lized from methanol (5 ml.). Recrystallization from methanol–ether yielded an analytical sample (780 mg.): λ_{max}^{KBr} 5.83 μ; $\lambda_{max}^{MeOH-HCl}$ 255 and 395 mμ (log ϵ 4.37 and 3.80): $\lambda_{max}^{MeOH-NaOH}$ 245, 345, and 420 mμ (log ϵ 4.41, 3.70, and 4.15).

Anal. Calcd. for $C_{30}H_{37}ClN_2O_8 \cdot C_7H_8O_3S$: C, 58.37; H, 5.96; Cl, 4.66; N, 3.68. Found: C, 58.38; H, 5.95; Cl, 4.67; N, 3.52.

7-Chloro-9-N-di-*t*-butyltetracycline (IIId).—The above compound IIe (720 mg.) was hydrogenated in ethanol (50 ml.) and 0.067 *M* pH 7 phosphate buffer (45 ml.) over palladium black (500 mg.) at 50 p.s.i. at room temperature for 30 min. The reaction mixture was filtered and added to a mixture of ethyl acetate, cyclohexane, and water. The organic layer was washed with water, dried, and evaporated. The residue (550 mg.) was dissolved in ether and added slowly to a stirred solution of *p*-toluenesulfonic acid (175 mg.) in ether (150 ml.). The resulting precipitate (218 mg.) was filtered. The filtrate was concentrated to yield pure product (45 mg.): $\lambda_{max}^{MeOH-HCl}$ 258, 342, and 373 mμ (log ϵ 4.32, 3.89, and 3.96); $\lambda_{max}^{MeOH-NaOH}$ 243, 270, and 391 mμ (log ϵ 4.33, 4.23, and 4.11).

Anal. Calcd. for $C_{30}H_{39}ClN_2O_8 \cdot C_7H_8O_3S$: C, 58.22; H, 6.21; Cl, 4.65. Found: C, 58.46; H, 6.32, Cl, 3.42.

9-N-Di-*t*-butyltetracycline (IIIc).—7-Chloro-9-N-di-*t*-butyl-6-deoxy-6-peroxydehydrotetracycline (IIc, 1.9 g.) was hydrogenated in ethanol (125 ml.) and benzene (25 ml.) over palladium black (1 g.) at room temperature at 50 p.s.i. for 18 hr. The reaction mixture was filtered and evaporated to dryness under reduced pressure. The residue was distributed between ether and pH 4.5 phosphate buffer and the ether phase was evaporated to dryness. The material obtained was again hydrogenated in ethanol (100 ml.) over palladium black (1 g.) for 3 hr. After filtration and evaporation to dryness the residue was distributed between ether and pH 4.5 buffer. The ether phase was dried and evaporated to yield the crude product (1.48 g.). This was dissolved in cyclohexane (400 ml.), and *p*-toluenesulfonic acid (445 mg.) dissolved in ethanol (2 ml.) was added. The resulting precipitate was purified by reprecipitation from methanol–ether: $\lambda_{max}^{MeOH-HCl}$ 271, 341, and 366 mμ (log ϵ 4.35, 4.06, and 4.07); $\lambda_{max}^{MeOH-NaOH}$ 269 and 380 mμ (log ϵ 4.26 and 4.23).

Anal. Calcd. for $C_{30}H_{40}N_2O_8 \cdot C_7H_8SO_3$: C, 60.97; H, 6.64; N, 3.84. Found: C, 60.53; H, 6.54; N, 3.75.

Anhydrotetracycline (1 g.) was irradiated and oxygenated in benzene solution (400 ml.) in the presence of 3,4-benzpyrene (15 mg.) for 7 hr. The solution was extracted with 0.01 *N* hydrochloric acid (100 ml.) and water (50 ml.) and the combined aqueous phases were hydrogenated at room temperature at 50 p.s.i. for 4 hr. over 5% palladium on carbon (500 mg.). The filtered solution contained, as shown by a bio-plated paper chromatogram, tetracycline as the only bio-active compound. The reaction mixture was freeze-dried to yield a crude product (486 mg.) containing anhydrotetracycline as well as tetracycline as indicated by a paper chromatogram. The crude product showed activity of 120 μ/mg. of tetracycline standard (1 mg. = 1000 μ), *K. pneumoniae* assay.

Dedimethylamino-7-chloroanhydrotetracycline also underwent the photooxidation process, as indicated during the reaction by the characteristic shift of ultraviolet absorption of the reaction mixture from an anhydro- to a dehydrotetracycline type.

Restricted Internal Reorientation in Large-Ring N-Methyllactams as Evidenced by Nuclear Magnetic Resonance[1]

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The nuclear magnetic resonance spectra of N-methylcaprolactam (I), N-methylcapryllactam (II), and N-methyllauryllactam (III) have been measured at various temperatures. The nine-membered lactam II displays singlet N-methyl absorption at temperatures as low as −30°, while the thirteen-membered lactam III possesses an N-methyl doublet at room temperature (δ_{AB} = 7 c.p.s.); coalescence occurs at 60°. Observation of the temperature-dependent N-methyl doublet in this latter case is considered to arise from *cis* and *trans* isomers about the amido group. The nature of the *cis* and *trans* isomers in large-membered N-methyl lactams is discussed as well as the mechanisms for interconversion. N-Methylation of lactams with sodium hydride and methyl iodide is described.

N.m.r. has proved extremely useful for the study of hindered internal rotation such as that occurring about the C–N bond in various N-methylamides.[2] Observation of a temperature-dependent N-methyl doublet signal corresponds to exchanging N-methyl rotamers which interconvert at a rate slower than the chemical shift difference between N-methyl *cis* and N-methyl *trans* to oxygen.[2] The mean lifetime in each state, $\tau_A\tau_B$, is therefore large compared with the inverse frequency separation $(\omega HA - \omega HB)^{-1}$. Application of this type of measurement to the cyclic analogs, N-methyl lactams, is of interest in order to determine the possible existence of *cis–trans* amido group exchange in large rings and to learn the range of ring sizes in which *trans* isomers may occur. Furthermore, in the case of coexisting *cis–trans* isomers, measurement of the relative absorption intensity of CH_3N *cis* to CO *vs.* CH_3N *trans* to CO should indicate the mean populations in each state, thus allowing the calculation of an equilibrium constant for a given system at constant conditions of temperature, solvent, and concentration. We wish to report experimental findings on these points.

Table I lists the chemical shifts for the ring CH_2, CH_2CO, CH_2–N, and CH_3–N for N-methylcaprolactam (I, seven-membered), N-methylcapryllactam (II, nine-membered), and N-methyllauryllactam (III thirteen-membered). The positions of the proton resonance are based upon abundant analogy; spectra have been reported for pyrrolidone, caprolactam, and N-methylpyrrolidone.[3] The most striking feature of these results is the doublet N-methyl resonance shown in the spectrum of the thirteen-membered example (Fig. 1). At 30° the peaks are separated by 7.1 c.p.s. Warming progressively to a temperature of 60° leads to coalescence of the two N-methyl components into a single peak (Fig. 1). Also the sharpness of both α-methylenes is

(1) Acknowledgment is made to the National Institutes of Health (GM11595-01) for support of this research.

(2) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 218–365.

(3) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, entries 68 and 116, respectively. Proton resonance values for caprolactam have been reported by G. Van Dyke Tiers, "Characteristic N.M.R. Shielding Values (Spectral Positions) for Hydrogen in Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958, pp. 16, 18.

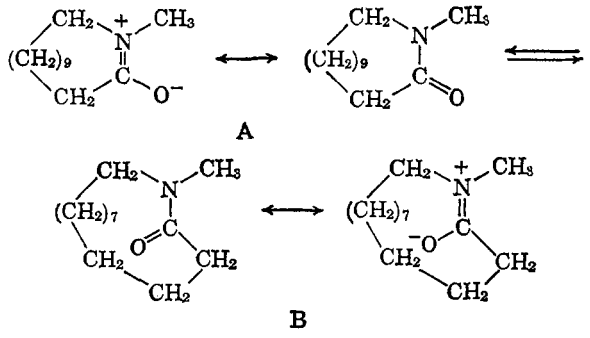
TABLE I[a]

CHEMICAL SHIFTS FOR PROTONS IN N-METHYLLACTAMS OF INCREASING RING SIZE AT 30°[b]

Lactam	Solvent[c]	CH_3N-	$-CH_2CO-$	$-CH_2N-$	$-CH_2-$	*trans–cis*
N-Methylcaprolactam (I)	CCl_4	2.96	2.40	3.32	1.67	Pure *cis*
N-Methylcapryllactam (II)	CCl_4	2.75[d]	2.40	3.50 triplet (J = 6 c.p.s.)	1.58	Pure *cis*
N-Methyllauryllactam (III)	Neat	2.78 (δ = 9.6 c.p.s.) 2.96	2.20	3.33	1.30	110:80
	CCl_4	2.85 (δ = 11.4 c.p.s.) 3.04	2.28	3.30	1.40	110:80
	$CDCl_3$	2.91 (δ = 7.1 c.p.s.) 3.04	2.48 triplet (J = 7 c.p.s.)	3.32 triplet (J = 7 c.p.s.)	1.40	100:90

[a] Spectra were taken with a Varian A-60 n.m.r. spectrometer; chemical shifts are in p.p.m. ±0.02 relative to tetramethylsilane as an internal standard. [b] Temperature was set using Varian V-6057 variable temperature accessory and is considered accurate to ±2°. [c] Solutions were 20% with respect to lactam. [d] Signal remained a sharp singlet upon cooling to −30°.

lost at higher temperatures. The possibility of the N-methyl doublet being due to dimerization or polymolecular association was excluded by a dilution study. The observed temperature *vs.* signal behavior is a diagnostic spectroscopic pattern for hindered internal reorientation,[2] and we believe in the present case the results may be explained in terms of an equilibrium between the two isomeric *cis* and *trans* forms (A and



B) possible for III. Since the isomers are undoubtedly of different energy, the mean lifetime (τ) in either state A or B is not necessarily the same; therefore, standard methods which require $\tau_A = \tau_B$ for the calculation of rate constants and activation parameters may not be applied.[4]

Piette and Anderson[5] have calculated rate constants and activations parameter for *cis* and *trans* rotational isomers of different τ_A and τ_B and where $\tau << T_2$ (transverse relaxation time). Such calculations applied to III will be reported separately. An approximate limit, however, can be placed upon the rate of reorientation. The N-methyl peaks at room temperature are separated by ν = 7.1 c.p.s.; therefore, reorientation between the two isomers must be occurring at a rate slower than $\delta\omega/\sqrt{2}$ or $2\pi(7.1 \text{ c.p.s.})/\sqrt{2}$ = 31.2 sec.$^{-1}$ The intensities of the two N-methyl peaks, and therefore the populations of A and B, are solvent dependent. Thus, with the pure amide (III) and in 20% solutions of III in carbon tetrachloride, the ratio of the high-field to low-field N-methyl peaks is 80:110. In deuteriochloroform the intensities are more nearly equal, 90:100. There is general agreement that in open-chain N-methylamides which display a doublet N-methyl resonance, the high-field peak is due to N-methyl *cis* to oxygen.[6] The above ratio for III corresponds to N-methyl *cis*–N-methyl *trans*, 80:110. The increase of *cis* isomer in deuteriochloroform is possibly due to a displacement of the equilibrium caused by hydrogen bonding of the negative carbonyl group with deuteriochloroform.

While N-methylcaprolactam (I) is necessarily in the *cis* form, inspection of models indicates that both a *cis* and *trans* arrangement is possible for N-methylcapryllactam (II). The N-methyl peak of II appears as a sharp singlet at room temperature and shows no change in appearance down to −30°. The high-field position (2.75 p.p.m.) of this peak leads us to believe that it exists purely in the *cis* form. The *cis* N-methyl peak in N-methylformamide appears at 2.74 p.p.m. The position of the N-methyl peak in N-methylcaprolactam (I) is at a lower field than either the *cis* N-methyl of N-methylformamide or the *cis* N-methyl of II or III. This may reflect the strain present in the seven-membered ring. The N-methyl peak of N-methylpyrrolidone appears at 2.83 p.p.m.[3]

Finally, mention should be made of mechanisms for the interconversion of the *cis* and *trans* isomers of III. In an N-methylamide, exchange between the two rotamers occurs by rotation about the C–N bond. The potential-energy barrier separating the two rotamers for dimethylacetamide is about 9 kcal./mole. The barrier is associated with the loss of resonance energy of the amide group in passing through the orthogonal transition state for exchange. A symmetrical sinusoidal potential-energy curve may be drawn for a plot of E *vs.* angle of rotation ϕ for ϕ = 0° to ϕ = 360°. Such a rotational pathway involves periodic rotation over a potential barrier, V_0, of the same height. Inspection of models of N-methyllauryllactam (III) indicates that a different pathway for isomer exchange may exist for this compound. A nonsymmetric potential-energy profile may be visualized for III. Reorientation between the *cis* and *trans* forms may proceed *via* a back and forth movement of the groups bound to the amido linkage. One exchange involves movement through 180°; beyond this point, a steep energy barrier exists for further movement towards the center of the ring where severe transannular interactions come into play. Energetically it is more feasible for the groups to retrace their steps. This process bears semblance to libration, that is, a periodic interchange in which a system point describes a closed orbit in

(4) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).
(5) L. H. Piette and W. A. Anderson, *ibid.*, **30**, 899 (1959).
(6) (a) D. G. de Kowalewski and V. J. Kowalewski, *Arkiv Kemi*, **16**, 373 (1960); (b) L. A. La Planche and M. T. Rogers, *J. Am. Chem. Soc.* **86**, 337 (1964).

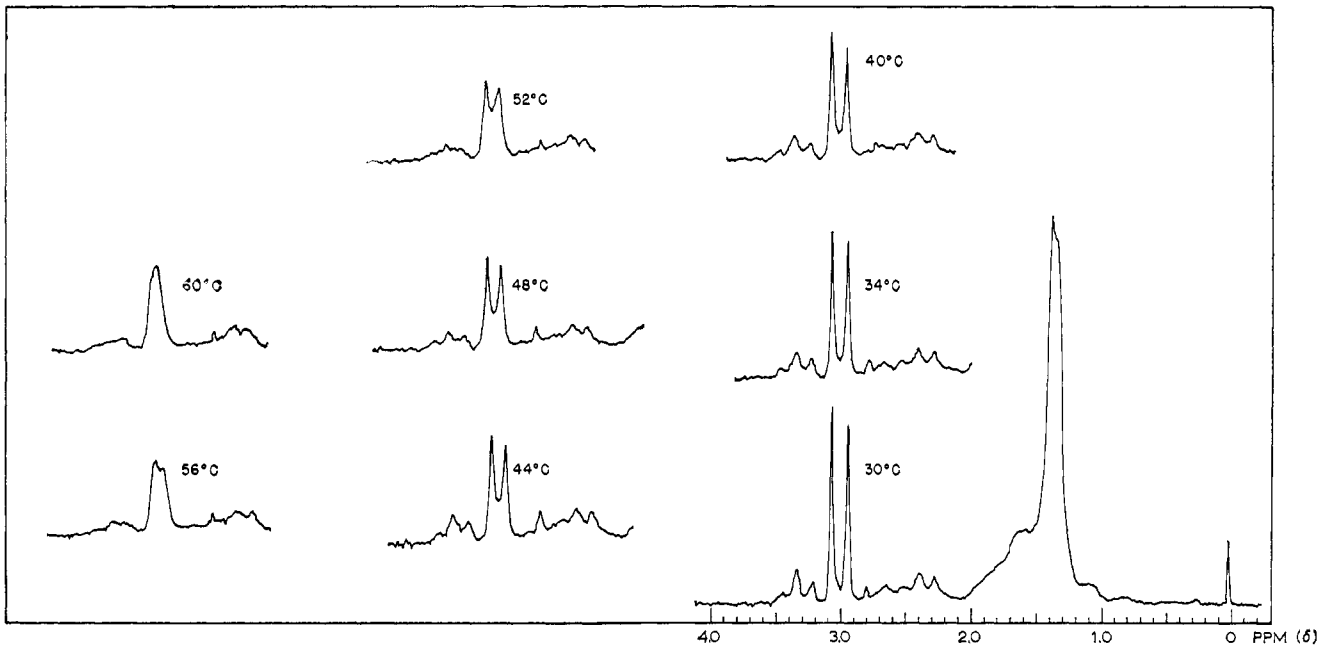


Fig. 1.—Effect of temperature upon the N-methyl absorption band of N-methyllaurylactam (III) in deuteriochloroform.

phase space.[7] The barrier to internal libration about the N–C bond for the A ⇌ B equilibrium would be the sum of nonbonded hydrogen–hydrogen repulsions, destabilizing torsional interactions, and loss of orbital overlap in passing through the transition state for isomer exchange.

Experimental

Procedure for N-Methylation of Lactams Using Sodium Hydride–Methyl Iodide.[8]—To a solution of 0.10 mole of the lactam[9] dissolved in 25 ml. of benzene, 0.30 mole of sodium hydride was added. With stirring under nitrogen, the solution was brought to reflux and 0.15 mole of methyl iodide in 20 ml. of benzene was added dropwise. The reaction system was kept at reflux for 7 hr. after completion of the dropwise addition. At the end of this time excess sodium hydride was cautiously decomposed by addition of 95% ethanol. Water was added and the benzene layer was separated and washed with 5% sodium chloride solution and water. The benzene solution was dried and distilled and the N-methyl lactams were purified by distillation at reduced pressure. The purity of the lactams was established by v.p.c. N-Methylcapryllactam (II) and N-methyllauryllactam (III) have been prepared in the laboratories of Badische Anilin and Soda Fabrik AG Ludwigshafen, Rhein, Germany. The properties of our synthetic materials agree with those communicated to us.[10]

(7) M. Goldstein, "Classical Mechanics," Addison-Wesley, Inc., Reading, Mass., 1959, p. 288.

(8) We wish to thank Professor R. Huisgen, University of Munich, for suggesting this method.

(9) Capryl- and lauryllactams were donated by the Badische Anilin and Soda Fabrik, A.G. Ludwigshafen, Rhein.

TABLE II

PHYSICAL PROPERTIES OF N-METHYLLACTAMS

Lactam	B.p., °C. (mm.)	$\nu_{C=O}^{CCl_4}$,[a] cm.$^{-1}$
N-Methylcaprolactam[b] (I)	120–22 (10)	1653
N-Methylcapryllactam[c] (II)	89–94 (1)	1644
N-Methyllauryllactam (III)	99–100 (1)	1650

[a] Recorded on a Beckman IR-9, resolution 1.68 cm.$^{-1}$ at 1600 cm.$^{-1}$ and sweep speed of 20 cm.$^{-1}$/min. [b] R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, **70**, 2115 (1948). [c] See ref. 10.

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(10) We wish to thank Dr. H. H. Lau, B.A.S.F., for communicating the physical properties of N-methylcapryllactam (II) and N-methyllauryllactam (III), and also for a handsome sample of III.