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Structure of an Ether Dimer of Deoxydihydroqinghaosu, a Potential Metabolite of the Antimalarial Arteether

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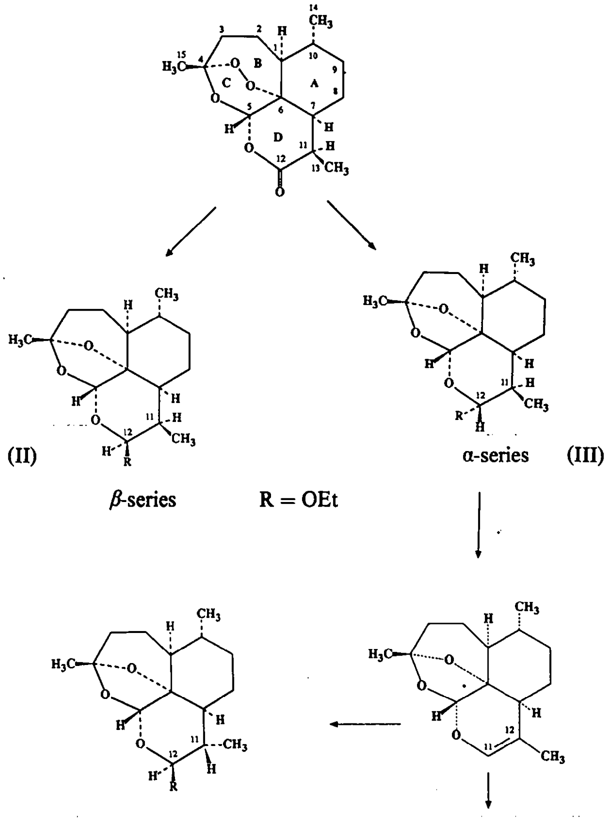
Abstract. $C_{30}H_{46}O_7$, $M_r = 518{\cdot}69$, triclinic, $P1$, $a = 9{\cdot}013\,(2)$, $b = 10{\cdot}520\,(2)$, $c = 15{\cdot}187\,(3)$ Å, $\alpha = 93{\cdot}3\,(2)$, $\beta = 93{\cdot}73\,(1)$, $\gamma = 95{\cdot}88\,(2)°$, $V = 1426{\cdot}2\,(5)$ Å^3, $Z = 2$, $D_x = 1{\cdot}21$ Mg m^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}54178$ Å, $\mu = 0{\cdot}65$ mm^{-1}, $F(000) = 564$, $T = 295$ K, final $R = 0{\cdot}043$, $wR = 0{\cdot}042$ for 3842 observed reflections. The dimer is formed such that the deoxyarteether moieties are *cis* to one another. Attempts to determine the absolute configuration of the molecule were inconclusive so the conformation corresponding to that found for qinghaosu was used for the refinement. Both halves of the dimer have the same chirality with five of the seven asymmetric carbons having an *S* conformation and two (C5 and C6) having an *R* conformation.

Introduction. Qinghaosu (I) (and more recently its semisynthetic analogs) have been clinically used in China for centuries as antimalarials (Luo & Shen, 1987). They are fast-acting blood schizontocides and their activity is directly related to the presence of a peroxide group in these molecules (Warhurst, 1986), whereas deoxy congeners (Brossi *et al.*, 1988) are inactive *in vitro* in assays measuring blood schizontocidal activity. Studies have shown that the loss of an O atom from the peroxide group was a route to its metabolism (Lou & Shen, 1987; Warhurst, 1986). The development of arteether, a *β*-ethyl ether isomer of dihydroqinghaosu, as a novel antimalarial in this series required preparation of analytical standards represented by the deoxy analogs shown below [(II), (III)] (Brossi *et al.*, 1988). Attempts to prepare these ethers from the corresponding alcohol (R = OH) with *p*-toluenesulfonic acid in ethanol afforded a new ethyl ether isomer (Gerpe, Yeh, Brossi & Flippen-Anderson, 1988) together with a dimer of formula $C_{30}H_{46}O_7$ (IV). This dimer is chemically related to dimers obtained in China in the qinghaosu family of compounds (China Cooperative Research Groups, 1982) and its conformation in the solid state and its relative configuration were, therefore, of interest. This information was provided by an X-ray analysis of the dimer, which showed it belongs to the C(11) epi series suggesting that conversion of the C(11) methyl group has taken place during the etherification of deoxydihydroqinghaosu.



(II) *β*-series R = OEt

α-series (III)

C(11) Epi series

Dimer (IV)

Experimental. Preparation of bis(epideoxydihydroqinghaosu) ether: deoxydihydroqinghaosu (200 mg) (Brossi *et al.*, 1988) in dry toluene (40 ml) was added with *p*-toluenesulfonic acid (20 mg) and refluxed under

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nitrogen with a Dean–Stark apparatus until the starting material had disappeared (TLC, silica gel, hexane–ethyl acetate = 9:1). The reaction mixture was concentrated to 5 ml, filtered through silica gel (5 g) and crystallized from ethyl ether–hexane to afford 75 mg of the dimer: m.p. > 511 K (softening), $[\alpha]^{20\,^\circ\mathrm{C}}$–43·1° ($c$ 1·0, $\mathrm{CHCl_3}$).

Data were collected from a colorless crystal of dimensions 0·32 × 0·42 × 0·08 mm on a Nicolet *R*3*mV* diffractometer with an incident-beam graphite monochromator. Cell dimensions were determined from a least-squares fit of 25 centered reflections within $42 < 2\theta < 55°$. Data collection parameters are: Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5417$ Å), $2\theta_{\max} = 125°$; range of *hkl*: $-10 \le h \le 0$, $-12 \le k \le 12$, $-17 \le l \le 17$, standards, 200, 030, 004, monitored every 100 reflections with random variation ±2·0% over data collection, θ–2θ mode, scan width $[2\theta(K\alpha_1)-1{\cdot}0$ to $2\theta(K\alpha_2)+1{\cdot}0]$, scan rate a function of count rate (10° min^{-1} minimum, 60° min^{-1} maximum), $\mu = 0{\cdot}65$ mm^{-1}; 5046 reflections measured, 4654 unique, $R_{\mathrm{int}} = 0{\cdot}020$ (from standard reflections), 3842 observed $[F_o > 3\sigma(F_o)]$. Data were corrected for Lorentz and polarization effects but absorption effects were ignored.

The structure was solved by direct methods. Least-squares refinement on F values was started with full-matrix methods and final cycles were performed with block-diagonal techniques, refining on one of the two molecules in the asymmetric unit per cycle. Programs used were provided with the MicroVAX versions of the *SHELXTL* system (Sheldrick, 1980). $\sum w(|F_o| - |F_c|)^2$ minimized where $w = 1/[\sigma^2(|F_o|) + g(F_o)^2]$, $g = 0{\cdot}00025$, secondary isotropic extinction from $F_c^* = F_c/[1{\cdot}0 + 0{\cdot}002(p)F_o^2/\sin 2\theta]^{0{\cdot}25}$ where $p = 0{\cdot}0045$ (4). 1018 parameters refined (519/cycle): atom coordinates for all atoms, anisotropic temperature factors for non-H atoms and isotropic temperature factors for H atoms; $(\Delta/\sigma)_{\max} = 0{\cdot}03$, $R = 0{\cdot}043$, $wR = 0{\cdot}042$, $S = 1{\cdot}35$. Final difference Fourier excursions 0·17 and –0·16 e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974).†

Discussion. Table 1 lists the atomic coordinates and U_{eq} values for the molecule. Atom numbering follows that shown in Fig. 1 (for the second molecule in the asymmetric unit add 20 to the number of the corresponding atom in the first molecule). An attempt was made to determine the absolute configuration of the dimer by refining each hand independently; however, the difference in final R factors was insignificant. Both molecules in the asymmetric unit have the same chirality, as do both halves of the dimer itself. The dimer was formed such that the two deoxyarteether moieties are *cis* to one another. The X-ray structures of

Table 1. *Atomic coordinates* (× 10^4) *and equivalent isotropic displacement parameters* (Å^2 × 10^3)

	x	y	z	U_{eq}*
O(1)	372 (3)	7728 (2)	9934 (2)	57 (1)
C(4)	−1026 (5)	8195 (4)	10103 (3)	63 (2)
C(3)	−1407 (6)	7883 (5)	11021 (3)	73 (2)
C(2)	−170 (5)	8473 (5)	11708 (3)	68 (2)
C(1)	1394 (5)	8338 (4)	11410 (3)	58 (1)
C(10)	2626 (5)	9103 (5)	12012 (3)	67 (2)
C(9)	4136 (6)	8988 (6)	11641 (3)	79 (2)
C(8)	4169 (5)	9363 (5)	10688 (3)	70 (2)
C(7)	2974 (4)	8535 (4)	10081 (3)	56 (1)
C(11)	3043 (5)	8886 (4)	9106 (3)	59 (1)
C(12)	1692 (5)	9571 (4)	8822 (3)	54 (1)
O(3)	1441 (3)	10495 (2)	9520 (2)	57 (1)
C(5)	833 (4)	9904 (4)	10237 (3)	53 (1)
C(6)	1440 (4)	8628 (3)	10433 (3)	50 (1)
O(2)	−723 (3)	9558 (3)	10061 (2)	63 (1)
C(13)	−2180 (6)	7667 (7)	9371 (4)	88 (2)
C(14)	2607 (9)	8681 (7)	12962 (4)	89 (3)
C(15)	3137 (7)	7734 (6)	8473 (4)	82 (2)
O(16)	2038 (3)	10251 (3)	8081 (2)	64 (1)
O(1′)	−1882 (3)	11884 (3)	7224 (2)	61 (1)
C(4′)	2993 (5)	11138 (5)	7627 (3)	77 (2)
C(3′)	−4478 (6)	11109 (7)	7063 (5)	93 (3)
C(2′)	−4311 (6)	10573 (6)	6131 (5)	95 (3)
C(1′)	−2820 (5)	11088 (4)	5755 (3)	68 (2)
C(10′)	−2489 (7)	10420 (5)	4873 (3)	83 (2)
C(9′)	−947 (6)	10880 (5)	4613 (3)	79 (2)
C(8′)	283 (6)	10776 (5)	5340 (3)	71 (2)
C(7′)	−14 (4)	11553 (4)	6186 (3)	54 (1)
C(11′)	1254 (5)	11523 (4)	6930 (3)	56 (1)
C(12′)	752 (4)	10663 (4)	7633 (3)	56 (1)
O(3′)	−107 (3)	9536 (3)	7231 (2)	62 (1)
C(5′)	−1555 (5)	9783 (4)	6892 (3)	65 (2)
C(6′)	−1541 (4)	11074 (3)	6483 (3)	55 (1)
O(2′)	−2524 (3)	9847 (3)	7577 (2)	78 (1)
C(13′)	−3060 (8)	11582 (8)	8570 (5)	101 (3)
C(14′)	−3679 (10)	10631 (8)	4136 (5)	114 (3)
C(15′)	1813 (7)	12847 (6)	7321 (4)	79 (2)
O(21′)	1553 (3)	2579 (2)	12138 (2)	52 (1)
C(24′)	2702 (4)	3098 (4)	12795 (3)	58 (1)
C(23′)	4192 (5)	2981 (5)	12408 (4)	71 (2)
C(22′)	4318 (5)	3708 (5)	11595 (4)	75 (2)
C(21′)	2879 (5)	3512 (4)	10961 (3)	62 (2)
C(30′)	2854 (6)	4414 (5)	10224 (3)	77 (2)
C(29′)	1362 (7)	4196 (6)	9683 (4)	84 (2)
C(28′)	35 (6)	4298 (5)	10247 (3)	70 (2)
C(27′)	16 (5)	3361 (4)	10971 (3)	52 (1)
C(31′)	−1312 (5)	3401 (4)	11560 (3)	54 (1)
C(32′)	−828 (5)	4168 (4)	12436 (3)	54 (1)
O(23′)	280 (3)	5198 (2)	12324 (2)	57 (1)
C(25′)	1669 (5)	4778 (4)	12135 (3)	55 (1)
C(26′)	1522 (4)	3562 (3)	11509 (3)	50 (1)
O(22′)	2456 (3)	4424 (3)	12920 (2)	62 (1)
C(33′)	2481 (7)	2455 (6)	13637 (3)	75 (2)
C(34′)	4132 (10)	4273 (10)	9612 (6)	122 (4)
C(35′)	−2036 (6)	2087 (5)	11726 (4)	75 (2)
O(36)	−2094 (3)	4706 (3)	12729 (2)	61 (1)
O(21)	−918 (3)	6901 (3)	15196 (2)	58 (1)
C(24)	436 (5)	6408 (4)	15489 (3)	67 (2)
C(23)	556 (6)	6480 (6)	16495 (3)	79 (2)
C(22)	−786 (6)	5744 (5)	16858 (3)	76 (2)
C(21)	−2287 (5)	5935 (4)	16350 (3)	62 (2)
C(30)	−3600 (7)	5037 (5)	16575 (3)	78 (2)
C(29)	−5013 (7)	5235 (6)	15999 (4)	88 (2)
C(28)	−4737 (6)	5111 (5)	15031 (3)	74 (2)
C(27)	−3481 (4)	6069 (4)	14783 (3)	56 (1)
C(31)	−3243 (5)	5965 (4)	13775 (3)	59 (1)
C(32)	−1877 (5)	5276 (4)	13602 (3)	54 (1)
O(23)	−1786 (3)	4241 (2)	14179 (2)	60 (1)
C(25)	−1349 (5)	4703 (4)	15055 (3)	57 (2)
C(26)	−2056 (5)	5905 (4)	15357 (3)	53 (1)
O(22)	218 (3)	5078 (3)	15160 (2)	66 (1)
C(33)	1698 (7)	7076 (8)	15055 (5)	96 (3)
C(34)	−3880 (10)	5163 (8)	17565 (4)	106 (3)
C(35)	−3110 (7)	7255 (5)	13369 (4)	81 (2)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{IJ} tensor.

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† Tables of bond lengths and angles, lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51374 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

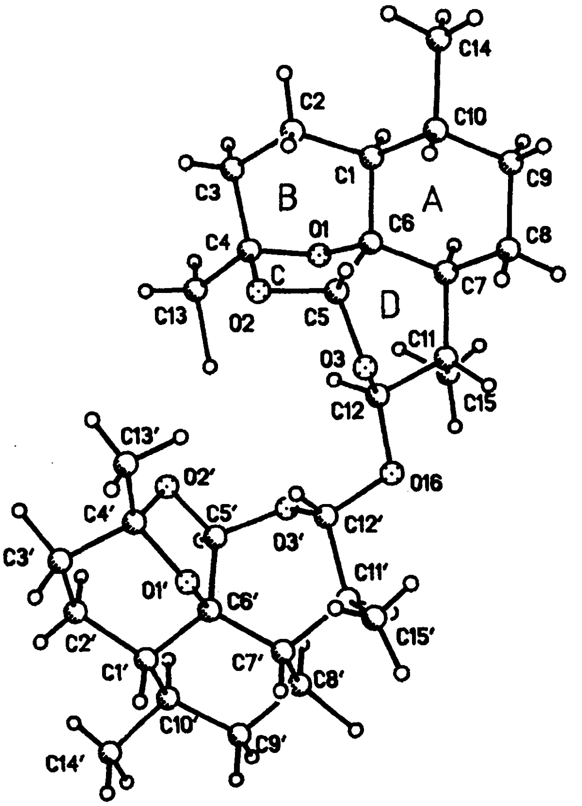

Fig. 1. Perspective drawing of the results of the X-ray study on the dimer. Only one of the two molecules in the asymmetric unit is shown.

both the *cis* (Brossi *et al.*, 1988) and *trans* (Gerpe, Yeh, Brossi & Flippen-Anderson, 1988) (C15 relative to O16) forms of the deoxyarteether monomer have been reported. In the present compound the conformation of the deoxyarteether moieties is the same as that found for the *trans* isomer. Ring *A* has a normal chair conformation while ring *B* has a slightly distorted chair conformation (absolute values for ring torsion angles vary from 48·5 to 59·1° for ring *A* and from 41·3 to 76·9° for ring *B*). Ring *D* has assumed a somewhat distorted conformation (absolute values for ring torsion angles vary from 15·0 to 73·5°) such that no unusual bond lengths or angles appear in the molecule. The five-membered ring has a normal envelope conformation with O1 being the out-of-plane atom. In the dimer, however, the methyl group on C11 and the oxygen atom on C12 are *gauche* with respect to one another (C15—C11—C12—O16 torsion angles range from −75·2 to −82·9°).

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A Tautomeric Form of Tetraethylammonium 1-Acrylamidononahydro-*closo*-decaborate(1−)

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Abstract. $C_8H_{20}N^+.C_3H_{14}B_{10}NO^-$, $M_r = 318·5$, monoclinic, $P2_1/c$, $a = 9·934\,(4)$, $b = 15·207\,(4)$, $c = 13·489\,(5)$ Å, $\beta = 94·16\,(3)°$, $V = 2032·5\,(11)$ Å^3, $Z = 4$, $D_x = 1·041$ g cm^{-3}, $\lambda(\text{Mo }K\alpha) = 0·71073$ Å, $\mu(\text{Mo }K\alpha) = 0·53$ cm^{-1}, $F(000) = 688$, $T = 295$ K. Final $R = 0·051$ for 1929 observed reflections. The

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