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Abstract

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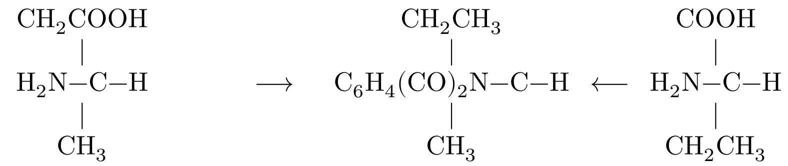
SYNTHESIS OF OPTICAL ISOMERS OF β-AMINOBUTYRIC ACID

Racemic β-aminobutyric acid is usually obtained by addition of ammonia to crotonic acid (^{1}). Addition of benzylamine (^{2}) to crotonic acid with subsequent hydrogenolysis of the N-substituted acid also leads to an optically inactive acid. At present, for the synthesis of β-amino acids, including β-aminobutyric acid, a method is widely used that consists in the interaction of aldehydes, malonic acid, and ammonia (^{3}).

In optically active form, β-aminobutyric acid was first obtained by Fischer (^{4}) by resolution of the racemate with camphorsulfonic acid. Racemic β-aminobutyric acid was obtained by him by hydrogenation of the phenylhydrazone of acetoacetic ester. Later (^{5}), β-aminobutyric acid was resolved with the aid of optically active α-phenylethylamine. In 1952 Balenovich and co-workers (^{6}) synthesized optically active (+)-β-aminobutyric acid, applying the Arndt—Eistert reaction to (—)-1-diazo-3-phthalimidobutan-2-one, obtained from *L*-alanine. The specific rotation of β-aminobutyric acid was +38.80°. Somewhat later the configuration of β-aminobutyric acid was established. (+)-β-Aminobutyric and *L*-α-aminobutyric acids were converted to 2-phthalimidobutane, and, by analogy with α-amino acids, β-aminobutyric acid was assigned to the *L*-series (^{7}).

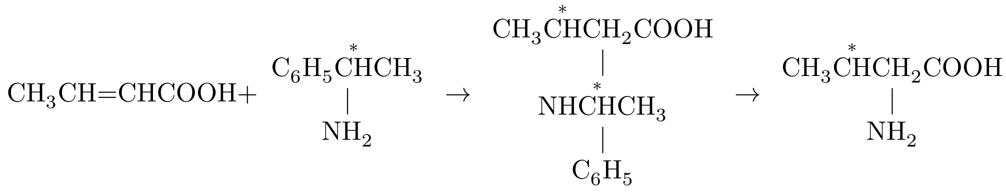


$$\begin{array}{c} \mathrm{CH_2COOH} \\ | \\ \mathrm{H_2N-C-H} \\ | \\ \mathrm{CH_3} \end{array} \longrightarrow \begin{array}{c} \mathrm{CH_2CH_3} \\ | \\ \mathrm{C_6H_4(CO)_2N-C-H} \\ | \\ \mathrm{CH_3} \end{array} \longleftarrow \begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H_2N-C-H} \\ | \\ \mathrm{CH_2CH_3} \end{array}$$

(+) 3s-aminobutyric acid

(—) 2s-aminobutyric acid

In the present work we propose a new method for the synthesis of both antipodes of β-aminobutyric acid, starting from crotonic acid and optically active α-phenylethylamine.



$$\mathrm{CH_3CH{=}CHCOOH} + \underset{\mathrm{NH_2}}{\underset{|}{\mathrm{C_6H_5\overset{*}{C}HCH_3}}} \rightarrow \underset{\mathrm{C_6H_5}}{\underset{|}{\underset{\mathrm{NH\overset{*}{C}HCH_3}}{\underset{|}{\mathrm{CH_3\overset{*}{C}HCH_2COOH}}}}}} \rightarrow \underset{\mathrm{NH_2}}{\underset{|}{\mathrm{CH_3\overset{*}{C}HCH_2COOH}}}$$

(I) (II) (IIIa, IIIb, IIIc, IIId) (IV)

When one of the antipodes of α-phenylethylamine is added to crotonic acid, two diastereomeric forms of N-substituted β-aminobutyric acid are formed. We separated the diastereomers IIIa and IIIb, using the greater solubility of one of them in acetone. When using α-phenylethylamine with $[\alpha]_D^{20} - 41°$, we isolated the N-substituted β-aminobutyric acids IIIa with $[\alpha]_D^{20} + 21.99°$ (yield 27%) and IIIb with $[\alpha]_D^{20} - 44.82°$ (yield 38.5%).

By hydrogenolysis of the N-substituted acids, (+)-β-aminobutyric acid with $[\alpha]_D^{20} + 35.69°$ (92% optical purity) and (−)-β-aminobutyric acid with $[\alpha]_D^{20} - 33.91°$ (87.4% optical purity) were obtained. In the case of addition

to crotonic acid, α-phenylethylamine with $[\alpha]_D^{20} + 41°$ gave N-substituted β-aminobutyric acids—IIIc with $[\alpha]_D^{20} - 18.29°$ (yield 28.8%) and IIIa with $[\alpha]_D^{20} + 30.69°$ (yield 42.3%). Hydrolysis of the N-substituted acids IIIc and IIIa led to β-aminobutyric acids with $[\alpha]_D^{20} - 34.91°$ (90% optical purity) and with $[\alpha]_D^{20} + 31.25°$ (81% optical purity). The total yield of the N-substituted β-aminobutyric acids IIIa and IIIb (IIIc and IIId) in both cases is $\sim$ 70%.

Table 1

Experimental data*

Name of acid	Yield, %	M.p., °C	(Butanol : water : acetic acid = 4 : 5 : 1)	$[\alpha]_D^{20}$, H_2O	$[\alpha]_D^{20}$, 2 N NaOH	$[\alpha]_D^{20}$, 2 N HCl
(−) α-Phenylethylamine						
(+) 3σ-(N-Phenylethyl)-aminobutyric acid	27	187-8	0.69	+21.99°; C = 1.4	−32.1°; C = 0.9	−6.66°; C = 1.2

Name of acid	Yield, %	M.p., °C	(Butanol : water : acetic acid = 4 : 5 : 1)	$[\alpha]_D^{20}$, H_2O	$[\alpha]_D^{20}$, 2 N NaOH	$[\alpha]_D^{20}$, 2 N HCl
(−) 3β-(N-Phenylethyl)-aminobutyric acid	38.5	150-151	0.69	−44.82°; C = 1.5	−71.08°; C = 1.4	−28.19°; C = 1.4
(+) 3σ-Aminobutyric acid	quant.	215-216	0.21	+35.69°; C = 2; $t = 21°$	+12.65°; C = 0.9	+16.26°; C = 1
(−) 3β-Aminobutyric acid	quant.	216	0.21	−33.91°; C = 1	–	–
(+) α-Phenylethylamine						
(−) 3β-(N-Phenylethyl)-aminobutyric acid	28.8	187-9	0.69	−18.29°; C = 1.4	+32.45°; C = 1.8	+4.5°; C = 1.5
(+) 3σ-(N-Phenylethyl)-aminobutyric acid	42.3	145-7	0.69	+30.69°; C = 1.5	+53.43°; C = 1.4	+18.95°; C = 1.4
(−) 3β-Aminobutyric acid	quant.	215-6	0.21	−34.91°; C = 2.2; $t = 21°$	−12.66°; C = 1.2	−18.5°; C = 1.2
(+) 3σ-Aminobutyric acid	quant.	215-7	0.21	+31.25°; C = 0.9	+11.02°; C = 0.8	+14.4°; C = 0.9

* Literature data: (+) β-aminobutyric acid—m.p. 200°; $[\alpha]_D^{20} + 35.3°$ (C = 9.6; H_2O); $[\alpha]_D^{20} + 14.7°$ (C = 9.8; 1 N NaOH) (4); $[\alpha]_D^{20} + 29.7°$ (C = 10; 1 N HCl); $[\alpha]_D^{18} + 38.8°$ (C = 0.5; H_2O) (6); (−) β-aminobutyric acid—m.p. 220°; $[\alpha]_D^{20} - 35.2°$ (C = 10; H_2O) (4).

By the method proposed by us, one of the diastereomers is isolated in the predominant amount (∼ by 14%). In order to decide the question of asymmetric induction in this reaction, we carried out hydrolysis of the mixture of diastereomers IIIa and IIIb (without separation) from α-phenylethylamine

Table 2

Molecular rotations of β-aminobutyric acids from (+) α-phenylethylamine*

Wavelength	(+) 3σ-N-Phenylethylaminobutyric acid, H_2O	(+) 3σ-N-Phenylethylaminobutyric acid, 2 N NaOH	(+) 3σ-N-Phenylethylaminobutyric acid, 2 N HCl	(−) 3β-N-Phenylethylaminobutyric acid, H_2O	(−) 3β-N-Phenylethylaminobutyric acid, 2 N NaOH	(−) 3β-N-Phenylethylaminobutyric acid, 2 N HCl	(−) 3β-Aminobutyric acid, H_2O	(−) 3β-Aminobutyric acid, 2 N NaOH	(−) 3β-Aminobutyric acid, 2 N HCl
589	+60.07°	+110.54°	+39.23°	−28.98°	+57.28°	+9.18°	−35.14°	−12.63°	−19.15°
578	+69.16°	+125.44°	+42.02°	−36.63°	+72.04°	+12.01°	−40.17°	−14.25°	−21.83°
546	+70.38°	+141.79°	+49.06°	−47.15°	+85.49°	+12.71°	−46.04°	−17.13°	−24.77°
436	+114.88°	+249.6°	+80.04°	−52.39°	+135.99°	+27.32°	−71.89°	−20.35°	−28.58°
405	+137.03°	+304.91°	+99.36°	−57.63°	+164.33°	+34.36°	−85.34°	−25.20°	−35.20°
382	–	–	–	−83.64°	+216.11°	+38.71°	−93.93°	−32.75°	−37.09°
365	+469.68°	+840.83°	+252.23°	−95.5°	–	–	−109.3°	−34.49°	−45.02°
356	–	–	–	−105.42°	–	–	−115.26°	–	−46.33°
334	+600.09°	+1074.3°	+230.69°	–	–	–	−145.55°	–	−53.37°
313	+704.63°	+1357.9°	+392.26°	–	–	–	−169.3°	–	−57.17°
302	+783.87°	+1548.36°	+432.60°	–	–	–	−173.89°	–	−56.67°
297	+838.97°	+1643.2°	+453.33°	–	–	–	−175°	–	−58.60°

* Values of the molecular rotations are given for only one antipode of β-aminobutyric acid.

with $[\alpha]_D^{20} - 41°$. After removal of the impurity of optically active α-phenylethylamine, the rotation of the acidic solution of β-aminobutyric acid was measured. At the sodium D-line it proved to be −4°. Thus, both experiments on the separation of diastereomers and experiments without separation indicate

for the fact that, on addition of optically active α-phenylethylamine to crotonic acid, asymmetric induction is observed.

For conclusions about the regularities of this reaction, further accumulation of experimental material is necessary.

For β-aminobutyric and N-substituted β-aminobutyric acids we have, for the first time, recorded optical rotatory dispersion curves. In Fig. 1 are shown the ORD curves of acids obtained using (−)-α-phenylethylamine; Table 2 gives the values of molecular rotations for β-aminobutyric acids isolated using (+)-α-phenylethylamine. To designate the configurations of optically active β-aminobutyric acids we used the ρ–σ system proposed by Terent' ev and co-workers (8).

Fig. 1. 1 –3σ-aminobutyric acid in 2 N NaOH; 2 –(+)3σ-aminobutyric acid

Figure 1

Figure 1: Figure 1

in 2 N HCl; 3 $-(+)3\sigma$-aminobutyric acid in H_2O; 4 $-(+)3\sigma$-(N-phenylethyl)-aminobutyric acid in H_2O; 5 $-(+)3\sigma$-(N-phenylethyl)-aminobutyric acid in 2 N HCl; 6 $-(+)3\sigma$-(N-phenylethyl)-aminobutyric acid in 2 N NaOH; 7 $-(-)3\rho$-(N-phenylethyl)-aminobutyric acid in H_2O; 8 $-(-)3\rho$-(N-phenylethyl)-aminobutyric acid in 2 N NaOH; 9 $-(-)3\rho$-(N-phenylethyl)-aminobutyric acid in 2 N HCl.

Experimental Part

Racemic β-N-phenylethylaminobutyric acid (III). To a solution of 2.2 g (0.026 mole) of crotonic acid in 6 ml of freshly distilled dry pyridine, 3 g (0.026 mole) of racemic α-phenylethylamine is added dropwise with shaking. The mixture is heated in an oil bath at 120–130° for 2 h. After cooling, the pyridine is distilled off in vacuo. The oily residue is treated with dry acetone; a white crystalline precipitate of β-N-phenylethylaminobutyric acid separates. Yield 3.4 g (65.4%); mp 189–190° (from acetone); R_f 0.69 (butanol : water : acetic acid = 4 : 5 : 1).

Found, %: C 69.15, 69.24; H 8.50, 8.59
Calculated, %: C 69.56; H 8.21

Racemic β-aminobutyric acid (IV). 0.5 g (0.002 mole) of III is dissolved in 10 ml of 30% ethyl alcohol. The mixture is hydrogenated over palladium black in a stream of hydrogen at 40° for 20 h. The catalyst is filtered off; the alcoholic solution of β-aminobutyric acid is evaporated to a volume of 1 ml. The acid is precipitated with acetone. Yield 0.2 g (100% based on III); mp 191–193° (2) (precipitated from 96% alcoholic solution with acetone); R_f 0.21 (butanol : water : acetic acid = 4 : 5 : 1).

Found, %: C 46.17, 46.32; H 8.85, 8.82
Calculated, %: C 46.60; H 8.74

(+) 3σ- and (−) 3ρ-N-phenylethylaminobutyric acids from α-phenylethylamine with $[\alpha]_D^{20} - 41°$. To a solution of 2.2 g (0.026 mole) of crotonic acid in 6 ml of dry, freshly distilled pyridine, 3 g (0.026 mole) of α-phenylethylamine with $[\alpha]_D^{20} - 41°$ is added dropwise with shaking. The reaction mixture is heated for 2 h in an oil bath at a temperature of 120–130°. The pyridine is distilled off in vacuo and freshly distilled acetone (~20 ml) is added to the residue. A white crystalline⋯

crystalline precipitate (IIIa). Yield 1.4 g (27%); mp 187–188°; $[\alpha]_D^{20}$ +21.99° ($C = 1.4$; H_2O); $[\alpha]_D^{20}$ −32.1° ($C = 0.9$; 2 N NaOH); $[\alpha]_D^{20}$ −6.66° ($C = 1.2$; 2 N HCl); R_f 0.69 (butanol : water : acetic acid = 4 : 5 : 1). Ether is added to the acetone mother liquor; a white, oily substance (IIIb) precipitates, crystallizing upon trituration with absolute ether. Yield of IIIb–2 g (38.5%); mp 150-151°; $[\alpha]_D^{20}$ −44.82° ($C = 1.5$; H_2O); $[\alpha]_D^{20}$ −71.08° ($C = 1.4$; 2 N NaOH); $[\alpha]_D^{20}$ −28.19° ($C = 1.4$; 2 N HCl).

(+)3σ- and (−)3ρ-Aminobutyric acids from α-phenylethylamine with $[\alpha]_D^{20}$ −41°. A solution of 0.5 g (0.002 mole) of the N-substituted acid with $[\alpha]_D^{20}$ +21.99° (IIIa) in 10 ml of 30% ethyl alcohol is hydrogenated over palladium black in a stream of hydrogen for 24 h. After separation of the catalyst, the solution is evaporated to a volume of 1 ml. The acid is precipitated with acetone. Yield 0.22 g (100% based on IIIa); mp 215-218°; $[\alpha]_D^{20}$ +35.69° ($C = 2$; H_2O); $[\alpha]_D^{20}$ +12.65° ($C = 0.9$; 2 N NaOH); $[\alpha]_D^{20}$ +16.26° ($C = 1.2$; 2 N HCl); R_f 0.21 (butanol : water : acetic acid = 4 : 5 : 1). Upon hydrogenation of 0.5 g (0.002 mole) of the N-substituted acid with $[\alpha]_D^{20}$ −44.82° (IIIb) under the same conditions, 0.22 g of β-aminobutyric acid is obtained, mp 215-216°; $[\alpha]_D^{20}$ −33.94° ($C = 1$; H_2O) (4); R_f 0.21 (in the same system).

(−)3ρ- and (+)3σ-N-Phenylethylaminobutyric acids from α-phenylethylamine with $[\alpha]_D^{20}$ +41°. From 2.2 g (0.026 mole) of crotonic acid in 6 ml of freshly distilled dry pyridine and 3 g (0.026 mole) of α-phenylethylamine with $[\alpha]_D^{20}$ +41°, 1.5 g (28.8%) of IIIc is obtained (from acetone); mp 187-189°; $[\alpha]_D^{20}$ −18.29° ($C = 1.4$; H_2O); $[\alpha]_D^{20}$ +32.45° ($C = 1.8$; 2 N NaOH); $[\alpha]_D^{20}$ +4.5° ($C = 1.5$; 2 N HCl); R_f 0.69 (butanol : water : acetic acid = 4 : 5 : 1).

After addition of ether to the acetone solution, an oily substance (IIId) precipitates, which is treated by the method described above. Yield 2.2 g (IIId; 42.3%); mp 145-147°; $[\alpha]_D^{20}$ +30.69° ($C = 1.5$; H_2O); $[\alpha]_D^{20}$ +53.43° ($C = 1.4$; 2 N NaOH); $[\alpha]_D^{20}$ +18.96° ($C = 1.4$; 2 N HCl); R_f 0.69 (in the same system).

(−)3ρ- and (+)3σ-Aminobutyric acids. Hydrogenation of 0.5 g (0.002 mole) of the N-substituted β-aminobutyric acid IIIc $[\alpha]_D^{20}$ −18.29° in 10 ml of 30% ethyl alcohol over palladium black in a stream of hydrogen under the conditions described above leads to β-aminobutyric acid with mp 215-216° (4); $[\alpha]_D^{21}$ −34.91° ($C = 2.2$; H_2O) (4); $[\alpha]_D^{20}$ −12.66° ($C = 1.2$; 2 N NaOH); $[\alpha]_D^{20}$ −18.5° ($C = 1.2$; 2 N HCl) R_f 0.21 (butanol : water : acetic acid = 4 : 5 : 1).

Upon hydrogenation of 0.5 g (0.002 mole) of the N-substituted β-aminobutyric acid (IIId) with $[\alpha]_D^{20}$ +30.69°, β-aminobutyric acid is obtained, mp 215-217°; $[\alpha]_D^{20}$ +31.25° ($C = 0.9$; H_2O); $[\alpha]_D^{20}$ +11.02° ($C = 0.8$; 2 N NaOH); $[\alpha]_D^{20}$ +14.4° ($C = 0.9$; 2 N HCl); R_f 0.21 (in the same system).

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