoxy-18 $\beta$ -olean-12-ene-3,11-dion-30-oate (III) (2). The produced A-norhydroxy-

acid is tentatively assigned Structure IV, in which the indicated stereochemistry of the ring A oxygen functions follows from the mechanism of the rearrangement where attack by hydroxyl ion at either C-2 or C-3 of the diketone form of II leads to a  $\beta$ -orientation of the resulting hydroxyl group (3).

Oxidative cleavage of ring A between C-2 and C-3 in glycyrrhetic acid, found not to be readily manageable by treatment of the appropriate glycol systems (1) with periodate, was accomplished by reaction of the diosphenol (II) with alkaline hydrogen peroxide. The resulting 2,3-*seco*-2,3,30-tricarboxylic acid (V), giving fitting spectral data, yielded a trimethyl ester and, upon heating in acetic anhydride, the corresponding anhydride (VI). The mass spectrum of V exhibited a very weak  $M^+$  ( $m/e$  516), and all fragmentations appear to result from the  $M^+ - H_2O$  ion ( $m/e$  498, VI) formed as a primary product. These include ions at  $m/e$  483, 465, and 437 (losses of  $CH_3$ ,  $H_2O + CH_3$ , and  $H_2O + CH_3 + CO$ , respectively, from the ion  $m/e$  498). Collapse of the anhydride ring A with losses of  $C_5H_7O_3$  and  $C_6H_9O_3$  gives ions ( $m/e$  383 and 369, respectively), which may have Structures *a* and *b*, respectively, produced by a mechanism involving transfer of the hydrogen atom on C-6. The base peak of the spectrum (at  $m/e$  315) appears to be the product of a dubious reaction type. The



familiar cleavages (4) across ring B (involving a McLafferty transfer of the C-1 hydrogen atom) and across ring C (by a retro-Diels-Alder type of reaction) are both observed giving ions at  $m/e$  303 (species *c*) and 262 (species *d*), respectively; the relatively low abundance of the first may be evidence that the original  $18\beta$  stereochemistry is retained.

## EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured in chloroform unless otherwise stated. UV spectra were taken in ethanol. The  $R_f$  values were taken on silica gel G chromatoplates, developed with toluene-ethyl acetate-acetic acid (12:4:0.5).

**2 $\beta$ -Hydroxy-A-nor-18 $\beta$ -olean-12-en-11-one-2 $\alpha$ ,30-dicarboxylic Acid (IV)**—*Method A*—A solution of methyl 2 $\alpha$ -acetoxy-18 $\beta$ -olean-12-ene-3,11-dion-30-oate (III) (2) (100 mg.) in ethanolic potassium hydroxide solution (10%, 5 ml.) was refluxed for 5 hr. After acidification, the precipitated solid matter (shown by TLC to be a mixture of two products,  $R_f$  0.20 and 0.43) was separated by fractional crystallization from acetone-benzene into: (a) 2-hydroxy-18 $\beta$ -oleana-1,12-dien-3,11-dion-30-oic acid (II) (1), obtained after purification from ethanol-benzene as needles (20 mg.,  $R_f$  0.43), m.p. and mixed m.p. 320–323°; and (b) the A-norhydroxy-acid (IV,  $R_f$  0.20) obtained as light-yellowish needles (35 mg., from acetone-hexane), m.p. 250°,  $[\alpha]_D^{25} + 176^\circ$ , giving one UV maximum at 250 nm. ( $\epsilon = 10,800$ ) and IR (KBr) bands near 3430, 3300, 1720, 1650, and 1630  $\text{cm}^{-1}$ .

*Anal.*—Calc. for  $\text{C}_{30}\text{H}_{44}\text{O}_6$ : C, 71.97; H, 8.86. Found: C, 71.75; H, 8.83.

*Method B*—A solution of the free acid of the diosphenol (II, 50 mg.) in ethanolic sodium hydroxide (10%, 5 ml.) was refluxed for 5 hr. followed by the usual workup. The isolated product, m.p. 250°, was shown to be identical (mixed melting point and co-TLC) with the previously described A-norhydroxy-acid (IV).

**2,3-*seco*-18 $\beta$ -Olean-12-en-11-one-2,3,30-tricarboxylic Acid (V)**—A refluxing solution of the free acid of the diosphenol (II, 1 g.) in ethanol (50 ml.) was treated with hydrogen peroxide solution (100 vol., 110 ml.) and potassium hydroxide solution (10%, 35 ml.), both being added in four equal portions at intervals of 15 min. After acidification, the precipitated product was washed with water and crystallized from *n*-hexane to give hexagonal plates of V ( $R_f$  0.30, 880 mg.), m.p. 205–208°,  $[\alpha]_D^{25} + 172.5^\circ$  (pyridine). The UV spec-

trum showed one maximum at 249 nm. ( $\epsilon = 12,700$ ), and the IR spectrum (mineral oil) contained bands near 3510 (broad), 1710, and 1655  $\text{cm}^{-1}$ .

*Anal.*—Calc. for  $\text{C}_{30}\text{H}_{44}\text{O}_7$ : C, 69.74; H, 8.58; mol. wt. 516. Found: C, 69.90; H, 8.64; mol. wt. (by mass spectrometry) 516.

**Trimethyl Ester of V**—Methylation of V (200 mg.) in chloroform (50 ml.) solution with ethereal diazomethane (from 4 g. *N*-nitrosomethylurea) afforded, after crystallization from chloroform-methanol, 150 mg. of the trimethyl ester ( $R_f$  0.57), m.p. 187–188°;  $[\alpha]_D^{25} + 37.6^\circ$ ; UV maximum at 250 nm. ( $\epsilon = 12,800$ ); IR (mineral oil) bands near 1730 and 1650  $\text{cm}^{-1}$ .

*Anal.*—Calc. for  $\text{C}_{33}\text{H}_{50}\text{O}_7$ : C, 70.93; H, 9.02. Found: C, 70.77; H, 9.11.

**Anhydride of V**—After refluxing a solution of the triacid (V, 160 mg.) in acetic anhydride for 1 hr., the residue remaining upon evaporation was crystallized from *n*-hexane to give the anhydride (VI) ( $R_f$  0.50, 60 mg.), m.p. 218–220°,  $[\alpha]_D^{25} + 180^\circ$ ; UV maximum at 250 nm. ( $\epsilon = 9900$ ); IR (KBr) bands near 3370, 1730, and 1660  $\text{cm}^{-1}$ .

*Anal.*—Calc. for  $\text{C}_{30}\text{H}_{42}\text{O}_6$ : C, 72.26; H, 8.49. Found: C, 71.86; H, 8.59.

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