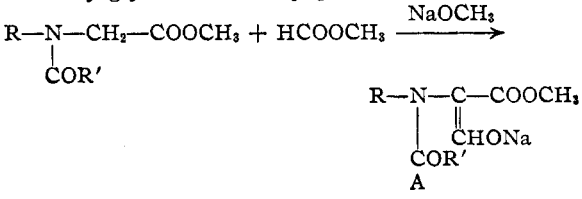
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Studies on Imidazoles. II. The Synthesis of 5-Imidazolecarboxylates from Glycine and Substituted Glycine Esters

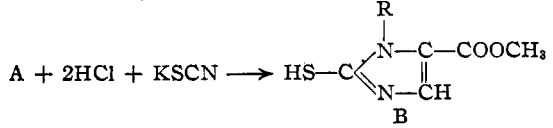
BY REUBEN G. JONES

A number of biologically important derivatives of imidazole including histamine, histidine, methylhistidine and pilocarpine have substituents attached to the 4- or 5-position of the imidazole ring. Although methods of synthesizing these compounds have been rather thoroughly investigated, the methods generally involve many tedious steps and low yields. Therefore, it was of interest to investigate more simple and direct ways of preparing imidazoles with suitable substituents in the 4(or 5)- and 1,5-positions.

This paper describes the synthesis of 5-imidazolecarboxylates from glycine and N-substituted glycine derivatives. It is known that N-acylated glycine esters may be formylated by the Claisen method to give the sodium enolate salts of N-acyl-C-formylglycine esters,[1] [A].



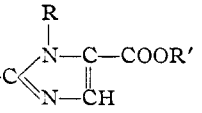
It has now been found that the sodium enolate salts (A) may be treated with acid and thiocyanate to yield 2-mercapto-5-imidazolecarboxylic acid esters,[2] (B).



This reaction takes place smoothly when the acyl group (—COR′) of A is formyl or acetyl but not when the acyl group is benzoyl. It was surprising to find that a pre-hydrolysis of A to form the intermediate, $RNHCH(CHO)COOCH_3$, was unnecessary. The reactions were best carried out by adding acid and thiocyanate simultaneously to a water or water–alcohol solution of A and heating. Under these conditions the N-acyl group appeared to be rapidly cleaved. A number of 2-mercapto-5-imidazolecarboxylates prepared in this way are presented in Table I.

TABLE I

2-MERCAPTO-5-IMIDAZOLECARBOXYLATES[2]



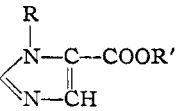
R	R′	Empirical formula	Yield, %[a]	M.p., °C.	Analyses,[b] % (C and H or N) Calcd.	Found
H	CH_3	$C_5H_6N_2O_2S$	50	190–191 (dec.)	17.70	17.24
H	C_2H_5	$C_6H_8N_2O_2S$	50–60	184	41.84, 4.68	42.03, 4.99
CH_3	CH_3	$C_6H_8N_2O_2S$	72–77	193–194	16.27	16.43
$(CH_3)_2CH$	CH_3	$C_8H_{12}N_2O_2S$	93	148–149	13.99	13.61
C_6H_{11}[c]	CH_3	$C_{11}H_{16}N_2O_2S$	90	171–172	11.66	11.56
$C_6H_5CH_2$	CH_3	$C_{12}H_{12}N_2O_2S$	97	174–175[d]	58.04, 4.87	58.00, 4.88
C_6H_5	CH_3	$C_{11}H_{10}N_2O_2S$	86	224–225 (dec.)	11.95	11.96
C_6H_5	C_2H_5	$C_{12}H_{12}N_2O_2S$	91	188–190	11.28	11.43

[a] Yields are based on the N-formylglycine esters (Table III) as starting materials. [b] Analytical samples were recrystallized from water or alcohol. [c] Cyclohexyl. [d] A second crystalline modification of this compound was also obtained which melted at 146–147°. When this melt was seeded with the higher melting form, it resolidified and then melted again at 174–175°.

The mercaptoimidazoles of Table I were oxidized by the well-known nitric acid method[3] to form the imidazoles listed in Table II. This nitric acid oxidation was modified in that lower tempera-

TABLE II

5-IMIDAZOLECARBOXYLATES[2]



R	R′	Empirical formula	Yield, %	M.p., °C.	Nitrogen analyses,[a] % Calcd.	Found
H	C_2H_5	$C_6H_8N_2O_2$[b]	80–86	157–158	20.00[c]	19.70
CH_3	CH_3	$C_6H_8N_2O_2$	82–86	56–57[d]	20.00	19.81
$(CH_3)_2CH$	CH_3	$C_8H_{12}N_2O_2$	72	liquid[e]	16.66	16.34
C_6H_{11}[f]	CH_3	$C_{11}H_{16}N_2O_2$	97	90–91	13.45	13.57
$C_6H_5CH_2$	CH_3	$C_{12}H_{12}N_2O_2$	83	63–64	[g]	
C_6H_5	C_2H_5	$C_{11}H_{10}N_2O_2$	98	80–81	12.96	13.21

[a] Samples for analyses were recrystallized from water and/or alcohol. [b] Previously prepared by a different method, see ref. 8. [c] *Anal.* Calcd.: C, 51.42; H, 5.75. Found: C, 51.47; H, 5.53. [d] B. p. 115° (8 mm.). [e] B. p. 129–131° (13 mm.). [f] Cyclohexyl. [g] Analyzed as the nitrate, see Experimental.

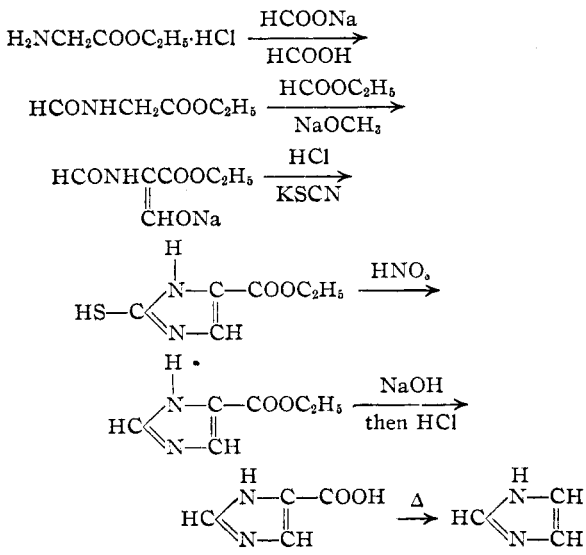
(1) Erlenmeyer and Stoop, *Ann.*, **337**, 236 (1904).

(2) When the substituent, R, is hydrogen the compound must be designated as a 4(or 5)-imidazolecarboxylate.

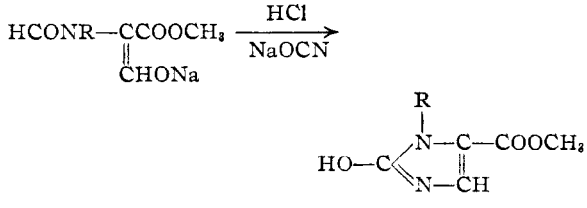
(3) Marckwald, *Ber.* **25**, 2354 (1892); Pyman, *J. Chem. Soc.*, **99**, 668 (1911).

tures and more concentrated nitric acid were used. It was observed that the oxidation of mercaptoimidazoles even in hot nitric acid did not take place unless oxides of nitrogen were present. However, by adding a little sodium nitrite to initiate the oxidation, it was possible to carry out the reaction at 25 or 30°, and under these conditions there was no significant hydrolysis of the ester groups.

Starting with the readily available glycine ethyl ester hydrochloride, the present imidazole synthesis constitutes an excellent method for the preparation of imidazole itself. By the following sequence of reactions, imidazole has been obtained in over-all yields of 35 to 40%



The condensation of the sodium enolate salts A with cyanate took place less satisfactorily than with thiocyanate, and only moderate yields of 1-substituted-2-hydroxy-5-imidazolecarboxylates were obtained.



It has been found that the carbalkoxy groups in imidazoles such as those of Table II can be readily converted to aldehyde, ketone, hydroxymethyl and other groups valuable for the synthesis of important imidazole derivatives. This work will be the subject of a separate publication.

Acknowledgment.—The writer expresses his appreciation to William L. Brown and Howard L. Hunter for the microanalyses reported herein, and to Keith C. McLaughlin for valuable assistance.

Experimental

N-Formyl-N-substituted-glycine Esters.—These compounds, listed in Table III, were prepared from the appropriate amine hydrochlorides by the method[4] illustrated in the following typical example.

A mixture of 272 g. (2.0 moles) of cyclohexylamine hydrochloride, 250 ml. of 40% formalin, and 100 ml. of water, in a flask provided with a stirrer, was cooled in an ice-bath, and with continuous stirring a cold concentrated, aqueous solution of 130 g. (2.0 moles) of potassium cyanide was added in portions over a period of two hours. The temperature was held below 10°, and a little solid carbon dioxide was added from time to time to maintain a carbon dioxide atmosphere. The mixture was stirred for one additional hour and then extracted with two 500-ml. portions of ether. After drying the solution over calcium oxide, the ether was removed by gentle warming, finally under vacuum. The crude cyclohexylaminoacetonitrile was dissolved in 2.5 l. of dry methanol which had been saturated in the cold with hydrogen chloride. This solution was allowed to stand overnight at room temperature and then heated under reflux for four hours. The ammonium chloride which had separated was removed by filtration. The filtrate was evaporated on the steam-bath under vacuum to a volume of about 800 ml. and again filtered through a pad of filter cell. Evaporation of this filtrate under vacuum left a residue of 340 g. of crude N-cyclohexylglycine methyl ester hydrochloride.

The crude ester hydrochloride was dissolved by warming in 250 ml. of 98% formic acid. To this solution was added a hot solution of 150 g. of sodium formate in 200 ml. of 98% formic acid. After the mixture had stood for one hour, the precipitated sodium chloride was removed by filtration through a layer of filter-cel, and 450 ml. of acetic anhydride was added in portions. When the vigorous reaction had subsided the mixture was heated on the steam-bath for one-half hour and then evaporated under vacuum to remove the formic and acetic acids. The residual liquid was taken into 1 l. of acetone whereupon a quantity of sodium chloride separated. The solution was filtered, the acetone distilled and, finally, the residual material was distilled under vacuum to yield pure N-formyl-N-cyclohexylglycine methyl ester as a colorless somewhat viscous liquid.

In the same way, N-formylglycine ethyl ester and methyl ester were prepared from glycine ethyl ester and methyl ester hydrochlorides respectively; and the N-formyl-N-

TABLE III

N-FORMYLGLYCINE ESTERS $\mathrm{HCON(R)CH_2COOCH_3}$

R	Empirical formula	Yield,[a] %	B. p., °C. (1.5 mm.)	$n^{25}D$	Nitrogen, analyses, % Calcd.	Found
H	$C_4H_7NO_3$	86[b]	110–112	1.4555	11.96	11.31
CH_3	$C_5H_9NO_3$	39	97–100[c]	1.4473	10.69	10.34
$(CH_3)_2CH$	$C_7H_{13}NO_3$	22	91–92	1.4503	8.80	8.67
C_6H_{11}[d]	$C_{10}H_{17}NO_3$	40	138–140	1.4808	7.05	7.35
$C_6H_5CH_2$	$C_{11}H_{13}NO_3$	39	144–145	1.5296	6.76	6.83
C_6H_5	$C_{10}H_{11}NO_3$[5]	76[e]	140–142			

[a] Yields are for the over-all process and are based on the amine hydrochloride used. [b] This yield is based on glycine methyl ester hydrochloride. The corresponding N-formylglycine ethyl ester, b. p. 110° (1 mm.) was prepared in 92% yield from glycine ethyl ester hydrochloride. [c] This boiling point is at 4 mm. pressure. The compound was first prepared by Dr. Q. F. Soper. [d] Cyclohexyl. [e] This yield is based on N-phenylglycine methyl ester hydrochloride. The corresponding N-formyl-N-phenylglycine ethyl ester,[5] b. p. 157–159° (7 mm.), was obtained in 90% yield from N-phenylglycine ethyl ester.

(4) The preparation of the substituted glycine ester hydrochlorides from amine hydrochlorides, formaldehyde and cyanide reported here is a modification of Staudt's method for the synthesis of sarcosine; see Staudt, *Z. physiol. Chem.*, **146**, 286 (1925).

phenylglycine ethyl and methyl esters[5] were prepared from the corresponding ethyl and methyl ester hydrochlorides of N-phenylglycine.

Condensation of N-Formylglycine Esters with Methyl Formate.—One example will suffice to illustrate the method by which the N-formylglycine esters of Table III were condensed with methyl formate.

In a three-necked flask provided with a stirrer and thermometer was placed 106 g. (0.67 mole) of N-formyl-N-isopropylglycine methyl ester and 120 g. (2.0 mole) of dry methyl formate. The flask was surrounded with an ice-bath and, with continuous stirring, a suspension of 40 g. (0.74 mole) of sodium methoxide[6] in 150 ml. of dry benzene was added in five portions during a period of one-half to one hour. The temperature of the reaction mixture was maintained below 15°, and stirring was continued for one hour after all of the sodium methoxide had been added. The mixture was then placed in the refrigerator and allowed to stand for twenty-four hours.

If it was desired to isolate the sodium enolate salt, dry ether was added to the reaction mixture, and the solid was collected on a filter, washed with dry ether and dried in vacuum.

2-Mercapto-5-imidazolecarboxylates.—The following example of the preparation of ethyl 2-mercapto 4(or 5)-imidazolecarboxylate shows the method by which the compounds of Table I were prepared.

The reaction mixture of 411 g. (3.12 moles) of N-formylglycine ethyl ester, 700 g. of ethyl formate, 700 ml. of benzene and 183 g. (3.4 moles) of sodium methoxide, carried out as described above, was shaken with 1 l. of water. When all solid had dissolved, the aqueous solution was separated, cooled in an ice-bath and stirred while 565 ml. (6.8 moles) of 12 *N* hydrochloric acid was added slowly. To the resulting solution was added 350 g. (3.6 moles) of crystalline potassium thiocyanate. The mixture was warmed on the steam-bath at 50–70° for two hours, allowed to stand overnight and finally cooled in an ice-bath. The crystalline ethyl 2-mercapto-4(or 5)-imidazolecarboxylate was collected on a filter, washed with a little water and air dried. The yield was 304 g. Yields for a number of experiments varied from 50 to 60% based on N-formylglycine ethyl ester.

N-Acetylglycine ethyl ester[7] (58 g., 0.4 mole) was condensed with 100 ml. of ethyl formate and 24 g. (0.44 mole) of sodium methoxide in 115 ml. of benzene by the procedure described above. The mixture was extracted with 200 ml. of water, 42 g. of potassium thiocyanate and 75 ml. of 12 *N* hydrochloric acid were added to the aqueous solution, and it was heated on the steam-bath for two hours. There was thus obtained 31 g. (43% yield) of ethyl 2-mercapto-4(or 5)-imidazolecarboxylate, identified by melting point and mixed melting point.

N-Benzoyl-C-formylglycine ethyl ester, when treated with thiocyanate under the same conditions as described above for the formyl and acetyl analogs, gave no imidazole compound.

The reactions of thiocyanate with the formyl-N-cyclohexyl, N-benzyl and N-phenylglycine derivatives were carried out in 50% alcohol. In most cases, after acidifying the sodium enolate solutions with two equivalents of hydrochloric acid it was not necessary to immediately add the thiocyanate. For example, 25.7 g. (0.10 mole) of the dry sodium enolate salt of N-formyl-N-benzyl-C-formylglycine methyl ester was dissolved in 100 ml. of 50% alcohol and 19 ml. (0.23 mole) of 12 *N* hydrochloric acid was added. After standing for twenty hours at room temperature, 15 g. (0.155 mole) of potassium thiocyanate was added and the mixture was heated on the steam-bath until most of the alcohol had evaporated. The methyl 1-benzyl-2-mercapto-5-imidazolecarboxylate was collected by filtration, washed with water and air dried. The yield was 24.0 g. (97%). A similar experiment, in which the thiocyanate was added immediately after the hydrochloric acid, yielded 90% of the desired imidazole.

In the case of N-formyl-N-phenyl-C-formylglycine esters it was necessary to add the thiocyanate simultaneously with the acid in order to get a good yield of the mercaptoimidazole. When acidified solutions were allowed to stand without the addition of thiocyanate a sparingly soluble crystalline substance was deposited, the nature of which has not as yet been determined. For example, from 24.3 g. (0.10 mole) of the sodium enolate salt of N-formyl-N-phenyl-C-formylglycine methyl ester and 19 ml. of 12 *N* hydrochloric acid in 100 ml. of 50% alcohol, there was obtained, after twelve hours, 12 g. of crystalline precipitate, m. p. 145–146° (*from alcohol*).

Anal. Found: C, 66.53; H, 5.79; N, 5.79.

Oxidation of 2-Mercapto-5-imidazolecarboxylates. 5-Imidazolecarboxylates.—A solution of 330 ml. of concentrated nitric acid in 950 ml. of water in a large beaker was mechanically stirred, and 2 g. of sodium nitrite was added. The beaker was then surrounded with an ice-bath, and with continuous stirring 300 g. (1.75 mole) of crude methyl 1-methyl-2-mercapto-5-imidazolecarboxylate was added portionwise at such a rate that the temperature of the mixture remained at about 25–35°. After all material had been added the solution was stirred for about ten minutes or until the evolution of nitrogen oxides had completely stopped. An excess of solid sodium carbonate was added carefully and with stirring. The mixture was extracted with four 200-ml. portions of chloroform; the extract was dried, the chloroform removed and the residual liquid distilled in vacuum. The distillate immediately crystallized.

By the same method the other compounds listed in Table II were prepared from the corresponding 2-mercapto compounds. The 1-isopropyl compound was purified by distillation. The 1-cyclohexyl and 1-phenyl compounds separated as crystalline solids and were purified by recrystallization from chloroform–petroleum ether.

Methyl 1-benzyl-5-imidazolecarboxylate separated from the oxidation mixture as the nitrate which did not decompose in the presence of cold excess sodium carbonate. A sample was recrystallized from alcohol; m. p. 170–171°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2 \cdot HNO_3$: C, 51.60; H, 4.76; N, 15.04. Found: C, 51.72; H, 4.52; N, 14.89.

The nitrate was boiled with sodium carbonate solution to liberate methyl 1-benzyl-5-imidazolecarboxylate.

The solution resulting from the oxidation of ethyl 2-mercapto-4(or 5)-imidazolecarboxylate was made basic with ammonium hydroxide (instead of sodium carbonate), chilled to 10° and the precipitated product collected and air dried.

Imidazole-4(or 5)-carboxylic Acid.[8]—Into 500 ml. of 6 *N* sodium hydroxide solution was stirred 250 g. (1.78 moles) of ethyl 4(or 5)-imidazolecarboxylate. The resulting solution was heated on the steam-bath for three hours and then cooled and acidified to *p*H 2.0 with concentrated hydrochloric acid. After standing for two hours the mixture was chilled to 0° and the white crystalline solid was collected on a filter. The product was stirred to a paste with 250 ml. of cold distilled water, filtered and washed on the filter with 200 ml. of alcohol followed by 200 ml. of ether. The yield of air dried product was 180 g. (84%); m.p. 271° (dec.) (lit.[8] 275°).

Anal. Calcd. for $C_4H_4N_2O_2$: N, 25.00. Found: N, 24.75.

Imidazole.—In a 200-ml. round-bottom flask carrying an eighteen-inch Vigreux column and a condenser set for distillation was placed 50 g. (0.45 mole) of 4(or 5)-imidazolecarboxylic acid. The flask was heated with a small flame and decarboxylation took place smoothly. The product was distilled under vacuum to yield 28.5 g. (94%) of pure imidazole, m.p. 90°.

1-Phenyl-2-mercapto-5-imidazolecarboxylic Acid.—A solution of 5 g. (0.02 mole) of ethyl 1-phenyl-2-mer-

(5) Paal and Otten, *Ber.*, **23**, 2587 (1890).

(6) Commercial sodium methoxide of good quality was satisfactory.

(7) Curtius, *Ber.*, **17**, 1663 (1884); *J. prakt. Chem.*, [2] **94**, 116 (1915).

(8) Pyman, *J. Chem. Soc.*, **109**, 186 (1916).

capto-5-imidazolecarboxylate in 12 ml. of 6 *N* sodium hydroxide solution was allowed to stand for forty-eight hours. The solution was acidified with acetic acid but nothing precipitated; therefore, hydrochloric acid was added whereupon a white precipitate of the desired acid seperated. The yield was 4.2 g. (95%). A sample was recrystallized from water for analysis; m.p. 198–200° (dec.).

Anal. Calcd. for $C_{10}H_8N_2O_2S$: N, 12.72. Found: N, 12.71.

1-Methyl-2-mercapto-5-imidazolecarboxylic Acid.—This was prepared from the methyl ester in the same way as described above for the corresponding phenyl compound m.p. 207–208°.

Anal. Calcd. for $C_5H_6N_2O_2S$: N, 17.71. Found: N, 17.55.

N-Formyl-C-formylglycine Ethyl Ester.—The dry sodium enolate salt from the condensation of 1.5 mole of N-formylglycine ethyl ester with ethyl formate was ground to a fine powder and added in one portion with stirring to a freshly prepared mixture of 135 ml. of 12 *N* hydrochloric acid and 200 g. of cracked-ice. As soon as all the salt had dissolved the solution was extracted with twenty 100-ml. portions of chloroform. The chloroform solution was dried with magnesium sulfate and evaporated in vacuum leaving 177 g. of crystalline residue. This was taken up in 1500 ml. of dry ether. The solution was decanted from a little insoluble gum, dried with magnesium sulfate, filtered and evaporated leaving 147 g. (62% yield) of white crystalline solid; m.p. 68–69°.

Anal. Calcd. for $C_6H_9NO_4$: C, 45.27; H, 5.70; N, 8.80. Found: C, 45.38; H, 6.32; N, 9.07.

The compound appeared to be somewhat hygroscopic; it was very soluble in alcohol or water, and slowly underwent decomposition at room temperature but could be kept for reasonably long periods of time at ice-box temperatures.

The corresponding methyl ester was also isolated but in lower yield because it was more water soluble and consequently more difficult to extract with chloroform. It was stable and not hygroscopic; m.p. 108–109°.

Anal. Calcd. for $C_5H_7NO_4$: N, 9.65. Found: N, 9.78.

1-Substituted-2-hydroxy-5-imidazolecarboxylates.—A solution of 20.9 g. (0.10 mole) of the sodium enolate salt of N-formyl-N-isopropyl-C-formylglycine methyl ester in 100 ml. of water was treated with 19 ml. of 12 *N* hydrochloric acid. The solution was allowed to stand for four hours then 9 g. of sodium cyanate was added. Effervescence took place. Gradually, a white crystalline precipitate of methyl 1-isopropyl-2-hydroxy-5-imidazolecarboxylate separated. After seven days the yield was 6.0 g. (32%). An analytical sample was recrystallized from alcohol; m.p. 174–175°.

Anal. Calcd. for $C_8H_{12}N_2O_3$: N, 15.21. Found: N, 14.87.

Methyl 1-cyclohexyl-2-hydroxy-5-imidazolecarboxylate was obtained in 22% yield from the sodium enolate salt of N-formyl-N-cyclohexyl-C-formylglycine methyl ester. It melted at 230–232°.

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: N, 12.50. Found: N, 12.61.

Methyl 1-benzyl-2-hydroxy-5-imidazolecarboxylate was obtained in 8.6% yield from the sodium enolate salt of N-formyl-N-benzyl-C-formyglycine methyl ester. It melted at 160–161°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: N, 12.07. Found: N, 12.20.

Ethyl 2-hydroxy-4-(or 5)-imidazolecarboxylate, obtained in 14% yield from the sodium enolate salt of N-formyl-C-formylglycine ethyl ester melted at 243–245°.

Anal. Calcd. for $C_6H_8N_2O_3$: N, 17.95. Found: N, 18.46.

Summary

A method for the preparation of 1-substituted-5-imidazolecarboxylates and 4(or 5)-imidazolecarboxylates from glycine derivatives is described. This method has also been shown to be a convenient synthesis of imidazole.

INDIANAPOLIS, INDIANA RECEIVED SEPTEMBER 24, 1948

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY,[1] PHILADELPHIA 18, PENNSYLVANIA]

Preparation of N-Alkyl Acrylamides and Methacrylamides by Pyrolysis of the Corresponding Acetoxy Amides

BY WILLIAM P. RATCHFORD, J. H. LENGEL AND C. H. FISHER

In a previous paper[2] it was shown that N,N-dimethylacrylamide (II) and acetic acid are obtained in high yields in the thermal decomposition of N,N-dimethyl-α-acetoxypropionamide (I). The present paper describes the preparation of certain acrylamides and methacrylamides (IV) by pyrolysis of appropriate acetoxy amides, and outlines some of the limitations of this method of making unsaturated amides.

$$\underset{\text{I}}{CH_3COOCH(CH_3)CON(CH_3)_2} \xrightarrow{520^\circ} \underset{\text{II}}{CH_2{=}CHCON(CH_3)_2} + CH_3COOH \quad (1)$$

$$\underset{\text{III}}{CH_3COOC(CH_3)_2CONHCH_3} \longrightarrow \underset{\text{IV}}{CH_2{=}C(CH_3)CONHCH_3} + CH_3COOH \quad (2)$$

N-Methyllactamide and N-methyl-α-hydroxyisobutyramide were made conveniently by allowing methyl lactate and methyl-α-hydroxyisobutyrate, respectively, to stand with methylamine at room temperature. N,N-Diethyllactamide, N,N-dibutyllactamide, and N,N-dimethylhydroxyisobutyramide could not be prepared satisfactorily by this method because of excessively low reaction rates. Diethylamine reacted slowly with polyactic acid[3] and with the methyl ester of polyactic acid, a moderate yield of N,N-diethyllactamide being obtained.

(1) 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 and Fisher, THIS JOURNAL, **69**, 1911 (1947).

(3) Filachione and Fisher, *Ind. Eng. Chem.*, **36**, 223 (1944).