PREPARATION AND PROPERTIES OF N-*n*-ALKYLLACTAMIDES[2]

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Although the preparation of lactamide (3–9) and certain N-substituted lactamides (1) has been described,[2] N-*n*-alkyllactamides have not been studied extensively (1, 10, 11). The effect of increasing the amine chain-length on the reaction of amine with lactic esters has not been investigated.

The purpose of the present work was to prepare and examine several N-*n*-alkyllactamides, determine qualitatively the reactivity of the primary-*n*-aliphatic amines toward methyl lactate, and develop correlations (12) among the various physical properties of the lactamides. Acetic acid esters of some of these lactamides were also prepared and examined.

Methyl lactate and mono-*n*-alkyl amines interacted readily at room temperature, giving excellent yields (Table I) of the corresponding lactamides; no added catalyst was necessary.

The lower reactivity of simpler esters, such as methyl acetate and methyl propionate, in this type of reaction has led to the suggestion that the *alpha* hydroxyl group promotes nucleophilic attack by the amine (1). This effect may mask any difference in reactivity of the amines as the amine chain-length is increased, for all the lactamides studied here were obtained without difficulty.

The lactamides were prepared by the previously described method; that is by mixing redistilled methyl lactate with a 10% excess of the amine, and allowing the mixture to stand for 7 or more days. The mixtures containing the amines of lower molecular weight through *n*-decylamine were kept at room temperature; the rest were kept liquid by storage at 50°. After distillation, a sample of each lactamide (except butyl) was crystallized several times from an appropriate solvent (Table I) and the melting point and analytical data were determined; the butyl derivative was redistilled prior to examination. The lactamides as distilled were of high purity; the yields in Table I refer to the distilled product.

The acetates of five lactamides (Table II) were obtained in 90–98% yield by acetylation with acetic anhydride in the presence of sulfuric acid catalyst.

Repellency and larvicidal tests. Tests conducted by the Bureau of Entomology and Plant Quarantine, U. S. Department of Agriculture, revealed that N-*n*-butyl- and N-*n*-amyllactamide applied to the skin had effective repelling times of 145 and 265 minutes, respectively, against *Aedes aegypti*, as compared with 180 and 360 minutes for dimethyl phthalate and ethyl hexanediol, respectively, the controls. At a concentration of 10 parts per million, N-*n*-tetradecyllactamide

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] For previous papers on lactamides see References (1) and (2). Reference (1) has an extensive bibliography on earlier work.

acetate gave 100% mortality against anopheline larvae in 48 hours. A lactamide described earlier, N-1,3-dimethylbutyllactamide (1), when applied to cotton stockings at 3.3 g. per square foot repelled *Aedes aegypti* for 15 days; five bites

TABLE I

PREPARATION AND PROPERTIES OF $HOCH(CH_3)CONH(CH_2)_nH$

n	YIELD,[a] %	REACTION TIME, DAYS	M.P., °C.	SOLUBILITY[b]	ANALYSES					
					C		H		N	
					Calc'd	Found	Calc'd	Found	Calc'd	Found
1	91	21	71.5–72[c]	—	46.6	46.8	8.8	8.9	13.6	13.9
2	97	14	44.5–45[d]	—	51.3	51.1	9.5	9.6	12.0	11.9
3	87	12	20[e,f]	—	54.9	55.5	10.0	10.4	10.7	10.7
4	98	10	25.5[e]	—	57.9	57.9	10.4	10.5	9.6	9.6
5	97	19	29.5[e,f]	6.60	60.3	60.8	10.8	10.7	8.8	8.8
6	98	15	41.5–42[f]	1.95	62.4	62.4[g]	—	—	8.1	8.2
8	96	13	52–52.5[h]	0.105	65.6	65.6[g]	—	—	7.0	6.9
10	98	10	61.5–62[h]	0.010	68.1	68.3	11.9	11.8	6.1	6.2
12	96.5	7[i]	68.5–69.5[h]	0.004	70.0	70.3	12.1	12.2	5.4	5.4
14	94.5	11[i]	74.5–75[h]	0.003	71.5	71.6	12.4	12.1	4.9	4.9
16	98	11[i]	79.5–80[j]	0.007	72.8	72.7	12.5	12.5	4.5	4.4
18	99	11[i]	83–84[j]	0.003	73.8	73.8	12.7	12.6	4.1	4.1

[a] Based on methyl lactate. [b] Grams per 100 ml. of water, at 25°; with an accuracy of 0.003 g.; the lower amides were completely soluble. [c] From benzene-acetone. [d] From petroleum ether-butanol; reference (10) gives m.p. 48°. [e] Freezing point. [f] From ether-petroleum ether. [g] Found by wet oxidation. [h] From ether. [i] At 50°. [j] From ethanol.

TABLE II

PROPERTIES OF $CH_3COOCH(CH_3)CONH(CH_2)_mH$

m	B.P., °C. (MM.)	M.P., °C.	n_D^{20}	ANALYSES							
				C		H		N		SAPON. EQUIV.	
				Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
2	110(1.5)	54–55[a]	1.4465[b]	52.8	53.0	8.2	8.5	8.8	8.6	159.2	143.2
4	120(1.8)	41.5–44	1.4480[b]	57.7	58.0	9.2	9.1	7.5	7.5	187.2	187.2
8	155(0.4)	10[c]	1.4525[d]	64.2	64.2	10.4	10.4	5.7	5.7	243.3	244.9
14	—	57.5–58.5[e]	—	69.7	70.0	11.4	11.6	4.3	4.3	327.5	316.5
18	—	71–72[f]	—	72.0	72.0	11.8	11.6	3.6	3.8	383.6	380.2

[a] From ether. [b] For the undercooled liquid. [c] Freezing point. [d] Density, d_D^{20} 0.9679; M_D^{20} Calc'd, 67.75; Found, 67.82. [e] From petroleum ether. [f] From ethanol-water.

then occurred in 28 days. The methods used in these tests have been described (13).

Hygroscopicity. Ethyl-, propyl-, butyl-, and amyl-lactamide were somewhat hygroscopic. Approximate equilibrium compositions at 25° of N-propyllactamide-water mixtures (expressed as weight % amide) at various relative humidities

were: 97% (22.5% relative humidity); 94% (32.5% relative humidity); 93% (48% relative humidity); and 89% (64.5% relative humidity). The propyl derivative appeared to be the most hygroscopic.

Physical constants. The boiling points at low pressures (Figures 1 and 2) were carefully determined in equipment known to give accurate results (14, 15). Lactamide and N-*n*-butyllactamide had almost identical boiling points in the

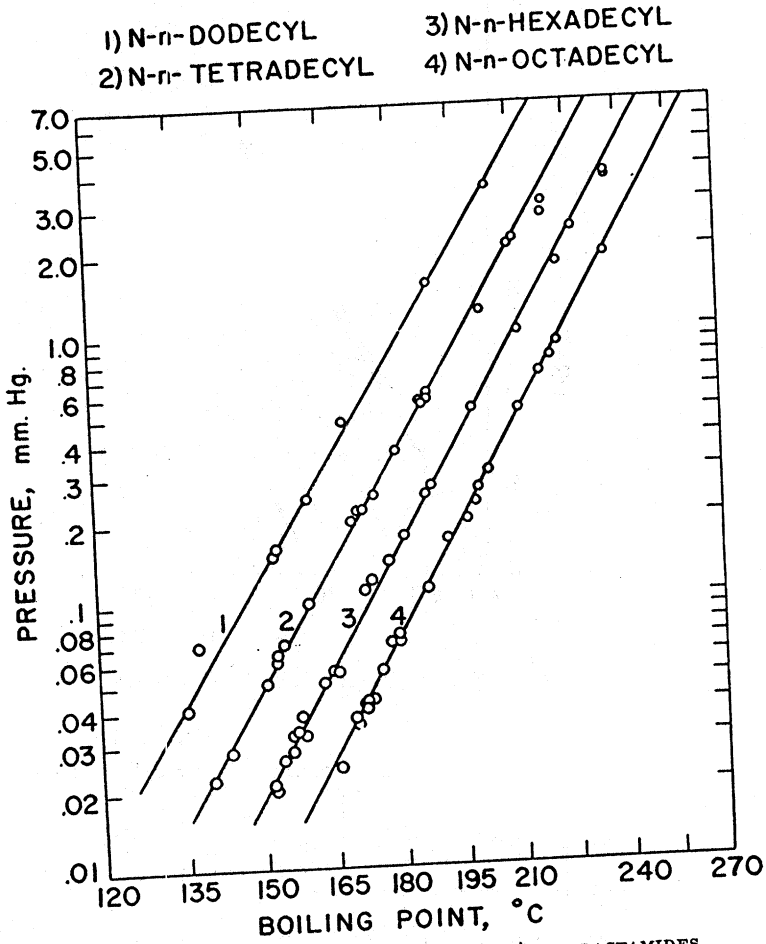

FIG. 1. BOILING POINTS OF LOWER N-*n*-ALKYLLACTAMIDES

range studied. In the figures, the ordinate is laid off as log ρ, the abscissa as 1/[T(°C.) + 273].

As observed previously (12, 16–18), it is possible to express the boiling points (in °K.) as a function of the total number of carbon atoms (x). For 10 mm. and 1.0 mm., the equations are

$$T_{10}^2 \times 10^{-4} = 0.7605\,x + 13.40 \qquad (x = 5 \text{ to } 21) \qquad [1]$$

$$T_{10}^2 \times 10^{-4} = 0.6620\,x + 10.78 \qquad (x = 5 \text{ to } 21) \qquad [2]$$

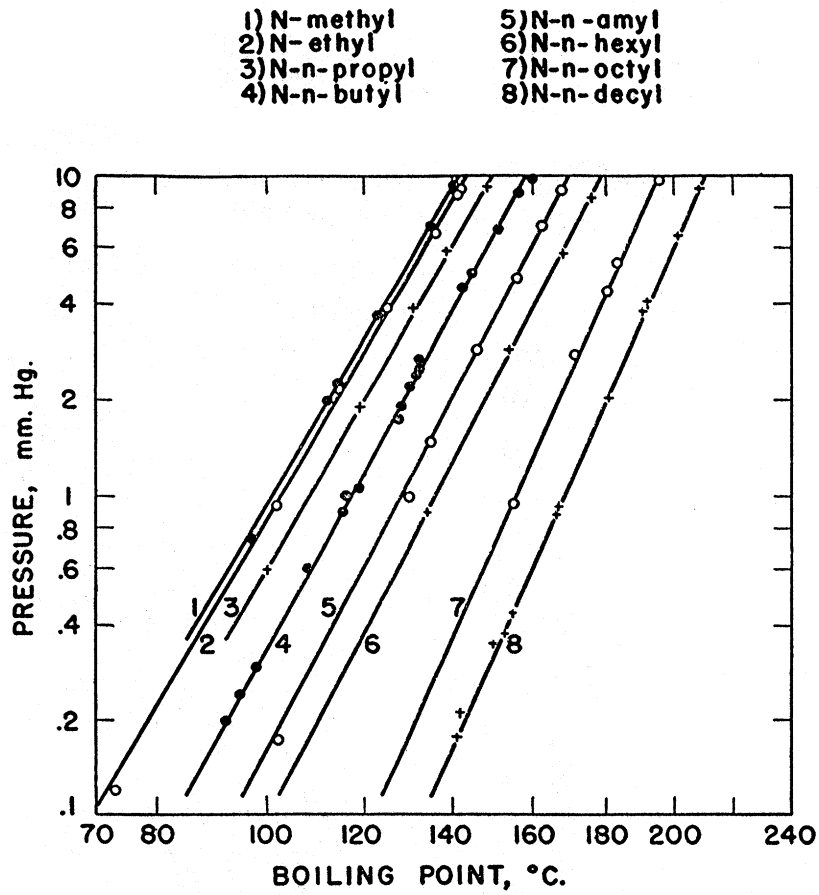

FIG. 2. BOILING POINTS OF HIGHER N-*n*-ALKYLLACTAMIDES

TABLE III

PHYSICAL CONSTANTS OF $HOCH(CH_3)CONH(CH_2)_mH$

m	d_4^{20}	n_D^{20}	M_D^{20}		d_4^{40}	n_D^{40}	M_D^{40}		VISCOSITY[b]
			Calc'd	Found			Calc'd	Found	
2	—	—	—	—	1.0290[a]	1.4480[a]	30.68	30.48	—
3	1.009	1.4560	35.30	35.33	0.9964	1.4487	35.30	35.29	34.6
4	0.9905[a]	1.4563[a]	39.92	39.87	.9764	1.4493	39.92	39.91	36.4
5	—	1.4569[a]	—	—	.9596	1.4496	44.54	44.55	38.1
6	—	1.4573[a]	—	—	—	—	—	—	—

[a] For the undercooled liquid. [b] Centipoises, at 40°.

Equations [1] and [2] give calculated boiling points which agree with the observed boiling points with an average deviation of 1°. They should be useful in estimating the boiling points of the missing members of the series. It was likewise possible

to relate refractive index (n_D^{20} and n_D^{40}) and density (d_4^{40}) (Table III) to the number of carbon atoms (x), using equations similar to those recently reported (12):

$$\frac{x}{d_4^{40}} = 1.1580x - 0.9310 \quad [3]$$

$$\frac{x}{n_D^{20}} = 0.6840x + 0.0189 \quad [4]$$

$$\frac{x}{n_D^{40}} = 0.6885x + 0.0105 \quad [5]$$

Equations [3], [4], and [5] give computed values of density and refractive index agreeing with the observed values with an average deviation of 0.0005 and 0.0001, respectively.

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EXPERIMENTAL

Materials. Commercial methyl lactate (made from fermentation acid) was carefully distilled *in vacuo*. This material had only slight optical activity. The ammonia, methylamine, and ethylamine were commercial anhydrous grade. The *n*-propylamine was Eastman Kodak best grade. The remaining amines were commercial samples; each was stored over potassium hydroxide for a few days, then filtered and distilled through a Fenske or Podbielniak column. In view of its catalytic activity (19), no precautions were taken to exclude traces of water. The refractive indices (n_D^{20}) of the liquid amines were: *n*-butyl-, 1.4013; *n*-amyl-, 1.4113; *n*-hexyl-, 1.4198; *n*-octyl-, 1.4300; and *n*-decyl-, 1.4361, all in good agreement with the literature values. For the higher amines neutral equivalents were determined: dodecyl-, 185.0, (calc'd, 185.2); tetradecyl-, 213.5, (calc'd, 213.3); hexadecyl-, 241.5, (calc'd, 241.3); and octadecyl-, 270.8, (calc'd, 269.3).

Lactamides. The preparation of N-*n*-hexyllactamide is typical, and is described in detail. To 208 g. (2.0 moles) of the ester was added 222 g. (2.2 moles) of the amine; after being shaken, the mixture was stored at room temperature. At the end of 15 days, the mixture was distilled (Vigreux column), and 55 g. of methanol (identified by boiling point and refractive index) was collected at atmospheric pressure. Vacuum was then applied (1 mm.), and 3 g. of an intermediate fraction was obtained at 28–120°. The lactamide was then collected at the ultimate pump vacuum, b.p. 120–128° (0.3 mm.); yield, 341 g. (98%). During the vacuum distillation, an additional 18 g. of material (identified as a mixture of methanol and amine) collected in a cooled trap in the vacuum line. A sample of the lactamide was recrystallized thrice from an ether-petroleum ether mixture, m.p. 41–41.5°. After being warmed at 36°/50 for 1.5 hours, the m.p. was 41.5–42°. The sample was then analyzed.

The octadecyl derivative, however, crystallized excessively in the stillhead and was obtained as a residue.

Lactamide was prepared from 1275 g. of methyl lactate by the method of Gucker and Allen (5); during addition of the ammonia the mixture was stirred and cooled with tap water to avoid the discoloration which occurred when the mixture was permitted to warm

spontaneously. When absorption of ammonia was complete, methanol and excess ammonia were evaporated at room temperature under vacuum (50 mm.) for 12 hours, and the crude product was obtained in 97% yield as a porous white mass, m.p. 67–73.5°.

Anal. Calc'd for $C_3H_7NO_2$: N, 15.7. Found: N, 15.4.

Michel (7) reports m.p. 76.4° for the racemic product.

Lactamide acetates. The lactamide acetates were prepared by the method of Fein and Fisher (12), except that the tetradecyl and octadecyl derivatives were isolated by washing the reaction mixture with hot water, filtering, and drying. The butyl and octyl compounds were not further purified before analysis; samples of each of the others were recrystallized several times from an appropriate solvent (Table II).

An attempt to acetylate N-ethyllactamide acetate further, to N-acetyl-N-ethyllactamide acetate, was not successful; a sample of the lactamide acetate was heated to reflux with 100% excess acetic anhydride in the presence of sulfuric acid as catalyst, but the compound was recovered unchanged. The agreement of the observed saponification equivalents (Table II) with those calculated for one saponifiable group indicates that the amide is more resistant than the acetoxy group under the conditions used (2b).

Physical constants. The boiling points (Fig. 1) of the first eight lactamides (Table I), with the exception of butyl, were determined in a tensimeter-still (15); an automanometer still (14) was used for the butyl derivative. For lactamide and for the dodecyl and higher lactamides (Fig. 2), a modification of the tensimeter-still was used, permitting the distillate to be kept molten until it reached the receiver.

Refractive indices, densities, and viscosities were measured by methods already described (12). Water solubility of the lactamides was determined by the method of Badgett, *et al.* (20), except for the amyl derivative, for which the method of Fordyce and Meyer (21) was used.

SUMMARY

N-*n*-alkyllactamides were obtained in 87–99% yield by the aminolysis of methyl lactate with methyl-, ethyl-, *n*-propyl-, *n*-butyl-, *n*-amyl-, *n*-hexyl-, *n*-octyl-, *n*-decyl-, *n*-dodecyl-, *n*-tetradecyl-, *n*-hexadecyl-, and *n*-octadecyl-amine. The acetates of ethyl-, butyl-, octyl-, tetradecyl-, and octadecyl-lactamide were made in 90–98% yield by acetylation with acetic anhydride. Three lactamides were mosquito repellents, and one lactamide acetate was a larvicide.

The properties measured for all the lactamides were the boiling points below a pressure of 10 mm. of mercury, and the melting points; for some, d_4^{20}, d_4^{40}, n_D^{20}, n_D^{40}, viscosity, and water solubility were also determined. The lactamides are low-melting, high-boiling compounds, and the higher homologs have low water-solubility.

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