[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

PREPARATION OF N-SUBSTITUTED LACTAMIDES BY AMINOLYSIS OF METHYL LACTATE[2, 3]

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Although several investigators have described the preparation of lactamide (1–3) and certain N-substituted lactamides (4–11), little is known about N-substituted lactamides and the relation between the structure of amines and their reactivity with lactic esters. The purpose of the work described here was to prepare and examine several N-substituted lactamides, and to determine qualitatively the reactivity of various types of amines toward methyl lactate. The discovery (10) that acrylamides can be made by pyrolysis of the acetyl derivative of certain lactamides was partially responsible for our interest in lactamides.

In most instances the lactamides were prepared by allowing a mixture of the amine and methyl lactate to stand at about 35° for several days. Inasmuch as the commercially available methyl lactate used was substantially the *dl*-mixture, the resulting lactamides (usually isolated by distillation) were optically inactive. Although methyl lactate was the only ester used in the present work, it is likely that certain other lactic esters could be employed conveniently to make the lactamides.

Methyl lactate and monoalkyl amines reacted readily at about room temperature, giving excellent yields (Table I) of the corresponding N-alkyl lactamides. A high yield of amide was obtained even with an amine of relatively high molecular weight, for example, *n*-octylamine. These and other experiments showed that methyl lactate is much more reactive toward amines than simpler esters such as methyl acetate and methyl propionate; other workers (12) have observed a similar difference in reactivity toward ammonia.

No added catalyst was necessary in the aminolyses, and none was employed in any of the lactamide preparations described. The data in Table I shows that branching on the carbon atom next to the amine nitrogen reduces the yield. The yields based on unrecovered ester were 5–10% higher than the yields listed in Table I for these branched compounds. Amines such as *tert*-butylamine were not studied, but presumably amines of this type would be less reactive toward methyl lactate than isopropyl- and *sec*-butylamine.[4] Unsaturated and hydroxy- and methoxy-substituted amides were obtained in good yield from allyl-, and β-hydroxyethyl-, and β-methoxyethyl-amine, respectively. 6-Aminocaproic acid

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

[2] Presented at 112th meeting of the American Chemical Society in New York, September 15–19, 1947.

[3] For previous papers, see reference (10).

[4] This statement is supported by the low reactivity of 2-amino-2-ethylpentane (13) and the failure of *tert*-butylamine to react with ethyl acetate and ethyl oxalate (14).

TABLE I

N-SUBSTITUTED LACTAMIDES FROM PRIMARY AND SECONDARY AMINES

AMINE	YIELD[a], %	ANALYSES						M.P., °C.	B.P., °C.	MM.	d_4^{20}	n_D^{20}	M_D^{20}	
		C		H		N								
		Calc'd	Found	Calc'd	Found	Calc'd	Found						Calc'd[b]	Found
n-Octyl-	96	65.6	65.6	—	—	7.0	6.9	52–52.5[c]	149–154	0.7	—	—	—	—
Isopropyl-	83	54.9	54.9	—	—	10.7	10.7	51–51.5[d]	94–97	0.3	—	—	—	—
Isobutyl-	95.6	57.9	58.1	—	—	9.7	9.7	47–48[d]	104–106	0.1	—	—	—	—
sec-Butyl[e]-	76	57.9	58.0	10.4	10.3	9.7	9.6	23.5–24[f]	98–99	0.6	0.9872	1.4523	39.92	39.70
Isoamyl[g]-	96	60.3	60.4	10.8	10.8	8.8	8.7	Liquid	116	0.7	0.9716	1.4557	44.54	44.51
4-Me-2-pentyl-	92	62.4	62.3	11.1	11.2	8.1	8.0	66–67[h]	113.5–116	0.3–0.5	—	1.4520[i]	—	—
Allyl[j]-	95	55.8	55.6	8.6	8.9	10.9	10.8	Liquid	86–87	0.2	1.0508	1.4753	34.84	34.62
Methallyl[k]-	92	58.7	58.5	9.2	8.8	9.8	9.7	Liquid	128.5–129	2.2	1.0249	1.4750	39.45	39.33
2-Hydroxyethyl[k]-	95	45.1	45.0	8.3	8.4	10.5	10.7	Liquid	137–139	0.003	1.1861	1.4862	32.21	32.16
2-Methoxyethyl-	87	49.0	49.0	8.9	8.6	9.5	9.5	48–50[c]	127	0.5	—	1.4610[i]	—	—
Cyclohexyl-	92	63.1	63.3	10.0	10.1	8.2	8.2	60–60.5[c]	125–136	0.2	—	—	—	—
Phenyl-	59	65.4	65.5	6.7	6.8	8.5	8.6	57–58[c]	147–156	0.1	—	1.5527[i]	—	—
Benzyl-	94[l]	67.0	66.9	7.3	7.2	7.8	7.8	47.5–48.5[h]	—	—	—	—	—	—
Pyrrolidine[k]	91	58.7	58.5	9.2	9.1	9.8	9.6	Liquid	134–135	7	1.1099	1.4900	37.45	37.29
Piperidine	84	61.1	60.8	9.6	9.1	8.9	8.7	Liquid	127–128.5	7	1.0728	1.4890	42.07	42.29
Morpholine	83	52.8	51.8	8.2	8.0	8.8	8.4	Liquid	110–111	1.4	1.1877	1.4940	39.12	39.01
Methylaniline	50	67.0	66.8	7.3	7.5	7.8	7.6	89.5–90.5[c]	—	—	—	—	—	—

[a] Of material isolated by distillation of the reaction mixture. Based on reagents charged. [b] For the atomic refraction of N in the disubstituted compounds the value 2.49 was used (reference 38); for N in the monosubstituted compounds, 2.76 (D'Alelio and Reid, *J. Am. Chem. Soc.*, **59**, 109 (1937); and for the other atoms the values of Eisenlohr (Gilman, *Organic Chemistry*, New York, 1938, p. 1739, John Wiley and Sons., Inc.). [c] From ether. [d] From ether-petroleum ether. [e] d_4^{40} 0.9713; n_D^{40} 1.4448. M_D^{40}: Calc'd, 39.92; Found, 39.76. [f] Freezing point. [g] d_4^{40} 0.9569; n_D^{40} 1.4483. M_D^{40}: Calc'd, 44.54; Found, 44.56. [h] From petroleum ether-benzene. [i] Undercooled liquid. [j] d_4^{40} 1.0372; n_D^{40} 1.4679. M_D^{40}: Calc'd, 34.84; Found, 34.60. [k] On the basis of titration data, the approximate rates of aminolysis were: Methallyl, 80% in 1 day; 2-hydroxyethyl, 75% in 2 hours and 91% in 1 day; and pyrrolidine, 75% in 30 minutes. [l] Of material isolated by crystallization.

reacted with methyl lactate, and methanol was distilled from the reaction mixture in high yield. The product, presumed to be N-5-carboxyamyllactamide, was not isolated in pure condition. Water distilled when the product was heated in a molecular still under a pressure of about 3 microns. Probably the viscous distillation residue contained the polymer $H[OCH(CH_3)CONH(CH_2)_5CO]_xOH$.

When the aminolysis study was extended to include cyclic and aromatic primary amines, aniline reacted incompletely, but both cyclohexyl- and benzylamine gave high yields (Table I). A second experiment with aniline, in which methanol was removed from the refluxing mixture by azeotropic distillation with cyclohexane (15), gave about the same yield (in both experiments the yields of lactanilide based on unrecovered ester were 15–20% higher than the yields given in Table I). The results shown in Table I suggest that primary amines generally are suitable for the preparation of lactamides under the conditions described. In connection with the decreased reactivity of aniline, the relatively low basicity of aromatic amines (16) and the fact that aniline is less reactive than primary aliphatic amines toward phenyl isocyanate (17) may be significant.

Dimethylamine (10), reacted readily with methyl lactate. Diethylamine did not react appreciably with methyl lactate at 35° even in the presence of water or sodium methoxide, both of which have been reported as catalysts for this type of reaction (12, 18–20). Diethylamine was substantially unreactive also toward methyl propionate and methyl glycolate. Diisobutyl-, diisoamyl-, di-*n*-amyl-, diphenyl-, dibenzyl-, diallyl-, and dibutyl-amine also were essentially nonreactive toward methyl lactate at 35°. It was shown by titration that the extent of aminolysis after 23 days at 35° was less than 3% for both diallylamine and dibutylamine.[5] The addition of water to the reaction mixtures caused these amines to be consumed at a higher rate, suggesting that the aminolyses had been accelerated. On examining the products, however, it was found that hydrolysis of methyl lactate and formation of amine lactates were primarily responsible for the utilization of free amine.

Although the results described above indicate that the higher dialkyl-, dialkenyl-, and diaryl-amines were relatively unreactive toward lactic esters under the experimental conditions, certain other secondary amines were reactive. N-Methylaniline for example, gave a moderate conversion (50%) to the corresponding lactamide (Table I). In a second preparation of N-methyl-N-phenyllactamide, methanol was removed during the reaction by azeotropic distillation with cyclohexane, but the conversion decreased to 27%. Possibly increased condensation-polymerization of the methyl lactate was responsible for the lower conversion to the amide.

Titration data indicated that *sym*-dimethylethylenediamine reacted readily with two moles of methyl lactate at 35°, and a high yield of methanol was obtained on distillation of the reaction mixture. Attempts to isolate the amide in pure condition, however, were unsuccessful. The experiments with this amine

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[5] Diethylamine and certain higher secondary amines have been observed to be relatively unreactive in the Mannich reaction (21, 22), in the aminolysis of ethyl oxalate (23), and in 1,4-addition to ethyl cinnamate (24).

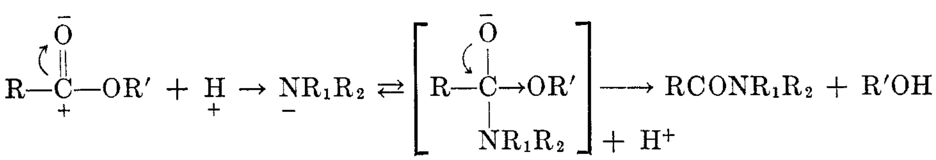
and with methylaniline suggest that methyl secondary amines (CH_3NHR) generally are moderately reactive toward methyl lactate.

Although diethylamine was unreactive toward methyl lactate, a related secondary amine, that is, diethanolamine, reacted readily, giving N,N-di-2-hydroxyethyllactamide in high yields. Attempts to distill the high-boiling, viscous product were unavailing. Ethylethanolamine ($EtNHCH_2CH_2OH$) also reacted with methyl lactate, but its rate of reaction was lower than that of diethanolamine. Presumably alkylethanolamines ($RNHCH_2CH_2OH$) in general are moderately reactive toward methyl lactate. This moderate reactivity can be attributed to the relatively low density of electrons around the nitrogen caused by the electron-attracting influence of the hydroxyl group.

Several cyclic secondary amines (pyrrolidine, piperidine, and morpholine) reacted readily with methyl lactate at 35° and gave high yields of the corresponding lactamides.[6]

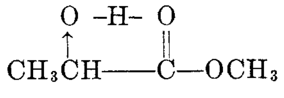
The results obtained with secondary amines indicate that, although amines of this class are generally much less reactive than primary amines, certain types of N,N-disubstituted lactamides can be made readily by the aminolysis of methyl lactate. Tertiary amines might be expected (28) to react with methyl lactate to yield quaternary ammonium lactates.

The following mechanism for the ammonolysis of lactic esters and esters in general has been proposed (12):



$$R-\underset{+}{\overset{\overset{\bar{O}}{\|}}{C}}-OR' + \underset{+}{H} \rightarrow \underset{-}{NR_1R_2} \rightleftarrows \left[R-\underset{\underset{NR_1R_2}{|}}{\overset{\overset{\bar{O}}{|}}{C}}\rightarrow OR' \right] \longrightarrow RCONR_1R_2 + R'OH + H^+$$

The electromeric shift in lactic esters would presumably be aided by the weak hydrogen bridge between the hydroxyl group and the carbonyl oxygen (29), and the fractional positive charge on the carbonyl carbon atom would probably be further increased by the inductive effect of the hydroxyl group:



$$CH_3\overset{\overset{O\ \text{-H-}}{\uparrow}}{C}H-\!\!\!-\overset{\overset{O}{\|}}{C}-OCH_3$$

This would facilitate the nucleophilic attack by amine (or amide ion) and may play a part in the reactivity of methyl lactate and methyl glycolate toward amines, as contrasted with the lower reactivity of methyl acetate and methyl propionate (12).

In evaluating the effect of the structure of the amine, there are at least two factors to be considered: (a) The inductive effect of substituents, operating to

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[6] Piperidine is more reactive than diethylamine to certain esters (25) in the Mannich reaction (21) and in addition to the vinyl group of vinylpyridine (26). It also reacts readily with ethyl formate under conditions where methylaniline and diphenylamine are unreactive (27).

make nucleophilic attack more or less easy by altering the electron density about the amino nitrogen; and (b) steric effects, described by Brown (30, 31) as "F-strain" and "B-strain." It is evident that in the case of the *n*-alkyl primary amines neither of these factors is interfering with the preparation; for the alkyl primary amines branched next to the amine nitrogen they may be exerting a slight inhibiting effect on the reaction.

The striking difference in the behavior of dimethyl- and diethyl-amine indicates a strong inhibiting force at work for the latter compound. It has been reported (32) that diethylamine is relatively unreactive toward several reagents.[6] Brown (30, 31) has shown that dimethylamine reacts with tri-*tert*-butylboron but that diethylamine fails to do so; this is ascribed to the presence of more "B-strain" in diethylamine and to the high "F-strain" (33) between the amine and the boron compound; that is, to steric factors. The "B-strain" is removed, in whole or in part, by "tying back" the ethyl groups in morpholine, pyrrolidine, and piperidine.

Dimethylamine reacts readily with methyl glycolate and methyl lactate at about 35°, but fails to react with methyl α-hydroxyisobutyrate under similar conditions. Probably steric factors of a different type, that is, those around the carbonyl group of the ester, are largely responsible for the relative nonreactivity of the methyl α-hydroxyisobutyrate.

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EXPERIMENTAL

Materials. Most of the amines were commercial samples. The pyrrolidine was kindly supplied by C. F. Woodward and Abner Eisner of this Laboratory. Octyl- and methoxyethyl-amine were dried over solid potassium hydroxide and then distilled. In the experiments, no attempt was made to exclude traces of water in view of its known catalytic effect in aminolysis reactions. The methyl lactate, obtained commercially, was carefully distilled through an efficient fractionating column. Refractive indices at 20° of amines after fractionation through Podbielniak or Fenske columns are: *sec*-butyl-, 1.3937; *n*-octyl-, 1.4300; 4-methyl-2-pentyl-, 1.4083; ethanol-, 1.4538; ethylethanol-, 1.4410; methallyl-, 1.4328; diallyl-, 1.4402; 2-methoxyethyl-, 1.4062; and dibutyl-, 1.4180. The literature gives the following values: *sec*-butyl-, 1.394 (34); *n*-octyl-, 1.430 (34); 4-methyl-2-pentyl-, 1.4086 (35); ethanol-, 1.4539 (34); ethylethanol-, 1.444 (36); methallyl-, 1.4303 (37); diallyl-, 1.4399 (37); and dibutyl-, 1.4186 (35).

Aminolysis. Most of the lactamides were made by mixing the reagents with the amine in 10% excess and storing at 35° for 1 to 3 weeks; the mixtures containing cyclohexyl-, benzyl-, and β-methoxyethyl-amine were stored for 4 weeks, and that with isopropylamine for 5 weeks.[7] It was established that incomplete reaction was not due to insufficient reaction

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[7] Glasoe and Audrieth (5) report a 50% yield of N-cyclohexyllactamide from ethyl lactate after 12 days at 25°. D'Ianni and Adkins (4) prepared N-pentamethylenelactamide in 70–80% yield by refluxing ethyl lactate with 10% excess piperidine for 20 hours. For the

time. In two experiments with *sec*-butylamine—one lasting 4 days, the other 2 weeks—the yields of the lactamide were essentially the same.

Because it typifies the procedures, the preparation of N-*n*-octyllactamide is described in detail: To 1.0 mole of methyl lactate was added 1.1 moles of *n*-octylamine; the mixture was stored for 2 weeks and then distilled through a 20-inch Vigreux column. The distillate collected at atmospheric pressure (24 g.) was identified as methanol (boiling point and refractive index); when the pressure was lowered (oil pump), 12 g. of an intermediate fraction distilled at 30°/30 to 148°/0.5. The last fraction (194 g.) was N-octyllactamide, b.p. 148–154°/0.5; yield, 96%. A sample was recrystallized from ether three times and its melting point and elementary composition were determined (Table I). The lactamides that were solid at room temperature were recrystallized; most of the liquid lactamides were carefully redistilled through the Vigreux column prior to determination of physical properties (Table I).

Because benzyllactamide crystallized in the stillhead and could not be conveniently distilled, it was isolated and purified by crystallization.

In the experiment with methylaniline, marked with a relatively low yield (50%), unreacted methyl lactate was not recovered. A high-boiling material, however, corresponding to 36% by weight of the initial ester, was obtained. This was tentatively identified as a partially aminolyzed polylactate.

When a mixture of ethylethanolamine (0.55 mole) and methyl lactate (0.5 mole) was allowed to stand at 35°, the aminolysis (as determined by titration) was about 70% after 4 days. Aminolysis did not proceed much further even in 5 weeks. On distillation, an 88% yield of methanol and several high-boiling fractions having different refractive indices were obtained. The largest fraction [30 g. distilling at 95–114° (3 to 7 microns)] might have been the impure N,N-ethylhydroxyethyllactamide; d^{20}_{4} 1.141 and n^{20}_{D} 1.4728. M^{20}_{D} Calc'd: 41.18; Found: 39.62. In a second experiment, six fractions (amounting to a conversion of 64% into the lactamide) were obtained by distillation in a molecular still. These had refractive indices (n^{20}_{D}) ranging from 1.4762 to 1.4811.

Anal. Calc'd for $C_7H_{15}NO_3$: N,8.7; Found: N,8.7.

Dibutylammonium lactate was obtained from a mixture of methyl lactate, dibutylamine and water that had stood for several weeks. After crystallization from ether, m.p. 77.5–79°.

Anal. Calc'd for $C_{11}H_{25}NO_3$: C, 60.2; H, 11.5; N, 6.4.
Found: C, 60.6; H, 11.7; N, 6.4.

Two mixtures of 0.10 mole of methyl lactate and 0.11 mole of diphenylamine—one stored at 35° for 15 days, the other at 100° for 13 days—failed to yield methanol on distillation.

Experiments with dimethylamine. (a) *Methyl propionate.* A mixture of 88 g. (1 mole) of the ester and 49.5 g. (1.1 moles) of amine was stored for 1 month. Titration indicated that only about half the amine had reacted, hence 1 ml. of water was added as catalyst (12). After an additional three months, titration indicated 85% reaction. After drying with calcium sulfate, dimethylpropionamide was distilled in 70% yield. The middle fraction (63% yield) had the following properties, in good agreement with the literature (38): b.p. 81.5–82°/26; n^{20}_{D} 1.4400; n^{25}_{D} 1.4382; d^{25}_{4} 0.9269; M^{20}_{D} 28.77.

Anal. Calc'd for $C_5H_{11}NO$: N, 13.8; Found: N, 13.9.

(b) *Methyl acetate.* A similar experiment with this ester showed 60% reaction after 1 month and 89% reaction after an additional 3 months in the presence of water; the yield of dimethylacetamide obtained by distillation was 69%. The middle fraction (58% yield) had the following properties, which are in good agreement with the literature (38): b.p. 74–74.5°/26; n^{20}_{D} 1.4373; n^{25}_{D} 1.4360; d^{20}_{4} 0.9429; M^{20}_{D} 24.22.

Anal. Calc'd for C_4H_9NO: N, 16.1; Found: N, 16.0.

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product, they reported b.p. 128–9°/7, n^{20}_{D} 1.4850, N, found 8.78. Bischoff and Walden (6) prepared N-methyl-N-phenyllactamide from the amine and lactic acid, lactide, and ethyl lactate, which gave the lowest yield even after 1 day's heating at 200°. They report m.p. 95–96°. Leipen (8) prepared lactanilide from the amine and ethyl lactate, and reports m.p. 58°.

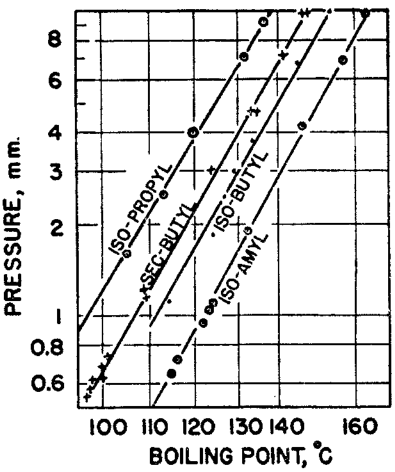

FIG. 1. BOILING POINTS OF N-ALKYL LACTAMIDES

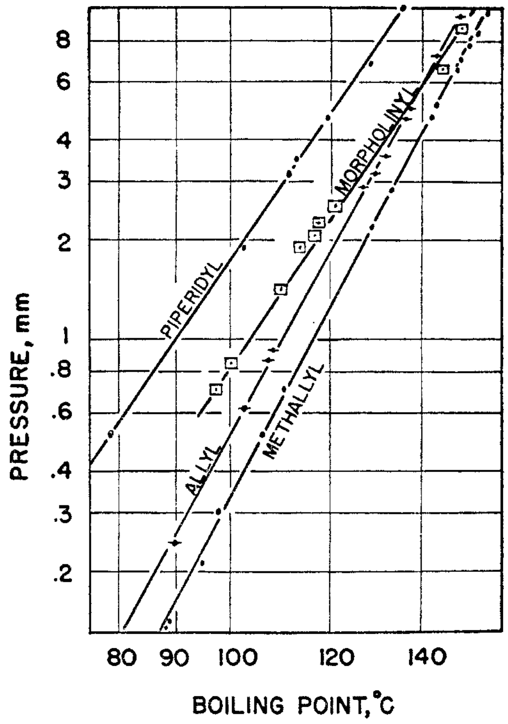

FIG. 2. BOILING POINTS OF N-SUBSTITUTED LACTAMIDES

(c) *Methyl glycolate.* Titration of a mixture of 90 g. (1 mole) of redistilled ester and 1.1 moles of amine that had been stored for 1 week showed 95% reaction; standing for an additional week produced no further change. After distillation of methanol and excess amine, dimethylglycolamide was collected at about 90°/0.5 in 89% yield. After several crystallizations from ether, and thorough drying, it melted at 43–45.5°. This material was deliquescent.

Anal. Calc'd for $C_4H_9NO_2$: N, 13.6; Found: N, 13.4.

Diethylamine was unreactive toward both methyl propionate and methyl glycolate.

Polymerization of N-allyllactamide. (a) Air was passed through allyllactamide containing 0.14% cobalt octanoate. After 10 days the mixture had darkened without perceptible polymerization.

(b) Sealed tubes containing allyllactamide and different amounts of benzoyl peroxide (some sealed under nitrogen and some under air) were kept at 100° for 8 days. Air and nitrogen had approximately the same effect. A 1% concentration of benzoyl peroxide was only slightly more effective than no peroxide, and 5% and 10% concentrations of benzoyl peroxide gave increasingly viscous solutions, indicating some polymerization.

Boiling points at different pressures of some of the lactamides (Figures 1 and 2) were carefully determined with an improved tensimeter-still (39). The boiling points of Table I were observed during the preparation.

SUMMARY

The aminolysis of methyl lactate with primary and secondary amines is shown to be a simple and convenient method for preparing many N-monosubstituted lactamides and certain types of N-disubstituted lactamides.

The preparation and properties of seventeen N-substituted lactamides are described.

PHILADELPHIA 18, PENNSYLVANIA

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