Synthesis of Optically Active 2-Aminoöctadecanes

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2-Octadecanone has been converted to DL-2-benzylaminoöctadecane by reductive amination with benzylamine. The resolution of the racemic base has been effected through its salts with benzoyl-L-alanine and benzoyl-D-alanine. Both enantiomeric bases were debenzylated hydrogenolytically to give (+) and (—)-2-aminoöctadecane. A series of derivatives of the racemic and of the optically active base has been prepared.

As part of an extensive investigation in the sphingosine field, it was found necessary to prepare the optically active 2-aminoöctadecane. There are no data in the literature about this compound. The conversion of 2-octadecanone into the desired base via the oxime and via the reductive amination was tried since both reactions had been successfully applied in our laboratory in the synthesis of sphingine[1].

For this purpose 2-octadecanone [I] was prepared in the reaction of 1-bromopentadecane with ethyl sodioacetoacetate and subsequent hydrolysis and decarboxylation of the intermediary formed β-keto ester. The readily available oxime [II] was reduced with lithium aluminum hydride giving racemic 2-aminoöctadecane [IV]. On the other hand, the reductive alkylation of benzylamine with [I] was performed to give a DL-2-benzylaminoöctadecane [III]. Hydrogenolysis of [III] in the presence of palladium catalyst also led to [IV]. The racemic base was characterized as its oxalate, D-tartarate, dibenzoyl-D-tartarate and as N-acetyl derivative.

Several attemps to resolve the DL-2-aminoöctadecane by means of usual resolving agents were unsuccessful. However, good results were obtained when benzoyl-L-alanine and benzoyl-D-alanine were used as resolving agents for DL-2-benzylaminoöctadecane. Both enantiomeric salts could be obtained in high purity and in good yields. The (+) and the (—)-base were debenzylated catalytically as described for the racemic base, giving the enantiomeric 2-aminoöctadecanes. Attempts to obtain the free bases in the analytically pure condition failed. Therefore, they were converted into the N-acetyl and N-phthalyl derivatives, which were found to be very convenient compounds for identification purposes. The specific rotations and melting points are listed in Table I.

TABLE I

Melting Points and Specific Rotations of Optically Active 2-Aminoöctadecanes and Derivatives

Compound	M. p., °C	$[\alpha]_D$ in °
(—)-2-Benzylaminoöctadecane benzoyl-L-alanine salt	80	+22.0
(—)-2-Aminoöctadecane	78—81	— 2.62
(+)-N-Acetyl	90—91	+ 4.34
(—)-N-Benzyl	—	— 8.95
(—)-N-Phthalyl	61—62	—11.07
(+)-2-Benzylaminoöctadecane benzoyl-D-alanine salt	80	—22.0
(+)-2-Aminoöctadecane	76—80	+ 2.80
(—)-N-Acetyl	90—91	— 4.75
(+)-N-Benzyl	—	+ 8.24
(+)-N-Phthalyl	61—62	+10.67

EXPERIMENTAL*

1-Bromopentadecane

The halide was prepared according to the method of Hunsdiecker, Hunsdiecker, and Vogt[2] in 77% yield (calculated on silver palmitate used).

2-Octadecanone [I]

1-Bromopentadecane (65.35 g., 0.225 mole) was added to ethyl sodioacetoacetate (from sodium [5.18 g.], ethanol [100 ml.] and ethyl acetoacetate [55 ml.]). The mixture was refluxed for 6 hr., potassium hydroxide (60 g.) in water (60 ml.) was added and the mixture kept at 60° for 0.5 hr. with frequent shaking. The clear solution was then refluxed with 400 ml. of 5 *N*-hydrochloric acid for 2 hr. The product was extracted with ether, washed successively with 5% potassium hydroxide and water, and dried. Evaporation gave the crude ketone, which was crystallized twice from 96% ethanol. Colorless plates (33.2 g., 55% yield), m. p. 53° (recorded m. p. 52°)[3].

2,4-Dinitrophenylhydrazone. — Orange colored needles from 96% ethanol, m. p. 92°.

Anal. 4.145 mg. subst.: 0.460 ml. N_2 (22.5°, 748 mm.)
$C_{24}H_{40}O_4N_4$ (448.60) calc'd: N 12.49%
found: N 12.65%

Oxime [II]. — A solution of 7.44 g. of [I] and hydroxylamine acetate (from 4.64 g. of hydroxylamine hydrochloride) in 100 ml. of absolute ethanol was refluxed for 6 hr. On cooling, colorless crystals separated. After two recrystallizations from 96% ethanol 5.37 g. needles (68% yield), m. p. 67—69°, were obtained.

Anal. 6.900 mg. subst.: 0.291 ml. N_2 (22°, 751 mm.)
$C_{18}H_{37}ON$ (283.48) calc'd: N 4.94%
found: N 4.82%

DL-*2-Benzylaminoöctadecane* [III]

A sample of 2.69 g. (0.01 mole) of [I], 5 ml. of freshly distilled benzylamine dissolved in 25 ml. of 96% ethanol was hydrogenated in the presence of Adams pla-

* The melting points are uncorrected.

tinum catalyst[4] (prepared from 45 mg. of platinum oxide). After 3.5 hr. 285 ml. (calc'd 252 ml.) of hydrogen was taken up at 26° and at 741 mm. The catalyst was filtered off, the solvent removed, and the residual oil distilled in vacuo. 3.23 g. (89.9% yield) of colorless oil, b. p. 200—205°/0.4 mm. was obtained.

Oxalate. — The neutral salt crystallizes from absolute ethanol in glistening leaflets, m. p. 131—133°.

Anal. 7.530 mg. subst.: 0.230 ml. N_2 (19.5°, 749 mm.)
$C_{52}H_{47}O_4N_2$ (809.27) calc'd: N 3.46%
found: N 3.50%

DL-*2-Aminoöctadecane* [IV]

Method A. — A solution of 5 g. of [II] in 100 ml. of absolute ether was added dropwise to a solution of 1.4 g. of lithium aluminum hydride in 75 ml. of absolute ether. The reaction mixture was refluxed for 1 hr. and then a little more than the theoretical amount of water was carefully added. The ether layer was dried and the solvent evaporated leaving 4.64 g. of a crude, crystalline amine, m. p. 45—55°.

Method B. — A solution of [III] (3 g.) in 25 ml. of 96% ethanol was reduced catalytically in the presence of 1 g. of palladium on barium sulphate catalyst[5] at 22° and 741 mm. Hg. After 3 hr. 1.15 moles of hydrogen was absorbed per mole of compound. The catalyst was filtered off and the filtrate evaporated to dryness. The oily residue was distilled in vacuo. 2.25 g. (98.7% yield) of a colorless oil, b. p. 135—137°/0.05 mm. was obtained, which solidified on standing for several hours; m. p. 65—75°.

Oxalate. — Glistening leaflets from absolute ethanol, m. p. 150—152°.

Anal. 6.030 mg. subst.: 0.207 ml. N_2 (17.5°, 745 mm.)
$C_{20}H_{41}O_4N$ (359.54) calc'd: N 3.90%
found: N 3.95%

D-Tartarate. — Neutral salt, colorless needles from 96% ethanol, m. p. 125—126°.

Anal. 9.000 mg. subst.: 23.000 mg. CO_2, 10.115 mg. H_2O
$C_{40}H_{84}O_6N_2$ (689.09) calc'd: C 69.71; H 12.29%
found: C 69.74; H 12.58%

Dibenzoyl-D-tartarate. — Neutral salt, colorless needles, from absolute ethanol, m. p. 160—162°.

Anal. 7.000 mg. subst.: 0.201 ml. N_2 (26°, 758 mm.)
$C_{54}H_{92}O_8N_2$ (897.29) calc'd: N 3.12%
found: N 3.27%

DL-*2-Acetamidoöctadecane*

[IV] (230 mg.), acetic anhydride (1 ml.) and pyridine (1 ml.) were heated at 100° for 0.5 hr. After cooling, the crystals were collected, washed with water and recrystallized from 96% ethanol. Colorless leaflets (210 mg.), m. p. 82°.

Anal. 9.145 mg. subst.: 25.750 mg. CO_2, 10.500 mg. H_2O
8.315 mg. subst.: 0.327 ml. N_2 (19°, 746 mm.)
$C_{20}H_{41}ON$ (311.54) calc'd: C 77.10, H 13.26, N 4.50%
found: C 76.84, H 12.85, N 4.52%

Resolution of the racemic 2-benzylaminoöctadecane

To a solution of 18 g. (50 mMoles) of [III] in 40 ml. of acetone 9.6 g. (50 mMoles) of benzoyl-L-alanine[6] was added. On heating on a steam bath a clear solution resulted, which was allowed to stand at room temperature overnight. Filtration gave

13.35 g. (96.7% calculated for one isomer) colorless crystals, which were recrystallized twice from 50 ml. of acetone. 8.84 g. (64% yield) of benzoyl-L-alanine salt, m. p. 80°, $[\alpha]_D^{20} = +22.0^0$ (c = 2.5, in 96% ethanol) was obtained.

Anal. 7.400 mg. subst.: 0.331 ml. N_2 (21°, 749 mm.)
$C_{35}H_{56}O_3N_2$ (552.81) calc'd: N 5.07%
found: N 5.12%

The sticky mother liquor from the above experiment was evaporated to dryness and the residue dissolved in ether. The solution was shaken with 2 *N*-sodium carbonate, washed with water and the solvent distilled off. There remained 8.96 g. of a crude, oily base, which was dissolved in 25 ml. of acetone and treated with 4.812 g. of benzoyl-D-alanine[6]. The resulting crystals were filtered and recrystallized twice from 35 ml. of acetone. 8.93 g. (64.7% yield) of the enantiomeric salt, m. p. 80°, $[\alpha]_D^{20} = -22.0^0$ (c = 2,5 in 96% ethanol) was obtained.

Anal. 7.485 mg. subst.: 0.323 ml. N_2 (20.5° 750 mm.)
$C_{35}H_{56}O_3N_2$ (552.81) calc'd: N 5.07%
found: N 4.96%

(—)-2-Benzylaminoöctadecane

The dextrorotatory benzoyl-L-alanine salt (5.96 g.) was dissolved in ether and decomposed with 2 *N*-sodium carbonate solution. The ether layer was washed with water, dried, the solvent evaporated and the oily residue distilled in vacuo. 3.59 g. colorless liquid, b. p. 153—156°/0.01 mm. was obtained, which crystallized on standing. Density 0.8690 at 20°, $[\alpha]_D^{20} = -8.95^0$ (homogeneous).

Anal. 7.760 mg. subst.: 0.277 ml. N_2 (19.5°, 748 mm.)
$C_{25}H_{45}N$ (359.62) calc'd: N 3.90%
found: N 4.10%

(—)-2-Aminoöctadecane

(—)-2-Benzylaminoöctadecane (2.59 g.) was debenzylated catalytically as described for the DL-base. Distillation gave 1.94 g. of crystalline base, b. p. 132—133°/0.02 mm., which could not be purified by crystallization. $[\alpha]_D^{18} = -2.62^0$ (c = 4.58, in chloroform).

(+)-2-Acetamidoöctadecane

A sample of 540 mg. of (—)-2-aminoöctadecane gave in usual manner 580 mg. of colorless needles, m. p. 90—91°, $[\alpha]_D^{17} = +4.34^0$ (c = 4.84, in chloroform).

Anal. 8.295 mg. subst.: 23.400 mg. CO_2, 9.620 mg. H_2O
$C_{20}H_{41}ON$ (311.54) calc'd: C 77.10; H 13.26%
found: C 76.98; H 12.98%

(—)-2-Phthalimidoöctadecane

A sample of 135 mg. of (—)-2-aminoöctadecane and 74 mg. of phthalic anhydride were heated at 140° for 1 hr. Crystallization from ethanol gave 165 mg. of colorless needles, m. p. 61—62°, $[\alpha]_D^{17} = -11.07^0$ (c = 2.8, in chloroform).

Anal. 9.535 mg. subst.: 27.220 mg. CO_2, 8.870 mg. H_2O
$C_{26}H_{41}O_2N$ (399.60) calc'd: C 78.14; H 10.34%
found: C 77.90; H 10.41%

(+)-2-Benzylaminoöctadecane

The levorotatory benzoyl-D-alanine salt (7.22 g.) gave 4.46 g. of colorless liquid, b. p. 153—155°/0.01 mm., which crystallizes on standing. $[\alpha]_D^{20} = +8.24^0$ (homogeneous).

Anal. 7.015 mg. subst.: 0.250 ml. N_2 (19°, 746 mm.)
$C_{25}H_{45}N$ (359.62) calc'd: N 3.90%
found: N 4.09%

(+)-2-Aminoöctadecane

The base, b. p. 132—134°/0.01 mm., could not be purified by crystallization. $[\alpha]_D^{17} = +2.80°$ (c = 5, in chloroform).

(—)-2-Acetamidoöctadecane

M. p. 90—91°, from 96% ethanol $[\alpha]_D^{19} = -4.75°$ (c = 4.84, in chloroform).

Anal. 8.960 mg. subst.: 25.250 mg. CO_2, 10.530 mg. H_2O
$C_{20}H_{41}ON$ (311.54) calc'd: C 77.10; H 13.26%
found: C 76.90; H 13.15%

(+)-2-Phthalimidoöctadecane

M. p. 61—62°, from 96% ethanol. $[\alpha]_D^{17} = +10.67°$ (c = 3, in chloroform).

Anal. 8.205 mg. subst.: 0.251 ml. N_2 (19°, 753 mm.)
$C_{26}H_{41}O_2N$ (399.60) calc'd: N 3.51%
found: N 3.54%

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IZVOD

Sinteza optički aktivnih 2-amino-oktadekana

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1. Izvedena je sinteza DL-2-benzilamino-oktadekana i DL-2-amino-oktadekana.
2. DL-2-benzilamino-oktadekan pocijepan je u optičke antipode s pomoću benzoil-L-alanina i benzoil-D-alanina.
3. Opisani su enantiomerni 2-amino-oktadekani i njihovi N-benzil-, N-acetil- i N-ftalil-derivati.

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