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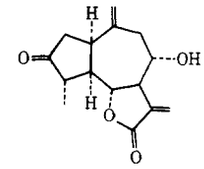

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New *ent*-Clerodane-Type Diterpenoids from *Baccharis trimera*[1a]

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The isolation of three new closely related *trans*-clerodane-type diterpenoids, **1a**, **1b**, and **2a**, from the medicinal plant *Baccharis trimera* (Less.) DC is described. Proof for the proposed structures and definite evidence for the stereochemistry were provided by x-ray analysis of **2a**. The flavone eupatorin was also isolated from *B. trimera* and the dihydroflavone sakuranetin from *B. retusa* DC.

Several members of the large Western hemisphere genus *Baccharis* (Compositae, tribe Astereae) are used as folk medicines by the populations of their respective habitats. In the present communication, we report on constituents of two such species which are native to São Paulo and neighboring states of Brazil.

Ethyl acetate extracts of *Baccharis trimera* (Less.) DC, a well-known medicinal plant of this region,[3,4] afforded protection against infection by cercaria of *Schistosoma mansoni*. Large-scale extraction and extensive chromatography afforded four crystalline compounds in relatively small amounts. One of these was eupatorin (3′,5-dihydroxy-4′,6,7-trimethoxyflavone, **3**)[8]; the others were three new apparently closely related diterpenoids: $C_{20}H_{28}O_4$, mp 151–153 °C (**1a**); $C_{20}H_{28}O_5$, mp 203–205 °C (**1b**); and $C_{20}H_{26}O_5$, mp 195–196 °C (**2a**).

The extra oxygen of **1b** and **2a** was that of a secondary hydroxyl group as evidenced by the IR spectra and the facile oxidation of **1b** and **2a** to the ketones **1c** and **2b** which exhibited new IR bands at 1705 and 1700 cm^{-1}, respectively, and lacked a multiplet near 4.1 ppm found in the NMR spectra of **1b** and **2a** (Table I). A pronounced diamagnetic shift of a doublet near 5.3 ppm (also present in the NMR spectrum of **1a**) to near 4 ppm accompanied these oxidations, the doublet being the downfield half of an AB system where B, near 3.9 ppm, was in turn coupled (J = 3 Hz) to another proton. The chemical shift of the AB system seemed characteristic of the methylene protons in the grouping –(O=)$COCH_2$– (A), with the B proton apparently long-range coupled to another proton.

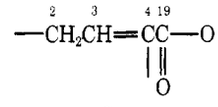
In the same region of the NMR spectra, **1a–c** also displayed the AB part of an ABX system near 4.45 and 3.95 ppm. The

Table I. ^{1}H NMR Spectra of 1b and 2a[a]

	1b	2a
H(1)	1.3 m	1.19 q,d (12,4)
	b	d
H(2)	2.39 m	2.4 m
	2.17 m	e
H(5)	6.71 dd (7, 2)	6.72 dd (7, 2)
H(6)	2.31 dd (14, 3)	2.34 dd (14, 3)
	b	1.37 ddd (14, 3, 2)
H(7)	4.09 m	4.13 m
H(8)	c	d
H(10)	b or c	e
H(11)	b or c	d
H(12)	1.3 m	2.28 m
	b or c	d
H(13)	2.47 m	
H(14)	2.67 dd (17, 8)	5.88 t (2)
	2.17 dd (17, 8)	
H(16)	4.46 dd (9, 7)	4.47[f]
	3.94 dd (9, 7)	
H(17)[g]	1.03 d (7)	1.06 d (7)
H(18)[g]	0.86	0.92
H(19)	5.31 d (7)	5.33 d (7)
	3.90 dd (7, 2)	3.92 dd (7, 2)

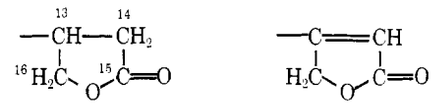
[a] Run in $CDCl_3$ solution on a Bruker 270-MHz spectrometer with Me_4Si as internal standard. Values are in ppm, figures in parentheses are coupling constants in hertz. Letters indicate multiplicities: d, doublet; t, triplet; q, quartet; m, multiplet whose center is given. Unmarked signals are singlets. [b] In four-proton multiplet near 1.4 ppm. [c] In three-proton multiplet near 1.6 ppm. [d] In five-proton multiplet near 1.6 ppm. [e] In three-proton multiplet near 2.15 ppm which contains -OH signal. [f] Slightly split, intensity two protons. [g] Intensity three protons.

chemical shift of these signals pointed to the presence of a second ester function of the type -(O=)$COCH_2CH<$ (B) which would account for the remaining two oxygen atoms of the empirical formulas. Furthermore, the IR spectra of **1a–c** which exhibited bands at 1770, 1740, and 1660 cm^{-1} and the strong UV absorption near 215 nm indicated that partial structures A and B were incorporated into two γ-lactone systems, one of which was α,β unsaturated as represented in C (numbering as in final formula) because of the appearance in all NMR spectra of a doublet of doublets near 6.7 ppm whose chemical shift is characteristic of β rather than α attachment. The ^{13}C NMR spectrum of **1b** (vide infra) revealed no center of unsaturation other than that of C.

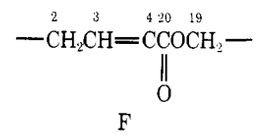


C

In the NMR spectra of **2a** and **2b**, the ABX system of partial structure B was replaced by a slightly broadened two-proton singlet whose appearance suggested the absence of the X proton, but the presence of some allylic coupling. These two compounds also exhibited a narrowly split triplet at 5.88 ppm which was responsible for the broadening of the two-proton singlet and whose chemical shift was characteristic of a proton on the α carbon of an α,β-unsaturated system. Moreover, the IR spectra of **2a** and **2b** displayed a new double-bond frequency at 1630 cm^{-1}, and the ^{13}C NMR spectrum of **2a** contained a second doublet and a second singlet in the vinylic carbon region. Consequently, B could be expanded to D (in **1a–c**) and to E (in **2a** and **2b**); hence, the methylene group of A must be attached to C as in F.

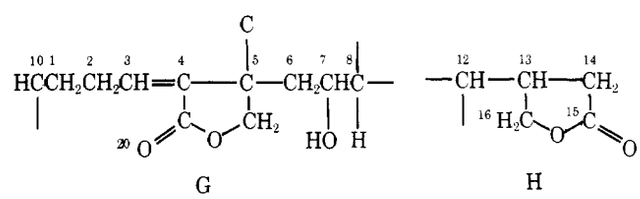


D E



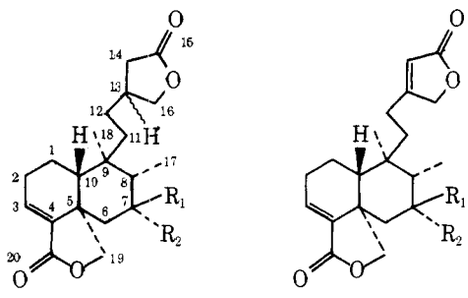
F

Extensive spin-decoupling experiments on **1b** and **2a** at 270 MHz, which will not be described in detail, permitted identification of H_{2a} and H_{2b} of F (see Table I) and showed that C(2) was adjacent to another methylene group ($-CH_2-$), which in turn was linked to a carbon atom [C(10)] carrying at least one proton. C(19) of F was next to a quaternary center; the proton which split H(19b) by W coupling was identified and shown to be part of the C(6) methylene group which was linked to the carbon atom [C(7)] carrying the secondary hydroxyl. Since C(8) carried at least one proton, partial structure F could be expanded to G. Identification of H(14a) and H(14b) (see partial structure D) in the NMR spectrum of **1b** was also possible, and it was shown that H(13) was coupled to at least one other proton as in H.



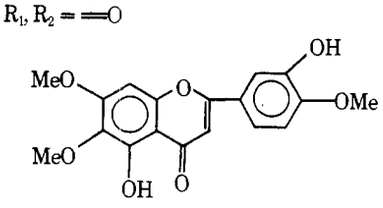
G H

The NMR spectra of all substances also exhibited a methyl singlet and a methyl doublet. Since the spin-decoupling experiments showed that C(12) of H was identical with C(10) of G and neither was identical with the carbon atom carrying the secondary methyl group (see Table I), partial formulas G and H together with the two methyl groups account for 25 of the 28 protons and at least 18 of the 20 carbon atoms required



1a, R_1, R_2 = H
b, R_1 = H; R_2 = OH
c, R_1, R_2 = =O

2a, R_1 = H; R_2 = OH
b, R_1, R_2 = =O



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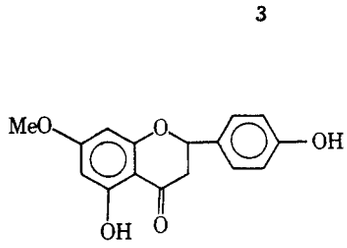

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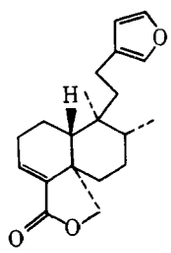

5

Table IV. Endocyclic Torsion Angles

Ring	Bond	Angle	Ring	Bond	Angle
A	C(1)–C(2)	−55.6°	γ-Lac-	C(4)–C(5)	34.4°
	C(2)–C(3)	24.9°	tone	C(5)–C(18)	−35.4°
	C(3)–C(4)	0.1°		C(18)–O(4)	26.0°
	C(4)–C(5)	6.1°		O(4)–C(19)	−3.5°
	C(5)–C(10)	−37.4°		C(19)–C(4)	−21.3°
	C(10)–C(1)	63.5°			
B	C(5)–C(6)	−54.4°	α,β-Unsatd	C(13)–C(14)	−0.6°
	C(6)–C(7)	48.6°	γ-lac-	C(14)–C(15)	0.0°
	C(7)–C(8)	−47.1°	tone	C(15)–O(3)	0.5°
	C(8)–C(9)	51.1°		O(3)–C(16)	−0.8°
	C(9)–C(10)	−61.7°		C(16)–C(13)	0.8°
	C(10)–C(5)	63.8°			

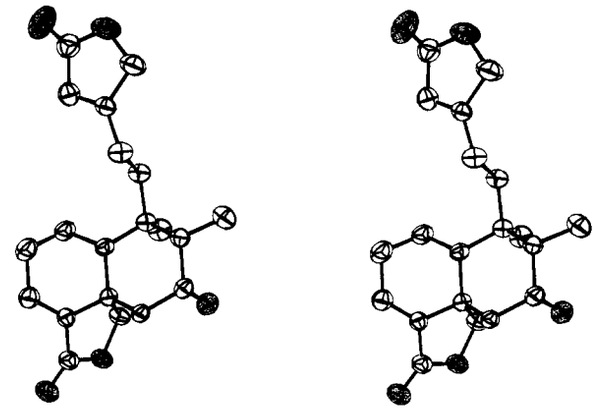

Figure 1. Stereoscopic view of **2a** (oxygen atoms shaded).

by the empirical formula of **1b.** Combination leads to the biogenetically plausible formulas **1b** and **2a** (exclusive of stereochemistry), which possess the same backbone-rearranged clerodane-type diterpenoid carbon skeleton as a lactone **5** previously[9] isolated from *Baccharis conferta* HBK. The unhydroxylated compound $C_{20}H_{28}O_4$ would then be **1a.**

The ^{13}C NMR spectra were fully in accord with this deduction. That of **1b** exhibited two carbonyl singlets (176.6, 169.8); 1 vinyl carbon singlet [139.2 for C(3)]; 1 vinyl carbon doublet [134.7 for C(4)]; two triplets characteristic of carbon carrying single-bonded oxygen [73.1 and 72.7 for C(16) and C(19)]; one doublet of carbon carrying single-bonded oxygen [C(7) at 72.2]; two methyl quartets (19.1 and 11.9); six methylene quartets at 40.5, 36.2, 34.6, 27.6, 26.5, and 19.4; three methinyl doublets at 48.3, 40.5, and 36.1, probably in the order C(10), C(8), and C(13); and two singlets at 44.9 and 38.4 ppm for C(5) and C(9), respectively. The corresponding signals for **2a** were two carbonyls (173.7, 169.8); two vinyl singlets at 170.0 and 139.2 for C(13) and C(4); two vinyl doublets at 134.7 and 115.4 for C(3) and C(14); two CH_2–O triplets [73.0, 72.6 for C(16) and C(19)]; one –CH–O doublet (C-7 at 72.1); two methyl quartets (19.0, 12.0); five methylene triplets at 40.6, 35.7, 27.7, 22.4, and 19.4; two methinyl doublets at 48.5 and 40.7 [C(10) and C(8)]; and two quaternary carbons at 44.9 [C(5)] and 38.9 ppm [C(9)]. Comparison of the two spectra, application of the usual shift parameters, and consultation of the literature[10] permitted assignment of most frequencies as specified, but no attempt was made to resolve ambiguities in the methylene and methinyl assignments by single-frequency off-resonance spin decoupling.

The proposed carbon skeleton was confirmed by selenium dehydrogenation of **1b** and **2b** which resulted in formation of 1,2-dimethylnaphthalene.

As for stereochemistry, the C-8 methyl group was equatorial, since **1c** and **2b** were apparently not epimerized on exposure to base. The magnitude of $J_{6,7}$ (3 and 2 Hz) showed that the hydroxyl group was axial which was confirmed by its deshielding effect on substituents at C(5) and C(9) (see below). While *cis*-clerodanes are known, the biogenetically plausible trans fusion of rings A and B, i.e., the axial orientation of the methylene group on C(5), and axial orientation of the C(9) methyl group, was supported by the existence of appreciable long-range coupling (2 Hz) between H(6b) and H(19b) and the upfield shifts (~1.3 and 0.25 ppm) which H(19a) and the C(19) methyl resonance experience on oxidation of **1b** and **2a** to the ketones **1c** and **2b,** respectively. Likewise, in **1a** which lacks the hydroxyl group, the chemical shifts of H(19a) and the C(9) methyl group are comparable to those prevailing in **1c** and **2b.** The stereochemistry at C(13) of **1a** and **1b** could not be deduced spectroscopically.

X-ray analysis of single crystals of **2a** confirmed the proposed structure and stereochemistry. The relative configuration of **2a** obtained from the structure determination is depicted in Figure 1. Tables II and III (Supplementary Material) give the atomic coordinates and temperature factors, and Table IV gives torsion angles in the rings in the molecule. Torsion angles reveal that ring A and B adopt approximately 1,2-diplanar and chair conformations, respectively.[11] The torsion angles involving the chain attached to C(9) are C(8)–C(9)–C(11)–C(12) (−63.6°), C(10)–C(9)–C(11)–C(12) (53.7°), C(9)–C(11)–C(12)–C(13) (−163.5°), C(11)–C(12)–C(13)–C(14) (84.1°), and C(11)–C(12)–C(13)–C(16) (−93.3°). Tables V and VI containing bond lengths and angles, respectively, are available as Supplementary Material. Bond lengths are, within the estimated standard deviations, essentially normal except for the rather long C(8)–C(9) bond [1.561 (4) Å]. This long bond may result from the high degree of substitution at the carbon atoms C(8) and C(9).

The CD curves of all substances exhibit a strong negative band at 242–244 nm which is attributed to the n to π* transition of the α,β-unsaturated lactone (or lactones) and corresponds in sign to the n to π* transition of the α,β-unsaturated ester of (−)-methyl hardwickiiate and methyl barbascoate of known absolute stereochemistry.[12] The CD curves of **1c** and **2b** display, in addition, a negative Cotton effect near 296 nm due to the n to π* transition of the newly introduced ketone; the sign is in keeping with the absolute stereochemistry depicted in the formulas, although the possible "antioctant" or "dissignate" effect[13] of the 3,4 double bond beclouds the argument.

Extraction of *Baccharis retusa* DC and extensive chromatography yielded the dihydroflavonol sakuranetin (**4**)[8] on the sole crystallizable constituent.

Experimental Section[15]

Extraction of *Baccharis Trimera.* Above-ground *Baccharis trimera* DC, wt 6.5 kg, collected by Dr. Hermógenes de Freitas Leitão Filho in Compos de Jordão, São Paulo State, Brazil, in July 1973, was extracted with ethyl acetate. The crude extract, wt 240 g, was chromatographed over 2 kg of silica gel, 250-mL fractions being collected in the following order: Fractions 1–17 (hexane), 18–52 (hexane–benzene, 20:1), 53–63 (idem, 13.5:1), 64–75 (idem, 6.5:1), 76–85 (idem, 5:1), 86–94 (idem, 4:1), 95–102 (idem, 3:1), 103–110 (idem, 2:1), 111–135 (benzene), 136–148 (benzene–$CHCl_3$, 20:1), 149–155 (idem, 10:1), 156–164 (idem, 5:1), 165–172 (idem, 2.5:1), 173–193 (idem, 1.5:1), 194–280 ($CHCl_3$), 281–291 ($CHCl_3$–ethyl acetate, 10:1), 292–300 (idem, 5:1), 301–320 (idem, 3:1), 321–340 (idem, 2.5:1), 341–359 (idem, 2:1), 360–378 (idem, 1.5:1), 379–396 (EtOAc), 397–417 (ethanol).

Fractions 217–226 (3 g) showed one major spot on TLC and were combined. Rechromatography over 40 g of silica gel and elution with CH_2Cl_2–EtOAc (100:1) gave 52 mg of solid **1a** which was purified by preparative TLC (silica gel, benzene–EtOAc, 3:1): yield 42 mg of **1a;** mp 151–153 °C; UV λ_{max} 215 nm (MeOH); CD curve $[\theta]_{243}$ −27 900, $[\theta]_{215}$ +11 000; IR (KBr) 1770 (satd lactone), 1750, and 1660 cm^{-1} (α,β-unsaturated γ-lactone); NMR (270 MHz) 6.75 [dd, 7, 2, H(3)],

4.45 (dd, 7, 5) and 3.92 [dd, 7, 5, H(16a) and H(16b)], 4.28 (d, 7) and 3.89 [dd, 7, 2, H(19a) and H(19b)], 2.66 (dd, 17, 8), 2.46 (m), 2.37 (m), 2.16 (dd, 17, 8) superimposed on 2.15 (m), 1.92 (dt, 12, 2), 1.56 (center of strong absorption corresponding to six protons), 1.34 (t, 7) superimposed on multiplets corresponding to four protons, 0.82 [d, 7, H(17)], and 0.58 ppm [H(18)]; significant peaks in low-resolution mass spectrum at *m/e* 332 (M^+, $C_{20}H_{28}O_4$, 0.2%), 278 ($M^+ - 54$, 10%), 167 ($M^+ - 54 - 111$, 30%), 149 (base peak).

Anal. Calcd for $C_{20}H_{28}O_4$: mol wt 332.2060. Found: mol wt (MS) 332.2068.

Elution of the combined fractions 217–226 with CH_2Cl_2–EtOAc, 3:1, gave 62 mg of eupatorin (3′,5-dihydroxy-4′,6,7-trimethoxyflavone) which was recrystallized from $CHCl_3$: mp 195–197 °C, lit.[8] mp 198–198 °C; UV λ_{max} 244 (23 600), 255 (27 100), 275 (22 900), and 342 nm (31 400). Acetylation with pyridine–acetic anhydride and recrystallization from benzene–petroleum ether afforded eupatorin diacetate, mp 176–177 °C, lit.[9] mp 176–177 °C. The NMR spectrum was superimposed on traces of eupatorin diacetate supplied by Professor S. M. Kupchan.

Fractions 233–242, wt 16 g, were combined and rechromatographed over 470 g of silica gel. The solid fractions eluted with CH_2Cl_2–EtOAc (50:1 and 20:1) were combined, wt 0.72 g. Recrystallization from EtOAc–MeOH (20:1) afforded 0.68 g of **1b**: mp 203–205 °C; UV λ_{max} 217.5 nm (MeOH); $[\alpha]^{22}_D$ −141 ° ($CHCl_3$); CD curve $[\theta]_{244}$ −31 000, $[\theta]_{216}$ +6900 (MeOH); IR (KBr) 3490 (–OH), 1765 (satd lactone), 1740 and 1650 cm^{-1} (unsatd lactone).

Anal. Calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10; mol wt, 348.1935. Found: C, 69.06; H, 8.07; mol wt (MS), 348.1949.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (composition, %) 330 ($C_{20}H_{26}O_4$, 9.0), 318 ($C_{19}H_{26}O_4$, 82.4), 312 ($C_{20}H_{24}O_3$, 14.7), 300 ($C_{19}H_{24}O_3$, 69.9), 299 ($C_{19}H_{23}O_3$, 10.1), 217 ($C_{14}H_{17}O_2$, 48.3), 205 ($C_{13}H_{17}O_2$, 31.1), 189 ($C_{13}H_{15}O$, 29.4), and 159 ($C_{11}H_{11}O$, 100).

Fractions 243–277, wt 24 g, were combined and rechromatographed over 600 g of silica gel (600 g). The fraction eluted with CH_2Cl_2–EtOAc (5:1) solidified, wt 0.622 g, and was purified by preparative TLC on silica gel (benzene–EtOAc, 2:1) to give 0.49 g of **2a**: mp 195–196 °C; UV λ_{max} 218.5 nm (MeOH); $[\alpha]^{22}_D$ −97° ($CHCl_3$); CD curve $[\theta]_{244}$ −31 000, $[\theta]_{216}$ +5000 (MeOH); IR (KBr) 3480 (–OH), 1770 (sh), 1735 (double strength), 1650, and 1630 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57; mol wt, 346.1779. Found: C, 69.26; H, 7.51; mol wt (MS), 346.1787.

Other significant peaks in the high-resolution mass spectrum were *m/e* (composition, %) 328 ($C_{20}H_{24}O_4$, 3.4), 316 ($C_{19}H_{24}O_4$, 27.5), 299 ($C_{19}H_{23}O_3$, 29), 298 ($C_{19}H_{22}O_3$, 10.6), 233 ($C_{14}H_{17}O_3$, 36), 219 ($C_{14}H_{19}O_2$, 15.3), and 203 ($C_{14}H_{17}O$, 23.1).

Oxidation of 1b and 2c. (a) To an ice-cold solution of 30 mg of **1b** in 5 mL of acetone was added dropwise, with stirring, 0.2 mL of Jones reagent. Stirring was continued for 10 min, after which period excess oxidant was destroyed by the addition of a few drops of MeOH. The solvents were removed at reduced pressure; the residue was diluted with ice-water and extracted with $CHCl_3$. The washed and dried extract was evaporated and the residue purified by preparative TLC (benzene–EtOAc, 3:1) to give 14 mg of gummy **1c**: IR (film) 1765 (double strength), 1705, and 1660 cm^{-1}; NMR (90 MHz) at 6.85 [dd, 7, 2, H(3)], 4.77 (dd, 9, 7) and 3.97 [dd, 9, 7, H(16a), and H(16b)], 3.95 [H(19a) and H(19b) center of AB system where A is narrowly split by coupling to H(6)], 0.97 [dd, 7, H(17)] and 0.61 ppm [H(18)]; CD curve (MeOH) $[\theta]_{242}$ −22 000, $[\theta]_{275}$ −3900 (min), $[\theta]_{293}$ −5400.

(b) Oxidation of 30 mg of **2a** in the same manner afforded 14 mg of gummy **2b**: IR (film) 1765, 1740, 1700, 1660, and 1630 cm^{-1}; NMR (90 MHz) 6.88 [dd, 7, 2, H(3)], 5.91 [br, H(14)], 4.79 [center of AB system where A is coupled to H(14), H(16a), and H(16b)], 4.02 (d, 7), and 3.93 [dd, 7, 2′, H(19a) and H(19b)], 1.02 [d, 7, H(17)], and 0.68 ppm [H(18)]; CD curve $[\theta]_{243}$ −24 500, $[\theta]_{275}$ −4800 (min), and $[\theta]_{295}$ −6000.

Dehydrogenation of 1b and 2a. A mixture of 0.1 g of **1b** and 0.3 g of selenium was heated at 345 °C for 3 h, cooled, and extracted with hexane. The residue from the hexane extract was placed on a TLC plate which was developed with benzene. The material which fluoresced under UV light was separated and extracted with spectroscopic grade benzene. Removal of benzene gave a small amount of residue whose ultraviolet spectrum in isooctane was identical with that of 1,2-dimethylnaphthalene.[16]

Dehydrogenation of 0.1 g of **2b** as described in the preceding paragraph also furnished 1,2-dimethylnaphthalene.

X-Ray Analysis of 2a. Compound **2a** crystallized in the orthorhombic space group $P2_12_12_1$, with a = 18.803 (4), b = 12.188 (4), c = 7.680 (2) Å, and Z = 4. Unit cell and intensity data were measured on a Philips PW 1100 diffractometer with Cu$K\alpha$ radiation and the $\theta - 2\theta$ scan technique. Unit cell parameters were refined by least squares from the observed 2θ values of 25 reflections. Of the 1957 independent reflextions with $2\theta \leq 140°$, 1741 had intensities greater than 3.3 $\sigma(I)$ [$\sigma(I)$ is based on counter statistics], and were used in the structure refinement. Lorentz and polarization corrections were applied, and the structure amplitudes derived. The structure was solved by direct methods with the multisolution procedure[17] and refined by the full-matrix least-squares method with the weighting scheme of Hughes.[18] The atomic scattering factors used were those of the *International Tables for X-ray Crystallography*.[19] Only the positional parameters of the hydrogen atoms were refined, resulting in an R value of 0.05 for all observed reflections. The isotropic temperature factor for each hydrogen atom was constrained to the same value as that of the carbon atom to which it is bonded.

Extraction of *Baccharis retusa*. Above-ground plant material, wt 5 kg, collected by Dr. Hermógenes de Freitas Leitão Filho in Campos de Jordão, São Paulo State, Brazil, in March 1974, was extracted with $CHCl_3$. The chloroform extract was evaporated and diluted with ethanol–water (1:3), allowed to stand, and filtered. The filtrate was extracted with $CHCl_3$; evaporation of the extract gave 5 g of gum which was chromatographed over 150 g of silica gel, 100-mL fractions being collected in the following order: Fractions 1–24 (hexane), 25–28 (hexane–EtOAc, 100:1), 29–32 (idem, 35:1), 33–43 (idem, 20:1), 44–54 (idem, 10:1), 55–65 (idem, 65:1), 66–72 (idem, 5:1), 73–80 (idem, 3:1), 81–92 (idem, 2:1), 93–100 (EtOAc), 101–108 (EtOAc–EtOH, 20:1), 109–115 (idem, 10:1), 116–123 (idem, 5:1), 124–131 (idem, 2:1), 132–139 (EtOH).

The solids from fractions 61–70, wt 0.335 g, were combined. Recrystallization from ethyl acetate furnished sakuranetin: mol wt (MS) 286; mp 144–145 °C, mixture melting point with authentic sample supplied by Professor Otto R. Gottlieb and Miss Rosely Maria Viégas Assumpcão undepressed; UV (EtOH) λ_{max} 335 (w), 289, 226, 216 and 209 nm, λ_{max} (EtOH–NaOAc) 335 and 287 nm, λ_{max} (EtOH–NaOH) 428, 285, and 245 nm (w); λ_{max} (EtOH–$AlCl_3$) 367, 309, and 281 nm; no change on addition of HCl; NMR signals identical with the one reported in the literature.[20]

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Supplementary Material Available. Tables II and III of atomic coordinates and temperature factors and Tables V and VI of bond lengths and bond distances (4 pages). Ordering information is given on any current masthead page.

Registry No.—**1a,** 63640-86-8; **1b,** 63640-87-9; **1c,** 63640-88-0; **2a,** 63640-89-1; **2b,** 63640-90-4; **3,** 855-96-9.

References and Notes

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Absolute Configuration at Chiral Nitrogen in Oxaziridines. 2[1]

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Peracid oxidation of chiral imines leads to diastereomeric oxaziridines in high optical yields. The chiral substituent connected to nitrogen and the carbon skeleton of the imine have a similar inductive effect on the newly created asymmetric center in the oxaziridine ring. A correlation of the chirality of new oxaziridines with those of known absolute configuration is made on the basis of changes in molecular rotation.

Pyramidal nitrogen stability in oxaziridines has been established by the separation of invertomers (enantiomers and diastereomers) of these compounds formed in asymmetric synthesis.[1-8]

Previously, we have found[1,2] that *m*-chloroperbenzoic acid oxidation of imines containing a chiral substituent linked to the nitrogen yielded diastereomeric oxaziridines in high optical yield. Thus, we were able to synthesize optically pure oxaziridines suitable for x-ray analysis (i.e., a compound containing a heavy atom and a chiral center of known configuration).

As described in a preliminary communication,[9] oxidation of optically active (*E*)-imine, obtained from *p*-bromobenzaldehyde and (*S*)-(−)-α-phenylethylamine, gave four nonracemic oxaziridines (Scheme I). The composition of the mixture was determined by integration of the signal produced by the proton at C-3. The pertinent δ values (CCl_4 s) are: **1**, 4.32; **2**, 4.38; **3**, 5.0, and **4**, 5.15 ppm. By analogy,[1,6] the trans configuration was assigned to **1** and **2**, and cis to **3** and **4**. The major product, diastereomer **1**, was isolated from the mixture by crystallization; the other three products were separated by chromatography (SiO_2; hexane–ether, 98:2).

Since the *S* chirality of the N substituent in the starting imine was known, and the x-ray study showed an opposite configuration at the carbon and nitrogen atoms in the oxaziridine ring, the absolute configuration of diastereomer **1** could be established as (2*R*,3*R*)-2-[(S)-1-phenylethyl]-3-*p*-bromophenyloxaziridine.[9] Consequently, the configuration of diastereomer **2** was (2*S*,3*S*)-2-[(S)-1-phenylethyl]-3-*p*-bromophenyloxaziridine.

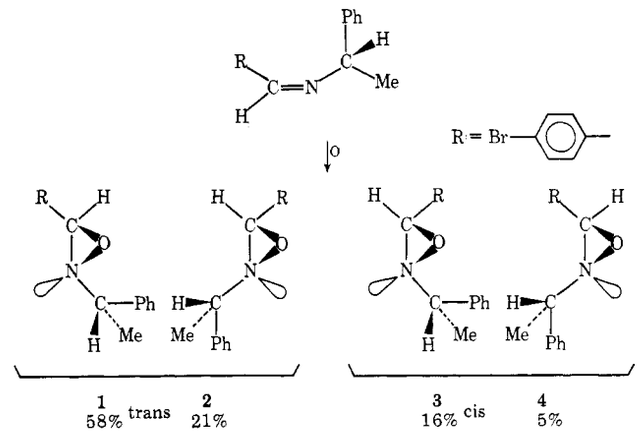
In order to investigate the relative configuration of the cis isomers, compounds **3** and **4** were each thermally isomerized (120 °C, tetrachloroethylene). The isomerization occurred in the direction **4** → **1** and **3** → **2**.

The interconversion of the trans and cis oxaziridine isomers proceeded exclusively by a nitrogen inversion mechanism.[10] Thus, the structural assignments could be made for compounds **3** and **4** as shown in Scheme I.

In previously reported syntheses of oxaziridines,[1,2,9] derivatives of α-phenylethylamine were used as substrates. Our present study concerns the effect of imine structure (i.e., the type of chiral substituent joined to the nitrogen or carbon in the imine) on the diastereoselectivity.

The use of (−)-menthylamine in the condensations with benzaldehyde and isobutyraldehyde provided optically active imines containing another kind of chiral substituent linked to nitrogen. The resulting imines turned out to be pure *E* isomer.

Scheme I



Oxidation of the benzaldehyde derivative (Scheme II, R = Ph) gave three of four possible diastereomeric oxaziridines (**5**, **6** and **7**; Table I) which were separated by silica gel column chromatography and elution with hexane or ether–hexane (2:98). The chemical shift of the C-3 proton in the ^1H NMR spectrum was used to determine the quantitative composition of the mixture and assign the relative geometry around the oxaziridine ring.

Oxidation of the isobutyraldehyde derivative (Scheme II, *R* = *i*-Pr) gave only two diastereomeric oxaziridines in a combined yield (**8** and **9**; Table II) of 67%. The C-3 proton signals were singlets at δ 3.48 and 3.25 ppm. The small difference in chemical shifts suggested that both compounds have the same configuration, most probably trans. The ratio of diastereomers in the mixture was determined by integration of the C-3 proton signals.

It was also of interest to investigate the effect of the chiral carbonyl component of the imine. Optically active imines of this type were derived from condensation of D-camphor with benzylamine and *n*-propylamine.

N-Benzylimine (Scheme III; **10a**, R = $PhCH_2$–) contains about 95% of the *E* isomer (^1H NMR), whereas the *n*-propylimine (Scheme III; **11a**, R = $CH_3CH_2CH_2$–) is essentially the pure *E* isomer. When these compounds were oxidized, the yield of oxaziridine determined iodometrically was about 50%.