Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. X (1). Correlation of the Dihedral Angles of Phenoxathiin Analogs with the 13C-NMR Chemical Shifts of the Sulfur Bearing 1a Carbon

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The observation of a linear relationship between the 13C-nmr chemical shifts of the C-1a carbon and the dihedral angle in a series of phenoxathiin analogs is reported. Presently available data, although limited, is presumed to be indicative of a more general behavior which has not been previously recognized or utilized. Extension of this observation to include other sulfur containing tricyclic systems may be expected to provide a useful means for the preliminary estimation of dihedral angles from solution 13C-nmr measurements after suitable parameterization.
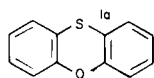
Sir:

We have investigated the synthesis of various annular nitrogen containing analogs of the phenoxathiin ring system as potential new psychoactive ring systems (4-7). A guiding premise in our selection of the phenoxathiin ring system as the heterocyclic nucleus for our exploratory studies was the isosteric equivalence of the phenoxathiin oxygen linkage and the phenothiazine -NH- linkage (4,7), as well as the close similarity between the dihedral angles

(∅) of phenoxathiin (8) and several neuroleptic phenothiazine analogs (9,10). The latter consideration seemed to be particularly germane to the design of these agents since, in the phenothiazine series, the increased planarity resulting from the replacement of the 2-chloro-substituent of chlorpromazine (∅ = 139.2°) (9) with a 2-methoxyl group to give 2-methoxypromazine (∅ = 157.4°) (11) is associated with a complete loss of pharmacologic activity (12). As an outgrowth of our utilization of 13C-nmr spectroscopy in the structure confirmation studies of these new compounds (4-7,13), we have observed a linear correlation between the dihedral angle of these systems and the chemical shift of the sulfur bearing 1a carbon (Table I). This relationship provides a convenient means for the estimation of dihedral angles in this and presumably, after suitable parameterization, other heterotricyclic systems of medicinal interest and is the basis for this communication.

Table I

Comparison of the 13C-nmr chemical shifts of the 1a carbon of phenoxathiin (1) and a series of analogs in deuteriochloroform with their respective crystallographically determined dihedral angles (∅).

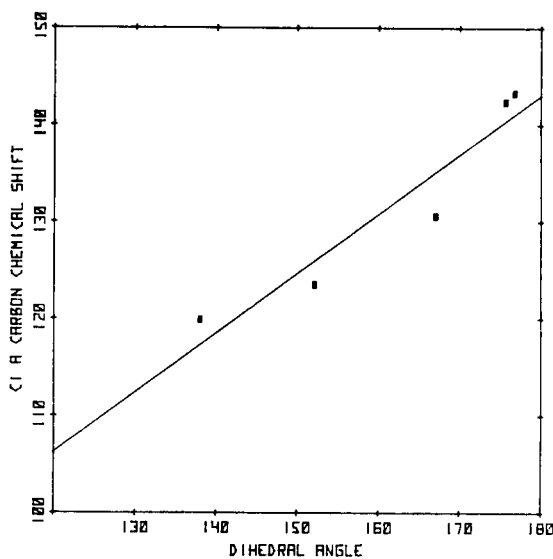| Compound		$\delta^{13}C_{1a}$	∅°
1		119.6 (18)	138.0 (8)
2		143.3 (4)	176.8 (7)
3		142.4 (7)	175.7 (7)
4		130.6 (19)	167.0 (20)
5		123.5 (21)	152.1 (22)

Figure 1. Plot of the 13C-nmr chemical shifts of the C1a carbons of selected phenoxathiin analogs vs. the corresponding dihedral angles.

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Correlation of various spectral parameters, *e.g.* chemical shift and coupling constants with physical quantities such as electron density have been attempted. Notable examples of such studies include the correlation of chemical shifts with electron densities in simple planar nitrogen containing systems (14,15). In contrast, similar attempts with more complex heterocycles have met with only very limited success, particularly in the case of non-planar systems, where attempts to correlate proton chemical shift with physical quantities gave no useful result. In light of the poor results previously obtained with non-planar systems, we were thus quite surprised to observe a linear relationship between the ^{13}C-nmr chemical shift of the 1a carbon and the respective dihedral angles in a series of phenoxathiin analogs. These data, although limited, are summarized in Table I and illustrated by Figure 1. Statistical evaluation of this data gives a correlation coefficient, r = 0.959, in direct contrast to the results of an earlier study which attempted a similar correlation and gave a correlation coefficient of r = −0.109. While arguments may certainly be advanced which challenge the validity of correlating solution and crystal measurements, the data, nonetheless, indicate that there is a direct correspondence between the overall molecular geometry and ^{13}C-nmr chemical shift behavior of the C1a position (17).

Further refinement of the reported relationship will require the complete analysis of the spin-spin and dipolar couplings of representative molecules oriented in the nematic phase. Completion of this detailed analysis should provide a firmer basis for comparing solution and crystallographic data. Preliminary studies with this direction are presently underway in these laboratories and will be reported.

REFERENCES AND NOTES

(1) For the preceeding paper in this series see, "Chemistry of the Phenoxathiins and Isosterically Related Heterocycles, IX.", *J. Heterocyclic Chem.*, **17**, 429, 1980.

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(17) In effect, plotting ^{13}C-nmr chemical shifts of C1a *vs* dihedral angle (∅), is analogous to correlating electron densities, which have been shown to be reflected linearly in aromatic carbon chemical shifts [G. A. Olah and G. D. Matescu, *J. Am. Chem. Soc.*, **92**, 1430 (1970)], with dihedral angles. Further, since sulfur containing tricycles have been shown to exhibit changes in dihedral angle as a result of changes in electron density ("Advances in Heterocyclic Chemistry," vols. 8 and 9, A. R. Katritzky and A. J. Bolton, Eds., Academic Press, New York.), it is not particularly surprising that such changes would conversely be reflected in ^{13}C-nmr chemical shifts.

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