Acta Chemica Scandinavica B 29 (1975) 93—98

A Facile Route to α-Hydrazinopropionic Acid of High Optical Purity. The Absolute Configuration of α-(4,5,6,7-Tetrahydroindazolyl-1 and -2)propionic Acid

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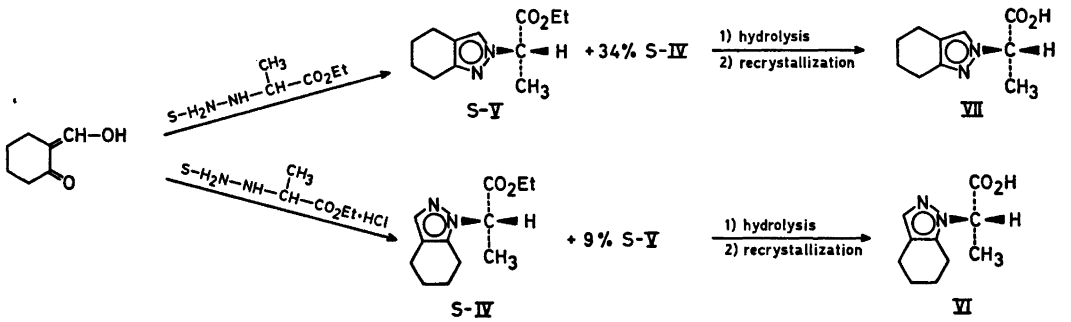
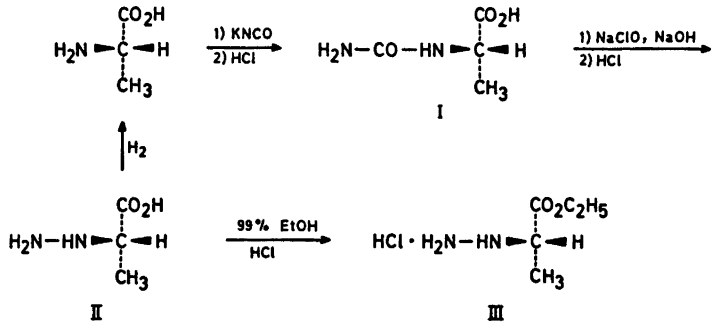
(*S*)(−)-α-Hydrazinopropionic acid (II) with $[\alpha]_D^{25} = -30°$ (6 M HCl) and an enantiomeric purity of 0.995 ± 0.002 has been synthesized *via* Hofmann rearrangement of (*S*)(−)-α-ureidopropionic acid (I). Ethyl α-hydrazinopropionate hydrochloride (III) was reacted with α-hydroxymethylenecyclohexanone to give a mixture of ethyl α-(4,5,6,7-tetrahydroindazolyl-1)propionate (IV) and ethyl α-(4,5,6,7-tetrahydroindazolyl-2)propionate (V). The ratio was influenced by the degree of protonation. (*S*)(+)-α-(4,5,6,7-tetrahydroindazolyl-1)propionic acid (VI) and (*S*)(+)-α-(4,5,6,7-tetrahydroindazolyl-2)propionic acid (VII) were synthesized for configurational assignment of some α-azolylpropionic acids.

The aim of the present work was to determine the absolute configuration of α-(indazolyl-2)-propionic acid,[1] α-(benzotriazolyl-2)-propionic acid [2] and a series of α-(cyclomethylenepyrazolyl-2)-propionic acids.[3,4] In the present case the quasi-racemate method [5,6] failed. The absolute configurations of the acids mentioned have now been determined by synthesis of (*S*)(+)-α-(4,5,6,7-tetrahydroindazolyl-2)propionic acid (VII) (Scheme 1) and CD measurements. Some of the results are given in Ref. 2—4. (−)-α-(Indazolyl-2)propionic acid was shown to have (*S*)-configuration by hydrogenation to VII. (*S*)(+)-α-(4,5,6,7-tetrahydroindazolyl-1)-propionic acid (VI) (Scheme 1) was also synthesized for the determination of the absolute configuration of α-(benzotriazolyl-1)-propionic acid.[7]

(*S*)(−)-α-Hydrazinopropionic acid (II) was obtained by Hofmann rearrangement of (*S*)(−)-α-ureidopropionic acid (I) with sodium hypochlorite in sodium hydroxide (Scheme 2). The mother liquor after separation of II gave a crystalline residue which was not further characterized. No II was obtained when using sodium hypobromite under different conditions instead of sodium hypochlorite. Separation of



Scheme 1.



Scheme 2.

II from the salt by means of ion exchange chromatography according to Carmi *et al.*[8] is not convenient for a separation on a large scale due to the large amount of salt formed. Purification via the ethyl ester of II and subsequent saponification with barium hydroxide according to Darapsky [9] was successful, but the method was tedious. In the present work most of the sodium chloride was separated off by treatment with acetic acid and a mixture of acetic acid and chloroform.

The enantiomeric purity of II defined according to Horeau [10] was determined by degradation to alanine, which was analyzed without purification according to Manning and Moore.[11] Using a method of Dakin [12] for preparation of I and performing the Hofmann reaction of I at room temperature, II was obtained with an enantiomeric purity of 0.995 ± 0.002. When the Hofmann reaction was done at 80 °C, II was obtained with enantiomeric purity of $0.97 - 0.98$.

A slight racemization also during the preparation of I with the Dakin method cannot be excluded. Therefore a milder method was worked out for its preparation. Alanine was reacted with potassium cyanate at room temperature for one day in a triethylamine-acetic acid buffer of pH 8. The preparation of II according to this method has not yet been done.

Examination of the IR spectrum of II reveals that it largely exists as a zwitterion. Absorption at 6.35 and 7.12 μm, typical for a carboxylate anion,[13] is found but absorption at 5.8 μm, normal for the carbonyl of an unionized carboxylic acid, is lacking. The IR spectrum of II is given in Fig. 1. The solubility properties of II, which are similar to those of alanine, and its high melting point support the zwitterionic character.

The cyclization of 1,3-dicarbonyl compounds or their sodium salts with hydrazines is a standard method for synthesis of pyrazoles.[14,15] β-Chlorovinylketones, β-alkoxyvinylketones, 1,3-diacetals, and β-aminovinylketones can be used instead of the 1,3-dicarbonyl compounds. 2-Chlorocyclohex-1-ene-1-carboxaldehyde and

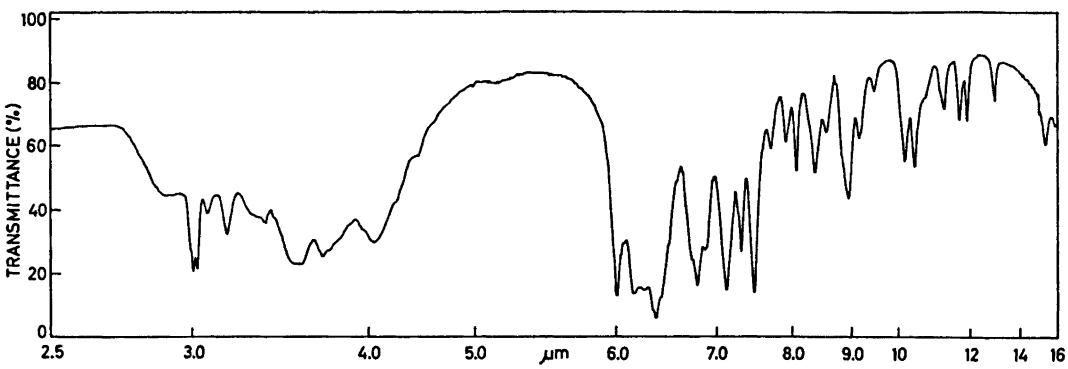


Fig. 1. IR spectrum of (S)(−)-α-hydrazinopropionic acid. Solid in KBr.

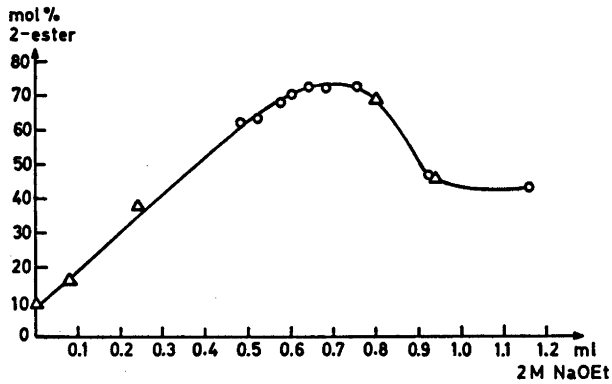


Fig. 2. Reaction of III with α-hydroxymethylenecyclohexanone upon addition of different amounts of sodium ethoxide. △ and ○ represent data obtained from ^{1}H NMR and GLC analysis, respectively.

benzylhydrazine in ethanol and hydrochloric acid are reported [16] to give exclusively 1-isomer, but no proof was given. The corresponding reaction with ethyl α-hydrazinopropionate hydrochloride (III), however, gives 1- and 2-isomer in the ratio 87:13.

A series of reactions was done with III and α-hydroxymethylenecyclohexanone in 99 % ethanol by adding sodium ethoxide in various amounts. The result is given in Fig. 2.

At strongly acidic or strongly basic conditions much of the 1-ester was formed in comparison to the 2-ester. The total yield of pyrazoles was high in the first case but rather low in the second case. At intermediary conditions more 2-ester than 1-ester was formed. These results are probably the consequence of the different degree of protonation in the different experiments. Protonation of the β-ketoaldehyde and the hydrazine compound as well as deprotonation of the β-ketoaldehyde ought to influence the course of reaction.

The reaction between α-hydroxymethylenecyclohexanone and β-hydroxyethylhydrazine in 99 % ethanol with or without addition of sodium ethoxide at −100 °C was followed by ^{1}H NMR spectroscopy. The reaction was quite fast and no intermediate was observed with certainty. Although the reaction between a β-ketoaldehyde and a hydrazine is a commonly used reaction, its mechanism is not known. Coispeau and Elguero [17] point out that the keto-enol equilibria and the two nucleophilic centra of monoalkyl-substituted hydrazines could give rise to twelve possible reaction mechanism and two isomers. Six of the mechanisms were ruled out. They do not discuss the influence of the degree of protonation on the reaction.

The reaction of II with α-hydroxymethylenecyclohexanone in absolute ethanol gave ~66 % VI and ~34 % VII. The same reaction but with triethylamine added (a drop of the reaction mixture on a moisted indicator paper gave pH 5.5) gave ~45 % VI and ~55 % VII. The reaction of α-hydroxymethylenecyclohexanone with ethyl (*S*)(−)-α-hydrazinopropionate and its hydrochloride was chosen for synthesis of VII and VI, respectively (Scheme 1), both of which thus have (*S*)-configuration.

The ester (*S*)-IV was easily racemized by hydrolysis with 2 M sodium hydroxide. A complete deuterium exchange of the α-proton by hydrolysis in 5 M sodium deuterium oxide at 100 °C was found by an ^{1}H NMR investigation. The acid isolated after acidification showed no or very low optical activity. Hydrolysis of IV with 2 M deuteriochloric acid at 100 °C did not give deuterium exchange and the acid isolated was optically active. The ester (*S*)-V, on the contrary, did not racemize on alkaline hydrolysis and the isolated acid had the maximal optical activity.

EXPERIMENTAL

The optical activity was measured with a Perkin-Elmer 141 spectropolarimeter in micro cells of 10 cm length. The CD curves were recorded in 1 ml cells in methanol solutions with

a Cary 60 spectropolarimeter equipped with a CD accessory. The ^{1}H NMR spectra were recorded on a Varian A-60 instrument with solutions of about 10 % using TMS as internal standard. The mass spectra were recorded at 70 eV with an LKB 9000 instrument and the IR spectra with a Perkin-Elmer 257 spectrophotometer in KBr pellets. The GLC analyses were performed with a Perkin-Elmer 990 instrument fitted with a flame ionization detector. Column temperature 160 °C, injection port temperature 240 °C and detector temperature 240 °C. Nitrogen carrier gas with flow rate 38 ml/min. The column was of 3.0 m length and made of glass, AW, DMCS-treated. I.D. 3.5 mm. It was packed with chromosorb W, AW, DMCS-treated, 100 – 200 mesh, coated with 7.5 % UCON 50LB-550 X. The column was conditioned at 200 °C for 24 h before use.

The thin layer chromatograms were run in butanol-glacial acetic acid-water (60:30:10) on non-activated plates (E. Merck) coated with silica gel F 254 with a nominal thickness of 0.25 mm. The chromatograms of α-hydrazinopropionic acid were developed with ninhydrin in 96 % ethanol (0.25 %, w/v) or molybdophosphoric acid (5 % in 96 % ethanol) according to Stahl.[18]

The melting points were determined with a hot stage microscope and are uncorrected. The microanalyses were carried out at the analytical department of the Institute.

The amino acid analyses were done with a Beckman Spinco automatic amino acid analyzer. The (*S*)-alanine used was purchased from Ajinomoto Co., Tokyo, Japan and contained less than 0.1 % (*R*)-alanine. The ligroin used had a specified b.p. of 60 – 71 °C.

(S)(−)-α-*Ureidopropionic acid (I).* 4.5 ml triethylamine and 4.5 ml water were mixed and glacial acetic acid was added to give a buffer of pH 8. 1.0 g (12.3 mmol) potassium cyanate was added to this buffer and then 1.0 g (11.2 mmol) of (*S*)-alanine in 3 ml of water. After one day at room temperature 2 M hydrochloric acid was added and I isolated, washed with ice-water and dried. 0.40 g (27 %) α-ureidopropionic acid was obtained with $[\alpha]_D^{25}$ −7.9°, $[\alpha]_{365}^{25}$ −17.9° (α_D^{52} −0.070°, α_{365}^{25} −0.159°, *c* 1.779; water) (lit.[12] $[\alpha]_D^{25}$ −9.4°). The product was not recrystallized to avoid eventual racemization.

(S)(−)-α-*Hydrazinopropionic acid (II).* An ice-cooled solution of 2.20 g (0.016 mol) of I was dissolved in 10 ml cooled 2 M sodium hydroxide, and 65 ml of 0.5 M sodium hypochlorite [20] in 10 % sodium hydroxide was added. The solution was kept at room temperature for 1.5 h. Then 1.6 ml of 99 % hydrazine hydrate was added (in another experiment sodium sulfite solution). The pH was adjusted to 3 with hydrochloric acid and the water distilled off in vacuo at 80 °C. The residue was suspended in acetic acid and most of the sodium chloride was filtered off. Chloroform was added in portions to the filtrate for selective precipitation of sodium chloride, I, and II in that order. II was dissolved in a small amount of water and precipitated by addition of 99 % ethanol. Yield 0.47 g (27 %). Recrystallization twice in the same way yielded II with m.p. 211 – 213 °C and $[\alpha]_D^{25}$ −30° (α_D^{25} −0.288°; *c* 0.964; 6 M HCl), R_F 0.38 (lit.[19] $[\alpha]_D^{25}$ −30.3°, m.p. 206 – 208 °C). The product contained a minor amount of sodium chloride; in another experiment 0.5 %.

Found: C 34.43; H 7.38; N 25.80. Calc. for $C_3H_8N_2O_2$ (104.11): C 34.61; H 7.75; N 26.91.

Deamination of (S)(−)-α-hydrazinopropionic acid. 0.2 mmol II was dissolved in 2 ml of water and 0.10 g 10 % palladium-on-charcoal was added. Hydrogenation was performed at a hydrogen pressure of 5 atm. in a Parr catalytic hydrogenation apparatus at room temperature for 24 h with continuous shaking. The catalyst was then filtered off, and the residue evaporated to dryness. The enantiomeric purity of the alanine formed was determined without purification. After the reaction, no II was detected in a TLC test. Neither absorption at 6.76 μm nor the double peak absorption at 3.0 μm typical for II was found.

Ethyl (S)(−)-α-hydrazinopropionate hydrochloride (III). (S)(−)-α-Hydrazinopropionic acid was esterfied before purification according to Darapsky.[9] The ester product was a viscous oil with $[\alpha]_D^{25}$ −23.3° (α_D^{25} −1.210°; *l* = 1; *c* 5.19; 99 % ethanol). The ester undergoes self-condensation upon standing (*cf.* Ref. 21). $[\alpha]_D^{25}$ of the ester hydrochloride was −2.8° (α_D^{25} −0.11°, *l* = 1, *c* 3.92; 99 % ethanol). ^{1}H NMR spectra showed that the ethyl α-hydrazinopropionate and its hydrochloride were not quite pure.

(S)(+)-α-(4,5,6,7-Tetrahydroindazolyl-1-)-propionic acid (VI). 0.40 g (3.2 mmol) α-hydroxymethylenecyclohexanone [22] was dissolved in 1.5 ml of 99 % ethanol. The solution was added dropwise at room temperature to 0.78 g (5.2 mmol) ethyl (*S*)(−)-α-hydrazinopropionate hydrochloride in 6 ml of 99 % ethanol. The temperature rose to 27 °C. The course of reaction was followed by ^{1}H NMR spectroscopy. After 10 min no further formation of IV and V was observed. After standing for half an hour the solvent was evaporated off at reduced pressure. The residue was warmed with 4 ml of 1 M hydrochloric acid on a boiling water bath for 90 min. 2 M sodium hydroxide was then added to pH 3.5 and the mixture was extracted with ether. Excess of sodium hydroxide should be avoided since the ester easily racemizes under alkaline conditions. The ether phase was dried with magnesium sulfate and treated with charcoal. The nearly colorless ether solution was evaporated to dryness. The residue (0.3 g) was dissolved in 1 ml of chloroform and precipitated by adding 6 ml of ligroin. After one further recrystallization in the same way and one from ethanol-water, a colorless product was obtained free from 2-isomer according to an IR and ^{1}H NMR analysis. 0. 06 g (10 %) of VI

was obtained with m.p. 139–140° C. $[\alpha]_D^{25}$ +16.8°, $[\alpha]_{365}^{25}$ +60.3° (α_D^{25} +0.219°, α_{365}^{25} +0.784°, *l* 1, *c* 1.30; $CHCl_3$). The specific rotation is strongly dependent on concentration. With *c* 3.518 an $[\alpha]_D^{25}$ value of +4.0° was obtained. IR (KBr), λ_{CO} 5.8 μm. UV λ_{max} 229.8 nm (log ε 3.67). CD, $[\theta]_{225}$ ±0, $[\theta]_{235}$ +1150 (in methanol). ^{1}H NMR ($CDCl_3$) $-CH_2-$ and $-CH_3$ (multiplet with the highest peak at δ 2.48), α-H (quartet at δ 4.90) and >CH= singlet at δ 7.30).

(S)(+)-α-(4,5,6,7-Tetrahydroindazolyl-2)-propionic acid (VII). Ethyl (S)(−)-α-hydrazinopropionate was isolated by suspending its hydrochloride in a mixture of chloroform and an excess of dry sodium carbonate. After stirring for some hours the chloroform solution was filtered and the chloroform evaporated off. It is advisable to prepare ethyl α-hydrazinopropionate just prior to use since it is not stable at room temperature.

0.5 g (4 mmol) of α-hydroxymethylenecyclohexanone was mixed with a solution of 0.5 g (3.8 mmol) of ethyl (*S*)(−)-α-hydrazinopropionate in 3 ml 99 % ethanol. The mixture was refluxed for 45 min. The solvent was distilled off and the residue was warmed for 2 h in a boiling water-bath. The hydrolyzate was extracted with ether and the water phase acidified to pH 3 with concentrated hydrochloric acid. The product was dissolved in 5 ml chloroform and 5 ml of ligroin was added. 0.05 g VII was obtained free from 1-acid according to IR and ^{1}H NMR data. M.p. 199–200 °C. $[\alpha]_D^{25}$ +41° (α_D^{25} +0.190°; *c* 0.464; $CHCl_3$).

The ratio of IV:V as a function of the amount of sodium ethoxide solution added. 0.200 g portions of racemic ethyl α-hydrazinopropionate hydrochloride were dissolved in 1.2 ml 99 % ethanol and various amounts of a 2 M solution of sodium ethoxide in 99 % ethanol were added. Then 0.40 ml of a solution of α-hydroxymethylenecyclohexanone in 99 % ethanol with a concentration of 0.5 g/ml was added to each portion under stirring and the mixture was warmed at 85 °C for 45 min. The solvent was distilled off and water was added to the residue. 2 M sodium hydroxide was added to slightly alkaline reaction if the water phase was acidic. The mixture was extracted with two portions of 5 ml ether and the ether phase was washed with a small amount of water and dried with magnesium sulfate. The ratio of IV:V in the ether solution was determined by GLC analysis. In some cases the ratios were determined by ^{1}H NMR analysis in DMSO solution of the residue after distilling off the solvent. The results are given in Fig. 2. Addition of more than 0.76 ml 2 M sodium ethoxide solution resulted in a marked decrease in the ester yield.

IV and V from 2-chlorocyclohexenecarboxaldehyde. 2-Chlorocyclohexenecarboxaldehyde was prepared according to Ziegenbein and Lang.[23] A solution of 1.0 g (5.4 mmol) rac. ethyl α-hydrazinopropionate hydrochloride in 1 ml 6 M hydrochloric acid and 2 ml 96 % ethanol was added at room temperature to 1.0 g (6.9 mmol) 2-chlorocyclohexenecarboxaldehyde dissolved in 3 ml 99 % ethanol. The course of reaction was followed by ^{1}H NMR spectroscopy using the difference in the vinyl proton shifts of the starting material, the intermediate and the products. A small amount of 2-chlorocyclohexenecarboxaldehyde remained after 30 min. After subsequent boiling for 30 min nearly no intermediate hydrazone was visible but much of the pyrazoles was observed. Boiling was continued for 30 min more. 2 M sodium hydroxide was then added to neutral reaction and the mixture was extracted with ether. The ether solution was dried, the ether distilled off and the residue analyzed by GLC. The compounds IV and V were formed in the ratio 87:13.

Acknowledgements. I want to thank Professor G. Bergson for his kind interest in this work and for all facilities placed at my disposal. I am much indebted to Dr. Ulf Ragnarsson for stimulating discussions and valuable advice and for performing the amino acid analyses. A grant from the Faculty of Science of the University of Uppsala is gratefully acknowledged.

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Received July 1, 1974.