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Resolution and Configurational Assignment of α(-Benzotriazolyl-2)propionic Acid. Synthesis of (+)-α-(4,5,6,7-Tetrahydrobenzotriazolyl-2)propionic Acid

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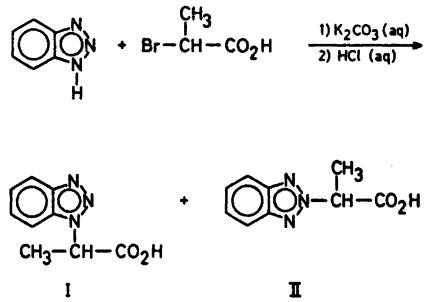
α-(Benzotriazolyl-2)propionic acid (II) has been resolved into its optical antipodes. The dextrorotary acid was obtained by fractional crystallization of its cinchonidine salt in methanol-water (7:1) and the levorotary form from (+)-α-methylbenzylamine with ethyl acetate as solvent. The specific rotation of the antipodes was $[\alpha]_D^{25} = +33.4°$ and $-33.2°$ in acetone. The acid (+)-II was hydrogenated to give (+)-α-(4,5,6,7-tetrahydrobenzotriazolyl-2)propionic acid (+III) with $[\alpha]_D^{25} = +16.4°$ in acetone. The dextrorotary acids were found to have *R*-configuration by CD measurements.

In connection with work on synthetic auxins at this Institute α-(benzotriazolyl-2)propionic acid (II) has now been investigated. Both of its antipodes exhibit antiauxin activity,[1] with (−)-II being the strongest antiauxin.

Racemic II and racemic α-(benzotriazolyl-1)-propionic acid (I) have also been tested [2] for activity against *Plasmodium berghei* in mice. The mean survival times for infected mice treated with I and II were zero.

Preliminary experiments on resolution of II were performed with the common alkaloids and synthetic bases in methanol-water ethanol, ethyl acetate, chloroform, and acetone. 0.001 mol acid and 0.001 mol base were dissolved in a small amount of solvent and the salt obtained after cooling was filtered off and dried. The acid was then liberated from the salt by addition of diluted sulfuric acid and the specific rotation determined in acetone. In most cases only oily products were obtained, but salts were obtained with cinchonidine in methanol-water, strychnine in ethyl acetate, dehydroabietyl amine in ethanol, and (+)-α-methylbenzylamine in ethyl acetate giving acid with $[\alpha]_D^{25} = +15°$, $+13°$, $+13°$ and $-9°$, respectively. According to the results the resolution was performed with cinchonidine and (+)-α-methylbenzylamine as bases.



Scheme 1.

DETERMINATION OF THE ABSOLUTE CONFIGURATION

Experiments were carried out in order to determine the absolute configuration of II by cleavage to active alanine. Reaction of II with sodium in ethanol according to Gattermann [3] yielded alanine as indicated by the ninhydrin test and by paper chromatography and *o*-phenylenediamine as indicated by specific reactions with 2,4-pentanedione [4] and phenanthrenequinone.[5] No experiments with optically active II were done due to problems with the isolation of alanine. Reduction of II according to Cappel and Fernelius [6] was not successful.

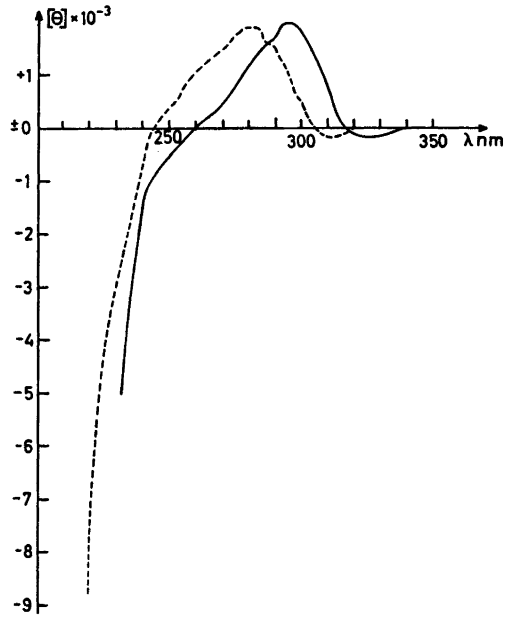


Fig. 1. CD curves of (+)-II ($c = 3.4 \times 10^{-2}$ g/100 ml) – – – –, and *R*-(+)-α-(indazolyl-2)-propionic acid ($c = 4.44 \times 10^{-2}$ g/100 ml) ——— in methanol.

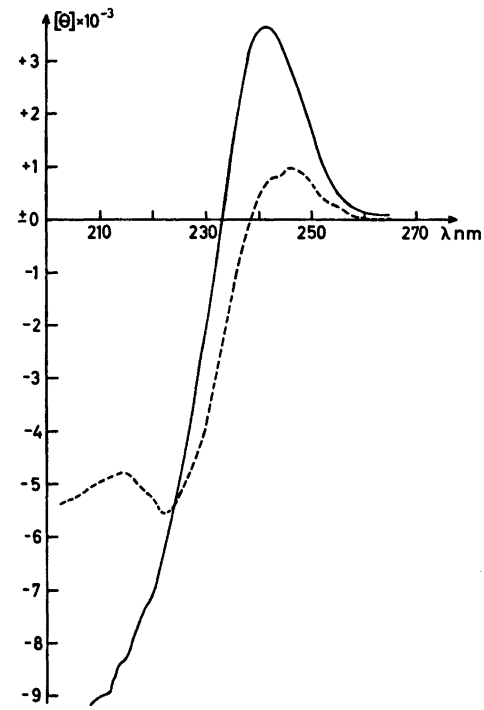
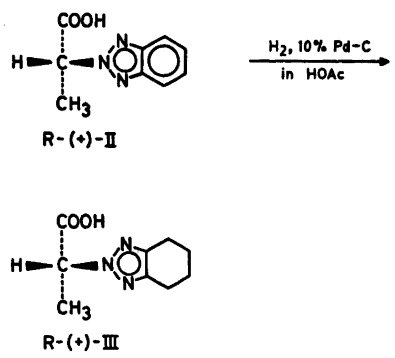


Fig. 2. CD curves of (+)-III ($c = 3.96 \times 10^{-2}$ g/100 ml) – – – and *R*-(+)-α-(4,5,6,7-tetrahydroindazolyl-2)propionic acid ($c = 3.56 \times 10^{-2}$ g/100 ml) ——— in methanol.

Attempts were also made to correlate the configuration of II with α-(indazolyl-2)propionic acid,[7] α-(thianaphthenyl-2)propionic acid [8] and the configuration of α-(4,5,6,7-tetrahydrobenzotriazolyl-2)propionic acid (III) with α-(4,5,6,7-tetrahydroindazolyl-2)propionic acid [7] by the quasi-racemate method.[9,10] No quasi-racemates were indicated by X-ray powder photograms, only solid solutions. (+)-III was obtained by hydrogenation of (+)-II (Scheme II). The CD curves of (+)-II and *R*-(+)-α-(indazolyl-2)propionic acid, however, show that (+)-II and (+)-III have *R*-configuration (Figs. 1 and 2).



Scheme 2.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian A-60 instrument with solutions of about 10 % using tetramethylsilane as internal standard. The mass spectra were recorded at 70 eV with an LKB 9000 instrument. The optical activity was measured with a Perkin-Elmer 141 spectropolarimeter in micro cells of 10 cm length or in cells of 20 cm length with an older instrument built at this institute. The CD curves were recorded in 1 ml cells in methanol solutions with a Cary 60 spectropolarimeter equipped with a CD accessory and the UV spectra on a Spectronic 505 spectrophotometer.

Thin layer chromatograms were run on non-activated plates (E. Merck) coated with silica gel F 254 with a nominal thickness of 0.25 mm. The chromatograms were examined

with UV light or developed with iodine vapour.

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

Racemic α-(benzotriazolyl-2)propionic acid (II). A mixture of II and its isomer α-(benzotriazolyl-1)propionic acid (I) was prepared according to Fredga and Lindgren[11] in 62 % yield. The isomers were separated utilizing their differing basicities[12] in a way described by Sparatore and Pagani.[13] 73 % I and 27 % II were obtained calculated on the total amount of acid. The separation was followed using the characteristic UV absorptions of I and II. The m.p. of II was 212–214 °C. Yield 17 % (lit. 20 %, 210–212 °C). R_F of I and II was 0.63 and 0.33, respectively, in 20 % acetic acid-benzene. ^{1}H NMR (DMSO-d_6) δ 7.19–7.86 (m, Ar-4 H, wt. 4), δ 5.76 (q, α-H, wt. 1), δ 1.90 (d, $-CH_3$, wt. 2).

R-(+)-α-*(Benzotriazolyl-2)propionic acid (+II).* 20.0 g (0.105 mol) α-(benzotriazolyl-2)-propionic acid and 30.8 g (0.105 mol) cinchonidine were dissolved in 320 ml boiling methanol-water (7:1). After one day in a refrigerator the salt obtained was filtered off. The acid was liberated from a small sample of the salt after each recrystallization and the rotary power was determined. The salt was recrystallized several times until the optical activity remained constant.

After nine recrystallizations the acid was liberated by addition of 2 M sulfuric acid. The acid obtained was extracted with ether and the ether evaporated *in vacuo*. 1.27 g (13 %) (+)-II was isolated, which was recrystallized from 170 ml boiling water and finally dried over concentrated sulfuric acid in a desiccator. M.p. 230–231 °C. $[\alpha]_D^{25} = +33.4°$, $[\alpha]_{365}^{25} = +74.4°$ ($c = 0.548$ g/100 ml $l = 1$ dm, $\alpha_D^{25} = +0.183°$, $\alpha_{365}^{25} = +0.408°$ in acetone). $[\theta]_{max}$ is +1945° at 280 nm in methanol solution.

S-(−)-α-*(Benzotriazolyl-2)propionic acid* [(−)*II*]. The mother liquor from the first crystallization was evaporated to dryness and the acid isolated as before. 7.5 g (0.04 mol) acid and 4.8 g (0.040 mol) (+)-α-methylbenzylamine was dissolved in 280 ml boiling ethyl acetate. The solution was cooled gently and then put in a refrigerator. 8.5 g salt was obtained, which was recrystallized until the optical activity remained constant.

The acid was isolated as described above. 2.33 g (11 %) acid was obtained. The acid was recrystallized from boiling water and dried over sulfuric acid in a desiccator. M.p. 230–231 °C. The rotatory power of the (−)-II acid in various solvents is given in Table 1.

Racemic α-(4,5,6,7-tetrahydrobenzotriazolyl-2)-propionic acid (III). Method A. 0.50 g (2.6 mmol) II was dissolved in 3 ml glacial acetic acid and 0.70 g 10 % palladium-on-charcoal was added. The reaction was carried out in a Parr catalytic hydrogenation apparatus in the usual way with hydrogen gas of 6 atm. pressure at room temperature during 15 h. The catalyst was then filtered off and the residue was evaporated to dryness and recrystallized from water. M.p. 148 °C.

Table 1. The optical activity of (−)-II in some different solvents. g = grams acid dissolved in the solvent to 10.0 ml. l = the tube length in dm.

Solvent	$[\alpha]_D^{25}$	l	g
Dimethylformamide	−42.6°	1	0.352
Acetone	−33.2°	1	0.750
Abs. ethanol	−7.7°	2	0.325
Water (neutral.[a])	+41.0°	2	0.305

[a] The acid was dissolved in 10.0 ml of 1.5 M ammonia solution.

Method B. 0.60 g (3.1 mmol) II was dissolved in 15 ml 99 % ethanol and 1.0 g 10 % palladium-on-charcoal was added. The hydrogenation was performed at 15 atm. hydrogen pressure and 75 °C with continuous shaking. After 18 h very little II remained. Another 0.50 g catalyst was added and the hydrogenation was continued for 5 h more. The catalyst was then filtered off and thoroughly washed with ethanol. After evaporating off the solvent 0.55 g of a faint yellow semisolid product remained. ^{1}H NMR, TLC, and MS analysis of the product showed that a minor amount of ethyl α-(4,5,6,7-tetrahydrobenzotriazolyl-2)propionate also was formed in addition to III. The product was dissolved in a small amount of diluted sodium hydroxide and extracted with chloroform. The acid was precipitated by addition of hydrochloric acid to pH 2 and then extracted with chloroform. The chloroform solution was washed with a small amount of water, dried with magnesium sulfate and then evaporated to dryness. The residue was dissolved in 2 ml chloroform. The acid III was crystallized out after addition of 5 ml ligroin. After another recrystallization in the same way, 0.33 g (55 %) III was obtained with m.p. 147.5–149 °C. $R_F = 0.57$ in 96 % ethanol. UV λ_{max} 236 nm (log ε 3.94). ^{1}H NMR ($CDCl_3$): $-CH_2-$ and CH_3- (multiplet with a doublet at δ 1.84, wt. 7), $-CH_2-\underset{|}{C}=$ (multiplet with the highest peak at δ 2.70, wt. 4), α-H (δ 5.35, wt. 1). (Found: (195.2, MS): C 54.69; H 6.63; N 21.12. Calc. for $C_9H_{13}N_3O_2$ (195.2): C 55.37; H 6.71; N 21.53).

R-(+)-α-*(4,5,6,7-Tetrahydrobenzotriazolyl-2)-propionic acid* (+*III*). 0.30 g *R*-(+)-II was hydrogenated according to method B to give 0.09 g (29 %) of (+)-III. M.p. 169–170.5 °C. $[\alpha]_D^{25} = +16.4°$, $[\alpha]_{365}^{25} = +41.5°$ ($\alpha_D^{25} = +0.053°$, $\alpha_{365}^{25} = +0.134°$, $c = 0.0323$ g/100 ml, $l = 1$ cm, acetone).

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