Synthesis of Unsaturated α-Amino-acids

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Unsaturated α-amino-acids or their esters can readily be prepared by reduction of unsaturated α-hydroxyimino-acids or their esters with aluminium amalgam.

SYNTHESES of α-amino-acids with unsaturated side chains have been based mainly on the acylaminomalonic ester approach [1] and have met with varying degrees of success. For example, in the preparation of 2-amino-pent-4-enoic acid (' allylglycine ') (Va), low yields have been recorded [2] as the result of competing acid-induced lactonisation to 2-amino-4-valerolactone (VI). Better yields were obtained [3] however in a two-stage hydrolysis and decarboxylation of ethyl allyl(formylamino)malonate, by using first basic and then mildly acidic conditions. This latter approach has been used successfully in the synthesis of several allenic α-amino-acids.[4] 2-Amino-4-methylpent-4-enoic acid (' methallylglycine ') (Vb) cannot be prepared by the acidic hydrolysis of ethyl (2-methylallyl)acetamidomalonate; the product of such treatment is entirely the α-amino-γ-lactone.[2] Moderate yields of this amino-acid have been obtained by prolonged alkaline hydrolysis of ethyl (2-methylallyl)-acetamidocyanoacetate.[1,2] 2-Aminohex-4-enoic acid (' crotylglycine ') (Vc) provides a further example of a compound whose preparation is complicated by its tendency to lactonise under the influence of acids.[2]

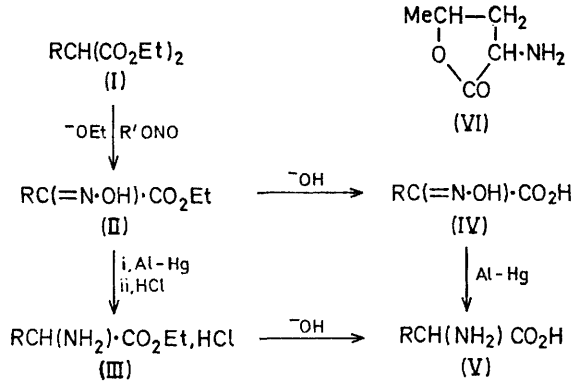
Investigating other routes for the synthesis of unsaturated amino-acids, we have found a method based on the preparation and reduction of α-hydroxyimino-derivatives [5] to be the most successful; this method can also be made to yield directly the ethyl esters of the amino-acids for use, for example, in peptide coupling reactions.

The alkenylmalonates (I) were prepared in the usual way by condensing the appropriate halides with malonic ester with the aid of sodium ethoxide. The products were studied by g.l.c.; it was found that, particularly in the case of the allylic halides, there was a tendency for disubstitution to occur,[6] and that the required monoalkenylated derivatives were difficult to obtain pure. The presence of some dialkenylated material however does not interfere with the next stage, which is the preparation of the α-hydroxyimino-ester (II) from

[1] N. F. Albertson, *J. Amer. Chem. Soc.*, 1946, **68**, 450, and references cited therein.
[2] H. L. Goering, S. J. Cristol, and K. Dittmer, *J. Amer. Chem. Soc.*, 1948, **70**, 3310.
[3] K. Schlogl and H. Fabitschowitz, *Monatsh.*, 1954, **85**, 1060.
[4] D. K. Black and S. R. Landor, *J. Chem. Soc.* (*C*), 1968, 283.
[5] K. E. Hamlin and W. H. Hartung, *J. Biol. Chem.*, 1942, **145**, 349; J. C. Shivers and C. R. Hauser, *J. Amer. Chem. Soc.*, 1947, **69**, 1264; R. H. Barry and W. H. Hartung, *J. Org. Chem.*, 1947, **12**, 460; N. F. Albertson, B. F. Tullar, J. A. King, B. B. Fishburn, and S. Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 1150.
[6] H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965, p. 184.

the malonate (I) and ethyl or pentyl nitrite in the presence of sodium ethoxide. Yields in this stage are usually good provided that the reaction is controlled by efficient stirring and cooling to keep the temperature below 0° during the addition of the ethoxide.

The usual method of reduction of the hydroxyimino-derivatives by catalytic hydrogenation [5] being useless



a; R = CH_2·CH:CH_2. b; R = CH_2·CMe:CH_2.
c; R = CH_2·CH:CHMe. d; R = $[CH_2]_2$·CH:CH_2.
e; R = $[CH_2]_3$·CH:CH_2.

for present purposes, aluminium amalgam [7] was selected as the reducing agent. In the reduction of the hydroxyimino-esters (II) directly to the amino-acid esters (III), the products were sometimes contaminated with the corresponding amino-acids. Re-esterification could usually be achieved by treatment with ethanolic hydrogen chloride. Best results were obtained by reduction with 1·6 equiv. of amalgam in ether which was approximately half saturated with water. The amino-acid esters were isolated as the hydrochlorides but none of these could be obtained in a satisfactorily crystalline condition. Hydrolysis converted them into the amino-acids in good yield.

The hydroxyimino-esters (II) were readily hydrolysed by warming with aqueous sodium hydroxide; the resulting hydroxyimino-acids (IV) were easily isolated and purified. The conditions necessary for the efficient reduction of these to the amino-acids (V) were less critical than those required for the reduction of the hydroxyimino-esters. Amino-acids obtained by this route however were found to contain traces of inorganic material.

EXPERIMENTAL

G.l.c. analyses were carried out with a Pye series 104 instrument [column (5 ft.) of Chromosorb W coated with silicone oil (10%)]. Retention times quoted (R_t') are relative to ethyl malonate. T.l.c. (ascending) was carried out on silica gel plates with butan-1-ol–acetic acid–water (3 : 1 : 1) as solvent. Spots were detected with ninhydrin, which gave yellow-brown colours with the unsaturated amino-acids, or by spraying lightly with acidified potassium permanganate solution.

The alkenyl halides used were purified commercial samples. After distillation, the following were homogeneous on g.l.c.: allyl chloride (B.D.H.), b.p. 45°; methallyl chloride (B.D.H.), b.p. 71—72°; 4-bromobut-1-ene (Koch–Light), b.p. 98—99°; and 5-bromopent-1-ene (Koch–Light), b.p. 126—127°. Redistilled but-2-enyl bromide (Koch–Light), b.p. 103—105°, was *ca.* 75% pure by g.l.c. A sample of 95% purity which was obtained by preparative g.l.c. was used in the condensations.

The ethyl alkenylmalonates were prepared by treating the halides with ethyl sodiomalonate (1 equiv.) in absolute ethanol. The products were purified by distillation and their purity was assessed by g.l.c. Ethyl allylmalonate gave three fractions, b.p. 195—210, 210—220, and 220—225°, of similar composition, which were combined to provide product, R_t' 2·4 (lit.,[8] b.p. 222—223°/766 mm.), of 80% purity which also contained some ethyl diallylmalonate (17%; R_t' 5·6) and a little ethyl malonate (3%; R_t' 1). Ethyl 2-methylprop-2-enylmalonate gave a fraction b.p. 91—92°/3 mm. (lit.,[9] 113—116°/14—17 mm.) which was 90% pure by g.l.c., R_t' 3·5. Ethyl but-2-enylmalonate after two distillations yielded a sample, b.p. 104—106°/5 mm. (lit.,[10] 132°/20 mm.) which was homogeneous on g.l.c., R_t' 3·6 (Found: C, 61·8; H, 8·3. Calc. for $C_{11}H_{18}O_4$: C, 61·7; H, 8·4%). Ethyl but-3-enylmalonate after two distillations yielded an homogeneous product, R_t' 3·9, b.p. 77—80°/0·5 mm. (lit.,[11] 116—121°/12 mm.) (Found: C, 61·4; H, 8·3%). Ethyl pent-4-enylmalonate gave a main fraction, b.p. 96—98°/0·5 mm., which was 90% pure. A small end-fraction, b.p. 98—100°/0·5 mm. (lit.,[12] 130—136°/14 mm.) was homogeneous, R_t' 6·5 (Found: C, 63·6; H, 8·6. Calc. for $C_{12}H_{20}O_4$: C, 63·2; H, 8·8%).

Preparation of the α-Hydroxyimino-esters (II).—The ethyl alkenylmalonate (x moles) was cooled to −10° in an ice–salt bath and ethyl (or pentyl) nitrite (x moles) was added. A solution of sodium (x g. atoms) in ethanol (30 ml. per g.) was run in slowly during 3 hr. with vigorous stirring, the temperature being maintained at −10°. The flask was then stoppered and kept at −10° overnight; ethanol was then removed under reduced pressure and the residue was mixed with an equal volume of iced water. The aqueous solution was washed with ether and brought to pH 5 by carefully adding concentrated hydrochloric acid, with cooling. The liberated product was then isolated by

α-Hydroxyimino-esters

	Scale (moles)	B.p.	M.p.	Found (%) C	H	N	Yield (%)
(IIa)	1	120°/3·5 mm.	24°	53·4	6·9	9·2 [a]	62
(IIb)	1	126°/4 mm.	35	55·9	7·4	8·0 [b]	52
(IIc)	0·1		59·5 [c]	55·9	7·6	8·2 [b]	87
(IId)	0·05		38—39 [d]	55·7	7·5	7·9 [b]	79
(IIe)	0·05						85 [e]

[a] $C_7H_{11}NO_3$ requires C, 53·5; H, 7·0; N, 8·9%. [b] $C_8H_{13}NO_3$ requires C, 56·1; H, 7·6; N, 8·2%. [c] From ether–light petroleum (b.p. 40—60°). [d] From light petroleum (b.p. 100—120°), raised to 43° on further crystallisation. [e] Product solidified at 0°; not purified further.

[7] M. S. Dunn, B. W. Smart, C. E. Redemann, and K. E. Brown, *J. Biol. Chem.*, 1931, **94**, 599.
[8] G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1948, 658.
[9] W. J. Doran and H. A. Shonle, *J. Amer. Chem. Soc.*, 1937, **59**, 1625.
[10] E. N. Eccott and R. P. Linstead, *J. Chem. Soc.*, 1929, 2153.
[11] R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1934, 1998.
[12] P. Gaubert, R. P. Linstead, and H. N. Rydon, *J. Chem. Soc.*, 1937, 1971.

continuous extraction with ether; the residue obtained by drying and evaporation was purified by distillation under reduced pressure or by crystallisation.

Reduction of the Hydroxyimino-esters.—Aluminium amalgam [13] [from the foil (6·2 g.)] was covered with moist ether, and ethyl 2-hydroxyiminopent-4-enoate (23·6 g., 0·15 mole) was added. A mildly exothermic reaction accompanied by the evolution of hydrogen ensued; this soon subsided and the mixture was set aside overnight. It was then heated and filtered and the filtrate was dried ($MgSO_4$) and evaporated. A solution of the resulting orange oil in dry ether was saturated with dry hydrogen chloride and left at room temperature overnight. Evaporation gave the hydrochloride of ethyl 2-aminopent-4-enoate (IIIa) (20 g., 95%) as a chromatographically homogeneous gum (R_F 0·64), positive to ninhydrin and to permanganate.

A portion (2·7 g., 0·015 mole) of the product was dissolved in water, and the solution was extracted with ether (7 ml.) and then added to a solution of sodium hydroxide (1·3 g., 0·033 mole) in water (7 ml.). After 2 hr. at room temperature the solution was made just acid with concentrated hydrochloric acid and then desalted by electrodialysis. Evaporation of the resulting solution under reduced pressure gave a solid (1·4 g.), m.p. 240—250° (decomp.). Recrystallisation from aqueous acetone gave 2-aminopent-4-enoic acid (1·15 g., 67%), m.p. 245—250° (decomp.), R_F 0·38; in agreement with values obtained for a sample of authentic material prepared by the acetamidomalonic ester route.[2]

The hydrochloride of ethyl 2-amino-4-methylpent-4-enoate (IIIb), prepared similarly, was obtained as a gum which was shown by chromatography to contain some of the corresponding amino-acid. The latter was largely but not completely esterified by treatment for 2 days with ethanolic 3M-hydrogen chloride. The reisolated amino-acid ester hydrochloride still could not be obtained crystalline. The hydrochlorides of ethyl 2-aminohex-4-enoate (IIIc) (R_F 0·56), ethyl 2-aminohex-5-enoate (IIId) (R_F 0·57), and ethyl 2-aminohept-6-enoate (IIIe) (R_F 0·62) were also prepared in the same way, and were obtained as hygroscopic solids.

Hydrolysis of the esters with aqueous sodium hydroxide followed by electrodialysis gave the corresponding amino-acids. 2-Amino-4-methylpent-4-enoic acid (Vb) (71% yield) had m.p. 212—214° (decomp.) (from aqueous acetone) [lit.[1], 214—215° (decomp.)], R_F 0·43. 2-Aminohex-4-enoic acid (Vc) (74% yield) had m.p. 255—260° (decomp.) (from aqueous ethanol) [lit.,[2] 260—270° (decomp.)], R_F 0·47 (Found: C, 55·7; H, 8·7; N, 10·8. Calc. for $C_6H_{11}NO_2$: C, 55·8; H, 8·5; N, 10·9%). *2-Aminohex-5-enoic acid* (Vd) (80% yield) had m.p. 250—255° (decomp.) (from water), R_F 0·46 (Found: C, 55·9; H, 8·6; N, 10·9%). *2-Aminohept-6-enoic acid* (Ve) (70% yield) had m.p. 258—262° (decomp.) (from water), R_F 0·55 (Found: C, 59·1; H, 9·1; N, 10·1. $C_7H_{13}NO_2$ requires C, 58·7; H, 9·1; N, 9·8%).

Hydrolysis and Reduction of the Hydroxyimino-esters.—A mixture of ethyl 2-hydroxyiminopent-4-enoate (42 g., 0·27 mole) and M-sodium hydroxide (300 ml., 0·3 mole) was warmed on a steam-bath for 10 min. The resulting solution was cooled, acidified with concentrated hydrochloric acid and extracted with ether. The extract was dried ($MgSO_4$) and evaporated, and the residue was crystallised from ether–light petroleum (b.p. 40—60°) to yield *2-hydroxyiminopent-4-enoic acid* (IVa) (20 g., 58%), m.p. 130° (Found: C, 46·6; H, 5·7; N, 10·5. $C_5H_7NO_3$ requires C, 46·5; H, 5·4; N, 10·8%). The hydroxyimino-acid (11 g., 0·085 mole) was added to aluminium amalgam [from aluminium (4·6 g., 0·17 g. atom.)] in moist ether, and the mixture was set aside overnight. Water was then added to decompose the excess of amalgam, and the solids were filtered off and washed well with water. The filtrate and washings were evaporated and the product (6·3 g.) gave chromatographically homogeneous 2-aminopent-4-enoic acid, m.p. 255—260° (decomp.) (from aqueous ethanol), R_F 0·38.

Similar hydrolysis of the other hydroxyimino-esters gave the following acids: *2-hydroxyimino-4-methylpent-4-enoic acid* (IVb) (57%), m.p. 119° [from ether–light petroleum (b.p. 40—60°)] (Found: C, 50·4; H, 6·4; N, 9·5. $C_6H_9NO_3$ requires C, 50·4; H, 6·3; N, 9·8%); *2-hydroxyiminohex-4-enoic acid* (IVc) (42%), m.p. 120·5° [from ethyl acetate–light petroleum (b.p. 40—60°)] (Found: C, 49·9; H, 6·0; N, 9·5%); *2-hydroxyiminohex-5-enoic acid* (IVd) (52%), m.p. 109° [from ethyl acetate–light petroleum (b.p. 40—60°)] (Found: C, 50·1; H, 6·1; N, 9·5%); *2-hydroxyiminohept-6-enoic acid* (IVe) (80%), m.p. 107·5° [from ethyl acetate–light petroleum (b.p. 40—60°)] (Found: C, 53·1; H, 6·9; N, 8·7. $C_7H_{11}NO_3$ requires C, 53·5; H, 7·0; N, 8·9%). Reduction of 2-hydroxyimino-4-methylpent-4-enoic acid with aluminium amalgam as already described gave 2-amino-4-methylpent-4-enoic acid (55%), m.p. 214° (decomp.) (from aqueous ethanol), R_F 0·43. Specimens of the corresponding amino-acids were likewise prepared from the other hydroxyimino-acids; they were chromatographically homogeneous after recrystallisation, but microanalysis established the presence of traces (*ca.* 1%) of inorganic material in these samples.

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[13] A. I. Vogel, 'Practical Organic Chemistry,' 3rd edn., Longmans Green and Co., London, 1957, p. 198.