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Some New α-(Cyclopolymethylenepyrazolyl-2)propionic Acids. Resolution of α-(Cycloheptapyrazolyl-2)propionic Acid and Determination of its Absolute Configuration

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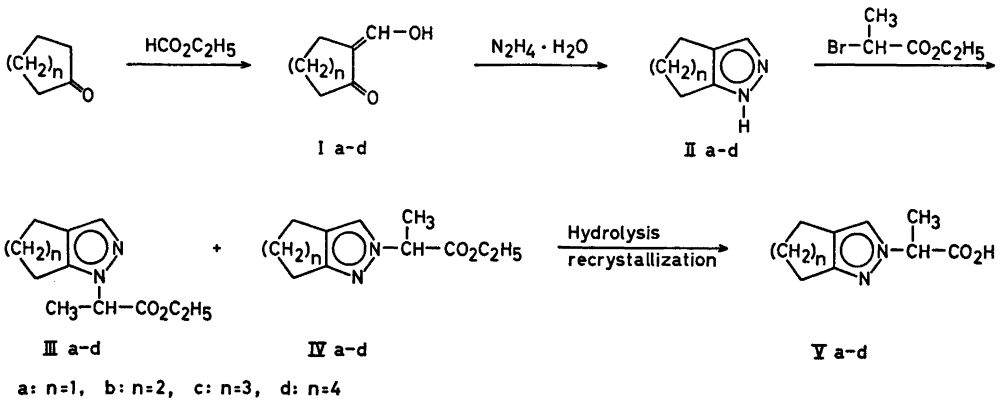
α-(Cyclopentapyrazolyl-2)propionic acid (Va), α-(cycloheptapyrazolyl-2)propionic acid (Vc), and α-(cyclooctapyrazolyl-2)propionic acid (Vd) have been synthesized from the corresponding cyclomethylenepyrazoles and ethyl α-bromopropionate by hydrolysis of the ester product. The reaction of cyclopentapyrazole (IIa) or 4,5,6,7-tetrahydroindazole (IIb) with ethyl α-bromopropionate in alcoholic sodium ethoxide solution gave a ratio of 1-ester to 2-ester of about 40:60. Alkylation of IIa with ethyl α-bromopropionate and without base yielded an ester ratio of 70:30, while IIb yielded the ratio 31:69. The acid Vc was resolved into its optical antipodes by fractional crystallization of its (−)-α-(β-naphthyl)ethylamine and (−)-ephedrine salts giving acids with $[\alpha]_D^{25} = +46.9$ and −46.5°, respectively, in chloroform. The absolute configuration of Vc was determined by means of circular dichroism measurements.

Some α-propionic acid derivatives of benzotriazole,[1,2] indazole,[3] and 4,5,6,7-tetrahydroindazole [4] have been synthesized earlier for stereochemical studies and studies of synthetic plant hormones. Three α-(cyclomethylenepyrazolyl-2)propionic acids have now been synthesized. The compounds are under examination with regard to auxin activity [5] and antimalarial action.[6]

The title compounds were synthesized from the corresponding cycloalkanones according to Scheme 1.

The cycloalkanones were formylated with ethyl formate in ether solution with sodium methoxide as base to give the α-hydroxymethylenecycloalkanones, which were then reacted



Scheme 1.

with hydrazine monohydrate under formation of the cyclopolymethylenepyrazoles IIa–d. The method used was, with slight modification, that of Ainsworth [7] for synthesis of 4,5,6,7-tetrahydroindazole. A higher yield of the cyclomethylenepyrazoles (IIa–c) was obtained by adding 99 % hydrazine hydrate directly to the dried ether solution of Ia–c.

The alkylation with alkylhalides of unsymmetrically substituted pyrazoles with unsubstituted nitrogen generally gives a mixture of isomers due to the ambident character of the pyrazole nucleus.[8] No rules have been established for predicting the course of reaction from the nature of the substituents in the pyrazole nucleus. The entering position is also influenced by the alkylating agent and the experimental conditions.[9]

The reaction between IIa–d and ethyl α-bromopropionate without solvent at 120° C gave both 1- and 2-ester. The ratio between 1-ester and 2-ester was dependent on the pyrazole used. IIa–c formed esters in the ratio 70:30, 31:69, and 19:81, respectively. A considerable amount of II remained unreacted. The analysis of the reaction products was done after neutralization with potassium carbonate solution and extraction with ether. The acid obtained after hydrolysis and recrystallization from ethanol-water was pure Va–d. Both IIa and IIb gave an ester ratio of about 40:60 on reaction with ethyl α-bromopropionate in alcoholic sodium ethoxide solution at room temperature.

The chemical shifts in DMSO-d_6 for the vinyl protons in II and the corresponding III and IV are well separated. The isomeric composition of the reaction mixture and the amount of unreacted IIa–d were determined from the peak areas of the different vinyl protons in the ^{1}H NMR spectra by cutting out and weighing the peaks and by GLC analysis. The position of the α-propionic acid group in Va–d was established by ^{1}H NMR spectroscopy according to Gustafsson.[10]

PRELIMINARY TESTS ON RESOLUTION

Preliminary tests for resolving Vc were done with the common alkaloids and some synthetic bases. Crystalline salts were formed with (–)-ephedrine, (+)-α-(β-naphthyl)ethylamine, dehydroabietylamine and (–)-α-phenethylamine in ethyl acetate giving levorotatory acid. The cinchonidine salt formed in ethyl acetate yielded dextrorotatory acid. Oils were obtained with cinchonine and brucine in ethyl acetate. On the basis of these results the resolution was performed with (–)-ephedrine and (–)-α-(β-naphthyl)ethylamine with ethyl acetate as solvent.

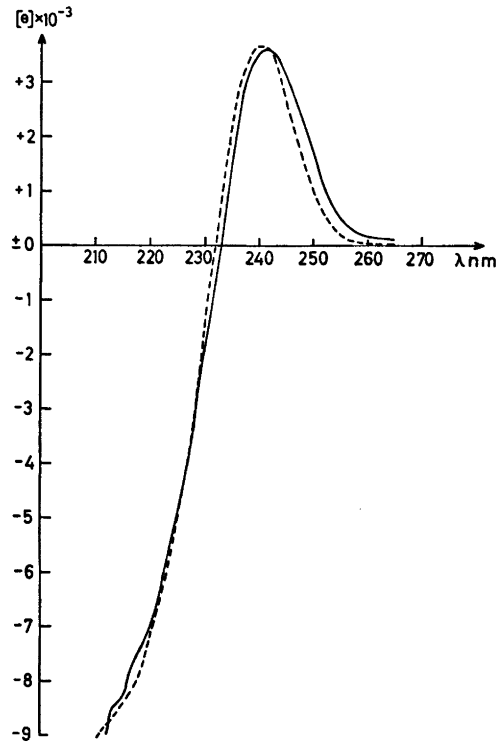


Fig. 1. CD spectra of D(–)Vb (——, $c = 3.96 \times 10^{-3}$ g/100 ml) and (–)Vc (- - -, $c = 3.88 \times 10^{-3}$ g/100 ml) in methanol.

DETERMINATION OF THE ABSOLUTE CONFIGURATION

The circular dichroism (CD) curves of D(–)Vb and (–)Vc were examined for configurational correlations. Fig. 1 clearly shows that (–)Vc has the D(*R*)-configuration. The absolute configuration of L(+)Vb was unequivocally established by direct synthesis *via* L(+)alanine.[11]

EXPERIMENTAL

The optical activity was measured with a Perkin-Elmer 141 spectropolarimeter in 1 ml micro cells of 10 cm length and with chloroform as solvent. The circular dichroism (CD) curves were recorded at 27 °C in 1 mm cells on a Cary 60 spectropolarimeter, equipped with a circular dichroism accessory. The IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer and the UV spectra on a Spectronic 505 spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian A-60 spectrometer in DMSO-d_6 solutions of about 15 % concentration with TMS as internal standard.

Gas-liquid chromatography (GLC) was performed on a Perkin-Elmer 990 gas chromatograph fitted with a flame ionization detector. Column temperature 150 °C, injection port temperature 240 °C and detector temperature 240 °C. Nitrogen carrier gas, flow rate 47 ml/min. Column: Chromosorb W, AW, DMCS-treated, 100 – 200 mesh, coated with 7.5 % UCON 50LB 550X, packed in a 3.0 m glass column AW, DMCS-treated, I.D. 3.5 mm. The column was conditioned at 200 °C before use. The mass spectra were recorded on an LKB 9000 A gas chromatograph-mass spectrometer operating at 70 eV. The melting points were determined with a hot stage microscope and are uncorrected. The microanalyses were carried out at the Analytical Department, Institute of Chemistry, University of Uppsala.

(+)-Ephedrine was isolated from its hydrochloride (Fluka AG $[\alpha]_{546}^{20} = +39 \pm 2°$ (*c* 11.5; water) by addition of 2 M sodium hydroxide and subsequent extraction with ether. The ether solution was dried over magnesium sulphate, the ether evaporated and the residue distilled. B.p.$_{0.2}$ 115 – 116 °C.

α-Hydroxymethylenecyclopentanone (Ia). A mixture of 84.0 g (1.0 mol) cyclopentanone distilled and dried over magnesium sulphate and 110 g (1.5 mol) dried ethyl formate was added with stirring at 15 °C to 54.0 g (1.0 mol) sodium methoxide in 2.0 l dry diethyl ether in a 5 l three-necked flask equipped with condenser, stirrer, dropping funnel, and drying tubes. The mixture was stirred at room temperature for 6 h, and allowed to stand overnight, after which 200 ml water was added and the mixture stirred until a solution was obtained. The ether phase was washed with 20 ml water. The combined water phase was acidified with 165 ml 6 M hydrochloric acid and extracted three times with 80 ml portions of ether. The ether solution was washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulphate. The boiling point from an earlier run was 67 – 73 °C at 1 mm torr (lit.[12,13] B.p.$_{11}$ 90 – 95 °C).

α-Hydroxymethylenecycloheptanone (Ic). A dry ether solution of α-hydroxymethylenecycloheptanone (Ic) was prepared in the same way from 44.5 g (0.40 mol) dried and distilled cycloheptanone, 44.4 g (0.60 mol) dried ethyl formate and 21.6 g (0.40 mol) sodium methoxide.

α-Hydroxymethylenecyclooctanone (Id). α-Hydroxymethylenecyclooctanone (Id) was prepared in the same way from 50.0 g (0.40 mol) cyclooctanone, 44.4 g (0.60 mol) ethyl formate and 21.6 g (0.40 mol) sodium methoxide in 1.0 l dried ether. 32.2 g (53 %) Id was obtained as a colourless viscous oil with b.p.$_{12}$ 104 – 106 °C and n_D^{22} 1.5154 (lit.[14] B.p.$_{0.1}$ 70 – 71 °C).

Cyclpolyomethylenepyrazoles (II). A slight excess of 99 % hydrazine hydrate (based on the amount of cycloalkanone used in the formylation step) was added dropwise with stirring to the ether solution of I in an ice bath. After standing at room temperature overnight the ether solution was concentrated in a rotary evaporator and the residue fractionated at reduced pressure. Distillation gave the corresponding cyclopolymethylenepyrazole as a clear viscous oil which crystallized to a white solid on standing at room temperature.

Cyclopentapyrazole (IIa). The ether solution of Ia previously described was reacted with 52.0 g (1.04 mol) 99 % hydrazine hydrate. Yield 50.2 g (46 % based on the amount of cyclopentanone used). B.p.$_{30}$ 165 °C. M.p. 57 °C (lit.[15] M.p. 57 – 59 °C). ^{1}H NMR (DMSO-d_6): δ 2.48 (m, $-CH_2-$), δ 7.15 (s, $-CH=$).

Cycloheptapyrazole (IIc). Cycloheptapyrazole was obtained from the ether solution of Ic and 21.0 g (0.42 mol) 99 % hydrazine hydrate. Yield 40.6 g (75 % based on the amount of cycloheptanone used). B. p.$_{1.2}$ 125 – 128 °C (lit.$_{0.5}$ [16,17] 118 – 120 °C) ^{1}H NMR (DMSO-d_6): δ 1.65 (m, $-CH_2-$), δ 2.50 (m, $-CH_2-C=$), δ 7.11 (s, $-CH=$).

Cyclooctapyrazole (IId). Cyclooctapyrazole was synthesized from 32.2 g (0.21 mol) of Id and 11.0 g (0.22 mol) 99 % hydrazine hydrate in 150 ml dry ether.

Yield 26.6 g (85 %). B.p.$_{1.5}$ 160 – 165 °C. M.p. 45 °C (lit.[18] M.p. 45 °C) ^{1}H NMR (DMSO-d_6): δ 1.42 (broad, $-CH_2-$), δ 2.54 (m, $-CH_2-C=$), δ 7.10 (s. $-CH=$).

D,L-α-*(Cyclopentapyrazolyl-2)propionic acid (Va).* 54.0 g (0.50 mol) of IIa and 108.6 g (0.60 mol) ethyl α-propionate were warmed at 120 °C for 4 h. After cooling, 100 ml water was added and the mixture was extracted three times with 100 ml portions of ether. The ether phase was washed with water and dried over magnesium sulphate. A GLC test showed that the ether solution contained 1-ester and 2-ester in the ratio 70:30. The ether was distilled off in a rotary evaporator and the residue was fractionated at reduced pressure. 34.1 g product with b.p.$_{0.5}$ 134 – 136° C was obtained. 20 % of IIa remained unreacted. ^{1}H NMR (DMSO-d_6): δ 6.95 (s, $-CH=$; IIIa), δ 7.21 (s, $-CH=$; IVa).

10.0 g of the product was hydrolyzed with

50 ml 2 M sodium hydroxide at 100 °C for 2 h. After cooling, the hydrolysate was extracted with ether. The water phase was then acidified with concentrated hydrochloric acid to pH 3.5 and placed in a refrigerator. 6.0 g product was obtained containing both 1-acid and 2-acid. After recrystallization twice from ethanol-water (2:1) and once from ethanol, no 1-isomer was found by ^{1}H NMR analysis. M.p. 170–171 °C. ^{1}H NMR (DMSO-d_6): δ 1.57 (d, 3 H, CH_3-), δ 2.46 (complex m, 6 H, $-CH_2-$), δ 4.89 (q, 1 H, α-H), δ 7.21 (s, 1 H, $-CH=$). IR (KBr), C=O 5.8 μ. UV, λ_{max} 233.4 nm (log ε 3.82). [Found (179.4, titration): C 59.87; H 8.73; N 15.65. Calc. for $C_9H_{12}N_2O_2$ (180.2): C 59.99;H 6.71; N 15.54].

D,L-α-*(Cycloheptapyrazolyl-2)propionic acid (Vc).* The acid Vc was synthesized in the same way from 40.0 g (0.29 mol) cycloheptapyrazole and 63.4 g (0.35 mol) ethyl α-bromopropionate. 33.8 g product was obtained after distillation. B.p. $_{0,1-0.2}$ 126–134 °C. Hydrolysis and recrystallization once from ethanol-water and twice from ethyl acetate yielded 18.5 g of Vc. M.p. 154–159 °C. IR (KBr) C=O 5.8 μ. UV λ_{max} 231.2 nm (log ε 3.83). ^{1}H NMR (DMSO-d_6): δ 1.55 (complex m and d, 9 H, $-CH_2-$ and CH_3-), δ 2.50 (complex m, 4 H, $-CH_2-\underset{|}{C}=$), δ 4.82 (q, 1 H, α-H), δ 7.28 (s, 1 H, $-CH=$). [Found (208.2, MS): C 63.36; H 7.64; N 13.54. Calc. for $C_{11}H_{16}N_2O_2$ (208.2): C 63.45; H 7.73; N 13.45].

D,L-α-*(Cyclooctapyrazolyl-2)propionic acid (Vd).* 58.6 g (0.39 mol) cyclooctapyrazole was reacted with 81.5 g (0.45 mol) of ethyl α-bromopropionate in the same way. 33.5 g product was obtained with b.p.$_{0.8}$ 153–156 °C. Hydrolysis and recrystallization from ethanol-water (2:1) yielded 16.2 g of Vd. M.p. 107 °C. IR (KBr) C=O 5.8 μ. UV λ_{max} 231.5 nm (log ε 3.76). ^{1}H NMR (DMSO-d_6): δ 1.57 (complex m and d, 11 H, $-CH_2-$ and CH_3-), δ 2.54 (complex m, 4 H, $-CH_2-\underset{|}{C}=$), δ 4.93 (q, 1 H, α-H), δ 7.36 (s, 1 H, $-CH=$). [Found (222.2, MS): C 64.61; H 8.19; N 12.43. Calc. for $C_{12}H_{18}N_2O_2$ (222.3): C 64.82; H 8.16; N 12.60].

Alkylation of cyclopentapyrazole and 4,5,6,7-tetrahydroindazole with ethyl α-bromopropionate in alkaline medium. 1.0 g (9 mmol) of IIa was dissolved in a sodium ethoxide solution made from 0.30 g (13 mmol) sodium in 7 ml 99 % ethanol. 5.0 g (22 mmol) ethyl α-bromopropionate was the added with stirring for a few minutes. The temperature increased to 52 °C and a white precipitate of sodium bromide was formed. After 25 min the reaction mixture became neutral. The mixture was concentrated in a rotary evaporator, and 5 ml of water was added to the residue. The mixture was extracted with three 10 ml portions of ether, the organic layer was dried, and the ether was distilled off. A ^{1}H NMR analysis of the mixture showed that 70 % of IIa was transformed into an ester mixture consisting of 42 % IIIa and 58 % IVa.

Alkylation of IIb in the same way gave 41 % IIIb and 59 % IVb of the total amount of ester formed. A good analytical separation of IIb, IIIb, and IVb by GLC was obtained with retention times 54, 93, and 102.5 min., respectively. The retention times for IIa, IIIa, and IVa were 27, 45, and 53 min.

Table 1.

Crystallization	Ethyl acetate (ml)	Salt obtained (g)	$[\alpha]_D^{25}$ of the acid (°)
1	780	12.5	−16
2	250	10.3	−27
3	180	8.8	−31
4	150	7.1	−37
5	130	6.0	−40
6	85	5.1	−45
7	65	4.3	−46
8	50	3.8	−45
9	50	3.2	−45

Preliminary tests on resolution of α-(cycloheptapyrazolyl-2)propionic acid (Vc). Preliminary experiments on resolution were performed with common alkaloids and some synthetic bases. 1 mmol of Vc and 1 mmol base were dissolved in a small amount of solvent and the salt obtained was filtered off and dried. The acid was liberated by adding 2 M sodium hydroxide. The organic base was removed by extraction several times with chloroform. The water solution was then acidified with 2 M hydrochloric acid to pH 3.5. The acid was filtered off and dried, and, the optical activity was determined in chloroform.

D*(R) (−)α-(Cycloheptapyrazolyl-2)propionic acid.* 12.5 g (0.060 mol) of Vc and 10.0 g (0.060 mol) (−)-ephedrine were dissolved in 780 ml of boiling ethyl acetate. After one night in a refrigerator the salt was filtered off and recrystallized several times from ethyl acetate. Acid was liberated from 0.10 g salt after each recrystallization and the optical activity was determined in chloroform. The results are given in Table 1.

The acid was liberated from its (−)-ephedrine salt by adding 2 M sodium hydroxide. After extraction with chloroform the water phase was acidified to pH 3.5 with concentrated hydrochloric acid. The product was recrystallized from ethanol–water (2:1) and dried over phosphorus pentoxide in vacuum. 1.1 g of Vc was obtained with m.p. 177–178.5 °C. The optical activity of (−)Vc in some different solvents is given in Table 2.

L(+)-α-*(Cycloheptapyrazolyl-2) propionic acid.* The mother liquor from the first crystallization

Table 2. The optical activity of (−)Vc in some different solvents. g = gram acid dissolved in the solvent to 10.0 ml

Solvent	$[\alpha]_D^{25}$ (°)	$[\alpha]_{365}^{25}$ (°)	g acid
Dimethyl formamide	+11.8	+33.8	0.0801
Glacial acetic acid	+1.5	+7.4	0.0830
Dimethyl sulphoxide	−0.4	−5.4	0.0790
Methanol	−7.5	−31.9	0.0800
Ethanol (abs.)	−11.8	−45.6	0.0811
Chloroform	−46.5	−156	0.0400

Table 3.

Crystallization	Ethyl acetate (ml)	Salt obtained (g)	$[\alpha]_D^{25}$ of the acid (°)
1	130	7.8	+24
2	120	6.6	+28
3	120	5.8	+30
4	120	5.1	+35
5	160	4.4	+37
6	190	3.7	+41
7	120	2.7	+42
8	160	2.2	+43
9	210	1.3	+42

was evaporated to dryness. 10.5 g salt was isolated from which the acid was liberated as described earlier. 4.6 g acid with $[\alpha]_D^{25} = +17°$ was obtained. This acid (0.022 mol) and 3.77 g (0.022 mol) (−)-α-(β-naphthyl)ethylamine [19] were dissolved in 130 ml of boiling ethyl acetate and the salt allowed to crystallize in a refrigerator. After nine recrystallizations the optical activity remained constant. The course of the resolution is given in Table 3. The acid was then liberated and recrystallized from ethanol–water (2:1). 0.50 g acid in white glistening crystals was obtained with m.p. 178–180 °C. $[\alpha]_D^{25} = +46.9°$ (*c* 0.398).

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