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ISOLABLE DIASTEREOISOMERS AS A RESULT OF RESTRICTED ROTATION ABOUT AN Ar-$\overset{S}{\overset{\|}{C}}$ BOND

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Recently, a considerable amount of interest has centered on the study of atropisomers, i.e. those resulting from slow rotation about a carbon-carbon single bond. In many cases the barriers to rotation are sufficiently high ($\geq$23 kcal/mole) to permit isolation of individual rotamers. Examples involving barriers between carbon-carbon bonds having sp^3-sp^3, sp^3-sp^2 and sp^2-sp^2 hybridization have been described.[1,2] In this paper we wish to report the measurement of high barriers to rotation about the Ar-C=O bond of a benzamide and the Ar-C=S bond of a thioamide. In the latter case we have been able to separate the individual rotamers, demonstrating a new type of atropisomerism. Isolation of these isomers provides additional evidence in support of an energetically favored perpendicular orientation of the aromatic ring relative to the N-C=O group of these *ortho*-disubstituted amides, notwithstanding recent claims to the contrary.[3]

The two compounds under study, 2-methoxy-1-naphthoyl-4-phenylpiperidine, 1, and 2-methoxy-1-thionaphthoyl-4-phenylpiperidine, 2, were synthesized by standard methods.[4] The ^{1}H n.m.r. spectrum of 1 in $CDCl_3$, showed two sharp equally intense singlets (δ4.01 and 3.98) in the methoxyl region indicating the presence of two isomers as depicted in Figure 1.[5] Upon experimentation it was found that the compound giving rise to the lower field singlet, 1-L, could be obtained free from its isomer by repeated washing of a semi-solid mass of 1 with acetone, which preferentially removed the isomer giving the high field singlet 1-H. By monitoring the methoxyl region the rate constant for isomerization of 1-L (at 18°C in $CDCl_3$) to the equilibrium position (50:50) was found to be 2.1×10^{-3} sec^{-1} ($\Delta G^{\ddagger}$ = 20.7 kcal/mole).

The corresponding thioamide also showed two singlets, δ 4.03 and 4.00, in its ^{1}H n.m.r. spectrum. One pure isomer giving rise to the lower field methoxy, 2-L, could be obtained by crystallization from hexane-ethyl acetate, m.p. 160-161°C. The second isomer 2-H was separated from 2-L by preparative thin layer chromatography on silica gel at 10°C using hexane-ethyl

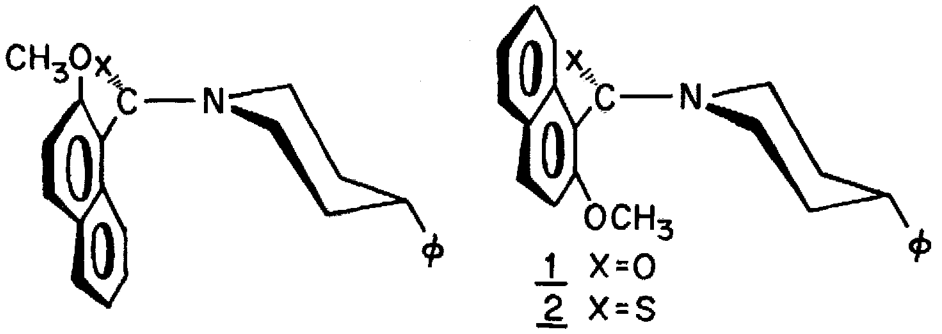

Fig. 1 Three dimensional formulae for the atropisomers of 1 and 2.

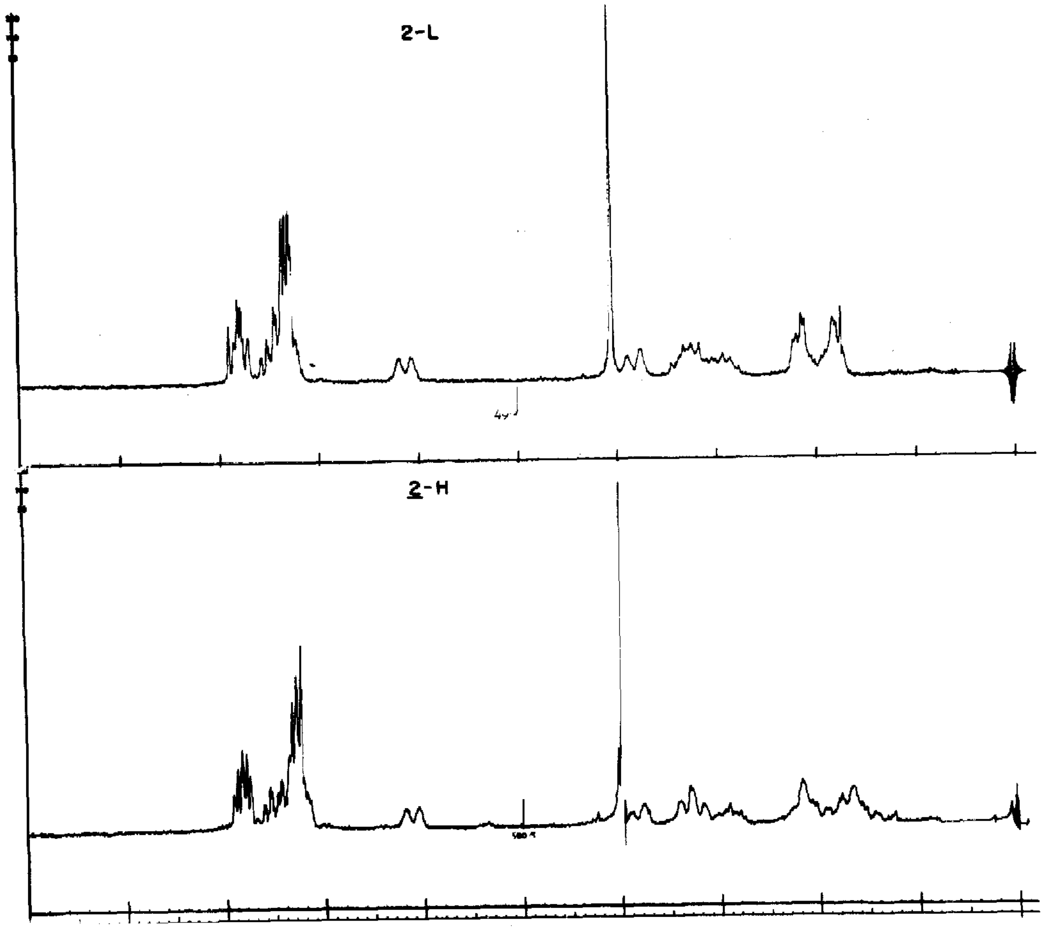

Fig. 2 The 100 MHz ^{1}H n.m.r. spectra of 2-L (top) and 2-H (bottom).

acetate, 3:1, as eluant (2-L had R_f=.32, 2-H=.21). The rate of isomerization of either isomer to the equilibrium distribution (50:50) determined by n.m.r. integration at 25°C was about 100 times slower than for 1, specifically 2.7×10^{-5} $\sec^{-1}$. This rate equates to a rotational barrier of 23.8 kcal/mole. Figure 2 shows the ^{1}H n.m.r. spectra of the separated isomers 2-L and 2-H. This novel example of separable atropisomers is readily accounted for by current knowledge of barriers to rotation in amides and thioamides.

The first report of a barrier to rotation about the $\mathrm{Ar{-}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}$ bond of an amide appeared in 1966.[6] Siddall and Garner found an activation energy of 20 kcal/mole for the process rendering the four methoxyl peaks equivalent to N-methyl, N-α-phenethyl-2,6-dimethoxybenzamide. They concluded that in the transition state the coplanar arrangement of the *O*-disubstituted aromatic ring and N-C=O atoms resulted in severe steric repulsions. Numerous additional examples followed[7] in which the changes in the barrier with the size of *ortho* substituents supported this explanation. It seems logical then that the greater bulk of the *ortho* substituents in the 2-methoxynaphthoic acid amide should increase the barrier as indeed happens in 1. Since equilibration of 1 can occur by either Ar-CO rotation or amide rotation we converted 1 to 2 in order to increase the amide barrier.[8] The fact that the barrier to isomerization also increased on thionation indicates isomerization to be occurring via C-N bond rotation. The barrier to Ar-CO rotation though not measurable must then be ⩾23.8 kcal/mole.

Recently[3] a rather unusual explanation was expressed to account for the coalescence of two doublets representing the *ortho* protons of p-nitrothiobenzoyl-3,5-dimethylmorpholine ($T_c \cong 0°$ in CS_2 using 220 MHz n.m.r.). The authors proposed that the aromatic ring underwent "librations" in a conformational energy minimum between two energy maxima associated with the coplanar and perpendicular orientations of the aryl versus amide groups.[9] In view of the aforementioned knowledge regarding such barriers, the coalescence observed simply constitutes an additional example of hindrance to rotation about both the thioamide and $\mathrm{Ar{-}}\overset{\mathrm{S}}{\overset{\|}{\mathrm{C}}}$ bonds. The results for 1 and 2 reinforce the reliability of this conclusion.

REFERENCES AND NOTES

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2. Recent examples of high barriers to rotation about sp^2-sp^2 carbon-carbon bonds have been reported for crowded butadienes, M. Rosner and G. Kobrich, *Angew. Chem. Int. Eng. Ed.*, *14*, 708 (1975); for diarylacenaphthenes, A.R. Miller and D.Y. Curtin, *J. Amer. Chem. Soc.*, *98*, 1860 (1976); and for 1,8-diarylnaphthalenes, R.L. Clough and J.D. Roberts, *J. Amer. Chem.*

Soc., *98*, 1020 (1976).

3. A.O. Fulea and P.J. Krueger, *Can. J. Chem.*, *53*, 3315 (1975).
4. Conversion of 2-methoxynapthoic acid, S.V. Sunthanker, H. Gilman, *J. Org. Chem.*, *16*, 8 (1951), to the acid chloride (with $SOCl_2$) then reaction with 4-phenylpiperidine gave amide *1*, m.p. 150-151°C (from ethyl ether). Thionation of *1* using the method of Kindler, *Ann.*, *431*, 207 (1923), gave *2* in 37% yield. Both compounds gave satisfactory combustion analyses.
5. The atropisomers, *1*-L and *1*-H can be readily seen to differ with respect to the *cis* or *trans* arrangement of the *ortho*-methoxyl with respect to the phenyl group at C-4 of the piperidine ring. It seems likely that the assignment of stereochemistry to the two isomers will only be possible by X-ray techniques.
6. T.H. Siddall, III and R.H. Garner, *Tetrahedron Letters*, 3513 (1966).
7. T.H. Siddall, III and R.H. Garner, *Can. J. Chem.*, *44*, 238 (1966); G.R. Bedford, D. Greatbanks and D.B. Rogers, *Chem. Commun.*, 330 (1966), corrigendum 144 (1967); A.H. Lewin and M. Frucht, *Tetrahedron Letters*, 1079 (1970); A.H. Lewin, M. Frucht, K.V.J. Chen, E. Benedetti and B. DiBlasio, *Tetrahedron*, *31*, 207 (1975); R. Lozac'h, L. Legrand and J. Sandstrom, *Org. Mag. Res.*, *7*, 54 (1975).
8. W.E. Stewart and T.H. Siddall, III, *Chem. Rev.*, *70*, 517 (1970).
9. The authors were attempting to explain the fact that part of the *ortho* absorption broadened and separated into two equal intensity doublets while a minor doublet remained sharp throughout. The thiobenzoyl morpholines studied were in all probability a mixture of *cis* and *trans* isomers. Only the *cis* isomer which is chiral could give rise to non-equivalent *ortho* protons and thus a temperature-dependent n.m.r. spectrum. The resolution of a somewhat related controversy appeared recently.[10]
10. W.B. Jennings and M.S. Tolley, *Tetrahedron Letters*, 695 (1976).
11. A comparison of the n.m.r. spectra of 2,6 dimethoxybenzoyl-piperidine and its 4-phenyl derivative also provides corroboration. The 4-phenyl derivative gives rise to two methoxyl peaks which coalesce at $62^{\circ}C$ ($\Delta G^{\neq}$ = 18.9 kcal/mole) while the parent, lacking asymmetry at C_4, has a singlet methoxyl.

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