Tetrahedron Vol. 42, No. 16, pp. 4437 to 4442, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00

STUDIES ON STRUCTURE AND SYNTHESIS OF ARTEANNUIN AND RELATED COMPOUND XX. THE STRUCTURE OF A NEW PEROXIDIC ARTEANNUIN DEGRADATION PRODUCT AND THE LACTONE CONFIGURATION OF RELATED COMPOUND

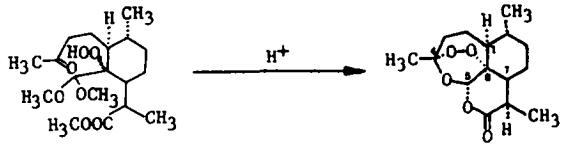
ZHOU Wei-Shan*, ZHANG Lian, FAN Zhao-Chang and XU Xing-Xiang

Shanghai Institute of Organic Chemistry, Academica Sinica
345 Lingling Lu, Shanghai, China

(*Received in Japan* 2 *May* 1986)

Abstract: Determination of structure of a new peroxidic product **3** obtained from the degradation of arteannuin **1** and lactone configuration of the related compound **4** by means of chemical transformation and X-ray analysis are described.

Arteannuin **1**, a new antimalarial isolated from Artemisia annua L., is a novel sesquiterpene lactone containing a unique endo-peroxide acetal[1]. Zhou et al[2] and Hofheinz et al[3] accomplished the construction of this peroxide unit by acid catalyzed cyclization of the key hydroperoxy keto acetal **2**.We have reported

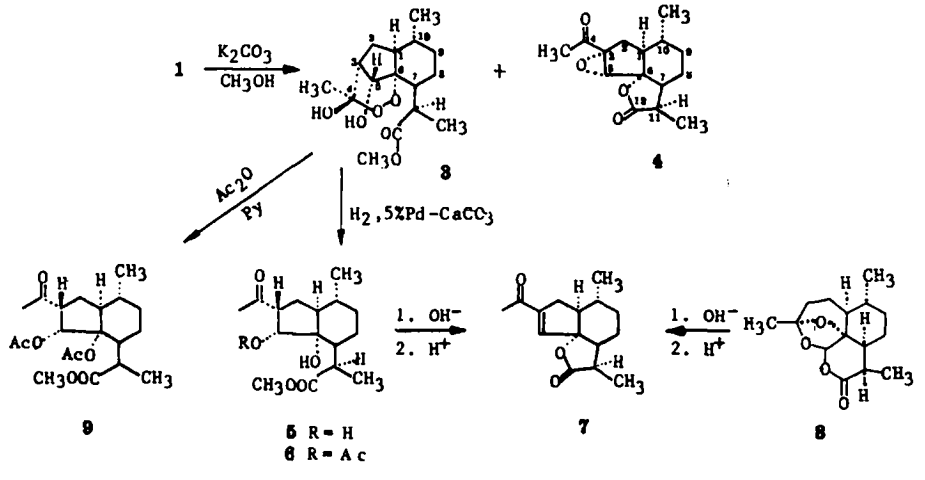


2 **1**

previously that arteannuin **1** on treatment with potassium carbonate in aqueous methanol at room temperature for an hour underwent an intramolecular epoxidation to form α-epoxide **4**[1], but the configuration of the lactone of **4** was not determined. During the course of continuing to study this reaction we isolated a new peroxidic product **3** in addition to **4**. In this paper we wish to report the determination of structure of this new compound and the lactone configuration of **4**.

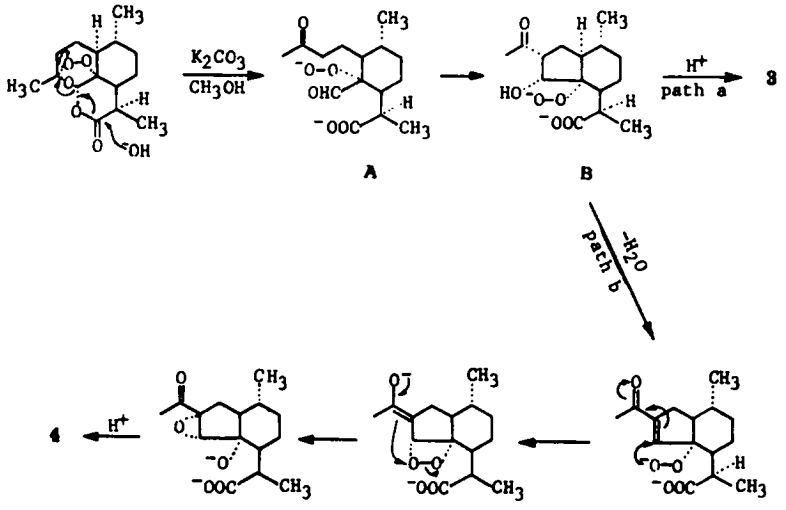
3 is a colorless crystalline compound with m.p.129-131°C. Its MS molecular weight and elemental analysis agreed with $C_{16}H_{26}O_6$. Laser-Raman spectrum at 730 cm^{-1} showed the existence of a peroxide group[4]. Hydroxy and ester carbonyl groups can be inferred from its IR spectrum (3430, 3340, 1700 cm^{-1}). The ^1H-NMR spectrum displayed a methyl ester at δ3.73 and two exchangeable hydroxy groups at δ6.78 and δ7.27. The wide band ^1H decoupling at ^{13}C-NMR of 3 showed 16 carbon resonances.The off resonance ^{13}C-NMR data allowed the observed resonances to be assigned to four primary, three secondary, six tertiary and two quaternary carbons along with one carbonyl carbon, in comparison with that of arteannuin 1 it appeared clearly that the peroxide bridge was attached to the two quaternary carbon atoms.

3 furnished the dihydroxy compound 5 in catalytic hydrogenation over 5% Pd-$CaCO_3$. The ^1H-NMR spectrum of 5 showed a methyl ketone (δ2.23,3H,s), and two exchangable hydroxy guoups at δ1.4-1.6. This led to the conclusion of existence of a peroxide hemiketal moiety. Acetylation of 5 with acetic anhydride and pyridine at room temperature gave acetate 6,indicating a secondary hydroxy group present in molecule 3. On treatment with potassium hydroxide 5 gave an α,β-unsaturated ketone 7 which was identical with that obtained from deoxyarteannuin 8 under the same condition[1], showing the secondary hydroxyl guoup was located at C-5 position. The endo-peroxide hemiketal 3 was converted into diacetate 9 with acetic anhydride and pyridine at room temperature through a cleavage of O-O bond of peroxide[5].



Scheme 1

Under basic condition, arteannuin 1 gave 3 through the ring opening intermediate A[1] and the intramolecular aldol condensation product B. Closure of this hydroperoxide onto the acetyl carbonyl generated this new bicyclic endo-peroxide hemiketal 3 through path a (**Scheme 2**). Owing to the fact that the hydroperoxy group did not leave from its ring, the configuration of peroxy group remained unchanged which should be the same as that of arteannuin 1 i.e.α -orientation. On observation of the molecular moldel of 3, the C-3 was likely to be in R-



Scheme 2

configuration, since S-configuration of C-3 would render the formation of the endo-peroxide hemiketal rather difficult. According to the coupling constant of 3-H and 5-H in ^{1}H-NMR of 3 ($J_{3,5}$=4.9Hz), the cis-relationship between the two protons could be assigned[6]. The result was further confirmed by the ^{1}H-NMR of the octahydroindene 5 ($J_{3,5}$=13.0Hz)[6]. Thus the C-5 configuration could also be assigned as R (axial hydroxy group). Concerning the C-4 configuration, owing to the lower frequency number of the hydroxy group of 3 in IR spectrum (3430, 3340cm^{-1}), which was regarded as the presence of a strong intramolecular hydrogen bond between C_4-OH and C_5-OH, the C_4 hydroxy group could be assigned as axial so that to make the bicyclic endo-peroxide hemiketal more stable. Thus the S-configuration of C_4 could be assigned, which was consistent with that of a known bicyclic endoperoxide compound[7].

Finally let us discuss the configuration of the lactone of 4. The β-orientation of the C-O bond at C-6 of 4 has been assigned by Zeng et al[8]. Nevertheless, based on the transformation of 3 in **Scheme 1**(from 3 through 5 to 6) and the mechanism shown in **Scheme 2** (path b), the assignment of α-orientation of the C-O bond at C-6 of 4 would be more reasonable. So the lactone ring of 4 is in a trans (6α, 7β) but not in a cis (6β, 7β) configuration[8]. This assignment was finally confirmed by X-ray analysis (Fig.1).

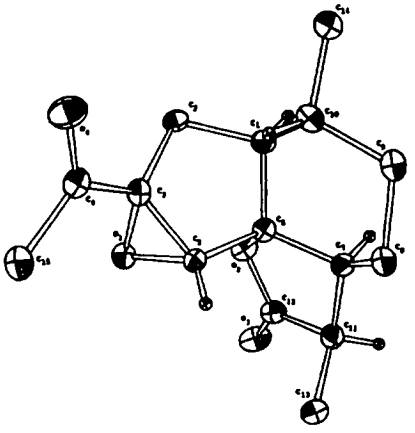


Fig 1 Structure of **4**

Experimental

M.ps were uncorrected. IR spectra were measured as films for oils or as Nujol mulls for solids on a shimadzu 440 spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded on a FX-90Q (90 MHz) or a Varian XL-200 (200 MHz) spectrometers with TMS as an internal standard in $CDCl_3$. MS spectra were run on a Finnign 4021 GC-MS instrument. Optical rotations were measured on an Autopol III automatic polarimeter. Silica gel used for flash column chromatography was silica-H (10-40 μ) purchased from Qingdao Haiyang Chemical Works and eluates used for the flash chromatography and TLC were aceton/ petroleum ether (60-90°C) in different ratio.

Isolation of endoperoxide 3 and epoxide lactone 4: To a solution of arteannuin 1 (5.0g) in methanol(100 ml) was added 10% potassium carbonate solution(40 ml). The reaction mixture was stirred at room temperature for one hour, then acidified to pH 2 with 10% hydrogon chloride solution. The methanol was removed under reduced pressure and the aqueous layer was extracted with ether for three times. The combined ether layer was washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of solvent under reduce pressure yielded crude product(5.0g) which was allowed to stand in a refrigerator after addition of a little amount of methanol to give a needle crystal **4** (0.51g) m.p. 222-4°C. It was no m.p.depression when admixed with an authentic sample (m.p. 222-223°C). Both samples have the sawe R_f values as well as IR, ^{1}H-NMR and MS spectra. A colorless crystal 3(0.53g) was obtained from the mother liquor after flash chromatography on silica gel. m.p.129-131°C. Caculated for $C_{16}H_{26}O_6$:

C; 61.13, H: 8.34; Found: C: 61.23, H: 8.74%. ^{1}H-NMR: 0.924 (3H, d, J=5.10Hz, 10-Me), 1.156 (3H,d, J=7.11Hz, 11-Me), 1.296(3H, s, 4-Me), 2.303(1H,t,J=5Hz, 3-H), 3.461(1H,brq, 11-H), 3.729(3H,s, -OMe), 4.273(1H,d,J=4.9Hz,5-H). ^{1}H-NMR decoupling experimental: irradiation of 5-H (δ4.273), 3-H (δ2.303) and 11-H (δ3.46) simplified the 3-H (δ2.303) 5-H(δ4.273) and 11-Me (δ1.16) to doublet, singlet and singlet respectively. ^{13}C-NMR: 178.8(s), 104.0(s),86.0(s), 71.2(d), 52.1(q),47.6(d), 47.1(d), 43.4(q),41.0(d), 36.5(d), 34.1(t), 30.2(t), 23.7(d) 23.5(t), 19.9(q), 17.8(q). IR(6.34x10^{-3} or 6.34x10^{-4} mol solution in CCl_4, recorded on Perkin-Elmer 983G ir instrument): 3430, 3340(-OH), 1700(ester)cm^{-1}. Laser-Raman: 730(peroxide)cm^{-1}. MS:314(M^+), 297(M^+-OH), 279(M^+-H_2O-OH).

Crystal data for 4: $C_{15}H_{20}O_4$, M=264.32, 4 was crystallized from methanol. The crystal was found to be the orthorhombic system with space group $P2_12_12_1$ and the unit cell parameters are precisely determined as a=5.945(6), b=14.171(2), c=16.264(3)Å , Vc=1370.2Å^3,Z=4 and Dc=1.28 g/cm^3 by means of Enraf-Nonius CAD4 four circle diffractometer.The intensity data were colleted on the same instrument by the ω-2 scan mode, with MoKα radiation (λ =0.7107Å) and a graphite monochromator and with 1069 independent observable reflections [$|F|>2\sigma(|F|)$] in the range $2° < 2\theta < 54°$. The intensity data were corrected for LP factors and for absorption based on scan technique. The nonhydrogen atoms were located by using the direct method and refined by block-diagonal least-squares technique with anisotropic thermal parameters. Hydrogen atoms were obtained from a difference Fourier map, and the final residual factor R was 0.067. The final atomic coordinates and the bond lengthes were deposited with Cambridge Crstallographic Data Centre, Lensfield Road, Cambridge CB21EW, U.K.

Hydrogenation of peroxide 3: To a hydrogen saturated solution of 5% Pd-$CaCO_3$ (0.20g) in 95% ethanol (5 ml) was added a solution of peroxide 3 (0.35 g) in the same solvent (10 ml). Under hydrogen atmosphere, the solution was stirred under ordinary pressure and temperature until no further hydrogen uptake occurred. The reaction solution was filted and concentrated under reduce pressure to give an oily product 5 (0.33g), in 99% yield. ^{1}H-NMR: 0.89 (3H, brs, 10-Me), 1.18 (3H, d J=8Hz, 11-Me), 2.23 (3H,s,4-Me), 3.70 (3H,s, -COOMe), 4.50 (1H, d, J=13Hz, 5-H). IR: 3400 (-OH), 1740 (ester), 1700 (ketone) cm^{-1}. MS: 299 (M^++1), 281(M^++1-H_2O), 263 (M^++1-2H_2O), 294 (M^++1-H_2O-MeO), 231 (M^++1-2H_2O-MeO).

Acetolysis of peroxide 3: To a solution of peroxide 3 (0.5 g) in dry pyridine (1ml) was added acetyl anhydride (1 ml). The reaction mixture was allowed to stand at room temperature for 48 h., then cooled to 0°C. Water (2 ml) was added and the resulted solution was stirred for half an hour. The reaction solution was further diluted with ethyl acetate (50 ml) and successively washed with 1% HCl, 5% $NaHCO_3$ and brine,dried over sodium sulfate and concentrated under reduce pressure to give a residue, which was separated by flash chromatography on silica gel to give a colorless solid 9 (0.47g) in 77% yield. Recrystallization from petroleum ether/acetone gave a colorless crystal m.p. 90.5-91.5°C, $[\alpha]_D^{18}$ -80.5°(C 1.03,$CHCl_3$); IR: 1780,1755,1740,1700 cm^{-1}; ^{1}H-NMR: 0.95 (3H,s,10-Me),

1.20(3H, d, J=7Hz, 11-Me), 1.95 (3H,s, 4-Me), 2.13 (3H,s, acetyl), 2.18(3H, s, acetyl), 3.23(1H,dd,J_1=10Hz, J_2=3Hz, 11-H, 3.53(3H,s, -OMe), 5.50(1H,d,J=11Hz, 5-H). MS(chemical ionization with methane): 383(M^++1).

Acetylation of diol 5: To a solution of diol 5 (0.17g) in dry pyridine (0.5 ml) was added acetyl anhydride (0.4 ml). The reaction mixture was allowed to stand at room temperature for 48 h. The ethyl acetate(20ml) was added and successively washed with 10% hydrogen chloride solution, 5% sodium bicarbonate and brine to neutrality, dried over sodium sulfate and concentrated under reduce pressure to give the residue which was separated by flash chromatography on silica gel to give an oily product 6 (0.16g). IR: 3450,1740, 1700cm^{-1}; ^{1}H-NMR: 0.90 (3H, brs, 10-Me), 1.25(3H,d,J=7Hz, 11-Me), 2.00(3H,s,4-Me), 2.17 (3H,s,acetyl), 3.55 (3H, s, OMe), 5.13 (1H, d, J=9Hz, 5-H). MS: 341 (M^++1), 281(M^++1-AcOH).

Reaction of diol 5 with sodium hydroxide: A mixture of diol 5 (0.20 g) in 95% ethanol (4ml) and 10% sodium hydroxide (1 ml) was heated under reflux for 2 h. The ethanol was removed under reduce pressure and water (2 ml) and dichloromethane (5 ml) were added. The mixture was acidified with 10% aqueous hydrogen chloride and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated under reduce pressure to give an oily mixture(0.20 g).To a solution of the mixture obtained above in dry dichloromethane (5 ml) was added a bit of p-toluene sulfonic acid for lactonization.The reaction mixture was stirred at room temperature for one hour. The solvent was removed under reduce pressure to give a residue, which was separated by flash chromatography on silica gel to give a colorless solid 7 (0.08 g). Recrystallization from acetone/petroleum ether furnished a pure 7 (0.05 g). m.p. 120-123°C. It showed no m.p. depression when admixed with the product obtained from deoxyarteannuin 8[1]. Both samples have the same R_f values as well as IR, ^{1}H-NMR and MS spectra.

Reference

1. Liu, Jing-Ming; Ni, Mu-Yun; Fan, Ju-Fen; Tu, You-You; Wu, Zhao-Hua; Wu, Yu-Lin; Zhou, Wei-Shan, Acta Chimica Sinica 37, 129 (1979).
2. Xu, Xing-Xiang; Zhu, Jie; Huang, Da-Zhong and Zhou, Wei-Shan, Acta Chimica Sinica 41, 574 (1983).
3. G.Schmid and W.Hofheinz, J.Amer.Chem.Soc. 105, 624 (1983).
4. Fang, Yi-Xing; Zhu, Zi-Ying; He Da-Jun, Acta Chimica Sinica 42, 1312 (1984).
5. Isao Saito and S,Sarma Nittala in "The Chemistry of Peroxides" p352, edited by S.Patai, John Wiley & Sons, 1983.
6. Liang Xiao-Tian, "Resultion and Application of High Resultion Hydrogen NMR" p 296-298, Science Press. Beijing, China. 1976.
7. Clark, G.R.; Nikaido,M.M.; Fair,C.K.; Lin,J., J.Org.Chem. 50,1944 (1985).
8. Zeng, Mei-Yi; Li, Lan-Na; Chen, Shu-Feng; Li, Guang-Yi; Liang, Xiao-Tian; Marie Chen and Jon Clardy, Tetrahedron 39, 2941 (1983).