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THE ABSOLUTE CONFIGURATION AND CONFORMATION OF NEOCURDIONE[1)]

Tamiko Ohkura,[a] Ji-Fu Gao ,[a,2a)] Kenzo Harimaya,[a] Manabu Hikichi,[a,2b)]
Yoichi Iitaka,[b] Takeshi Kawamata,[a] Masanori Kuroyanagi,[c]
Seigo Fukushima[c] and Seiichi Inayama [*,a]

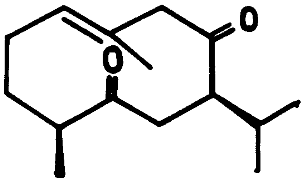
Pharmaceutical Institute, School of Medicine, Keio University,[a]
35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan, Faculty of
Pharmaceutical Sciences, The Universtiy of Tokyo,[b] 7-3-1 Hongo,
Bunkyo-ku, Tokyo 113, Japan, and Shizuoka College of Pharmacy,[c]
2-2-1 Kojika, Shizuoka-shi, Shizuoka 442, Japan

The complete stereostructure of neocurdione (1a) from *Curcuma wenyujin* and *C. aromatica* was determined unequivocally on the basis of chemical transformation of curdione (2a) to 4-epicurdione (1b) as well as X-ray crystallography of the *p*-bromobenzoate (3b) of 8αH-dihydro-4-epicurdione (3a). The preferred conformation of 1a in solution was found to be A [C(10)-CH_3/C(5)=O: *anti*] based on ^{1}H-NMR spectrometry at various temperatures, and NOE measurements, especially at -60°C. In contrast, the preferred conformation of 1a in crystals (X-ray) was found to be B [C(10)-CH_3/C(5)=O: *syn*] . A conformational analysis of 1a, 1b and 2a is also presented based on molecular dynamics calculations using MM2.

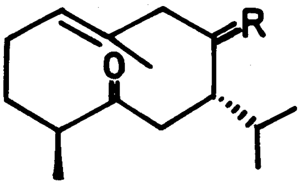
KEYWORDS ——— neocurdione; *Curcuma wenyujin*; *Curcuma aromatica*; Zingiberaceae; germacranoid; absolute configuration; ^{1}H-NMR (500 MHz); variable-temperature; NOE; X-ray diffraction

In our continuous study on bioactive sesquiterpenoid constituents in *Curcuma wenyujin*, the structure of neocurdione, a new isomer of curdione (2a), has been deduced to be 7-epicurdione (1a)(4α,7αH) or its antipode, 4-epicurdione (1b)(4β,7βH).[3)] This communication concerns the unambiguous elucidation of the absolute configuration of 1a (4*S*, 7*R*) on the basis of the chemical transformation to 4-epicurdione (1b)(4*R*, 7*S*), i.e., the antipode of naturally occurring neocurdione (1a) from curdione (2a)(4*S*, 7*S*), whose absolute configuration has been established.[4)] The complete stereostructure of 1a was determined by an X-ray diffraction study of the *P*-bromo-benzoate (3b) of 8αH-dihydro-4-epicurdione (3a)(4*S*, 7*S*, 8*R*) obtained from 8βH-dihydro-4-epicurdione (2c)(4*R*, 7*S*, 8*S*) which was derived by epimerization of 8βH-dihydrocurdione (2b)(4*S*, 7*S*, 8*S*).[5)]

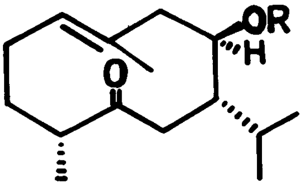
In order to decide which is the correct structure of neocurdione, 1a or 1b, the following chemical transformations were carried out. Curdione (2a) was reduced with sodium borohydride in methanol at room temperature for 3 h to give ketol (2b):



1a
1b: 1a(4β, 7βH)



2a (R=O)
2b (R=αOH)
2c: 2b(4βH)

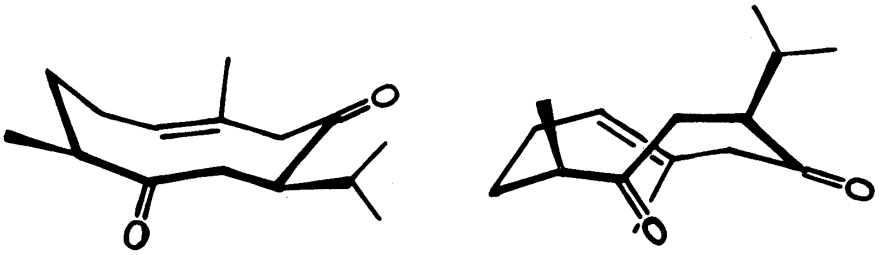


3a (R=H)
3b (R=COC$_6$H$_4$Br)

$C_{15}H_{26}O_2$, mp 55-58°C, $[\alpha]_D^{19}$ +70.25° (c, 2.10; $CHCl_3$), EI-MS m/z 238 (M^+) [cf. 8αH-dihydro-curdione, mp 163-164°C; $[\alpha]_D^{24}$ +3.07° (c, 3.58; $CHCl_3$)[4b]]. 2b was treated with potassium tert-butoxide in benzene in a 4:1 mixture of the starting material (2b) and its C(4)-epimer (2c). The 2c was separated by silica gel chromatography using hexane-ether. 8βH-dihydro-4-epicurdione (2c) $C_{15}H_{26}O_2$, oil, $[\alpha]_D^{20}$ -0.26° (c, 3.82; $CHCl_3$), EI-MS (M^+) 238, was oxidized with chromic anhydride in pyridine to give 4-epicurdione (1b): $C_{15}H_{24}O_2$, mp 45-47°C, $[\alpha]_D^{22}$ +65.88° (c, 1.20; $CHCl_3$), EI-MS m/z 236 (M^+), CD $[\theta]_{300}$ +36,585; $[\theta]_{223}$ -12,589 (c = 3,800, MeOH). The physical characteristics of 1b were identical in every respect with those of neocurdione (1a), except the sign of optical rotation $[\alpha]_D^{22}$ -65.80° (c, 1.20; $CHCl_3$)[3] and the sign of the CD Cotton effect [$[\theta]_{299.5}$ -36,060; $[\theta]_{223}$ +12,368 (c = 5,084, MeOH)].[3] This clearly shows that neocurdione is the antipode of 4-epicurdione (1b) and should be expressed as 1a. In addition a rapid reduction of 1b with lithium aluminum hydride in tetrahydrofurane afforded the oily 2c (80%) together with its crystalline 8αH-epimer (3a)(8%) (mp 102-103°C).

To further confirm the absolute structure (1a) thus deduced, *p*-bromobenzoate (3b)(4*S*, 7*S*, 8*R*), which was prepared in good yield by treatment of 3a with *p*-bromobenzoyl chloride in pyridine in the presence of 4-dimethylaminopyridine, was submitted to X-ray crystallographic analysis. 3b: $C_{22}H_{29}O_3Br$, mp 123-124°C, $[\alpha]_D^{20}$ -11.36° (c, 0.352; $CHCl_3$), IR ν_{max}^{KBr} (cm^{-1}): 1718, 1700, 1593, EI-MS m/z 220 ($M^+-BrC_6H_4COOH$), ^1H-NMR ($CDCl_3$) δ: 7.90 (2H, d, J = 7.0, arom.-H), 7.59 (2H, d, J = 6.5, arom.-H), 5.13 (2H, br s, 1- and 8αH), 2.63 (1H, br s, 4-H), 1.86 (3H, s, 10-CH_3), 1.15 (3H, d, J = 7.32, 4-CH_3), 0.83 (3H, d, J = 6.84, 11-CH_3), 0.67 (3H, d, J = 6.59, 11-CH_3).

The absolute configuration of 3b was determined by the anomalous dispersion of CuKα radiation by the bromine atom. The crystal data are as follows: $C_{22}H_{29}O_3Br$, MW = 421.4, orthorbombic, space group $P2_12_12_1$, lattice constants a = 13.569(1), b = 18.887(2), c = 8.382(0) Å, α = β = γ = 90°, U = 2151.4 $Å^3$, Z = 4, D_{calc} = 1.289 gcm^{-3}. The intensity data of a total of 1720 reflections were collected within the 2θ angle of 156° by graphite monochromated CuKα radiation. The structure was determined by the heavy atom method and refined by the method of least-squares. The final R-value was 0.047.[6] Fig. 1 shows a stereoview of the molecular structure of 3b. Thus, the absolute structure of synthetic 4-epicurdione was independently established to be 1b, and that of naturally occurring neocurdione is automatically expressed as 1a. The crystal structure and conformation of 1a was depicted in a previous paper.[3]



A B

Fig.1. Stereoview of *p*-Bromobenzoate (3b) of 8αH-Dihydro-4-epicurdione (3a)

It is evident that, in the crystalline state,[3] 1a adopts conformation B with a *syn* relationship between C(5)=O and C(10)-CH$_3$, as mentioned above for 3b. This is in sharp contrast with the conformation of curdione (2a),[1,4] in which C(5)=O and C(10)-CH$_3$ was arranged in the *anti*-relationship, solely in the crystal state and predominantly in solution. This prompted us to examine the preferred conformation of 1a in solution. Thus, variable-temperature NMR studies of 1a in solution using 500 MHz ^{1}H-NMR spectrometer were undertaken. While the spectrum showed a set of well-separated proton signals at C(1)-H and C(10)-CH$_3$ at room temperature, at -60°C two sets of signals appeared with an intensity ratio of approximately 2:1 [i.e. C(1)-H: δ 4.98 and 5.48; C(10)-CH$_3$: δ 1.76 and 1.59]. This indicates that each of the signals is assigned to the respective conformers. This would be represented by conformation A and B by analogy with curdione (2a).[4a] To determine the conformation of the major one, the intramolecular nuclear Overhauser effect (NOE) was measured at -60°C. When the frequency corresponding to the C(10)-CH$_3$ of the predominant conformer was saturated, 3% of NOE was observed in C(9)-αH. In addition, the C(1)-H signal of the major conformer (δ 4.98) appears to be upward compared to the corresponding proton of the minor one (δ 5.48). In contrast, the C(10)-CH$_3$ signal of the major one is observed at a lower field (δ 1.76) than that of the minor conformer (δ 1.59). It is of special interest that neocrudione (1a) is considered to adopt mainly more stable conformations such as conformation A [C(10)-CH$_3$/C(5)=O: *anti*] in solution but less stable conformations such as conformation B [C(10)-CH$_3$/C(5)=O: *syn*] in crystals.[3]

To assess this problem further, the relative strain energies of both the *anti* and *syn* type conformations were calculated using the MM2 force field program.[7] The calculated ratio between the *anti* and *syn* type conformations was 68:32.[1,8] The ratio coincided with that obtained experimentally by the ^{1}H-NMR studies described above. This shows that the *syn* type conformation of neocurdione (1a) in crystals was relatively unstable both in solution (^{1}H-NMR studies) and in the gas phase (MM2 calculations). The existence of the unusually labile structure depicted by the X-ray analysis may be explained by stabilization due to interactions with neighboring molecules in the crystalline state. More precise calculations and discussions about the conformation of 1a and 2a will be reported in a following paper.

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REFERENCES AND NOTES

1) Presented at the 106th annual meeting of Pharmaceutical Society of Japan, Chiba, Paper abstract, p. 198, Apr. 2, 1986.

2) a) Visiting Research Associate of Keio University on leave from the Dalian Institute of Medicinal and Pharmaceutical Sciences; b) Visiting Lecturer of Keio University from Yakult Institute for a joint project.

3) T. Ohkura, Ji-Fu Gao, K. Harimaya, M. Hikichi, T. Kawamata, Y. Iitaka, Wu-Xiu Yiṅg, T. Nishishita, and S. Inayama, Jpn. J. Pharmacog., *40*, 352 (1986). The curdione isomer isolated from *C. aromatica* by two of the authors (M.K. and S.F.)cf.3) has finally been found by our careful comparative reexamination to coincide in every respect with the neocurdione isolated from *C. wenyujin*.3)

4) a) S. Inayama, Ji-Fu Gao, K. Harimaya, Y. Iitaka, Yong-Tian Guo and T. Kawamata, Chem. Pharm. Bull., *33*, 1323 (1985); b) S. Inayama, Ji-Fu Gao, K. Harimaya, M. Hikichi, Y. Iitaka, Yong-Tian Guo and T. Kawamata, *ibid.*, *33*, 2179 (1985).

5) Loc. cit. ref. 5 in **4**b: cf. H. Hikino, Y. Sakurai, H. Takahashi and T. Takemoto, Chem. Pharm. Bull., *15*, 1390 (1960).

6) The final atomic parameters will be deposited with the Cambridge Crystallographic Data Center and the F_o, F_c table may be obtained upon request from one of the authors (Y.I.).

7) N. L. Allinger, J. Am. Chem. Soc., *99*, 8127(1977).

8) As a comparative example, the calculated ratio of the major conformations of curdione (2a) represented by conformation **A** [C(10)-CH_3/C(5)=O: *anti*]4a) to the minor conformations represented by conformation **B** [C(10)-CH_3/C(5)=O: *syn*]4a) was shown to be 70:30. This accorded with the ratio (5:1) in solution (-70°C).4a)

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