tional 1.2 g of trifluoroacetic anhydride was added. Following an additional 15 min of stirring, the reaction mixture was concentrated to about 2 mL, and a solution of NaCN (1.5 g, 30 mmol in 50 mL H_2O) was added followed by trifluoroacetic acid to pH 4. After the mixture was stirred at room temperature for 20 min, the pH was adjusted to 8 and the α-cyano adduct 8-d_3 was extracted with 3 × 60 mL of CH_2Cl_2. The combined extracts were washed with H_2O, dried ($MgSO_4$), and filtered through neutral alumina. The residue in 30 mL of MeOH was cooled in an ice bath and treated dropwise with 1.5 mL (22 mmol) of 70% $HClO_4$. After the mixture stood overnight, 1.56 g (6 mmol, 24%) of pure $MPDP^+$-d_3 was obtained: mp 119–120 °C (lit.[3] mp for the d_0 compound 119–120 °C); UV (MeOH) λ_{max} 345 nm (ε 19 000); ^1H NMR (CD_3CN) δ 3.21 (s, 2 H, CH_2), 3.62 (s, 3 H, CH_3), 6.89 [s, 1 H, C(5)-H]; and 7.57 (m, 5 H, Ar H). Anal. Calcd for $C_{12}H_{11}D_3NClO_4$: C, 52.47; H, 5.14; N, 5.1. Found: C, 52.09; H, 5.04; N, 5.07.

Acknowledgment. We thank Dr. Timothy MacDonald for directing our attention to the Diels–Alder pathway. We acknowledge the Bio-organic, Biomedical Mass Spectrometry Resource at the University of California, San Francisco (A. L. Burlingame, Director), supported by NIH Division of Research Resources Grant RR-01614. This research was supported by Public Health Service Research Grant NS230366.

Registry No. 1-d_4, 118459-65-7; 1-d_4·HCl, 118459-68-0; 2·perchlorate, 97467-07-7; 2-d_3·perchlorate, 118473-79-3; 7-d_4, 118459-66-8; 8-d_3, 118459-67-9; 13, 118459-64-6.

Molecular Structure of a Chiral 3,5-Bridged Pyridine and the Effect of Structure on Circular Dichroic Spectra

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The crystal structure of the 3,5-bridged chiral macrocyclic pyridine (4*S*,14*S*)-4,14-di(2-propyl)-6,9,12-trioxa-3,15,19-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,5,13,16-tetrone (**5a**) has been determined by crystallographic means. Each unit cell contains two nonequivalent molecules. In each molecule the amide groups are twisted out-of-plane in a conrotatory fashion righ-handedly with respect to the molecular C_2 axis viewed along the line from C4 to N1 of the pyridine ring. This twist allows avoidance of potential interaction between the amide nitrogen bonded protons and that bonded to C4 of the pyridine ring. The macrocyclic framework is inherently dissymmetric as a result of this helical twist. This is reflected in the circular dichroism spectrum of **5a**, which has two strongly negative effects in the 200–400-nm region, at 218 nm, [θ] −58 800 and 273 nm, [θ] −45 600. Very similar CD effects are found for analogues of **5a** with at the chiral atoms at the 4,14-positions, methyl groups (**6a**), *tert*-butyl groups (**6b**), and proline (**7**). Comparisons are also made with compounds (**8b**) derived (in thought) from **5a** by transposition of the macrocyclic bridge from the 3,5- to the 2,6-positions. Compound **8a** is analogous to **8b** save that it is a benzene rather than a pyridine derivative. Several nonmacrocyclic analogues of **5a** have also been examined as well as the thioamide derivative of **5a** (compound **9**) for which a synthesis has been developed. The longer wavelength CD effect in **5a** is assigned to the *pyridine* n–π* transition and the shorter wavelength effect to π–π* transitions. Attempts to correlate the absolute signs with a recently postulated model fail. A method for synthesis of the unnatural amino acids, (*S*)-(+)-2-amino-3,3-dimethylbutanoic acid (**13**), in enantiomerically pure form is described as well as an NMR method for the determination of the enantiomeric purity of samples of **13**.

In the presence of an electrophile like Mg^{2+} macrocycles **1** transfer hydride at room temperature with excellent enantioselectivity to the *re* face of activated ketone **2** as shown in Scheme I.[1] In this sense they are NADH mimics. Groups other than hydride may also be transferred.[2] The effect of variation in the amino acids incorporated, an example being L-valine in **1** as illustrated, and of bridge length and composition (a diethylene glycol unit for the case of **1**) has been investigated systematically.[1] Further development of these macrocyclic systems has been hampered by the fact that all attempts to determine crystal structures have failed. The information forthcoming from crystallographic studies is virtually indispensable for understanding the stereochemical intricacies of the complexes formed as well as spectroscopic details. Although the structure of **1** or a related 1,4-dihydropyridine still has not been obtained, we have now solved the structure of bridged *pyridine* **5a**.[3] This structure provides considerable insight

(1) See, for example: Talma, A. G.; Jouin, P.; De Vries, J. G.; Troostwijk, C. B.; Werumeus Buning, G. H.; Waninge, J. K.; Visscher, J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 3981.

(2) (a) Mashraqui, S. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1983**, *105*, 7792. (b) Van Keulen, B. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1984**, *106*, 6029.

(3) Several structures of other 1,4-dihydropyridines have been obtained, however. In general, the 1,4-dihydropyridine ring is either planar or adopts a shallow boat conformation: (a) Van der Veen, R. H.; Kellogg, R. M.; Vos, A.; Van Bergen, T. J. *J. Chem. Soc., Chem. Commun.* **1978**, 923. (b) Karle, I. L. *Acta Crystallogr.* **1961**, *14*, 497. (c) Krajewski, J.; Urbanczyk-Lipkowska, Z.; Gluzinski, P. *Cryst. Struct. Commun.* **1977**, *6*, 787. (d) Krajewski, J.; Urbanczyk-Lipowska, Z. *Acta Crystallogr.* **1977**, *B33*, 2967. (e) Hempel, A.; Gupta, M. P. *Acta Crystallogr.* **1978**, *B34*, 3815. (f) Triggle, A. M.; Shefter, E.; Triggle, D. J. *J. Med. Chem.* **1980**, *23*, 1442. (g) See also: Hays, G. R.; Huis, R.; Coleman, B.; Clague, D.; Verhoeven, J.; Rob, F. *J. Am. Chem. Soc.* **1981**, *103*, 5140.

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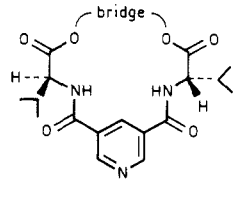


5

bridge

a) $-(CH_2)_5-$

b) $-(CH_2)_2O(CH_2)_2-$

c) $-(CH_2)_4-$

d) $-(CH_2)_6-$

into the interplay of steric factors that determine the overall morphology of the molecule. This structural information is used to clarify circular dichroism (CD) spectra for **5a** and some structurally related macrocycles.

Results

Details of the determination of structure and the relevant structure factors are discussed in the Experimental Section. PLUTO drawings of the two crystallographically independent molecules of **5a** are given in Figure 1 and in Figure 2 a stereoview of the cell packing arrangement is presented.

The differences between the two crystallographically independent molecules of **5a** lie in relatively minor variations in the conformations of the pentamethylene bridge and the two carbonyl groups to which the pentane-1,5-diol fragment is attached.

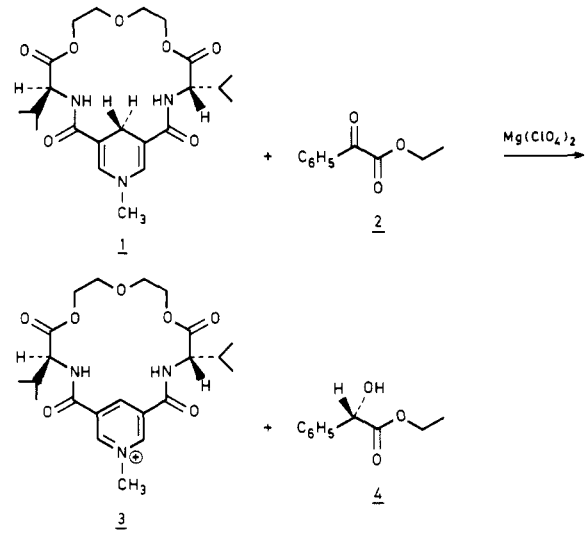
The amide protons, those bonded to N120/N18 and N220/N28, would, were they coplanar with the aromatic ring, interact sterically with the hydrogen attached to respectively C14 and C24 (4-position of the pyridine ring in heterocyclic numbering). The possibility of interactions between the amide oxygen atoms O131/O122 and O231/O222 with hydrogens bonded to C16/C12 and C26/C22 (2,6-positions of the pyridine ring in heterocyclic numbering) is also present although the potential interactions at the 4-position of the pyridine ring seem more severe. This potential interaction is avoided by an out-of-plane twisting of the amide groups. This twisting occurs in a single absolute sense owing to the presence of the two stereogenic centers of L configuration. The amide groups remain, as expected, relatively planar and tilt out-of-plane in such a fashion that the isopropyl substituents attached to the stereogenic carbon atoms rotate *outward* from the macrocyclic ring. This is illustrated in Figure 3, which is a schematic drawing of this *conrotatory* molecular movement viewed down the C_2 axis through the macrocyclic ring looking at C4 (heterocyclic numbering, C14/C24 in crystallographic numbering). The nonbonded interactions of the substituents on the amino acid with the macrocyclic ring are lessened by this outward rotation.

This right-handed twisting of the amide groups out-of-plane causes the pyridine to become inherently dissymmetric.[4] The helicity thereby generated should be reflected in spectroscopic properties sensitive to molecular asymmetry like circular dichroism (CD). Similar spectral behavior in a series of compounds would be an indication that this twisting effect occurs in all structurally similar molecules.

Compounds **5b,c** based on L-valine were available from previous work[1] and could readily be used for such a comparative examination. For macrocycles derived from other amino acids we turned to **6a** (L-alanine) and **7** (L-proline). We also wished to incorporate an amino acid with as bulky as possible side-chain substituent. *tert*-Leucine (**13**) seemed most appropriate in this regard. This is not available from natural sources. After considerable difficulty enantiomerically pure L-*tert*-leucine was synthesized as outlined in Scheme II, which is a modification of literature procedures.[5] Many of the procedures described lead only to optically enriched **13**. There is also considerable confusion in the literature with regard to the correct optical rotation for optically (and enantiomerically) pure **13**. The experimental details for our synthesis of **13**, an NMR procedure for establishment of the enantiomeric excess together with pertinent rotational values, and the procedures for the synthesis of macrocycle **6b** in which L-**13** is incorporated are given in the Experimental Section.

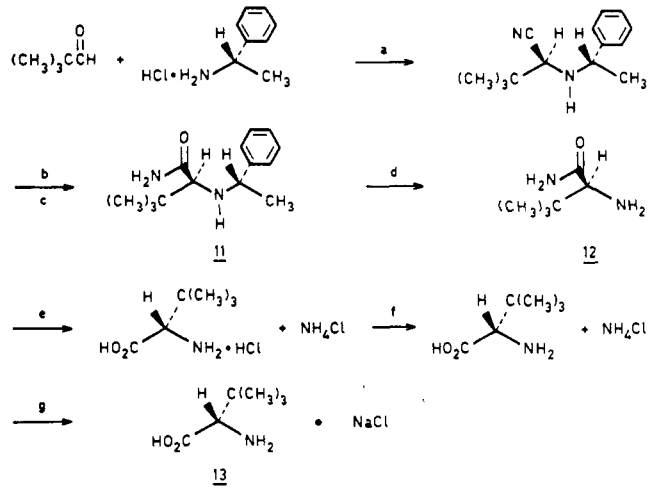
In addition, thioamide derivative **9** was prepared from **5a** as shown in Scheme III. The "turned over" pyridine

Scheme I. Enantioselective Hydride Transfer to Activated Ketone by 1,4-Dihydropyridine



1 + 2 → 3 + 4

Scheme II. Synthesis of Optically Pure 13[a]

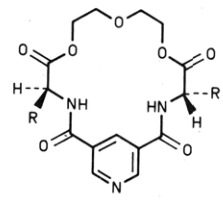


11 12 13

[a] (a) CH_3OH, NaCN; (b) concentrated H_2SO_4; (c) NH_4OH; (d) 10% Pd/C, 3 atm H_2, 96% C_2H_5OH; (e) HCl; (f) propylene oxide, C_2H_5OH; (g) 1 equiv of NaOH, H_2O.

(4) See, for example: Mason, S. F. *Molecular Optical Activity and the Chiral Discriminations*; Cambridge University Press, 1982; pp 51–71.

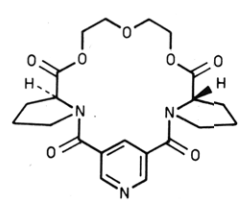
(5) (a) Fauchere, J.-L.; Petermann, C. *Helv. Chim. Acta* **1980**, *63*, 824. (b) Do, K. Q.; Caviezel, M.; Schwyzer, R. *Helv. Chim. Acta* **1979**, *62*, 956. (c) Subramanian, P. K.; Woodard, R. W. *Synth. Commun.* **1986**, *16*, 337.



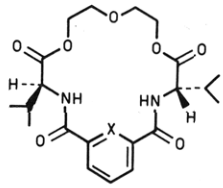
6

a) R = CH_3

b) R = $(CH_3)_3C$



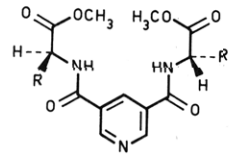
7



8

a) X = CH

b) X = N



10

a) R = $(CH_3)_2CH$

b) R = $(CH_3)_3$

8a as well as the benzene analogue **8b** were also available from previous work.[1]

The first task is to assign the major electronic transitions. In compounds like **5** the pyridine-3,5-dicarboxamide unit is the predominant contributor to the near ultraviolet region. The *ester* linkages incorporated in the macrocyclic framework should have weak n–π* absorbtions in the ultraviolet at around 260 nm.[6] Nonconjugated amide carbonyl groups also have weak n–π* transitions around this or shorter wavelengths.[6] In compounds **5** the amide carbonyls are, however, in conjugation with the pyridine and form in fact a single chromophoric system. However, to a first approximation we anticipate that the ester and amide n–π* transitions will not be major contributors to the longer wavelength portion of the spectra. What is an important consideration is the pyridine n–π* transition. For the well-studied pyridine-3,5-dicarboxylates this transition has been observed at around 290 nm.[7] It can have a significant intensity compared to the π–π* absorptions.[8] In pyridine itself a dispersion-induced CD effect in the presence of (+)-diethyl tartrate is observed at the wavelength expected for the n–π* transition.[9]

Ultraviolet (UV) spectra of **5b** have been measured in CH_2Cl_2/cyclohexane (1:9) and ethanol and are shown in Figure 4a. The red shift in the long wavelength tail in the less polar (than ethanol) solvent system CH_2Cl_2/cyclohexane is indicative of a n–π* transition. Owing to the broadness of the spectral bands, this assignment is not absolutely certain. Absence (Figure 4b) of any trace of this longer wavelength absorption in **8a**, which is a benzene rather than pyridine derivative, strengthens the supposition that the bands around 270 nm in **5** and **6** are chiefly n–π*. The CD spectra of **8a,b** (see later) will provide further support for this argument. The allowed benzenoid $^1L_b \leftarrow {}^1A$ and $^1L_a \leftarrow {}^1A$ transitions must lie in the shorter

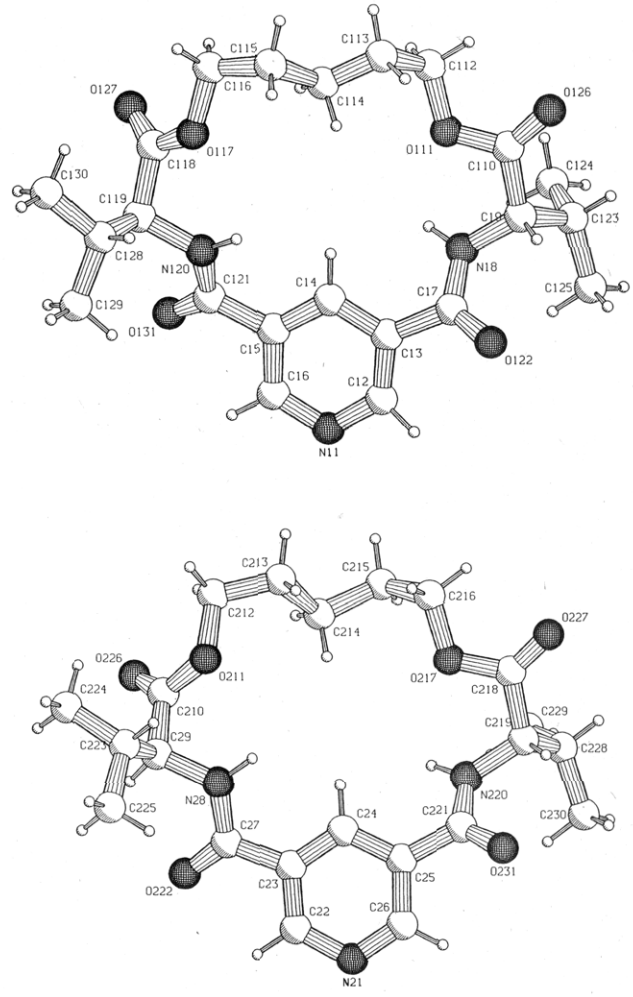


Figure 1. PLUTO drawing of the two crystallographically independent molecules of **5a**.

wavelength envelope, with a maximum at 225 nm.

The CD spectral data for **5a–d**, **6a,b**, **7**, **8a,b**, and **9** are compiled in Table I.[10] In Figure 5 the CD spectra of the enantiomers of **5b** are illustrated. Two major Cotton effects at 218 and 271 nm, both negative, for the enantiomer derived from L-valine appear in mirror image in the enantiomer derived from D-valine. These bands are strong. Values for $[\theta]$ lie in the range of $5–7 \times 10^4$. These molar ellipticities are only roughly an order of magnitude less than those observed for inherently dissymmetric chromophores with perturbed σ skeletons such as found in optically active helicenes[11a] and heterohelicenes.[11b]

This general pattern of two major negative Cotton effects is observed also in **6a,b**, which are derived from L-alanine and L-*tert*-leucine, respectively (Figure 6). The shorter wavelength band is shifted slightly to the red in proline derivative **7** (Figure 7). The "turned over" pyridine **8b** (Figure 8) also exhibits the same general band structure. In accord with the suggested band assignments the benzene derivative **8a**, which cannot have a pyridine n–π* absorption, indeed lacks any appreciable CD effect around 275 nm (Figure 8). This observation supports the hypothesis that the long wavelength absorption in the chiral

(6) Calvert, J.; Pitts, J. N., Jr. *Photochemistry*; Wiley: New York, 1967; pp 427, 434.

(7) Van Bergen, T. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 8451.

(8) Jaffe, H. H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*; John Wiley: New York, 1962. (b) See also Gotarelli and Samori [Gotarelli, G.; Samori, B. *Tetrahedron Lett.* **1970**, 2055] for some pyridine UV and CD spectra. For discussions of spectral bands, see: (c) Klevens, H. B.; Platt, J. R. *J. Chem. Phys.* **1949**, *17*, 470. (d) Platt, J. R. *J. Chem. Phys.* **1951**, *19*, 263. (e) Schellman, J. A. *Acc. Chem. Res.* **1968**, *1*, 144.

(9) Schipper, P. E.; Norden, B. *Chem. Phys. Lett.* **1979**, *67*, 99.

(10) For an excellent discussion of the principle and practice of CD spectroscopy, see: Legrand, M.; Rougier, M. J. *Stereochemistry. Fundamentals and Methods*, Vol 2; Kagan, H., Ed.; Georg Thieme: Stuttgart, 1977; pp 33–183.

(11) (a) Newman, M. S.; Darlak, R. S.; Tsal, L. *J. Am. Chem. Soc.* **1967**, *89*, 6191. (b) Groen, M. B.; Wynberg, H. *J. Am. Chem. Soc.* **1971**, *93*, 2968.

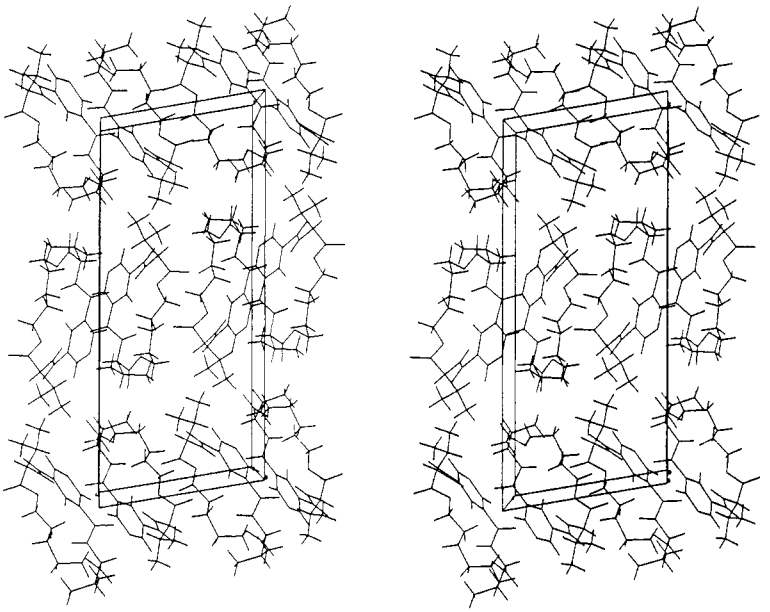


Figure 2. Stereoview of the cell packing of compound **5a**.

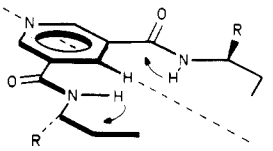


Figure 3. Schematic drawing of the conrotatory molecular movement of the N–H groups.

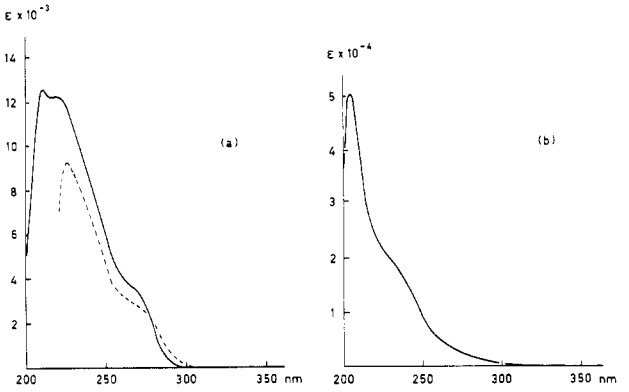


Figure 4. Ultraviolet spectra of (a) **5b** in 95% ethanol (—) and CH_2Cl_2/cyclohexane (1:9) (- - -) and (b) **8a** in 95% ethanol.

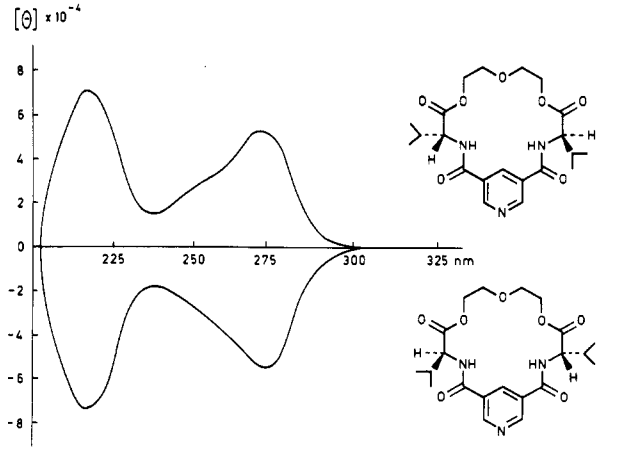


Figure 5. Circular dichroism spectra of the enantiomers of **5b** in 95% ethanol.

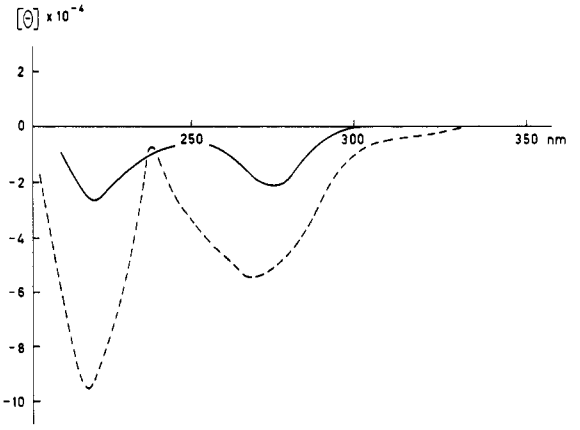


Figure 6. Circular dichroism spectra of **6a** (—) and **6b** (- - -) in 95% ethanol.

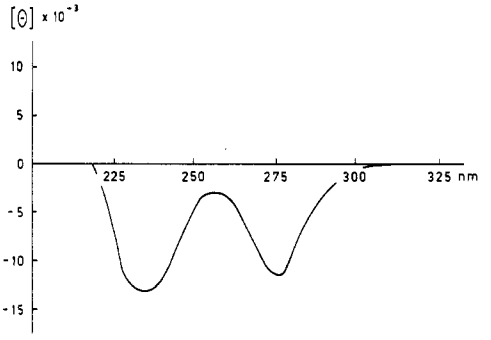


Figure 7. Circular dichroism spectrum of **7** in 95% ethanol.

bridged pyridine macrocycles is indeed chiefly that from the pyridine n–π^* transition. The magnitude and sign of the CD effects in **8b** suggest that the same dissymmetric twist of the amide groups can be realized in the absence of a hydrogen atom (but a lone pair in this case) juxapositioned between the two amide groups.

The final spectrum to be illustrated is that for the thioamide **9**, which also has two negative Cotton effects at around 300 and 390 nm (Figure 9). There is also a positive short wavelength CD contribution. Compounds **10a,b** have the same chromophoric system but lack the

Scheme III. Conversion of the Amide Groups into Thioamide Group by Lawesson's Reagent

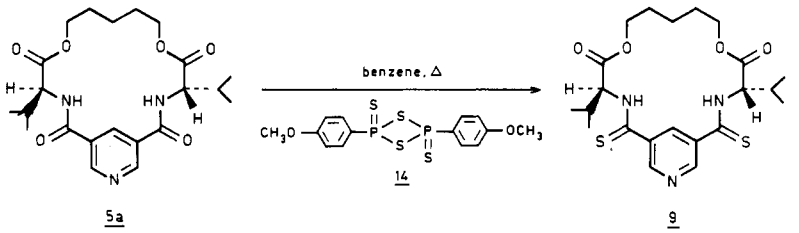


Table I. Circular Dichroism Data for Chiral 3,5-Bridged Pyridines

compd	bridge	γ, [θ][a,b]		
5a	$-(CH_2)_5-$	218, −58 800		273, −45 600
5b[c]	$-(CH_2)_2O(CH_2)_2-$	218, −75 300		271, −57 500
5b[d]	$-(CH_2)_2O(CH_2)_2-$	218, +70 600		271, +51 200
5c	$-(CH_2)_4-$	219, −69 600		271, −58 600
5d	$-(CH_2)_6-$	219, −48 400	244, +11 100	276, −18 900
6a	$-(CH_2)_2O(CH_2)_2-$	222, −26 200		276, −21 800
6b	$-(CH_2)_2O(CH_2)_2-$	216, −98 100		267, −56 700
7	$-(CH_2)_2O(CH_2)_2-$	235, −13 800		276, −11 400
8a	$-(CH_2)_2O(CH_2)_2-$	221, −112 900		245, −42 300
8b	$-(CH_2)_2O(CH_2)_2-$	220, −47 200		275, −21 600
9	$-(CH_2)_5-$	230, +143 000	300, −39 500	392, −20 200
10a	none	237, −4650		273, +3750
10b	none	222, −3930		274, +1730

[a] Maxima or shoulder wavelength in nanometers. [b] All spectra measured in spectrograde 96% ethanol at ambient temperature. [c] Prepared from (*S*)-valine. [d] Prepared from (*R*)-valine; differences in [θ] values between (+) and (−) enantiomers of **5b** probably reflect different dilution procedures used by two different operators working at widely separated times.

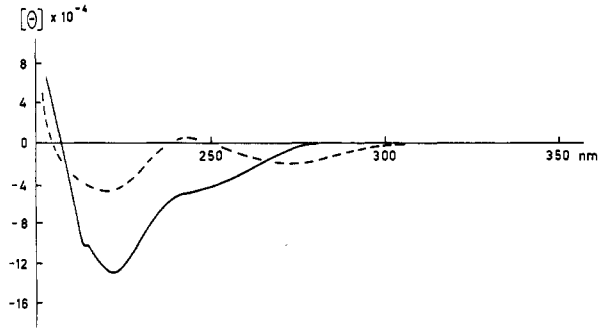


Figure 8. Circular dichroism spectra of **8a** (—) and **8b** (- - -) in 95% ethanol.

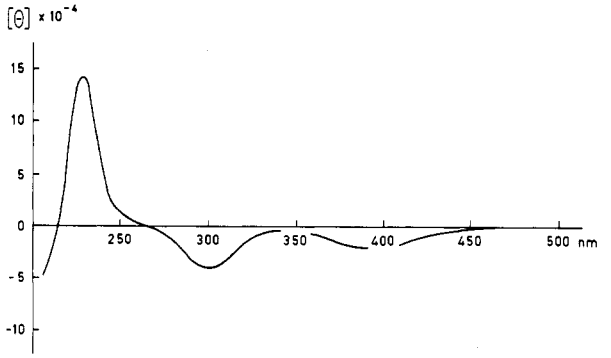


Figure 9. Circular dichroism spectrum of **9** in 95% ethanol.

bridge of the macrocycles. Their conformational flexibility should be much greater. They exhibit (Table I) CD effects at roughly the same wavelengths as the corresponding macrocycles but the longer wavelength CD effect in this case is clearly positive. The [θ] values for the CD effects are now, however, at least an order of magnitude less than those for the corresponding amide derivatives.

Discussion

The single-crystal X-ray crystal structure of **5a** reveals unambiguously the inherent dissymmetry of the pyridine-3,5-dicarboxamide unit. In CPK molecular models the interactions between the amide hydrogens and C4 of the pyridine ring are sufficient to prevent ready passage of the planar amide groups. The direction of rotation of the amide group out of plane in macrocyclic compounds like **5a** (not true in open-chain compounds) is dictated by the substituent on the chiral carbon of the amino acid; this substituent is forced outward from the ring. The absolute helicity observed in the crystal is preserved in solution, judged on the basis of the intensity of the CD effects. Reasoning by analogy one expects similar helicity to pertain in the other macrocycles studied. This is, of course, not rigidly established in the absence of additional crystal structures. The obvious similarities in the CD spectra between the various macrocycles studied here leads us to think that the analogy is nevertheless correct.

Relatively little has been done on the CD spectra of chiral pyridines so that there is a dearth of information for correlation of the spectra. An investigation that does bear on the results given here is that of Dyer et al.,[12] on some chiral 2,6-bridged macrocyclic pyridines. In essence the sphere model of Snatzke[13] developed for disubstituted benzene derivatives was modified for the case of pyridines that possess overall C_2 molecular symmetry; the pyridine is embedded by means of attachment at the 2,6-positions in a macrocyclic ring that bears two chiral carbon atoms.

Snatzke introduced the very useful convention of consideration of the CD effects in these types of aromatic systems in terms of spheres. The first sphere is the aromatic system itself, the second is formed by chiral atoms embedded in, say, a ring attached to the aromatic system, and the third sphere effects are just removed from the

(12) Sector rules for some macrocyclic derivatives of pyridine-2,6-dicarboxylic acid have recently been described: Dyer, R. B.; Palmer, R. A.; Ghirardelli, R. G.; Bradshaw, J. S.; Jones, B. A. *J. Am. Chem. Soc.* **1987**, *109*, 4780. A review of pertinent literature is given.

(13) See, for example: Snatzke, G.; Ho, P. C. *Tetrahedron* **1971**, *27*, 3645.

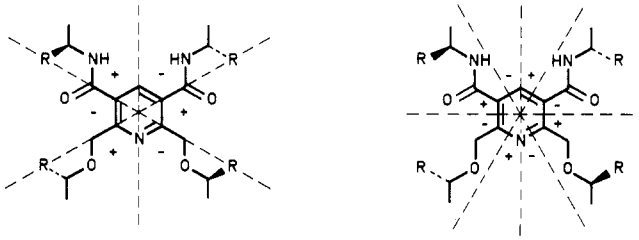


Figure 10. Proposed[12] sector rules for π–π^* (left) and n–π^* (right) CD transitions in pyridines. These drawings have been also adapted to the 3,5-disubstituted examples discussed in this article.

second sphere, and so on. The intensity of the CD effect in general diminishes as the spheres become farther removed from the aromatic chromophore. The "third sphere" model suggested by Dyer et al.[12] is illustrated for 2,6-disubstituted compounds in Figure 10 for n–π^* and π–π^* transitions together with the corresponding projection of a 3,5-bridged pyridine. The signs given for the sectors are those above the plane of the paper; they have the opposite sign on the underside of the paper.

Inspection of Figure 10 indicates that for **5a** and related macrocyclic systems a positive CD effect both for the n–π^* and π–π^* is predicted on the basis of the model presented in Figure 10. This is clearly in disagreement with observation. The failure to obtain agreement between this model and the macrocycles investigated here may lie in the effect of the helicity of the chromophoric system induced by the amide groups. This perturbs the σ skeleton of the chromophore and may overwhelm third-sphere effects induced by perturbing chiral atoms farther removed from the chromophore.

We hope in a separate publication to consider this problem in more detail. There is in any case now a fairly appreciable body of data on chiral 3,5-bridged pyridines that indicates like CD behavior for structurally analogous systems. These data can be used for the development of theoretical models.

Experimental Section

General. All compounds cited without reference are either commercially available or have been described previously in the literature. Melting points are uncorrected and were determined either on a Reichert hot stage provided with a microscope or on a Mettler automatic melting point apparatus. Ultraviolet spectra were measured with a Perkin-Elmer Lambda V apparatus and CD spectra were taken on a Jobin Yvon Auto Dichrograph Mark V instrument. Mass spectra were determined on a MS 9 instrument and NMR spectra were obtained for routine purposes on a Perkin-Elmer 21 60-MHz NMR spectrometer. Other spectra were measured with a Varian XL-100 (100 MHz), a Nicolet 200-MHz, or a Varian 300-MHz NMR spectrometer.

In conjunction with common practice L and D nomenclature for amino acids is used in the body of the text. In this section the Cahn–Prelog–Ingold *R* (equivalent to D for amino acids) and *S* (equivalent to L) nomenclature will be used.

Crystal Structure Determination. A crystal of **5** of dimensions approximately 0.1 × 0.28 × 0.28 mm was grown from $CH_3OH/CHCl_3$ solution. The colorless plate-shaped crystal was glued to the top of a glass fiber and was transferred to the cold nitrogen stream of the low temperature unit mounted on an Enraf-Nonius CAD4F diffractometer. Unit cell parameters and their standard deviations were determined from a least-squares analysis of the setting angles of 20 reflections in the range $18.97° < \theta < 21.14°$.[14] Three reference reflections measured at every 200 min of X-ray exposure time showed a variation of less than 2%. The intensities were corrected for these variations as well as for Lorentz and polarization effects, but not for absorption. The variance $\sigma^2(I)$ was calculated on the basis of counting statistics and a term $(PI)^2$ where P is the instability constant as derived from the excess variance in the reference reflections.[15] Attempts to solve the structure by direct methods did not lead to a reasonable result. The data were then subjected to the latest version of DIRDIF,[16] employing automated vector-search rotation functions (ORIENT), followed by reciprocal space translation functions (TRACOR) using the following search fragments. Carbonyl groups were placed at the 3,5-positions of the pyridine moiety and the conformations of these groups relative to the aromatic plane were varied in steps of 15°. One of these trials met with success and revealed two crystallographically independent molecules. Refinement on F was carried out by block-diagonal least-squares techniques with anisotropic thermal parameters for the non-hydrogen atooms. Hydrogen atoms were introduced at the calculated positions (C–H bond distance of 1.0×) and were refined with fixed geometry with respect to their carrier atoms and with one overall temperature factor. The four starred atoms have unrealistically large thermal parameters and bond distances, which suggests some degree of disorder. For this reason C(113) was constrained. Isotropic secondary extinction corrections were applied.[17] Scattering factors are taken from Cromer and Mann.[18] Anomalous dispersion values are those given by Cromer and Liberman.[19] All calculations were carried out on the CDC-Cyber 170/760 computer of the University of Groningen with the program XTAL,[20] the EUCLID[21] package, and a locally modified version of the program PLUTO.[22]

In the supplementary material (see paragraph at end of this article) the crystal data and other details (Table A), final values of the refined positional parameters for both independent molecules (Table B), and interatomic bond distances, bond angles, and torsional angles (Table C) are given.

Table II. Some Reported Optical Rotations for *tert*-Leucine (13)

confgn	rotation, deg	concn and solvent	ref
S	$[\alpha]^{28.5}_D$ −10.15	*c* 4.63, H_2O	24
S	$[\alpha]^{28.5}_D$ +8.36	*c* 4.78, 20% HCl	24
S	$[\alpha]^{20}_{546}$ −10.9	*c* 2.0, H_2O	25a
S	$[\alpha]^{26}_D$ +30.0	*c* 1.0, CH_3CO_2H	25b
S	$[\alpha]_D$ −10.9	*c* 1.0, H_2O	25c
R	$[\alpha]^{25}_D$ −31.4	*c* 1.0, CH_3CO_2H	25c
S	$[\alpha]^{25}_D$ +30.0	*c* 1.0, CH_3CO_2H	25c
S	$[\alpha]^{21}_D$ −9.4	*c* 1.0, H_2O	25d
R	$[\alpha]^{19}_D$ +9.2	*c* 1.0, H_2O	25d
S	$[\alpha]^{25}_{589}$ −8.2	*c* 1.01, H_2O	25e
S	$[\alpha]^{25}_D$ −9.5	*c* 3.0, H_2O	26a
S	$[\alpha]^{25}_D$ +8.7	*c* 3.0, 5 N HCl	26a

General Remarks on the Synthesis of 3,3-Dimethyl-2-aminobutanoic Acid (13). This compound is known also as *tert*-butylglycine, *tert*-leucine, pseudoleucine, α-methylvaline, terleucine, or trimethylglycine. The racemic compound was first synthesized in 1914[23] and was first resolved in 1934 via the brucine salt of the *N*-formyl derivative.[24] Many chemical[25] and recently

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enzymatic[26] procedures for resolution have been described.

There is, however, much confusion with regard to optical purity of samples of **13**. In Table II various optical rotations reported for **13** are compiled. The most reliable value appears to be that of Viret, Patzelt, and Collet[25c] who report resolution of the racemate with camphor-10-sulfonic acid. The enantiomeric excess was determined by means of HPLC on derivatives of **13** on chiral columns.

We experienced great experimental difficulties in resolution procedures. Large losses of material were encountered and experimental operations were often excessively time consuming. We turned therefore to asymmetric synthesis. Modification of a reported route[5] wherein α-phenylethylamine is used as chiral auxiliary proved acceptable. This synthesis is in essence a combination of two known routes to optically pure unnatural amino acids.[5]

2-[(*S*)-Methyl(phenylmethyl)amino]-3,3-dimethylbutanamide (11). To a stirred suspension of potassium cyanide (1.84 g, 28.2 mmol) in 25 mL of dry methanol was added (*S*)-(-)-α-methyl-*N*-benzenemethanamine hydrochloride (4.45 g, 28.2 mmol, $[\alpha]^D$ -7.10° (*c* 2.0, absolute C_2H_5OH)).[5c] The suspension was cooled to 5 °C. A solution of freshly distilled pivaldehyde (2.43 g, 28.3 mmol) in 5 mL of dry methanol was added slowly. The mixture was stirred at room temperature for 20 h and filtered. The mother liquor was concentrated in vacuo. The oil was recrystallized twice from CH_3OH/H_2O to yield 5.0 g (23.1 mmol, 82% yield) of 2-[(*S*)-(methylphenylmethyl)amino]-2,2-dimethylpropanecarbonitrile as white crystals, mp 41.6 °C (lit.[5a] mp 40 °C): IR 3330, 2850, and 2235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 9 H, $(CH_3)_3C$), 1.30 (d, 3 H, CH_3CH), 2.81 (s, 1 H, *H*CCN), 3.03 (br s, 1 H, N*H*), 4.01 (q, 1 H, CH_3CH), and 7.25 (br s, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 25.1 (q), 26.6 (q), 34.8 (s), 58.1 (d), 60.1 (d), 120.8 (s), 128.0 (d), 128.5 (d), 129.6 (d), and 145.2 (s); $[\alpha]_D$ -200.4°, $[\alpha]_{578}$ -210.8°, $[\alpha]_{546}$ -239.3°, $[\alpha]_{436}$ -409.4°, $[\alpha]_{365}$ -651.0° (*c* 1.0, CH_3OH) (lit.[5a] $[\alpha]^{23}_D$ -203.9° (*c* 1.0, CH_3OH)). This nitrile (4.5 g, 20.6 mmol) was added slowly to stirred, cold (-5 °C), concentrated sulfuric acid (50 mL). The mixture was heated to room temperature and was stirred for 48 h and thereafter was poured onto chopped ice (200 g) and was neutralized with concentrated NH_4OH. The solid product was extracted into ethyl acetate (100 mL). The water layer was extracted twice more with ethyl acetate (50 mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed. The solid material was recrystallized from diethyl ether/hexane. Material recovered from the mother liquor was recrystallized from hexane. In total there was obtained 3.7 g (15.8 mmol, 77% yield) of product, mp 113–115.5 °C (lit.[5a] mp 113 °C): IR (KBr) 3490, 3290, 1680, and 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 9 H, $(CH_3)_3C$), 1.31 (d, 3 H, CH_3CH), 1.83 (br s, 1 H, N*H*), 2.45 (s, 1 H, $NHCHC(CH_3)_3$), 3.58 (q, 1 H, $CHCH_3$), 6.16 (br s, 2 H, $CONH_2$), and 7.20 (s, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 24.7 (q), 26.8 (q), 33.1 (s), 56.8 (d), 68.8 (d), 126.6 (d), 126.9 (d), 128.2 (d), 144.8 (s), and 176.5 (s); $[\alpha]_D$ -88.9°, $[\alpha]_{578}$ - 93.2°, $[\alpha]_{546}$ -105.3°, $[\alpha]_{436}$ -177.3°, and $[\alpha]_{365}$ -278.3° (*c* 1.0, CH_3OH) (lit.[5a] $[\alpha]^{23}_D$ -88.9° (*c* 1, CH_3OH)).

(*S*)-(+)-2-Amino-3,3-dimethylbutanamide (12). A mixture of 3.0 g (12.8 mmol) of **11** and 200 mg of 10% Pd/C in 200 mL of 90% ethanol was shaken for 1 night under 3 atm of H_2 in a Parr apparatus. The mixture was filtered through a Celite filter, and, after removal of the solvent, the product was isolated (1.6 g, 12.3 mmol, 96% yield) as a white solid, mp 98–100 °C (lit.[25g] mp 97–99 °C); IR (KBr) 3220 and 1685 cm^{-1}; ^{13}C NMR (CD_3OD) δ 24.5 (q), 33.5 (s), 62.4 (d), and 177.2 (s); $[\alpha]_D$ +41.0°, $[\alpha]_{578}$ +43.4°, $[\alpha]_{546}$ +49.6°, and $[\alpha]_{436}$ +87.2° (*c* 2.4, 5 N HCl) (lit.[25h] $[\alpha]_D$ -35.0° (*c* 3.0, H_2O) for D enantiomer).

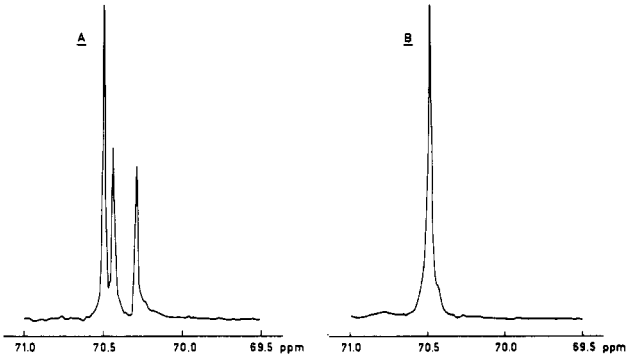

Figure 11. ^{31}P NMR spectra of the phosphonothioic amides of the methyl ester of (A) racemic **13** and (B) optically pure **13**.

(*S*)-(+)-2-Amino-3,3-dimethylbutanoic Acid (13). A portion of 2.8 g (21.5 mmol) of **12** ($[\alpha]_{578}$ +43.4°) was heated in 25 mL of concentrated HCl at 100 °C overnight. The solvent was removed and the crude product was dissolved in 30 mL of absolute ethanol. The solution was cooled to 0 °C and 3 mL of propylene oxide was added. After stirring for 30 min, the solvent was removed and the residue was dissolved in 25 mL of H_2O. The solution was extracted with three 20-mL portions of diethyl ether. The water layer was evaporated to provide 3.0 g (16.3 mmol) of amino acid containing 1 equiv of NH_4Cl. The product was dissolved in 20 mL of H_2O and 650 mg of NaOH (16.3 mmol) was added. The solution was heated on a water bath at 40 °C for 15 min (pH = 7). After evaporation of the H_2O, there was obtained 3.1 g (16.3 mmol, 76% yield) of amino acid **13** with 1 equiv of NaCl, mp (dec); IR (KBr) 3150, 2960, 1620, 1410, and 1395 cm^{-1}; ^1H NMR (D_2O) δ 1.02 (s, 9 H, $(CH_3)_3C$) and 3.40 (s, 1 H, $(CH_3)_3CH$); ^{13}C NMR (D_2O) δ 26.3 (q), 32.2 (s), 64.5 (d), and 173.3 (s). This mixture of **13** and NaCl is acceptable for most synthetic purposes.

Amino acid **13** (920 mg) with 1 equiv of NaCl was brought onto a Dowex ion-exchange column (column 2.5 × 7 cm, 20 g Dowex 1 × 4, 200–400 mesh) and was eluted with H_2O. The first 25 mL of eluate contained amino acid and NaCl (680 mg). The pH changed from 8 to 6.5. The second 25 mL of eluate contained amino acid and hardly any NaCl. Evaporation of this fraction under vacuum yielded 140 mg of white product. Analysis for Cl: 0.07% Cl. $[\alpha]_D$ -10.9°, $[\alpha]_{578}$ -11.0°, $[\alpha]_{546}$ -11.4°, $[\alpha]_{436}$ -17.8°, and $[\alpha]_{365}$ -24.1° (*c* 0.90, H_2O).

The enantiomeric excess of the sample of **13** prepared as described was established by the method of Feringa, Strijtveen, and Kellogg.[27] A sample of **13** containing 1 equiv of NaCl (1.0 g, 5.3 mmol) was treated with methanol and HCl gas. After reflux followed by workup, there was obtained a colorless oil (0.41 g, 2.8 mmol, 52%): $[\alpha]_D$ +62.9°, $[\alpha]_{578}$ +65.7°, $[\alpha]_{546}$ +75.9°, $[\alpha]_{436}$ +136°, $[\alpha]_{365}$ +232° (*c* 0.82, $CHCl_3$). This material was dissolved in $CDCl_3$ and was treated in an NMR tube with excess CH_3PSCl_2. The same experiment was done with racemic **13**. The ^{31}P NMR spectra obtained are illustrated in Figure 11. For racemic material the base-line separation is not complete for the *d,l* and one meso form; the second meso peak is well separated from the others. Within the limitations of integration accuracy the enantiomeric excess of the optically active **13** that we prepared is at least 98% (spectrum b).

***N,N'*-Bis[(1*S*)-1-carboxy-2,2-dimethylpropyl]-3,5-bis(aminocarbonyl)pyridine.** This compound was prepared according to a described procedure from pyridine-3,5-dicarboxylic acid (1.36 g, 8.14 mmol) and (*S*)-*tert*-leucine with 1 equiv of NaCl (3.08 g, 16.3 mmol). The yield was 1.55 g (3.43 mmol, 48%), mp 180.5–182 °C; ^1H NMR (CD_3OD) δ 1.27 (s, 18 H, $(CH_3)_3C$), 4.78 (s, 2 H, NHC*H*), 8.78 (s, 1 H, pyr-4*H*), and 9.21 (br, 2 H, pyr-2,6*H*); ^{13}C NMR (CD_3OD) δ 27.3 (q), 35.3 (s), 62.6 (d), 131.5 (s), 136.2 (d), 151.7 (d), 167.6 (s), and 173.9 (s).

(4*S*,14*S*)-4,14-Bis(2-methyl-2-propyl)-6,9,12-trioxa-3,15,19-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-

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2,5,13,16-tetrone (6b). This compound was prepared analogously to a described procedure from the bis((*S*)-*tert*-leucine amide) of pyridine-3,5-dicarboxylic acid (800 mg, 2.0 mmol) and 1,5-dibromo-3-oxapentane (470 mg, 2.0 mmol). The compound was isolated as a yellow powder, which was purified by flash chromatography (column 10 cm × 25 mm diameter, 15 g of Kieselgel Merck 60, 230–240-mesh ASTM) with ethyl acetate (200 mL) as eluent. The material obtained was recrystallized from CH_2Cl_2–diethyl ether (1:1). There was obtained 460 mg (1.03 mmol, 48% yield) of product as a white powder, mp 295 °C dec: IR (KBr) 3300, 1735, 1645, and 1535 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 18 H, $(CH_3)_3C$), 3.77–3.81 (m, 4 H, $CO_2CH_2CH_2O$), 4.23–4.28 + 4.53–4.75 (2 × m, 4 H, CO_2CH_2), 4.78 (d, 2 H, NHCH), 7.11 (d, 2 H, NH), 8.00 (t, 1 H, pyr-4H), and 8.96 (d, 2 H, pyr-2,6H); ^{13}C NMR ($CDCl_3$, CD_3OD) δ 26.2 (q), 35.2 (s), 61.0 (d), 63.3 (t), 69.7 (t), 128.3 (s), 130.9 (d), 152.1 (d), 164.4 (s), and 168.2 (s); $[\alpha]_{578}$ −129.8°, $[\alpha]_{546}$ −153.9°, $[\alpha]_{436}$ −336.5°, $[\alpha]_{365}$ −767.4° (*c* 0.18, DMF); exact mass spectrum, *m/e* calcd for $C_{23}H_{33}N_3O_7$ 463.231, found 463.231; UV (95% ethanol) λ_{max} 258 (ϵ 3700) and 214 nm (ϵ 11 700).

(4*S*,14*S*)-4,14-Di(2-propyl)-5,13-dioxo-6,12-dioxa-3,15,19-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dithione (9). The bridged pyridine 1 (300 mg, 0.69 mmol) and Lawesson reagent[28] (14) (310 mg, 0.76 mmol) were dissolved in 25 mL of dry benzene. The solution was refluxed under a nitrogen atmosphere for 3 h. The solvent was removed under reduced pressure, and the remaining yellow sticky mass was flash chromatographed (column 8 cm × 2.5 cm, 15 g of Kieselgel Merck 60, 230–400-mesh ASTM) with CH_2Cl_2 (100 mL), followed by CH_2Cl_2/ethyl acetate (1:1, 100 mL) as eluents. There was obtained 320 mg (0.69 mmol, 100% yield) of product as a yellow powder, mp 194.3–195.8 °C: IR (KBr) 3180, 1740, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (dd, 12 H, $(CH_3)_2CH$), 1.76 (br s, 6 H, $OCH_2(CH_2)$, CH_2O), 2.06–2.61 (m, 2 H, $(CH_3)_2CH$-), 3.98–4.72 (m, 4 H, CO_2CH_2), 5.10 (dd, 2 H, CSNHCH), 7.23 (br s, 1 H, pyr-4H), 8.38 (br s, 2 H, pyr-2,6H), and 9.21 (d, 2 H, NH); ^{13}C NMR ($CDCl_3$) δ 18.5 (d), 18.9 (d), 25.0 (t), 28.8 (t), 31.3 (d), 64.7 (d), 65.9 (t), 127.9 (d), 136.0 (s), 149.4 (d), 168.2 (s), and 195.0; $[\alpha]_{578}$ −427.5°, $[\alpha]_{546}$ −567.5° (*c* 0.91, CH_2Cl_2); exact mass spectrum, *m/e* calcd for $C_{22}H_{31}N_3O_4S_2$ 465.176, found 465.177; UV (95% ethanol) λ_{max} 372 (ϵ 510), 276 (ϵ 12 200), and 224 nm (ϵ 16 800).

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Supplementary Material Available: Tables A–C (Experimental) with crystal data, final atomic coordinates and equivalent isotropic thermal parameters, and selected interatomic bond distances, bond angles, and torsional angles (13 pages). Ordering information is given on any current masthead page.

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One-Carbon Compounds as Synthetic Intermediates. The Synthesis of Hydropyrimidines and Hydroquinazolines by Sequential Nucleophilic Addition to Diphenyl Cyanocarbonimidate with Concomitant Cyclization

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Diphenyl cyanocarbonimidate (1) undergoes nucleophilic addition with ω-amino esters and amines in a sequential manner to give guanidine derivatives that, for the most part, spontaneously cyclize to give hydropyrimidines or hydroquinazolines. The hydropyrimidines could be dehydrogenated to dihydropyrimidines, and the NCN group could be hydrolyzed to a carbonyl or amine group in the pyrimidine and to an amine group in the quinazoline series. The regiospecificity of the cyclization was determined by a combination of spectroscopic methods and comparison of compounds synthesized by standard routes. The scope of the synthetic route is indicated. Some of the acyclic *N*-cyano-*O*-phenylisoureas formed by the first nucleophilic addition exist as mixtures of isomers, and the barriers to interconversion have been determined by NMR spectroscopy.

One-carbon compounds in which the carbon is divalently bonded to a heteroatom and has two singly bonded electron-withdrawing substituents have found considerable use both as reagents and as synthetic intermediates. Thus 1,1′-carbonyldiimidazole,[2] 1,1′-thiocarbonyldiimidazole,[3] and methyl cyanoformate[4] have been used as reagents or for the introduction of functional groups whereas *N*-arylchloroformimidoyl chlorides[5] and diphenyl and dimethyl cyanocarbonthioimidate[6] have been used as intermediates, particularly in the synthesis of heterocycles. Diphenyl cyanocarbonimidate (1) has also been used in the synthesis of heterocycles,[7] and it has advantages over its sulfur analogues. In many of the cases in which 1 has been used to prepare heterocycles, the cyano group has been involved in the resulting ring system.[8] Thus reaction of

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