CHEMICAL TRANSFORMATIONS OF QINGHAOSU, A PEROXIDIC ANTIMALARIAL, II*

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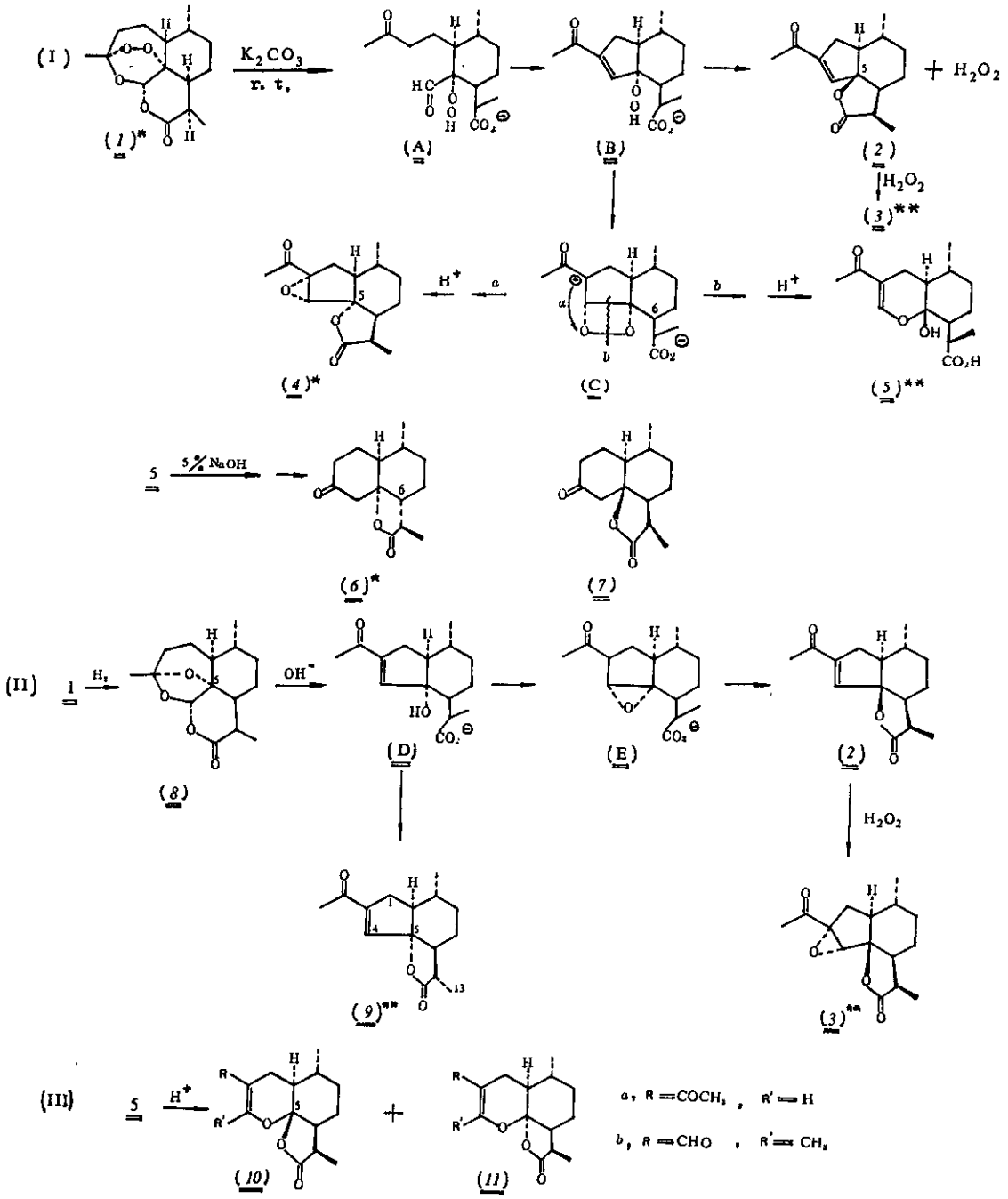
Abstract— Qinghaosu (1) is known to give a plethora of products in alkaline media. This paper is concerned with the amended stereochemistry of products 3, 4 and 5, with attendant mechanistic implications. Lactonization of 5 is also discussed.

This paper reports some new results on the chemistry of the peroxidic antimalarial, qinghaosu (also known as arteannuin, 1)[1]. In addition, the stereochemistry of some of the transformation products reported earlier[1] became suspect in the course of time and had to be amended (3 and 5 in this paper, 4 by other authors[2]). In alkaline media (K_2CO_3 or NaOH) qinghaosu (1) suffers lactonic ring opening with simultaneous unlocking of all the latent functionalities to give A, as shown in the Scheme. Subsequent condensation of the aldehydic group onto the active methylene gives B which in turn by internal Michael-type reaction gives C, a key intermediate with a dioxetane ring. Rupture of the dioxetane ring (path b) is the major route in aqueous solution (containing 20% methanol for solubility reasons) with an optimized conversion of better than 88%, a fact that has been exploited for the quantitative analysis of qinghaosu[1]. Here the stereochemistry of the product (5) at C-6 has to be amended as shown. The proposed inversion of this center occurs only under slightly more drastic conditions (5% NaOH under reflux), furnishing 6. A synthetic specimen (7)[3] with retention at C-6 was found to be distinctly different from 6 by direct comparison (e.g., Rf values). When the mixed solvent becomes much richer in alcohol (MeOH or EtOH), the yield of 5 drops sharply, giving way to the formation of 4, among others. Evidently 4 has its genesis from C via an internal attack of the peroxidic linkage by the enolate anion (path a). This anion is probably better solvated in aqueous media and hence less aggressive. Note the non-inversion at C-5 of compound 4, which was previously wrongly assigned as 3 (with inversion at C-5)[1]. As previously proposed[1], the formation of 3 requires an intermolecular reaction between 2 and hydrogen peroxide. Now we did detect a very small amount of 2 in the reaction mixture. (The configuration at C-5 follows from that of 3). Free hydrogen peroxide was also detected by several independent experiments, including polarography. However, compound 3 was not present in detectable amounts and was to be obtained from an unexpected source (vide infra).

*Dedicated to Professor D.H.R. Barton on the occasion of his 70th birthday.

Scheme 1. Transformations of qinghaosu (1). Structures labeled with capital letters are proposed intermediates. Compounds labeled with asterisks have been analyzed by X-ray diffraction (* previously; ** this work).



Catalytic hydrogenation of qinghaosu (1) gives deoxyqinghaosu (8)[4]. Quite unexpectedly, the product (2) has suffered an inversion at C-5 (Reaction II). This is attributable to the intervention of E, an internal Michael-type adduct, the epoxide of which is vulnerable to a back-side attack by the carboxylate anion (incidently, further treatment of 2 with H_2O_2 gives 3[4], which was fully characterized by X-ray diffraction). We did also isolate another minor isomer 9 with intact C-5 stereochemistry. NOE evidence is only compatible with C-5α and C-13α configurations, confirmed by X-ray diffraction. The inversion at C-13 can be rationalized by the need of releasing steric congestion. The C-13 methyl group of 4 is also subject to severe steric congestion, yet somehow it managed to preserve stereochemical integrity under apparently similar conditions.
The hydroxy-acid (5) can be lactonized by storage in acidic media. Since the hydroxy group of 5 is part of a hemi-ketal, reversion to the keto-form sets free the bidentate β-dicarbonyl system, thus offering two choices of re-closure in addition to the two epimeric alternatives at C-5. Altogether there are four isomeric products upon lactonization with the 10a and 10b pair predominating. The C-5 epimers can be easily separated, but each epimer still contains a regioisomeric pair (10a and 10b; 11a and 11b; a:b ≃ 4:1), as evidenced by ^1H and ^{13}C nmr. C-5 configurational homogeneity in the two isolates, aside from the coincident Rf values within each regio-isomeric pair, is strongly supported by smooth pseudo first-order kinetics. The 10a and 10b pair is faster than the 11 pair by a factor of 2 (monitored by the development of the enolate absorption at 292 nm with dil. NaOH in large excess).
The aldehydic form (ca. 20%) of 5 is also detected in solution.

EXPERIMENTAL

M.p.s are uncorrected. Optical rotations were measured with Perkin-Elmer 241 Polarimeter. Uv spectra were recorded with a Shimadzu UV-240 spectrophotometer. Nmr spectra were recorded in $CDCl_3$ with a JEOL FX-90Q spectrometer. Ms were recorded with a VG ZAB-2F spectrometer in the EI mode. X-Ray single crystal analyses were performed on a Nicolet R3M/E diffractometer, using SHELXTL program for the direct method. The absolute configuration of 1 has been established[4], from which follow all the other configurational representations.
The isolation and spectral data of 3 (from Reaction II), 4, 5, 6 and 8 have been fully described previously[1,4].
Identification of 2 in the reaction mixture (Reaction I). With an authentic sample of 2 (from Reaction II) at hand, it became convenient to detect 2 from the K_2CO_3 treatment[4] of qinghaosu (1) in aqueous methanol. It was found to occur as a "contaminant" of 4. Epoxidation[4] gave 3 which can be easily separated (Estimated yield, under 5%).
Isolation and characterization of 9
The mother liquor[4] of 2 (Reaction II, 28% yield), by repeated preparative tlc (silica, 1:1 BuOAc- pet. ether) afforded 9 in 0.8% yield. Mp. 151.5-152.5°C, $[\alpha]_D^{15}$ -179° (c, 0.1, $CHCl_3$). Ms m/z 248 (M^+). Uv (95% EtOH) 229nm (13000). Ir (KBr), 3070, 1767, 1667 cm^{-1}. ^1H Nmr, δ1.05 (3H, d, J=7.2), 1.27 (3H, d,

J= 7.2), 2.25 (3H, s), 2.40 (1H, d, J=16.8 Hz, 1α-H), 2.54 (1H, quint, J=7.2), 2.84 (1H, ddd, J=16.8, 5.13, 2.92, 1β-H), 6.71 (1H, s, 4-H). NOE (4-H): 2.25 (2.4%), 2.54 (8%).

Isolation of 10 and 11.

Qinghaosu (2.4 g) in 95% EtOH (100 ml) was mixed with 0.2% aqueous NaOH (400 ml) and allowed to react at 50°C for 2.5 h. The usual work-up[1] gave 5. Silica gel chromatography of the mother liquor gave 10 (290 mg) and 11 (92 mg).

Compound 10: Mp. 100.5-102.5°C, $[\alpha]_D^{25}$ +13.5° (c, 0.5, $CHCl_3$). Ms m/z 264 (M^+). Uv (95% EtOH), 244 nm (10,000). Ir (film), 3090, 1790, 1060, 1627 cm^{-1}. ^1H Nmr, δ 1.03 (3H, d, J=7.2), 1.20 (3H, d, J=7.2), 2.26 (3H, s), 3.38 (1H, quint, J=7.2), 7.44 (0.8H, d, J=0.5), 10.00 (0.2H, s). ^{13}C Nmr, δ 8.7 (q), 19.8 (t), 24.8 (q), 25.0 (t), 32.2 (t), 32.7 (d), 38.7 (d), 42.5 (d), 43.4 (d), 105.3 (s), 152.3 (d), 178.0 (s), 195.9 (s), 119.5 (s).

Compound 11. Mp. 114-117°C, Ms, m/z 264 (M^+). Uv (95% EtOH), 250 nm (13200). Ir (KBr), 3090, 1795, 1658, 1635 cm^{-1}. ^1H Nmr, δ 1.03 (3H, d, J=7.2), 1.18 (3H, d, J=7.2), 2.28 (3H, s), 3.32 (1H, quint, J=7.2), 7.54 (0.8H, br s), 10.00 (0.2H, s). ^{13}C Nmr, δ 8.8 (q), 15.9 (t), 18.1 (q), 24.8 (q), 25.9 (t), 30.2 (d), 36.0 (d), 38.6 (d), 40.4 (d), 108.3 (s), 152.8 (d), 177.8 (s), 195.7 s), 40.6 (d), 116.2 (s), along with a small peak at 188.4 (d).

Compound 10 and 11 were interconvertible upon storage in chloroform solution.

X-Ray diffraction analysis showed 3, 5 and 9 to belong to the space group $P2_12_12_1$, with 4 molecules per unit cell. MoKα ($\theta \leq 23^\circ$) was used for 3, cell dimensions 5.496 (4), 12.633 (3) and 20.768 (7) Å, 997 observable reflections out of 1163, R= 0.0585. CuKα ($\theta \leq 57^\circ$) was used for both 5 and 9. For 5, cell dimensions 6.922 (1), 12.122 (1) and 17.543 (3) Å, 1097 observable reflections out of 1174, R= 0.0391. For 9, cell dimensions 8.575 (5), 10.398 (5) and 15.404 (7) Å, 1003 observable reflections out of 1098, R= 0.0490. Bond lengths and bond angles are all within normal ranges.

REFERENCES AND NOTES

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3. We thank Prof. X.X.Xu, Shanghai Institute of Organic Chemistry, for a gift of this compound.
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