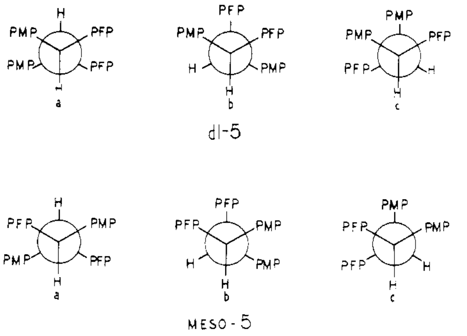

Figure 1. Conformations of 1,2-bis(pentafluorophenyl)-1,2-bis(*p*-methoxyphenyl)ethane. PMP = *p*-methoxyphenyl; PFP = perfluorophenyl.

were prepared and analyzed.

(Pentafluorophenyl)(*p*-methoxyphenyl)methanol was coupled in the presence of chromium(II) chloride to yield an equimolar (by NMR analysis) mixture of the diastereomeric 1,2-bis(*p*-methoxyphenyl)-1,2-bis(pentafluorophenyl)ethanes (*meso*- and *dl*-**5**).[15] The separation of the diastereomers was readily accomplished by successive crystallizations. In CDCl$_3$ one diastereomer exhibited the ethano methine proton resonance at 5.55 ppm while the second diastereomer's methine resonance appeared at 5.35 ppm; the respective melting points of the compounds are 199–202 °C and 140–143 °C. Employing the arguments advanced by Huang et al.,[16,17] the higher melting diastereomer is tentatively assigned the *meso* configuration.[18]

If polar interactions were to govern the conformations of *meso*-**5**, it would be expected that the preferred conformation of *meso*-**5** would be **5a** (Figure 1); there exists in this conformation two pairs of attractive interactions (pentafluorophenyl–*p*-methoxyphenyl), while in conformers **5b** and **5c** two pairs of repulsive interactions exist with only a single attractive interaction. For *dl*-**5**, conformer **5a** exhibits two pairs of repulsive interactions while both **5b** and **5c** exhibit two attractive and one repulsive interaction each. Assuming that the repulsive interaction between pentafluorophenyl groups would exceed that of *p*-methoxyphenyl groups, the preferred conformer of *dl*-**5** would be **5c**.

Nuclear magnetic resonance analysis of the two diastereomers was conducted at 300 MHz employing the ^{13}C satellite method.[3] In CCl$_4$ solution the 5.55 ppm diastereomer (*meso*) has $^3J_{\mathrm{HH}} = 13.25 \pm 0.15$ Hz while the 5.35-ppm diastereomer (*dl*) has $^3J_{\mathrm{HH}} = 12.65 \pm 0.05$ Hz. It is clear that both diastereomers exist predominantly in the H–H anti conformation and that the anticipated ring–ring interactions do not, in this case, overcome the repulsive steric interactions encountered in H–H gauche conformations. It should be noted, however, that the coupling constants observed are in agreement with the tentative configurational assignments, i.e., the *meso* diastereomer should prefer the H–H anti conformation to a greater extent than the *dl* diastereomer with a resultant greater vicinal coupling constant.

Experimental Section

(Pentafluorophenyl)(*p*-methoxyphenyl)methanol was prepared by the addition of 5.44 g (0.04 mol) of *p*-anisaldehyde to the Grignard reagent prepared from 12.35 g (0.05 mol) of bromopentafluorobenzene and 1.22 g (0.05 mol) of Mg turnings in 70 mL of anhydrous ether. Stirring was continued for 2 h after the addition was completed. The reaction mixture was cooled in an ice bath and the reaction was quenched with 10% aqueous HCl. The ether layer was separated and dried over anhydrous sodium sulfate. Removal of the ether under reduced pressure followed by distillation of the crude product at 141–143 °C at 0.4 mm afforded 7.9 g (65%) of the alcohol: ^{1}H NMR (CDCl$_3$) methine, δ 6.2; OCH$_3$, 3.8; aromatic, AA′BB′ quartet centered at 7.1.

***meso*- and *dl*-1,2-Bis(pentafluorophenyl)-1,2-bis(*p*-methoxyphenyl)ethane** were prepared by a method analogous to that reported by Finocchiaro et al.[15] for similar compounds. (Pentafluorophenyl)(*p*-methoxyphenyl)methanol (7.4 g, 0.024 mol) was dissolved in a mixture of 100 mL of acetone and 50 mL of concentrated hydrochloric acid. The solution was flushed with nitrogen and 8.43 g (0.068 mol) of chromium(II) chloride was added. The resultant reaction mixture was stirred under nitrogen for 3 h at room temperature. The suspension was filtered and the precipitate was washed with several portions of water. The precipitate was extracted with ether, the ether layer dried over anhydrous sodium sulfate was filtered, and the solvent was removed. ^{1}H NMR analysis (CDCl$_3$) indicated a 50:50 mixture of diastereomers. Recrystallization of the crude solid from hexane afforded two fractions: fraction 1, δ(methine) 5.55 ppm, mp 199–202 °C; fraction 2, δ(methine) 5.35 ppm, mp 140–143 °C. Anal. (Fraction 1). Calcd C, 58.45; H, 2.79. Found: C, 58.48; H, 2.92.

Registry No. *meso*-**5**, 95216-89-0; *dl*-**5**, 95216-90-3; (pentafluorophenyl)(*p*-methoxyphenyl)methanol, 95216-88-9; *p*-anisaldehyde, 123-11-5; bromopentafluorobenzene, 344-04-7.

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(15) The coupling reaction is analogous to one reported previously by Finnoccharo et al. (Finnacchario, P.; Gust, G.; Hounshell, W. D.; Hummel, J.; Maravigna, P.; Mislow, K. *J. Am. Chem. Soc.* **1976**, *98*, 4945).

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(18) See, however, the caveat and exception listed in ref 8.

Attractive Nonbonded Interactions. The Solution Conformation of *N*-(1-Phenyl-2-propyl)nicotinamide Chloride

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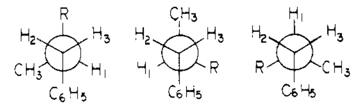
We[1] and others[2] have determined the solution conformation of 1,2-diphenylpropane. The predominant conformation in solution is, as expected on the basis of repulsive nonbonded interactions between contiguous phenyl groups, phenyl–phenyl anti (**1a**; R = C$_6$H$_5$). Similarly, we[3] and others[4-6] have determined that amphetamine (**1**; R = NH$_2$) and its hydrochloride (**1**; R = NH$_3^+$Cl$^-$) prefer the phenyl–amino gauche, phenyl–methyl anti conformation (**1b**, R = NH$_2$ or NH$_3^+$Cl$^-$) in aqueous solution. As an extension of this work, investigation of a corresponding pyridinium salt (**2**) was undertaken. Comparison of 1,2-



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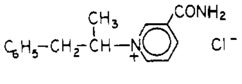
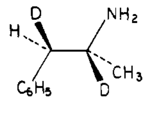
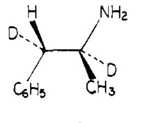
diphenylpropane and *N*-(1-phenyl-2-propyl)nicotinamide chloride (*N*-amphetamylnicotinamide chloride) (2) should provide valuable information relative to the influence of steric interactions of the pyridinium group in aqueous solution.



Preparation of *N*-(1-Phenyl-2-propyl)nicotinamide Chloride. In order to determine the conformation of a molecule possessing an ethane-like fragment consisting of three nonequivalent protons ($-CH_AH_BCH_X-$), it is necessary to assign the chemical shift of either proton A or proton B such that the vicinal coupling constants $^3J_{AX}$ and $^3J_{BX}$ can be unequivocally assigned. We have previously described the synthesis of (1*R*,2*R*)- and (1*S*,2*S*)-1,2-dideuterio-1-phenyl-2-propylamine (dideuterioamphetamine, **3**-d_2) in which the assignment of the chemical shift of one

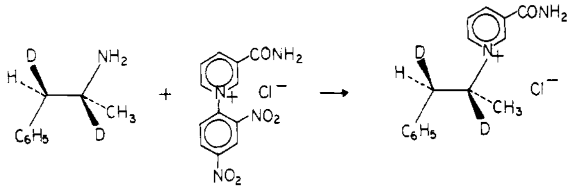




of the methylene group protons (*pro-S* and *pro-R* in the 1*R*,2*R* and 1*S*,2*S* enantiomers, respectively) is readily made. The lone methylene protons of the enantiomeric dideuterioamphetamines are enantiotopic by external comparison and are thus magnetically equivalent, giving rise to a single resonance (in the ^2H-decoupled spectrum).

Thus, for the three-spin ethano bridge system of amphetamine itself, the three chemical shifts and three coupling constants associated with the ethane fragment (CH_3-decoupled) were assigned. Our original assignment has recently been confirmed.[5]

N-(1-Phenyl-2-propyl)nicotinamide chloride (**2**) and its dideuterated analogue (**2**-d_2) were prepared by the addition



of amphetamine and dideuterioamphetamine (**3**), respectively, to *N*-(2,4-dinitrophenyl)nicotinamide chloride (**4**). The mechanism of this reaction, originally discovered by Zincke,[7] has been determined.[8] The nitrogen atom of the amine reactant becomes the pyridine ring nitrogen in the final product via a ring opening–ring closure sequence. We have confirmed this mechanism by labeling studies involving ^{15}N-labeled amines in which the ^{15}N of the reactant amine appears as the pyridine nitrogen of the final product.[9]

The importance of this result is that since the amine nitrogen appears as the pyridine nitrogen in the final product the stereochemistry of the reaction is determined, i.e., the amine is introduced with retention of configuration and any stereochemistry and/or labeling of the reactant amine is established in the final product. When specifically deuterium-labeled amphetamine **3** is reacted with **4**, the assignment of the chemical shift of the lone remaining methylene proton in labeled **2** is possible and by comparison of labeled and unlabeled **2** all chemical shifts and coupling constants can be assigned.

Table I. NMR Parameters and Populations

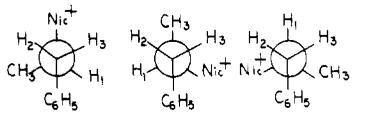
		$^3J_{HH}$		conformer populations[a]		
no.	solvent	J_{12}	J_{13}	a	b	c
1 (R = C_6H_5)	CCl_4	8.20	6.50	0.52	0.35	0.13
2	D_2O	5.14	9.45	0.21	0.64	0.15

[a] See text.

Table II. Vicinal Coupling Constants

no.	$^3J_{12}$ (Hz)	$^3J_{13}$ (Hz)
p-CH_3O-**2**	4.98	9.47
2	5.14	9.45
p-NO_2-**2**	5.93	9.02

Conformation of *N*-(1-Phenyl-2-propyl)nicotinamide Chloride. The pertinent NMR parameters for **2** are δ_1 (methine) 5.54, δ_2 (methylene) 3.81, and δ_3 (methylene) 3.54, while for **2**-d_2 the methylene chemical shift is δ 3.81, establishing all three chemical shifts. The coupling constants ($^3J_{HH}$) for **2** are $^3J_{12}$ = 5.29 Hz, $^3J_{13}$ = 9.50 Hz, and $^3J_{23}$ = −14.48 Hz. The relative magnitudes of the two vicinal coupling constants ($^3J_{12}$ and $^3J_{13}$) are surprising; if conformer **2a** were the major conformer, it would be expected that $^3J_{12}$ would be greater than $^3J_{13}$. Therefore, it is apparent that the major conformer of **2** is not **2a** but rather that it is **2b** possessing the phenyl and nicotinamide moieties in a gauche relationship, in marked contrast to the hydrocarbon analogue 1,2-diphenylpropane. A comparison of the two systems is presented in Table I.



The conformer populations presented in Table I were calculated from the equations $^3J_{12} = n_aJ_t + n_bJ_g + n_cJ_g$, $^3J_{13} = n_aJ_g + n_bJ_t + n_cJ_g$, and $1 = n_a + n_b + n_c$, with the assumption that the theoretical trans and gauche coupling constants J_t and J_g are 13.0 and 3.0 Hz, respectively, in all conformations.

Symmetry considerations alone invalidate the later assumption, but order of magnitude *estimates* of populations can be obtained. Further, changes in J_t and J_g resulting from group electronegativity differences have been ignored; corrections, if made, would not be expected to significantly alter the results.[10] Over a wide range of possible theoretical values ($10 \leq J_t \leq 15$; $2 \leq J_g \leq 6$) it can only be concluded that the preferred solution conformations of **2** and its hydrocarbon counterpart **1** (R = C_6H_5) differ; the former perfers the aryl moities gauche while in the latter they are anti.

Nature of the Nonbonded Interaction. The interaction that destabilizes the phenyl–phenyl gauche, phenyl–methyl trans conformation of 1,2-diphenylpropane (**1b**) is steric in nature. Were the same interaction dominant in *N*-amphetamylnicotinamide chloride (**2**), it would be expected that the preferred conformer of **2** would be **2a**. Pyridinium compounds are known to form both inter- and intramolecular charge-transfer complexes with aromatics.[11,12] It is likely that an intramolecular attractive charge-transfer interaction stabilizes the unexpected aryl–aryl gauche conformation of **2**.

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Credance for this explanation is gained by comparison of the vicinal coupling constants of **2** with those of the p-NO_2- and p-CH_3O-phenyl derivatives of **2** (p-NO_2-**2** and p-CH_3O-**2**, respectively) given in Table II. Granted that remote (para) substitution does not markedly alter the adjacent methylene groups electronegatively which in turn could alter the magnitudes of the observed vicinal coupling constants,[10] qualitative analysis indicates that as conformer population **2b** is diminished relative to **2a**, J_{12} should increase and J_{13} should decrease; conversely, as conformer population **2b** is increased relative to **2a**, J_{12} should decrease and J_{13} should increase. The electron-donating methoxy group causes J_{13} to increase while the electron-withdrawing nitro group causes J_{13} to decrease relative to the unsubstituted molecule **2**. Although only small conformer population changes are observed, the coupling constant and conformer population trends are what should be expected for an attractive electronic interaction.

Finally, it should be noted that the angle between two aryl rings on contiguous carbons of an ethane-like fragment (assuming idealized carbon hybridization) is 39° and the centers of the two rings are separated by ca. 3.5 Å (in an eclipsed conformation). Neither the inter-ring angle nor the inter-ring separation is optimal for charge-transfer interaction;[13] for maximum charge transfer the rings should be coplanar.

Experimental Section

All melting points are uncorrected. Micro analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY. All NMR spectra were determined on 5% (wt/vol) D_2O solutions containing DSS as internal standard. Theoretical spectra were calculated with the LAOCN 3 program.[14]

(±)-Amphetamine was prepared by a previously reported procedure[15] as was dideuterioamphetamine (**3**-d_2).[3]

1-(2,4-Dinitrophenyl)nicotinamide chloride was prepared by the method of Lettre[16] and was used without further purification.

***p*-Nitroamphetamine** was prepared by the method of Patrick[17] and exhibited bp 115–117 °C (Kugelrohr) at 1.0 mm (lit.[17] bp 115–116 °C at 1.0 mm). The ^1H NMR spectrum is consistent with the structure.

***p*-Methoxyamphetamine** was prepared by lithium aluminum hydride reduction[18,19] of 1-(p-methoxyphenyl)-2-nitroprop-1-ene[19] which exhibited bp 142–146 °C at 1 mm and mp 42–44 °C (lit.[20] bp 176.2–178.8 °C at 8 mm and mp 43–44 °C). The product exhibited bp 87–89 °C at 0.6 mm (lit.[18] bp 141 °C at 14 mm; lit.[19] bp 129–132 °C at 8 mm). The ^1H NMR spectrum is consistent with the structure.

***N*-(1-Phenyl-2-propyl)nicotinamide chloride** was prepared by adding 5.4 g (0.04 mol) of amphetamine to a solution of 13.0 g (0.04 mol) of 1-(2,4-dinitrophenyl)nicotinamide chloride in 65 mL of methyl alcohol cooled to 0 °C. Upon addition of the amine the solution turns red-black. The reaction mixture was stirred for 18 h at room temperature during which time the color of the mixture changed to yellow-orange. The solvent was removed on a rotary evaporator and the solid residue was extracted with 100 mL of water; the remaining solid was removed by filtration and was discarded. The aqueous filtrate was decolorized with activated carbon and filtered, and the solvent was removed on a rotary evaporator. The residue was crystallized from methanol–ether; after three crystallizations the melting point of the colorless solid is 206.5–208 °C; yield 9.3 g (84% of theoretical). Anal. Calcd for $C_{15}H_{17}N_2OCl$: C, 65.10; H, 6.15. Found: C, 65.07; H, 6.09.

***N*-[1-(4-Nitrophenyl)-2-propyl]nicotinamide chloride** was prepared analoguously to the unsubstituted derivative (above). Product crystallized from ethanol–ether exhibited mp 192–194 °C. Anal. Calcd for $C_{15}H_{16}N_3O_3Cl$: C, 55.99; H, 4.98; N, 13.06; Cl, 11.04. Found: C, 56.20; H, 5.28; N, 13.10; Cl, 11.00.

***N*-[1-(4-Methoxyphenyl)-2-propyl]nicotinamide chloride** was similarly prepared (above). Product crystallized from ethanol–ether exhibited mp 185–187 °C. Anal. Calcd for $C_{16}H_{19}N_2O_2Cl$: C, 62.64; H, 6.20; N, 9.14; Cl, 11.58. Found: C, 62.56; H, 6.11; N, 9.31; Cl, 11.49.

Registry No. N-(1-phenyl-2-propyl)nicotinamide chloride, 95249-96-0; amphetamine, 300-62-9; 1-(2,4-dinitrophenyl)nicotinamide chloride, 53406-00-1; N-[1-(4-nitrophenyl)-2-propyl]nicotinamide chloride, 95249-97-1; N-[1-(4-methoxyphenyl)-2-propyl]nicotinamide chloride, 95249-98-2.

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Synthesis of Methyl 3,5,9,11,13-Pentaoxotetradecanoate, a "Skipped" Heptaketide, via Ozonolysis of a Hydroaromatic System

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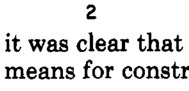
The synthesis of carbon chains possessing alternating methylene and carbonyl groups ("polyketides", **1**) has provided valuable materials for verification of the acetate–malonate pathway of biosynthesis[1] as well as useful precursors to certain acetate-derived natural products.[2] As synthetic entities, higher order polyketides present difficult objectives due to their inherent instability, the limited access to unprotected versions, and a proclivity, when unmasked, for these systems to undergo indiscriminate, internal condensation. Notable success in counteracting these properties has been achieved by Harris, who developed a stepwise, iterative process for homologation of polyketides via their polyenolate anions,[3] and by Money and Scott, who succeeded in deploying polyketides within cleverly contrived pyrone structures.[4]

Our approach to the synthesis of polyketides had, as its antecedent, a report by Birch, which described an attempt to prepare **3** by ozonolysis of the dihydroaromatic system **2**.[5] Although **3** was not fully characterized in that study, it was clear that this tactic offered a potentially valuable means for construction of extended polyketide (**1**, $n \geq 4$)

$CH_3(COCH_2)_nCO_2R$

1



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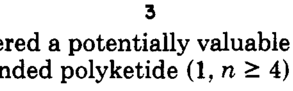

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