C-(11)-EPI-DEOXYARTEETHER: FORMATION AND STRUCTURE

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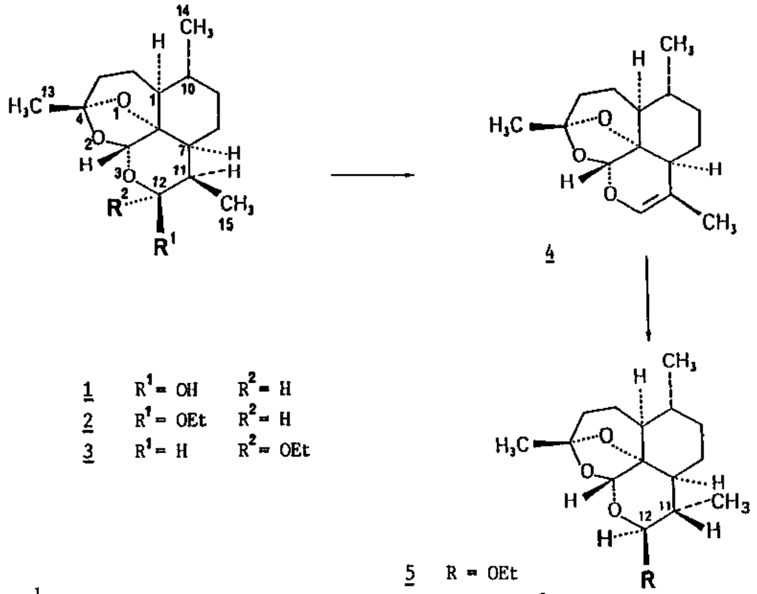
Abstract - Acid catalyzed etherification of deoxydihydroqinghaosu (1) with ethanol saturated with hydrogen chloride afforded 11-epi-deoxyarteether (5). Compound 5 also was obtained from deoxyethers 2 and 3 and the vinylic ether 4 under the same reaction conditions. The configuration at C-11 and C-12 of 5, strongly supported by ^{1}H-nmr data, has been confirmed by X-ray analysis.

Arteether, a crystalline compound derived from the Chinese antimalarial qinghaosu (QHS), is prepared by treatment of dihydro-QHS with ethanol and boron trifluoride etherate, and separated from its oily α-epimer by crystallization or by chromatography.[1,2] Studies of QHS and artemether (methyl ether analog of arteether) as antimalarial drugs carried out in China revealed that loss of an oxygen atom from the peroxide group was a route of its metabolism[3,4], also expected to hold for arteether.[2] The two deoxyethers 2 and 3 of the ethyl ether series were prepared from their peroxy-precursors as analytical standards.[2] Deoxy-QHS prepared from QHS,[4,5] failed to react with sodium borohydride in contrast to QHS which is converted into dihydro-QHS.[1,6] The desired deoxy-compound 1, however, was obtained from dihydro-QHS by catalytic deoxygenation. Etherification of 1 with ethanol saturated with HCl[7] afforded the novel ether 5 (90% yield) which was also obtained from 2 or 3 under these reaction conditions (Fig 1). ^{1}H-nmr of 5 showed a coupling constant $^{3}J_{7,11}$ of 1 Hz which is very small in comparison with that of the ethyl ethers of the dihydro-QHS and deoxydihydro-QHS series where vicinal couplings between H-C(7) and H-C(11) in the α and β isomers are in the range of 4.3-5.0 Hz.[2] Based on a Dreiding model and Karplus relation,[8] this small value of $^{3}J_{7,11}$ (1.0 Hz) (which suggests a near 90° dihedral angle between the coupled protons), together with a large $^{3}J_{11,12}$ (8.1 Hz) in 5 is consistent with the proposed structure 5 having an inverted methyl group at C(11), and a β confi- guration of the ethyl ether group in a quasi-equatorial position at C(12). The observed large upfield shift for H-C(11) in 5 (δ 1.41), as compared to dihydro-QHS and deoxydihydro-QHS ethyl ethers (δ 2.3-2.4), is also in line with the conclusion that H-C(11) in 5 is positioned trans to the peroxide or ether O-(1) group respectively, receiving less magnetic shielding from these groups than in the correspondent cis series. Epimerization of 2 and 3 into 5 by acid catalysis in $CDCl_3$ is accompanied by a slow formation of the vinylic ether 4. In fact, new resonances corresponding to 3, 4 and 5 were detected in a solution of 2 over a period of time (see Table 1). The resonances at 6.04 (1H, quartet) and 1.63 (3H, doublet) with a mutual coupling constant of 1.1 Hz, verified by a decoupling experiment, are consistent with a typical allylic group, and were assigned to the H-C(12) and CH_3-C(11) of 4. Based on these studies, it is postulated that the reaction sequence for the acid catalysed conversion of 2 into 5 is: 2 or 3 → 4 → 5.

Fig 1



4

1 R^1= OH R^2= H
2 R^1= OEt R^2= H
3 R^1= H R^2= OEt

5 R = OEt

Table 1. Selected ^{1}H-nmr data (δ, 300 MHz, in $CDCl_3$) of 1 to 5.[a]

Compound	δH-5		δH-12		δH-11		δCH_3-15		$^3J_{11,12}$		$^3J_{7,11}$	
	α	β	α	β	α	β	α	β	α	β	α	β
1[a]	(5.35)	5.36	(4.77)	5.31	(2.32)	2.46	(1.01)	0.91	(6.3)	5.3	(4.8)	6.4.
2	-	5.30	-	4.79	-	2.42	-	0.91	-	4.5	-	5.4
3	5.29	-	4.43	-	2.40	-	0.97	-	6.2	-	5.0	-
4	5.48		6.04[b]		-		1.60[b]		-		-	
5	-	5.42	-	4.69	-	1.41	-	1.07	-	8.1	-	1.0

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a, The numbers in the parenthesis of compound 1 are derived from spectrum containing both the α and β species after equilibration. For comparison, data of 2, 3 and 5 are also categorized in terms of α and β isomers. b, $^4J_{H-12,Me-15}$=1.1 Hz.

The reaction sequence for the acid catalyzed conversion of 2 into 5 suggested by the spectral analysis was proven to be correct since 4, prepared from 1 by the procedure used in the QHS-series of compounds,[1] formed quantitatively 5 when treated in ethanol with HCl gas.

The configuration of 5 assigned by ^{1}H-nmr analysis has been confirmed by an X-ray analysis which led to the structure illustrated in Fig 2. Of the six-membered rings, ring A has a normal chair conformation and ring B has a slightly distorted chair conformations (absolute values for ring torsion angles range from 52.9-57.5° for ring A, 43.4-76.1° for ring B). Ring D has assumed a somewhat distorted conformation (absolute values for ring torsion angles vary from 24.4-67.1°) such that no significant strain is noted in the molecule. The five-membered ring has an envelope conformation with O(1) being the out of plane atom. The x-ray results confirmed the prediction that the $-CH_3$ and $-O-CH_2-CH_3$ moieties on ring D are trans to one another (C15-C11-C12-O4 = - 149.9°).

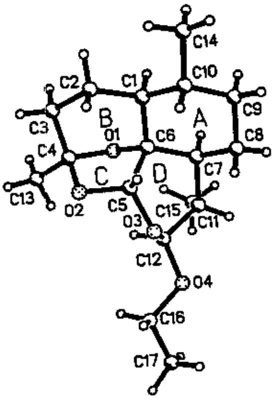

Fig 2: Diagram showing the structure and conformation of 5. The figure is drawn using the experimentally determined coordinates with arbitrary thermal parameters.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Fisher-Johns apparatus and are uncorrected. The optical rotations were measured on a Perkin Elmer 141 polarimeters. Ir spectra were recorded on a Perkin Elmer 257 grating infrared spectrophotometer instrument. ^{1}H-nmr spectra were taken on a Varian XL-300 spectrometer with $(CH_3)_4Si$ as the internal reference. EI mass spectra values were carried out on a V. G. MICROMASS LTD 7070F spectrometer. Elemental analysis were performed by Microlit Laboratories Inc.

Reaction of Deoxydihydroqinghaosu (1), Deoxyarteether (2), α-Deoxydihydroqinghaosu Ethyl Ether (3) and Vinylic Ether(4)with Ethanol Saturated with HCl[7]: A solution of deoxyarteether 2 (192 mg, 0.65 mmol), or oily α-deoxydihydroqinghaosu ethyl ether 3 (239 mg, 0.81 mmol), or deoxydihydroqinghaosu 1 (46 mg, 0.17 mmol), or vinylic ether 4 (20 mg, 0.08 mmol), in ethanol saturated with HCl[7] (15 ml, 15 ml, 5 ml and 5 ml respectively) was stirred at r.t. until the starting material had disappeared (TLC: ethyl acetate/hexane = 1:9). Conversion of the starting material was observed (TLC: ethyl acetate/hexane=1:9). The reaction mixture was concentrated to dryness, extracted with ethyl ether, washed with aqueous sodium bicarbonate and distilled water, dried over sodium sulfate and concentrated to give 5 as a white solid (86% yield from 2, 78% from 3, 90% from 1 and 84% from 4): mp 89-90°C (ethyl ether-hexane); $[\alpha]_D^{22}$ = -10.3° (c 1.12, $CHCl_3$); ms m/z = 296 (M^+); ^{1}H-nmr ($CDCl_3$): δ 5.42 (s, 1H, H-5), 4.69 (d, 1H, J = 8.1, H-12); 3.92 (qd, 1H, ^2J=9.8, $OC\underline{H}_2CH_3$)[9], 3.54 (qd, 1H, $OC\underline{H}_2CH_3$)[9], 1.25(t,3H,$OCH_2C\underline{H}_3$); ir (KBr) νmax 2950, 1500 cm^{-1}, Anal. Cal. for $C_{17}H_{28}O_4$: C, 68.88; H, 9.52. Found: C, 68.73; H, 9.57. Vinylic ether 4: From 1 as described in the QHS-series of compounds: mp 91-93°C; $[\alpha]_D$22 = + 11.76° (c 0.3, $CHCl_3$); ms: m/z 250 (M^+).

X-ray Crystallographic Data: $C_{17}H_{28}O_4$, molecular weight = 296.40, orthorhombic, space group $P2_12_12_1$, a = 9.035(2), b = 10.581(2), c = 17.589(3), dcalc = 1.17 gcm^{-3}, μ = 0.58 mm^{-1}, 1529 independent reflections were measured out to $2\theta_{max}$ = 112° with a Nicolet R3M diffractometer using CuKa radiation (=1.5178 A) with a graphite monochromator in the incident beam. The data were collected at room temperature using the $\theta/_{2\theta}$ scan technique with a variable scan rate ranging from 12°/min minimum to 30°/min maximum, depending upon the intensity of a reflection. The structure was solved by direct methods as implemented by the SHELXTL system of programs.[9] Full-matrix least-squares refinement on 202 parameters (coordinates and anisotropic thermal parameters for non-hydrogen atoms; hydrogen atoms placed at calculated positions, C-H =0.96 Å, and allowed to ride on covalently bonded atoms), using the 1393 reflections for which /Fo/>3 σ/ Fo/ gave a final R-factor of 5.7% (Rw = 5.3%). The goodness of fit parameters was 2.32 and the final difference map was featureless. Tables of hydrogen coordinates, bond lengths and angles have been deposited with the Crystallographic Data Centre, Cambrige University Chemical Laboratory, Cambridge CB2 1EW, England.

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