the catalyst and solvent left a red sirup which readily crystallized to a yellow solid when heated with 100 ml. of water and 20 ml. of concentrated ammonium hydroxide. Most of the color could be removed by slurrying with cold ethyl acetate. Three experiments gave 25.2, 23.2 and 26.5 g. of crude product (melting above 146°) suitable for the next step. A sample recrystallized from ethanol melted at 154–155° uncor.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.11; H, 7.44; N, 5.37.

1-Cyclohexylmethyl-5-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline.—Reduction of 12.7 g. of the above 1-benzyl compound in 100 ml. of acetic acid in the presence of 0.4 g. of Adams platinum oxide catalyst took about eight hours at 50° and 50 lb. initial hydrogen pressure; yield 10.7 g. melting at 147–149° uncor. A sample, recrystallized from methanol, melted at 153.6–154.6° cor. Both the solubility in sodium hydroxide, the melting point and the ultraviolet absorption spectra of this compound indicated that the benzene ring and not the phenolic ring had been reduced.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71; N, 5.40. Found: C, 78.61; H, 9.53; N, 5.28.

The hydrochloride, recrystallized from isopropyl alcohol, melted at 264.0–266.0° cor.

Anal. Calcd. for $C_{17}H_{25}NO \cdot HCl$: C, 69.00; H, 8.86; N, 4.73; Cl, 11.98. Found: C, 68.97; H, 8.58; N, 4.65; Cl, 12.07.

1-Benzyl-2-methyl-5-hydroxydecahydroisoquinoline (IX).—A solution of 26.5 g. of 1-benzyl-2-methyl-5-hydroxy-1,2,3,4-tetrahydroisoquinoline in 150 ml. of 2 *N* sodium hydroxide to which Raney nickel catalyst had been added was shaken with hydrogen at an initial pressure of 825 lb. The temperature was raised until reduction started (at 175°) and then gradually increased to 195°. Reduction was continued for six hours. The product separated as a separate phase. It was extracted with benzene and distilled at 0.4 mm. to give 14.8 g. boiling from 120 to 143°. Since not all of this material was soluble in dilute hydrochloric acid, 6.6 g. of the product was taken up in benzene and washed with 8 ml. of phosphoric acid in water. Addition of potassium carbonate yielded 3.7 g. of oil which was distilled; b.p. 141–146° (0.3 mm.). The product, though not analytically pure, was used for the last step without further purification.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71; N, 5.40. Found: C, 79.95; H, 10.20; N, 5.93.

N-Methylmorphinane (X).—A solution of 2.7 g. of the decahydro compound in 25 ml. of 85% phosphoric acid was refluxed for 70 hours and then poured onto ice. The aqueous phase was extracted with ether and the product then salted out with potassium carbonate. It was taken up in ether, dried and distilled to give 1.0 g. of pale yellow oil boiling at 130–132° at 0.7 mm. The odor was quite similar to several derivatives of the 1-azabicyclo[3.3.1]nonane ring system which have been prepared by one of us.

Anal. Calcd. for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.33; H, 9.50; N, 5.51.

Failure to form a crystalline derivative (picrate, hydrochloride, picrolonate) indicated that the product was a mixture. A test showed high analgesic activity for the mixture. The product decolorized permanganate readily suggesting the presence of 1-benzyl-2-methyl-Δ^5-octahydroisoquinoline.

The material was chromatographed by pouring a solution of 0.484 g. in 3.7 ml. of low boiling petroleum ether onto the top of 30 g. of aluminum oxide in a 50-ml. buret. The column was eluted with 20-ml. portions of low boiling petroleum ether to which was added 0, 0, 0, 1, 3, 5, 5 and 5 ml. of ether, respectively. The last three solvents eluted 0.10, 0.12 and 0.12 g. The latter two samples crystallized; m.p. 50–54°. They gave a picrate melting at 172–174°, not depressed when mixed with a sample of Dr. Grewe's N-methylmorphinane picrate kindly furnished to us by Dr. Nolte. The first fraction gave a picrate which, after one recrystallization, softened at 171° and melted at 178°. It gave a large melting point depression with N-methylmorphinane picrate and was not further investigated.

Acknowledgment.—The authors are indebted to Mr. Morris Auerbach and Kenneth Fleischer and staff for analytical results and also to Dr. Rudolph Grewe and Dr. Elisabeth Nolte for a generous sample of N-methylmorphinane picrate.

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

N-Substituted Lactamides

BY M. L. FEIN AND E. M. FILACHIONE

RECEIVED JANUARY 2, 1953

N,N-Disubstituted lactamides that are difficult to obtain by aminolysis of methyl lactate with secondary amines were readily prepared by dehydration of the lactic acid-secondary amine salt. The preparation and properties of various dialkyl, alkyl aryl, aralkyl and hydroxyalkyl lactamides are reported.

Previous papers from this Laboratory reported that N-monosubstituted lactamides can be prepared in excellent yields by aminolysis of methyl lactate with primary aliphatic amines.[2,3] The reaction is simple, proceeds readily at room temperature, and in most instances results in almost quantitative yields of the substituted lactamide. With a few exceptions, the N,N-disubstituted lactamides, however, were extremely difficult to prepare by such an aminolysis reaction. The notable exceptions were aminolysis of methyl lactate with dimethylamine, piperidine, morpholine, pyrrolidine and diethanolamine, in which instances the yields of N,N-disubstituted lactamide were extremely high.[4,5,6] Thus, N,N-dimethyllactamide was obtained in 90% yield, whereas N,N-dibutyllactamide was virtually unobtainable by aminolysis of methyl lactate with the appropriate secondary amine.

In the study reported here, the preparation of dialkyl lactamides by dehydration of the lactic acid-secondary amine salt was investigated. This general method for the preparation of amides has been applied previously in making aromatic derivatives such as lactanilide.[7,8] N,N-Dibutyllactamide has been suggested as a plasticizer for

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) W. P. Ratchford, *J. Org. Chem.*, **15**, 326 (1950).

(3) W. P. Ratchford and C. H. Fisher, *ibid.*, **15**, 317 (1950).

(4) W. P. Ratchford and C. H. Fisher, THIS JOURNAL, **69**, 1911 (1947).

(5) W. P. Ratchford, J. H. Lengel and C. H. Fisher, *ibid.*, **71**, 647 (1949).

(6) W. P. Ratchford, *Ind. Eng. Chem.*, **42**, 1565 (1950).

(7) Leipen, *Monatsh.*, **9**, 45 (1888).

(8) C. A. Bischoff and P. Walden, *Ann.*, **279**, 71 (1894).

TABLE I

PREPARATION AND PROPERTIES OF N-SUBSTITUTED LACTAMIDES

Lactamide	Reaction conditions[a] Temp., °C.	Time, hr.	Conversion, %	B.p., °C.	Mm.	M.p.,[c] °C.	Physical constants and analysis[b] $n^{20}D$	d^{20}_4	η at 20° c.p.s.	Nitrogen, % Found	Calcd.
N,N-Diallyl	141–160	8	68	111	5.0		1.4792	1.0115	14.38	8.01	8.28
N,N-Di-*n*-butyl	165–187	7	83	145	10.0		1.4540	0.9413	22.05	6.81	6.96
N,N-Di-*n*-amyl	151–158	8	80	150	5.0		1.4552	.9227	27.27	6.09	6.11
N,N-Di-*n*-hexyl	147–161	8	81	154	2.0		1.4566	.9158	34.89	5.32	5.44
N,N-Di-*n*-octyl[h]	170–183	5	77[d]	204	4.0		1.4590	.9018	45.89	4.34	4.47
N,N-Di-2-ethylhexyl[i]	162–184	5	60[d]	179	4.0		1.4612	.9108	94.85	4.33	4.47
N,N-Di-*n*-decyl[j]	149–156	8	83	145	0.004		1.4605	.8892	55.71	3.68	3.79
N,N-Dibenzyl	176–182	6	75	134	.015	73–74	1.5700[e]			5.22	5.20
N-Butyl-N-phenyl	159–172	7	28[d]	134	1.7	38.5–39.5	1.5159[e]			6.21	6.33
N-Methyl-N-phenyl	153–164	11	50[d]			89–90				7.75	7.82
N-Phenyl[f]	110–134	5	87	149	0.9	57–58	1.5635[e]				
N-*t*-Octyl	136–146	9	44	80	.01		1.4585	.9530	202.4	6.78	6.96
N-(α-Methylbenzyl)[g]			50	102	.001	92–94	1.5338[e]			7.28	7.25
N-(β-Phenylethyl)[g]			95			86–87				7.28	7.25
N-(3-Hydroxypropyl)[g]			91	116	.001		1.4848	1.1507		9.64	9.52
N-(1-Hydroxy-2-butyl)[g]			88	111	.02		1.4781	1.1052		8.56	8.69
N,N-Dibutylpropionamide	163–181	11	53	122	10.0		1.4469	0.8758	4.43	7.42	7.56

[a] Reaction temperature and time were recorded after free water from the 80% lactic acid had been removed. [b] Determined on redistilled or recrystallized materials. [c] N-Methyl-N-phenyllactamide was recrystallized from acetone, the others from ether. [d] Unreacted amine was also recovered in appreciable quantity (10 to 60%). [e] Supercooled liquid. [f] Previously reported (ref. 7 and 8). [g] Prepared by aminolysis of methyl lactate with the appropriate amine. [h] Calcd. for $C_{19}H_{39}O_2N$: C, 72.79; H, 12.54. Found: C, 72.70; H, 12.55. [i] Calcd. for $C_{19}H_{39}O_2N$: C, 72.79; H, 12.54. Found: C, 72.69; H, 12.52. [j] Calcd. for $C_{23}H_{47}O_2N$: C, 74.74; H, 12.82. Found: C, 74.71; H, 12.96.

zein,[9] but its preparation and physical properties were not described. Dehydration of the lactic acid-secondary amine salt proved to be a highly satisfactory method for preparing the disubstituted lactamides. The procedure was simple; it consisted in neutralizing aqueous lactic acid with the amine, then dehydrating by refluxing with a high-boiling entraining agent such as xylene.

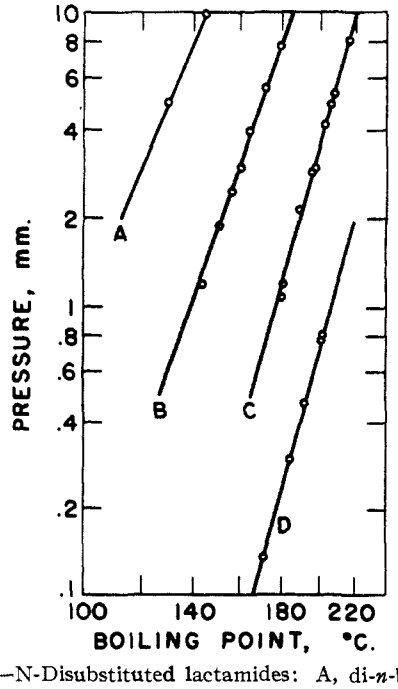

Fig. 1.—N-Disubstituted lactamides: A, di-*n*-butyllactamide; B, di-*n*-hexyllactamide; C, di-*n*-octyllactamide; D, di-*n*-decyllactamide.

(9) C. D. Evans and R. H. Manley, U. S. Patent 2,437,946, March 16, 1948.

Water present as solvent was removed rapidly, whereas dehydration of the salt to amide occurred more slowly and at temperatures in the neighborhood of 150°. In general, conversion into the amide was in the range of 70 to 85%. Secondary amines containing one aryl substituent on the nitrogen and primary aliphatic amines derived from a tertiary alkyl group, such as *t*-octylamine, were not so satisfactory as the simpler secondary amines in this reaction, and were also non-reactive in the aminolysis of methyl lactate. The lactamides were high-boiling materials; those containing an aromatic ring were solids at room temperature. In the preparation of N-methyl-N-phenyl- and N-butyl-N-phenyllactamides large amounts of unreacted amine were recovered and a considerable quantity of lactide was formed.

Experimental

Amines.—Commercial materials were redistilled; they had the following constants: Diallylamine, b.p. 110° at about 760 mm., $n^{20}D$ 1.4402; di-*n*-butylamine, b.p. 158.5° at about 760 mm., $n^{20}D$ 1.4182; di-*n*-amylamine, b.p. 77.5° at 9 mm., $n^{20}D$ 1.4270; di-*n*-hexylamine, b.p. 104° at 7 mm., $n^{20}D$ 1.4338; di-(2-ethylhexyl)-amine, b.p. 126° at 4.0 mm., $n^{20}D$ 1.4431; di-*n*-octylamine, b.p. 151° at 5.0 mm., $n^{20}D$ 1.4345; didecylamine, b.p. 184–186° at 3.0 mm.; dibenzylamine, b.p. 151.5–152° at 5.0 mm., $n^{20}D$ 1.5760; aniline, b.p. 75–76° at 15 mm.; N-methylaniline, b.p. 79.5–81° at 12 mm., $n^{20}D$ 1.5697; and N-butylaniline, b.p. 111–112° at 10 mm., $n^{20}D$ 1.5339.

Lactamides Obtained by Dehydration of Lactic Acid-amine Salts.—The following procedure for the preparation of N,N-dibutyllactamide was typical of the preparation of the various lactamides.

Edible grade 80% lactic acid (112 g., 1 mole of total available lactic acid) was neutralized with the equivalent amount of dibutylamine (129 g., 1.0 mole) which was added portionwise and with occasional cooling and shaking. Then xylene (100 ml.) was added, and the two-phase reaction mixture, continuously stirred, was refluxed under a water-separating trap, commonly used for removing water formed in esterification reactions. Thus water was continuously removed by xylene, the entraining agent. The water normally

present in the 80% lactic acid (*ca.* 22 ml.) was removed rapidly, but the water resulting from dehydration of the amine lactate was formed at higher temperature and at a considerably slower rate. After removal of free water, 11 hours of refluxing at 154 to 166° was required to collect 18 ml. (1 mole) of water formed by dehydration of the salt. By using less entraining agent (50 ml. instead of 100 ml.) the reaction temperature was increased, and dehydration was completed considerably faster (7 hours instead of 11).

Upon completion of the reaction, the xylene was removed by distillation at 40–50 mm., and the dibutyllactamide was isolated by distillation at 5.0 mm.

The preparation of other substituted lactamides is summarized in Table I. The physical constants and analytical data were determined on redistilled or recrystallized samples. The solid lactamide derivatives were recrystallized from ether, except N-β-phenylethyllactamide, which was recrystallized from acetone. For purposes of comparison, N,N-dibutylpropionamide was also prepared.

Lactamides by Aminolysis of Methyl Lactate.—N-(α-methylbenzyl)-, N-(β-phenylethyl)-, N-3-hydroxypropyl- and N-(1-hydroxy-2-butyl)-lactamides were prepared by aminolysis of methyl lactate with an equivalent amount of α-methylbenzylamine, β-phenylethylamine, 3-aminopropanol and 2-amino-1-butanol, respectively. This method has been described previously.[3,6] The results are shown in Table I.

Boiling points of dibutyl, dihexyl, dioctyl and didecyl lactamides were determined at various pressures in the range of 0.1 to 10.0 mm. with a tensimeter still.[10] The results are shown in Fig. 1.

Acknowledgment.—The authors wish to thank Mary Jane Welsh and Ruth Kelly of this Laboratory for the analyses and T. J. Fitzpatrick for help in several preparations. They also thank the following companies[11] for generous samples: Sharples Chemical, Inc., for dibutylamine, diamylamine, dihexylamine, didecylamine, N-butylaniline; Heyden Chemical Company for dibenzylamine; Carbide and Carbon Chemicals Corp. for di-2-ethylhexylamine, N-α-methylbenzylamine; Rohm and Haas Co. for *t*-octylamine; Monsanto Chemical Co. for β-phenylethylamine; Shell Development Co. for diallylamine; Commercial Solvents Company for 2-amino-1-butanol; American Cyanamid Co. for 3-aminopropanol.

(10) W. P. Ratchford and C. E. Rehberg, *Anal. Chem.*, **21**, 1417 (1949).

(11) Mention of names, brands or companies should not be construed as a recommendation or endorsement by the Department of Agriculture over those not mentioned.

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Ester-amides of Lactic Acid

BY M. L. FEIN AND E. M. FILACHIONE

RECEIVED JANUARY 2, 1953

Various esters of N-substituted lactamides, particularly dialkyl-, hydroxyalkyl- and di-(hydroxyalkyl)-lactamides, were prepared. Concurrent esterification and dehydration to produce satisfactory yields of esters of lactamides was accomplished by heating a mixture of the lactic acid–amine salt, fatty acid, and an entraining agent.

Because lactic acid contains both hydroxyl and carboxyl groups it is capable of being transformed into numerous derivatives which are simultaneously an ester and an amide. However, comparatively little information has been reported concerning these ester-amide derivatives of lactic acid. Earlier investigators have reported a few esters of lactamide, dimethyllactamide and lactanilide.[2–7]

More recently some acetates, acrylates and methacrylates of substituted lactamides have been reported.[8–11]

This paper reports various additional ester-amides of lactic acid particularly esters of the N,N-disubstituted lactamides and the hydroxyalkyl lactamides. The preparation of some of these ester-amides by simultaneous direct esterification and dehydration of the lactic acid–amine salt was also investigated.

The pure ester-amides were prepared by acylation of the lactamide with acid anhydrides or chlorides. Subsequently it was found practical to prepare at least some of these derivatives by direct esterification in which carboxylic acids were employed. The direct esterification of N,N-dibutyllactamide with lauric acid proceeded very slowly, and only approximately 40% esterification occurred as judged by the amount of water removed during the reaction. The yield of desired ester-amide was very poor. It was of interest that if the esterification was conducted with the lactic acid–amine salt in place of the lactamide the esterification proceeded satisfactorily with concurrent dehydration of the amine salt, and good yields of the ester of the substituted lactamide were obtained. Similarly a satisfactory yield of hydroxyethyllactamide dipelargonate was obtained by this method.

Experimental

Preparation of Lactamides.—Butyllactamide and the hydroxyalkyllactamides were prepared in almost quantitative yields by aminolysis of methyl lactate as previously described.[9–12] Lactanilide, *t*-octyllactamide and the dialkyllactamides were prepared in satisfactory yield by dehydration of the corresponding lactic acid–amine salt as reported recently.[13]

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Lambling, *Bull. soc. chim.*, [3] **17**, 356 (1897).

(3) E. E. Blaise, *ibid.*, [4] **15**, 661 (1914); [4] **15**, 666 (1914).

(4) R. Anschütz and W. Bertram, *Ber.*, **37**, 3971 (1904).

(5) K. Freudenberg and L. Markert, *ibid.*, **60**, 2447 (1927).

(6) K. Freudenberg and M. Meister, *Ann.*, **518**, 86 (1935).

(7) C. M. Bean, J. Kenyon and H. Phillips, *J. Chem. Soc.*, 303 (1936).

(8) W. P. Ratchford, J. H. Lengel and C. H. Fisher, THIS JOURNAL, **71**, 647 (1949).

(9) W. P. Ratchford, *J. Org. Chem.*, **15**, 326 (1950).

(10) D. D. Reynolds and W. O. Kenyon, U. S. Patents 2,458,420 (Jan. 4, 1949) and 2,458,421 (Jan. 4, 1949).

(11) D. D. Reynolds and J. H. Van Campen, U. S. Patent 2,458,422 (Jan. 4, 1949).

(12) W. P. Ratchford, *Ind. Eng. Chem.*, **42**, 1565 (1950).

(13) M. L. Fein and E. M. Filachione, THIS JOURNAL, **75**, 2097 (1953).