Communications to the Editor

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STEREOSTRUCTURE OF CURDIONE

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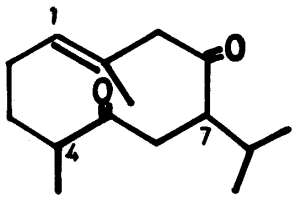
The stereostructure of curdione (1) isolated from Curcuma wenyujin together with curcumol (2a) was determined as 1a on the basis of its direct X-ray crystallography and transformation to 2a. The preferred conformation of 1a in solution was found to be CC/syn (C(5)=O/C(1)-H) (3a) rather than CC/anti (3b) as in crystal based on ^{1}H-NMR variable-temperature and NOE measurements, especially at -70°C. A possible biogenetic pathway from 1a through conformational change (3a to 3b) to 2a and the absolute configuration were proposed.

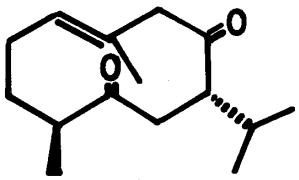
KEYWORDS——curdione; germacranoid; Curcuma wenyujin; Zingiberaceae; stereostructure; ^{1}H-NMR (400 MHz); variable-temperature; NOE; X-ray diffraction

The gross structure of curdione isolated from Zedoariae rhizoma was assigned as 1. In the course of our study on the bio-active terpenoid constituents in Curcuma wenyujin (Zingiberaceae), curdione (1)[2] was isolated from its essential oil together with the major sesquiterpene hemiacetal, curcumol (2a), whose absolute stereostructure had recently been determined.[3] Since 1 is assumed to be a possible biogenetic precursor of 2a, the elucidation of the stereostructure of 1 with a flexible conformation is not only of much interest, but also essential to clarify the biogenetic pathway from 1 to 2a. Hence, a direct X-ray diffraction study of 1 was first executed to establish its relative stereochemistry. The physical data for 1 are as follows: $C_{15}H_{24}O_2$; mp 61-62°C[2]; $[\alpha]_D^{25}$ +26.0° (c, 1.00; $CHCl_3$); IR ν_{max}^{KBr} (cm^{-1}): 1704 (C=O), 1667 (C=C); EI-MS m/z 236 (M^+); high-resolution mass (MS) m/z 236.1778 (Theor. 236.1770); ^{1}H-NMR ($CDCl_3$, 400 MHz)[4] δ: 0.88, 0.95 (3H x 2, each d, J = 6.6, $-CH(CH_3)_2$), 0.98 (3H, d, J = 6.6, $>CH-CH_3$), 1.57 (1H, m, 3α-H), 1.66 (3H, s, $>C=CH-CH_3$), 1.88 (1H, m, 12-H), 2.09~2.15 (3H, br, 3α-H, 2α-H, 2β-H), 2.34 (1H, m, 4α-H), 2.40 (1H, d,d, J = 18, J = 2.2, 6β-H), 2.69 (1H, m, 6α-H), 2.85 (1H, d,d,d, J = 8.8, J = 8.8, J = 2.2, 7β-H), 2.94 (1H, d, J = 11, 9α-H), 3.07 (1H, d, J = 11, 9β-H), 5.17 (1H, S, 1-H).

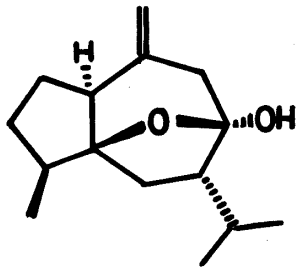
The crystal data are: $C_{15}H_{24}O_2$, MW 236, orthorhombic, space group $P2_12_12_1$, lattice constant a = 10.758(5), b = 13.164(7), c = 10.176(5), U = 1441.1 Å^3, z = 4, D_{calc} = 1.0895 gm^{-3}. The intensity data were collected on a Philips PW 1100



1



1a
1b (4β, 7αH)



2a
2b (7αH)

diffractometer using graphite monochromated CuKα radiation. 1229 Reflections up to 155° (2θ) were used. The structure was solved by the direct method using a MULTAN[5] program and refined by the method of least-squares with block-diagonal matrix approximations. The final R value was 0.05 including 24 hydrogen atoms with isotropic temperature factors. The molecular structure in crystal and the relative stereochemistry of 1 thus depicted in Fig. 1 reveal that curdione (1) exists in a CC conformation[6] possessing a trans relationship between C(4)-methyl and C(7)-isopropyl side chain. Moreover, this conformation is characteristic of the syn-arrangement[7] of C(5)=O and C(1)-H i.e. oriented on the same side of the plane put through the ten-member ring.

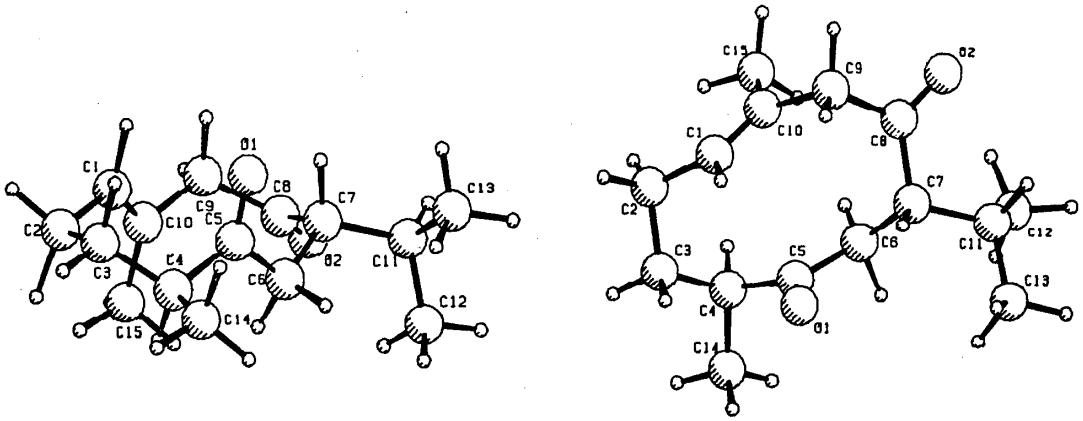
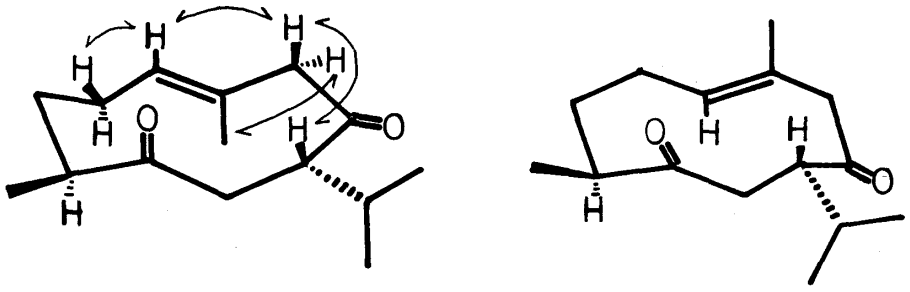


Fig. 1 Perspective Views of Curdione (1a)

An examination of Dreiding models shows that two major conformations are possible for 1. In order to verify the co-existence of more than two diverse conformers, variable-temperature studies of 400 MHz ^{1}H-NMR spectroscopy of 1 were performed. The spectrum showed a set of well-separated peaks at room temperature in spite of broad signals at -30°C. At the temperatures less than -50°C, especially at -70°C, two sets of signals with an intensity ratio of approximately 5:1 (e.g. C(1)-H 5.06 and 5.63; C(10)-CH_3 1.76 and 1.48 ppm) were observed. This indicates that each of the signals arose from the two CC conformers, i.e. conformation A (3a) and conformation B (3b), the latter of which takes the anti-arrangement[7] of C(5)=O and C(1)-H. For the determination of the stereostructures of each conformer, intramolecular nuclear Overhauser effect (NOE) measurements were carried out at -70°C. When the frequency corresponding to C(1)-H of the major isomer was sat-



3a 3b

Fig. 2 Conformation A (3a) and B (3b) of Curdione (1a)

urated, 6% of NOE was observed both in C(9)-βH and C(2)-βH. Irradiation of the frequency at C(10)-CH_3 was effected by 3% C(9)-αH, but not C(9)-βH. When C(9)-βH was irradiated, 6% of NOE appeared both in C(1)-H and C(7)-βH (Fig. 2). Due to the anisotropic effect of both carbonyl groups in 1, C(1)-H signal of the major conformer (δ 5.06) appears upward in comparison with the corresponding proton of the minor one (δ 5.63). On the contrary, C(10)-CH_3 of the former is observed at the lower field (δ 1.76) rather than that of the latter (δ 1.48). These results clearly suggest that the predominant conformer and the minority should be represented as conformation A (3a)(C(5)=O/C(10)-CH_3: anti) and conformation B (3b)(C(5)=O/C(10)-CH_3: syn), respectively, (Fig. 2). Furthermore, as the dominant spectrum of each set of signals measured at -70°C was closely similar to that observed at ambient temperature, 3a proves to be the preferred conformation in solution at room temperature as well as in the crystals shown in Fig. 1.

Since 2a was exclusively produced only by heating 1a at 200°C in ethanol,[9] it seems to be suggested that curdione (1a) mainly existing in conformation A (3a) could transform via conformation B (3b) to curcumol (2a) with retention of C(7)-configuration, not to the hypothetical C(7)-β-epimer (2b)[10] in a possible biogenetic pathway. As the absolute configuration of curcumol[3] has been established as 2a possessing C(7)-α-isopropyl side chain, which is more stable than 2b with C(7)-β-substituent,[10] the absolute stereostructure of curdione (1) should be presumably represented as 1a, rather than its mirror image (1b), providing that the transformation from 1a to 2a proceeded without epimerization.

Further studies obtaining the concrete proof about this point are now in progress.

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REFERENCES AND NOTES

1) Visiting Research Associate of Keio University on leave from Dalian Institute of Medicinal and Pharmaceutical Sciences.
2) H. Hikino, Y. Sakurai, S. Takahashi and T. Takemoto, Chem. Pharm. Bull., 15, 1390 (1967).
3) S. Inayama, Gao Ji-Fu, K. Harimaya, T. Kawamata, Y. Iitaka and Guo Yong-Tian, Chem. Pharm. Bull., 32, 3783 (1984).
4) Spin-decoupling experiments at 400 MHz permitted the assignment of all the protons in the molecule.
5) G. Germain, P. Main and M.M. Woolfson, (1971). MULTAN. A Computer Program for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. Universities of York and Louvain.
6) W.C. Still and I. Galynker, Tetrahedron, 37, 3981 (1981).
7) W. Parker, J.S. Roberts and R. Ramage, Quart. Rev. (London), 21, 331 (1967).
8) It should be noted that the minor conformation B (3b) is designated to be a typical one with similar conformations with respect to the syn-arrangement.
9) Ji Zhe-Zhong, Yin De-Zhoug, Zeng Shao-Juen, Xu Hong-Xia, Journal of Shemyang College of Pharmacy, Sum 13, 86 (1981).
10) Molecular mechanics calculation (MM2[11] and MM2'[12]) for the steric energies and heats of formation were carried out with respect to the conformations in question (3a and 3b). This calculation suggested that 2a and 3a should be thermodynamically more stable than 2b and 3b, respectively. Details will be soon reported elsewhere.
11) N.L. Allinger, J. Am. Chem. Soc., 99, 8127 (1977).
12) C. Jaine and E. Osawa, Tetrahedron, 39, 2769 (1983).

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