Dipole Moments and Pharmacological Activity of Cyclic Ureas, Cyclic Thioureas, and the N,N′-Dimethylated Compounds

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The synthesis, dipole moments, and pharmacological properties of five-, six-, and seven-membered cyclic ureas, cyclic thioureas, and the corresponding N,N′-dimethylated compounds are reported. The difference between the dipole moments in dioxane and benzene are much larger for the nonmethylated than for the methylated compounds. The sulfur compounds all have larger moments than the corresponding oxygen compounds and this difference is greater for the ring than for chain compounds. The reasons for these observations are discussed. Four new compounds are reported. The ratios of the frequencies of their carbonyl and thiocarbonyl bands is greater for the unsubstituted compounds than for the dimethylated compounds. The hydrogen bonding in the former which is not possible in the latter is responsible for the difference. The reason for the extremely hygroscopic character of the N,N′-cyclic ureas is discussed. The protons in the spectra of the sulfur compounds appear at a lower field than those in the corresponding oxygen compounds indicating greater contributions from the forms with a separation of charge which was also indicated by the higher dipole moments. N,N′-Dimethyltetramethylenethiourea was found to be the most potent convulsant among the compounds studied and more toxic than pentylenetetrazole on the basis of millimoles per kilogram required to kill 50% of the mice tested. It caused clonic convulsion within 1 min and death in a few minutes after intraperitoneal injection (100 mg/kg). N,N′-Dimethyltrimethylenethiourea was found to be the most potent respiratory stimulant in these series on the basis of millimoles per kilogram required to increase the rate of respiration by 50% in mice. Intraperitoneal injection of 30 mg/kg increased the respiration rate by 52% and shortened the sleeping time by 28% in a group of 12 mice pretreated with 60 mg/kg of sodium pentobarbital. A t test gave $P < 0.01$ and 0.10 for the respiration rate and the sleeping time, respectively.

A number of CNS depressants have a ureide structure and others have an imide structure. These have in common a resonating structure

$$>N-C(=A)- \longleftrightarrow >N^{+}=C(-A^{-})-$$

where A = O or S, which is also present in many CNS stimulants.[2-9] These drugs also have groups such as alkyl, alkenyl, or aryl which can provide regions for hydrophobic interaction and lipoid solubility. Some have active hydrogens that can hydrogen bond and others do not. Therefore it is of interest to study the physical and pharmacological properties of a series of cyclic ureas, cyclic thioureas, and the corresponding dimethylated compounds with five-, six-, and seven-membered rings. All of these contain the resonating structures, the dimethylated compounds do not have active hydrogens while the others do, and the change in ring size alters the dipole moment and the hydrophilic character of the molecules.

Experimental Section

The procedure of Allen, *et al.*,[10] was used to prepare the cyclic thioureas which were then desulfurized by the method of Mecke[11] to give the corresponding cyclic ureas (Table I). Absolute alcohol was used to extract the final product which gave better results than vacuum distillation.

TABLE I

Deriv of urea	%, yield	Bp (mm) or mp, °C Lit.	Obsd	Formula	Analyses[a]
N,N′-Ethylenethio-	81.3	197[b]	198–200		
N,N′-Trimethylene-thio-	88.4	207[c]	210–211.5	$C_4H_8N_2S$	C, H, N, S
N,N′-Tetramethyl-enethio-	73.5	178[d]	179–181		
N,N′-Ethylene-	70.3	131[e]	130–133	$C_3H_6N_2O$	
N,N′-Trimethylene-	72.7	266[f]	260	$C_4H_8N_2O$	
N,N′-Tetramethyl-ene-	66.3	168[d]	175–177	$C_5H_{10}N_2O$	C, H, N
N,N′-Dimethylethyl-enethio-	78.6	110–112[g]	110–113		
N,N′-Dimethyltri-methylenethio-	53.4		78.5–79.5	$C_5H_{10}N_2S$	C, H, N, S
N,N′-Dimethyl-tetramethylene-thio-	18.8		61–63	$C_6H_{12}N_2S$	C, H, N, S
N,N′-Dimethyl-ethylene	71.0	104–151	67–68 (2)	$C_4H_8N_2O$	C, H, N
N,N′-Dimethyltri-methylene-	63.5		84–85 (2)	$C_5H_{10}N_2O$	C, H, N
N,N′-Dimethyl-tetramethylene-	61.9		91–94 (6)	$C_6H_{12}N_2O$	C, H, N

[a] All analytical values were within ±0.5% of the calculated values. [b] F. K. Beilstein, "Handbuch der Organischen Chemie," Vol. 24, 1936, p 4. [c] Footnote *b*, p 5. [d] H. K. Hall, Jr., and A. K. Schneider, *J. Am. Chem. Soc.*, **80**, 6409 (1958). [e] Footnote *b*, p 2. [f] C. V. Stead, *Rept. Progr. Appl. Chem.*, **46**, 92 (1961).

The four new compounds were made as follows.

N,N′-Dimethyltrimethylenethiourea.—N,N′-Dimethyl-1,3-propanediamine was treated with CS_2 using the previous method[10] with a reflux period of 3 days.

N,N′-Dimethyltetramethylenethiourea.—To 6.5 g of N,N′-tetramethylenethiourea and 4.9 g of NaH dispersion (56.8%) under N_2, 250 ml of freshly distilled dioxane was added slowly with stirring. The reaction mixture was maintained between 55–60° for 3 hr, then cooled to room temperature, and the flow of N_2 was stopped. MeI (50 g) was added, and the same temperature was maintained for another 2 hr. The clear supernatant showed pH 7, and the precipitate of NaI was removed by filtration, then triturated and washed with DMF. The

(1) (a) From the Ph.D. thesis of E. J. Lien, 1966. (b) To whom inquiries concerning this work should be addressed.

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solvent was removed, the residue was dissolved in boiling H_2O, and the mineral oil was removed with decolorizing charcoal. The volume was reduced to 15 ml, and 25 ml of dioxane was added to precipitate NaI. Filtration, removal of dioxane, and distillation gave 1.5 g of crude product, yield 18.8%, bp 96–136° (3 mm). Repeated recrystallization from ether–heptane mixture gave the pure product.

N,N'-Dimethyltrimethyleneurea and N,N'-Dimethyltetramethyleneurea.—The same procedure was used for the N,N'-dimethylated cyclic ureas as was used for N,N'-dimethyltetramethylenethiourea except the cyclic ureas were used as starting material and a reflux period of 3 hr was used after addition of MeI. After NaI and dioxane were removed the mineral oil from the NaH separated upon cooling. Fractional distillation of the bottom layer gave the desired product.

The elementary analyses were done by the Microanalysis Laboratory, Department of Chemistry, University of California. The melting points were corrected. The dipole moments were measured with a WTW dipole meter Model DM01 using a DFL 2 cell. The method of Halverstadt and Kumler,[12] programmed for an IBM 1401 computer by Simpson,[13] was used to calculate the moments. The electronic polarizations were calculated from the electron group refractions given by Smyth.[14] Solute atomic polarizations were neglected. The standard errors in moments were calculated as before.[15] Ir spectra were measured on a Beckman IR8 spectrophotometer either in KBr or in 0.5–1.5% solution in CCl_4. The uv spectra were measured on a Cary recording spectrometer Model 11 in solution in heptane, EtOH, and H_2O, and the nmr spectra on a Varian A-60A spectrometer sometimes using a time-averaging computer (CAT) C-1024 The position of the peaks are with reference to that of TMS.

Since not much pharmacological "history" of these compounds has been reported in the literature, the "blind screening" method of Turner[16] was used. Groups of four Swiss Webster albino mice, two male and two female (25–27 g), were injected intraperitoneally with a series of logarithmic dosages, starting from 30 mg/kg, and the symptoms were observed continuously for 2 hr, then at intervals for 5 days. A 0.2% water solution was used for dosage equal to or below 100 mg/kg; 2% solution was used for dosage of 300 and 1000 mg/kg. For dosage higher than 1000 mg/kg, higher concentration and only two mice were used because of the limited amount of the compound available.

Results and Discussion

Table II gives the results of the dipole moment measurements in dioxane and in benzene and the difference between the results in dioxane and benzene and the difference between the moments of the S and O compounds.

TABLE II

Compd	Dipole moment (μ), D: Dioxane	Benzene	Diff
N,N'-Ethyleneurea	4.01 ± 0.02	2.94 ± 0.02	1.07
N,N'-Trimethyleneurea	4.67 ± 0.04		
N,N'-Tetramethyleneurea	4.43 ± 0.01	2.83 ± 0.02	1.60
N,N'-Ethylenethiourea	5.60 ± 0.02	4.51 ± 0.06	1.09
N,N'-Trimethylenethiourea	5.79 ± 0.05	4.69 ± 0.06	1.10
N,N'-Tetramethylenethiourea	5.36 ± 0.02	4.20 ± 0.02	1.16
N,N'-Dimethylethyleneurea	4.09 ± 0.01	4.05 ± 0.01	0.04
N,N'-Dimethyltrimethyleneurea	4.23 ± 0.01	4.17 ± 0.01	0.06
N,N'-Dimethyltetramethyleneurea	3.75 ± 0.02	3.76 ± 0.01	−0.01
N,N'-Dimethylethylenethiourea	5.32 ± 0.02	5.19 ± 0.01	0.13
N,N'-Dimethyltrimethylenethiourea	5.63 ± 0.02	5.48 ± 0.01	0.15
N,N'-Dimethyltetramethylenethiourea	5.29 ± 0.02	5.03 ± 0.01	0.26

Ring members	Dipole moment (μ), D: Dioxane S	Dioxane O	Dioxane Diff	Benzene S	Benzene O	Benzene Diff
Unsubstituted						
Five	5.60	4.01	1.59	4.51	2.94	1.57
Six	5.79	4.67	1.12	4.69		
Seven	5.36	4.43	0.93	4.20	2.83	1.37
Dimethyl						
Five	5.32	4.09	1.23	5.19	4.05	1.14
Six	5.63	4.23	1.40	5.48	4.17	1.31
Seven	5.29	3.75	1.54	5.03	3.76	1.27

The difference between the moments in dioxane and benzene are much larger, 1.07–1.60 D, for the nonmethylated compounds than for the dimethylated compounds, 0.01–0.26 D. The difference for the nonmethylated sulfur compounds are all close to 1.1 D (1.09–1.16), those for the dimethylated sulfur compounds close to 0.2 D (0.13–0.26 D), those for the dimethylated oxygen compounds close to 0 (−0.01 to 0.06), and those for the two nonmethylated oxygen compounds 1.07 and 1.62 D. The third nonmethylated oxygen compound could not be measured in benzene because of low solubility.

In seeking a reason for the large difference between the moments in dioxane and benzene for the nonmethylated compounds compared with the dimethylated compounds, the fact that the former can hydrogen bond and the latter cannot is pertinent. A possible explanation is that in benzene one is actually measuring a mixture of a monomer and a hydrogen-bonded dimer which has a lower moment, while in dioxane the dimers are broken up by the solvent. This explanation does not seem valid, however, because if it were so the dielectric constant–weight fraction plots would not be straight lines and pains were taken to have the solutions dilute enough so these plots were straight lines.

A more reasonable way of accounting for the observation is that the local dipoles of the dioxane can get closer to the dipoles in the nonmethylated compounds and increase the contributions of the forms with a separation of charge, thus giving rise to a higher observed moment. The local dipoles of dioxane are more effective in polarizing the nonmethylated compounds than for the dimethylated ones. The fact that the differences between the moments in dioxane and benzene are greater for the dimethyl sulfur compounds than for the dimethyl oxygen compounds lends support to this view because sulfur is inherently more polarizable than oxygen.

The cyclic sulfur compounds all have higher moments than the corresponding oxygen compounds, and the differences here are considerably greater, 0.93–1.59 D, than was the difference between the moments of urea and thiourea, $\Delta\mu = 0.33$ D.[17] The reason sulfur compounds of this type have higher moments than the corresponding oxygen compounds have been discussed previously,[18,19] and is due in the sulfur compounds to the

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labilization of the ground state due to "strain" in the thiocarbonyl group and stabilization of the activated state through acceptance of electrons in the 3d orbitals. These effects are enhanced in the cyclic compounds because of the assistance they give to flatness and this in effect is greatest for the five-, less for the six-, and still less for the seven-membered rings. The $\Delta\mu$ from S to O in dioxane for the five-, six-, and seven-membered rings are, in this order, namely, 1.59, 1.12, and 0.93 D.

The contribution of the dipolar structures to urea and thiourea was previously estimated at 20 and 30%.[17] The contribution of the dipolar form to the structure of N,N'-trimethylenethiourea can be calculated using Pauling's equation,[20] $Dn = D_1 - (D_1 - D_2)\{1.84(n - 1)^3 0.84n - 0.16\}$, and the X-ray crystallographic data[21] for the C=S and C–N bond distances in this molecule. The value of n, the bond number, comes out 1.3 for the C=S bond and 1.7 for the C–N bond thus indicating a 70% contribution from the resonating forms with a separation of charge. The large contribution of these forms is responsible for the observed bond distances in N,N'-trimethylenethiourea and the larger dipole moments of the sulfur compounds compared with the corresponding oxygen compounds.

The order of the difference between the moments of the sulfur and oxygen compound for the dimethylated compound is the reverse of that for the unsubstituted compounds, being 1.23, 1.40, and 1.54 D for the five-, six-, and seven-membered dimethylated ring compounds, respectively. The major reduction in moment on dimethylation occurs with the six- and seven-membered ring oxygen compounds and only small changes occur with the others. The smaller effect shown by the sulfur compounds is probably due to the fact that, although sulfur is larger and therefore more steric hindrance is expected, the lack of coplanarity may reduce the contribution of the dipolar forms less in case of the sulfur compounds than in case of the oxygen compounds since it has been shown that the sp–3d orbital bonding[22] is much less sensitive to the angle of rotation from coplanarity than is the 2p–2p π bonding present in the oxygen compounds. A slight increase in moment on dimethylation in the case of the five-membered ring oxygen compound is probably the result of the methyl groups stabilizing the forms with a separation of charge because of their ability to supply electrons and no steric hindrance is present that would prevent coplanarity because of the more favorable angles in the five-membered ring.

Ir Spectra.—The ratios of $\nu_{C=O}$ $\nu_{C=S}$ vary from 1.35 to 1.38 for the unsubstituted compounds and from 1.21 to 1.27 for the dimethylated compounds. The reason for this difference is undoubtedly the hydrogen bonding that is known to be present in the unsubstituted carbamoyl and thiocarbamoyl compounds[23] and not in the methylated ones. Since it is known that hydrogen bonding decreases the carbamoyl and thiocarbamoyl frequencies, the fact that the ratio of $\nu_{C=O}/\nu_{C=S}$ is larger for the unsubstituted compounds suggests that the hydrogen bonding decreases the thiocarbamoyl frequency more than it does the carbamoyl frequency, in spite of the fact that the hydrogen bond is stronger in the C=O than in the C=S compounds. The C=S bond is weaker, 128 kcal/mole, than the C=O bond (166–179 kcal/mole) and any constraint would have much more effect on the C=S than on the C=O bond. If this effect is greater than the effect of the increased strength of the hydrogen bond to the C=O, then the ratio will be larger in the unsubstituted compounds as observed.

We were not able to get the N,N'-dimethylated cyclic ureas free of an O–H band in the 3200–3600-cm^{-1} region. Even a carefully dried freshly distilled sample between NaCl plates gave a weak band in this region and on exposure to the air for 15 min this band grew in size to equal that for the C–H band. This hygroscopicity is evidence of the great tendency of the oxygen in these compounds to form hydrogen bonds with water.

Uv Spectra.—The cyclic ureas and dimethylureas have no absorption peak between 225–400 mμ. Cyclic thioureas were found by others[24] to have a λ_{max} that increased from 238 to 252 mμ as the ring size increased from 5 to 7 but on further increasing the ring size to 11 the λ_{max} stayed in the range 234–250.

Limited data on the five-membered ring compound have been published.[25] All three compounds have two strong bands in heptane and a shoulder at long wavelength. These bands appear to be similar to those found in tetramethylthiourea[25–27] at 220, 262, and 330 mμ and probably arise from similar transitions.

Nmr Spectra.—All of the protons on the sulfur compounds appear at a lower field than those on the corresponding oxygen compounds. This is explainable in terms of sulfur having a higher electron density than oxygen in these compounds, thus causing the neighboring methylene and N-methyl groups to be more electron deficient and their signals to appear at lower fields.[28] The N–H bands are broad due in part to coupling with nitrogen.[29] The sharpness of the methylene peaks of the five-membered ring compounds are indicative of methylene protons being equivalent and of the molecules being flat. The evidence from nmr that the sulfur has a higher electron density is in keeping with the findings that the sulfur compounds had higher dipole moments and greater contributions from forms with a separation of charge.

Respiratory and Other CNS Effects.—Respiratory stimulation was observed for all of the compounds studied except for ethyleneurea and trimethyleneurea, which were inactive as respiratory stimulants at a dose as high as 4 g/kg. A component of sedation was observed for every compound at different dosage levels except N,N'-dimethyltetramethylenethiourea, which showed transient stimulation, then sedation at 30 mg/kg, but only stimulation was observed at 75 mg/kg.

Clonic convulsions were observed for tetramethyleneurea (4 g/kg), N,N'-dimethyltetramethyleneurea

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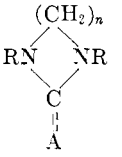
TABLE III

MOLECULAR WEIGHT, DIPOLE MOMENT (μ), MEDIAN EFFECTIVE DOSE (ED_{50}), AND MEDIAN LETHAL DOSE (LD_{50}) OF THE CYCLIC UREAS, AND THE N,N′-DIMETHYLATED COMPOUNDS



Compd	Mol wt	μ, D	ED_{50} mg/kg	ED_{50} (mmoles/kg)	LD_{50} mg/kg	LD_{50} (mmoles/kg)
R = H, A = O						
n = 2	86.1	4.01 ± 0.02[a]	...	...	>4000	(>46.5)
n = 3	100.1	4.67 ± 0.04	...	...	>4000	(>40.0)
n = 4	114.1	4.43 ± 0.01	2760	(24.2 ± 1.64[b])	2840	(24.9 ± 1.09[a])
R = H, A = S						
n = 2	102.2	5.60 ± 0.02	605	(14.2 ± 0.78)	>2000	(>19.6)
n = 3	116.2	5.79 ± 0.05	900 (extrapolated)	(7.75 ± 0.28)	560	(4.8 ± 0.25)
n = 4	130.2	5.36 ± 0.02	530 (extrapolated)	(4.1 ± 0.37)	215	(1.7 ± 0.11)
R = CH_3, A = O						
n = 2	114.2	4.09 ± 0.01	1300	(11.4 ± 1.42)	2840	(24.9 ± 1.09)
n = 3	128.2	4.23 ± 0.01	900	(7.0 ± 1.38)	1300	(10.1 ± 0.47)
n = 4	142.2	3.75 ± 0.02	3000 (extrapolated)	(21.1 ± 11.5)	700	(4.9 ± 0.36)
R = CH_3, A = S						
n = 2	130.2	5.32 ± 0.02	30.5	(0.23 ± 0.01)	175	(1.3 ± 0.06)
n = 3	144.2	5.56 ± 0.02	10	(0.07 ± 0.002)	118	(0.8 ± 0.03)
n = 4	158.3	5.29 ± 0.02	32	(0.20 ± 0.003)	82	(0.5 ± 0.01)

[a] Standard error. [b] One standard deviation.

(1 g/kg), and all of the thiourea derivatives except ethylenethiourea. The dosage for the thioureas causing convulsion was 1 g/kg for trimethylenethiourea, 300 mg/kg for tetramethylenethiourea and N,N′-dimethylethylenethiourea, 100 mg/kg for N,N′-dimethyltrimethylenethiourea, and 75 mg/kg for N,N′-dimethyltetramethylenethiourea, respectively.

Ataxia was observed for ethylenethiourea (2 g/kg) and N,N′-dimethylethyleneurea (2 g/kg). Initial stimulation of respiration followed by progressive depression of respiration, diaphragmatic respiration, and finally asphyxia were observed for N,N′-dimethyltrimethyleneurea (2 g/kg).

The median effective dose (ED_{50}), which was arbitrarily defined as the dose required to increase the respiration rate by 50%, the median lethal dose (LD_{50}), the dipole moment, and the molecular weight are summarized in Table III. The ED_{50} and LD_{50} were obtained by the graphic calculation of Miller and Tainter.[30]

Among these compounds, N,N′-dimethyltrimethylenethiourea is the most potent respiratory stimulant; it increased the respiration rate by 50% at 10 mg/kg (0.07 mmole/kg); its LD_{50}/ED_{50} is 11.5. N,N′-Dimethyltetramethylenethiourea is the most potent convulsant with an LD_{50} of 79 mg/kg (0.5 mmole/kg). This compound is more toxic than pentylenetetrazole which has an LD_{50} of 92 mg/kg (0.67 mmole/kg) in mice by intraperitoneal injection.[31]

Analeptic Action.—Since N,N′-dimethyltrimethylenethiourea was the most potent respiratory stimulant in the series studied, it was chosen for further study against the CNS depression of barbiturate. Two groups of 12 Swiss Webster mice (both sexes, weighing 25–27 g) were injected with sodium pentobarbital (60 mg/kg) intraperitoneally.[32] To one group, 30 mg/kg of N,N′-dimethyltrimethylenethiourea was given by the same route 10 min after the injection of sodium pentobarbital. The respiration rate counted at 20 min after the injection of pentobarbital and the sleeping time, which was defined as the interval between the loss and the spontaneous return of the righting reflex,[33] are summarized in Table IV.

TABLE IV

ANALEPTIC EFFECT OF N,N′-DIMETHYLTRIMETHYLENETHIOUREA IN MICE PRETREATED WITH SODIUM PENTOBARBITAL

Group	Drug(s) injected (mg/kg)	Resp rate, times/min	Sleeping time, min
A	Sodium pentobarbital (60)	89 ± 10[a]	54 ± 14[a]
B	Sodium pentobarbital (60) + N,N′-dimethyltrimethylenethiourea (30)	135 ± 32, ↑ 52%	39 ± 10, ↓ 28%

[a] 95% confidence limits using Student's t distribution.

The data show that in mice pretreated with pentobarbital (60 mg/kg) the respiration rate was increased about 52% ($P < 0.01$), and the sleeping time was shortened about 28% ($P < 0.10$) by N,N′-dimethyltrimethylenethiourea (30 mg/kg). This compound failed to antagonize the pentobarbital-caused CNS depression in Sprague–Dawley rats or in guinea pigs and the respiratory depression in these animals caused by morphine.

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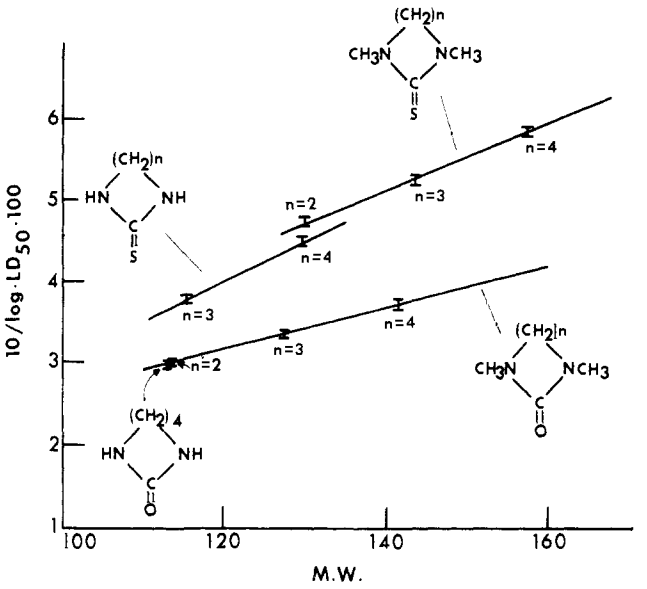

Figure 1.—Plot of 10/log [LD_{50} (mmoles/kg) × 10^2] *vs.* the molecular weight. I = 10/log [LD_{50} (mmoles/kg) ± 1 standard deviation × 10^2].

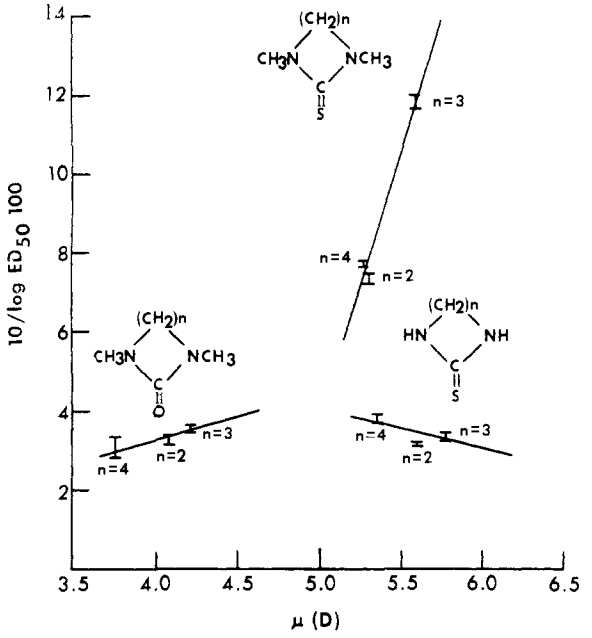

Figure 2.—Plot of 10/log [ED_{50} (mmoles/kg) × 10^2] *vs.* the dipole moment. I = 10/log [LD_{50} (mmoles/kg) ± 1 standard deviation × 10^2].

Structure–Activity Relationship.—Among this wide spectrum of activity some correlations with the structure can be made. First of all, in a homologous series the acute lethal toxicity was found to be related to the molecular weight. The plots of 10/log [LD_{50} (mmoles/kg) × 10^2] *vs.* the molecular weight were straight lines for three series (see Figure 1). This can be explained since in a homologous series of compounds the lipid/water partition coefficient increases as the molecular weight increases, and this appears to be the determining factor for the acute lethal toxicity either due to CNS depression or stimulation in the series of compounds we studied.

Addition of one methylene group in the ring increases the toxicity two- to threefold. N,N′-Dimethylation increases the toxicity four- to sixfold. The sulfur compounds are about 11 to 25 times more toxic than the corresponding oxygen compounds.

Second, for the N,N′-dimethylated compounds, the respiratory stimulation activity was found to be related to the dipole moment of the molecule, the best-fitted line of the plots of 10/log[ED_{50} (mmoles/kg) × 10^2] *vs.* dipole moment μ had a positive sign for the slope. For the nonmethylated sulfur compounds, the sign for the slope of the line was negative (see Figure 2).

For the N,N′-dimethylated compounds the sedation observed may possibly be due to the demethylated products, but further study is needed to establish whether this is true.

The lack of activity for ethyleneurea and trimethyleneurea can be attributed to their low lipid/water partition coefficients, since their dipole moments could not be measured or barely measured in benzene and dioxane (more waterlike solvent) had to be used.

It is known that nonalkylated amides are less soluble in water than the mono- and dialkylated amides because they form so many and such strong hydrogen bonds among themselves that the interaction with the water when placed in it is not strong enough to break up the crystal. A nonpolar solvent would have less effect than water. The dialkylamides do not have any hydrogens which can form hydrogen bonds so the intermolecular forces are weak and only oxygen and nitrogen atoms are available to hydrogen bond with the hydrogen of water. The fact that the dialkylamides have a much higher water solubility than the nonalkylated amides does not mean that nonalkylated amides will not have a lower lipid/water partition coefficient because the solubility in lipid will certainly be much less for the nonalkylated amides than their solubility in water. The fact that water solubility goes dialkyl- > monoalkyl- > nonalkylamides does not mean that their lipid/water partition coefficients are the reverse, but their lipid/water partition coefficients could very well be and are in fact likely to be in the ratio dialkyl > monoalkyl > nonalkyl. One may convince himself by comparing the log P values (P = the partition coefficient in 1-octanol/water) of N-phenyl-N′-dimethylurea (0.98) and N-phenyl-N′-methylurea (0.42).[34]

If we examine the plots of 10/log ED_{50} *vs.* μ, the different signs for the slopes of the plots suggest that different types of binding with the receptors may be involved. Conceivably, dipole–dipole interaction is operating for the dimethylated compounds, and hydrogen bonding is operating for the nonmethylated compounds. A higher dipole moment of a molecule would certainly lead to a better dipole–dipole interaction with the receptor. Careful examination of the plots showed that all of the five-membered rings fell below the line. This may be due to inadequate lipid/water partition to allow them to get to the site of action and/or due to inadequate hydrophobic interaction with the receptor.

For hydrogen bonding, a higher dipole moment would cause the >NH hydrogen to be more electron deficient, and the >C=S grouping to have a higher

(34) Professor C. Hansch, private communication.

electron density; these two effects would provide a stronger hydrogen bond. Since hydrogen bonding tends to stabilize the conformation of a receptor, it would then compensate the effect caused by the hydrophobic interaction of the alkylene group; consequently, less stimulation would be observed.

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Stereochemical Studies on Medicinal Agents. VI.[1] Bicyclic Bases.[2] Synthesis and Pharmacology of Epimeric Bridged Analogs of Meperidine, 2-Methyl-5-phenyl-5-carbethoxy-2-azabicyclo[2.2.1]heptane[3]

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Epimeric 2-methyl-5-phenyl-5-carbethoxy-2-azabicyclo[2.2.1]heptanes were elaborated from N,O,O-tritosylhydroxyprolinol, and the stereochemistry was determined from physicochemical studies. The benzoquinone-induced writhing test indicated the *endo*-phenyl epimer to be twice as potent as meperidine and six times more potent than the *exo* isomer. In terms of brain concentrations, however, the *endo*–*exo* potency ratio is 3.7. Evidence is presented which quantitatively relates difference in brain levels between the epimers to their partition coefficients. The large difference in geometry between the *exo* and *endo* epimers suggests that their comparable activities are due to differing modes of interaction with analgetic receptors.

The importance of steric factors on the action of strong analgetics has received considerable attention.[4] Most of the research in this area has been focused on the relationship between absolute stereochemistry of conformationally mobile compounds and analgetic activity. While it is generally believed that differences in potencies which are observed with enantiomeric analgetics are a consequence of events at the receptor level, the role of conformational factors in influencing analgetic activity has remained controversial.[4,5]

The recognition[6] of the structural relationship between morphine and meperidine led to the postulate[7] that the axial-phenyl conformer of meperidine would be expected to "fit" the receptor surface better than the equatorial conformer. This conclusion was based on the known conformation[8] of the phenylpiperidine moiety in morphine, which contains an aromatic group that is held rigidly in an axial position relative to the piperidine ring.

Evidence consistent with this view[7] was obtained from the stereostructure–activity relationship of prodine diastereomers. As it was known[9] that β-prodine is more potent than the α isomer, it was concluded that this was because the conformational equilibrium for the former analgetic favors more of the axial species than the latter.

On the other hand, the work of Ziering, *et al.*,[9] suggested that the steric relationship of the phenyl group with respect to the piperidine ring is of minimal importance. This was supported by the fact that the 3-ethyl analogs show a reversal in the potency ratio when compared to the prodines. Since modification of the 3 substituent from methyl to ethyl to allyl should cause only minor changes in the conformational equilibria, this suggests that other overriding factors are responsible for the differences in potency between *cis* and *trans* racemates in the prodine series. This is supported further by a recent study[10] on the brain concentrations of α- and β-prodine in rats. It has been found that higher brain levels of β-prodine fully account for the observed difference in potency[9,11] between the α and β isomers.

Analysis of the stereostructure–activity relationship of other conformationally mobile, prodine-type[12–14] analgetics also suggested[4] that both equatorial- and axial-phenyl conformations have the ability to produce comparable analgetic activity.

The question of the identity of a favorable pharmacophoric conformation for the piperidine ring in 4-phenylpiperidine analgetics also remains unanswered. The work of Bell and Archer[15,16] on the analgetically active tropane analog (**1**) of meperidine suggests that this compound may exist primarily in the boat conformation.

Although the above analyses suggest that the conformational requirements of the aromatic group in 4-

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