are much less soluble than the semicarbazones of the corresponding levulinic esters. The semicarbazones isolated in this way were identical in m.p. and mixed m.p. with those obtained from the products of the Wolff synthesis (Table II).

TABLE II

SEMICARBAZONES OF THE ACETYLACRYLIC ESTERS

Alkyl	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	193–194[a,b]		
Ethyl	199–200[b]	21.10	21.08
Propyl	161–163[c]	19.71	19.75
Butyl	135–136	18.50	18.39
Benzyl	165–166[c]	16.10	16.22

[a] Rinkes and v. Hasselt, *Chem. Centr.*, **87**, II, 390 (1916); *cf.* **88**, I, 208 (1917), give m.p. 196°. [b] Mixture of methyl and ethyl semicarbazones melted at 188–191°. [c] Mixture of propyl and benzyl semicarbazones melted at 138–150°.

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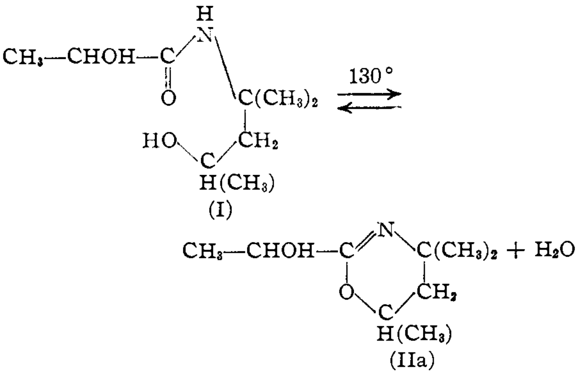
Lactic Acid Derivatives. 4,4,6-Trimethyl-2-(1-hydroxyethyl)-5,6-dihydro-1,3,4H-oxazine[1]

BY WILLIAM P. RATCHFORD

Although hydroxy alkyl amides of lactic acid are generally prepared from methyl lactate without difficulty[2] the attempted preparation of N-(1,1-dimethyl-3-hydroxybutyl)-lactamide (I), from 4-methyl-4-amino-2-pentanol and methyl lactate has led instead to the formation (at 130°) of an anhydro compound of empirical formula $C_9H_{17}O_2N$ (II), which we believe to be 4,4,6-trimethyl-2-(1-hydroxyethyl)-5,6-dihydro-1,3,4H-oxazine (IIa).



The lactamide (I) was obtained in 12% yield by crystallization from the aminolysis mixture and also by reversal of the above reaction. The evidence on which we assign the structure (IIa) is (1) empirical formula, (2) neutralization equivalent, (3) hydroxyl analysis, (4) conversion of (II) to (I) by an equivalent of water, (5) analysis of the picrate of (II), (6) molecular refraction (the observed molecular refraction, 47.75, agreed more closely with that calculated[3] for (IIa), 47.76, than with that for an N-alkene lactamide, 48.72), and (7) analogy with the work of Smith and Adkins,[4] who attempted to distil N-(1,1-dimethyl-3-hydroxybutyl)-acetamide at 130–140°, and obtained instead 2,4,4,6-tetramethyl-5,6-dihydro-1,3,4H-oxazine.

The two methyl groups on the carbon adjacent to the amide nitrogen promote the dehydration of (I) to (II), for N-(3-hydroxybutyl)-lactamide (which lacks these two methyl groups) was distilled in a tensimeter-still[5] without difficulty.

Experimental[6]

Materials.—The methyl lactate, a commercial material, was redistilled in vacuum. The 4-methyl-4-amino-2-pentanol was distilled in vacuum in an efficient still; b. p. 83° (22 mm.); n^{20}_D 1.4362; neut. equiv., 116.4 (calcd., 117.2).

4,4,6-Trimethyl-2-(1-hydroxyethyl)-5,6-dihydro-1,3,-4H-oxazine.—To 128 g. (1.1 moles) of the amine was added 104 g. (1.0 mole) of methyl lactate; after storage at room temperature for seven days, a sample of the mixture showed 97% reaction. Methanol and excess amine (and possibly water) were removed under vacuum (Vigreux column); the pressure was gradually lowered so that the temperature of the liquid did not exceed 130°. The remaining liquid was transferred to the tensimeter-still. It had a higher vapor pressure than expected; it distilled at 92° (14.5 mm.) to 97° (9.5 mm.) in 90% yield (computed as (II)). The temperature of the liquid did not exceed 130°. After redistillation twice in vacuum (Vigreux column), b. p. 97° (18.5 mm.), the following properties were determined: n^{20}_D 1.4481; d^{20}_4 0.9679; neut. equiv. (in ice-water), 171.6, 171.1 (basic). *Anal.* Calcd. for $C_9H_{17}O_2N$: C, 63.1; H, 10.0; N, 8.18; neut. equiv., 171.2; OH, 9.9. Found: C, 63.1; H, 10.2; N, 8.08; OH, 10.5.[7]

Base Picrate.—The picrate of (II) was formed in good yield by treatment with picric acid in benzene, and was recrystallized thrice from benzene, m. p. 147°. *Anal.* Calcd. for $C_{15}H_{20}O_9N_4$: C, 45.0; H, 5.04; N, 14.0. Found: C, 45.7; H, 5.18; N, 13.8. A picrate of 4-methyl-4-amino-2-pentanol was prepared, m. p. 146–147°; mixed m. p. with the oxazine picrate 120–125°.

Attempts to characterize (II) through the 3,5-dinitrobenzoate and the *p*-nitrobenzoate were unsuccessful; the former was a gummy mass and the latter an oil. Toward benzenesulfonyl chloride, (II) was unreactive.

Hydrolysis of (II) to (I).—To an 8.0-g. (0.047 mole) sample of (II) was added 0.85 g. (0.047 mole) of water. After ten days, the mixture solidified. It was recrystal-

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[1] Contribution from one of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

[2] Ratchford, *Ind. Eng. Chem.*, in press,

[3] Using 4.10 for the atomic refraction of N in the group C—N=C of (IIa) (von Auwers, *Z. physik. Chem.*, **147**, 436 (1930)); 2.76 for N in the unsaturated lactamide (D'Alelio and Reid, THIS JOURNAL, **59**, 109–111 (1937)), and the customary values for the other atoms (Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1751).

[4] Smith and Adkins, THIS JOURNAL, **60**, 407 (1938).

[5] Ratchford and Rehberg, *Anal. Chem.*, **21**, 1417 (1949).

[6] All melting points are uncorrected.

[7] Hydroxyl determination by the method of Ogg, Porter and Willits, *Ind. Eng. Chem., Anal. Ed.*, **17**, 394 (1945).

lized thrice from ether-ethanol, m. p. 93-95.5°; mixed m. p. with authentic (I) 93-93.5°. *Anal.* Calcd. for $C_9H_{19}O_3N$: N, 7.40. Found: N, 7.36.

N-(1,1-Dimethyl-3-hydroxybutyl)-lactamide (I).—The aminolysis reaction was repeated, using 1 mole each of ester and amine; after sixteen days, titration indicated 89% reaction. An aliquot was seeded with (I) and cooled; it became a semi-solid mass. This was filtered, and the solid was crystallized once from ether-ethanol yielding 12% of crude (I) (m. p. 88-90°). The crude (I) was recrystallized several times from ether-ethanol, m. p. 94-95.5°. *Anal.* Calcd. for $C_9H_{19}O_3N$: C, 57.1; H, 10.1; OH, 18.1. Found: C, 56.8; H, 10.0; N, 7.52; OH, 18.5.[7]

Acknowledgment.—The author is indebted to Ruth W. Brand for the analyses, to Robert J. Gallagher for assistance, and to the Shell Chemical Corporation for a generous sample of the amine.

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Synthetic Analogs of Oxytocic Drugs. IV. Miscellaneous Substituted-β-alanine Esters

BY ARTHUR P. PHILLIPS

Oxytocic activity having been discovered in a series of phenethyl-β-alanine esters[1] an exploration was made of the effect of modifying various portions of the molecular structure.[2,3] This paper reports the preparation of a variety of β-alanine ester types: (1) bearing purely aliphatic substituents on the nitrogen; (2) N-benzyl or N-phenethyl derivatives having not one but two 2-carbomethoxyethyl groups on the nitrogen; and (3) in which the β-nitrogen is part of a saturated heterocyclic ring.

None of these compounds possessed significant oxytocic activity, but most of them are of extremely low toxicity.

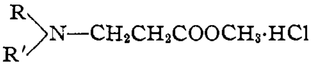
The substances included were all synthesized by reaction of the appropriate amine with methyl acrylate giving excellent yields in most cases. The substituted bis-2-carbomethoxyethylamines were made by heating under reflux a mixture of the particular primary amine and about five moles of methyl acrylate for from ten to twenty hours.

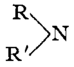
Experimental

Data on the compounds are included in Table I. The method of preparation and isolation are illustrated by a few examples.

6,7-Dimethoxy-N-(2-carbomethoxyethyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride.—A mixture of 10 g. (0.05 mole) of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with 12 cc. (nearly 0.15 mole) of methyl acrylate in 25 cc. of benzene was refluxed for twenty-four hours. Basic material was extracted from benzene with 3 *N* hydrochloric acid. The aqueous acid extracts were basified with potassium carbonate and liberated base was extracted with ether. After drying over anhydrous potassium carbonate addition of a slight excess of methanolic hydrogen chloride to the ethereal solution precipitated the product as the hydrochloride. The yield of white crystals was 8 g. (50%) and after several crystallizations from methanol-ether mixtures these melted at 177-178°.

TABLE I

MISCELLANEOUS SUBSTITUTED-β-ALANINE ESTER SALTS 
$\left.\begin{matrix}R\\R'\end{matrix}\right\rangle N—CH_2CH_2COOCH_3\cdot HCl$

R	R'	Crystn. solvent[a]	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
(1) R and R' = simple aliphatic groups (or hydrogen)								
CH_3	H[b]	Free base	44	B. p. 71-73, 29 mm.				
n-C_3H_7	n-C_3H_7[c]	Ac	67	134-135	51.99	51.87	8.37	8.31
n-C_4H_9	n-C_4H_9[c,d]	Ac. E.	50	125-126.5	55.08	55.15	8.92	8.72
n-C_5H_{11}	n-C_5H_{11}[c]	M. Ac. E.	80	232-234	57.60	57.55	9.38	9.74
(2) R' = $CH_2CH_2COOCH_3$								
CH_3[b]		Free base	37	B. p. 133-135, 12 mm.				
$C_6H_5CH_2$		M. Ac. E.	80	85.5-87	57.02	56.78	7.03	7.05
4-$CH_3OC_6H_4CH_2CH_2$		M. Ac. E.	100	118-119	56.71	56.73	7.29	7.62
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$		Ac. E.	90	124-125	55.42	55.66	7.25	7.44
(3)  $\left.\begin{matrix}R\\R'\end{matrix}\right\rangle N$ = a saturated heterocyclic ring								
$C_5H_{10}N$[e,f]		M. E.	90	195-196	52.05	52.57	9.35	9.13
$C_9H_{10}N$[g]		M. E.	100	157-158	61.02	60.85	7.10	6.89
$C_{11}H_{14}NO_2$[h]		M. E.	50	177-178	57.02	57.01	7.02	7.34
$C_{12}H_{16}NO_2$[i]		M. E.	90	192-193	58.23	58.55	7.34	7.33
$C_{11}H_{15}N_2$[j,k]		M. Ac.	95	225-226	53.70	53.84	7.22	7.58

[a] Ac = acetone; E = ether; M = methanol. [b] Known compound; see Morsch, *Monatsh.*, **63**, 220 (1933). [c] Acid oxalate salt since the hydrochloride seemed intractable. [d] The base had b. p. 108° (6 mm.). [e] The base had b. p. 110-111° (21 mm.). [f] $C_5H_{10}N$ = 1-piperidino-. [g] $C_9H_{10}N$ = 1,2,3,4-tetrahydro-2-isoquinolino-. [h] $C_{11}H_{14}NO_2$ = 6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolino-. [i] $C_{12}H_{16}NO_2$ = 6-ethoxy-7-methoxy-1,2,3,4-tetrahydro-2-isoquinolino-. [j] $C_{11}H_{15}N_2$ = N'-benzyl-N-piperazino-. [k] The dihydrochloride.

N,N-Bis-(2-carbomethoxyethyl)-homoveratrylamine Hydrochloride.—A mixture of 36 g. (0.2 mole) of homoveratrylamine and 120 g. (1.3 moles) of methyl acrylate was refluxed for twenty-four hours on a steam-bath. The

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(1) Baltzly, Dvorkovitz and Phillips, THIS JOURNAL, **71**, 1162 (1949).

(2) Baltzly and Phillips, *ibid.*, **71**, 3419 (1949).

(3) Baltzly and Phillips, *ibid.*, **71**, 3421 (1949).