NADPH. After protein precipitation by the addition of acetone and extraction of the aqueous phase at pH 8 with ethyl acetate, the reaction mixture was separated by thin-layer chromatography (SiO_2, 99.75:0.25 AcOEt–NH_4OH) and each fraction analyzed by HPLC (μ-Porasil column, 99.75:0.25:0.02 CH_2Cl_2–CH_3OH–$(CH_3)_3N$).

Formation of 20-*epi*-ervatamine under these conditions was unambiguously shown by comparison of the TLC and HPLC retention time and mass and UV spectral data for the metabolite purified with those of an authentic sample.[9] The major metabolite[12] of dregamine is its N-demethylation product **3**, the structure of which has been shown by the mass spectrum of a sample purified by HPLC ($M^{+\cdot}$ 254) and its transformation back to dregamine (**1**) upon Eschweiler–Clark reductive methylation.[13]

About 4 and 140 nmol of **2** and **3** are, respectively, formed per mg of protein and per 30 min in the aforementioned conditions.

Table I shows the influence of various factors on the yields of formation of metabolites **2** and **3**. The yields were dramatically reduced upon heat denaturation of the protein before incubation, showing that formation of **2** and **3** is almost totally enzyme dependent. These yields were very low in the absence of NADPH or O_2, the necessary cofactors of cytochrome P-450 dependent microsomal monooxygenases,[14] and were greatly decreased in the presence of ellipticine (1 mM), known to be an efficient inhibitor of these monooxygenases[15] (Table I).

Furthermore, dregamine (**1**) readily binds to the hydrophobic active site of microsomal cytochrome P-450 as shown by visible spectroscopy. The difference spectrum produced by progressive addition of dregamine to a rat liver microsomal suspension exhibits a peak around 395 nm and a trough at 420 nm. It corresponds to the transition of originally low-spin cytochrome P-450 iron(III) to the high-spin state upon binding of **1** to a protein active site near the heme and is characteristic of the formation of a cytochrome P-450 substrate complex.[14] The binding affinity of **1** for cytochrome P-450 from liver microsomes of phenobarbital pretreated rats is relatively high since the concentration of **1** producing the half-maximum formation of the difference spectrum is about 10^{-5} M.

Taken together, these results are in agreement with the involvement of cytochrome P-450 in the microsomal oxidative demethylation of dregamine to the secondary amine **3** and its isomerization to 20-*epi*-ervatamine (**2**).

Oxidations of tertiary amines resulting in *N*-oxide formation or N-dealkylation are well-known microsomal reactions;[3] radical cations[16] of the starting amines ($RCH_2NR'R''^{+\cdot}$) iminium ions ($RCH{=}NR'R''^{+}$) and carbinolamines ($RCHOHNR'R''$) have been proposed as intermediates in these N-dealkylation reactions.[17]

It seems possible that 20-*epi*-ervatamine was derived either from a rearrangement of the *N*-oxide of **1** catalyzed by the iron cytochrome P-450 (iron(III) playing the same role as $COCF_3$ in the modified Polonovski reaction) or from a free-radical rearrangement of the radical cation formed by one-electron oxidation of **1**.

Whatever the exact mechanism may be, the present results describe an enzymatic equivalent of the modified Polonovski reaction for the conversion of vobasine to ervatamine-type alkaloids, providing a further argument in favor of the previously proposed biogenetic filiation between alkaloids of the vobasine and ervatamine types. It also supports the hypothesis of the modified Polonovski reaction being "biomimetic".

(12) HPLC analysis reveals the presence of many other products in the reaction mixture, either derived from **1** or from low-molecular weight compounds from microsomes. This made quantitative analysis difficult and explains the relatively high errors on some determinations (Table I).

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Effect of Molecular Structure on Mesomorphism. 12.[1] Flexible-Center Siamese-Twin Liquid Crystalline Diesters—A "Prepolymer" Model

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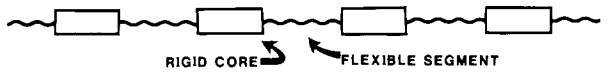
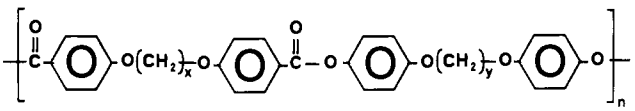
The vast majority of mesogenic (liquid crystalline) molecules are cigar-shaped structures having a rigid central core. This core is often composed of aromatic rings (or conformationally locked saturated rings) joined through a linking group such as —COO—, —CH=N— or —N=NO—.[2] In fact, the structural requirement of a rigid core is often given as necessary for nematic behavior in small molecule liquid crystals.[3,4] There have been recent reports of polymeric liquid crystals in which a small molecule liquid crystal moiety has been incorporated into the polymer backbone.[5,6] This is schematically shown below. An example of such a polymer



is compound **1**.[5d] All 30 polymers exhibited nematic phases on



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heating. Using calorimetrically determined (DSC) binary phase diagrams, we have established the nematic nature of the polymeric mesophase.[7] This phase assignment is supported by X-ray diffraction photographs of this mesophase in which only a single, diffuse ring at 4.4 Å was observed.[8] From viscosity data, the polymers **1** have estimated average molecular weights, M_w, ranging from 16200 to 19200.[8] These polymers (**1**) are structurally related to the mesogenic small molecule family of 4-alkoxyphenyl 4′-alkoxybenzoates (**2**) which have a rigid central core with flexible tail groups.

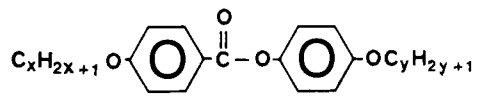

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Table I. Thermal Analysis of Siamese Twins (3)

x	$T_{K \rightarrow N}$,[a] °C	$T_{N \rightarrow I}$, °C
2	154.5	177.8
3	138.7	160.1
4	128.7	159.9
5	122.8	149.0
6	120.3	149.5
7	124.0	143.0
8	124.3	146.1
9	118.2	133.0
10	122.7	136.2

[a] All compounds upon heating underwent at least one solid–solid transition before the nematic phase was reached. A detailed study of thermal properties of these materials is planned.

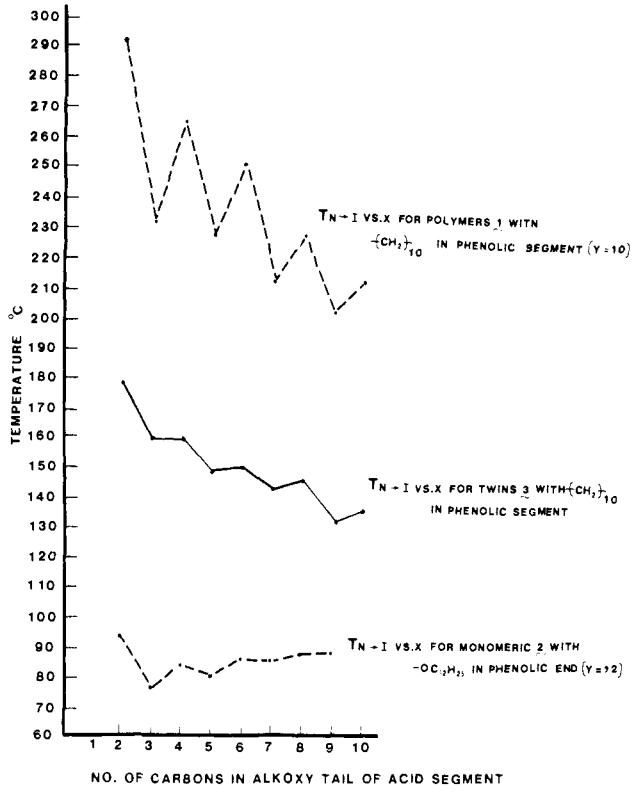
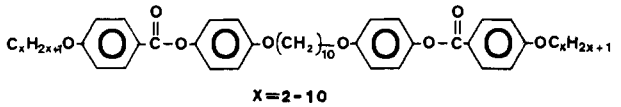


Figure 1. Plot of N → I transition temperatures for structurally similar nematogenic compounds.

We wish to report the synthesis and characterization of a series of Siamese-twin diesters which are of interest because they have not a rigid center but a flexible center, and because, we feel, they can be considered as oligomer models having chemical structures intermediate between those of small molecules liquid crystals and polymeric liquid crystals.

The diesters were made by reaction of 2 mol of the appropriate 4-*n*-alkoxybenzoic acid with 1 mol of 4,4′-dihydroxy-1,10-diphenoxydecane by the method of Hassner.[9] Infrared and proton NMR spectra along with elemental analyses were consistent with the structure shown below. Opitcal microscopy was performed



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on a Reichert Thermovar polarizing light microscope equipped with a Mettler FP5/52 heating stage. A du Pont 990 differential scanning calorimeter was used for thermal measurements. The nematic nature of these compounds was established by optical textures (Schlieren) and miscibility with standard reference nematic materials. X-ray diffraction by this mesophase was consistent with a nematic classification. Transition temperatures for **3** are given in Table I and a plot of these temperatures vs. alkoxy carbon number is presented in the center of Figure 1.

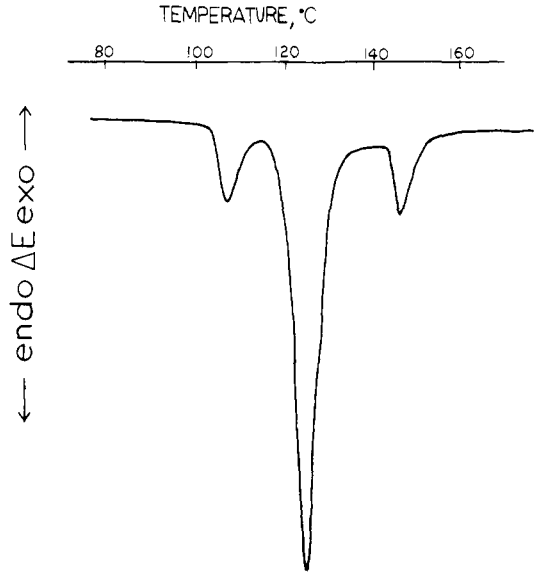

Figure 2. DSC curve for compound with $x = 8$ in series **3**.

All nine homologues show stable, enantiotropic nematic phases. There is the ususal odd–even effect in the nematic → isotropic (N → I) temperatures.[3] Melting points do not show random scatter typical of many liquid crystalline series but instead seem to fall on or near a smooth, descending curve. Figure 2 shows a DSC curve for twin compound with $x = 8$ in series **3**. The sequence of phase transitions (on heating) is as follows: solid–solid, solid–nematic, nematic–isotropic. There is considerable structural similarity between the twin molecules and the simple 4-alkoxyphenyl 4′-alkoxybenzoates. (The twins are simply two phenyl benzoates joined through a diether linkage, i.e., tail to tail).

Examination of mesogenic behavior of our twins (**3**) and series **2** compounds as reported in the literature[2] reveals the following: increasing alkoxy tail length in **2** leads to a smectic mesophase, often to a high degree of smectic polymorphism. Series **3** compounds show only nematic phases. These nematogens (**3**) have no rigid central core. It may be argued that there are *two* rigid cores joined by a flexible segment, but nevertheless the "center" of the structure is flexible. This flexibility is usually considered deleterious to mesogenic behavior because of the large number of nonlinear geometries the molecule could adopt if the center were flexible. It should be noted that Vorlander,[10] some time ago, prepared nematic mesogens by using aliphatic diacid chlorides to join segments. The chemical structure of the twins (**3**) is similar to what may be the structure of oligomers formed in the buildup of polymers such as **1**. These polymers are nematogenic only as are the twins (**3**). Thus it appears smectic tendencies of the small molecule series **2** are lost in the first coupling. It is our conclusion that there is a continuum of nematic behavior from small molecule **2** to polymer **1** through nematic structures such as **3**. Plotted in Figure 1 are N → I transition temperatures for similarly constituted molecules of series **1**–**3**. A dodecyloxy tail was used for series **2** compounds due to the unavailability of data on decyloxy. It can be seen that series **3** twins lie at intermediate temperatures and show odd–even alternation in the same sense as in polymers **1** and small molecules **2**. Although many series **2** compounds have smectic phases as well as a nematic phase, only the N → I temperature is plotted in Figure 1.

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Stereocontrolled Trans and Cis Nucleophilic Attack by Acetate on π-Allylpalladium Complexes. Applications to Stereoselective Palladium-Catalyzed 1,4-Diacetoxylation of Cyclic 1,3-Dienes

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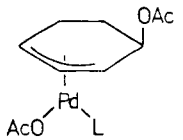
The control of stereochemistry in nucleophilic additions to unsaturated hydrocarbons coordinated to a metal is of great importance in organic synthesis.[1] Much work has been devoted to the stereochemistry of nucleophilic additions to π-allyl- and π-olefinpalladium complexes[2-7] and applications of such reactions is stereoselective organic transformations.[1b,7-10] Although both cis and trans attack by acetate on π-allylpalladium complexes appears to take place,[2,3] there are so far no methods for selecting the stereochemistry of nucleophilic attack, e.g., turning an external trans attack into an intramolecular cis attack for a given nucleophile. We recently reported that cis migration of acetate from palladium to carbon takes place in π-allylpalladium acetate complexes on treatment with carbon monoxide.[3] We have now found a very simple way of controlling the stereochemistry of nucleophilic attack by acetate on π-allylpalladium complexes.

It is known that palladium-catalyzed oxidation of 1,3-cyclohexadiene in acetic acid results in the formation of 1,4-diacetoxy-2-cyclohexene of undetermined stereochemistry.[11] Although a free radical chain process was suggested by the authors, a more likely mechanism is that the reaction proceeds via nucleophilic addition of acetate to an intermediate π-allylpalladium complex **1**, formed by trans acetoxypalladation of one of the double bonds.



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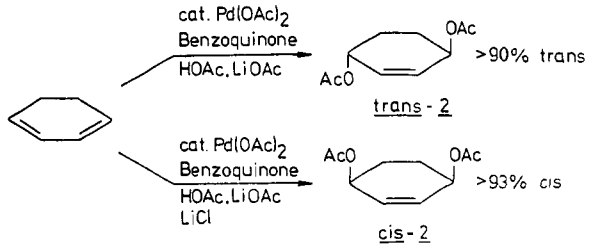
Scheme I



We have studied the stereochemistry of the 1,4-diacetoxylation and found that the presence of lithium chloride and/or lithium acetate has a profound effect on the stereochemical outcome. Oxidation of 1,3-cyclohexadiene using benzoquinone and catalytic amounts of palladium acetate in acetic acid gave a 1:1 mixture of *cis*- and *trans*-1,4-diacetoxy-2-cyclohexene (**2**). When the same oxidation was performed in the presence of lithium acetate, the main product was the *trans*-diacetate (*trans*-**2**). A remarkable change in stereochemistry was observed on the addition of small amounts of lithium chloride. Thus in the presence of both lithium acetate and lithium chloride the *cis*-diacetate (*cis*-**2**) was formed with high stereoselectivity (Scheme I). The latter reaction was more conveniently performed by using Li_2PdCl_4 as catalyst and lithium acetate as the only added salt.

The stereochemical analyses of products **2** obtained from 1,3-cyclohexadiene was accomplished by using ^1H NMR spectroscopy. The diacetates *cis*-**2** and *trans*-**2** have characteristic NMR spectra with the CH_2CH_2 grouping at 2.1 and 1.7 ppm for trans-**2** but concentrated at 1.9 ppm for *cis*-**2**.[12] Further characterization was obtained by hydrolysis of cis-**2** to the known cyclohex-2-ene-1,4-diol.[13]

In a typical procedure 1,3-cyclohexadiene (1.2 g, 15 mmol) was added during 4 h to a solution of Li_2PdCl_4 (315 mg, 1.2 mmol), LiOAc (10.2 g of the dihydrate, 100 mmol), and benzoquinone (3.0 g, 28 mmol) in acetic acid (50 mL) at 25 °C. The mixture was stirred for another 4 h at 25 °C and then filtered, diluted with brine (30 mL), and extracted with pentane. The pentane phase was washed (water, 2 M NaOH), dried ($MgSO_4$), and evaporated to give 2.02 g (68%) of essentially pure *cis*-**2** (>95% cis). Using the same procedure (only 50 mmol of LiOAc) but replacing Li_2PdCl_4 with $Pd(OAc)_2$ as catalyst gave 2.21 g (74%) of crystalline *trans*-**2** (>90% trans), mp 49–50 °C. In the same manner cyclopentadiene, 1,3-cycloheptadiene, and 1,3-cyclooctadiene were oxidized to *cis*-1,4-diacetoxy-2-cyclopentene (>95% cis),[13] *cis*-1,4-diacetoxy-2-cycloheptane (>95% cis),[14] and cis-1,4-diacetoxy-2-cyclooctene (>83% cis) in 21, 57, and 41% isolated yield respectively.[15]

The change in stereochemistry found in the palladium-catalyzed oxidation of 1,3-cyclohexadiene on addition of lithium salts is best explained by a change in the mode of acetate attack on the intermediate π-allylpalladium complex **1**. To obtain more convincing evidence for such a stereocontrolled attack, we studied the stoichiometric reactions with the π-allylpalladium complex **3**,[3,16] related to the putative intermediate **1** (Scheme II). Thus treatment of complex **3b** with benzoquinone in acetic acid at room temperature resulted in cis attack by coordinated acetate to give

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(11) Brown, R. G.; Davidson, J. M. *J. Chem. Soc. A* **1971**, 1321.

(12) A quantitative analysis was possible since the signal for δ_{CHOAc} of *cis*-**2** separates from the one of trans-**2** [$(\delta_{CHOAc})_{trans}$ 5.31, $(\delta_{CHOAc})_{cis}$ 5.23 ($CDCl_3$, 200 MHz)].

(13) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876.

(14) Mp 79–80 °C. Characterized by ^1H NMR, IR, and mass spectra. ^1H NMR spectra ($CDCl_3$) for the cis and trans isomer are different. Cis isomer: δ 5.67 (s, 2, CH=CH), 5.37 (br d, J = 10.5 Hz, 2, CH-O). Trans isomer δ 5.77 (s, 2, CH=CH), 5.41 (br d, J = 6.4 Hz, 2, CH-O). Further characterization according to: Cope, A. C.; Liss, T. H.; Wood, G. W. *J. Am. Chem. Soc.* **1957**, *79*, 6287.

(15) Cyclooctadiene could also be oxidized to the *trans*-diacetate ($Pd(OAc)_2$, LiOAc) whereas the highest relative yield of *trans*-diacetate from cycloheptadiene was 50% (no lithium salts). Acyclic 1,3-dienes selectively gave 1,4-diacetate, but except for butadiene, yields were poor (isoprene, 1,3-pentadiene) due to competing Diels–Alder addition with benzoquinone.

(16) Complex **3a** is known to be of trans configuration; cf. ref 3.

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