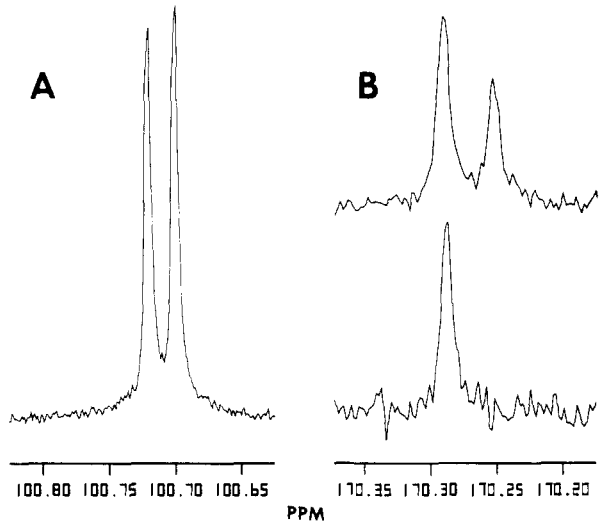

Figure 1. 50.3-MHz $^{13}C\{^1H\}$ NMR spectra recorded on a Varian XL-200 as noted (A) (±)-[1′-^{18}O,5′-^{13}C]averufin (**5**, 17 mg in 2.5 mL of 1:1 Me_2SO-d_6/$CDCl_3$) sweep width 200 Hz, 4000 points, 32 transients, zero filling. (B) Top: [5′-^{13}C,^{18}O]versiconal acetate (**8**, 8.5 mg in 2.5 mL of Me_2SO-d_6), sweep width 1600 Hz, 16000 points, 12896 transients, line broadening 0.25 Hz, zero filling. Bottom: versiconal acetate (natural abundance, 34 mg in 2.5 mL of Me_2SO-d_6), acquisition parameters as above, 3136 transients.

with ^{18}O (●) and C-5′ with ^{13}C (■) and, further, if oxygen exchange of the proposed methyl ketone intermediate **7** were not too rapid, a heavy isotope at the carbonyl oxygen of **8** would be expected to be revealed in the upfield shift[11] of the 5′-carbon in its $^{13}C\{^1H\}$ NMR spectrum.[12] In contrast to this highly restrictive criterion, a large number of other mechanistic possibilities may be represented by path B which, as a group, are distinguished by hydrolytic opening of the averufin ketal and hence cleavage of the 1′-oxygen/5′-carbon bond with ^{18}O label being lost rapidly in **11**.

Therefore, 2,6-bis(methoxymethyl)benzaldehyde was exchanged with ^{18}O water, elaborated to (±)-[1′-^{18}O,5′-^{13}C]averufin (**5**) as before[2,6] and administered to cultures of *A. parasiticus* (ATCC 15517) in the presence of dichlorovos.[10] Figure 1A depicts a portion of the 50.3-MHz $^{13}C\{^1H\}$NMR spectrum of averufin (**5**) indicating about a 48/52 $^{16}O/^{18}O$ ratio at C-5′ as revealed in the 0.02 ppm ^{18}O-induced upfield shift.[11] Examination of the analogous spectrum (Figure 1B, top) of the isolated versiconal acetate (**8**) showed an upfield shift of the C-5′ resonance of 0.04 ppm consistent with the location of heavy isotope at the carbonyl oxygen,[11] as hoped. When normalized for natural abundance contributions (Figure 1B, bottom), it could be shown that approximately 80% of the ^{18}O label originally present in averufin (**5**) survived in the derived versiconal acetate (**8**).

In conclusion, neither nidurufin (**3**) nor pseudonidurufin (**4**) under two distinct feeding regimens serves as an effective precursor of aflatoxin B_1. However, the established facile and intact incorporation of averufin into aflatoxin[1,2] and versiconal acetate[10] is further refined herein to require that the side-chain branching and cleavage steps proceed in such a way that the 1′-oxygen/5′-carbon bond remains intact to versiconal acetate. Scheme 1A is one of a very narrow spectrum of possibilities that satisfies this mechanistic stricture.[14]

Acknowledgment. We are deeply indebted to Dr. S. L. Pratt (Varian Instrument Group) for running the spectra shown in Figure 1, to Professor J. W. Bennett (Tulane) for providing advice and laboratory space for the microbiological portion of this work, and to C. A. Lisek and the NSF-supported Middle Atlantic Mass Spectrometry Laboratory at Hopkins and J. B. Stanley (Southern Regional Research Center, USDA) for mass spectra. We are pleased to acknowledge the financial support of the NIH (ES01670) and of the A. P. Sloan Foundation.

Note Added in Proof. Very recent relative stereochemical assignments of nidurufin and pseudonidurufin, based on model systems,[13] confirm those made earlier for the natural product and its 2′-epimer from unambiguous total synthesis.[3-5] While we concur that π-participation in the chain-branching reaction is possible,[11,14] the details of the mechanism proposed by these authors must be revised in light of the findings presented herein.

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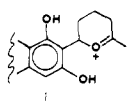
(12) Net retention of the 1′-oxygen/5′-carbon bond could result from radical or cation formation and migration of the anthraquinone nucleus either directly or through π participation and spiro cyclopropane formation (see: Murphy, W. S.; Wattanasin, S. *Chem. Soc. Rev.* **1983**, *12*, 213-250). Alternative fates of an intermediate as i also may be visualized.



(13) Murphy, R. A., Jr.; Cava, M. P. *J. Am. Chem. Soc.* **1984**, *106*, 7630-7632.

(14) Townsend, C. A.; Davis, S. G.; Koreeda, M.; Hulin, B., unpublished results. A summary of these studies was made at the 188th ACS National Meeting, Philadelphia, PA, August, 1984, ORGN 211.

Solid-State Conformations of Linear Oligopeptides and Aliphatic Amides. A Model of Chiral Perturbation of a Conjugated System

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The out-of-plane distortions of an amide bond may result from two kinds of torsion, and are correspondingly described by the angles τ, $\theta_{C'}$, and θ_N, where the latter two reflect the degree of pyramidalization of the C′ and N atoms[1] (see Scheme I). Such a pyramidalization does not require large energy expenditure[2] and is in fact often observed in the solid state.[3] Since a nonplanar amide bond is chiral, introduction of chirality in the C_i^α and C_{i+1}^α allylic rotors could in principle affect the magnitude and sign of the $\theta_{C'}$ and θ_N values. Furthermore, it appears that an amide bond interacts differently with the two allylic rotors C_i^α and C_{i+1}^α; as shown by ^{13}C NMR studies, there is an electron density shift into the C_i^α–H bond overlapping the $2\pi_\pi$ system, but this is not seen in the case of the C_{i+1}^α–H bond.[4] Therefore aliphatic amides present an interesting and convenient model for studying the effect

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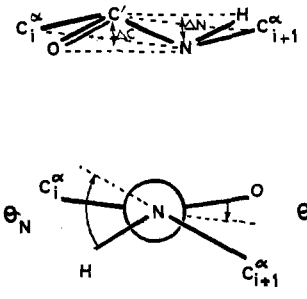
Table I.

type of structure	no. of entries	syn pyram, %	av C'N bond length, Å		av $\theta_{C'}$		av θ_N	
			syn	anti	syn	anti	syn	anti
I. RR'XCCONHCH$_3$[a]	25	32	1.315 (7)	1.327 (7)	4.0	2.6	11.3	8.0
II. CH$_3$CONHCRR'COZ[b]	43	34	1.332 (6)	1.336 (6)	1.5	1.1	6.9	4.7
III. RR'XCCONHCX'R''R'''[c]	138	49	1.328 (6)	1.335 (6)	2.4	2.4	6.7	8.4
IV. CH$_3$CONHCHRR'[d]	14	50	1.327 (4)	1.337 (7)	1.6	1.3	7.3	8.4
V. RR'XCCONHCH(CH$_3$)$_2$[e]	8	75	1.341 (8)		2.7		12.3	
VI. (CH$_3$)$_3$CCONHCRR'X[f]	7	86	1.345 (6)		1.3		8.2	
VII. RR'XCCO-D-Pro[g]	40	52	1.338 (7)	1.335 (9)	2.3	2.1	3.9	7.7
VIII. RR'XCCON(R'')$_2$[h]	23	65	1.322 (11)	1.339 (9)	2.9	2.5	4.3	4.8

[a] *N*-Methyl amides of Gly, D,L-aa, and Aib; correspondingly R = R' = H, R = H, R' = alkyl, or R = R' = CH$_3$ and X = N$_i$. In single cases X = O and X = *n*-propyl. [b] *N*-acetyl-Gly, D,L-aa, and Aib; R, R' cf *a*. In three cases *N*-acetyl "peptidelike" derivatives, i.e., NCCOZ moiety present while R, R' are different. [c] Peptides and amides derived from Gly, D,L-aa, and Aib, i.e., either X = N$_i$, R, R' cf *a*, and X' = C, O, P, etc., R'', R''' = H, C or X' = COZ, R'', R''' cf *a*, and X = C, N, O, Cl, etc., R, R' = H, C. For other amides either X or X' have to carry an electron-withdrawing substituent. [d] *N*-Acetyl amino sugars; i.e., CHRR' = a pyranosyl or a furanosyl ring. [e] *N*-Isopropyl amides of Gly and D,L-aa; R, R', X cf *a*. In one case R = R' = X = H. [f] *N*-Pivaloyl-Gly and D,L-aa; R, R' cf a, *X* = COZ. [g] *N*-Acylprolines; the acyl moiety either Gly, D,L-aa, or Aib; i.e., X = N$_i$, R, R' cf *a*, or acetyl X = R = R' = H, pivaloyl X = R = R' = CH$_3$, and isobutyryl X = R = CH$_3$, R' = H. [h] R'' = CH$_3$, C$_2$H$_5$, or other alkyl; the acyl moiety D,L-aa(6), CH$_3$(8), or other X = N, O, C and R, R' = H, alkyl.

Scheme I



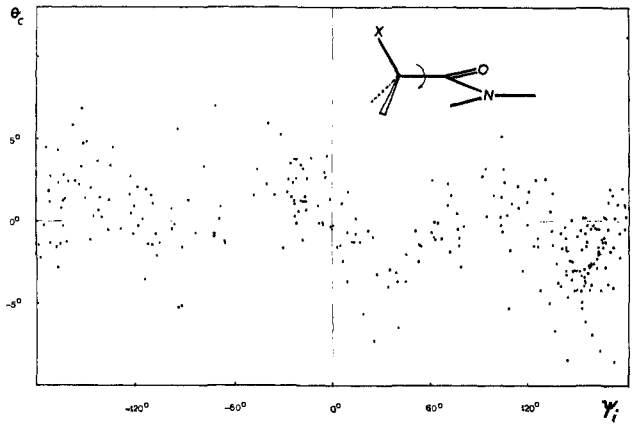


Figure 1. Relationship between the magnitude and direction of partial pyramidalization of the amide carbonyl carbon atom ($\theta_{C'}$) and the conformation of the C_i^α group (see Scheme I). The $\theta_{C'}$ and ψ_i values are plotted for all the entries, I–VIII, in the table except those acetamides (II, IV, and VIII) where the methyl hydrogen atoms could not be satisfactorily located and, in addition, for a number of β-lactam- and sarcosine-derived amides. Thus X = N$_i$ or otherwise an atom of highest priority, except for acetamides, isobutyramides, and pivalamides, where X = H or CH$_3$ of ψ_1 closest to ±90°.

of chiral substitution on the conformational equilibrium of a planar conjugated system.

In order to address this problem, we have examined out-of-plane distortions of about 300 amide bonds in the crystal structures of linear oligopeptides and aliphatic amides[5] and have found that the pyramidalization of the carbonyl carbon atom ($\theta_{C'}$), in contrast to the pyramidalization of the nitrogen atom (θ_N), appears to correlate with the overlap and electron affinity of the σ bond

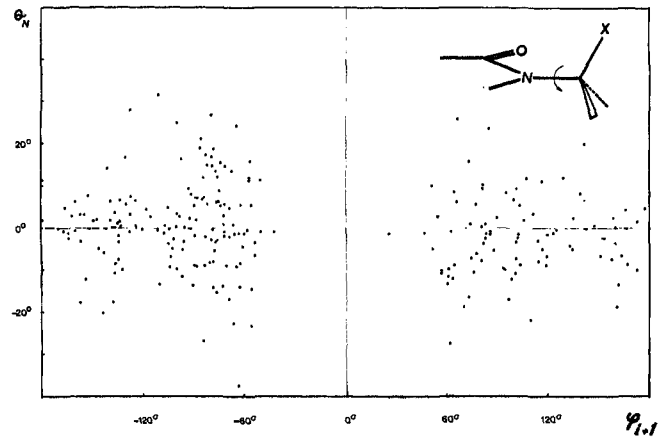
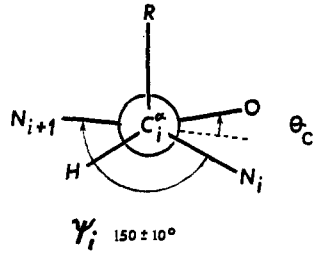


Figure 2. Relationship between the magnitude and direction of partial pyramidalization of the amide nitrogen atom (θ_N) and the conformation of the C_{i+1}^α group (see Scheme I). The θ_N and φ_{i+1} values are plotted for all the secondary amides in the table, entries I–VI, except for those *N*-methyl amides where the methyl hydrogen atoms could not be satisfactorily located. Thus X = COZ or otherwise an atom of highest priority, except for *N*-isopropyl amides, X = CH$_3$ of φ_{i+1} closer to ±90°.

Scheme II



aligned with the 2p$_\pi$ system. In addition, we have found that the structural data suggest a tendency of polarized amide bonds to pyramidalize syn ($\theta_{C'}\cdot\theta_N < 0$) and nonpolarized amide bonds to pyramidalize anti ($\theta_{C'}\cdot\theta_N > 0$).

The first relation is shown in the plot $\theta_{C'}$ vs. ψ_i (Figure 1), where ψ_i corresponds to the standard angle employed to describe the peptide backbone conformation.[6] The pattern visible in the plot indicates that the favored direction of pyramidalization of the carbonyl carbon atom is antiperiplanar to the allylic bond overlapping the 2p$_\pi$ system (ψ_i = ±30°, ±90°, ±150°) and that the $\theta_{C'}$ value tends to decrease in the staggered or eclipsed conformations (ψ_i = ±60°, ±120°, ±180°), which makes the absolute change reminiscent of the 6-fold potential for the sp^2–sp^3 rotation.

(5) A search in *Chemical Abstracts* through spring 1983 yielded 208 structures 91% $R < 080$, where *H* coordinates were determined from the Fourier differences maps and the reported bond length and angles were reproduced in our computations. 317 amide bonds were found, selected on the basis of the esd of the C'N bond, 93% <0.010 Å (none higher than 0.015 Å), and on the basis of the structure type (see Table I).

(6) IUPAC–IUB Commission on Biological Nomenclature: *Biochemistry*, **1970**, *9*, 3471.

A plot of the θ_N vs. ϕ_{i+1} values is shown in the Figure 2.[7] There seems to be no discernible pattern in this case.

Since the amide nitrogen $2p_\pi$ orbital is a poor electron donor in the allylic interaction as compared to the C′ $2p_\pi$ orbital,[4] the observed difference in the θ_N and $\theta_{C'}$ behavior suggests that such a donation is an important interaction in staggering of allylic moieties on the sp^2–sp^3 bonds. This explanation is supported by the fact that a rotational variance of θ_N is found in the case of *N*-glycosides[8] and by the fact that $\theta_{C'}$ increases when the electron affinity of the bond overlapping the $2p\pi$ system increases.

Examination of the points for the bonds from group III in the table, in the region 150 ± 10° of Figure 1 (the corresponding conformation is shown in Scheme II), indicates that the average $\theta_{C'}$ value equals 2.7° if the antiperiplanar bond is CH, 3.3° if it is C–CH_3 and 3.8° if it is C–CHRR′ (for 12 Gly, 9 L-Ala, and 8 additional L-amino acid, excluding L-Pro, entries, respectively), whereas the average $\theta_{C'}$ values for all the remaining points are 2.2°, 2.8°, and 1.8° (26 Gly, 12 L-Ala, and 19 additional L-amino acid, excluding L-Pro, entries).[9]

The second important aspect of conformational equilibria of the planar conjugated systems is relative stability of the syn- and anti-pyramidalized sp^2–sp^2 bonds. This question has been addressed in computational studies of olefins, which indicate a greater stability of the anti form.[10] The pertinent experimental data are collected in the table. It can be seen that the substitution of the amide bond which increases the degree of its polarization, as indicated by lowering of the C=O stretching frequency,[11] also increases stability of the syn-pyramidalized form. Furthermore, if the bonds that are more polarized toward $>C^+—N^-< \leftrightarrow >C=N^+<$ mezomeric structures do tend to pyramidalize in the same direction on the C′ and N atoms, the average C′N bond length of the syn-pyramidalized amides is expected to be smaller. A trend in this direction is indeed observed.[12]

As previously mentioned, the occurrence of out-of-plane distortions attracted a good deal of attention in the structural studies of amides,[2,3] and such distortions were invoked to explain chirooptical properties of amides,[13] chiral folding of polypeptide chains in proteins,[14] in particular systematic right-handed twist of β-sheet structures,[15] reactivity of β-lactam antibiotics,[16] and the mechanism of enzymic cleavage of peptide bonds.[17] Nonetheless, there has been no attempt at explanation of the direction and magnitude of these seemingly incidental features, except for the proposition that they might be determined by hydrogen bonding in the crystal lattice,[18] polypeptide chain,[19] or the active site.[17] The energy of the $2p_\pi,\sigma^*$ two-electron stabilizing interactions, which we believe largely determine the direction and extent of staggering on the sp^2–sp^3 bonds, might be significantly higher than the energy of hydrogen bonding.[20] It seems then that the data reported here are relevant for a number of problems in structural chemistry of peptides and proteins.

On the other hand, however, these data may well reflect generally valid principles of behavior of the delocalized $2p_\pi$ systems on chiral perturbation, and we have attempted to extend these observations, using our incipient bond model of 1,2-asymmetric induction,[21] into a rule of selection for 1,N-π^n-diastereoface-differentiating reactions, i.e., the reactions where the incipient and the inducing chiral centers are separated by one, two, or more atoms of a planar $2p_\pi$ skeleton.[22]

Acknowledgment. I express my gratitude to Professor Sir Derek Barton and Dr. Maurice M. Pechet for the generous support at the Research Institute for Medicine and Chemistry, Cambridge, MA, where this study was initiated, and to Dr. Robert H. Hesse for the numerous invaluable discussions.

(7) The ϕ_{i+1} angle is defined according to the IUPAC–IUB Commission rules.[6]

(8) Cieplak, A. S., submitted for publication. The *N*-glycoside nitrogen is, presumably, less electron deficient than the amide nitrogen.

(9) The esd values for the $\theta_{C'}$ angles are about 0.3–0.5°.

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(11) Dolphin, D.; Wick, A. "Tabulation of Infrared Spectral Data"; Wiley: New York, 1977; Chapter 4.3, pp 241–262.

(12) Possibly with the exception of proline amides, group IV in the Table, where the increase of steric hindrance in the syn form might be more severe.

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(21) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(22) Cieplak, A. S. *J. Am. Chem. Soc.*, submitted for publication.

Enantioselective Synthesis of Quaternary Carbon Centers through Michael-Type Alkylation of Chiral Imines[1]

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Although quaternary carbon centers are challenging structural components of many complex natural compounds,[2] only a few methods for generating this moiety in an efficient enantioselective manner exist to date.[3]

We now report a novel and general process for the synthesis of chiral 2,2-disubstituted cycloalkanones **2**, in high enantiomeric purity. The reaction involves a new type of "*deracemizing alkylation*" of 2-monosubstituted cycloalkanones **1**, as chiral imine derivatives, by means of electron-deficient alkenes (Scheme I).

Thus imine **3**, bp 110 °C (0.1 torr) (prepared in 89% yield from *rac*-2-methylcyclohexanone and (*S*)-(−)-1-phenylethylamine[4] **7** by azeotropic removal of water, toluene, *p*-TsOH, 1 h) with 1 equiv of methyl vinyl ketone (THF, 20 °C, 3 days) led to adduct **5** (Scheme II). Hydrolysis (AcOH 10%, 20 °C, 1 h) of crude compound **5** afforded (*R*)-(+)-diketone[5] **6**, bp 130 °C (9 torr),

(1) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J., paper presented in part at the EUCHEM Conference on Asymmetric Formation of C–C Bonds, Port-Camargue, France, April 25–27, 1984.

(2) For an excellent review on the construction of quaternary carbon centers, see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419–460.

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(4) Commercial amine **7**, $[\alpha]^{20}_D$ −39.4° (neat), was used.

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