Communications to the Editor

[Chem. Pharm. Bull. 23(2) 460—462 (1975)]

UDC 547.92.02.04 : 581.192

Correlation of Protolyofoligenic Acid with Cycloartenol

Correlation of protolyofoligenic acid (II) with cycloartenol (III) was established to certify the stereostructure of II.

Protolyofoligenic acid (II) was derived to 24,25-di-O-isopropylidene-9(10)-cyclolanostane-3α-ol (VIII) through protolyofoligenol (VI) and the corresponding aldehyde (VII).

Cycloartenol (III) was acetylated, epoxidized, and benzoylated. The product, dibenzoate, was separated into 24*R* and 24*S* isomers by column and preparative thin-layer chromatography. Hydrolyzed product of 24*R* isomer, which has 3β-hydroxyl group, was derived to isopropylidene derivative, oxidized to 3-oxo compound and reduced by Meerwein–Ponndorf method to yield 3α-hydroxyl compound. The final product was identified with (VIII), which was derived from protolyofoligenic acid.

Lyofolic acid (I) is a new triterpene glucoside isolated from the leaves of *Lyonia ovalifolia* var. *elliptica*. Acid hydrolysis of I gave lyofoligenic acid, an artifact, and glucose, while the genuine aglycone protolyofoligenic acid (II) was isolated from the extract of the leaves along with the other triterpenoids.[1] Although some investigations on the functional groups were made previously, the structure of the genuine aglycone has not been elucidated.

Since protolyofoligenic acid was assumed to have the same carbon skeleton as cycloartenol (III) by comparison of the ORD curve of the 3-keto derivative (IV) with that of cycloartenone (V), the chemical correlation of protolyofoligenic acid (II) with cycloartenol (III) has been attempted and accomplished as described in this communication.

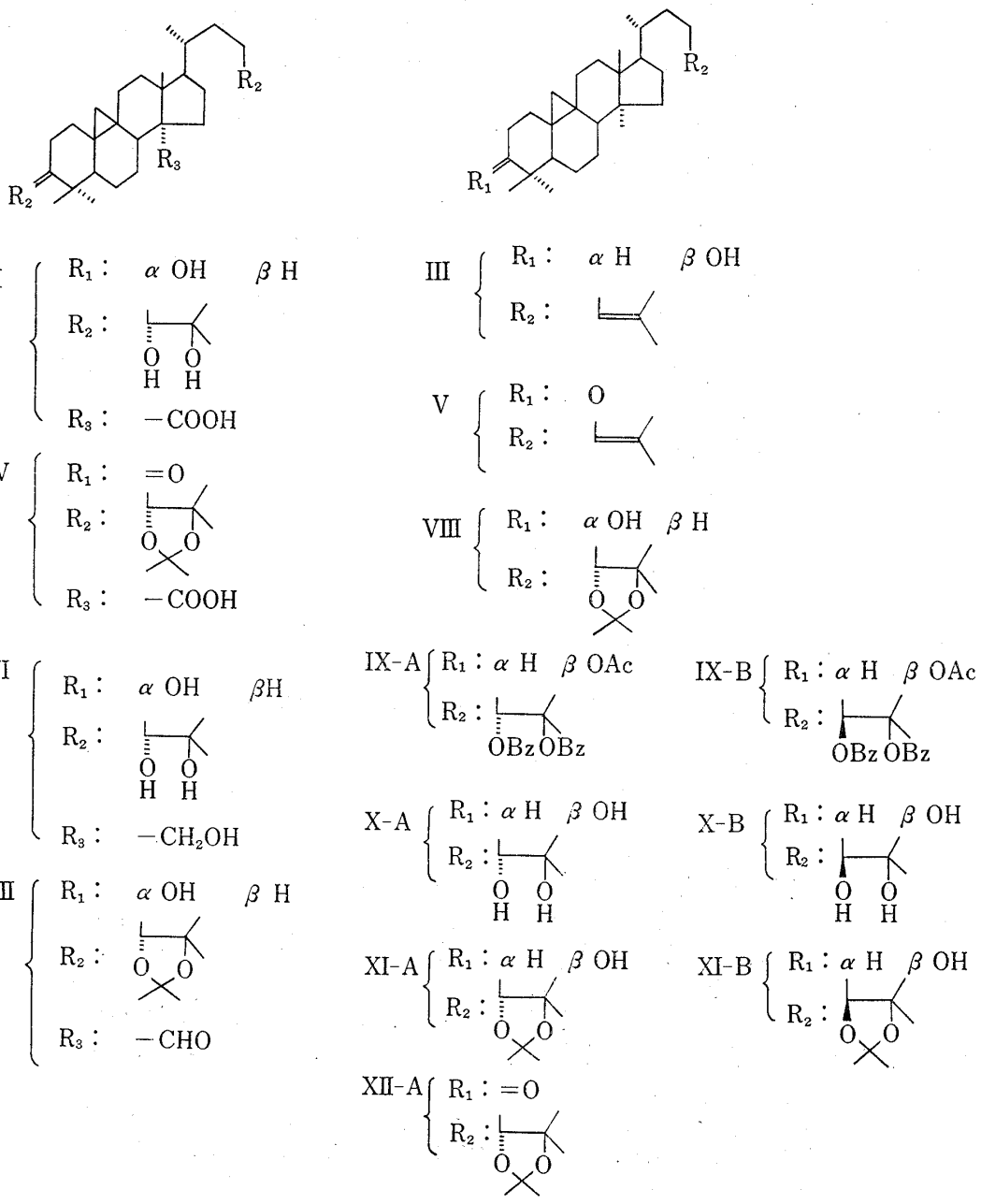
Prolonged treatment of protolyofoligenic acid (II) with vitride[2] in diglyme under reflux yielded protolyofoligenol (VI), colorless needles (ethyl acetate), mp 229—231°, IR ν_{max}^{KBr} cm^{-1}: 3400 (broad). The isopropylidene derivative of VI was oxidized with chromium trioxide in pyridine at 0° to yield the corresponding aldehyde VII, isopropylideneprotolyofoligenal, which was without purification subjected to Wolff-Kishner reduction to give 24,25-di-O-isopropylidene-9,19-cyclo-9β-lanostan-3α-ol (VIII), colorless needles (methanol–acetone), mp 179—182°. Mass Spectrum Calcd. for $C_{33}H_{56}O_3$: 500. Found: *m/e*: 500. IR ν_{max}^{KBr} cm^{-1}: 3500. NMR $\delta_{ppm}^{CDCl_3}$: 0.33, 0.52 (each 1H, ABq, J=4.0 Hz, cyclopropane methylene proton), 0.88 (3H, d, J=6.0 Hz, CH–C<u>H</u>$_3$), 0.88 (6H, s, C–CH$_3$×2), 0.94, 0.96, 1.09, 1.24, 1.32, 1.41 (each 3H, s, C–CH$_3$), 1.61 (1H, s, OH), 3.47 (1H, m, $W_{h/2}$=6.0 Hz, C3-H), 3.65 (1H, br. d, J=7.0 Hz, C24-H).

On the other hand, cycloartenol (III), obtained by alkali hydrolysis of γ-orizanol,[3] was acetylated and oxidized with *m*-chloroperbenzoic acid in dichloromethane to yield a mixture of two epoxides epimeric at C-24. The mixture was treated with diluted sulfuric acid in tetrahydrofuran and the resulting glycols were benzoylated and separated by silica gel column and preparative thin-layer chromatography into 24*R*, 25- and 24*S*, 25-dibenzoyloxy-9,19-cyclo-9β-lanostan-3β-yl acetate (IX-A and IX-B). Each product was hydrolyzed with ethanolic alkali to yield the corresponding triols (X-A and X-B). The absolute configurations of the hydroxy groups at C-24 of these compounds were established by the modified Horeau's method[4] that X-A possesses *R* whereas X-B possesses *S*-configuration. X-A: colorless needles (methanol), mp 160.5—161.5°. *Anal.* Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found: C, 78.44; H, 11.63. IR ν_{max}^{KBr} cm^{-1}: 3400 (broad). Mass Spectrum *m/e*: 460 (M$^+$). X-B: colorless

1) J. Sakakibara, Y. Hotta, and M. Yasue, *Yakugaku Zasshi*, **91**, 1318 (1971).
2) Sodium bis-(2-methoxyethoxy)aluminium hydride $NaAlH_2(OCH_2CH_2OCH_3)_2$ (70% in benzene).
3) G. Ohta and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **5**, 40 (1957).
4) C.J.W. Brooks and J.D. Gilbert, *Chem. Commun.*, **1973**, 194.

plates (methanol), mp 191.0—193.0°. *Anal.* Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found: C, 78.00; 11.47. IR ν_{max}^{KBr} cm^{-1}: 3400 (broad). Mass Spectrum *m/e*: 460 (M^+).

The isopropylidene derivatives of X-A and X-B, namely XI-A and XI-B, were prepared by treatment with *p*-toluenesulfonic acid in acetone. XI-A: colorless rods (acetone–methanol), mp 198.0—199.5°. *Anal.* Calcd. for $C_{33}H_{56}O_3$: C, 79.14; H, 11.27. Found: C, 79.09; H, 11.34. IR ν_{max}^{KBr} cm^{-1}: 3500, 1375, 1370. NMR $\delta_{ppm}^{CDCl_3}$: 0.32, 0.58 (each 1H, ABq, J=4.0 Hz, cyclopropane methylene proton), 0.82 (3H, s, C–CH_3), 0.90 (3H, d, J=6.0 Hz, CH–C$\underline{H}_3$), 0.90 (3H, s, C–CH_3), 0.98 (6H, s, C–CH_3×2), 1.10, 1.26, 1.34, 1.42 (each 3H, s, C–CH_3), 2.08 (1H, s, OH), 3.28 (1H, q, J=5.5, 10.0 Hz, C3-H), 3.66 (1H, br. d, J=7.0 Hz, C24-H). Mass Spectrum *m/e*: 500 (M^+). XI-B: colorless needles (methanol), mp 177.0—178.5°. *Anal.* Calcd. for $C_{33}H_{56}O_3$: C, 79.14; H, 11.27. Found: C, 78.98; H, 11.08. IR ν_{max}^{KBr} cm^{-1}: 3500, 1380, 1370. NMR $\delta_{ppm}^{CDCl_3}$: 0.32, 0.58 (each 1H, ABq, J=4.0 Hz, cyclopropane methylene proton), 0.82 (3H, s, C–CH_3), 0.90 (3H, d, J=6.0 Hz, CH–C$\underline{H}_3$), 0.90 (3H, s, C–CH_3), 0.98 (6H, s, C–CH_3×2), 1.10, 1.26, 1.34, 1.42 (each 3H, s, C–CH_3), 2.16 (1H, s, OH), 3.28 (1H, q, J=5.5, 10.0 Hz, C3-H),



Chart

3.64 (1H, br. t, J=6.0 Hz, C24-H). Mass Spectrum m/e: 500 (M^+).

It is a noticeable finding in the ^{1}H-NMR spectra that the C24-proton signal of 24*R*-derivative (XI-A) and that of IV are observed as the similar broad doublet (J=7.0 Hz), while that of 24*S*-derivative (XI-B) is observed as a broad triplet (J=6.0 Hz). Therefore, XI-A was oxidized to the corresponding 3-oxo compound XII-A with chromium trioxide in pyridine. XII-A: colorless rods (acetone), mp 145—146°. *Anal.* Calcd. for $C_{33}H_{54}O_3$: C, 79.46; H, 10.92. Found: C, 79.58; H, 11.18. IR ν_{max}^{KBr} cm^{-1}: 1705, 1378, 1368. NMR $\delta_{ppm}^{CDCl_3}$: 0.59, 0.82 (each 1H, ABq. J=4.0 Hz, cyclopropane methylene proton), 0.91 (3H, s, C–CH_3), 0.93 (3H, d, J=6.0 Hz, CH–C$\underline{H}_3$), 1.02, 1.06 (each 3H, s, C–CH_3), 1.12 (6H, s, C–$CH_3\times2$), 1.27, 1.38, 1.42 (each 3H, s, C–CH_3), 3.66 (1H, br. d, J=7.0 Hz, C24-H). Mass Spectrum m/e: 498 (M^+).

The carbonyl group of XII-A was then reduced under the Meerwein-Ponndorf conditions to yield a 3α-hydroxy derivative: colorless needles (methanol–acetone), mp 179—182°. *Anal.* Calcd. for $C_{33}H_{56}O_3$: C, 79.14; H, 11.27. Found: C, 79.36; H, 11.48. IR ν_{max}^{KBr} cm^{-1}: 3500. Mass Spectrum m/e 500 (M^+). The final product was identified with VIII by mixed melting point determination, IR and mass spectrometry.

Finally, the position of the carboxyl function in protolyofoligenic acid (II) is considered to be at C-14 on the basis of the recent X-ray analysis of a derivative of lyofoligenic acid,[5] since lyofoligenic acid was already shown to possess the carboxyl function at the same position as II.[1]

Based on the accumulated evidence the stereostructure II has been established for protolyofoligenic acid.

Faculty of Pharmaceutical Sciences,
Nagoya City University,
Tanabe-dori, Mizuho-ku, Nagoya, 467,
Japan

Jinsaku Sakakibara
Yoshihiro Hotta
Masaiti Yasue

Received August 15, 1974

5) J. Sakakibara, Y. Hotta, M. Yasue, Y. Iitaka, and K. Yamazaki, *Chem. Commun.*, **1974**, 839.

[Chem. Pharm. Bull. 23(2) 462—464 (1975)]

UDC 547.92.04

Facile Preparation of Pregn-14-ene-20,21-diones

A practical synthetic method of 21-dimethoxypregn-14-en-20-ones which are key intermediates in bufadienolide syntheses is described. It involves 21-thiomethylation of pregn-14-en-20-ones followed by oxidation with N-chlorosuccinimide in methanol.

As demonstrated by Stache, *et al.*[1] in their syntheses of scillarenin and 5α-bufalin, facile synthesis of the title compounds is a crucial requirement for establishing practical synthetic method of natural bufadienolides.[2] We herein describe an effective method for the preparation of pregn-14-ene-20,21-diones from readily available pregnan-20-ones or pregn-16-en-20-ones. It involves in the key step a new oxidation method of methylketone to α-ketoaldehyde *via* thiomethyl derivative which will find general applicability. Exemplified below are the con-

1) U. Stache, K. Radscheit, W. Fritsch, H. Kohl, W. Haede, and H. Ruschig, *Tetrahedron Letters*, **1969**, 3033; *Ann. Chem.*, **750**, 149 (1971). See also, W. Haede, W. Fritsch, K. Radscheit, U. Stache, and H. Ruschig, *ibid.*, **741**, 92 (1970).
2) F. Sondheimer, *Chemistry in Britain*, **1965**, 454.