Registry No. 1(Ar = Ph), 71734-80-0; **3**, 1022-45-3; **7**, 71734-82-2; **8**, 16776-73-1; **I** Li salt, 71734-83-3; **9a**, 71734-84-4; **9b**, 71734-85-5; tosyl chloride, 98-59-9; isopropylamine, 75-31-0.

Crystal Structure and Stereochemistry of Ivalbin, a Xanthanolide[1]

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Our X-ray analysis of parthemollin (**1**)[2] established the stereochemistry of a number of xanthanolides with a cis-fused γ-lactone ring closed toward C-6[3] and showed that in this series neither the Stöcklin–Waddell–Geissman rule[4] for predicting the nature of the ring fusion from the lactone Cotton effect nor Beecham's suggestion[5] that the sign of the lactone Cotton effect is determined by the chirality of the C=C—C=O chromophore is valid. It was therefore of interest to examine a xanthanolide with a lactone ring closed toward C-8; we selected ivalbin (**2**)[6,7] because some doubt remained[7] about its configuration at C-2.

Crystal data for ivalbin are listed in the Experimental Section. Figure 1 is a stereoscopic drawing of the molecule which shows that our original[7] stereochemical assignments were correct. Figure 1 also represents the absolute configuration for two reasons. (1) Application of the Horeau method to two derivatives of ivalbin showed[7] that its configuration of C-4 was *S*; (2) ivalbin was correlated[6-8] with xanthinin (**3**) without altering the stereochemistry at C-10. Xanthinin, in turn, was degraded to (−)-*S*-methylsuccinic acid. Hence the configuration of ivalbin at C-10 is also *S*.

The lactone ring fusion of ivalbin is trans with H-7α, i.e., it is 7*R*,8*S* as originally deduced[7] on biogenetic grounds and on the basis of the positive Cotton effect in a lactone closed to C-8 (Stöcklin–Waddell–Geissman rule). The analysis thus provides independent evidence for the stereochemistry assigned[8] to C-7 and C-8 of xanthinin and various congeners which have been correlated with ivalbin; the configuration of these compounds at C-2 (and in the case of xanthanol and isoxanthanol, at C-4 as well) remains unknown.

Tables I–IV listing final atomic and final anisotropic thermal parameters, bond lengths, and bond angles of ivalbin are available as supplementary material. Table V lists selected torsion angles. As is also apparent from Figure 1, the cycloheptene ring in the crystal adopts a chair conformation which is slightly distorted from C_s symmetry, possibly as the result of a serious C-10, methyl, C-1 side-chain interaction which would develop in a distorted boat.[9] The ^{1}H NMR coupling constants (see Table VI) indicate that this is also the conformation adopted in solution. The α-methylene γ-lactone ring is much less flattened than in parthemollin, the sum of the internal torsion angles (Table V) being 101° instead of 39°, and deviates significantly from the envelope conformation, with C(8)–O(3)–C(12)–C(11) and O(3)–C(12)–C(7) torsion angles of 11.3 and 8.8° (±0.5°), respectively. The C(13)–C(11)–C(12)–O(4) angle is 10.5°; the chirality of the C=C—C=O chromophore

Table V. Torsion Angles (deg) in Ivalbin[a]

C(10)-C(1)-C(5)-C(6)	−7.5
C(1)-C(5)-C(6)-C(7)	−41.0
C(5)-C(6)-C(7)-C(8)	67.7
C(6)-C(7)-C(8)-C(9)	−80.7
C(7)-C(8)-C(9)-C(10)	76.7
C(11)-C(7)-C(8)-O(3)	30.3
C(7)-C(8)-O(3)-C(12)	−27.0
C(8)-O(3)-C(12)-C(11)	11.3
O(3)-C(12)-C(11)-C(7)	8.8
C(12)-C(11)-C(7)-C(8)	−23.9
C(13)-C(11)-C(12)-O(4)	10.5
C(6)-C(5)-C(1)-C(2)	173.2
C(5)-C(1)-C(2)-C(3)	−107.3
C(1)-C(2)-C(3)-C(4)	173.3
C(2)-C(3)-C(4)-C(15)	−74.1

[a] Estimated standard deviation for a typical C-C-C-C torsion angle is 0.5°.

Table VI. 270-MHz ^{1}H NMR Spectrum of Ivalbin[a,b]

H-2	4.03 dt	H-9a	2.18 ddd
H-3a	1.5 m[b]	H-9b	1.5 m[b]
H-3b	1.37 dt	H-10	2.71 m
H-4	3.64 m	H-13a	5.98 d
H-5	5.69 dd	H-13b	5.59 d
H-6a	2.53 ddd	H-14	1.05 d[c]
H-6b	2.07 ddd	H-15	1.11 d[c]
H-7	2.40 m	2-OH	4.70 d (5)
H-8	4.37 ddd	4-OH	4.43 d (4)

[a] Run in Me_2SO-d_6 with Me_4Si as internal standard. Values in ppm. [b] Superimposed signals. [c] Intensity three protons. *J*'s (in Hz): 2,3a = 2,3b = 4,15 = 10,14 = 7; 5,6a = 10; 5,6b = 3; 6a,6b = 14; 6a,7 = 2; 6b,7 = 11.5; 7,8 = 12; 7,13a = 3.5; 7,13b = 3; 8,9a = 12.5; 8,9b = 2; 9a,9b = 13; 9a,10 = 3.5; 9b,10 = 10.

Table VII. ^{13}C NMR Spectra[a]

carbon	1	2	3	4
1	143.60	150.06	145.12	139.17
2	65.72 d	76.42 d	66.25 d	25.58 t
3	50.73 t	44.60 t	46.77 t	41.03 t
4	206.58	65.08 d	63.26 d	207.10
5	120.52 d	122.64 d	119.49 d	123.52 d
6	78.65 d	24.73 t	78.91 d	78.02 d
7	37.85 d	48.28 d	38.13 d	38.90 d
8	28.32 d	82.35 d	28.48 t	34.68 t
9	29.77 t	36.79 t	30.20 t	72.48 d
10	32.41 d	28.72 d	32.76 d	33.91 d
11	139.83	139.96	139.14	139.95
12	169.30	169.65	169.36	169.03
13	122.15 t	118.21 t	121.86 t	122.50 t
14	16.48 q	19.50 q	16.56 q	13.51 q
15	30.46 q	23.94 q	24.13 q	29.57
Ac				170.11, 20.96 q

[a] Run in Me_2SO-d_6 at 67.09 MHz with Me_4Si as internal standard. Frequencies are in ppm. All unmarked signals are singlets.

(1) Work at the Florida State University was supported by a grant (CA-13121) from the U.S. Public Health Service through the National Cancer Institute.

(2) (a) Sundararaman, P; McEwen, R. S.; Herz, W. *Tetrahedron Lett.* **1973**, 3809. (b) Sundararaman, P; McEwen, R. S. *J. Chem. Soc., Perkin Trans. 2* **1975**, 440.

(3) In ref 2a through an error in drawing, the C-2 configurations of apachin and ivambrin which are 2*S*, 4*R*, 6*S*, and 10*S*, were incorrectly shown as 4*S*.

(4) Stöcklin, W.; Waddell, T. G.; Geissman, T. A. *Tetrahedron* **1970**, *26*, 2397.

(5) Beecham, A. F. *Tetrahedron* **1972**, *28*, 5543.

(6) Herz, W.; Chikamatsu, H.; Viswanathan, H.; Sudarsanam, V. *J. Org. Chem.* **1967**, *32*, 682.

(7) Chikamatsu, H.; Herz, W. *J. Org. Chem.* **1973**, *38*, 585.

(8) Winters, T. E.; Geissman, T. A.; Safir, D. *J. Org. Chem.* **1969**, *34*, 153.

(9) Such an interaction has been invoked[2b] to explain the observation that the cycloheptene ring of parthemollin adopts a slightly distorted C_s-boat rather than a twist-boat conformation.

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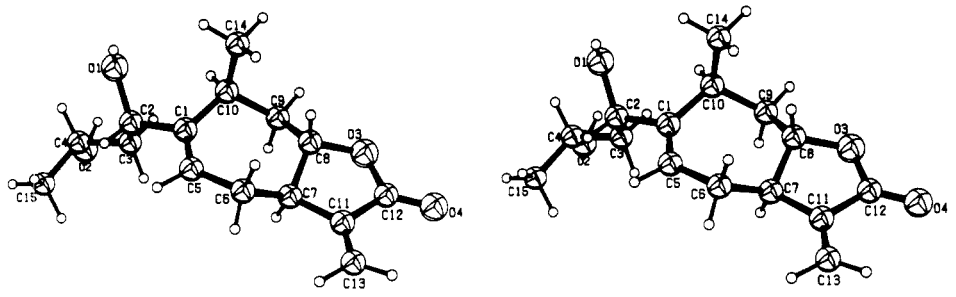
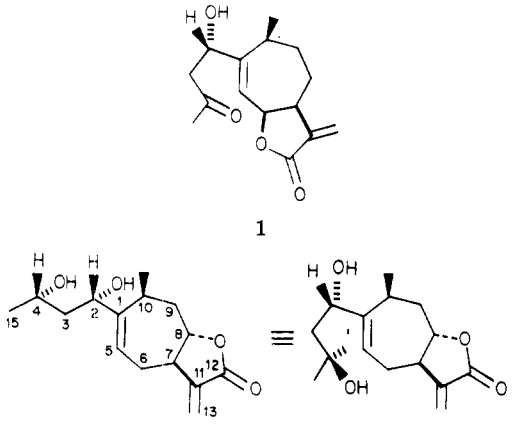


Figure 1. Stereoscopic view of ivalbin.

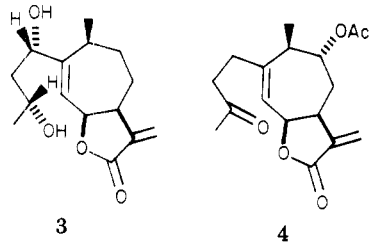
thus corresponds with the observed[7] (positive) Cotton effect (Beecham's generalization) as appears to be generally true for trans-fused lactones on six- or seven-membered rings. McPhail and Sim[10] have pointed out that because of the relative regidity of trans-fused lactone systems it would be expected that the chirality of the C=C—C=O chromophore would be determined by the position of the ring junction, whereas in the case of cis-fused lactones, such as parthemollin, the flexibility of the lactone ring allows no such generalization. They also noted that in both cis and trans lactones the signs of the C=C—C=O and C-(α)-C(β)-C(γ)-O torsion angles were paired. This is true for ivalbin where C(O(3))-C(8)-C(7)-C(11) is 30°; however, parthemollin[2b] and more recently alatolide,[11] a *trans,trans*-1(10),4,5-germacradienolide, constitute exceptions.

Since ^{13}C NMR spectra of xanthanolides have not been reported previously, we list in Table VII ^{13}C NMR spectra of ivalbin (2) parthemollin (1), ivambrin (3)[12] and ivalbatin acetate (4)[7] which will facilitate further work in this area.



1

2



3 4

Multiplets were assigned by single-frequency off-resonance decoupling. The observed chemical shift differences are self-explanatory except for the C-2 signal in **2** and **3** for which $\Delta\delta$, due primarily to the difference in stereochemistry at C-4, seems unusually large. The 10-ppm upfield shift of C-2 in ivambrin probably reflects a large rotamer population with steric interactions between substituents on C-2 and C-4 whereas, at least in the crystalline state of ivalbin (Figure 1), such interactions seem to be minimized.

Experimental Section

Single crystals of ivalbin were prepared by slow crystallization from methanol and were monoclinic, space group $P2_1$, with a = 7.271 (1) Å, b = 6.829 (1) Å, c = 14.739 (2) Å, β = 97.22 (1)° and d_{calcd} = 1.215 g cm^{-3} for z = 2 ($C_{15}H_{22}O_4$, M_r = 266.34). The intensity data were measured on a Hilger-Watts diffractometer (Ni filtered Cu Kα radiation, θ-2θ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.20 × 0.25 × 0.5 mm. A total of 1073 reflections were measured for θ < 57°, of which 1049 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[13] and was refined by full-matrix least-squares methods. Seven reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement anisotropic thermal parameters were used for the heavier atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.033 and R_w = 0.045 for the remaining 1042 observed reflections. The final difference map had no peaks greater than ±0.2 e Å^{-3}.

Registry No. 1, 23264-32-6; 2, 7544-65-2; 3, 33204-43-2; 4, 37163-91-0.

Supplementary Material Available: Tables I–IV listing final atomic parameters, final thermal parameters, bond lengths, and bond angles of ivalbin (3 pages). Ordering information is given on any current masthead page.

(10) McPhail, A. T.; Sim, G. A. *Tetrahedron* **1973**, *29*, 1751.
(11) Cox, P. J.; Sim, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 255.
(12) Yoshioka, H.; Higo, A.; Mabry, T. J.; Herz, W.; Anderson, G. D. *Phytochemistry* **1971**, *10*, 401.
(13) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.

Chlorination and Deoxygenation in the Vilsmeier Reaction of 1-Hydroxypyrazoles and 1-Hydroxypyrazole 2-Oxides

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Pyrazole does not undergo formylation under the conditions of the Vilsmeier reaction, but various 1-substituted pyrazoles do react to give pyrazole-4-carboxaldehydes.[2,3] We wish to report the results of an investigation of the

(1) Visiting Research Professor, on leave from Hong-Ik University, Seoul, Korea.
(2) Mal'tseva, S. P.; Borodulina, Z. A.; Stepanov, B. I. *J. Org. Chem. USSR (Engl. Transl.)* **1973** *9*, 840.
(3) Schofield, K.; Grimmett, M. R.; Keene, B. R. T. "Heteroaromatic Nitrogen Compounds—The Azoles"; Cambridge University Press: Cambridge, England, 1976; p 31.

0022-3263/79/1944-4438$01.00/0