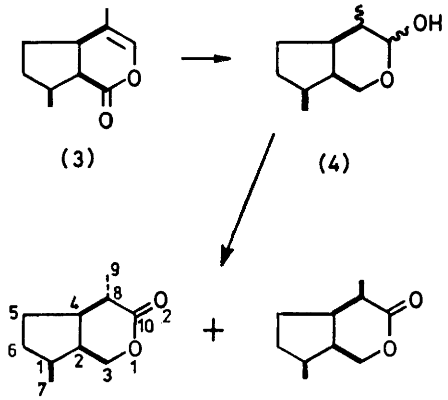
Synthesis and Molecular Structures of (1*S*)-*cis,cis*-Iridolactones

By **Franco Bellesia, Ugo M. Pagnoni,*** and **Roberto Trave,** Istituto di Chimica Organica, Università di Modena, Via Campi 183, 41100 Modena, Italy
Giovanni Dario Andreetti,* Gabriele Bocelli, and **Paolo Sgarabotto,** Istituto di Strutturistica Chimica dell'Università di Parma, C.N.R. Centro di Studio per la Strutturistica Diffrattometrica, Via M. D'Azeglio 85, 43100 Parma, Italy

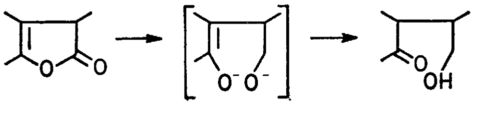
Two *cis,cis*-iridolactones (1) and (2) with a natural (*S*)-configuration at C(1) have been synthesized and their crystal and molecular structures determined by direct methods and refined by least-squares to *R* 0.109 and 0.064. As in the natural *trans,cis*-isomers (iridomirmecines), (5) and (6), the heterocyclic ring has a boat conformation which allows the C(8) methyl group to assume an equatorial position. Spectroscopic measurements indicate that this type of geometry, which has the lowest strain-energy as calculated by molecular mechanics (GEMO program), is also present in solution.

DURING our studies [1] concerning the elucidation of minor components of plants with a structurally simple iridoid skeleton, we have prepared the *cis,cis*-iridolactones (1) and (2), starting from the unsaturated lactone (3), an intermediate we have used previously.[2] The key step in this transformation is the reduction of the lactone system of (3), for which we adopted conditions which would avoid immediate ring-opening, since we have often found this to involve isomerization at C(2). After many unsuccessful attempts, we used the experimental method reported [3] for the reduction of some butenolides to keto-alcohols by $LiAlH_4$ under carefully controlled conditions. When (3) was thus treated, the intermediate aldehydo-alcohol afforded directly the product of intramolecular acetalization (4).



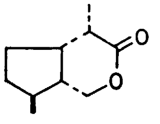
(3) (4) (2) (1)

Crystallographic atom numbering system

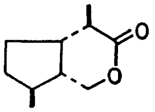


Subsequent oxidation by CrO_3 in pyridine yielded [55% from (3)] a mixture of *cis,cis*-iridolactones; the two irido- (1) and isoirido-type (2) epimers (15 : 85, by g.l.c.) were separated by preparative gas–liquid chromatography.

The synthesis of the enantiomers of (1) and (2) has been previously reported by Wolinsky *et al.*[4] from carvone tribromide; assignment of the irido- or isorido-type structure relied on comparison of the optical rotations with those of the natural *trans,cis*-iridolactones (5) and (6), and assuming that variation in configuration of the methyl group at C(1) does not alter drastically the conformation of the whole molecule.



(5)



(6)

The conformations of the natural iridolactones (iridomirmecines) have been investigated both for the solid state and for solution. *X*-Ray analysis has shown [5a,6] that they have the boat structures indicated in Figure 1a and b, with the methyl group on the lactone ring equatorial as expected.[5]

There is much spectral evidence for such conformations in solution. The i.r. absorptions [7] of the natural irido- and isoirido-mirmecines (1 758 and 1 761 cm^{-1}) are in the range [8] for boat-type δ-lactones [$\nu_{max.}$ (CCl_4) 1 758—1 765 cm^{-1}] rather than that normally accepted for δ-lactones of different conformation (1 730—1 750 cm).[9] In n.m.r. analysis, the shape of the signal related to CH_2–O–C(O) changes according to the geometry of the lactone ring and shows which of the two boat conformations is present. Dreiding models show that the dihedral angles differ between protons of the C(3)–C(2) bond (Figure 2). The coupling constants J_{AX} and J_{BX} are [10] in fact small and of equal value (3 Hz) in the irido-isomer (giving place to a slightly broadened AB singlet), while they are different (10.1 and 5.9 Hz) in the isoirido-isomer (yielding a group of eight lines scattered on *ca.* 1 p.p.m.).

It has been suggested [11,12] that the chirality of the boat form of the lactone ring determines the sign of the n–π^* Cotton effect and that such a sign is opposed to that of the dihedral angle C–C–C(O)–O in the ring.[13] The Cotton effects for irido- and isoirido-mirmecine isolated from *Iridomyrmex humilis* [14] are in agreement with this empirical rule (Table 1).

By assuming boat conformations for the *cis,cis*-iridolactones also, the *cis*-relationship between the cyclopentane methyl and the lactone group may produce a greater strain-energy than in the natural isomers,

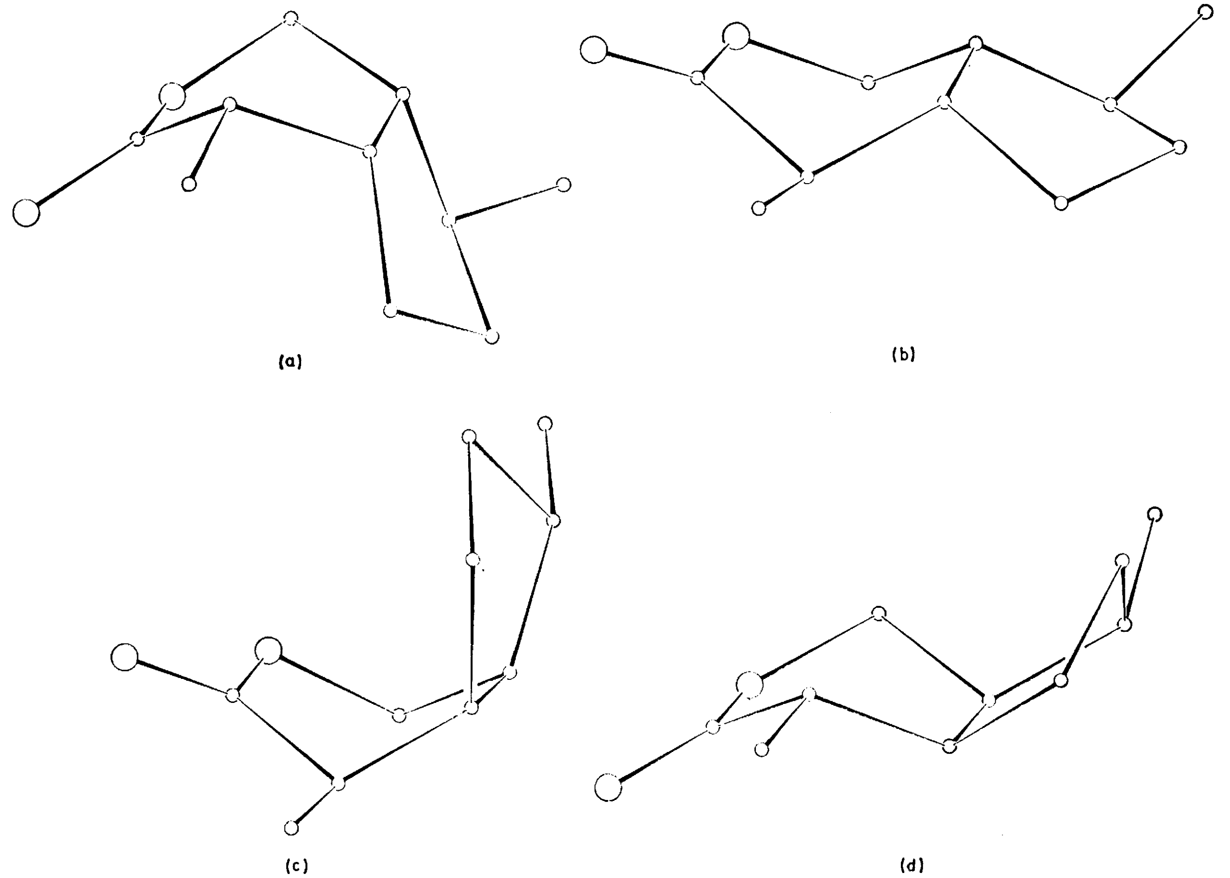


FIGURE 1 Clinographic view of (a) *trans,cis*-iridolactone (5), (b) *trans,cis*-isoiridolactone (6), (c) *cis,cis*-iridolactone (1), and (d) *cis,cis*-isoiridolactone (2)

especially in an *endo*-conformation such as that expected for isomer (1). Since the lactone ring in the boat or half-chair[9] conformation appeared to have some flexibility in certain steric circumstances, we undertook a conformational analysis of (1) and (2), in connection with our studies on the biological activity of this class of monoterpene.

The spectroscopic results (i.r., n.m.r., c.d.) for the *cis,cis*-iridolactones we have synthesized are shown in Table 1, and comparison with data for the natural *trans,cis*-isomers shows that (1) may have an irido-type and (2) an isoirido-type boat structure, in all cases the C(8) methyl group being (see Dreiding models) equatorial. These suggested boat conformations for (1) and (2) have been confirmed in the solid state by *X*-ray crystal structure determinations.

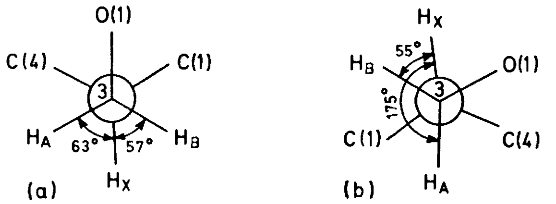


FIGURE 2 a, Irido-type; b, isoirido-type

Molecular Geometry.—Bond distances and angles for (1) and (2) are listed in Table 2; clinographic views, seen along the basal plane of the six-membered ring, are shown in Figure 1, together with those of the natural irido- and isoirido-mirmecines (5) and (6). Both epimers (1) and (2) therefore exhibit a boat conformation of the six-membered ring and the torsion angle C(8)–C(10)–O(1)–C(3) is close to 0°.

Unfortunately the geometry of epimer (1), owing to the low m.p. and consequent high thermal motion, has not been determined very accurately, and discussion of the π delocalization through the lactone group must be limited to epimer (2).

The C–O bond distances are C(10)–O(1) 1.35(2) and O(1)–C(3) 1.45(1) Å [corresponding values for irido- (5) and isoirido-mirmecine (6) are 1.365(30) and 1.360(30), and 1.428(30) and 1.488(30) Å]. Comparison of these values with those [1.312(5) Å] for carboxylic acid esters,[15] paraffinic and saturated heterocyclic compounds [1.426(5) Å],[15] compounds with *C*(*ar*)–O bonds [1.379—1.393(4) Å],[16] and furan (1.362 Å),[17] together with the quasi-coplanarity of C(8), C(10), O(2), O(1), C(3) suggests that conjugation through the lactone group significantly contributes to the conformation of the six-membered ring.

All four molecules (Figure 1) have a zig-zag segmented shape, the dihedral angles being acute or obtuse according to whether the rings are folded in an *endo*- or *exo*-conformation. The angles formed by the normals to

TABLE 1

Spectroscopic and physical data for iridolactones

		N.m.r.^{b,c}/Hz		C.d.^{d}	
Irido-type	I.r.^{a}/cm^{-1}	J_{AX}	J_{BX}	$[\theta]_{225}$ $\times 10^3$/°	$[\alpha]_D^{20}$ ^{a}/°
cis,cis (1)	1 757	3	3	−12.2	−169.4
trans,cis (5)	1 758 ^{e}	3	3	13.4	210
Isoirido-type					
cis,cis (2)	1 755	10.2	6.4	14.5	51.8
trans,cis (6)	1 761 ^{e}	10.1 ^{f}	5.9 ^{f}	−12.9	−59

^{a} CCl_4. ^{b} $CDCl_3$. ^{c} As observed by direct inspection. ^{d} Cyclohexane. ^{e} Ref. 7. ^{f} Ref. 10.

various mean planes are reported in Table 3; a positive sign indicates the normals cross above, and a negative sign that they cross below the molecular plane, as seen in Figure 1. These angles give some indication of steric effects due to the methyl substituents and to ring–ring interactions. In *cis,cis*-iridolactone (1), with an all-*endo*-conformation, these steric effects are quite large and clearly indicated by the corresponding angles between planes (2)–(3) and (3)–(4) which are significantly different from those of natural isoiridomirmecine (6), which has a stretched conformation.

The packing (Figure 3) is consistent with van der Waals interactions.

DISCUSSION

The structures of crystals of (1) and (2) are very like those reported for the natural *trans,cis*-isomers (5) and (6); the *cis*-relationship between the methyl group on the cyclopentane ring and the lactone group does not cause a significative shift in the six-membered ring from a boat geometry with the methyl substituent equatorial. This was largely as expected, from consideration of the planarity of the lactone group, the geometrical restrictions due to the *cis*-fused junction, and that the alternative boat conformation would put the C(8) methyl group in the improbable ' bowsprit ' position.

TABLE 2

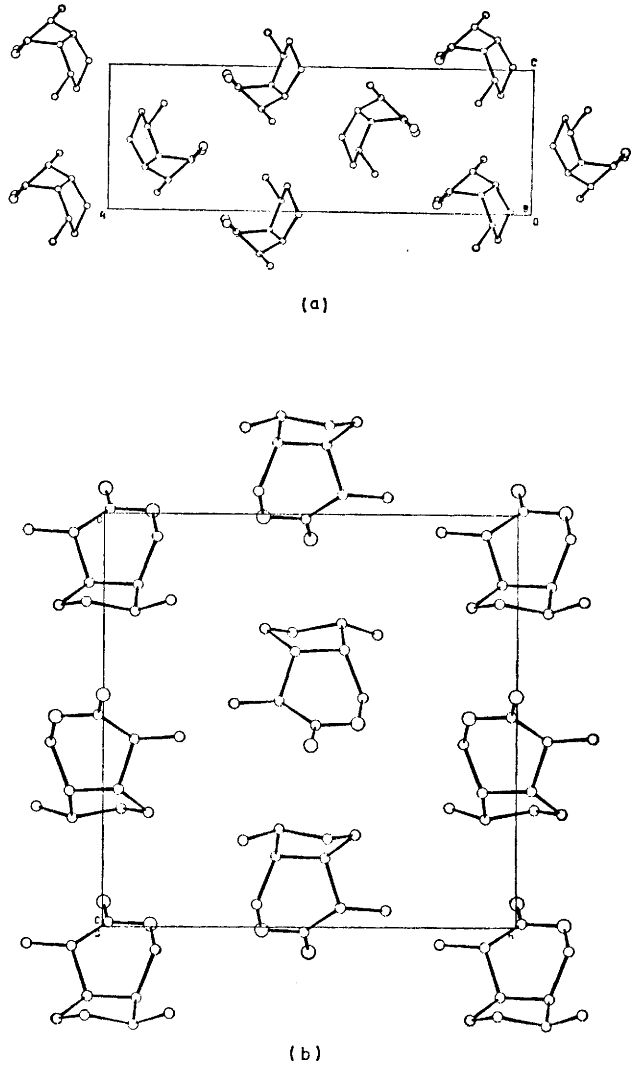
Bond lengths (Å) and angles (°) for (1) and (2)

(*a*) Intramolecular distances

	(2)	(1)		(2)	(1)
O(1)–C(3)	1.45(1)	1.51(1)	C(2)–C(4)	1.55(2)	1.56(2)
O(1)–C(10)	1.35(2)	1.41(2)	C(4)–C(5)	1.56(1)	1.58(3)
O(2)–C(10)	1.20(1)	1.23(3)	C(4)–C(8)	1.55(1)	1.52(2)
C(1)–C(2)	1.54(1)	1.50(3)	C(5)–C(6)	1.52(1)	1.58(3)
C(1)–C(6)	1.53(1)	1.65(3)	C(8)–C(9)	1.50(1)	1.55(3)
C(1)–C(7)	1.51(1)	1.57(3)	C(8)–C(10)	1.49(2)	1.52(3)
C(2)–C(3)	1.52(1)	1.52(3)			

(*b*) Bond angles

	(2)	(1)
C(3)–O(1)–C(10)	117(1)	113(2)
C(2)–C(1)–C(6)	104(1)	107(2)
C(2)–C(1)–C(7)	116(1)	123(2)
C(6)–C(1)–C(7)	113(1)	107(2)
C(1)–C(2)–C(3)	114(1)	117(2)
C(1)–C(2)–C(4)	106(1)	107(2)
C(3)–C(2)–C(4)	110(1)	111(2)
O(1)–C(3)–C(2)	111(1)	109(2)
C(2)–C(4)–C(5)	105(1)	106(2)
C(2)–C(4)–C(8)	112(1)	110(2)
C(5)–C(4)–C(8)	112(1)	114(2)
C(4)–C(5)–C(6)	105(1)	108(2)
C(1)–C(6)–C(5)	102(1)	98(2)
C(4)–C(8)–C(9)	114(1)	115(2)
C(4)–C(8)–C(10)	109(1)	110(2)
C(9)–C(8)–C(10)	112(1)	111(1)
O(1)–C(10)–O(2)	118(1)	119(2)
O(1)–C(10)–C(8)	116(1)	115(2)
O(2)–C(10)–C(8)	126(1)	127(2)



(a)

(b)

FIGURE 3 Molecular packing of (a) (1) and (b) (2)

The aforementioned hypotheses concerning higher strain-energies in the *cis,cis*-isomers have been checked by equilibration experiments and by theoretical calculations.

The equilibrations at C(8) for the two pairs [(1) and (2), (5) and (6)] of epimers have been made simultane-

TABLE 3

Angles (°) formed by the normals to planes

Planes (1): C(8), C(10), O(1), C(3)
(2): C(8), C(2)—(4)
(3): C(5), C(4), C(2), C(1)
(4): C(1), C(6), C(5)

Iridolactone	(1)–(2)	(2)–(3)	(3)–(4)
cis,cis (1)	54.2	54.0	34.8
trans,cis (5)	−53.3	−55.4	37.3
Isoiridolactone			
cis,cis (2)	−53.7	57.6	40.7
trans,cis (6)	53.8	−57.9	39.5

ously under identical conditions, since the literature data [7,18] are at variance. In 0.5N-MeONa in MeOH, the ratio between irido- and isoirido-type structures is 1 : 3 for the natural *trans,cis*-isomers [(5), (6)], whereas it is 1 : 5 for our *cis,cis*-isomers [(1), (2)]. These results seem therefore to confirm the expected relative increase in strain-energy for the *cis,cis*-iridolactone (1) with an *endo*-conformation.

Theoretical computations were based on a program (GEMO) [19] of molecular mechanics, derived from Westheimer concepts of minimization of strain-energy. The use of such a program in the case of germacrane sesquiterpenes, with various geometrical restrictions of the cyclodecane ring, has revealed [20,21] that geometries very like those which have been observed in the crystals have the lowest strain-energy values. Since mathematical procedures of this type do not avoid the problem of the false minima in three-dimensional space, we have examined for each initial boat conformation some probable, but differently distorted, geometries. The results of the calculation are shown in Figure 4; it can be seen that the values of total strain-energy are in good agreement with the aforementioned hypotheses and the results of equilibration experiments, and that the torsion angles of the conformations so calculated are very close to those obtained from the X-ray analysis.

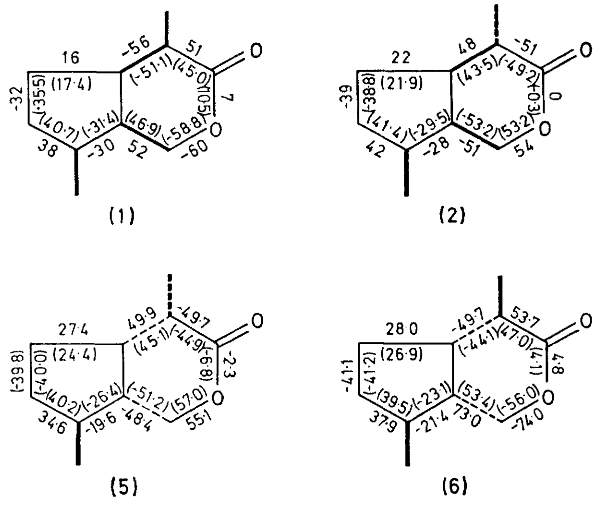


FIGURE 4 Experimental (X-ray) and calculated (GEMO, in parentheses) torsion angles taken round the rings in synthetic [(1) and (2)] and natural [(5) and (6)] iridolactones; calculated strain energies are: (1) 22.437, (2) 21.063, (5) 19.818, and (6) 19.299 kcal mol^{-1}

Examination of the geometrical data reported in Figure 4 shows that the conformations of the four iridolactones with a *cis*-fused junction seem to be completely determined by the two methyl substituents. In all the isomers, the geometry of the cyclopentane ring is identical and allows the methyl group to assume a quasi-equatorial orientation, and the lactone ring has a quasi-ideal boat conformation with the methyl group equatorial.

Furthermore, the geometries observed in the crystals correspond to conformations having the least strain-energy values and agree with the spectroscopic results (n.m.r., i.r., and c.d.) measured for solutions.

EXPERIMENTAL

General Method.—I.r. spectra were taken with a Perkin-Elmer 257 spectrophotometer, n.m.r. spectra with a JEOL C 60 spectrometer with tetramethylsilane as internal standard, c.d. curves with a Roussel-Jouan CD II dichrograph, and mass spectra with a Varian Mat 112 at 70 eV by g.l.c. insertion. M.p.s were measured on a Mel-Temp apparatus; optical rotations were measured with a Perkin-Elmer 141.

Hemiacetal (4).—$LiAlH_4$ (0.338 g, 8.9 mmol) was added during 10 min to a well stirred solution of (3) (1.66 g, 10.0 mmol) in anhydrous diethyl ether (550 ml) cooled to 0 °C. The reaction course was monitored by t.l.c. and after 15 min a few drops of water–methanol (1 : 1) were added. After drying ($MgSO_4$), solvent was evaporated off and the residue chromatographed over silica gel, eluting with a gradient of benzene–acetone. The isolated hemiacetal (4) was purified by distillation (1.25 g, 7.3 mmol) (73%), b.p. 88—90 °C at 0.1 mmHg; $\nu_{max.}$ (film) 3 400 (OH) cm^{-1}; $\delta(CCl_4)$ 0.98 and 1.03 (3 H each, d, J 4 Hz, CH_3C), 3.3—4.2 (2 H, m, CH_2O), and 4.62 (1 H, d, J 5 Hz, OCHO); m/e 170 (M^+) (Found: C, 70.35; H, 10.8. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66%).

(1S)-cis,cis-*Iridolactones* (1) *and* (2).—To a solution of hemiacetal (4) (1.18 g, 6.9 mmol) in pyridine (25 ml) Cornforth oxidation reagent [22] (16 ml) was added dropwise. After 20 h at room temp. the reaction mixture was poured into water, filtered through Celite, and extracted with ether (4 × 50 ml). The ethereal solution was dried ($MgSO_4$) and evaporated to give a residue which was distilled (1.05 g), b.p. 78—80 °C at 0.1 mmHg. G.l.c. analysis (3% WEAS on Chromosorb W AW-DMCS) has shown the presence of two products, (1) and (2), in a ratio of 15:85. Crystallization (24 h at −30 °C) from n-pentane enabled separation of pure (g.l.c., t.l.c.) (1*S*)-*cis,cis*-isoiridolactone (2) (0.485 g), m.p. 63—64 °C; $[\alpha]_D^{20}$ +51.8 (c, 3.3 in CCl_4) [lit.[4] for the enantiomer, $[\alpha]_D^{25}$ −53.2° (c, 3.58 in CCl_4)]; $\nu_{max.}$ (CCl_4) 1 755 (CO) cm^{-1}; $\delta(CDCl_3)$ 0.96 (3 H, d, J 7 Hz, CH_3C), 1.20 (3 H, d, J 5 Hz, CH_3C), and 3.8—4.4 (2 H, AB portion of ABX system, J_{AX} 10.2, J_{BX} 6.4 Hz, CH_2O), m/e 168 (M^+) (Found: C, 71.5; H, 9.65. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%).

The residue obtained from the mother-liquor was fractionated by preparative g.l.c. (5% WEAS on Chromosorb W 30—60 mesh) to give pure (g.l.c., t.l.c.) (1*S*)-*cis,cis*-iridolactone (1) (0.073 g), which was crystallized from n-pentane, m.p. 31—32 °C; $[\alpha]_D^{20}$ −169.4° (c, 3.5 in CCl_4) [lit.[4] for the enantiomer, $[\alpha]_D^{25}$ +172° (c, 2.40 in CCl_4)]; $\nu_{max.}$ (CCl_4) 1 757 (CO) cm^{-1}; $\delta(CDCl_3)$ 1.07 and 1.20 (3 H each, d, J 6 Hz, CH_3C), and 4.0—4.6 (2 H, AB portion of ABX system, J_{AX} 3, J_{BX} 3 Hz, CH_2O); m/e 168 (M^+) (Found: C, 71.20; H, 9.70. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%).

Procedure for Equilibration at C(8) *of Iridolactones.*—The pure lactone isomer (10—15 mg) was dissolved in 0.5N-methanolic MeONa (10—15 ml) containing methylnaphthalene as internal standard (the use of an internal standard revealed some decomposition in the iridolactones under the conditions used). The mixture was set aside for 24 h, then acidified (dilute H_2SO_4), and extracted with ether. After drying ($MgSO_4$) and concentration the organic layer was directly examined by g.l.c. (2% WEAS on Chromosorb W AW-DMCS 80—100 mesh). Results are in the Discussion section.

X-*Ray Structure Analysis*

(1S)-cis,cis-*Isoiridolactone* (2).—Crystals are colourless prisms elongated on [001]. Preliminary cell-dimensions and space-group data were obtained from oscillation and Weissenberg photographs. Lattice parameters were then refined by least-squares by use of 15 $(\theta, \chi, \phi)_{hkl}$ measurements taken on a Siemens single-crystal diffractometer. The crystal used for data collection was 0.3 × 0.4 × 0.6 mm.

Crystal data. $C_{10}H_{16}O_2$, $M = 168.1$. Orthorhombic, $a = 12.085(3)$, $b = 12.038(3)$, $c = 6.497(2)$ Å, $U = 945.2$ Å^3, $Z = 4$, $D_c = 1.17$ g cm^{-3}, $F(000) = 368$. Cu-K_α radiation, $\lambda = 1.5418$ Å, μ(Cu-K_α) = 5.7 cm^{-1}. Absent spectra: $h00$ $h \neq 2n$, $0k0$ $k \neq 2n$, $00l$ $l \neq 2n$ define space group $P2_12_12_1$ (D_2^4. No. 19).

Intensity data were collected up to θ 70° by use of the ω—2θ scan method and the ' five-points ' technique [23] with nickel-filtered Cu-K_α radiation on a Siemens single-crystal diffractometer. Of 1 055 independent reflections measured 306 were not used in the crystal analysis having intensities $<2[\sigma^2(I) + 10^{-4}I^2]^{\frac{1}{2}}$, where I is the relative intensity and $\sigma^2(I)$ its variance from counting statistics. No corrections were made for absorption.

Structure analysis and refinement. The structure was solved by direct methods with $150|E_{hkl}| > 1.46$ by use of the MULTAN [24] program system by fixing the origin with the reflections 0,7,1, 9,3,0, 1,2,0, and permuting the phases of 8.11.2 and 2,9,3, taking care of the enantiomorph. An E map computed by use of the most consistent set of phases revealed the position of all non-hydrogen atoms. The structure was refined by full-matrix least-squares. A difference-Fourier synthesis revealed the positions of all the hydrogen atoms; those belonging to the methyl groups were rather smeared. All atom parameters were then refined (heavy atoms anisotropically and hydrogen atoms isotropically) with a weighting function of the form $1/w = \sigma^2(F_o) + 0.005|F_o|^2$. The hydrogen atoms of the methyl groups were refined as rigid groups, assuming C–H 1.08 Å. The final value of R was 0.064 and of R' 0.072.

TABLE 4

Fractional co-ordinates (× 10^4; × 10^3 for H atoms) with standard deviations in parentheses for epimer (2)

	x	y	z
O(1)	3 843(4)	−65(4)	−1 004(9)
O(2)	4 983(6)	−599(5)	−3 425(9)
C(1)	4 254(5)	2 367(5)	2 711(9)
C(2)	4 180(4)	1 720(4)	672(8)
C(3)	3 722(5)	553(6)	906(11)
C(4)	5 368(3)	1 678(4)	−210(8)
H(1)	402(5)	322(5)	−196(10)
H(2)	380(4)	220(5)	37(9)
H(3,1)	399(6)	14(7)	−199(13)
H(3,2)	284(5)	51(4)	−89(9)
H(4)	538(5)	211(6)	189(9)
H(5,1)	623(5)	306(5)	−102(9)
H(5,2)	717(8)	176(7)	−169(15)
H(6,1)	565(7)	260(7)	−496(12)
C(5)	6 099(4)	2 234(5)	1 471(10)
C(6)	5 433(5)	2 141(6)	3 449(9)
C(7)	3 384(6)	2 094(7)	4 305(14)
C(8)	5 752(5)	472(4)	−677(8)
C(9)	6 844(6)	407(6)	−1 780(12)
C(10)	4 867(7)	−112(5)	−1 834(12)
H(6,2)	563(9)	143(9)	−421(16)
H(7,1)	255(6)	231(7)	−385(14)
H(7,2)	342(6)	122(7)	−464(14)
H(7,3)	361(6)	256(7)	−566(14)
H(8)	572(7)	15(7)	−49(12)
H(9,1)	744(6)	95(6)	104(12)
H(9,2)	724(6)	−37(6)	217(12)
H(9,3)	654(6)	80(6)	316(12)

Final positional parameters together with their standard deviations are given in Table 4. Hydrogen atoms have been assigned the same numbers as the carbon atoms to which they are bonded.

(1S)-cis,cis-*Iridolactone* (1).—Crystals are colourless prisms elongated on [001]. Cell parameters and space group were determined as before and lattice parameters were refined from 15 measurements. The crystal used for data collection was 0.2 × 0.4 × 0.4 mm.

Crystal data. $C_{10}H_{14}O_2$, $M = 168.1$. Orthorhombic, $a = 19.805(5)$, $b = 7.223(2)$, $c = 6.736(2)$ Å, $U = 963.6$ Å^3, $Z = 4$, $D_c = 1.14$ g cm^{-3}, $F(000) = 368$. μ(Cu-K_α) = 5.6 cm^{-1}. Absent spectra: $h00$ $h \neq 2n$, $0k0$ $k \neq 2n$, $00l$ $l \neq 2n$ define space group $P2_12_12_1$ (D_2^4, No. 19).

TABLE 5

Fractional co-ordinates (× 10^4) with standard deviations in parentheses for epimer (1)

	x	y	z
O(1)	7 229(8)	−1 149(32)	−601(28)
O(2)	7 197(10)	1 982(30)	−874(29)
C(1)	5 916(12)	−3 227(38)	726(48)
C(2)	6 185(12)	−2 877(37)	−1 313(35)
C(3)	6 946(13)	−2 872(41)	−1 553(56)
C(4)	5 868(11)	−1 028(30)	−2 048(31)
C(5)	5 500(14)	−152(39)	−192(48)
C(6)	5 775(15)	−1 167(38)	1 732(42)
C(7)	6 292(14)	−4 414(39)	2 323(52)
C(8)	6 411(10)	199(31)	−2 953(38)
C(9)	6 157(12)	2 065(34)	−3 799(42)
C(10)	6 974(13)	494(41)	−1 452(47)

Intensity data were collected similarly up to θ 55° and of 735 independent reflections 362 were not used in the crystal analysis. The crystal specimen was sealed in a Lindeman capillary to prevent sublimation. Absorption effects were ignored.

Structure analysis and refinement. The structure was solved by direct methods as before. Refinement was by full-matrix least-squares cycles with unit weights, at first isotropically down to R 0.180 and then anisotropically to a final R of 0.109.

The limitations of the experimental data (*ca.* 3 reflections per parameter) reflected in the estimated standard deviations. No attempts were made to locate hydrogen atoms.

Final positional parameters together with their standard deviations are given in Table 5.

For both compounds, observed and calculated structure factors and thermal parameters are listed in Supplementary Publication No. SUP 22525 (10 pp., 1 microfiche).*

All calculations were performed on a Cyber 76 computer at the Centro di Calcolo Interuniversitario dell'Italia Nord-Orientale, Casalecchio (Bologna), with financial support from the University of Parma.

Strain-energy Minimization Procedure.—The GEMO calculations were carried out on a CY 7600 computer (of CINECA, Centro Interuniversitario di Calcolo dell'Italia Nord-Orientale), by use of the strain-energy minimization program of Cohen.[19] The molecules required in media 1 min

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* See Notice to Authors No. 7, in *J.C.S. Perkin II*, 1978, Index issue.

of computer time. The following energy functions were used, with parameters taken from appropriate references:[19,20,25]

Bond stretching, $E(l) = K_l(l - l_0)^2$;

Angle bending, $E(\theta) = K_\Theta(\theta - \theta_0)^2$;

Torsion around a single bond, $E(\phi) = q[1 + \cos n\,(|\phi| + s)]$;

Torsion around a double bond, $E(\phi) = a[|\phi| - t]^2$;

Non-bonded interactions, $E(\mathrm{nb}) = (A/d^9) - (B/d^6)$.

[8/1869 *Received*, 24*th October*, 1978]

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