MOLECULAR PHARMACOLOGY, 7, 674–682

Thioxanthones

II. Studies on the Hydrogen-Bonding Capacity of Lucanthone

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(Received April 7, 1971)

SUMMARY

Lucanthone (1-diethylaminoethylamino-4-methylthioxanthone) is a bacteriostatic and carcinostatic agent, and combines readily with DNA. N_{11}-Methyl substitution results in virtual deletion of these activities. It has been postulated that this effect is due to loss of the capacity to form in an intermolecular hydrogen bond.

Suitable investigations of electronic and vibrational spectra indicate the presence of a stable intramolecular amino-carbonyl proton bond in lucanthone. The studies reveal no evidence of interaction between strong hydrogen-bonding acids or bases and the carbonyl or secondary amine substituents.

Consequently, the reduced biological and biochemical activity concomitant with N-methyl substitution is not attributable to a diminished capacity to form intermolecular proton bonds. In fact, the capability of lucanthone in this regard is lower than that of the less active N-methyl derivative, in which the nonbonding $2p$ orbital of the carbonyl function is free to interact with hydrogen-bonding acids.

INTRODUCTION

N_{11}-Methyl substitution of 1-dialkylaminoalkylamino-4-methylthioxanthones (Fig. 1)[1] is generally associated with a striking reduction in bacteriostatic (1) and carcinostatic (2) activity. In addition, the above compositional change is accompanied by complete loss of the capacities to inhibit RNA polymerase, to stabilize DNA against heat denaturation, and to increase the viscosity of DNA solutions (1, 3).

Spectrophotometric studies and ionization constants indicate that N_{11}-methyl substitution results in steric interference between the N-methyl group and the oxygen atom on C_9. This necessitates a rotation of the amine side chain on the C_1—N_{11} bond axis to permit these substituents to achieve their approximate van der Waals separation (4). On the basis of the above data and interpretations, the following hypotheses were suggested: (a) coplanarity of the thioxanthone ring and amine side chain may be requisite to *optimum* biological activity, or (b) changes in physical properties concomitant with steric inhibition of resonance

[1] All numerical subscripts refer to the assignments in Fig. 1. The following terms are used: monohydrochloride, N_{14}-protonated; dihydrochloride, N_{11}- and N_{14}-protonated. The expression n-π^* transition refers to the excitation of an electron from a nonbonding atomic to an antibonding molecular orbital. π-π^* transitions involve the promotion of an electron from a bonding to an antibonding molecular orbital.

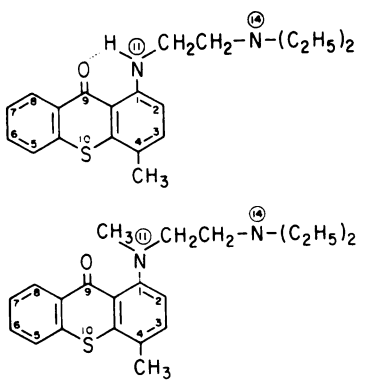

FIG. 1. *Structural formulae of lucanthone (upper) and 11-methyllucanthone*

may account for the observed differences in cytotoxic and biochemical effects (4).

An alternative explanation has been proposed by Blanz and French (2), who suggested that diminished hydrogen-bonding capacity may be responsible for the reduced carcinostatic activity of the *N*-methyl derivatives. It has also been suggested that the lucanthone-DNA complex is stabilized by proton bonds involving the carbonyl oxygen and secondary amine substituents of the thioxanthone and the base residues of the DNA helix[2]. The present study was undertaken to determine whether the intrinsic physicochemical properties of lucanthone and 11-methyllucanthone are compatible with these proposed mechanisms of action.

MATERIALS AND METHODS

The pertinent properties of lucanthone (Burroughs Wellcome & Company, Inc.) and its *N*-methyl derivative (Parke, Davis & Company) have been described (5, 6). Methods of purification and criteria for purity are given in ref. 4.

Electronic spectra were determined on a Cary 15 recording spectrophotometer by methods defined previously (4).

Infrared spectra were obtained on a Perkin-Elmer model 257 grating spectrophotometer and on a Perkin-Elmer model 137 spectrophotometer with NaCl optics (4).

In order to rule out possible artifacts associated with the KBr disc technique (7), discs were prepared from samples ground by several methods and for various periods of time as recommended by Baker (7). In addition, spectra of the KBr discs were compared with those of mineral oil mulls and with solid films deposited on sodium chloride plates from solutions in *n*-hexane. The N—H stretching absorption was well resolved in all solid films examined; however, a number of artifactual distortions were found in the 1600 cm^{-1} region, and the carbonyl frequencies of these specimens (approximately 1620 cm^{-1}) are not included in Table 2. The band frequencies obtained by the various methods described were virtually identical.

All solvents used in the determination of visible, ultraviolet, and infrared spectra, and in the preparation of solid films, were of spectroscopic quality.

RESULTS

Ultraviolet spectra. The ultraviolet spectra of lucanthone and 11-methyllucanthone are depicted in Fig. 2. Differences in the frequency, molar absorptivity, bandwidth, and fine structure in the recorded spectra of the two thioxanthones are attributable to steric inhibition of resonance in the *N*-methyl derivative (4).

The influence of various solvents on the ultraviolet absorption bands of the compounds, as well as pertinent physical constants, are described in Table 1. Ideally, the reference frequency should be the 0—0 transition of the vapor. When this is not feasible, however, a solution in the nonpolar solvent of lowest refractive index (*n*-hexane) is chosen as the most suitable standard (13–15). The results are not suitable for rigorous theoretical analysis, but are entirely adequate to define semiquantitatively the nature and extent of certain solute-solvent interactions. The utility of such studies in the investigation of inter- and intramolecular hydrogen bonds is well documented (14–18). In several instances this method alone has been considered sufficient to establish the presence of intramolecular proton bonds (17, 18).

In nonpolar solvents the 30,000 cm^{-1} bands of lucanthone and 11-methyllucanthone manifest bathochromic shifts of com-

[2] G. Hite, cited by Hirschberg *et al.* (1).

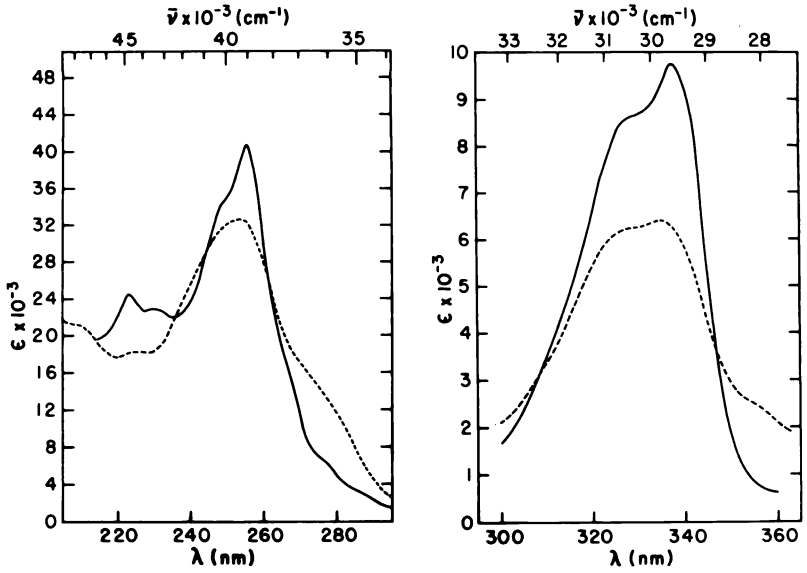

FIG. 2. *Ultraviolet absorption spectra of lucanthone* (——) *and 11-methyllucanthone* (- - -) The solvent was *n*-hexane. λ = wavelength; $\bar{\nu}$ = wave number; ε = molar absorptivity.

parable magnitude. Both derivatives exhibit small hypsochromic shifts in the polar hydrogen-bonding base, acetone. However, a striking and, in fact, the only significant difference in the behavior of the two thioxanthones occurs in solutions in the hydrogen-bonding acid, methanol. The magnitude of the shift of 11-methyllucanthone is well within the range of hydrogen bond enthalpies: 1–7 kcal/mole; 350–2500 cm^{-1} (14). The direction and magnitude of the shift indicate weakening of an intermolecular hydrogen bond in the excited relative to the ground state of the solute. The data in Table 1 clearly indicate that the difference in the solvent effect on the spectra of the two thioxanthones is not related to the refractive index, dipole moment, or dielectric constant of the solvent, but is attributable to the hydrogen-bonding capacity of methanol.

The high-frequency region of the ultraviolet spectrum is inaccessible to most of the solvents used in the study of the 30,000 cm^{-1} band. In methanol, however, the frequency shifts of the 39,000 cm^{-1} band complexes of the two derivatives differ considerably, and the magnitude of the shift for 11-methyllucanthone is again compatible with the presence of an intermolecular hydrogen bond between solute and solvent.

Both compounds have absorption bands in the visible portion of the spectrum. The major absorption maxima of lucanthone and its *N*-methyl derivative, in *n*-hexane, are 22,730 cm^{-1} (440.0 nm) and 23,230 cm^{-1} (430.5 nm), respectively (4). Neither band exhibits solvent effects attributable to hydrogen bonding.

Both the 22,700 and 30,000 cm^{-1} band complexes of lucanthone are quite sensitive to variations in configuration and charge density involving the proximal (N_{11}) amine substituent. Yet neither manifests significant changes in frequency or intensity on passing from *n*-hexane to the hydrogen-bonding base, acetone. These findings suggest, although negatively, that the proton on N_{11} is not available for hydrogen-bonding interaction with the solvent.

The solvent effects described imply that lucanthone comprises a highly stable N – H···O=C intramolecular proton bond (14, 16–18).

The criteria described are similar to those adduced by Pimentel and McClellan (14), in relating solvent-induced spectral shifts to hydrogen bonding interactions; by Morton

TABLE 1

Influence of various solvents on frequencies of ultraviolet absorption maxima of lucanthone and 11-methyllucanthone

$\tilde{\nu}$ = wave number; $\Delta\tilde{\nu}$ = wave number shift relative to *n*-hexane; n = solvent refractive index at the indicated temperature (superscript) and wavelength (subscript) (8–10); u = solvent dipole moment (11); D = solvent static dielectric constant at 20° (12). *n*-Hexane was the reference solvent throughout.

Solvent	$n_{340nm}^{20\pm2°}$	u (gas)	$D^{20°}$	$\Delta\tilde{\nu}$	
				Lucanthone ($\tilde{\nu}$ = 29,630 cm^{-1})	11-methyl-lucanthone ($\tilde{\nu}$ = 29,850 cm^{-1})
		esu × 10^{18}		cm^{-1}	cm^{-1}
n-Hexane	1.400[a]	0	1.890	0	0
Cyclohexane	1.449	0	2.203	−40	−40
CCl_4	1.492	0	2.239	−300	−260
Benzene	1.561	0	2.284	−170	−180
Acetone	1.389	2.84	21.40	+40	+50
Methanol	1.346	1.71	33.58	+220	+920

Solvent	$n_{250nm}^{19\pm1°}$	$\Delta\tilde{\nu}$	
		Lucanthone ($\tilde{\nu}$ = 39,140 cm^{-1})	11-Methyl-lucanthone ($\tilde{\nu}$ = 39,450 cm^{-1})
		cm^{-1}	cm^{-1}
n-Hexane	1.434[b]	0	0
Cyclohexane	1.483	−150	−160
Methanol	1.372	−80	−990

[a] $n_{350nm}^{15°}$ (8).
[b] $n_{250nm}^{15°}$ (8).

TABLE 2

Infrared absorption frequencies of N—H and C=O stretching vibrations of lucanthone in the solid state and in dilute solution

Each frequency represents the average of several determinations. Solution spectra: concentration, 0.003–0.15 M; solvent, CCl_4; cells, NaCl; cell path, 0.1–1 mm.

Sample	$\tilde{\nu}$ N—H	$\tilde{\nu}$ C=O
	cm^{-1}	cm^{-1}
KBr disc	3257	1618
Solid film	3259	
Mineral oil mull	3256	1618
Solution in CCl_4	3254	1617

and Stubbs (17), in establishing the presence of internal hydrogen bonds in *o*-hydroxy-aldehydes and -ketones; and by Conover (18), in similar studies of 8-hydroxytetralone, 7-hydroxy-3-methylindanone, and oxy- and chlor-tetracycline.

In the present case, consideration of the possible effects of steric inhibition of resonance in 11-methyllucanthone requires an analysis of the solvent-induced frequency shifts in terms of the pertinent intermolecular forces, as well as an evaluation of the electronic structure of the diamine side chain.

Vibrational spectra. The stretching frequencies of the carbonyl and amine bonds of lucanthone in the solid state and in dilute solution are presented in Table 2. The interpreted functional group region of the infrared spectrum is depicted in Fig. 3. The low transition energy of the N—H vibration and the constancy of the absorption frequencies of the N—H and C=O bonds, despite changes in phase and concentration, are entirely compatible with the presence of a stable intramolecular amino-carbonyl hydrogen bond.

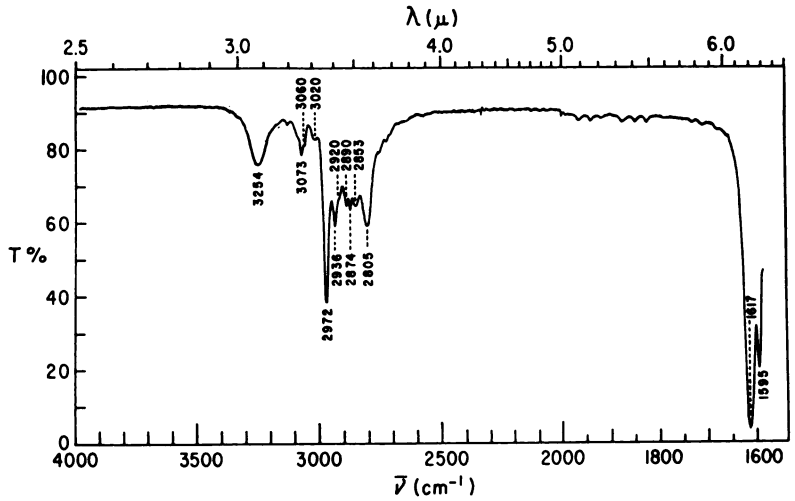

FIG. 3. *Infrared absorption spectrum of lucanthone*

Note 2-fold abscissa expansion for frequencies below 2000 cm^{-1}. λ = wavelength; $\bar{\nu}$ = wave number; T = transmittance. The sample melting point was 65.5–65.8°; concentration, 0.15 M; solvent, CCl_4; cell path, 0.1 mm. A Perkin-Elmer 257 spectrophotometer was used, with gratings adjusted to maximum deviations of ±2 cm^{-1} for the bands of polystyrene. All frequencies are averages of several determinations. The N—H stretching frequency is 3254 cm^{-1}. The C=O stretching vibration is assigned to the strong absorption at 1617 cm^{-1}. This interpretation is somewhat tentative, since aromatic C=C vibrations also absorb in this region of the spectrum (19). The several absorptions between 3073 and 3020 cm^{-1} represent C—H stretching vibrations of the thioxanthone ring. The bands between 3000 and 2800 cm^{-1} comprise the fundamental frequencies of the various alkyl C—H stretching vibrations and, possibly, overtones of the deformations of the methyl and methylene groups (20). The absorption maximum at 2972 cm^{-1} almost certainly represents an asymmetrical CH_3 vibration (20). The band at 2805 cm^{-1} vanishes on conversion to the monohydrochloride (see Fig. 3 of ref. 4), and is attributable to a vibration of the free tertiary (N_{14}) amine substituent of the base. Similar bands have been described for various free amines, including di- and triethylamine (21). The remaining C—H absorptions cannot be unambiguously assigned, since band resolution may be incomplete, and the perturbations induced by the 2 nitrogen atoms and the heteroaromatic ring cannot be directly assessed. Some of the pertinent problems are discussed in ref. 22. The band at 1595 cm^{-1} in all probability represents a C=C vibration of the thioxanthone ring (19).

DISCUSSION

Electronic spectra. N_{11}-Methyl substitution in lucanthone results in steric inhibition of resonance. This not only affects molecular configuration but also induces significant changes in the distribution of charge density. The pK_a of the proximal (N_{11}) amine constituent is increased [ΔpK_a = 3.61 (4)], the basicity of the terminal (N_{14}) amine is enhanced because of altered inductive and field effects, and variable changes in electron density throughout the conjugated system may be present. Consequently, the solvation energies of the two thioxanthones in the ground electronic state may differ appreciably. Electronic spectra are particularly advantageous to the present investigation, since solvent-induced frequency shifts represent *differences* between the solvation energies of the ground and excited states.

Solvation energies are determined by dispersion forces, by dipole-dipole and dipole-induced dipole interactions, and, where applicable, by solute-solvent hydrogen bonds (14, 15, 23–27). Because the required time interval of the electronic transition is much shorter than the relaxation time of the solvent, the excited state of the solute interacts with the configuration of solvent molecules that was in approximate equilibrium with the solute prior to photoexcitation. This Franck-Condon effect (23, 27) is of con-

siderable importance when both solute and solvent possess permanent dipole moments.

Dispersion forces are invariably augmented subsequent to an allowed electronic transition, and induce a bathochromic shift (24). Frequency shifts due to electrostatic forces reflect changes in the dipole moment of the solute concomitant with excitation, and altered excited state solvation energies due to the Franck-Condon effect. Generally an increase in polarity enhances and a decrease opposes the effect of dispersive interactions (23, 25–27).

The frequency shifts of the 30,000 cm^{-1} transitions in nonpolar solvents indicate that the combined effect of dispersion and dipole polarization forces is virtually identical for the two thioxanthones (23–27). The shifts in acetone represent the composite influence of dispersion forces, electrostatic interactions, and the Franck-Condon effect (23, 25–27). Again, the changes in frequency are almost identical. It may be inferred that changes in molecular polarity concomitant with the 30,000 cm^{-1} transition are comparable for lucanthone and its *N*-methyl derivative.

The above considerations also clearly indicate that the difference observed in the solvent effect of methanol on the spectra of the two thioxanthones is attributable solely to its hydrogen-bonding capacity.

The spectral perturbation induced by proton bonding between solute and solvent normally overshadows the effects of the intermolecular forces considered above (14, 15). Changes in hydrogen bond energies due to electronic excitation specifically reflect altered electron densities at a proton-bonding substituent. The dominant Franck-Condon effect, in this instance, is mediated by differences in the equilibrium bond length of the proton bond in the ground and excited states of the solute (14, 15).

The magnitude of solvent shifts due to hydrogen bonding is normally in the range of 350–2500 cm^{-1} (1–7 kcal/bond-mole) (14, 15). Bathochromic shifts indicate an increase, and hypsochromic shifts a decrease, in hydrogen bond strength in the excited relative to the ground electronic state of the solute.

Both the magnitude and direction of the frequency change of the 39,000 cm^{-1} band complex of 11-methyllucanthone in methanol are those normally anticipated for π-π^* transitions of hydrogen-bonding bases[1] (14–16).

The hypsochromic shift of the 30,000 cm^{-1} band complex of 11-methyllucanthone in methanol is somewhat unusual for a π-π^* transition of a proton-bonding base[2] (14, 15). Such shifts have been noted, however, for a number of conjugated compounds, which, like the thioxanthone, comprise an electropositive nitrogen and a strongly electronegative oxygen atom. Examples include 1-methyl-2- and 1-methyl-4-pyridone (33), 1-phenyl-2,3-dimethyl-5-pyrazolone (antipyrine) (34, 35), and highly polar merocyanine dyes (36, 37). All these compounds are characterized by the presence of an oxygen atom possessing an unusually high electron density in the ground electronic state (28). This net charge is reduced in the course of the pertinent π-π^* transition, with concomitant diminutions in polarity and hydrogen-bonding capacity (28, 37).

It is highly unlikely that the amine substituents of 11-methyllucanthone contribute significantly to its enhanced hydrogen-bonding capacity as measured by electronic spectra. The interpretation of the 30,000 cm^{-1} band complex given above clearly implicates the carbonyl function as the principal determinant of spectral shifts due to protonic interaction with a hydrogen-bonding acid. Furthermore, the possible influence of the diamine side chain can be excluded specifically on the basis of spectrophotometric criteria, which apply to the 39,000 as well as the 30,000 cm^{-1} absorption band.

The terminal (N^{14}) amine moiety is in-

[2] Hypsochromic shifts in hydroxylic solvents are characteristic of the n-π^* transitions of hydrogen-bonding bases (13, 14, 28). However, the high intensity of the 30,000 cm^{-1} band militates strongly against the possibility that an n-π^* transition contributes significantly to the total absorption of the band complex (29, 30). Intense n-π^* transitions (ϵ = 100–6000) have been noted in isolated instances (31), but the electronic structural concomitants of such n-π^* intensification (32) do not apply to the thioxanthones.

sulated from the thioxanthone ring by 2 methylene residues. Hence it should effect only a slight perturbation on the electronic transitions of the conjugated portion of the molecule. Spectral studies of a number of thioxanthone derivatives, performed in this laboratory, amply confirm the insensitivity of the band frequency to various structural alterations in this region of the side chain.

Spectra of the base and the mono- and dihydrochloride[1] of 11-methyllucanthone indicate that the proximal (N_{11}) amine group exerts strong conjugation effects despite steric inhibition of resonance. Consequently its lone pair electrons are not readily available for hydrogen bonding.

In view of the above, the spectral shifts of the 39,000 and 30,000 cm^{-1} band envelopes of the N_{11}-methyl derivative in methanol may be attributed primarily to proton bonding between the solvent and the nonbonding $2p$ orbital of the carbonyl function. The absence of a shift of comparable magnitude in the spectrum of lucanthone indicates that the lone pair electrons of its oxygen atom are unavailable for protonic interaction with the solvent.

The failure of either the 22,700 or 30,000 cm^{-1} band of lucanthone to manifest significant spectral shifts in acetone suggests that the proton on N_{11} is similarly incapable of participating in the formation of an intermolecular hydrogen bond.

The findings and interpretations cited are in all respects compatible with the presence of a stable, intramolecular N—H···O=C hydrogen bond.

In summary, the solvent-induced frequency shifts due to various combinations of dispersion forces, dipole orientation and induction forces, and the electrostatic Franck-Condon effect are virtually identical for the two thioxanthone derivatives. The two compounds differ significantly only in their capacity to function as hydrogen-bonding bases. The structural basis for this difference resides primarily, if not exclusively, in the nature of the carbonyl substituent: specifically, the availability of its $2p$ lone pair electrons for interaction with a hydrogen-bonding acid. The above considerations establish the presence of a strong intramolecular amino-carbonyl proton bond in lucanthone.

Vibrational spectra. The infrared absorption frequency of the N—H stretching vibration of unassociated secondary amines is 3500–3300 cm^{-1} (38). Aryl- and heteroaromatic-alkylamines are assigned to the upper portion of this region, at approximately 3450 cm^{-1} (38, 39). It is well established that high electron affinities of the aromatic or heteroaromatic ring (19, 39, 40) and low electron densities of the amine nitrogen atom (41, 42) are associated with high N—H stretching frequencies. This relationship holds for conjugated ring systems comprising both amine and carbonyl functions (40), and applies equally to primary and secondary amines (20, 39, 40). The potent electron-withdrawing effect of the thioxanthone ring is evidenced by the very low ionization constant of the proximal (N_{11}) amine substituent of lucanthone [pK_a = −0.20 (4)]. Accordingly, in the absence of other influences, a high N—H stretching frequency might be reasonably anticipated.

Hydrogen bonding commonly results in a small but significant decrease in absorption frequency (14, 20). Sutherland (43) specified the N—H stretching frequency of the proton-bonded amino-carbonyl complex (—N—H···O=C—) as 3320–3240 cm^{-1}. The pertinent band frequency of lucanthone, approximately 3255 cm^{-1}, is well within this range.

The carbonyl stretching frequency of *unsubstituted* thioxanthone has been identified as a multiplet with an absorption maximum at 1650 cm^{-1} (44). The low frequency of this band in polynuclear, aromatic, and sulfur-containing heteroaromatic ketones is well documented (19, 20, 44, 45). The additional decrease in the frequency of this absorption band in lucanthone relative to unsubstituted thioxanthone is consistent with hydrogen bonding. However, the observed difference is equally attributable to a decrease in the carbonyl bond order concomitant with ring substitution, particularly to the presence of the electron-donating, mesomeric amine moiety at C_1 (45).

The preceding discussion suggests that infrared absorption frequencies are indeed

compatible with, but do not unequivocally define, the presence of hydrogen bonds. Proton-bonded systems absorb over a wide range of frequencies. The magnitude of the anticipated changes in wavelength, bandwidth, or intensity is variable and, in the case of amines, may be quite small (20, 39, 46). Finally, as in the case of the carbonyl band, an alternative explanation for the spectral findings may be applicable. Vibrational spectra may be used in a much more definitive manner if the initial observations are supplemented by studies of phase and concentration dependence (14).

The lucanthone molecule comprises a hydrogen-bonding acid, the secondary amine; and two proton-bonding bases, the carbonyl and tertiary amine substituents. Such compounds normally form intermolecular hydrogen bonds in concentrated solution, and particularly in the solid phase (14). Consequently the pertinent stretching frequencies are concentration-dependent, since the change from concentrated solution, or solid, to dilute solution in an inert medium involves rupture of the intermolecular proton bonds. Typically the infrared spectra of such substances reveal hypsochromic shifts, reduced bandwidth, and decreased relative intensity of the affected absorption bands concomitant with dilution. The reduction in concentration may be accompanied by band splitting, indicating the simultaneous presence of both free and associated forms (14). The pertinent infrared absorption bands of lucanthone manifest no significant variation on changing from the solid phase to dilute solutions in carbon tetrachloride.

The combination of a low transition energy for the N—H stretching vibration with the virtual absence of concentration or phase dependence for both the N—H and C=O absorption frequencies indicates the presence of a stable intramolecular amino-carbonyl proton bond in lucanthone.

The above findings and interpretations imply that the reduced biological and biochemical activity concomitant with N_{11}-methyl substitution of 1-dialkylaminoalkylamino-4-methylthioxanthones is not attributable to a diminished capacity to form intermolecular hydrogen bonds. In fact, the studies of solvent effects on electronic spectra indicate that the capability of lucanthone in this regard is lower than that of its biologically and biochemically less active *N*-methyl derivative.

ACKNOWLEDGMENTS

I thank Dr. I. B. Weinstein and Dr. E. Hirschberg for supplying lucanthone and its *N*-methyl derivative, and Mrs. E. Felten for preparing the illustrations.

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