Acta Chemica Scandinavica B 29 (1975) 88—92

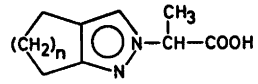
^{1}H NMR Spectroscopy of Some α-(Cyclopolymethylenepyrazolyl)-propionic Acids. Resolution and Configurational Assignment of α-(Cyclopentapyrazolyl-2)propionic Acid

HÅKAN GUSTAFSSON

Department of Organic Chemistry, Institute of Chemistry, University of Uppsala, S-751 21 Uppsala, Sweden

α-(4,5,6,7-Tetrahydroindazolyl-1)propionic acid (V) has been synthesized by catalytic hydrogenation of α-(indazolyl-1)propionic acid (IX) with 10 % palladium-on-charcoal as catalyst. The difference in the chemical shifts for the 3-proton in 1- and 2-substituted pyrazoles was used for determination of the structure of α-(cyclopentapyrazolyl-2)propionic acid (I), α-(cycloheptapyrazolyl-2)propionic acid (III) and α-(cyclooctapyrazolyl-2)propionic acid (IV). I was resolved *via* the brucine salt in ethyl acetate giving the acid with $[\alpha]_D^{25} = +26.7°$ in chloroform. The absolute configuration of I was determined by circular dichroism measurements. The rubidium salt of (−)-III was prepared for an unequivocal X-ray determination of the structure of I−V, IX and α-(indazolyl-2)-propionic acid (X) and the absolute configuration of active I−III.

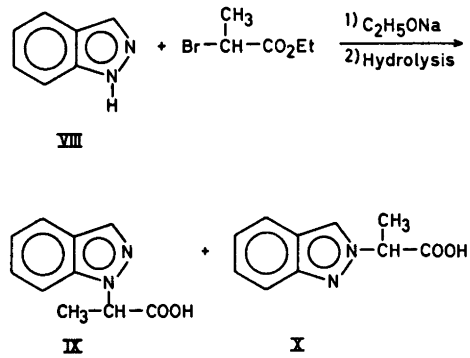
A series of α-(cyclomethylenepyrazolyl-2)propionic acids (I−IV) has been synthesized earlier.[1,2] The present investigation deals with the structure determination of these compounds.



I: n=1, II: n=2, III: n=3, IV: n=4.

The substitution of II was decided by hydrogenation of α-(indazolyl-2)propionic acid (X),[1] but its position in I, III, and IV, however, was not settled. To elucidate this question α-(4,5,6,7-tetrahydroindazolyl-1)propionic acid (V) was prepared.

Indazole (VIII) was reacted under reflux with ethyl α-bromopropionate in a solution of sodium ethoxide in absolute ethanol according to von Auwers and Allardt [3] giving a mixture of 1- and 2-esters (Scheme 1).



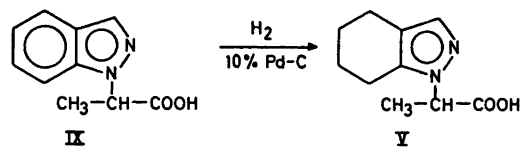
Scheme 1.

IX and X were successfully separated without prior picrate formation by column chromatography on silica gel. IX and X was also separated by recrystallization from hydrochloric acid of suitable concentration in which X, the more basic, is more soluble than IX.

The ^{1}H NMR data of IX and X and their ethyl esters in Table 1 show that the 3-proton shift in DMSO-d_6 appears at a higher field for the 1-isomers than for the 2-isomers.

Table 1. Chemical shifts (δ; ppm rel. TMS) of some 1- and 2-substituted indazoles and indazole in DMSO-d_6 and trifluoroacetic acid.

Compound	DMSO-d_6		Trifluoro-acetic acid	
	3-H	α-H	3-H	α-H
IX	8.01	5.57	8.84	6.02
IX, ethyl ester	8.02	5.64	8.75	5.93
X	8.34	5.50	8.87	5.91
X, ethyl ester	8.34	5.54	8.75	5.82
VIII	8.13		8.68	



IX V

Scheme 2.

STRUCTURAL DETERMINATION

von Auwers and Düesberg [4] found that the lower boiling isomers obtained by alkylation of indazole with alkylhalides in the presence of alkali were identical with those obtained according to the method of Fischer and Tafel [5] which gives exclusively the 1-isomer. Due to this and the mode of synthesis the 2-structure was assigned to the higher boiling isomer. The correctness of this structural assignment is supported by work of Grandberg *et al.*[9] and Schwan and Davis.[10] The structural determination of 1- and 2-alkylated indazoles is now easily done by means of their characteristic UV absorption properties.[6–8]

The structure of IX and X were determined by comparison of their UV spectra with those of 1- and 2-methylindazoles. IX and X were hydrogenated to V and II, respectively (Scheme 2 and Ref. 1). The 1-substitution of V and 2-substitution of II was further confirmed by ^{1}H NMR spectroscopy using the difference in chemical shifts of the vinylproton on 1,3,4- and 1,4,5-trialkylated pyrazoles.[12] III was used as a reference substance. The 2-substitution of III was determined by an X-ray crystallographic investigation [11] of its rubidium salt. The latter determination of the structure of II independently proves the correctness of the structure assignment of IX and X and that one of von Auwers and Düesberg of other indazoles. The chemical shifts of the vinyl protons of the compounds listed in Table 2 show that also I and IV are 2-substituted.

IR data on I–V were not useful for the structural determination, and the difference in UV maxima between I–IV and V was too small for a safe structural assignment.

PRELIMINARY TESTS ON RESOLUTION

Preliminary tests on resolution of racemic I were done with the common alkaloids and also with some synthetic bases in different solvents and solvent mixtures. In most cases only oils were formed, but salts were obtained with cinchonidine, (−)-ephedrine, brucine, and dehydroabietyl amine in ethyl acetate. The cinchonidine and (−)-ephedrine salts gave acid with $[\alpha]_D$ −2°, brucine +4°, and dehydroabietyl amine +1 and −1° in two different experiments. Brucine and cinchonidine were chosen for a full scale resolution. After four crystallizations of the brucine salt, an $[\alpha]_D$ value of +25° was obtained which did not change upon further recrystal-

Table 2. Chemical shifts of some pyrazoles in $CDCl_3$, DMSO-d_6 and CF_3COOH.

Compound	$CDCl_3$		DMSO-d_6		CF_3COOH	
	3-H	α-H	3-H	α-H	3-H	α-H
I	7.00	4.92	7.21	4.88	7.82	5.56
II	7.11	5.00	7.35	4.93	7.87	5.53
II ethyl ester			7.37	5.05		
III	7.11	4.99	7.28	4.82	7.87	5.48
IV	7.12	5.04	7.36	4.93	7.92	5.54
V	7.35	4.93	7.13	4.93	7.92	5.53
V ethyl ester			7.15	5.04		

lization. The cinchonidine salt of the acid obtained from the mother liquor after resolution with brucine gave after the first crystallization acid with $[\alpha]_D$ −11.7°. For some reason the specific rotation diminished upon further recrystallization.

DETERMINATION OF THE ABSOLUTE CONFIGURATION

The absolute configuration of (+)-I was determined from the CD data of (+)-I and(*R*)-(−)-II.[14] Fig. 1 clearly shows that (+)-I has the *S*-configuration.

The rubidium salt of (−)-III was synthesized for a crystallographic X-ray investigation in order to confirm unequivocally the 2-substitution of III and the absolute configuration of I−III. The X-ray investigation is under progress.[11]

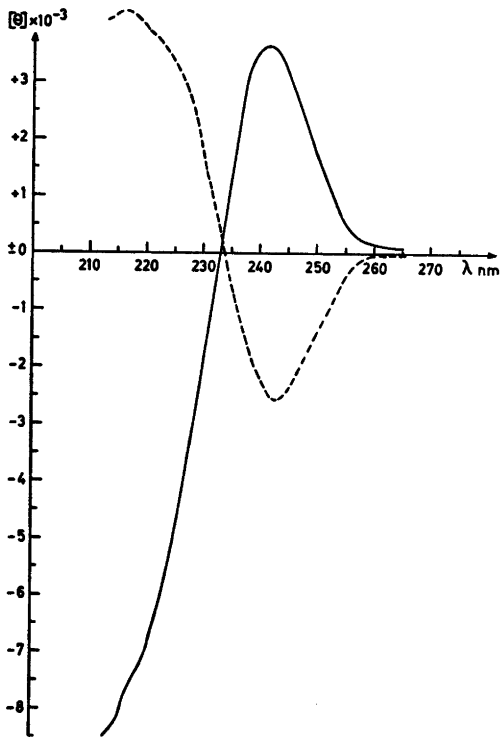


Fig. 1. CD spectra of (+)-I (- - -, $c = 3.90 \times 10^{-2}$) and (*R*)-(−)-II (———, c 3.56×10^{-2}) in methanol.

EXPERIMENTAL

The CD curves were recorded in 1 mm cells at 27 °C with a Cary 60 spectropolarimeter equipped with a circular dichroism accessory. The optical activity was measured with a Perkin-Elmer 141 spectropolarimeter in 1 ml micro cells of 10 cm length with chloroform as solvent. The IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian A-60 spectrometer with solutions of about 15 % concentration, when possible, using TMS as internal standard. The mass spectra were recorded at 70 eV with an LKB 9000 instrument.

GLC was performed on a Perkin-Elmer 900 gas chromatograph fitted with a flame ionization detector. Column temperature 200 °C, injection port temperature 230 °C, detector temp. 250 °C. Nitrogen carrier gas, flow rate 70 ml/min. Column: Varaport 30, AW, DMCS, 100−120 mesh, coated with 5 % Carbowax 20 M AW, DMCS-treated, packed in a 2.8 m glass column AW, DMCS-treated, I.D. 3.5 mm. The column was conditioned at 230 °C before use. Column chromatography was performed on silica gel (0.05−0.2 mm, 70−325 mesh ASTM, E. Merck). The thin layer chromatograms were run in glacial acetic acid/benzene (4/1) on non-activated 5 × 20 cm plates coated with silica gel F 254 (E. Merck) with a nominal thickness of 0.25 mm and analyzed with UV light or developed with iodine vapor.

All melting points were taken with a hot-stage microscope and are corrected. The microanalyses were carried out at the Analytical Department, Institute of Chemistry, Uppsala University.

(+)-Ephedrine was isolated from its hydrochloride (Fluka AG $[\alpha]_{546}^{20}$ +39±2° (*c* 11.5; water) by addition of 2 M sodium hydroxide and subsequent extraction with ether. The ether solution was dried over magnesium sulfate, the ether evaporated and the residue distilled *in vacuo*. M.p. 39 °C (lit[13] m.p. 40 °C).

rac-*Ethyl α-(indazolyl-1 and -2)propionate.* A mixture of racemic ethyl α-(indazolyl-1 and -2)-propionate was synthesized according to von Auwers and Allardt.[3]

I. Without sodium ethoxide. 1.0 g (8.5 mmol) indazole and 2.9 g (16.0 mmol) ethyl α-bromopropionate were warmed at 120 °C for 3 h. A slight excess of 2 M sodium hydroxide was then added. The mixture was extracted with three 6 ml portions of ether, the ether solution dried over magnesium sulfate and the ether distilled off. A GLC and a NMR analysis of the residue showed that it contained the 1-ester and 2-ester in the ratio 6:94 together with a minor amount of unreacted indazole. The retention times were 42, 85, and 55 min, respectively.

II. With sodium ethoxide. 1.50 g (13 mmol) indazole was dissolved in a solution of 0.437 g (19 mmol) sodium in 10 ml absolute ethanol, and 4.00 g (22 mmol) ethyl α-bromopropionate was

added. The temperature rose to 55 °C within a few minutes. The mixture was then refluxed until it was neutral and worked up as described earlier. A GLC analysis showed that 1- and 2-esters were formed in the ratio 66:34. 13.6 g of product was obtained after distillation from a run with 10 times the amounts given above. 4 g indazole was recovered upon distillation. The isomeric composition was not changed significantly after the distillation.

rac α-*(Indazolyl-1)propionic acid.* A. The isomeric esters were separated via the picrate of the 2-ester.[3] The acid obtained after hydrolysis was not quite free from X. Therefore the product (0.150 g) was chromatographed on a 28 × 1 cm column of 17.0 g silica gel. The column was eluted at a flow rate of 1 ml min^{-1} with 220 ml benzene, 50 ml 3 % (v/v) acetic acid/benzene, and 450 ml 5 % acetic acid/benzene. 5 ml fractions were collected and analyzed by TLC. Fractions 77 – 100 were pooled and evaporated to dryness yielding 0.134 g pure IX. M.p. 113 – 114.5 °C. IR (KBr) λ_{CO} 5.80 μ: UV (99 % EtOH) λ_{max} 254.9 nm (log ε 3.68) and 290.8 nm (log ε 3.76). R_F 0.52. (Found: C 63.11; H 5.30; N 14.73. Calc. for $C_{10}H_{10}N_2O_2$ (190.2): C 63.14; H 5.30; N 14.73).

B. 15.0 g ester mixture was hydrolyzed in 60 ml 2 M sodium hydroxide at 110 °C for 2 h. The alkaline solution was extracted with ether and concentrated hydrochloric acid was added to pH 2. After one night in a refrigerator, 11.5 g acid mixture was obtained. A ^{1}H NMR investigation showed that the product contained 59 % IX and 41 % X.

1.5 g of the acid mixture was dissolved in a mixture of 7.5 ml 2 M and 1.2 ml concentrated hydrochloric acid. The pH of the solution was 1.5 – 2.0. After cooling 0.55 g IX nearly free from X was isolated. After another recrystallization and thorough washing with water 0.42 g pure IX was obtained.

rac α-*(4,5,6,7-Tetrahydroindazolyl-1)propionic acid (V).* The conditions for the hydrogenation of IX were worked out on the 5 mg scale. Thin layer chromatography followed by mass spectrometry was used to test the hydrogenation product for the presence of V. Hydrogenation of IX in a Parr apparatus at 5 atm for one day at room temperature with 10 % palladium-on-charcoal as catalyst and glacial acetic acid as solvent yielded at least four products. No IX remained. Hydrogenation in 96 % ethanol at a higher pressure and temperature gave a more uniform product and was therefore chosen for hydrogenation on a larger scale. Only two spots were seen in the TLC test, a large one from V and a small one which probably was the ethyl ester of V. No IX remained.

0.40 g (2.1 mmol) IX was dissolved in 4 ml of 96 % ethanol and hydrogenated by shaking with hydrogen gas at 110 atm and 70 °C with 0.80 g 10 % palladium-on-charcoal as catalyst. After hydrogenation for 15 h a TLC test showed that only a small amount of IX remained. A further 0.50 g catalyst was then added and the hydrogenation continued for another 9 h. No or very little IX remained, but more by-product, probably the ethyl ester of V, was formed. The filtrate was then evaporated to dryness and the residue dissolved in 3 ml of chloroform, filtered and added to 10 ml of ligroin (b.p. 60 – 71 °C). An oil was first obtained, which crystallized on scratching. The product was made alkaline with 2 M sodium hydroxide and extracted with chloroform. The alkaline solution was filtered and then acidified by addition of hydrochloric acid to pH 3.5. The solid product was washed with ice water and dried. 0.20 g acid was obtained with m.p. 140 – 141 °C and R_F 0.43. UV (99 % EtOH) λ_{max} 229.8 nm (log ε 2.67). IR (KBr) λ_{CO} 5.75 μ. (Found: C 61.79; H 7.30; N 14.28. Calc. for $C_{10}H_{14}N_2O_2$ (194.2): C 61.81; H 7.27; N 14.44).

(S)-(+)-α-(Cyclopentapyrazolyl-2)propionic acid ((+)-I). Racemic α-(cyclopentapyrazolyl-2)propionic acid (I) was synthesized according to Gustafsson *et al.*[2] M.p. 170 – 71 °C. 13.5 g (0.075 mol) I and 32.2 g (0.075 mol) brucine were dissolved in 620 ml of boiling ethyl acetate and allowed to crystallize overnight in a refrigerator. The salt obtained was then recrystallized. After each crystallization, acid was liberated from 0.10 g salt by addition of 2 M sodium hydroxide, extraction with chloroform several times and subsequent acidification with hydrochloric acid to pH 5. The acid was filtered off and dried, and the optical activity was measured in chloroform. After five recrystallizations the acid was liberated from its salt by addition of 2 M sodium hydroxide. The brucine was filtered off and the filtrate acidified to pH 3.5 with concentrated hydrochloric acid. The course of the resolution is given in Table 3. After recrystallization from 5 ml ethanol/water (2/1) 0.50 g acid was obtained with m.p. 180 – 87 °C. $[\alpha]_D^{25}$ +26.7°, $[\alpha]_{365}^{25}$ +95.8° (*c* 0.524). CD: $[\alpha]_{234}$ ±0, $[\theta]_{242}$ −2590. The somewhat low $[\theta]$ value at λ_{max} 242 and the broad melting point interval make it probable that the acid was not quite optically

Table 3. Resolution of α-(cyclopentapyrazolyl-2)propionic acid (I).

Crystallization	1	2	3	4	5	6
Solvent, ml	620	100	75	80	40	40
Salt, g	16.0	13.3	10.9	7.8	5.3	4.1
$[\alpha]_D^{25}$, deg	13.6	18.8	19.3	25.5	25.5	25.7

pure. (Found: C 59.98; H 6.74; N 15.44. Calc. for $C_9H_{12}N_2O_2$ (180.2): C 59.99; H 6.71; N 15.54).

The rubidium salt of (−)-α-(cycloheptapyrazolyl-2)propionic acid. A concentrated solution of 0.0924 g (−)-III in acetone was mixed with an equimolar amount of rubidium hydroxide in a minimal amount of water. The combined solution was slightly alkaline. More (−)-III was added to neutral reaction. The mixture was evaporated to dryness and 8 ml warm acetone was added. The salt was dissolved by adding a minimal amount of water (~0.25 ml) to the warm mixture. After cooling, 0.060 g (41 %) rubidium salt monohydrate of (−)-III was obtained. The salt was recrystallized from acetone with a small amount of water. The rubidium and potassium salts of II were made in the same way. (Found: C 42.58; H 5.48; N 8.79. Calc. for $C_{11}H_{17}N_2O_3Rb$ (310.74): C 42.52; H 5.51; N 9.02).

Acknowledgements. I wish to thank Professors A. Fredga and G. Bergson for their kind interest in this work and for all facilities placed at my disposal. I am also indebted to Dr. R. Håkansson for valuable advice concerning the circular dichroism spectra and to Mr. K. Janné for recording the mass spectra. A grant from the Faculty of Science of the University of Uppsala is gratefully acknowledged.

REFERENCES

1. Gustafsson, H. *Ark. Kemi 29* (1969) 587.
2. Gustafsson, H., Ericsson, H. and Lindqvist, S. *Acta Chem. Scand. B 28* (1974) 1069.
3. von Auwers, K. and Allardt, H. G. *Ber. Deut. Chem. Ges. 59* (1926) 95.
4. von Auwers, K. and Düesberg, M. *Ber. Deut. Chem. Ges. 53* (1920) 1179.
5. Fischer, E. and Tafel, J. *Justus Liebigs Ann. Chem. 227* (1885) 303.
6. Ramart-Lucas, P. *Bull. Soc. Chim. Fr.* (1950) 317.
7. Rousseau, V. and Lindwall, H. G. *J. Amer. Chem. Soc. 72* (1950) 3047.
8. Bellotti, A. and Pappalardo, G. *Boll. Sci. Fac. Chim. Ind. Bologna 16* (1958) 29.
9. Grandberg, I. I., Kost, A. N. and Yaguzhinskii, L. S. *J. Gen. Chem. USSR 29* (1959) 2499.
10. Schwan, T. J. and Davis, C. S. *J. Pharm. Sci. 57* (1968) 877.
11. Aleby, S. *To be published.*
12. Albright, J. D. and Goldman, L. *J. Org. Chem. 31* (1966) 273.
13. *Handbook of Chemistry and Physics*, 48th Ed. 1967–1968. The Chemical Rubber Co., Cleveland, Ohio, USA.
14. Gustafsson, H. *Acta Chem. Scand. B 29* (1975) 93.

Received June 17, 1974.