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Crystal Structure of Byakangelicin ($C_{17}H_{18}O_7$)

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The crystal structure of byakangelicin, one of furanocoumarin aldose reductase inhibitors, was determined by X-ray diffraction method. The crystal is triclinic, with a = 8.114(1), b = 10.194(1), c = 11.428(1)Å, α = 111.50(1), β= 95.57(1), γ= 112.52(1)°, D_x = 1.41, D_m = 1.39 g/cm^3, space group P1 and Z = 2. The intensity data were collected by ω-2θ scan method with CuK_a radiations. The structure was solved by direct method and refined by full matrix least-squares procedure to the final *R*-value of 0.056. There are two molecules with different conformations in an asymmetric unit. The molecules are kept by two intermolecular O-HO type hydrogen bonds and van der Waal's forces in the crystal. The absolute configuration of the molecules was estimated to S-form by the 'Eta refinement' procedure.

Key words: Byakangelicin, Aldose reductase inhibitor (ARI), Absolute configuration, X-ray diffraction

INTRODUCTION

Several furanocoumarins isolated from *Angelicae* plants most frequently prescribed in Chinese medicines, have been found to cause a profound inhibitory activity of the hepatic microsomal cytochrome *P-450* dependent mixed-function oxidase (*MFO*) system, and this activity was accompanied by the loss of cytochrome *P-450* itself (Shin and Moo, 1986, 1990).

Furanocoumarins such as byakangelicin, neobyakangelicol and isopimpinellin strongly inhibit insulin-stimulated lipogenesis. Therefore, the crude drug *Byakuchi* may activate the actions of lipolytic hormones and selectively inhibit the effects of antilipolytic hormones (Kimura and Arichi, 1982).

The enzyme aldose reductase (*AR*) which brings about intracellular accumulation of sorbitol or galactitol in the polyol pathway of aldose metabolism has been demonstrated to play important roles not only in the cataract formation in the lens (Van Heyningen, 1959; Pirie and Van Heyningen, 1964) but also in the pathogenesis of diabetic complications such as neuropathy (Ward, 1973), retinopathy (Engerman and Kern, 1984) and nephropathy (Beyer-Mears *et al.*, 1984).

Evidence, therefore, suggests that compounds which inhibit *AR* are expected to be effective in preventing the sugar cataract formation as well as in the diabetic complications. Recently, a number of structurally diverse *AR* inhibitors (*ARI*) not only of synthetic but also of natural origin, have been extensively studied to clarify their *in vivo* effects for prevention of cataract formation as well as diabetic complications in experimental animals (Dvornic *et al.*, 1973) and even in clinical trials (Handelsman and Turtle, 1981).

Several synthetic *ARI*s are currently available and many have been tested for their clinical use, albeit with limited success (Raskin and Rosenstock, 1987), i.e.; Synthetic compounds with diverse structures such as sorbinil (Beyer-Mears and Cruz, 1985), epalrestat (Terashima et al., 1982), flavonoids (Shimazu, 1984) and isoliquiritigenin (Aida et al., 1990) from natural origin have been extensively studied and reported to inhibit *AR*. Shin and co-workers carried out the research for a new potential *AR* inhibitor useful for the treatment of galactosemic as well as for the diabetic cataract from *Angelica dahurica* roots and they found that byakangelicin is the most promising active principles utilizable as a lead compound,

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because this compound not only inhibited AR *in vitro* but also prevented from formation of galactosemic cataract *in vivo*, and furthermore, it was a main component peculiar to the plant part.

In this work, the three dimensional structure of byakangelicin,7-(2,3-dihydroxy-3-methylbutoxy)-6-hydroxy-4-methoxy-5-benzofuranacrylic acid, extracted from the roots of *Angelica dahuria (Umbelliferae)*, was determined by X-ray diffraction method in order to provide useful information for the understanding of the structure-activity relationship.

METHODS

Yellowish prismatic crystals were grown by slow evaporation from a mixture of methanol and ether at room temperature.

Crystal data

$C_{17}H_{18}O_7$	CuK radiation
M_r = 334.33	λ= 1.5418
Triclinic	Cell parameters from 25
P1	reflections (range 11.7-18.7°)
a = 8.114(1) Å	
b = 10.194(1)Å	m= 0.872
c = 11.428(1)Å	*T*= 293 K
α= 111.50(1)°	Colourless Prism
β= 95.57(1)°	0.3 × 0.3 × 0.2 mm^3
γ= 112.52(1)°	
V = 780.8(2)Å^3	*Z* = 2
D_x = 1.41 g/cm^3	
D_m = 1.39 g/cm^3 (measured by flotation in KI solution)	

Data collection

Enraf-Nonius CAD4	R_{int} = 0.025
diffractometer	q_{max} = 70.0°
w/2q scans	*h* = -9 → 9
Absorption correction:	*k* = -11 → 11
none	*l* = 0 → 13
2927 measured reflections	3 standard reflections
2731 unique reflections	frequency: 60 min
2584 observed reflections	intensity decay: 1.2%
[$F > 3\sigma(F)$]	

Table I. Fractional atomic coordinates and equivalent isotropic displacement parameters(Å ^{2}, X10^4) with their e.s.d's. $U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

Atom	[Molecule A] x/a	y/b	z/c	Ueq	[Molecule A] x/a	y/b	z/c	Ueq
O(1)	9780(6)	3145(5)	1277(4)	63(2)	-204(5)	6459(5)	8421(4)	61(2)
O(2)	11084(6)	5954(5)	3492(4)	76(2)	-1362(6)	3754(5)	6226(4)	75(2)
O(3)	13752(6)	8719(4)	3414(4)	55(2)	-4090(6)	928(5)	6318(4)	67(2)
O(4)	13767(6)	5638(5)	-878(4)	73(2)	-4019(7)	3978(5)	10581(4)	76(2)
O(5)	8035(8)	627(6)	358(7)	111(3)	1621(7)	9059(6)	9385(5)	92(3)
O(6)	7745(8)	4872(6)	4401(5)	89(2)	-931(8)	2694(7)	3806(5)	103(3)
O(7)	9444(8)	9140(5)	5863(6)	86(2)	2 08(7)	491(5)	3882(5)	79(2)
C(8)	15012(8)	9698(7)	3016(6)	63(2)	-5380(9)	-53(8)	6713(7)	71(3)
C(9)	15111(9)	8921(7)	1793(7)	72(3)	-5390(8)	714(7)	7910(6)	58(3)
C(10)	13773(7)	7278(5)	1338(5)	42(2)	-4074(7)	2346(7)	8375(6)	57(2)
C(11)	12987(7)	7238(6)	2383(5)	46(2)	-3342(8)	2400(6)	7331(5)	53(2)
C(12)	11699(7)	5919(7)	2419(5)	56(2)	-2042(8)	3735(7)	7299(5)	53(2)
C(13)	11164(6)	4519(6)	1287(5)	42(2)	-1457(7)	5116(7)	8398(5)	59(3)
C(14)	9172(9)	1698(7)	239(7)	69(3)	4 75(8)	7946(8)	9476(6)	67(3)
C(15)	9943(10)	1640(8)	-831(7)	64(3)	-286(10)	8010(8)	10576(7)	70(3)
C(16)	11199(8)	2942(7)	-845(6)	59(3)	-1547(9)	6720(7)	10580(5)	57(3)
C(17)	11844(7)	4456(6)	205(5)	48(2)	-2190(7)	5174(6)	9472(5)	48(2)
C(18)	13130(8)	5818(7)	214(5)	59(2)	-3497(7)	3770(6)	9481(5)	46(2)
C(19)	14548(13)	6906(11)	-1194(8)	82(4)	-4847(11)	2693(8)	10905(7)	79(3)
C(20)	9812(9)	6593(8)	3695(5)	61(3)	-187(9)	2942(7)	5999(6)	71(3)
C(21)	9122(7)	6510(6)	4838(5)	53(2)	608(8)	3184(7)	4894(5)	55(2)
C(22)	8125(8)	7500(7)	5280(5)	58(2)	1625(8)	2122(6)	4427(5)	55(2)
C(23)	7202(10)	7214(10)	6322(7)	80(4)	2398(13)	2387(10)	3335(9)	78(4)
C(24)	6633(11)	7241(11)	4162(7)	84(4)	3114(13)	2427(12)	5528(9)	99(5)

Table II. The bond lengths(Å) of byakangelicin with their e.s.d's.

	[Mol. A]	[Mol. B]		[Mol. A]	[Mol. B]
O(1)-C(13)	1.416(6)	1.346(6)	O(1)-C(14)	1.368(7)	1.395(7)
O(2)-C(12)	1.361(6)	1.396(6)	O(2)-C(20)	1.412(6)	1.469(6)
O(3)-C(8)	1.375(7)	1.387(8)	O(3)-C(11)	1.374(6)	1.361(7)
O(4)-C(18)	1.374(6)	1.335(6)	O(4)-C(19)	1.401(9)	1.425(7)
O(5)-C(14)	1.193(7)	1.209(7)	O(6)-C(21)	1.462(7)	1.456(7)
O(7)-C(22)	1.435(7)	1.453(7)	C(8)-C(9)	1.359(9)	1.306(9)
C(9)-C(10)	1.454(8)	1.440(8)	C(10)-C(11)	1.413(7)	1.394(7)
C(10)-C(18)	1.418(7)	1.394(8)	C(11)-C(12)	1.370(8)	1.382(8)
C(12)-C(13)	1.401(7)	1.364(8)	C(13)-C(17)	1.392(7)	1.407(7)
C(14)-C(15)	1.420(1)	1.445(9)	C(15)-C(16)	1.336(9)	1.324(9)
C(16)-C(17)	1.413(8)	1.462(7)	C(17)-C(18)	1.377(8)	1.423(7)
C(20)-C(21)	1.488(7)	1.529(7)	C(21)-C(22)	1.503(7)	1.576(7)
C(22)-C(23)	1.525(8)	1.514(8)	C(22)-C(24)	1.541(8)	1.506(9)

Table III. The bond angles(°) of byakangelicin with their e.s.d's.

C(14)-O(1)-C(13)	120.7(5)	123.9(4)	C(20)-O(2)-C(12)	114.6(4)	111.6(4)
C(11)-O(3)-C(8)	105.6(4)	105.8(5)	C(19)-O(4)-C(18)	121.0(5)	121.2(5)
C(9)-C(8)-O(3)	12.9(5)	111.6(6)	C(10)-C(9)-C(8)	105.7(6)	107.9(6)
C(11)-C(10)-C(9)	105.0(5)	104.4(5)	C(18)-C(10)-C(9)	138.3(5)	137.8(5)
C(18)-C(10)-C(11)	16.7(5)	117.6(5)	C(10)-C(11)-O(3)	110.7(5)	110.2(5)
C(12)-C(11)-O(3)	123.2(5)	123.7(5)	C(12)-C(11)-C(10)	126.0(5)	126.1(5)
C(11)-C(12)-O(2)	122.9(5)	124.7(5)	C(13)-C(12)-O(2)	123.1(5)	119.5(5)
C(13)-C(12)-C(11)	113.9(4)	115.8(5)	C(12)-C(13)-O(1)	115.1(4)	118.5(5)
C(17)-C(13)-O(1)	121.1(4)	119.7(5)	C(17)-C(13)-C(12)	123.7(5)	121.7(5)
O(5)-C(14)-O(1)	114.5(7)	117.6(6)	C(15)-C(14)-O(1)	117.5(5)	116.5(5)
C(15)-C(14)-O(5)	128.0(7)	126.0(6)	C(16)-C(15)-C(14)	121.8(6)	121.4(6)
C(17)-C(16)-C(15)	122.0(6)	120.6(6)	C(16)-C(17)-C(13)	116.6(5)	117.8(5)
C(18)-C(17)-C(13)	120.1(5)	120.9(5)	C(18)-C(17)-C(16)	123.2(5)	121.3(5)
C(10)-C(18)-O(4)	124.3(5)	127.1(5)	C(17)-C(18)-O(4)	116.1(5)	115.0(4)
C(17)-C(18)-C(10)	119.5(5)	117.9(5)	C(21)-C(20)-O(2)	111.5(4)	106.2(4)
C(20)-C(21)-O(6)	106.5(5)	108.0(5)	C(22)-C(21)-O(6)	106.1(4)	108.9(4)
C(22)-C(21)-C(20)	113.1(4)	109.7(5)	C(21)-C(22)-O(7)	109.1(5)	106.5(4)
C(23)-C(22)-O(7)	106.8(5)	107.9(5)	C(23)-C(22)-C(21)	111.9(5)	108.4(5)
C(24)-C(22)-O(7)	107.0(5)	109.6(6)	C(24)-C(22)-C(21)	113.8(5)	112.6(5)
C(24)-C(22)-C(23)	107.9(5)	111.6(6)			

Refinement

Refinement on F
R = 0.056
wR^2 = 0.081
S = 0.605
2534 reflections
563 parameters
All H-atom parameters refined

Unit weights applied
$(\triangle/\sigma)_{max}$ = 0.17
$\triangle\rho_{max}$ = 0.250Å^{-3}
$\triangle\rho_{min}$ = -0.020Å^{-3}
atomic scattering factors from *SHELX76* (Sheldrick,1976)

Intensity data were collected with a scan width of $\triangle\omega$= (1.2 ± 0.15θ)°(estimated from ω-θ plots). The counter aperture was also adjusted as a function of θ. The horizontal aperture width ranged from 2.0 to 3.1 mm, while the vertical one was set at 4 mm. All reflections were corrected for the usual Lp effects and decay compensation was applied.

Data collection: CAD-4 software (Enraf-Nonius, 1989). Cell refinement: CAD-4 software (Enraf-Nonius, 1989). Data reduction: MolEN (Fair,1990). Program(s) used to

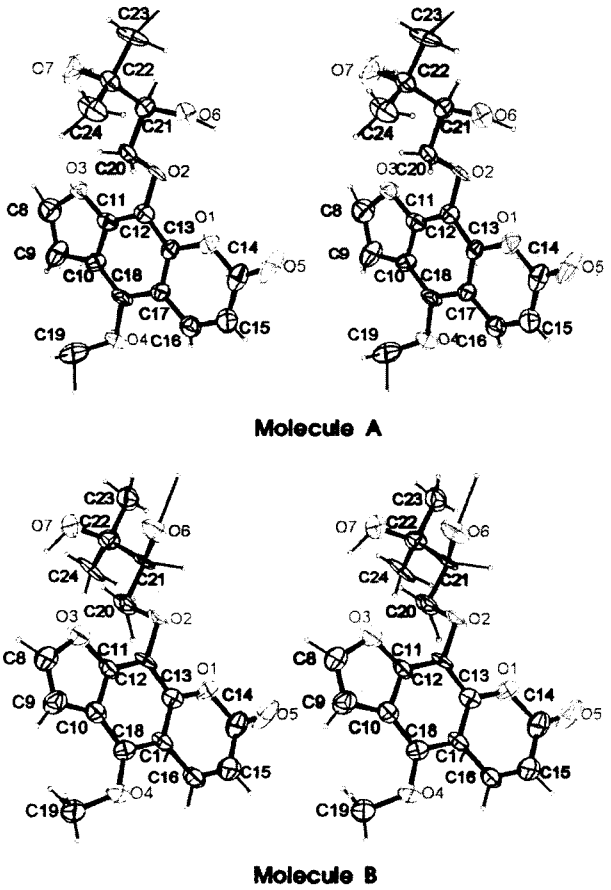

Fig. 1. ORTEPII (Johnson, 1976) drawing of byakangelicin with the atomic numbering scheme. The displacement ellipsoids are drawn at the 50% probability level. H atoms are drawn as small circles of arbitrary radii.

solve structure : MULTAN84 (Main, Germain & Woolfson,1984). Program(s) used to refine structure: SHELX76 (Sheldrick, 1976). Molecular graphics: ORTEP (Johnson, 1976). Software used to prepare material for publication: MolEN (Fair,1990).

RESULTS AND DISCUSSION

There are two byakangelicin molecules in an asymmetric unit, which are tentatively named as molecule A and molecule B. The atomic parameters are presented in Table I.

Bond lengths and angles of this molecule are within the range of chemically reasonable values (Table II, III). The stereoscopic views of both The conformations of both molecules are slightly different. The torsion angles of O(6)-C(21)-C(22)-C(24) are -67.12° (*gauche*) in molecule A and molecules, drawn by *ORTEP* II (Johnson, C.K., 1976), are presented in Fig.1.

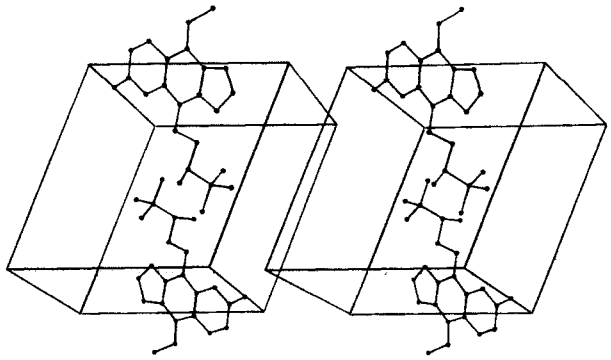

Fig. 2. Crystal packing of byakangelicin

-173.93° (*trans*) in molecule B. However, those of O(6)-C(21)-C(22)-O7 are 173.45° (*trans*) in molecule A and -53.78° (*gauche*) in molecule B.

The molecules in crystal state are kept by two intermolecular O-HO type hydrogen bonds. The distance of O6(A)(x,y,z)-HO6(B)(x+1,y,z) is 2.694 Å and that of O7(A)(x,y,z)H-O7(B)(x+1,y+1,z) is 3.079 Å. The molecules are kept by *van der Waal's* forces in crystal.

The absolute configuration was estimated by using the '*Eta* refinement' in the *MolEN* program package to refine the final atomic coordinates together with the eta parameter. After *Eta* refinement with the value of *Eta* parameter ; -1, the final R value was 7.6%. This result shows that present configuration is reasonable and both molecules have *S* forms.

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REFERENCES

Aida K., Tawata M., Shindo H., Onaya T., Sasaki H., Yamaguch T., Chin M. and Mitsuhashi H., Isoliquiritigenin; A new aldose reductase inhibitor from *Glycyrrhizae Radix*. *Planta Medica* 56, 255 (1990).

Beyer-Mears A., Ku L. and Cohen M., Glomerular polyol accumulation in diabetes and its prevention by oral sorbinil. *Diabetes* 33, 604 (1984).

Beyer-Mears A. and Cruz E., Reversal of diabetic cataract by sorbinil, an aldose reductase inhibitor. *Diabetes* 34, 15 (1985).

C. Kay Fair, *MolEN, Structure Determination System* (1990).

Donald R., On the application of Hamilton's Ratio Test to the Assignment of absolute configuration and an Alternative Test. *Acta Cryst.* 37(A), 734 (1981).

Dvornic D., Simard-Duguesne N, Krami M., Sestanj K., Gabbay K H., Kinoshita J. H., Varma S. D. and Merola L. O., Polyol accumulation in galactosemic inhibitor. *Science(Wash. D. C.)* 182,1146 (1973).

Engerman R. L and Kern T. S., Experimental galactosemia produces diabetic-like retinopathy. *Diabetes*, 33, 97 (1984).

Enraf-Nonius, *CAD-4* software. *Version 5*. Enraf-Nonius, Delft, The Netherlands. (1989).

Fair, C. K., *MolEN. An Interactive Intelligent System for Crystal Structure Analysis*. Enraf-Nonius, Delft, The Netherlands. (1990).

Handelsman D. J. and Turtle J. R., Clinical trial of a aldose reductase inhibitor in diabetic neuropathy. *Diabetes* 30, 459 (1931).

Inagaki K., Miwa I., Yashiro T. and Okuda J., Inhibition of aldose reductase from rat and bovine lenses by hydantoin derivatives. *Chem. Pharm. Bull.* 30, 3244 (1982).

Johnson C. K., *ORTEP, A FORTRAN Thermal Ellipsoid Plot Program for Crystal Structure Illustrations* (ORNL-5138). *Oak Ridge National University, ennessee* (1976).

Kimura Y., Ohminami H., Arichi H., Okuda H., Baba K., Kozawa M., Arichi S., Effects of various coumarins from roots of *Angelica Dahurica* on actions of adrenaline, ACTH and insulin in fat cells. *Planta Med.*, 45, 183 (1982).

Main P., Germain G. and Woolfson M.M., *MULTAN, A Computer Program for Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univ. of York, England (1976).

Pirie A. and Van Heyningen R., The effect of diabetes on the content of the sorbitol, glucose, fructose and inositol in the human lens. *Exp. Eye Res.* 3, 124 (1965).

Raskin P. and Rosenstock J., Aldose reductase inhibitors and diabetic complications. *AM. J. Med.* 83, 298 (1987).

Terashima H., Hama K., Yamamoto R., Tsuboshima M., Kikkawa R., Hatanaka I. and Shigeta Y., Effects of a new aldose reductase inhibitor on various tissues *in vitro*. *J. Pharm. Exp. Ther.* 229(1), 226 (1984).

Shimazu M., Ito T., Terashima S., Hayashi T., Arisawa M., Morita N. Kurokawa S., Ito K. and Hashmoto Y., Inhibition of lens aldose reductase by flavonoids. *Phytochem.* 23, 1885 (1984).

Sheldrick G.M., *SHELX, Program for Crystal Structure Determination*, Univ.of Cambridge, England (1976).

Shin, K. H., and Woo, W. S., Inhibition of hepatic microsomal drug-metabolizing enzymes by imperatorin, *Arch. Pharm. Res.*, 9, 81 (1986).

Shin, K. H., Kim, Woo, W. S., The mode of the activity of naturally occurring furanocoumarins on hepatic cytochrome P-450 enzyme system. *Kor. J. Pharmacogn.*, 21, 74 (1990).

Shin K. H., Chung M. S., Chae Y. J., Yoon K. Y. and Cho T. S., A survey for aldose reductase inhibition of some herbal medicines. *Fitoterapia* LXIV(2), 130 (1993a).

Shin K. H., Woo W. S., Moon K. H. and Yoo S. J., Effects of naturally occurring furanocoumarins of lipid peroxidation and carbon tetrachloride-induced hepatotoxicity in mice. *Arch. Pharm. Res.* 16, 13 (1993b).

Shin K. H., Chung M. S., and Cho T. S., Effects of Furanocoumarins from *Angelica Dahurica* on Aldose Reductase and galactosemic cataract formation in rats. *Arch. Pharm. Res.* 17, 331 (1994).

Van Heyningen R., Formation of polyol by the lens of the rat with sugar cataract. *Nature*, 184, 194 (1959).

Ward J. D., The polyol pathway in the neuropathy of early diabetes. In "*Advances in Metabolic Disorders (Suppl.2)*" *ed. by R. A. Camerini-Davalos and H. S. Cole, Academic Press, New York*, p.425 (1973).