

TABLE II
SUMMARY OF CALCULATIONS

Compound	μ free rotation	μ maximum	μ minimum
IVb	3.03	3.40	2.58
IVd	2.07	2.84	0.77
i	2.07	2.84	0.77
ii	2.41	2.95	1.94

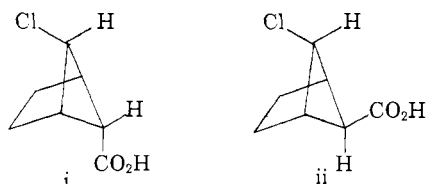
result which coincides with the steric course recently determined for the analogous ring contraction of diazocamphor (V).¹³

Acknowledgments.—The support of this work by the Alfred P. Sloan Foundation and the National Science Foundation is acknowledged with pleasure.

Experimental

The dielectric constants were measured with the Dipolemeter DMOI made by the Wissenschaftlich-Technische Werkstätten. The dipole moments were calculated using the equation and method of Halverstadt and Kumler.¹⁴

and the *endo* isomer a value of 2.41 D. These data, along with the relevant μ_{\max} and μ_{\min} calculations, are summarized in Table II.



(13) J. Meinwald, A. Lewis and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 2649 (1960); see also ref. 2.

$$p_{20} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta) \frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{20} = p_{20} M$$

$$\mu = 0.01281 \sqrt{(P_{20} - P_{E_2}) T}$$

The plots of ϵ_{12} versus ω_2 and v_{12} versus ω_2 were straight lines within the limits of experimental error. The value of ϵ_1 and v_1 were calculated by the method of least squares. The standard error in the dipole moments was calculated from the equation $\delta\mu = 0.004 (M/\mu)\delta\alpha^{15}$ and the standard error in α from the equation¹⁶

$$\delta\alpha = \pm \left\{ \frac{n}{n-2} \left[\frac{\Sigma(\epsilon' - \epsilon_{12})^2}{n\Sigma\omega_2^2 - (\Sigma\omega_2)^2} \right] \right\}^{1/2}$$

where n is the number of solutions taken and ϵ' is the value from the best straight line. Errors from the scatter of the points for specific volume do not need to be considered since large errors in β produce only negligible errors in the dipole moments.¹⁷

The P_{E_2} values are from the molar refractions as calculated from the electron group refractions.

Camphorquinone, m.p. 198°, was made in the usual way by selenium dioxide oxidation of *d*-camphor.¹⁸

7-Chloronorcaphorquinone, m.p. 111.5–112°, was made in an analogous way by selenium dioxide oxidation of *syn*-7-chlorobicyclo[2.2.1]heptan-2-one.⁴

(14) I. F. Halverstadt and W. D. Kumler, *ibid.*, **64**, 2988 (1942).

(15) E. W. Randall and Rodger Raab, private communication.

(16) C. G. Le Fevre and R. J. W. Le Fevre, *J. Chem. Soc.*, 4041 (1953).

(17) K. B. Everard, R. A. W. Hill and L. E. Sutton, *Trans. Faraday Soc.*, **46**, 417 (1950).

(18) Elsevier's "Encyclopedia of Organic Chemistry," Elsevier Publishing Co., Inc., New York, N. Y., 1948, Vol. 12 A, p. 888.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO MEDICAL CENTER, SAN FRANCISCO, CALIF.]

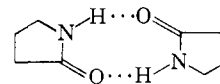
The Dipole Moment and Structure of Five- and Six-membered Lactams

BY CALVIN M. LEE AND W. D. KUMLER

RECEIVED JULY 1, 1961

The dipole moment of 2-pyrrolidone (I), 3.79 D., is like that of a straight chain amide. The addition of a methyl group one carbon removed or on the nitrogen increases the moment (*ca.* 0.3 D.) by stabilizing the plus charge on the nitrogen in the ionic form. Spiro-(cyclohexane-1,5'-pyrrolidone) (IV) has an appreciably higher moment, 4.56 D., than I. The addition of a carbonyl group to the nitrogen of a 5- or 6-membered-lactam (N-acetyl) decreases the moment, indicating that the compound is in the *cis-trans* conformation where the carbonyl groups are farthest apart. The decrease in moment in the 6-membered ring lactam, 0.6 D., is less than the decrease in moment in the 5-membered ring lactam, 0.8 D., as the angle between the carbonyl groups in the 6-membered ring compound is less than in the 5-membered ring compound. The addition of a carbonyl group in the lactam ring forms an imide which must be in the *cis-cis* conformation. The decrease in the dipole moment in the 6-membered rings is about 1.3 D. while the decrease in the 5-membered ring is about 2.4 D. The greater decrease in the 5-membered rings is due to the greater angle between the two ring carbonyls and the opposition of the N⁺O⁻ dipoles to the carbonyl resultant in the 5-membered ring. The substitution of a methyl group for hydrogen on lactams or imides raises the dipole moment by about 0.15 D.

The dipole moment of simple amides in dioxane at 30° is in the range of 3.7–3.9 D.¹ The dipole moment of pyrrolidone (I) in dioxane at 30°, 3.79 D is like that of the straight chain amides. Fischer² reported a value of 3.7 D. in benzene for I and Huisgen and Waltz³ give a value of 3.55 D. in benzene at 25°. In 1933, Devoto⁴ calculated a value of 2.3 D. for pyrrolidone in benzene; this low moment has been attributed to the formation of a dimer of low dipole moment²



The dipole moment of the cyclic dimer of pyrrolidone is said³ to have a value of 2.2 D. in benzene at 25°.

One cannot make a model of pyrrolidone with Stuart-Briegleb models as the compression of angles from 120° to 108° is too great. It is peculiar then that the moment of the compound is like a straight chain amide. The 5-membered ring would be expected to have more *s*-character in the exocyclic bonds and more *p*-character in the ring bonds.⁵

(1) W. D. Kumler and C. W. Porter, *J. Am. Chem. Soc.*, **56**, 2549 (1934).

(2) E. Fischer, *J. Chem. Soc.*, 1382 (1955).

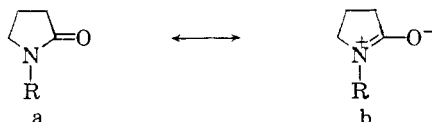
(3) R. Huisgen and H. Waltz, *Chem. Ber.*, **89**, 2616 (1953).

(4) G. Devoto, *Gazz. chim. Ital.*, **63**, 495 (1933).

(5) C. M. Lee and W. D. Kumler, submitted for publication.

It might be expected that the normal carbonyl resonance $\text{C}=\text{O} \leftrightarrow \text{C}^+-\text{O}^-$ would be stabilized by the greater *s*-character in the exocyclic bond and raise the dipole moment. However, the ring resonance is destabilized by the smaller amount of *s*-character in the ring bonds which would cause a lower moment. Evidently the effects cancel.

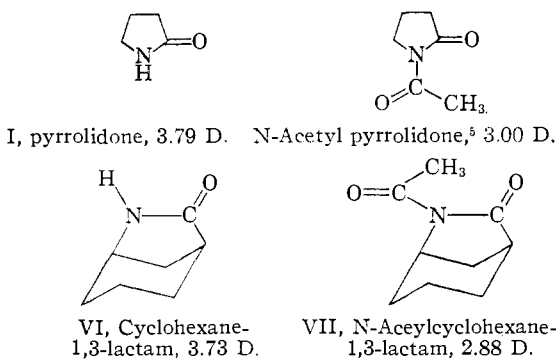
One might expect a methyl group on the nitrogen or one carbon removed to increase the dipole moment of pyrrolidone by stabilizing the positive charge on resonance form b. Both the 5-methyl-



(II), and 5,5-dimethylpyrrolidone (III) have higher moments (*ca.* 0.3 D.) than pyrrolidone itself. The fusion of a pyrrolidone ring to the axial and equatorial bonds of cyclohexane does not affect the pyrrolidone ring appreciably, as there is only a slight distortion of ring angles from 108° to $109^\circ 28'$. The inductive effect of the cyclohexane ring is greater than that of two methyl groups as the moment of compound IV is 0.5 D. higher than that of 5,5-dimethylpyrrolidone (III).

N-Methylpyrrolidone (V) has a moment of 4.06 D., which is 0.27 D. higher than pyrrolidone (I). Fischer² reported a value of 4.09 D. for V in benzene at 30° .

COMPARISON OF DIPOLE MOMENTS OF PYRROLIDONES AND N-ACETYLPIRROLIDONES

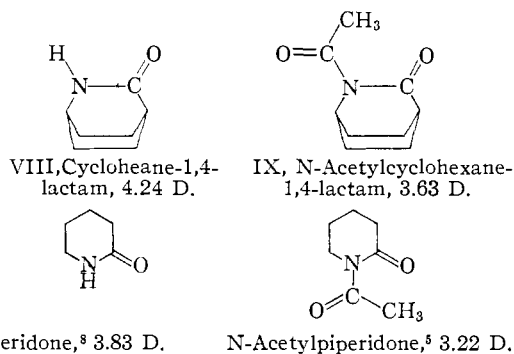


When an amide group is fused to the diaxial positions of the chair form of cyclohexane there is some distortion of ring angles; the angle between the $\text{C}=\text{O}$ and $\text{N}-\text{H}$ is increased slightly so the

moment of the 5-membered ring lactam formed is a little less than pyrrolidone, 3.73 D., compared with 3.79 D. for I. N-Acetylpyrrolidone has a moment of 3.00 D. which is 0.79 D. less than pyrrolidone. This low moment is due to the presence of most of the molecules of the compound in the *cis-trans* conformation where the carbonyl groups are farthest apart. The addition of an acetyl group to cyclohexane-1,3-lactam would be predicted to have the same effect; indeed, the dipole moment is lowered by about the same amount, 0.85 D. This low moment indicates that imide

VII is also in the *cis-trans* conformation for the *cis-cis* conformation would be expected to have a moment higher than pyrrolidone itself.

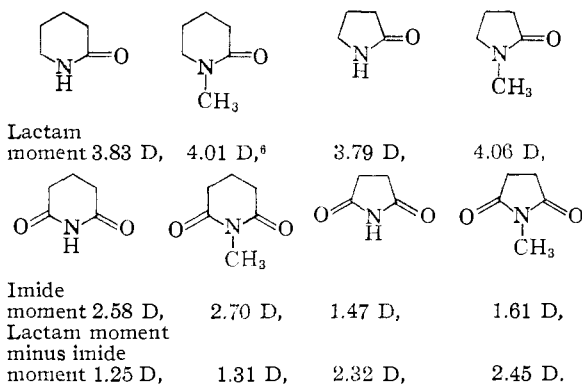
THE DIPOLE MOMENTS OF PIPERIDONES AND N-ACETYLPIPERIDONES



In contrast to the 1,3-lactams, the formation of a 6-membered ring lactam as in cyclohexane-1,4-lactam causes distortion of the lactam ring. Attached to the "bowsplits" of the boat form of cyclohexane the angle between the $\text{N}-\text{H}$ and the $\text{C}=\text{O}$ dipoles decreases slightly so that the mo-

ment of cyclohexane-1,4-lactam, 4.24 D., is 0.41 D. higher than piperidone. N-Acetyl piperidone is 0.61 less than piperidone itself; it is thus in the favored *cis-trans* conformation. The addition of an acetyl group to cyclohexane-1,4-lactam also decreases the dipole moment by 0.61 D. The addition of an acetyl group to a 6-membered ring lactam decreases the dipole moment by a smaller amount (0.6 D. compared with 0.8 D.) than the addition to a 5-membered ring lactam. The reason for this is that the angle between the two carbonyl groups in the 5-membered ring is greater than in the 6-membered ring, and since the angle is greater than 120° , the additional carbonyl causes a reduction of the resultant moment which is greater in the 5-membered ring compound.

Comparison of Dipole Moments of Lactams and Imides Effect of N-Methyl Group on Dipole Moments.—It seems appropriate here to compare the dipole moments of lactams with those of imides. The effect of an N-methyl group on the dipole moment can also be determined.



(6) J. Syrkin and E. A. Shott-Lvova, *Acta Physicochim. URSS*, **20**, 397 (1945).

TABLE I

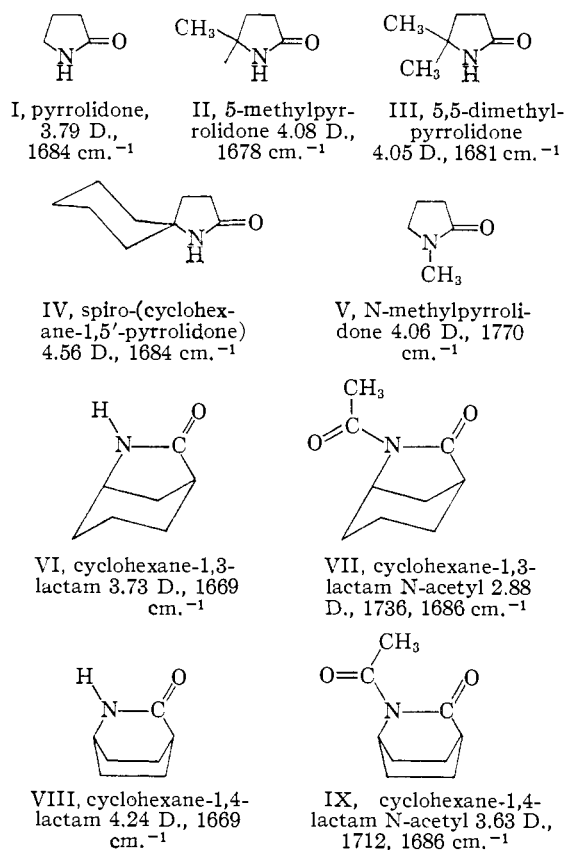
DIPOLE MOMENTS OF PYRROLIDONES AND PIPERIDONES IN DIOXANE AT 30°

	ω_2	ϵ_{12}	ν_{12}
I, Pyrrolidone	0.00	2.20756	0.97395
	.0003979	2.21706	.97395
μ 3.79 \pm 0.02 D.	.0010982	2.22981	.97395
	.0018179	2.24702	.97395
	.0044715	2.30018	.97395
	.0059181	2.32911	.97395
Mol. wt. 85.11			
ϵ_1 2.208337	ν_1 0.97395	P_{20} 311.44	
α 20.48489	β 0.00	P_E 22.16	calcd.
II, 5-Methylpyrrolidone	0.00	2.19986
	.0009372	2.21912	0.97828
μ 4.08 \pm 0.04 D.	.0015375	2.23176	.97827
	.0020990	2.24196	.97824
	.0024450	2.24972	.97822
	.0029351	2.25957	.97822
Mol. wt. 99.14			
ϵ_1 2.20003	ν_1 0.97832	P_{20} 360.96	
α 20.2716	β -0.03953	P_E 26.68	calcd.
III, 5,5-Dimethylpyrrolidone	0.0008207	2.21712	0.97832
	.0018956	2.23568	.97833
μ 4.05 \pm 0.03 D.	.0021512	2.24091	.97823
	.0030086	2.25591	.97837
	.0034088	2.26201	.97839
Mol. wt. 113.16			
ϵ_1 2.20285	ν_1 0.97828	P_{20} 361.43	
α 17.4890	β +0.02855	P_E 31.33	calcd.
IV, Spiro-(cyclohexane-1,5'-pyrrolidone)	0.00	2.19968	0.97391
	.0007459	2.21149	.97366
	.0018157	2.22264	.97337
μ 4.56 \pm 0.04 D.	.0022856	2.23461	.97328
	.0028301	2.24368	.97318
	.0031705	2.24873	.97309
Mol. wt. 167.10			
ϵ_1 2.19951	ν_1 0.97387	P_{20} 461.62	
α 15.43170	β -0.25244	P_E 43.34	calcd.
V, N-methylpyrrolidone	0.00	2.20143	0.97833
	.0015128	2.22950	.97827
	.0020145	2.23917	.97831
μ 4.06 \pm 0.03 D.	.0021383	2.24710	.97823
	.0029667	2.25843	.97823
	.0033808	2.26732	.97820
Mol. wt. 99.13			
ϵ_1 2.20074	ν_1 0.97834	P_{20} 347.51	
α 19.4603	β -0.03769	P_E 16.89	calcd.
VI, Cyclohexane-1,3-lactam	0.00	2.20567	0.97422
	.0009078	2.21783	.97407
	.0012920	2.22296	.97397
μ 3.73 \pm 0.02 D.	.0021798	2.23520	.97377
	.0025419	2.24085	.97367
	.0037001	2.25635	.97357
Mol. wt. 125.17			
ϵ_1 2.20544	ν_1 0.97421	P_{20} 312.95	
α 13.76538	β -0.18790	P_E 34.05	calcd.
VII, N-acetylcyclohexane-1,3-lactam	0.00	2.19925	0.97337
	.0011795	2.20961	.97337
	.0019459	2.21449	.97337
μ 3.63 \pm 0.05 D.	.0028752	2.22279	.97337
	.0033077	2.22664	.97337
	.0046748	2.23957	.97337
Mol. wt. 181.21			
ϵ_1 2.21989	ν_1 0.97337	P_{20} 306.10	
α 8.52085	β 0.00	P_E 4.19	calcd.
VIII, Cyclohexane-1,4-lactam	0.00	2.19771	0.97427
	.0015304	2.22348	.97407
	.0019234	2.23289	.97392
μ 4.24 \pm 0.05 D.	.0028839	2.24719	.97377
	.0034361	2.25789	.97367
	.0042267	2.27287	.97347

ϵ_1 2.19744	ν_1 0.97430	P_{20} 395.01
α 17.67219	β -0.18947	P_E 34.05
VIII, N-acetylcyclohexane-1,4-lactam	0.00	2.20987
	.0020609	2.22065
	.0027630	2.22485
μ 2.88 \pm 0.02 D.	.0043163	2.23358
	.0053979	2.23897
	.0064278	2.24505
Mol. wt. 181.21		
ϵ_1 2.20970	ν_1 0.97392	P_{20} 209.15
α 5.47518	β -0.10111	P_E 41.94

When the carbonyl group is inserted in the lactam ring, the dipole moment of the imide formed is lower than that of the original lactam. This decrease is caused by the opposition of the new carbonyl dipole to the lactam dipole. In the two cases involving 6-membered rings, the decrease is about 1.3 D.; the decrease in the 5-membered rings is almost double that or 2.4 D. As previously explained, the greater decrease in the moment of the 5-membered ring compounds is due to the greater angle between the carbonyl groups and the opposition of the N⁺O⁻ dipoles to the carbonyl resultant in the 5-membered ring.

Fig. 1.—The dipole moments of pyrrolidones and piperidones in dioxane at 30°, and infrared carbonyl frequency.



While Fischer² suggested that an N-methyl group decreased the dipole moment of a lactam, the four sets of data here show that the N-methyl group causes an increase in the moment of about 0.15 D.

Infrared and Ultraviolet Spectra.—The infrared carbonyl frequency of pyrrolidones I–V is 1678–1684 cm.⁻¹ (Fig. 1). Parsons⁷ has discussed the

(7) A. E. Parsons, *J. Mol. Spec.*, **6**, 201 (1961).

vibration spectra of 2-pyrrolidone (I). The carbonyl frequency of the two lactams fused to cyclohexane, VI, VIII, are both 1669 cm.^{-1} . The 5-membered lactam N-acetylcyclohexane-1,3-lactam (VII) has two sharp bands at 1736 and 1686 cm.^{-1} . The 6-membered ring N-acetylcyclohexane-1,4-lactam also has two sharp bands, one at 1712 and the other at 1686 cm.^{-1} . The two bands in each of the above two cases are of equal intensity. Presumably the band at 1686 is the normal ring lactam carbonyl (1678 – 1684 cm.^{-1} for I–V) while the band at higher frequency is the acetyl carbonyl band. N-Acetylpyrrolidone⁵ has two bands, one at 1730 cm.^{-1} and the other at 1686 cm.^{-1} . However, N-acetylpiperidone shows only one band at 1686 cm.^{-1} .

None of the lactams except N-methylpyrrolidone (V) show any ultraviolet absorption band above $200\text{ m}\mu$; there appears to be a band of high extinction just below $200\text{ m}\mu$ for the lactams which is the limit on the Cary model 11. N-Methylsuccinimide (VI) has a band at $202\text{ m}\mu$ with a molar extinction coefficient of about 5000. The 5-membered N-acetyl lactam (VII) has a peak at $217\text{ m}\mu$ with an extinction of 8700 while the 6-membered N-acetyl lactam (IX) has a peak at $218\text{ m}\mu$ molar

extinction coefficient of about 10,100. While it is true that the greater the dipole moment the lower the extinction, there is no parallel between the slopes of the plot of the maximum extinction and the dipole moment as reported for N-acetyl and N-benzoyl lactams.⁵ The fact that the 5-membered ring VII is attached to the chair form of cyclohexane, while the 6-membered ring IX is attached to the boat form of cyclohexane alters the dipole moment appreciably. N-Acetylpyrrolidone has a peak at $216\text{ m}\mu$ with extinction coefficient of 11,300, while N-acetylpiperidone has a peak at $218\text{ m}\mu$ with extinction coefficient of 8900.

Experimental

All dipole moments were measured in dioxane at 30° and calculations made using the equation and method of Halverstadt and Kumler.⁸

We wish to thank Dr. H. K. Hall, Jr., of du Pont for providing the compounds.⁹

All spectrographic measurements were made by Mr. M. K. Hrenoff of the Spectrographic Laboratory of the School of Pharmacy. Infrared spectra were run on Perkin-Elmer model 21 and ultraviolet spectra on Cary model 11.

(8) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2933 (1942).

(9) H. K. Hall, Jr., *ibid.*, **80**, 6404 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO MEDICAL CENTER, SAN FRANCISCO, CALIF.]

The Dipole Moment and Structure of the Carbamate Group

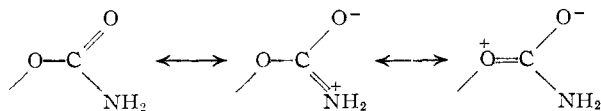
BY CALVIN M. LEE AND W. D. KUMLER

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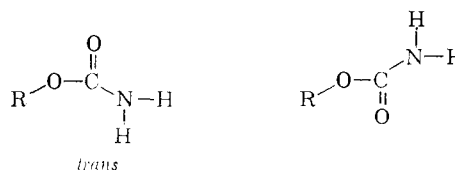
The carbamate group, $\text{O}=\text{C}-\text{N}<$, can theoretically be in two conformations, the *cis* and the *trans* (position of the carbonyl group with respect to the R group) (Fig. 1). In cyclic carbamates of ring size five to seven only the *trans* conformation is permitted. The dipole moments of the free carbamates ethyl carbamate (I) and emylcalmate (II) are 2.59 and 2.64 D., resp. The moments of the five- and six-membered cyclic carbamates III and IV are 5.07 and 5.10 D., resp. Comparison of these experimental moments with theoretical moments indicates that the free carbamate group takes up the *cis* conformation while the cyclic carbamates of low ring size are in the *trans* conformation. Fusion of the carbamate group to the 1,3- and 1,4-position of cyclohexane (V, VI) show a slightly increased moment (0.6 D.) over the cyclic carbamates; an explanation in terms of rehybridization of ring bonds is offered. The low dipole moment of N-acetyloxazolidone (VII), 2.81 D., indicates that it is in the *cis-trans* conformation where the carbonyl groups are farthest apart. Low dipole moments (1.7 D.), examination of models, infrared and ultraviolet spectra of some oxazolidine 2,4-diones VIII and IX all indicate that there is only a very small amount of resonance in these compounds as would be predicted.

Introduction

The carbamate group, $\text{O}=\text{C}-\text{NH}_2$, has increasingly appeared in many drug classes such as hypnotics, muscle relaxants, antiepileptics and anticancer agents. It is flat because of the resonance and there are two possible conformations,



cis and *trans*, depending on the position of the carbonyl group with respect to the R group. Either the *cis* or *trans* conformations might be expected in free carbamates while only the *trans* conformation would be expected in five-, six- and seven-



membered cyclic carbamates. The dipole moments of free and cyclic carbamates and related compounds were measured to determine which conformations are present.

Results and Discussion

Figure 2 gives the dipole moments in dioxane at 30° for these compounds. Free carbamates have a much lower moment than cyclic carbamates (compare I–IV).

Both urethan (I), a hypnotic and anticancer agent, and emylcalmate (II), a "tranquilizing and