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Synthesis of α -Amino-1-Adamantylacetic and α -Amino-2-Adamantylacetic Acid*

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α -Amino-2-adamantylacetic acid (VII) was obtained when 2-adamantylcyanoacetylhydrazide (IX) was subjected to Curtius rearrangement or 2-(2-adamantyl)-malonic acid (XII) to Hofmann degradation. The same amino acid was obtained when α -bromo-2-adamantylacetic acid (VI) was treated with ammonia.

Partial hydrolysis of diethyl adamantyl-(1)-malonate (XIV) yielded ethyl adamantyl-(1)-malonate (XV) which, after treatment with thionyl chloride and then ammonia, gave 2-(1-adamantyl)-malonic acid ethyl ester (XVII). Hofmann degradation of 2-(1-adamantyl)-malonic acid ethyl ester gave α -amino-1-adamantylacetic acid (XVIII).

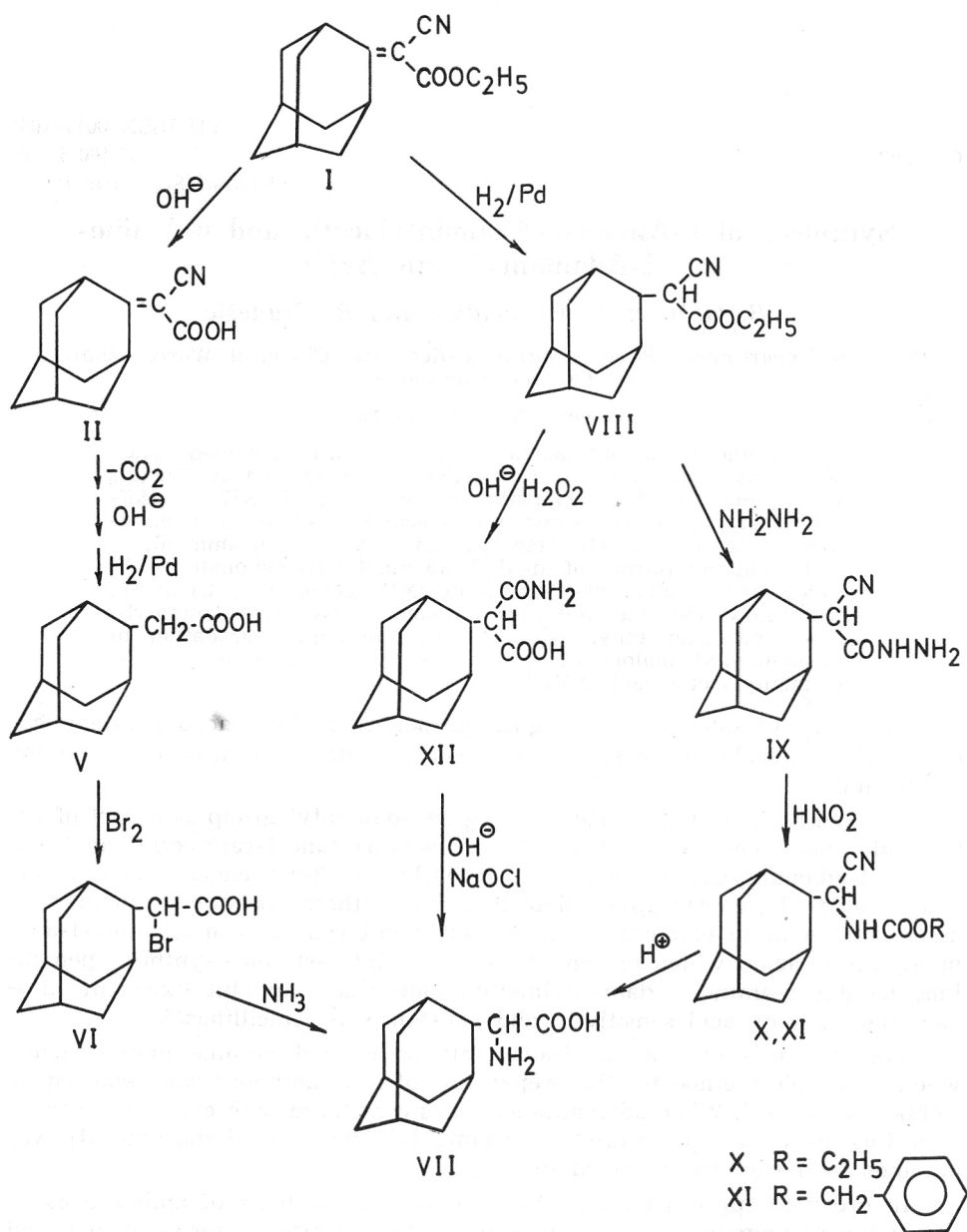
Discovery of interesting biological properties of 1-aminoadamantane hydrochloride¹ stimulated the synthesis of a large number of structurally related compounds.

The synthesis of amino acids, having an adamantyl group as a part of the molecule, has been reported for 3-aminoadamantane-1-carboxylic acid², α -amino-1-adamantylacetic acid³ and recently for 2-aminoadamantane-2-carboxylic acid⁴. It seemed appropriate to us to synthesise α -amino-2-adamantylacetic acid⁵ and to elaborate a more convenient synthesis of α -amino-1-adamantylacetic acid⁶, which presented the added interest since synthetic penicillins, having α -amino-1-adamantylmethyl side chain, exhibit excellent antibacterial activity, acid sensitivity and resistance to penicillinase².

The synthesis of α -amino-2-adamantylacetic acid became more feasible when a suitable method for the preparation of adamantanone was reported by Geluk and Keizer⁷. When adamantanone was condensed with cyanoacetic ester, according to Cope's procedure^{8,9}, 2-adamantylidenecyanoethylacetate (I) was obtained as a starting intermediate.

In order to apply a classical method for the synthesis of amino acids — the action of ammonia upon α -halogen substituted acid — series of new and described experiments were designed to prepare α -bromo-2-adamantylacetic acid (VI). 2-Adamantylidenecyanoethylacetate (I) upon alkaline hydrolysis and decarboxylation of the resulting 2-adamantylidenecyanoacetic acid (II) according to Burkhard¹⁰, gave 2-adamantylideneacetonitrile (III). Hydrolysis of III with potassium hydroxide gave 2-adamantylideneacetic acid (IV) which,

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on catalytic hydrogenation quantitatively yielded 2-adamantylacetic acid (V). This method for the preparation of 2-adamantylacetic acid is different than that described previously by Landa¹¹. Bromination of 2-adamantylacetic acid (V), in presence of red phosphorus, led to the formation of α -bromo-2-ada-

mantylacetic acid (VI) which in a reaction with liquid ammonia afforded α -amino-2-adamantylacetic acid (VII) in 12% overall yield.

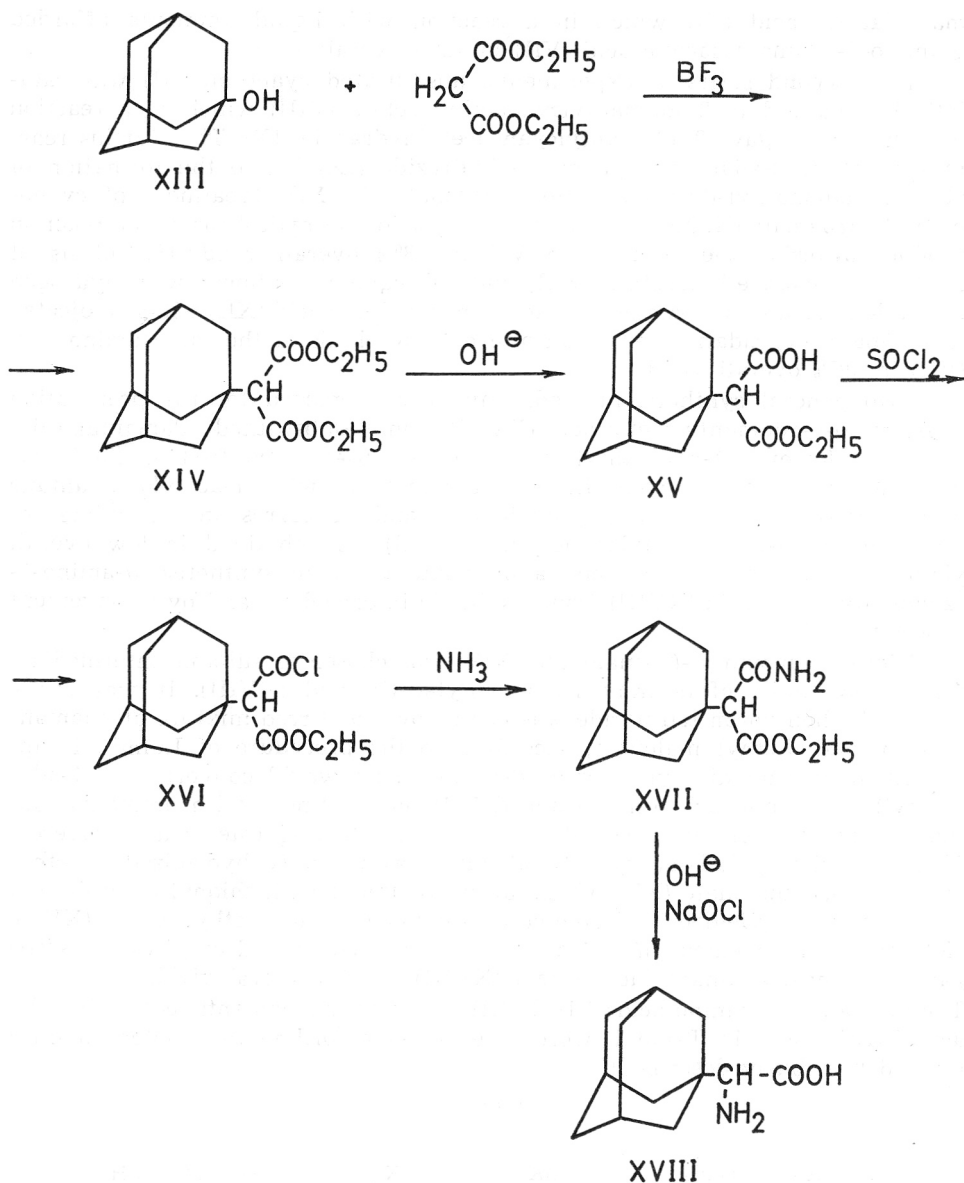
In a second series of experiments, unsaturated cyanoester (I) was catalytically reduced to 2-adamantylcyanoethylacetate (VIII) which in a reaction with hydrazine gave 2-adamantylcyanoacetylhydrazide (IX). The Curtius rearrangement of 2-adamantylcyanoacetylhydrazide (IX) led to the formation of alkyl *N*-adamantyl-(2)-cyanomethyl/carbamate (X, XI). Treatment of cyanomethyl carbamate (X, XI) with hydrobromic acid and hydrolysis of the reaction product afforded the amino acid VII in 38% overall yield. Hydrolysis of 2-adamantylcyanoethylacetate (VIII) and subsequent treatment with hydrogen peroxide gave the monoamide of 2-adamantylmalonic acid (XII) which subjected to Hofmann degradation led to an alternate synthesis of the same amino acid (VII) in 39% overall yield.

Two general synthetic methods have been reported for the preparation of α -amino-1-adamantylacetic acid (XVIII) from 1-substituted adamantane derivatives. However, 1-adamantylcarboxaldehyde, used in the first method³, was not a suitable starting reagent. In the second method³, when 1-acetyladamantane was oxidised to 1-adamantylglyoxylic acid and its corresponding oxime reduced, α -amino-1-adamantylacetic acid (XVIII) was obtained in low overall yield (6%). Therefore it seemed appropriate to us to synthesise α -amino-1-adamantylacetic acid (XVIII) from a suitable intermediate and by a convenient procedure.

Diethyl adamantyl-(1)-malonate (XIV) was chosen as suitable intermediate for the synthesis of α -amino-1-adamantylacetic acid (XVIII). It was easily prepared when boron trifluoride was passed over a stirred mixture of adamantan-1-ol and diethyl malonate, according to the procedure of Lunn¹². It appeared likely that diethyl adamantyl-(1)-malonate would convert to 2-(1-adamantyl)-malonamic acid ethyl ester (XVII) on treatment with ammonia, but these attempts were unsuccessful and only the starting ester was recovered. Therefore, diethyl adamantyl-(1)-malonate was partially hydrolyzed in ethyl adamantyl-(1)-malonate (XV) which, after treatment with thionyl chloride and then ammonia, yielded 2-(1-adamantyl)-malonamic acid ethyl ester (XVII). Hofmann rearrangement of 2-(1-adamantyl)-malonamic acid ethyl ester (XVII) gave α -amino-1-adamantylacetic acid (XVIII) in 30% overall yield. The pK values of amino acids VII, XVIII and 2-aminoadamantane-2-carboxylic acid (XIX) listed in Table I, were determined according to a potentiometric method previously described¹³.

TABLE I

Amino acids	pK' ₁	pK' ₂	Isoelectric pH
α -amino-1-adamantylacetic acid (XVIII)	2.87	8.52	5.695
α -amino-2-adamantylacetic acid (VII)	2.75	8.36	5.545
2-aminoadamantane-2-carboxylic acid (XIX)	2.98	8.02	5.500



There are no significant difference in pK and pH values of isoelectric points between adamantane substituted α -amino acids and geminally functionalized, achiral aminoadamantane carboxylic acid.

The amino acids VII and XVIII exhibit very low water solubility, which presents a problem in biological evaluation of adamantyl amino acids VII and XVIII. This low solubility may be associated not only with the α -amino acid

zwitterionic character, but also with the lypophilic character of adamantane part of the molecule. Nevertheless, amino acids VII and XVIII are more soluble in water (1 g/l for VII and 1.7 g/l for XVIII) at room temperature over pH range 2—8.5 than 2-aminoadamantane-2-carboxylic acid (0.3 g/l).

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded, unless otherwise stated, in potassium bromide plates on a Perkin-Elmer Infracord model 257 and are reported in wavelenghts followed by relative intensities in brackets. pH Values were measured on a pH-meter Methrom model E 300 B.

2-Adamantylidenecyanoethylacetate (I)

2-Adamantylidenecyanoethylacetate⁹ (I) was prepared from adamantanone according to Cope's⁸ procedure (Yield 87%).

2-Adamantylidenecyanoacetic Acid (II)

2-Adamantylidenecyanoethylacetate (2.04 g, 8.2 mmol) in absolute ethanol (2 ml) was added into a stirred solution of potassium hydroxide (1.06 g, 20 mmol) in absolute ethanol (12 ml). After about 10 minutes a white product started to precipitate. Stirring was continued for additional 4 hours. The reaction mixture was evaporated to dryness, water (5 ml) was added and undissolved material filtered. The filtrate was extracted with benzene, the aqueous layer acidified with 10% hydrochloric acid and obtained crystals filtered. Yield 1.0 g (58.5%), m. p. 182—184 °C. (Lit.¹⁰: m. p. 184.4—185.9 °C).

2-Adamantylideneacetonitrile (III)

2-Adamantylideneacetonitrile (III) was prepared according to the procedure given by Burkhard¹⁰ (yield 85%).

2-Adamantylideneacetic Acid (IV)

A solution of 2-adamantylideneacetonitrile (2 g, 11.5 mmol) and potassium hydroxide (2 g, 35.5 mmol) in water (4 ml) and ethylene glycol (18 ml) was heated at 120—128 °C for 24 hours. The mixture was evaporated to dryness under reduced pressure and the residual solid acidified with 10% hydrochloric acid. Crude 2-adamantylideneacetic acid was recrystallized from ethanol-water. Yield 1.18 g (53.5%), m. p. 135—138 °C (Lit.¹⁰ m. p. 135.5—136.7 °C).

2-Adamantylacetic Acid (V)

2-Adamantylideneacetic acid (2 g, 10 mmol) in absolute ethanol (68 ml) was hydrogenated over palladium (5% Pd/C, 0.3 g) at 22 °C and 2 atm for 1 hour. The catalyst was filtered and the filtrate evaporated to dryness under reduced pressure. Yield 2.25 g (100%). Pure 2-adamantylacetic acid was obtained by recrystallization from methanol-water, m. p. 133—134 °C. (Lit.¹¹ m. p. 136 °C).

 α -Bromo-2-adamantylacetic Acid (VI)

A mixture of 2-adamantylacetic acid (0.8 g, 4.11 mmol), benzene (10 ml) and red phosphorus (0.5 g) was heated at 50 °C and an excess of bromine (26.1 g, 0.163 mmol) was added. The reaction was slightly exothermic. After heating at 80 °C for 3 hours, the excess of bromine was removed by distillation and cold water (20 ml) was added. The mixture was heated at 100 °C for another 30 minutes, then treated with some sodium bisulphite and extracted with ether. After evaporation of ether the crystalline residue was treated with petroleum ether (15 ml) and the crystals filtered. Recrystallization from benzene gave 0.77 g (yield 70%) of the product, m. p. 178—181 °C. Further crystallization from benzene gave the analytical sample as colourless needles, m. p. 184 °C.

Anal. C₁₂H₁₇O₂Br (273.17) calc'd.: C 52.76; H 6.27; Br 29.26%
found: C 53.01; H 6.14; Br 29.70%

Ir spectrum: 1710 (vs) cm⁻¹.

α-Amino-2-adamantylacetic Acid (VII)

Into a mixture of *α*-bromo-2-adamantylacetic acid (1.36 g, 5 mmol) and methanol (6 ml) cooled in a glass tube at -50 °C, liquid ammonia (about 5 ml) was introduced. The glass tube was sealed and after staying at 22 °C for 5 days, the solvent was evaporated to dryness. The crystalline residue was treated with water, the crystals filtered and washed with water. Yield 0.62 g (59%), m. p. 250 °C. Pure *α*-amino-2-adamantylacetic acid was obtained when the crude product was dissolved in 10% hydrochloric acid and precipitated with 0.1 M sodium hydroxide at pH 5.6, m. p. 258–260 °C (in a sealed tube), undepressed with the sample obtained by Curtius rearrangement of 2-adamantylcyanoacetylhydrazide.

2-Adamantylcyanoethylacetate (VIII)

To a solution of 2-adamantylidenecyanoethylacetate (10 g) in ethanol (250 ml) 5% palladium on carbon (1 g) was added. The mixture was hydrogenated under pressure of 1 atm at room temperature for 2 hours. The catalyst was filtered off and the filtrate evaporated to a colourless oil (yield 9.9 g, 98%), distilled at 130–160 °C/0.08 mm.

Anal. C₁₅H₂₁NO₂ (247.36) calc'd.: C 72.84; H 8.56; N 5.66%
found: C 72.94; H 8.63; N 5.68%

Ir spectrum (film): 2250(w), 1745(vs) cm⁻¹.

2-Adamantylcyanoacetylhydrazide (IX)

To a solution of 2-adamantylcyanoethylacetate (9.38 g, 37 mmol) in ethanol (20 ml), 80% solution of hydrazine hydrate (5.5 ml, 90.5 mmol) was added. The solution was heated under reflux for 1 hour. Upon cooling 7.6 g (yield 86%) of 2-adamantylcyanoacetylhydrazide crystallized out of the solution in form of colourless needles, m. p. 157–158 °C. For analysis a sample was sublimed (m. p. 160–161 °C) at 160 °C/0.1 mm.

Anal. C₁₃H₁₉N₃O (233.31) calc'd.: C 66.92; H 8.21; N 18.01%
found: C 67.17; H 7.94; N 17.83%

Ir spectrum: 3300(m), 2240(w), 1660(m), 1620(w) cm⁻¹.

Ethyl N-/adamantyl-(2)-cyanomethyl/urethane (X)

To a suspension of 2-adamantylcyanoacetylhydrazide (2 g, 86 mmol) in water (7 ml) 2.5 M hydrochloric acid (4 ml), ether (20 ml) and an aqueous solution of sodium nitrite (0.620 g/9 mmol in 2 ml water) were added stirring vigorously at 0 °C. The reaction mixture was stirred at 15 °C for 1 hour. The ether layer was separated and the aqueous phase extracted twice with 20 ml portions of ether. The ethereal extracts were combined, dried over magnesium sulphate and added to absolute ethanol (30 ml). Ether was largely evaporated and the residual solution was refluxed until nitrogen evolution ceased. After concentration to a shorter volume a crystalline precipitate was separated, m. p. 155–157 °C. Yield 1.55 g (69%). Crystallization from 20% ethanol gave analytical sample, m. p. 157–158 °C.

Anal. C₁₅H₂₂N₂O₂ (262.34) calc'd.: C 68.67; H 8.45; N 10.68%
found: C 68.95; H 8.65; N 10.77%

Ir spectrum: 3300(m), 2240(w), 1695(s) cm⁻¹.

Benzyl N-/adamantyl-(2)-cyanomethyl/urethane (XI)

Benzyl *N*-/adamantyl-(2)-cyanomethyl/urethane was prepared according to the procedure described for the preparation of ethyl *N*-/adamantyl-(2)-cyanomethyl/urethane using benzyl alcohol instead of ethanol. Yield 60%, m. p. 171—172 °C. Recrystallization from chloroform gave colourless needles, m. p. 173—173.5 °C.

Anal. C₂₀H₂₄N₂O₂ (324.41) calc'd.: C 74.04; H 7.46; N 8.64%
found: C 73.96; H 7.28; N 8.91%

Ir spectrum: 3300(m), 3040(w), 2240(w), 1695(s), 1535(s) cm⁻¹.

2-(2-Adamantyl)-malonamic Acid (XII)

To a solution of 2-adamantylcyanoethylacetate (8.39 g, 34 mmol) in absolute ethanol (20 ml), a solution of potassium hydroxide (4.4 g, 78.2 mmol) in absolute ethanol (40 ml) was added dropwise and the solution was stirred at 25 °C for 5 hours. The separated solid product was dissolved in 1 M sodium hydroxide (20 ml). To this solution 30% hydrogen peroxide (7.7 ml, 90 mmol) was added with stirring. After the addition of hydrogen peroxide was completed it was stirred further for 30 minutes at 20 °C. While stirring the solid partly separated and upon cooling the complete amount of potassium salt of 2-(2-adamantyl)-malonamic acid separated. Yield 7.2 g (80%). For analysis, a sample was dissolved in water and the solution acidified with hydrochloric acid. Separated 2-(2-adamantyl)-malonamic acid was recrystallized from ethanol, m. p. 159—160 °C.

Anal. C₁₃H₁₉NO₃ (237.29) calc'd.: C 65.80; H 8.07; N 5.90%
found: C 65.50; H 7.99; N 5.61%

Ir spectrum: 3430(m), 3290(w), 1725(m), 1650(s), 1585(w) cm⁻¹.

α-Amino-2-adamantylacetic Acid (VII)

a) From ethyl *N*-/adamantyl-(2)-cyanomethyl/urethane. — Ethyl *N*-/adamantyl-(2)-cyanomethyl/urethane (2 g, 7.65 mmol) was gradually added into 63% bromic acid (16 ml) at 60 °C. The reaction solution was heated at 90 °C for 30 minutes, water (50 ml) was added, and the reaction mixture was refluxed for 4 hours. The solid separated out of the solution upon cooling, was dissolved in water (40 ml), the impurities were filtered and the filtrate was adjusted to pH 5.6. A colourless solid separated (1.19 g, 75%), m. p. 255—258 °C (in a sealed tube). Precipitation from 1 M sodium hydroxide with hydrochloric acid gave analytical sample, m. p. 258—260 °C (in a sealed tube).

Anal. C₁₂H₁₉NO₂ (209.28) calc'd. C 68.86; H 9.15; N 6.69%
found: C 69.01; H 8.89; N 6.79%

Ir spectrum: 3500—3300(b), 1665(m), 1630(w), 1585(w), 1505(m) cm⁻¹.

b) From benzyl *N*-/adamantyl-(2)-cyanomethyl/urethane. — *α*-Amino-2-adamantylacetic acid (0.8 g, 62%) was prepared according to the procedure described for the preparation of the amino acid starting from ethyl *N*-/adamantyl-(2)-cyanomethyl/urethane.

c) From potassium salt of 2-(2-adamantyl)-malonamic Acid. — To the cold solution of sodium hypochlorite (3.1 ml, 10.3 g NaOCl/100 ml — 4.3 mmol) and sodium hydroxide (0.175 g, 4.5 mmol), potassium salt of 2-(2-adamantyl)-malonamic acid dissolved in water (20 ml) was added. To this reaction mixture 0.5 M sodium hydroxide (20 ml) was added and the mixture was refluxed for 1 hour. Upon cooling the crude impurities were filtered and the filtrate was acidified with hydrochloric acid to pH 5.6. A colourless solid separated (0.44 g, 57%), m. p. 252—256 °C (in a sealed tube). Precipitation from 1 M hydrochloric acid with sodium hydroxide gave analytical sample, m. p. 258—260 °C (in a sealed tube).

The ir spectra of all three amino acids were superimposable.

The *N*-trifluoroacetyl derivative of *α*-amino-2-adamantylacetic acid was prepared by adding trifluoroacetic anhydride (2 ml, 13.7 mmol) to the solution of the

amino acid (2 g, 9.6 mmol) in 15 ml anhydrous trifluoroacetic acid at -15°C and stirring the reaction solution at $10-15^{\circ}\text{C}$ for 1 hour. The excess anhydride and trifluoroacetic acid were distilled under reduced pressure, the residue was extracted with dry ether and the ethereal extract filtered and concentrated. Crystallization was achieved from *n*-hexane — petroleum ether. Yield 1.52 g (52%), m. p. $190-192^{\circ}\text{C}$. Recrystallization from methylenechloride — *n*-hexane gave analytical sample, m. p. $192-194^{\circ}\text{C}$.

Anal. $\text{C}_{14}\text{H}_{18}\text{NO}_3\text{F}_3$ (305.29) calc'd.: C 55.08; H 5.94; N 4.59%
found: C 55.34; H 5.74; N 4.71%

Ir spectrum: 3300(m), 1725(vs), 1710(vs), 1560(m) cm^{-1} .

Diethyl Adamantyl-(1)-malonate (XIV)

Diethyl adamantyl-(1)-malonate (XIV) was prepared from adamantan-1-ol according to the Lunn's procedure¹².

Ethyl Adamantyl-(1)-malonate (XV)

To a solution of diethyl adamantyl-(1)-malonate (5.71 g, 19.5 mmol) in absolute ethanol (20 ml), 1 M alcoholic solution of potassium hydroxide (39 ml, 39.2 mmol) was added dropwise during 1 hour at 25°C . The mixture was then stirred 6 hours at room temperature, alcohol was evaporated and the residual solid washed with ether and dissolved in water (35 ml). To the water solution, covered with ether, DOWEX 50 (H^+) (25 ml) was added slowly vigorously stirring. After all divided precipitate of ethyl adamantyl-(1)-malonate has gone into the ether layer, ether was dried over magnesium sulphate and evaporated to dryness giving a colourless solid (4.73 g, 91%), m. p. $82-84^{\circ}\text{C}$. For analysis, a sample was recrystallized from *n*-hexane, m. p. $86-87^{\circ}\text{C}$.

Anal. $\text{C}_{15}\text{H}_{22}\text{O}_4$ (266.33) calc'd.: C 67.64; H 8.33%
found: C 67.88; H 8.42%

Ir spectrum: 1740(s), 1715(s) cm^{-1} .

Adamantyl-(1)-carbethoxyacetylchloride (XVI)

To a solution of ethyl adamantyl-(1)-malonate (5 g, 18 mmol) in dry benzene (50 ml) thionyl chloride (5 ml, 69 mmol) was added dropwise. The reaction solution was heated at 60°C for 4 hours. Benzene was distilled and traces of thionyl chloride were removed by repeated distillations with benzene. A residual redish oil (5.35 g, 100%) of acid chloride was taken crude in the next reaction. Ir spectrum (film): 1820(s), 1740(s) cm^{-1} .

2-(1-Adamantyl)-malonamic Acid Ethyl Ester (XVII)

A stream of dry gaseous ammonia was passed through a stirred solution of adamantyl-(1)-carbethoxyacetylchloride (5 g) in 50 ml of dry methylenechloride, with external cooling to 0°C for 40 minutes. The separated solid was removed and the filtrate was evaporated to dryness giving 2-(1-adamantyl)-malonamic acid ethyl ester. Yield 3.96 g (85%), m. p. $136-138^{\circ}\text{C}$. Recrystallization from chloroform-petroleum ether gave analytical sample, m. p. $138-140^{\circ}\text{C}$.

Anal. $\text{C}_{15}\text{H}_{23}\text{O}_3\text{N}$ (265.34) calc'd.: C 67.89; H 8.74; N 5.28%
found: C 68.13; H 8.59; N 5.33%

Ir spectrum: 3430(m), 3350(w), 3290(w), 3180(m), 1730(m), 1690(s), 1615(m) cm^{-1} .

α -Amino-1-adamantylacetic Acid (XVIII)

To a solution of 2-(1-adamantyl)-malonamic acid ethyl ester (1.5 g, 5.68 mmol) in absolute ethanol, 1 M alcoholic potassium hydroxide (15 ml, 15 mmol) was added dropwise while stirring. Reaction mixture was left for 24 hours at room tem-

perature, ethanol was then distilled and the residual solid dissolved in water (40 ml). To this solution, a solution of sodium hydroxide (0.260 g, 6.6 mmol) in sodium hypochlorite (5 ml, 10.3 g/100 ml, 7 mmol) was added and the reaction mixture was refluxed for 1 hour. Upon cooling crude impurities were filtered and the filtrate was acidified with 5 M hydrochloric acid to pH 5.7. A colourless solid separated (0.8 g, 67.5%), m.p. 265—269 °C (in a sealed tube).

Ir spectrum: 3500—3400(w), 1620(b), 1490(m) cm^{-1} .

A sample of α -amino-1-adamantylacetic acid (0.2 g) was suspended in absolute methanol (10 ml) and a stream of dry hydrogen chloride was passed through the suspension at 0 °C until the whole amino acid was dissolved. Methanol was then evaporated and the residual hydrochloride of α -amino-1-adamantylacetic acid was recrystallized from methanol-ether. Yield 0.210 g (89.5%), m.p. 320—321 °C (decomp. in a sealed tube). (Hermann³ reported m.p. decomp. over 320 °C).

Anal. $\text{C}_{12}\text{H}_{20}\text{NO}_2\text{Cl}$ (245.75) calc'd.: C 58.64; H 8.20; N 5.70%
found: C 58.30; H 7.88; N 5.37%

Ir spectrum: 1745(s), 1600(m), 1495(s) cm^{-1} .

The *N*-trifluoroacetyl derivative of α -amino-1-adamantylacetic acid was prepared by adding trifluoroacetic anhydride (1 ml, 6.85 mmol) to the solution of the amino acid (0.8 g, 3.8 mmol) in 6 ml of anhydrous trifluoroacetic acid at -10 °C and stirring the reaction solution at 10—15 °C for 1 hour. The excess anhydride and trifluoroacetic acid were distilled under reduced pressure, the residue was extracted with dry ether and the ethereal extract filtered and concentrated. Crystallization was achieved from *n*-hexane — petroleum ether. Yield 0.480 g (41%), m.p. 198—201 °C. For analysis a sample was sublimed (m.p. 220—221 °C) at 158 °C/0.05 mm.

Anal. $\text{C}_{14}\text{H}_{18}\text{O}_3\text{NF}_3$ (305.29) calc'd.: C 55.08; H 5.94; N 4.59%
found: C 55.10; H 6.00; N 4.71%

Ir spectrum: 3280(m), 1740(s), 1690(s), 1560(m) cm^{-1} .

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SAŽETAK

Sinteza α -amino-1-adamantiloctene i α -amino-2-adamantiloctene kiseline

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Sintetizirane su α -amino-1-adamantil- i α -amino-2-adamantiloctena kiselina.

α -Amino-2-adamantiloctena kiselina pripravljena je Curtiusovom pregradnjom 2-adamantilcijanoacetilhidrazida, odnosno Hofmannovom odgradnjom monoamida 2-adamantilmalonske kiseline. Ista kiselina dobivena je reakcijom amonijaka s α -brom-2-adamantiloctenom kiselinom.

Parcijalnom hidrolizom dietil-1-adamantilmalonata dobiven je etil-1-adamantilmalonat koji je preveden u etilni ester 2-(1-adamantil)-malonamid-kiseline. Hofmannovom odgradnjom etilnog estera 2-(1-adamantil)-malonamid-kiseline dobivena je α -amino-1-adamantiloctena kiselina.

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