# THE CHEMISTRY OF DRUGS. VI[1]

# THERMAL DECOMPOSITION OF QINGHAOSU

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Abstract - Heating qinghaosu in refluxing xylene for 22 h afforded decomposition products 2 and 4 in 15% yield each. Structures of 2 and 4 were assigned based on their $^{1}$H-NMR and $^{13}$C-NMR data and the former confirmed by a single crystal X-ray analysis. Structure 4, supported by spectral data and a successful O-acetylation of the OH group remains tentative. Structures 2 and 4 contain a newly formed tetrahydrofuran ring, originating by breakage of the original peroxide group.

Thermal decomposition of the antimalarial sesquiterpene qinghaosu (1, QHS), was hoped to afford products which could be connected with intermediates of its total synthesis.[2] It was expected that such studies would in addition provide valuable first hand information on the thermal stability of the peroxide group in QHS and the course of its fragmentation. We now would like to report our findings made by heating QHS in refluxing xylene for 22 h. In contrast to heating 1 in toluene which afforded practically no decomposition products, or tetralin, which afforded too many decomposition products, heating 1 in xylene under reflux afforded 2 and 4 in 15% each, isolated by chromatography on silica gel. Mass spectrometry (mass 282) and $^{1}$H-NMR and $^{13}$C-NMR data (22 protons and 15 carbons)

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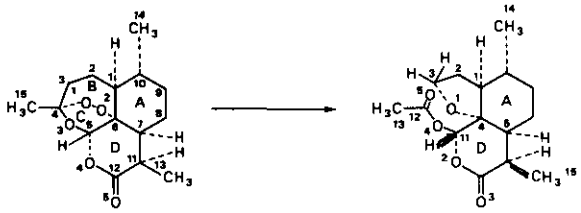
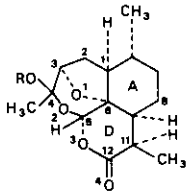
revealed that 2 and 4 were thermal rearrangement products of QHS. Comparision of NMR spectra of 2, 4 and QHS suggested that both A and D rings of QHS remained intact during the thermal reaction. The faster moving compound assigned to structure 2 contained a newly formed tetrahydrofuran ring and an acetate side chain. The formation of a tetrahydrofuran was supported from two newly formed proton signals at δ 4.20 and 3.91, characteristic chemical shifts for an α-proton of a tetrahydrofuran ring. This was further supported by a C-13 DEPT experiment, which showed that one of the four $-CH_2-$ carbons in QHS was largely shifted downfield to δ 69.19, typical for an α-positioned carbon in a tetrahydrofuran ring and resulting from the presence of a directed bond oxygen atom. The existence of an acetate side chain was evidenced from a newly formed



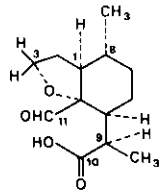
1. QINGHAOSU



2.



4. R = H
5. R = Ac



3.

carbonyl carbon at δ 168.4 originating from C-4 (δ 105.32) of QHS. Structure 2 was further confirmed by a single crystal X-ray analysis (see below). The slower moving compound 4 contained a tetrahydrofuran ring incorporated into the 7-membered ring B+C of 1 and a newly formed OH group at C-4. This was supported by new resonances at δ 3.62 (1H) and 2.10 (1H, exchangeable) which were assigned to H-C(3) and the hydroxy proton at C-4 in 4, respectively. Observation of a C-13 signal at δ 68.96 with doublet multiplicity assigned to C-3 also supported the above structural assignment. The stereochemistry at C-4, however, remains unresolved. Hydrolysis of 2 with sodium carbonate in MeOH at room temperature afforded the aldehyde 3 of mass 240, and acetylation of 4 with glacial acetic acid in dry methylene chloride in the presence of 4-dimethylaminopyridine afforded an acetate 5 of mass 324, supporting the new structural features present in the two thermolysis products. $^{1}$H-NMR and $^{13}$C-NMR spectra of 2 and 4 suggested that protons and carbon atoms of rings A and D in 2 and 4 were similarly arranged as in qinghaosu.[3] No interconversion between 2 and 4 was found, suggesting that both compounds originated in principle from a breakage of the peroxide group followed by an intramolecular recombination of fragments. The numbering used for interpreting the NMR-spectra and for discussing the X-ray analysis is shown in the formulae. Compounds 4 and 5 did not give crystals which were suitable for an X-ray analysis, and the relative configuration at C-4, therefore, remains undetermined.

EXPERIMENTAL SECTION

Melting points were taken on a Fisher-Johns apparatus and uncorrected. Silica gel 60 (particle size 0.040-0.063 mm or 0.015-0.040 mm) from Merck was used for column chromatography with a flash-chromatography column (Aldrich Chemical Co.). Silica gel GF plates from Analtech, Inc. was used for thin layer chromatography (tlc) with the solvent systems petroleum ether/ethyl acetate = 7:3. Optical rotations were measured with a Perkin-Elmer Model 241 MC polarimeter in $CHCl_3$ and concentrations specified. IR spectra (in $cm^{-1}$) were obtained on a Beckman 4230 instrument as KBr tablet. Chemical Ionization (CI) mass spectra (m/z) were obtained by using a Finnigan 1015 D spectrometer. $^{1}$H-NMR and proton noise decoupled $^{13}$C-NMR spectra were obtained using a Varian XL-300 spectrometer with $Me_4Si$ as internal reference (δ in ppm, J in Hz).

Stability of Qinghaosu to Heat: Qinghaosu (1) was heated in several solvents. Changes were noticed on tlc after spraying with a solution of 2% vanillin in conc. sulfuric acid. QHS did not change when refluxed in EtOH for two days. In toluene, after refluxing for four days, QHS was still the major product. When heated in tetralin for

5 h at 200°C many new products were formed. When QHS was heated in xylene for 22 h at 180-185°C QHS had disappeared and two new products could be seen after spraying with vanillin reagent, a faster moving compound 2 which gave a red color on tlc after spraying, and a slower moving compound 4 which gave a blue color. Both compounds were prepared on a larger scale.

Heating Qinghaosu (1) in Xylene: Qinghaosu (1,2g) in xylene (10 ml) was heated for 22 h at 178-182°C. The solution was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate mixtures, followed by ethyl acetate afforded in the ethyl acetate fractions first the faster moving compound 2 (325.4 mg 16.3%): mp 89.5-90.5°C; $[\alpha]_D^{23}$ +94.39° (c, 0.7, $CHCl_3$); IR 2920, 1730 (lactone); CI-MS ($NH_3$): 283 ($M^+$+1); $^1$H-NMR δ 5.62(s,1H, C11-H), 4.20(m, 1H, C3-H), 3.91(m,1H,C3-H'), 3.14 (m,1H,C9-H), 1.86(m,1H,C5-H), 2.12(s, 3H,C13-$CH_3$), 1.19(d,3H,C15-$CH_3$), 0.98(d,3H,C14-$CH_3$); $^{13}$C-NMR: δ 171.61(C-10), 168.40(C-12), 92.94(C-11), 79.29(C-4), 69.19(C-3). Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85%. Found: C, 63.81; H, 7.71%.
The slower moving compound 4 was crystallized from isopropanol (282 mg, 14%): mp 191-192°C; $[\alpha]_D^{23}$ -129.1° (c, 1.0, $CHCl_3$); IR: 3480 (OH), 2920, 1700, 850; CI-MS ($NH_3$): 283 ($M^+$+1); $^1$H-NMR: δ 5.64(s,1H,C5-H), 3.62(s,1H,C3-H), 3.20(m,1H,C11-H), 2.07(m,1H,C7-H), 1.58(s,3H,C15-$CH_3$), 1.20(d,3H,C13-$CH_3$), 0.93(d,3H,C14-$CH_3$); $^{13}$C-NMR: δ 171.38(C-12), 108.87(C-4), 98.90(C-5), 82.87(C-6) 68.96(C-3). Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.81; H, 8.11%.

Hydrolysis of 2 to 3: Compound 2 (18.3 mg, 0.065 mmole) in methanol (2 ml) and anhydrous sodium carbonate (50 mg) were stirred for 1 h at room temperature. The solvent was removed in vacuo, then water (2 ml) added. The solution was neutralized with glacial acetic acid (pH 6.7) and extracted with chloroform (3 x 3 ml). The organic layer was dried ($Na_2SO_4$), filtered and evaporated to give a yellow gum (3, 7 mg), showing one spot by tlc. IR ($CH_2Cl_2$): 2960, 1710 (CO); CI-MS ($NH_3$): 241 ($M^+$+1). $^1$H-NMR: δ 9.70(s,1H,C11-H), 4.06(m,1H,C3-H), 3.88(m,1H,C3-H'), 2.40(m,1H,C9-H), 1.22(d,3H,C12-$CH_3$), 0.89(d,3H, C13-$CH_3$);

Acetylation of 4: A mixture of 4 (96 mg, 0.34 mmol), acetic acid (0.1 ml, 1.75 mmol), 4-dimethylaminopyridine (DMAP, 20 mg) and N,N'-dicyclohexylcarbodiimide (51 mg, 0.25 mmol in dry methylene chloride (10 ml) was stirred at room temperature for 2 days. The mixture was filtered and the filtrate washed with 0.1 N HCl, water, and 10% aqueous

$NaHCO_3$, dried ($Na_2SO_4$) and filtered. The yellow oil obtained after evaporation of the solvent was chromatographed on a silica gel column with mixtures of petroleum ether - ethyl acetate (8:2 and 7:3), to give a white solid (43.5 mg) which seems to be a mixture of two compounds. Crystallization from isopropyl ether afforded a small sample of compound 5 (6 mg): mp 172-174°C; IR ($CH_2Cl_2$) 1740 (CO): CI-MS ($NH_3$): 325 ($M^+$+1).

NMR-Data for QHS (1): $^1$H-NMR: δ5.84(s,1H,C5-H), 3.37(m,1H,C11-H,$J_{7,11}$=5.3 Hz,$J_{11,13}$=7.3 Hz), 2.40(m,1H,C3-H), 2.03(m,1H,C3-H'), 1.97(m,1H,C2-H), 1.84(m,1H,C8-H), 1.78(m,1H,C9-H), 1.75(m,1H,C7-H); 1.50(m,1H,C2-H'), 1.41(s,3H,C15-$CH_3$), 1.22-1.34(m,2H,C1-H,C10-H), 1.19(d,3H,C13-$CH_3$,$J_{11,13}$=7.3 Hz), 0.98-1.10 (m,2H,C8-H',C9-H'), 0.98(d,3H,C14-$CH_3$,$J_{10,14}$=6.0 Hz); $^{13}$C-NMR: δ172.01(C-12), 105.32(C-4), 93.64(C-5), 79.45(C-6), 50.01, 44.91, 37.47, 32.84 (remaining 4 CH carbons), 35.84, 33.54, 24.78, 23.33 (4 $CH_2$ carbons), 25.15, 19.78, 12.51 (3 $CH_3$ carbons).

X-Ray Crystallographic Data for 2: $C_{15}H_{21}O_5$, molecular weight = 281.36, monoclinic, space group C2, a = 29.181(5)Å, b = 8.152(2)Å, c = 12.648(2)Å β = 98.65(2)Å, z = 8, $d_{calc}$ = 1.26 $gcm^{-3}$, μ = 7.9 $cm^{-1}$. 2396 independent reflections were measured out to $2\theta_{max}$ = 120° with a Nicolet R3 diffractometer using CuKα radiation (λ = 1.54178Å) with a graphite monochromator on the incident beam. The data were collected at room temperature using the θ/2θ scan technique with a variable scan rate related to the intensity of a reflection. Monitor relections, collected at regular intervals, indicated that the crystal remained stable during data collection. The structure, which contained two molecules per asymmetric unit, was solved by direct methods[4,5] as inplemented by the SHELXTL system of programs[6]. Full-matrix least-squares refinement on 380 parameters (coordinates and anisotropic thermal parameters for non-hydrogen atoms: hydrogens placed at calculated positions and allowed to ride on covalently bonded atoms), using the 2187 reflections for which $|F_o| > 3\sigma F_o$ gave a final R factor of 4.0% (Rw = 4.7%). The goodness of fit parameter was 1.5 and the final difference map was featureless. Coordinates, thermal parameters and bond lengths and angles for this molecule have been deposited with the Crystallographic Data Centre, Cambridge University Chemical Laboratory, Cambridge CB2 1EW, England.

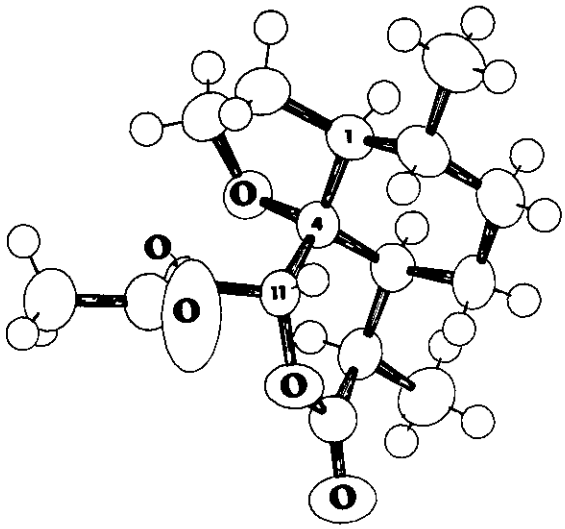



Fig.1 : CRYSTAL CONFORMATION 2a

Legend

Figure 1. Diagram showing the structure and conformation of 2a. Only one of the two molecules in the asymmetric unit is shown. The figure is drawn using the experimentally determined coordinates with arbitrary thermal parameters for the hydrogen atoms.

Discussion: The results of the X-ray study on 2 are illustrated in Figure 1. The two molecules in the asymmetric unit are essentially the same. Bond distances and angles agree well between the two molecules and both have the same overall relative conformation. The five-membered ring is a flattened envelope with C-1 being the out-of-plane atom. The all carbon six-membered ring has a normal chair conformation. The two molecules in the asymmetric unit (2a and 2b) show small conformational differences. In both cases the six-membered lactone ring is flattened in the vicinity of O-2, however, it is much more pronounced in one molecule. In 2a, C10-O2-C11-C4 = -4.4°, C9-C10-O2-C11 = -2.3° and O2-C11-C4-C5 = -23.1°. The corresponding values in molecule 2b are 27.4°, -11.8°, and -50.9° respectively. The conformation of the fused six-membered ring system in qinghaosu itself[7] is very similar to that found for

molecule 2b (corresponding torsion angles are 23.3° -16.1° and -44.1°). In 2 the acetyl group on C-11 is on the same side of the molecule as is O-1, (O1-C4-C11-O4 torsion angle is -20.3° in 2a and -46.3° in 2b) and there has been a rotation about the C11-O4 bond such that O-5 is point away from O-1. In qinghaosu the corresponding torsion angle (O2-C6-C5-O3) is -51.6° and O-1 and O-2 (corresponding to O-1 and O-5 in 2) are bonded to form a peroxide bridge from C-6 to C-4 (corresponding to C-12 and C-4 in 2).

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