Allenes. Part XVII.† The Synthesis of Allenic Cyanohydrins, Amino-nitriles, and Amino-acids from Allenic Aldehydes

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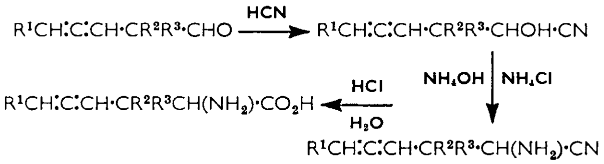
Application of a modified Strecker synthesis to 2,2-dimethylalka-3,4-dienals gives good yields of cyanohydrins, amino-nitriles and amino-acids. Allenic amino-acids are obtained, but only in low yield, from allenic aldehydes with no blocking group in the 2-position.

A NUMBER of unsaturated amino-acids show hypoglycaemic activity in mammals and inhibit fatty acid oxidation.[1] As part of a programme to investigate the biological activity of unsaturated amino-acids, a series of new allenic amino-acids has been prepared.

The synthesis of allenic aldehydes by the Claisen rearrangement of propynyl vinyl ethers has already been described.[2] The Strecker synthesis is still the best for the preparation of α-amino-acids from aldehydes. The modifications of Zelinsky and Stadnikoff,[3] who used potassium cyanide and ammonium chloride for the preparation of amino-nitriles which were then hydrolysed to α-amino-acids, and of Ultee,[4] who used anhydrous hydrogen cyanide at 0° to prepare cyanohydrins and then converted these into α-amino-nitriles, were applied to five allenic aldehydes.



Penta-3,4-dienal [2] and hexa-3,4-dienal [2] were converted into the corresponding α-amino-nitriles by shaking with a mixture of potassium cyanide, ammonium chloride, and concentrated aqueous ammonia. Hydrolysis with 10N-hydrochloric acid gave 2-aminohexa-4,5-dienoic acid ($R^1 = R^2 = R^3 = H$) and 2-aminohepta-4,5-dienoic acid ($R^1 = Me$, $R^2 = R^3 = H$) in low yield, identified by comparative paper chromatography. As both the 3,4-dienals rearrange readily under basic conditions to 2,4-dienals, this route is not suitable for preparative work. A cyanohydrin was formed under non-basic conditions by adding anhydrous hydrogen cyanide to penta-3,4-dienal but the cyanohydrin polymerised when distilled.

However, 2,2-dimethylalka-3,4-dienals ($R^2 = R^3 = Me$), which are readily available from Claisen rearrangement of prop-2-ynyl vinyl ethers,[2] were converted into the corresponding cyanohydrins, amino-nitriles, and amino-acids in good yield. An example of the general applicability of this method to the synthesis of other non-allenic, unsaturated 3,3-dimethyl-2-aminoalkanoic acids is given in the Experimental section (2,2-dimethylpent-4-enal was converted into 2-amino-3,3-dimethylhex-5-enoic acid).

Amino-acid	R_F *
$CH_2{:}C{:}CH{\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$	0·51
$MeCH{:}C{:}CH{\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$	0·61
$CH_2{:}C{:}CH{\cdot}CMe_2{\cdot}CH(NH_2){\cdot}CO_2H$	0·75
$MeCH{:}C{:}CH{\cdot}CMe_2{\cdot}CH(NH_2){\cdot}CO_2H$	0·83
$Pr^nCH{:}C{:}CH{\cdot}CMe_2{\cdot}CH(NH_2){\cdot}CO_2H$	0·84

* In n-butanol–glacial acetic acid–water (4 : 1 : 5).

EXPERIMENTAL

Infrared spectra were determined with a Perkin-Elmer Infracord spectrometer for liquid films, for Nujol mulls, or for potassium chloride discs. Paper chromatography was carried out on Whatman No. 1 paper; see Table for R_F values. Papers were equilibrated at room temperature for 2 hr. before spots were eluted with solvent. Amino-acids were detected by spraying with a solution of ninhydrin in ethanol (0·2%) followed by heating at 75°.

2-Hydroxy-3,3-dimethylhex-5-enenitrile.— 2,2-Dimethylpent-4-enal (5·0 g., 0·045 mole), prepared from allyl 2-methylprop-1-enyl ether [5] (85%) by heating for 3 hr. at 150° under reflux (2,4-dinitrophenylhydrazone, m. p. 117—118°; lit.,[6] 117—118°), was added slowly to liquid hydrogen cyanide (6·7 g., 0·25 mole) cooled at 0°. A saturated aqueous solution of potassium cyanide (0·1 ml.) was added and the mixture was shaken for 5 min. and left at 0° for 5 hr. and at room temperature for 2 days. Ether (20 ml.) and water (20 ml.) were added, the aqueous layer was extracted with ether (2 × 15 ml.), and the combined organic layers were dried ($MgSO_4$) and distilled to give the *cyanohydrin* (5·2 g., 84%), b. p. 70—71°/0·5 mm. (Found: C, 69·0; H, 9·3; N, 10·0. $C_{18}H_{14}N$ requires C, 69·1; H, 9·4; N, 10·1%), $\nu_{max.}$ 1645m (C=C), 3400s (O–H), and 2230 (C≡N) cm.$^{-1}$.

2-Amino-3,3-dimethylhex-5-enenitrile.—2,2-Dimethylpent-4-enal (3·5 g., 0·032 mole) and ammonium chloride (0·2 g.) were added to aqueous ammonia (30 ml.; *d* 0·880), ammonia gas was passed through for 10 min., and the mixture was shaken for 1 hr. and cooled to 0°. Liquid hydrogen cyanide (20 g., 0·74 mole) was added slowly, and the mixture was shaken for 12 hr. Water (30 ml.) and ether (30 ml.) were added, the aqueous phase was extracted with ether (4 × 20 ml.), and the combined organic layers were dried ($MgSO_4$). Distillation gave 3-fractions: (i) b. p. 48—50°/0·8 mm. (2·7 g., 61%), (ii) b. p. 70—78°/0·9 mm. (0·2 g.), and (iii) b. p. 80—81°/0·9 mm. (1·3 g., 29%). Fraction (i) was the

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† Part XVI, D. K. Black, S. R. Landor, A. N. Patel, and P. F. Whiter, *J. Chem. Soc.* (*C*), 1967, 2260.

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[3] N. Zelinsky and C. Stadnikoff, *Ber.*, 1906, **39**, 1722.

[4] M. A. J. Ultee, *Rec. Trav. chim.*, 1909, **28**, 248.

[5] D. K. Black and S. R. Landor, *J. Chem. Soc.*, 1965, 5225.

[6] K. K. Brannocc, *J. Amer. Chem. Soc.*, 1959, **81**, 3379.

amino-nitrile (Found: C, 69·5; H, 10·3; N, 20·3. $C_8H_{14}N_2$ requires C, 69·6; H, 10·1; N, 20·3%), $\nu_{max.}$ 3400m (N–H stretch), 1650m (C=C), 2230w (C≡N), and 1520s (N–H deformation) cm.$^{-1}$. Fraction (iii) was the cyanohydrin prepared in the previous experiment (identified by comparison of i.r. spectra).

2-*Amino*-3,3-*dimethylhex*-5-*enoic Acid*.— 2-Amino-3,3-dimethyl-hex-5-enenitrile (2·0 g., 0·014 mole) was heated under reflux with 10N-hydrochloric acid (50 ml.) for 1 hr. The mixture was set aside overnight at room temperature and evaporated *in vacuo* to small bulk. Hydrochloric acid (30 ml.; 10N) was added and the mixture was heated under reflux for a further 3 hr. Water (30 ml.) was added, the mixture was evaporated *in vacuo* to dryness, and the residue was dissolved in water (10 ml.). Aqueous ammonia was then added (to pH 4) and the mixture was cooled at 0° for 3 days to give the solid *amino-acid* (1·4 g., 62%) (Found: C, 61·1; H, 9·4; N, 8·9. $C_8H_{15}NO_2$ requires C, 61·2; H, 9·6; N, 8·9%), $\nu_{max.}$ 3200—2900vs (C–H and N–H stretch), 1520—1500vs ($\overset{+}{N}H_3$ deformation), and 1650—1580 (CO_2^- and C=C) cm.$^{-1}$.

2-*Aminohexa*-4,5-*dienoic Acid*.—Penta-3,4-dienal [5] (1·0 g.), was added to a mixture of ammonium chloride (0·4 g.), potassium cyanide (0·4 g.), aqueous ammonium hydroxide (4 ml.), and water (5 ml.), and the mixture was shaken for 12 hr. at room temperature. It was then heated at 50° for 3 hr., 10N hydrochloric acid (50 ml.) was added, and the mixture shaken for 2 hr. and heated under reflux for 1 hr. It was evaporated *in vacuo* to small bulk and 10N hydrochloric acid (10 ml.) was added. The mixture was then heated under reflux for 1 hr. and evaporated to dryness. Water (10 ml.) was added and the mixture was again evaporated to dryness. The residue was dissolved in water (10 ml.), and the solution was neutralised with saturated sodium hydrogen carbonate solution, evaporated to small bulk, and chromatographed on paper. 2-Aminohexa-4,5-dienoic acid was identified as the only ninhydrin-sensitive component, R_F 0·51, in agreement with that of an authentic sample.[7]

2-*Hydroxy*-3,3-*dimethylhexa*-4,5-*dienitrile*.— 2,2-Dimethylpenta-3,4-dienal [5] (5·5 g., 0·05 mole) was added to liquid hydrogen cyanide (20 g., 0·74 mole) cooled at 0°. Saturated potassium cyanide solution (0·2 ml.) was added and the mixture was shaken for 3 hr. and set aside at room temperature for 2 days. Ether (20 ml.) and water (50 ml.) were added, and the aqueous phase was extracted with ether (3 × 20 ml.). The combined organic layers were dried ($MgSO_4$) and distilled to give the *cyanohydrin* (3·0 g., 44%), b. p. 80—81°/0·7 mm. (Found: C, 69·3; H, 8·2; N, 10·2. $C_8H_{11}NO$ requires C, 70·1; H, 8·0; N, 10·2%), $\nu_{max.}$ 3400vs (O–H), 1960s (C=C=C), 850vs (=C=CH_2), and 2260w (C≡N) cm.$^{-1}$, and a polymeric residue (4 g.).

2-*Amino*-3,3-*dimethylhexa*-4,5-*dienenitrile*.— 2-Hydroxy-3,3-dimethylhexa-4,5-dienenitrile (5·0 g., 0·036 mole), ammonium chloride (1·5 g.), and aqueous ammonia (250 ml.; *d* 0·880) were shaken at 20° for 7 days. Ether (50 ml.) was added, the aqueous layer was extracted with ether (4 × 30 ml.), and the combined organic layers were dried ($MgSO_4$). After removal of ether, distillation gave the *amino-nitrile* (4·1 g., 83%), b. p. 75—77°/2 mm. (Found: C, 70·4; H, 9·1; N, 20·10. $C_8H_{12}N_2$ requires C, 70·6; H, 8·8; N, 20·6%), $\nu_{max.}$ 1950s (C=C=C), 850s (=C=CH_2), 3300s (N–H stretch), and 2230w (C≡N) cm.$^{-1}$.

2-*Amino*-3,3-*dimethylhexa*-4,5-*dienoic Acid*.—Concentrated hydrochloric acid (50 ml.) was added slowly to 2-amino-3,3-dimethylhexa-4,5-dienenitrile (3·2 g. 0·024 mole) with continuous agitation. The solid hydrochloride formed initially dissolved on addition of an excess of acid. After 1·2 hr. at 20° the mixture was refluxed for 1 hr., decolourised with charcoal, and filtered; the filtrate was evaporated *in vacuo* (5 mm.) to half-bulk. Water (30 ml.) was added, and the solution was neutralised with saturated sodium hydrogen carbonate solution and again evaporated *in vacuo*. The resulting solid was dissolved in water (10 ml.) and the solution subjected to preparative paper chromatography (Whatman No. 3). Elution, with water, of the band containing the component, R_F 0·75, gave the *amino-acid* as a solid (0·8 g., 22%) (Found: C, 62·1; H, 8·4; N, 9·1. $C_8H_{13}NO_2$ requires C, 61·9; H, 8·4; N, 9·0%), $\nu_{max.}$ 1965m (C=C=C), 2800—3400vs (C–H and N–H stretch), and 1590—1620vs (zwitterion C=O and N–H deformations).

2-*Aminohepta*-4,5-*dienoic Acid*.—Impure hexa-3,4-dienal [5] (1·5 g.), by a similar procedure as used for penta-3,4-dienal, gave a solid which on paper chromatography showed the presence of a major component, R_F 0·61, and two minor components, R_F 0·72 and 0·47. Paper chromatography with an authentic sample [7] showed the component, R_F 0·61, to be 2-aminohepta-4,5-dienoic acid; the other two components were not identified.

2-*Hydroxy*-3,3-*dimethylhepta*-4,5-*dienenitrile*.— 2,2-Dimethylhexa-3,4-dienal [5] (5·0 g., 0·04 mole) was added to liquid hydrogen cyanide (30 g., 1·11 mole) cooled to 0°. A saturated solution of potassium cyanide (0·4 ml.) was added, and the mixture was left at −10° for 3 hr. After 2 days at room temperature, water (10 ml.) and ether (3 × 20 ml.) were added, and the combined organic layers were dried ($MgSO_4$). Distillation gave the *cyanohydrin* (4·4 g., 73·2%), b. p. 85—87°/2·5 mm., (Found: C, 71·4; H, 8·6; N, 9·2. $C_9H_{13}NO$ requires C, 71·5; H, 8·6; N, 9·3%), $\nu_{max.}$ 3500s (O–H), 1960s (C=C=C), 870s (=C=CH–), and 2230m (C≡N) cm.$^{-1}$.

2-*Amino*-3,3-*dimethylhepta*-4,5-*dienenitrile*.— 2-Hydroxy-3,3-dimethylhepta-4,5-dienenitrile (4·0 g., 0·026 mole), ammonium chloride (1·0 g.), and aqueous ammonia (300 ml., *d* 0·880) were shaken at 20° for 1 week. Extraction with ether (5 × 20 ml.) and distillation gave the *amino-nitrile* (2·6 g., 66%), b. p. 62—63°/1·9 mm. (Found: C, 71·5; H, 9·1; N, 18·5. $C_9H_{14}N_2$ requires C, 72·0; H, 9·3; N, 18·7%), $\nu_{max.}$ 1960s (C=C=C), 875m (=C=CH–), 3400m (N–H stretch), and 2230 (C≡N) cm.$^{-1}$.

2-*Amino*-3,3-*dimethylhepta*-4,5-*dienoic Acid*.—2-Amino-3,3-dimethylhepta-4,5-dienenitrile (0·8 g., 0·0053 mole) was cooled in an ice-bath and concentrated hydrochloric acid was added slowly with constant agitation. After 5 hr. at 20°, water (15 ml.) was added and the mixture was refluxed for 2 hr. Concentration *in vacuo* (2 mm.) to half-bulk, addition of water (20 ml.), and evaporation *in vacuo* gave a solid (0·6 g.) containing ammonium chloride. Paper chromatography showed the presence of a single ninhydrin-sensitive component, R_F 0·85. Preparative paper chromatography gave the *amino-acid* (R_F 0·83) in poor yield (0·005 g.).

2-*Amino*-3,3-*dimethylnona*-4,5-*dienoic Acid*.—A mixture of 2,2-dimethylocta-3,4-dienal [5] (2·0 g., 0·013 mole), aqueous ammonia (8 ml.; *d* 0·880), potassium cyanide (1 g.), and ammonium chloride (1 g.) was heated at 60° for 5 hr. Hydrochloric acid (25 ml.; 10N) was added, and the mixture was refluxed for 1 hr. and left overnight at room

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[7] D. K. Black and S. R. Landor, following Paper.

temperature. The mixture was evaporated *in vacuo* to small bulk, and 10N-hydrochloric acid (15 ml.) was added. The solution was refluxed for 3 hr. and again evaporated *in vacuo*. The residue was dissolved in water (10 ml.) and the solution was passed through a column of Deacidite ' E ' ion-exchange resin (2 × 30 cm.). The column was washed with water until a negative test for chloride ion was obtained. The eluate was concentrated *in vacuo* to give the solid (0·5 g., 32%) *amino-acid* (Found: C, 69·7; H, 8·9; H, 6·9. $C_{11}H_{19}NO_2$ requires C, 70·6; H, 8·9; H, 6·9%), $\nu_{max.}$ 1960m (C=C=C), 860m (=C=CH–), 2800—3400vs (C–H and N–H stretch), and 1590—1610m (NH_3 deformation and CO_2^- Paper chromatography showed a major ninhydrin-sensitive component, R_F 0·84 and a trace of impurity, R_F 0·75.

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