Dehydrogenation of II. To 0.0114 mol of II in 35 mL of benzene under N_2 was added slowly 0.25 mol of DDQ dissolved in 70 mL of benzene. After the mixture was refluxed for 30 h, the benzene was evaporated to dryness. The residue was extracted with ligroin, and this solution was passed through an alumina column, which removed a slight green color. Evaporation of the petroleum solvent yielded white crystals of compound I in 12% yield: mp 126–128 °C; IR (KRr pellet) 1600, 1665 cm^{-1}; ^1H NMR (CCl_4) δ 2.7 (m, 4), 6.4 (m, 2), 7.2 (s, 10); UV (cyclohexane) 295 nm, 305, 320.

Anal. Calcd for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.79; H, 6.40.

Preparation of *p*-Benzylbenzohydrol (III). The general procedure of Wiselogle and Sonnenborn[8] for the synthesis of benzohydrol was modified: A mixture of 20 g (0.074 mol) of *p*-benzoyldiphenylmethane,[9] 20 g (0.5 mol) of technical sodium hydroxide pellets, and 20 g (0.305 mol) of zinc dust in 200 mL of 95% alcohol was stirred. The mixture spontaneously warmed to about 65 °C. After 3 h, the cool mixture was suction filtered and the residue washed with alcohol. The filtrate was poured into 5 volumes of ice water acidified with 44 mL of concentrated HCl. A white cloudiness indicated the separation of the product. Filtration and drying under vacuum at 40 °C gave 19.5 g (98% yield) of III: mp 62–65 °C; IR (KBr pellet) 3300; ^1H NMR (CCl_4) δ 2.9 (s, 1), 3.8 (s, 2), 5.5 (s, 1), 7.2 (m, 14).

Anal. Calcd for $C_{20}H_{18}O$: C, 87.55; H, 6.61. Found: C, 87.71; H, 6.71.

Preparation of Bis[α-(*p*-benzylphenyl)benzyl] Ether (IV). Attempts to synthesize I led instead to the ether bis[α-(*p*-benzylphenyl)benzyl] ether (IV). A mixture of 0.7 g (2.5 mol) of *p*-benzylbenzohydrol and 50 mL of a 10% solution of H_2SO_4 in water was stirred under reflux for 48 h. The lump of hard white solid that formed was filtered from the acid. The lump was powdered with a glass rod and washed with water and methanol to yield 0.645 g (95%). This ether is insoluble in CS_2, ethanol, DMS, very slightly soluble in boiling CCl_4, and soluble in hot benzene and hexachloro-1,3-butadiene. This product was extracted in a Soxhlet extraction apparatus with benzene and recrystallized by cooling the benzene solution: mp 191–192 °C; IR (KBr pellet) shows no OH or C=C bands; ^1H NMR (hexachloro-1,3-butadiene) δ 3.9 (s, 4), 5.4 (s, 2), 7.1 (s, 28).

Anal. Calcd for $C_{40}H_{34}O$: C, 90.55; H, 6.45. Found: C, 89.85; H, 6.51.

Preparation of α,α'-Diphenyl-α-bromo-*p*-xylene (V). Two methods were followed to obtain this compound.

Method 1. Monobromination of *p*-Dibenzylbenzene. A solution of 2.58 g (0.10 mol) of *p*-dibenzylbenzene[10] in 25 mL of CCl_4 was heated to reflux in a water bath, and 1.60 g (0.10 mol) of Br_2, dissolved in 25 mL of CCl_4, was added over a period of 3 h under a UV lamp. The evolved HBr was collected in a water trap. The mixture was left refluxing for 12 h under the UV lamp, when the solution was clear yellow. The solution was cooled, washed with water, 5% NaOH, and finally water and then dried with $MgSO_4$ overnight and filtered, and the solvent was removed by distillation. The residue crystallized after 2 days to yield 1.71 g (53%) of white crystals, mp 60–62 °C.

Method 2. Bromination of III. Although the NMR spectrum of the product obtained by method I indicated that there was bromination and the relative areas of the peaks were in accordance with the given structure, proof of structure is not conclusive because a mixture of unbrominated, monobrominated, and dibrominated compounds would give a very similar or identical spectrum. To avoid this uncertainty the hydroxyl group of III was substituted with a bromine atom. An excess of 48% solution of HBr in water was added to 2.74 g (0.10 mol) of III and the mixture stirred at room temperature for 3 h. When the mixture was heated to reflux, two layers immediately appeared. After 1 h the mixture was cooled, and the oily layer was extracted with CCl_4, washed several times with water, sodium bicarbonate, and water again to eliminate any traces of acid. The CCl_4 solution was dried overnight with $MgSO_4$ and filtered, and the solvent was removed by distillation. The monobromo compound crystallized, giving a total yield of 2.96 g (92%). This product was recrystallized from petroleum ether, giving white crystals melting at 60–62 °C. Both ^1H NMR and IR spectra were identical with those obtained by method 1: ^1H NMR (CCl_4) δ 3.8 (s, 2), 6.1 (s, 1), 7.1 (m, 14).

Anal. Calcd for $C_{20}H_{17}Br$: C, 71.22; H, 5.08; Br, 23.70. Found: C, 71.15; H, 5.12; Br, 23.63.

Attempted Reaction of V with Potassium *tert*-Butoxide. In an attempt to obtain I by 1,6-dehydrohalogenation of V, 1.05 g (3.1 mmol) of this reagent was mixed with 1.10 g (9.8 mmol) of potassium *tert*-butoxide in 40 mL. The mixture was heated under reflux under nitrogen atmosphere for 30 min. At the end of this period dehydrohalogenation had not occurred as indicated by IR and ^1H NMR spectra.

Preparation of 1,4-Bis(α-bromobenzyl)-1,4-dibromocyclohexane (VI). To 0.585 g (2.25 mmol) of II dissolved in 5 mL of CCl_4 was added 45.8 mL (4.58 mmol) of a 0.1 M solution of Br_2 in CCl_4 until the color did not fade. The CCl_4 was evaporated almost totally and ethyl ether was added to precipitate the product. The solid was filtered, redissolved in chloroform, and reprecipitated with ethyl ether. The white crystals were dried for 24 h under vacuum at 60 °C: mp 195.5–197.5 °C; ^1H NMR (CCl_4, 80 °C) δ 2.3 (s, 8), 5.1 (s, 2), 7.2 (m, 10).

Anal. Calcd for $C_{20}H_{20}Br_4$: C, 41.42; H, 3.48; Br, 55.11. Found: C, 41.23; H, 3.41; Br, 55.31.

Preparation of 1,4-Bis(α-bromobenzylidene)cyclohexane (VII). To 0.245 g (0.42 mmol) of VI was added 5 mL of a 20% solution of KOH in 95% ethanol and the mixture was heated under reflux in a water bath for 2 h. VII was filtered from the alcoholic solution and washed with water and alcohol several times. It was purified by crystallization from ligroin and from chloroform to yield 0.16 g (90%;) of white crystals: mp 175–180 °C; IR (KBr pellet) 1660 cm^{-1}; ^1H NMR (CCl_4, 85 °C) δ 2.5 (s, 8), 7.3 (s, 10).

Anal. Calcd for $C_{20}H_{18}Br_2$: C, 57.44; H, 4.34; Br, 38.22. Found: C, 57.30; H, 4.29; Br, 38.38.

Attempted Preparation of I. A procedure similar to that used by Velluz[11] was followed. To a solution of 0.691 g (2.66 mmol) of II in 10 mL of CCl_4 was added 2.0 g (11.25 mmol) of commercial *N*-bromosuccinimide and the mixture was refluxed for 30 min under UV light. The succinimide formed was removed by filtration and the solvent evaporated. The residue was purified by column chromatography and found to be a mixture of VI and I. To increase the ratio of I to VI, we carried out the same experiment under the same conditions, using freshly purified NBS; however, the purification of NBS did not affect the distribution of products. The cream-colored product could not be purified to yield a pure product as evidenced by poor elemental analyses.

Registry No. I, 82639-38-1; II, 82639-39-2; III, 82639-40-5; IV, 82639-41-6; V, 82639-42-7; VI, 82639-43-8; VII, 82639-44-9; benzyltriphenylphosphonium chloride, 1100-88-5; 1,4-cyclohexanedione, 637-88-7; *p*-benzoyldiphenylmethane, 58280-04-9; *p*-dibenzylbenzene, 793-23-7.

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Absolute Configuration Determinations of Chiral α-Substituted Benzylamines Using Liquid Crystal Induced Circular Dichroism

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Introduction

Absolute configurations of chiral compounds are routinely assigned on the basis of the rotation sign of plane polarized light at 589 nm. While this method has been useful, it is out of line with modern analytical techniques from the viewpoint of sensitivity. Chemical structures can

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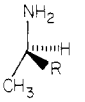
Table I. Liquid Crystal Induced Optical Activity for Chiral α-Substituted Benzylamines

compd	R	R'	sign of $[\alpha]_D$ (neat)	LCICD[a] 1% in MBBA
2a	phenyl	Me	–	–
2b	phenyl	Et	–	–[b]
2c	phenyl	*i*-Pr	–	–[b]
2d	phenyl	cyclohexyl	–	–[b]
2e	phenyl	*t*-Bu	–	–[b]
2f	phenyl	benzyl	+	–[b]
2g	*p*-nitrophenyl	Me	–	–
2h	*p*-bromophenyl	Me	–	–
2i	*p*-methylphenyl	Me	–	–
2j	2-thienyl	Me	–	–[c]
2k	2-naphthyl	Me	–	–[c]
2m	1-naphthyl	Me	–	–
2n	2,4,5-trimethylphenyl	Me	–	–[b]
3a	phenyl	Me	–	–
3b	phenyl	Et	–	–[b]
3e	phenyl	*t*-Bu	–	–[b]

[a] Determined from the sign of the Cotton effect in the CD spectrum of the MBBA chromophore between 390 and 400 nm. [b] The *R* enantiomer of this compound was actually studied and was found to exhibit a positive LCICD. [c] Both enantiomers of this compound were studied and showed opposite LCICD signs.

be assigned on the basis of IR, NMR, and mass spectral data obtained from submilligram quantities of materials. However, even in the most favorable cases, for compounds with high specific rotations, much larger quantities of material are desirable to obtain reliable rotation data. In less favorable cases, where the substituents on the chiral center have high electronic symmetry, gram quantities of material may not give reliable rotations for configurational assignments.[1] Furthermore, the rotations in a homologous series of compounds are not always constant for the same absolute configuration. Such is the case for the series of amines **1a**–**1e**, where $[\alpha]^{20}_D$ (neat) is negative for all but compound **1c**.



1a, R = Et
b, R = *n*-Pro
c, R = *i*-Pro
d, R = *t*-Bu
e, R = cyclohexyl

Observation of CD or ORD spectra alleviates the sensitivity problem to a certain degree, and in many cases the sign of the Cotton effect is considered more reliable for the assignment of absolute configuration. However, commonly the chromophore, whose Cotton effect can be related to absolute configuration, is not in an accessible region of the electronic spectrum, and the sign of the Cotton effect must be inferred from the plain ORD curve. This is unreliable in many instances as well.

The plain ORD curves between 350 and 600 nm for neat *S*-α-substituted benzylamines (**2**, Table I) are a good example. *The ORD spectra of compounds* ***2e*** *and* ***2f*** *exhibit positive plain curves,* ***2a***, ***2b***, *and* ***2d*** *exhibit negative plain curves, and* ***2c*** *exhibits a weak positive plain curve even though the configurations are identical.*

Recently, a liquid-crystal technique has been shown to be useful for configurational assignments of chiral alcohols.[2,3] By preparing ca. 1% solution of a chiral substrate in a liquid-crystal solvent such as *N*-(*p*-methoxybenzylidene)-*p*-*n*-butylaniline (MBBA), a helical arrangement of liquid-crystal molecules was formed. (*S*)-1-Phenylethanol was found to form a right-handed helical arrangement,[2,4] while the *R* enantiomer formed a left-handed helical arrangement. The helix sense could easily be determined because the helical arrangement of MBBA molecules resulted in an amplified rotation resulting from the conjugated imine chromophore of the solvent at ca. 400 nm. One percent solutions prepared from 0.1 mg of alcohol in MBBA yield observed rotations between 10° and 100°. The chirality amplification is large enough to allow distinction between compounds that are enantiomeric by virtue of deuterium substitution.[5]

In addition to achieving the large chirality amplification, several other advantages result from using this liquid crystal induced circular dichroism (LCICD) technique. Since the solute is present in such small quantities, the optical activity measured is only that arising from the conjugated imine chromophore of the solvent. Thus, variables introduced by changing the positions of absorption maxima as a result of substituent variations on the solute are eliminated. Since the chromophore is at relatively long wavelength (ca. 400 nm for MBBA), the optical activity can be measured by using CD, ORD, or conventional polarimetric techniques, although caution should be exercised in utilizing the latter technique (see below).

Results and Discussion

Shown in Table I are the signs of the LCICD Cotton effects induced in MBBA, by the additions of optically active amines **2a**–**2n**. All 13 amines exhibit negative LCICD's, indicating the formation of cholesteric phases with left-handed helix senses. While there is only one deviation from a negative rotation at 589 nm in isotropic solution, the plain ORD curves of three, **2c**, **2e**, and **2f** deviate from the behavior of the rest of the series.

(1) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1979**, *44*, 1025.
(2) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1980**, *45*, 1379.
(3) Gottarelli, G.; Samori, B.; Marzochi, S.; Stremmenos, C. *Tetrahedron Lett.* **1975**, 1981.
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(5) Gottarelli, G.; Samori, B.; Fuganti, C.; Grasselli, P. *J. Am. Chem. Soc.* **1981**, *103*, 471.

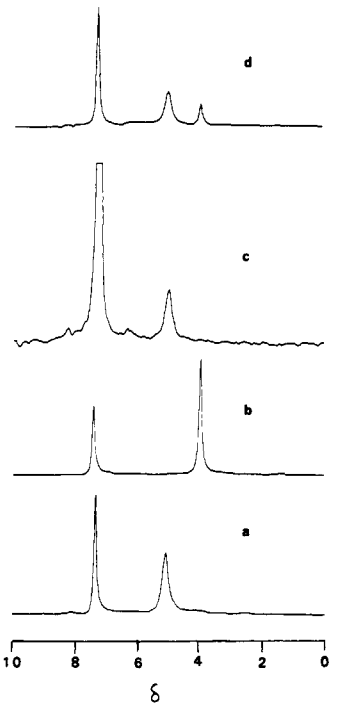
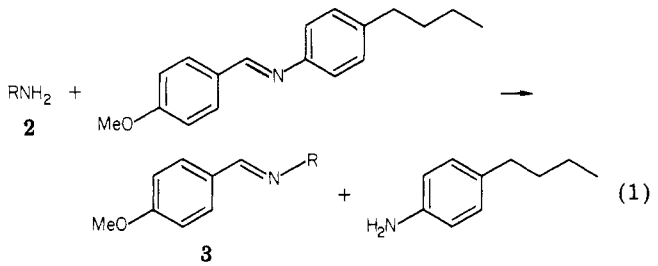


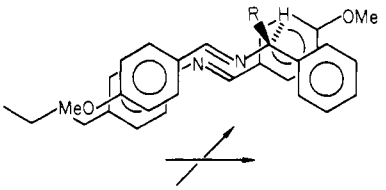
Figure 1. 15.1-MHz ^2H NMR spectra in α,α,α-trifluorotoluene at 25 °C. The downfield in all cases corresponds to $CDCl_3$, added as an internal reference. The spectra were obtained under the following circumstance: (a) authentic *N*-(*p*-methoxybenzylidene)-α,α-dideuteriobenzylamine (**3o**) in $PhCF_3$ solvent, (b) authentic **2o** in $PhCF_3$, (c) α,α-dideuteriobenzylamine (**2o**), was dissolved in liquid crystalline MBBA solvent (5% solution) and after mixing, a 10% solution of this mixture in $PhCF_3$ was prepared for measurement, (d) ca. 50 mg of authentic **2o** was added to the solution used to obtain c.

Initially, it is surprising that (*S*)-1-phenylethylamine (**2a**) induces the formation of a left-handed helix (negative rotation). This is opposite to that of (*S*)-1-phenylethanol, and to a first approximation one would expect the two compounds to interact similarly with MBBA. We have determined by NMR that, in fact, benzylamines, when dissolved in MBBA, undergo a transamination reaction described by eq 1. We have verified this by preparing



α,α-dideuteriobenzylamine (**2o**) and monitoring its reaction in MBBA by ^2H NMR. The 15-MHz ^2H NMR spectra of α,α-dideuteriobenzylamine (**2o**) and its *N*-*p*-methoxybenzylidene derivative (**3o**) are shown in Figure 1b and 1a, respectively. When a 5% solution of α,α-dideuteriobenzylamine in MBBA is prepared and then quickly dissolved in α,α,α-trifluorotoluene, the spectrum in Figure 1c results, indicating the presence of *N*-(*p*-methoxybenzylidene)-α,α,-dideuteriobenzylamine (**3o**) alone. When additional α,α-dideuteriobenzylamine (**2o**) is added to the mixture whose spectrum is shown in Figure **1c**, unreacted **2o** is detected. Attempts to follow the reaction above 10° by NMR failed due to the rapid reaction of the amine. Since the MBBA is present in large excess, virtually all the optically active amine is in the form of its *N*-*p*-methoxybenzylidene derivative. The sense of the induced helix in

Scheme I



MBBA must therefore be described in terms of the interaction of **3** with the liquid-crystal solvent molecules.

As further verification, compounds **3a**, **3b**, and **3e** were synthesized and isolated, and their LCICD measured in MBBA. These rotations are shown in the last three entries of Table I and are consistent with the observed LCICD behavior when the corresponding amines are dissolved in MBBA.

Molecules such as **3** will align with their long axes parallel to the long axes of MBBA.[4b] The solute–solvent interaction can be depicted by the diagram in Scheme I. The aryl rings of **3** intercalate between the corresponding aryl rings of the solvent molecules. The benzyl substituents then project perpendicular to the long axis of **3**, above and below the molecular plane. MBBA molecules above and below the plane of **3** interact with these substituents. In the case of Scheme I, the interaction with the benzylic proton is not as severe as the interaction with the R substituent; the MBBA molecule therefore skews to avoid this latter interaction, resulting in the formation of a segment of a left-handed helix when the configuration of **3** is *S*. While other interactions such as repulsion of the methoxy group could cause helix formation, these interactions are achiral and would not result in the formation of one chiral helix sense in preference to the other. The LCICD of **2a–2n**, in Table I are all determined in this way.

Initially, the helix senses were inferred from the polarimetrically determined rotation signs at 589 nm. Under these conditions, compounds **2e** and **2f** at first appeared to be exceptions, exhibiting positive rotations for the *S* enantiomers. When the CD spectra were obtained, negative Cotton effects were consistently observed for both **2e** and **2f**. Dilution studies using the polarimeter to measure optical activity indicated that the initial rotations were larger than 180°, giving the appearance of a positive rotation. Consequently all the LCICD signs in Table I were verified by use of CD measurements.

In conclusion, by application of the LCICD technique to chiral substituted benzylamines, it is possible to amplify the effects of chirality by many orders of magnitude over normal optical activity measurements in isotropic solutions. The correlation of the absolute configuration with the sense of the helix formed in the liquid crystal and ultimately with the sign of LCICD Cotton effect can be accomplished by considering the orientation of the amine's *N*-*p*-methoxybenzylidene derivative in MBBA. When the sign of the LCICD is determined polarimetrically, dilution studies should be used to verify the sign of rotation.

Experimental Section

Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. CD and ORD spectra were determined with a Cary-60 ORD instrument with a CD accessory. NMR spectra were recorded with Varian EM-360 and XL-100 instruments, IR spectra were obtained on a Sargeant-Welch Pye Unicam 3-100 instrument, and mass spectra were obtained with a Du Pont 2-490B instrument.

Preparation and Resolution of Amines. Compound **2a** was purchased from Aldrich Chemical Co. and **2k** was provided by Professor W. H. Pirkle, University of Illinois, Urbana, IL. Racemic amines **2i**, **2j**, **2k**, and **2n** were prepared by reductive amination

Table II. Properties of Chiral Amines 2a-2n

	$[\alpha]^{25}\lambda$ [a]						literature		
compd	589	578	546	436	365	bp, °C (mm)	$[\alpha]_{589}$ (max)[a]	bp, °C (mm)	ref
2a	−37.8	−39.5	−45.0	−76.8	b		−40.3	184-186	9
2b	+19.2	+19.7	+22.2	+36.2	+50.75	87-90 (15)	+20.15	204-206	10
2c	+1.15	+1.10	+1.00	+0.40	+0.38	96-97 (15)	+14.1	95 (14)	11
2d	+4.02	+4.12	+4.57	+6.23	b	83-85 (0.6)	+9.8	96 (1.5)	12
2e	+2.55	+2.54	+2.54	+0.67	−7.8	103-105 (15)	+9.1	99-101 (14)	13
2f	−9.1	−9.27	−12.0	−25.4	b	115-120 (0.35)	−11.8	159 (9)	14
2g	−14.9[c]	−15.2	−16.1	b	b	91-92 (0.3)	+16.7	120-140 (1.5)	8, 15[d]
2h	−22.1[c]	−23.1	−26.3	−46.0	b	60-62 (0.3)	−20.3[e]		8, 16[d]
2i	−28.5	−29.8	−33.8	−57.3	>−75	85-86 (30)	−34.5	205	17
2j	+12.0[f]	+12.6	+14.3	+24.8	+40.2	75-77 (35)	−13	95-96 (30)	18
2k	−11.1[c]	−11.5	−13.0	−22.0	−31.9	75-76 (0.75)	−19	53 (mp)	19
2m	+47.6[g]	+49.9	+57.3	+104	+182		+62		20
2n	+13.3	+13.8	+15.8	+27.2	b	125-127 (20)			9

[a] Rotations were measured on neat samples unless otherwise specified. [b] Optical density too large to measure optical activity. [c] c 10, ethanol. [d] Prepared as described in ref 8, second reference describes physical and optical properties of optical isomers. [e] c 2, methanol. [f] c 4, methanol (literature value: c 5, methanol). [g] c 3, ethanol (literature value: c 5, methanol).

of the corresponding ketones with formamide and formic acid.[6] Racemic **2b**, **2c**, **2e**, and **2f** were obtained by addition of phenylmagnesium bromide to the corresponding nitrile followed by reduction with $LiAlH_4$, and **2d** was prepared in a similar manner from cyclohexylmagnesium bromide and cyanobenzene.[7] Compounds **2g** and **2h** were prepared from **2a** as previously reported.[8] NMR and IR spectra were consistent with the desired products.

α,α-Dideuteriobenzylamine (**2o**) was prepared from $LiAlD_4$ reduction of benzonitrile in tetrahydrofuran and was isolated as a clear colorless liquid: (bp (63–65 °C (20 mm); NMR ($CDCl_3$) δ 7.32 (s, 5 H, C_6H_5), 1.50 (s, 2 H, NH_2); IR (neat) 3380, 3300, 3050, 3020, 2200, 2140, 2060, 1600, 1490, 1450, 840, 790, 700 cm^{-1}; MS (70 eV), *m/e* (relative intensity), 109 (M^+, 99), 108 (100), 93 (84), 80 (26), 79 (31), 78 (27), 77 (21), 67 (8), 66 (10), 58 (17), 51 (17), 43 (29), 32 (25).

Resolutions were performed by multiple recrystallizations of amine salts with chiral carboxylic acids to yield samples with optical purities varying between 10% and 79.5%. Observed specific rotations, boiling points and literature citations for the resolutions are given in Table II. Absolute configurations are based on the assignments cited in ref 20.

Preparation of *N*-*p*-Methoxybenzylidene Derivatives 3a, 3b, 3e, and 3o. Optically active amines were added to 1.1 equiv of *p*-methoxy-benzaldehyde (10% in CH_2Cl_2). The mixture was refluxed on a steam bath for 30 min and dried with K_2CO_3, and the solvent was removed on a rotary evaporator. The residue was distilled at reduced pressure to yield pure **3a**, **3b**, and **3e**.

Compound **3a** was obtained from **2a** ($[\alpha]^{20}_D$ −37.8°, neat) as a clear viscous yellow liquid: bp 128–138 °C (0.15 mm); $[\alpha]^{25}_\lambda$ (*c* 10, $CHCl_3$) $+101_{589}$, $+106_{578}$, $+126_{546}$, $+284_{436}$; NMR ($CDCl_3$)δ 8.30 (s, 1 H, CH=N), 7.70 and 6.83 (AA′BB′, 4 H, $C_6H_4OCH_3$) 7.1–7.6 (m, 5 H, C_6H_5), 4.43 (q, 1 H, $CHCH_3$), 3.70 (s, 3 H, OCH_3), 1.55 (d, 3 H, CH_3); IR (neat) 3080, 3060, 2980, 2850, 1650, 1610, 1580, 1500, 1450, 1420, 1380, 1300, 1270, 1190, 1100, 1090, 1050, 980, 910, 870, 840, 760, 700 cm^{-1}; MS (70 eV), *m/e* (relative intensity), 240 (M^+ + 1, 9), 239 (M^+, 48), 238 (17), 224 (51), 105 (100).

Compound **3b** was obtained from **2b** ($[\alpha^{20}_D$ +19.2, neat) as a clear colorless liquid: bp 128–131 °C (0.15 mm); $[\alpha]^{25}_\lambda$ (*c* 10, $CHCl_3$), -83.5_{589}, -88.1_{578}, -105.3_{546}, -241.9_{436}; NMR ($CDCl_3$) δ 8.27 (s, 1 H, CH=N), 7.67 and 6.87 (AA′BB′, 4 H, $C_6H_4OCH_3$), 7.0–7.4 (m, 5 H, C_6H_5), 4.10 (t, 1 H, $CHCH_2CH_3$), 3.80 (s, 3 H, OCH_3), 1.90 (m, 2 H, $CHCH_2CH_3$), 0.83 (t, 3 H, CH_2CH_3); IR (neat), 3070, 3050, 2890, 2880, 2790, 2780, 1640, 1600, 1580, 1510, 1480, 1420, 1380, 1300, 1250, 1160, 1100, 1030, 970, 820, 760, 700 cm^{-1}; MS (70 eV), *m/e* (relative intensity), 254 (M^+ + 1, 1.5), 253 (M^+, 9.4), 224 (100), 119 (6), 91 (29), 77 (6).

Compound **3e** was obtained from **2e** ($[\alpha]^{20}_D$ +2.55, neat) as a clear colorless liquid, bp 158–168 °C (1.5 mm), which solidified to a white crystalline solid, mp 61–63 °C, on standing; $[\alpha]^{25}_\lambda$ (*c* 5, $CHCl_3$) -55.4_{589}, -58.6_{578}, -68.6_{546}, -143.8_{436}, -294_{365}; NMR ($CDCl_3$) δ 8.13 (s, 1 H, CH=N), 7.70 and 6.84 (AA′BB′, 4 H, $C_6H_4OCH_3$), 7.0–7.6 (m, 5 H, C_6H_5), 3.87 (s, 1 H, CHN), 3.78 (s, 3 H, OCH_3), 0.91 (s, 9 H, $C(CH_3)_3$); IR (neat) 3080, 3040, 2980, 2930, 2880, 2860, 1650, 1610, 1580, 1520, 1460, 1420, 1400, 1360, 1300, 1250, 1170, 1060, 1040, 840, 740, 700 cm^{-1}; MS (70 eV), *m/e* (relative intensity), 281 (M^+, 3), 266 (3), 224 (100), 91 (7), 77 (4).

Compound **3o** was obtained from **2o**. Molecular distillation yielded a clear colorless liquid: NMR ($CDCl_3$) δ 8.22 (s, 1 H, CH=N), 7.67 and 6.85 (AA′BB′ 4 H, $C_6H_4OCH_3$), 7.28 (s, 5 H, C_6H_5), 3.78 (s, 3 H, OCH_3); IR (neat), 3100, 3020, 2880, 2780, 2170, 2110, 2050, 1620, 1500, 1450, 1430, 1320, 1250 1160, 1100, 1025, 830, 715 cm^{-1}; MS (70 eV), *m/e* (relative intensity), 228 (M^+ + 1, 8), 227 (M^+, 49), 226 (33), 135 (15), 134 (17), 133 (12), 93 (100), 77 (13).

LCICD Determinations. Samples were prepared by adding 5–10 mg of chiral solute to 1 mL of MBBA. The resulting mixture was warmed to ca. 50 °C until an isotropic liquid had formed. One drop (ca. 5 mg) of this solution was sandwiched between two quartz plates with a 20-μm silver spacer. The resulting sample was mounted on a brass block and the resulting optical activity was measured by CD, ORD, and polarimetry. Care was taken not to mechanically twist the plates, and the resulting optical activity was not evident until the sample had cooled to form a liquid-crystal film. A minimum of three measurements were made on different sample preparations of each solution, and in all instances, the CD sign was reliably reproduced, in most instances giving an off-scale reading at the least sensitive setting on our instrument. Polarimetry was found to be unreliable since at higher concentrations the rotations tended to be out of the range of our instrument. However, by examining more dilute solutions (0.05%) and observing the plain ORD curve from 800 down to 550–600 nm, the sign of the Cotton effect for the imine chromophore could

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be determined. The magnitudes of the induced activity when measurable could not be reproduced reliably due to variations in sample thickness and temperature.

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Crystal Structure and Stereochemistry of Ivaxillin[1]

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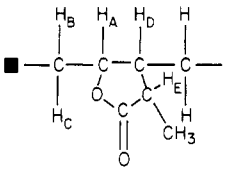
A number of years ago[2] one of us described isolation from *Iva axillaris* of the three cyclopropanoid guaianolides axivalin (**1**), ivaxillarin (**2**), and anhydroivaxillarin (**3**) which have so far remained the only representatives of their type (see Chart I). The stereochemistry of axivalin which has been correlated with **2** and **3** was subsequently[3] established by X-ray crystallography.

Two other constituents of *I. axillaris* were the previously known[4] eudesmanolide microcephalin (**4**) and a saturated sesquiterpene lactone $C_{15}H_{22}O_4$ (mp 173–176 °C) which appeared to be new and was named ivaxillin. As the substance lacked hydroxyl and ketone groups, it was tentatively formulated as a diepoxyguaianolide,[2] but this is clearly incompatible with the empirical formula which, if the presence of two oxirane functions is postulated, imposes an upper limit of one alicyclic ring.

Indeed, ^{13}C NMR and 270-MHz ^1H NMR spectra of the small sample of ivaxillin still extant from the earlier work suggested that the substance was a diepoxygermacranolide of structural type **5**, exclusive of stereochemistry. The presence of partial structure A was deduced by spin de-



A

Chart I

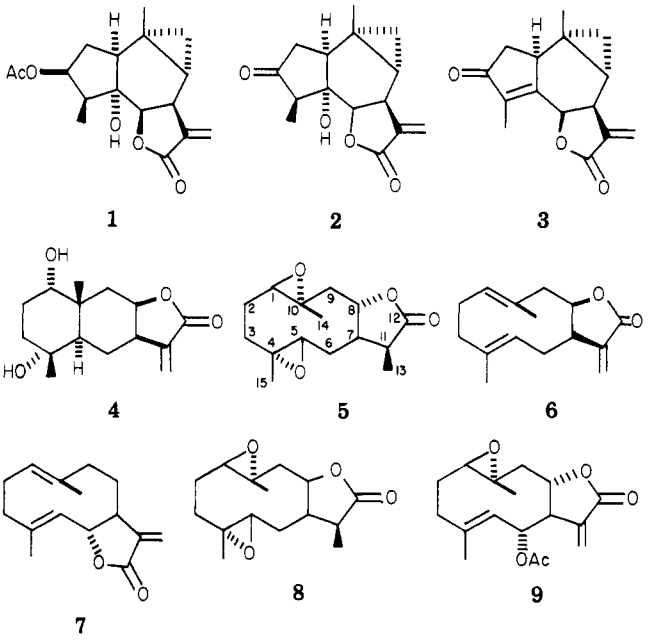


Table I. ^{13}C NMR Spectral Data of Ivaxillin[a]

shift, δ	carbon	shift, δ	carbon
177.91 s	C-12	40.59 d	C-11[b]
82.02 d	C-8[b]	35.73 t	C-3[c]
65.13 d	C-1,5	26.33 t	C-6[c]
64.39 d		24.00 t	C-2[c]
61.02 s	C-4[c]	18.19 q	C-14[c]
57.66 s	C-10[c]	16.33 q	C-15[c]
45.57 d	C-7[b]	11.54 q	C-13[b]
45.11 t	C-9[c]		

[a] Run at 67.9 MHz in $CDCl_3$. [b] Assignment by selective decoupling. [c] Assignment based on predicted shifts and comparison with the ^{13}C NMR spectrum of **9** (Joseph, Nathan-P. *Rev. Latinoam. Quim.* **1978**, *9*, 36).

coupling. In $CDCl_3$, H_A (ddd at 4.30 ppm) was coupled to H_B (br d at 2.78 ppm, $J_{A,B}$ 1.5 Hz) and H_C (partially buried in a four-proton multiplet centered at 1.45 ppm but clearly visible in C_6D_6 as a dd at 1.08 ppm, $J_{A,C}$ = 10 Hz) as well as to H_D (m at 2.45 ppm, $J_{A,D}$ = 10 Hz). H_B and H_C were mutually coupled ($J_{B,C}$ = 14 Hz), the absence of further splitting indicating that the neighboring carbon was quaternary. H_D was also coupled to H_E (quintet at 2.82 ppm, $J_{D,E}$ = 7.5 Hz) which in turn was coupled to a methyl doublet at 1.23 ppm. The appearance of the H_D signal indicated that it adjoined a methylene, at least one of whose protons was part of the four-proton multiplet at 1.45 ppm.

As the ^1H NMR spectrum of ivaxillin also displayed two methyl singlets at 1.39 and 1.27 ppm and two signals at 2.79 (br d, J = 14 Hz) and 2.74 ppm (br d, J = 10 Hz) characteristic of protons on an oxirane ring, gross structure **5** which was consonant with the ^{13}C NMR spectrum (Table I) and biogenetically plausible seemed likely. As to stereochemistry, if ivaxillin were derived by epoxidation of a *trans*-1(10),*trans*-4,5-germacradienolide and hence in the favored crown conformation when in solution,[5,6] the lactone ring had to be trans-fused to account for the observed coupling constants involving H-7 and H-8. Furthermore, the value of $J_{7,11}$ (7.5 Hz) and the large solvent shift observed for the C-11 methyl signal ($\delta_{CDCl_3} - \delta_{C_6D_6}$ = −0.46

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