419. *Experiments in the Synthesis of Derivatives of α-Aminoacrylic Acid from Serine and* N-*Substituted Serines.*

By Eugene Rothstein.

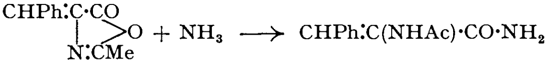
The condensation of acetamide with pyruvic acid affords αα-diacetamidopropionic acid which eliminates acetamide yielding α-acetamidoacrylic acid (Bergmann and Grafe, *Z. physiol. Chem.*, 1930, **187**, 187). The *methyl* ester, but no other derivative, could be obtained from this acid directly. When treated with alkali under various conditions, *methyl β-chloro-α-acetamidopropionate*, prepared from serine, affords methyl α-acetamido-β-methoxypropionate, *β-chloro-α-acetamidopropionamide*, and *α-acetamidoacrylamide*, as well as methyl acetamidoacrylate. The yields, however, are small and the methods employed are not suitable for preparing these compounds in quantity. Most of the corresponding alkylamino-compounds were not similarly obtainable from N-*methyl*- or NN-*diethyl-serine* (*α-methylamino*- or *α-diethylamino-β-hydroxypropionic acid*).

The amino-derivatives of acrylic acid are comparatively difficult of access, one of the easier routes being the condensation of acetamide with pyruvic acid, followed by the elimination of one molecule of acetamide from the diacetamidopropionic acid (I) so obtained (Bergmann and Grafe, *Z. physiol. Chem.*, 1930, **187**, 187):

$$\underset{\text{(I.)}}{\mathrm{CMe(NHAc)_2{\cdot}CO_2H}} \longrightarrow \underset{\text{(II.)}}{\mathrm{CH_2{:}C(NHAc){\cdot}CO_2H}} + \mathrm{NH_2Ac}$$

This method is of limited application; the synthesis of derivatives of α-acetamidoacrylic acid (II) in this way is at the best troublesome and is usually impossible owing to the reactivity of the acid towards the usual reagents. Diacetamidopropionic acid (I) is more stable but only the acid itself decomposes to the unsaturated compound.

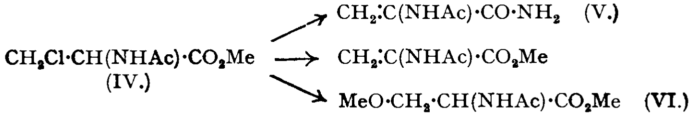
Methyl α-*acetamidoacrylate* has been obtained from the acid by means of the silver salt and methyl iodide, but even here direct esterification was not successful and the use of methyl sulphate was also unsatisfactory. Since methyl α-acetamidoacrylate afforded a polymer with somewhat unusual properties, syntheses in this series were further investigated. In the case of α-acetamidocinnamic acid the *amide* could be prepared quite easily from the corresponding azlactone and ammonia:



$$\begin{matrix}\mathrm{CHPh{:}C{\cdot}CO} & & \\ \vert \quad > \mathrm{O} & + \mathrm{NH_3} \longrightarrow & \mathrm{CHPh{:}C(NHAc){\cdot}CO{\cdot}NH_2} \\ \mathrm{N{:}CMe} & & \end{matrix}$$

but even in this case the *methyl* ester was best obtained from the silver salt; dehydration of the amide to the nitrile could not be accomplished owing to complete decomposition. The azlactone of α-acetamidoacrylic acid is unknown and in consequence other possible methods for the synthesis of the amide and of other derivatives had to be devised.

The starting material was serine (*Org. Synth.*, 1940, **20**, 81) which was esterified and converted into methyl β-chloro-α-aminopropionate hydrochloride, $\mathrm{CH_2Cl{\cdot}CH(NH_2,HCl){\cdot}CO_2Me}$ (III), by a slight modification of the method of Fischer and Rasche (*Ber.*, 1907, **40**, 3723). Not very large amounts of this substance could be obtained because the yields are extremely irregular and appear to depend on the purity of both the ester hydrochloride and the phosphorus pentachloride. *Methyl* β-*chloro*-α-*acetamidopropionate* (IV) was produced when (III) was boiled with acetyl chloride in benzene suspension, and (IV) was converted by alkali into α-*acetamidoacrylamide* (V), methyl α-acetamidoacrylate, or methyl α-acetamido-β-methoxypropionate (VI) according to the conditions:



$$\begin{matrix} & \nearrow & \mathrm{CH_2{:}C(NHAc){\cdot}CO{\cdot}NH_2} \quad \text{(V.)} \\ \underset{\text{(IV.)}}{\mathrm{CH_2Cl{\cdot}CH(NHAc){\cdot}CO_2Me}} & \longrightarrow & \mathrm{CH_2{:}C(NHAc){\cdot}CO_2Me} \\ & \searrow & \mathrm{MeO{\cdot}CH_2{\cdot}CH(NHAc){\cdot}CO_2Me} \quad \text{(VI.)} \end{matrix}$$

The methoxy-ester (VI), previously synthesised by Synge (*Biochem. J.*, 1939, **33**, 1931) using a different method, was formed when methyl-alcoholic potash was used. Removal of hydrogen halide with ethereal ammonia furnished mainly the methyl acrylate accompanied by a small quantity of the amide (V). The latter, however, must have been derived directly from (IV) because methyl acetamidoacrylate is either unreactive or suffers complete decomposition when mixed with ammonia in various proportions. In fact, (IV) with cold concentrated aqueous ammonia yielded *β-chloro-α-acetamidopropionamide*, $\mathrm{CH_2Cl{\cdot}CH(NHAc){\cdot}CO{\cdot}NH_2}$ (VII), but useful quantities were unobtainable by this method.

Attempts to prepare the amide (VII) in larger amounts were unsuccessful. Neither *α-amino-β-hydroxypropionamide hydrochloride*, $\mathrm{HO{\cdot}CH_2{\cdot}CH(NH_2,HCl){\cdot}CO{\cdot}NH_2}$, nor its *N-acetyl* derivative (IX), prepared by the hydrolysis of *methyl α-acetamido-β-acetoxypropionate* (VIII) with ammonia, would react with a halogenating agent to yield the corresponding β-chloro-compound, *e.g.*, (VII) :

$$\mathrm{HO{\cdot}CH_2{\cdot}CH(NH_2,HCl){\cdot}CO_2Me} \xrightarrow{\mathrm{AcCl}} \underset{\text{(VIII.)}}{\mathrm{AcO{\cdot}CH_2{\cdot}CH(NHAc){\cdot}CO_2Me}} \xrightarrow{\text{aq. NH}_3} \underset{\text{(IX.)}}{\mathrm{HO{\cdot}CH_2{\cdot}CH(NHAc){\cdot}CO{\cdot}NH_2}} \overset{\mathrm{PCl_5}}{\dashrightarrow} \text{(VII)}$$

nor was it possible to dehydrate (IX) to the acryloamide (V). A similar difficulty attended the replacement of the hydroxyl group in *methyl α-diethylamino-β-hydroxypropionate* (XI), prepared from methyl α-bromo-β-methoxypropionate (X) :

$$\underset{\text{(X.)}}{\mathrm{MeO{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2Me}} \longrightarrow \mathrm{MeO{\cdot}CH_2{\cdot}CH(NEt_2){\cdot}CO_2Me} \longrightarrow \underset{\text{(XI.)}}{\mathrm{HO{\cdot}CH_2{\cdot}CH(NEt_2){\cdot}CO_2H}}$$

Reaction between (XI) and phosphorus pentachloride afforded a base containing less than 25% of the calculated percentage of chlorine. Since alkali failed to remove all the halogen the experiments in this case were not pursued further.

The *N*-methyl derivatives of α-aminoacrylic acid could not be prepared. Direct methylation of α-acetamidoacrylic acid or of αα-diacetamidopropionic acid and condensation of pyruvic acid with acetomethylamide failed. Next, the reactions of the *N*-methyl derivatives of serine were examined. Ethyl α-bromo-β-ethoxypropionate (XII) (Wood and Vigneaud, *J. Biol. Chem.*, 1940, **134**, 414) gave *α-methylamino-β-ethoxypropionomethylamide* (XIII) and thence *α-methylamino-β-hydroxypropionic acid* (XIV) :

$$\underset{\text{(XII.)}}{\mathrm{EtO{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2Et}} \longrightarrow \underset{\text{(XIII.)}}{\mathrm{EtO{\cdot}CH_2{\cdot}CH(NHMe){\cdot}CO{\cdot}NH_2}} \longrightarrow \underset{\text{(XIV.)}}{\mathrm{HO{\cdot}CH_2{\cdot}CH(NHMe){\cdot}CO_2H}}$$

No difficulty was encountered in obtaining *methyl α-acetomethylamido-β-acetoxypropionate* $\mathrm{AcO{\cdot}CH_2{\cdot}CH(NMeAc){\cdot}CO_2Me}$, from the *hydrochloride* of the *methyl* ester of (XIV), but, unlike the unmethylated homologue, it could not be satisfactorily hydrolysed to the β-hydroxy-compound.

On the other hand, although *methyl β-chloro-α-methylaminopropionate hydrochloride* (XV) was produced by addition of phosphorus pentachloride to a chloroform solution of the methyl ester hydrochloride, the halogen atom was replaced by an acetoxy-group when (XV) was warmed with acetyl chloride, yielding the *methyl α-methylamino-β-acetoxypropionate hydrochloride* (XVI), and not the *N*-acetyl derivative :

$$\underset{\text{(XV.)}}{\mathrm{CH_2Cl{\cdot}CH(NHMe,HCl){\cdot}CO_2Me}} \longrightarrow \underset{\text{(XVI.)}}{\mathrm{AcO{\cdot}CH_2{\cdot}CH(NHMe,HCl){\cdot}CO_2Me}}$$

The ester (XVI) is apparently also formed when methyl α-acetomethylamido-β-hydroxypropionate is boiled first with acetyl chloride and then with phosphorus pentachloride, but the melting point is somewhat lower and there is a slight depression when the substance is mixed with (XVI). The only alternative structure for (XVI) is methyl β-chloro-α-methylaminopropionate acetate, $\mathrm{CH_2Cl{\cdot}CH(CO_2Me){\cdot}NHMe,AcOH}$, but the substance contained *ionic* halogen and did not afford an unsaturated derivative when warmed with piperidine.

EXPERIMENTAL.

Acetamidoacrylic Acid.—αα-Diacetamidopropionic acid was prepared from acetamide (480 g.) and freshly distilled pyruvic acid (390 g.) (Bergmann and Grafe, *loc. cit.*). The yield after three extractions with ethyl acetate was 357 g. (43%), the acid separating from water or ethanol in needles, m. p. 195—196° (decomp.) [Bergman and Grafe record m. p. 189—190° (corr.; decomp.)]. The extracts afforded a mixture (132 g.) of this acid with α-acetamidoacrylic acid. The total quantity of the acetamidoacrylic acid finally obtained from the above products was 136 g. (40%); this acid crystallised from ethanol in needles, m. p. 204° (decomp.) [Bergmann and Grafe give m. p. 198—200° (corr.)]. For complete conversion of the diacetamido-compound into the unsaturated acid, the former must be mixed with *cold* glacial acetic acid, the temperature then being gradually raised to the boiling point.

Acetamidoacrylic acid decomposes when mixed with thionyl chloride (alone or in pyridine), phosphorus pentachloride, or phosphorus oxychloride. Direct esterification failed. The silver salt (80%) was precipitated by the addition of a slight excess of concentrated silver nitrate solution to a solution of the sodium salt of the acid; unchanged acid could be recovered by acidifying the filtrate with a slight excess of concentrated hydrochloric acid. *Methyl α-acetamidoacrylate*, obtained by boiling the silver salt with excess of methyl iodide and a small quantity of quinol, separated from light petroleum (b. p. 40—60°) in short prisms, m. p. 52—54° (yield 66—70% based on the silver salt) and distils without decomposition (b. p. 104°/8 mm.) but is liable to polymerise unless quinol is present (Found: C, 50·5; H, 6·2; *M*, 154. $C_6H_9O_3N$ requires C, 50·3; H, 6·3%; *M*, 143). The ester when first prepared has a pleasant heliotrope odour, but when kept develops the odour characteristic of pyruvic acid. It is unsaturated to permanaganate and quickly decolorises bromine water. The preparation using methyl sulphate is illustrated in the two typical examples below:

(i) A solution of the acid (6 g.) in warm methanol (100 c.c.) was made slightly alkaline to methyl-orange with 6% sodium methoxide solution, and to it were added quinol (1 g.), anhydrous sodium carbonate (3·0 g.), and methyl sulphate (9·0 g.). The liquid was boiled under reflux for 2 hours and then cooled, an excess of dry ether was added, and the precipitated sodium salts were filtered off. The filtrate was distilled to dryness in a vacuum, and the residue repeatedly extracted with ether. The yield of recrystallised ester was 3 g. (45%).

(ii) A methanolic (50 c.c.) solution of the acid (5 g.), when boiled under reflux for 20 hours with quinol (1 g.), sodium carbonate (6 g.), and methyl sulphate (9 c.c.) and then treated as in (i), gave 2·0 g. (36%) of recrystallised ester.

Synthesis of Methyl β-Chloro-α-acetamidopropionate from Serine.—Methyl β-chloro-α-aminopropionate hydrochloride (III) was prepared by Fischer and Rasche's method (*loc. cit.*), adapted for larger quantities. A cooled suspension of dry serine methyl ester hydrochloride (Fischer and Suzuki, *Ber.*, 1907, **40**, 4193) (22·3 g.) in acetyl chloride (200 c.c.) was stirred vigorously during the addition of phosphorus pentachloride (34 g.). There was a slow evolution of hydrogen chloride and at the end of two hours the liquid which had become homogeneous deposited the chloro-ester hydrochloride as a white powder. This was filtered off and washed with acetyl chloride and petrol; yield, 12·6 g. (50·5%). A further quantity (6·6 g.) of very impure material could be obtained from the filtrate by precipitation with light petroleum, but was not easily purified and was unsuitable for further synthetic work.

The chloro-ester hydrochloride (56 g.) was suspended in dry benzene (400 c.c.) and boiled under reflux with freshly distilled acetyl chloride (45 c.c.) until dissolution was complete. Addition of an excess of light petroleum (b. p. 40—60°) precipitated *methyl β-chloro-α-acetamidopropionate* (IV) which crystallised from ether–light petroleum (b. p. 40—60°) in micro-crystals, m. p. 79—80° (24·5 g., 46%) (Found: C, 40·5; H, 5·7; Cl, 19·5. $C_6H_{10}O_3NCl$ requires C, 40·1; H, 5·6; Cl, 19·8%).

Removal of Hydrogen Chloride from Methyl β-Chloro-α-acetamidopropionate.—(a) *With potassium methoxide.* The chloro-ester (6·5 g.) was set aside with 2N-potassium methoxide (18 c.c.) and quinol (0·05 g.) for several hours, filtered, and evaporated to dryness in a vacuum. A warm ethereal extract deposited, on cooling, a crystalline product, m. p. 65—70°. After three extractions with boiling light petroleum (b. p. 40—60°), it crystallised from ether in stellate clusters, m. p. 72—73° (2·4 g., 38%). The substance was evidently methyl α-acetamido-β-methoxypropionate (Synge, *loc. cit.*, gave m. p. 70—71°) but could not be entirely freed from the accompanying methyl acetamidoacrylate which could be detected by its odour (Found: C, 48·7; H, 7·2; N, 7·8. Calc. for $C_7H_{13}O_4N$: C, 48·0; H, 7·4; N, 8·0%). The light petroleum extracts afforded the acrylate in 37% yield.

(b) *With methyl-alcoholic potash.* The ester (1·8 g.) was mixed with a solution of potassium hydroxide (0·6 g.) and quinol (0·01 g.) in methanol (5 c.c.). Potassium chloride was precipitated, heat being evolved, and the odour of methyl acetamidoacrylate became perceptible. Filtration and removal of the solvent left a residue from which 0·4 g. (28%) of the ester was obtained.

(c) *With methyl-alcoholic ammonia.* The chloro-ester (0·45 g.) with 25% methanolic ammonia (5 c.c.) (but no quinol) furnished polymerised methyl acetamidoacrylate.

(d) *With ethereal ammonia.* The chloro-ester (3 g.) was boiled with dry ether (300 c.c.), filtered from a small amount of undissolved substance, and, following the addition of a small quantity of quinol, saturated with ammonia. After being kept in a refrigerator for 2 days, the liquid was filtered and the solvent removed in the usual manner. The semi-solid residue was extracted with two successive quantities of boiling light petroleum (b. p. 40—60°) which, when evaporated, yielded methyl acetamidoacrylate (1·3 g., 54%). The residue from the extractions was recrystallised from ethanol, whence separated *α-acetamidoacrylamide* (V) as clusters of prisms, m. p. 161—162° (Found: C, 47·2; H, 6·3; N, 21·7. $C_5H_8O_2N_2$ requires C, 46·9; H, 6·2; N, 21·9%). The substance rapidly decolorised bromine water and alkaline permanganate solution.

(e) *With ethereal piperidine.* A filtered solution of the ester (1·8 g.) in ether (150 c.c.) containing quinol was mixed with piperidine (0·85 g.). The theoretical amount of piperidine hydrochloride was precipitated and filtered off. Distillation of the solvent gave nearly pure methyl α-acetamidoacrylate (0·8 g., 56%).

Derivatives of Serine.—*β-Chloro-α-acetamidopropionamide* (VII) was formed by the gradual addition of methyl β-chloro-α-acetamidopropionate (3·0 g.) to ammonia (*d*, 0·88; 20 c.c.), containing a little quinol and cooled in a freezing mixture. The mixture was shaken from time to time and after about 1½ hours the dark-red, nearly homogeneous solution deposited a small quantity of the amide which separated from ethanol in micro-crystals, m. p. 167° (decomp.) (Found: C, 36·8; H, 5·6; N, 16·7; Cl, 21·9. $C_5H_9O_2N_2Cl$ requires C, 36·5; H, 5·5; N, 17·0; Cl, 21·6%).

The preparation of *methyl α-acetamido-β-acetoxypropionate* (VIII) was carried out by boiling under reflux a suspension of serine methyl ester hydrochloride (17·5 g.) in benzene (100 c.c.) with acetyl chloride (18 c.c.) for 2 hours, the reaction being completed by the further addition of acetyl chloride (5 c.c.).

Removal of the solvent from the now homogeneous solution yielded the diacetyl compound, b. p. 160°/8 mm., 135°/0·8 mm. (22 g., 96·5%). The substance solidified below 0° but could not be recrystallised satisfactorily (Found: C, 47·9; H, 6·5; N, 7·5. $C_8H_{13}O_5N$ requires C, 47·3; H, 6·4; N, 6·9%). Conversion into α-acetamido-β-hydroxypropionamide (IX) took place when a solution of (VIII) (22 g.) in methanol (100 c.c.) was saturated with ammonia at 0° and set aside for 2 days. Evaporation of the solvent yielded the amide which, after rubbing with methanol, crystallised from ethanol; m. p. 138—139°; yield, 7·5 g. (47·5%) (Found: C, 41·2; H, 6·6; N, 19·1. $C_5H_{10}O_3N_2$ requires C, 41·1; H, 6·9; N, 19·2%). A further small quantity of the substance could be obtained by saturating the methanolic extract with ammonia. The amide could also be prepared by evaporating, on the steam-bath, an aqueous-ammoniacal solution of the diacetyl compound, but the subsequent purification was more laborious.

Substitution of the hydroxyl group by halogen was impossible owing to the decomposition caused by the usual reagents. Direct dehydration by heat was also impossible, only very slight reaction occurring at 160—180°.

α-Amino-β-hydroxypropionamide hydrochloride resulted when the methyl ester hydrochloride was mixed with methanolic ammonia below 0°. The residue obtained by distilling off the solvent in a vacuum was dissolved in methanol, filtered, and again evaporated. The residue separated from a concentrated solution in the same solvent as a crystalline power, m. p. 192—193° (decomp.) (Found: C, 25·6; H, 7·1. $C_3H_9O_2N_2Cl$ requires C, 25·6; H, 6·4%).

Derivatives of Diethylaminopropionic Acid.—Methyl α-bromo-β-methoxypropionate (30 g.) was boiled for 2 hours under reflux with diethylamine (30 g.) and methanol (30 c.c.), excess of alkali added, and the base extracted with ether. The ethereal layer yielded a product containing unchanged bromo-ester. The mixture was shaken with dilute acetic acid and extracted with ether, and the aqueous layer basified and extracted as before, thus yielding pure *methyl α-diethylamino-β-methoxypropionate*, b. p. 83—85°/8 mm., (12·3 g., 43%) (Found: 57·5; H, 9·8. $C_9H_{19}O_3N$ requires C, 57·1; H, 10·1%).

Methyl α-diethylamino-β-hydroxypropionate, b. p. 100°/10 mm., was prepared by boiling the methoxy-ester (16 g.) with hydrobromic acid (48%; 200 c.c.) for 2 hours. After removal of the acid, etc., in a vacuum, water (250 c.c.) was added, the solution distilled to dryness, and the procedure repeated using the same quantity of methanol. Finally, a methanolic solution of the residue was saturated with dry hydrogen chloride and then evaporated to dryness, and the residue basified. The ethereal extract of the liquid was dried (Na_2SO_4) and from it were isolated 2 g. (13·5%) of the amino-ester (Found: C, 55·1; H, 9·6; N, 8·2. $C_8H_{17}O_3N$ requires C, 54·9; H, 9·7; N, 8·0%).

Attempted Preparation of Methyl β-Chloro-α-diethylaminopropionate.—The hydrochloride of the above ester (22 g.), dried over phosphoric oxide, was dissolved in freshly redistilled acetyl chloride (200 c.c.) and stirred with phosphorus pentachloride (26 g., 25% excess) for 2 hours, after which the liquid was boiled under reflux until no more hydrogen chloride was evolved (20 minutes). The base obtained by this reaction had b. p. 89°/8 mm. and contained only a small proportion of the theoretical quantity of chlorine (see analysis), but even this small amount was not removed by ethereal piperidine or methanolic ammonia over a period of a week and no further attempt was made to obtain the pure chloro-ester (Found: C, 52·8; H, 9·1; Cl, 4·4. Calc. for $C_8H_{16}O_2NCl$: C, 49·6; H, 8·3; Cl, 4·4%). It is evident that not more than about 25% of the mixture was the required base.

Acetamidocinnamic Acid Derivatives.—The azlactone of α-acetamidocinnamic acid (*Org. Synth.*, Coll. Vol. II, 1) (90 g.) was suspended in ethanol (500 c.c.) and saturated with ammonia at 0°. The precipitate was washed with the solvent and crystallised therefrom. *α-Acetamidocinnamide* separated in colourless needles, m. p. 205° (decomp.) (68 g., 70%) (Found: C, 64·3; H, 5·7. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9%).

The *methyl* ester, prepared by boiling the silver salt of the acid with methyl iodide, crystallised from benzene in fine needles, m. p. 119—120° (Found: C, 65·8; H, 6·2; N, 6·2. $C_{12}H_{13}O_3N$ requires C, 65·8; H, 5·9; N, 6·4%).

Methylamino-derivatives.—(a) *Attempted preparation of α-acetomethylamidoacrylic acid.* When freshly distilled pyruvic acid (1 mol.) was mixed with acetomethylamide (2 mols.), heat was evolved but no condensation took place, in contrast to the corresponding experiments with acetamide. The experiment, repeated with use of diethylamine, piperidine, or sodium ethoxide as catalyst, was equally unfruitful, nor was it possible to methylate α-acetamidoacrylic acid directly with either methyl sulphate or methyl *o*-nitrobenzenesulphonate.

(b) *Derivatives of α-methylamino-β-hydroxypropionic acid.* Ethyl α-bromo-β-ethoxypropionate (Wood and Vigneaud, *loc. cit.*) (40 g.) was heated for 12 hours at 100° with 33% ethanolic methylamine (50 g.) in a sealed tube. Addition of dry ether precipitated most of the excess of methylamine as hydrobromide. This was filtered off, the filtrate extracted with dilute acid, and the aqueous layer concentrated. An excess of solid potassium carbonate was then added, the liberated base extracted with ether, and the solution dried (K_2CO_3). Removal of the ether yielded *α-methylamino-β-ethoxypropionomethylamide* (XIII), b. p. 86°/1 mm. (14·7 g., 52%) (Found: C, 52·2; H, 10·1; N, 18·2. $C_7H_{16}O_2N_2$ requires C, 52·5; H, 10·0; N, 17·5%). Hydrolysis was carried out by boiling the amide with excess of 48% hydrobromic acid, the hydrobromide being isolated in the usual way; the free acid was obtained by boiling an aqueous solution of this salt with freshly precipitated white lead oxide as described in the next experiment.

It was found advantageous (cf. preparation of serine, *Org. Synth., loc. cit.*) to use the α-bromo-β-ethoxy-acid for the condensation with methylamine. The ester was hydrolysed with cold sodium hydroxide, and a nearly theoretical yield of the acid obtained by acidification with 7N-sulphuric acid and extraction with ether. The product (352 g.) was heated with 30% aqueous methylamine (700 g.) at 100° in an autoclave for 20 hours. After hydrolysis with hydrobromic acid, the methylamino-acid was boiled with lead oxide until no further bromine ions were present in the solution. Several successive quantities of the oxide were necessary, the lead bromide being filtered off before each new addition. The final filtrate was heated to the boiling point and saturated with hydrogen sulphide. Removal of the precipitated lead sulphide was followed by evaporation in a vacuum. The residue, washed with ethanol, was recrystallised from this solvent with the addition of a very small amount of water, and the *α-methylamino-β-hydroxy-*

propionic acid (XIV) dried in a vacuum over phosphoric oxide; m. p. 210° (decomp.); yield, 66 g. (31% based on the bromo-acid) (Found : C, 40·4; H, 7·4; N, 11·8. $C_4H_9O_3N$ requires C, 40·3; H, 7·6; N, 11·8%).

Methyl α-methylamino-β-hydroxypropionate hydrochloride was prepared by saturating a solution of the acid (10 g.) in methanol (250 c.c.) with dry hydrogen chloride. After isolation by the usual method it was dried over phosphoric oxide (yield, 12·4 g., 86·5%). Recrystallisation from ethanol–light petroleum (b. p. 60—80°) afforded a product, m. p. 115—116° (Found : C, 35·4; H, 6·9; N, 8·7; Cl, 21·2. $C_5H_{12}O_3NCl$ requires C, 35·4; H, 7·1; N, 8·3; Cl, 20·9%).

Methyl α-acetomethylamido-β-acetoxypropionate (4·7 g., 65%) resulted when a mixture of the above methyl ester (5·65 g.), acetyl chloride (7 g.), and benzene (50 c.c.) was boiled under reflux for 24 hours. It had b. p. 132°/0·3 mm. (Found : C, 49·9; H, 6·9. $C_9H_{15}O_5N$ requires C, 49·8; H, 6·9%). Unlike that of the unmethylated derivative, its satisfactory hydrolysis could not be achieved. Decomposition ensued when ammonia was added.

Methyl β-Chloro-α-methylaminopropionate Hydrochloride (XV).—Methyl α-methylamino-β-hydroxypropionate (2 g.) was dissolved in chloroform (10 c.c.), and phosphorus pentachloride (2·7 g.) added in three portions to the liquid cooled in water. The mixture was then cooled to below 0°. After 2 days, the *chloro*-ester *hydrochloride* was deposited as a white solid (1·1 g.). This was washed with chloroform and ether and recrystallised from methanol–ether whence it separated in stellate clusters, m. p. 143° (decomp.) (Found : C, 31·9; H, 5·9; N, 7·2; Cl, 37·2. $C_5H_{11}O_2NCl_2$ requires C, 31·9; H, 5·9; N, 7·4; Cl, 37·8%). The same substance was obtained by mixing, with ice-cooling, the β-hydroxy-derivative (2 g.), freshly distilled acetyl chloride (10 c.c.) and phosphorus pentachloride (2·7 g.); the reaction was completed by boiling the liquid for 30 minutes. When cold, a small crystalline deposit (0·7 g.) was formed. The melting point, after crystallisation from ethanol, was slightly lower than that given above (Found : C, 31·8; H, 6·2%).

Reaction of (XV) *with Acetyl Chloride*.—The dichloro-compound (0·4 g.) in benzene (20 c.c.) was boiled under reflux with acetyl chloride (0·3 c.c.) until dissolution was almost complete. After decantation and evaporation to dryness, the residual syrup was carefully washed with ether containing a trace of ethanol and recrystallised first from this mixture and then from ether–methanol. The m. p. was then 118—119° and was slightly depressed when the substance was mixed with that described in the next paragraph. The analytical figures appeared to indicate the identity of the two compounds (Found : C, 40·4; H, 6·8; N, 6·9; Cl, 17·4. Calc. for $CH_2Cl\cdot CH(NMeAc)\cdot CO_2Me$: C, 43·4; H, 6·2; N, 7·3; Cl, 18·4%). Other experiments using different samples of the starting material yielded compounds with slightly lower melting points, the analytical figures being nearer those below. It is possible that these were mixtures.

Methyl α-methylamino-β-acetoxypropionate hydrochloride (XVI) was formed in an experiment designed to prepare in one operation the β-chloro-*N*-acetyl ester from methyl α-methylamino-β-hydroxypropionate hydrochloride. The latter (7 g.) was boiled under reflux with acetyl chloride (15 c.c.) for 1 hour and then treated with phosphorus pentachloride (7·7 g.). The liquid was boiled for a further 15 minutes and set aside at 0° overnight. The supernatant liquid was decanted and the residue washed with ether, mixed with alcohol and ether to decompose any remaining phosphorus halides, and after filtration again washed with ether. Three recrystallisations from ethanol furnished the acetoxy-ester, m. p. 110—112° (Found : C, 39·5; H, 6·7; N, 6·7; Cl, 16·6. $C_7H_{14}O_4NCl$ requires C, 39·7; H, 6·6; N, 6·6; Cl, 16·8%).

Attempted Replacement of the Hydroxyl Group by Bromine.—Methylaminohydroxypropionic acid (1 g.) was mixed with 80% hydrobromic acid (4 g.). After 48 hours, the liquid was distilled in a vacuum to dryness and the residue allowed to crystallise in a vacuum desiccator over phosphoric oxide. The crystals were mixed with absolute ethanol and the process repeated. The *hydrobromide* so obtained had a somewhat indefinite m. p. of 160° (decomp.) and may have contained traces of the β-bromo-derivative (Found : C, 23·5; H, 5·0; N, 6·7; Br, 40·8. $C_4H_{10}O_3NBr$ requires C, 24·0; H, 5·0; N, 7·0; Br, 40·0%).

The foregoing has been put on record as the investigation has now been discontinued. The author thanks Messrs. Imperial Chemical Industries Limited, Dyestuffs Division, for a grant and for gifts of chemicals.

THE UNIVERSITY, LEEDS.

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