On the Absolute Configuration of threo-1, 2-Diphenyl-2-hydroxyethylamine

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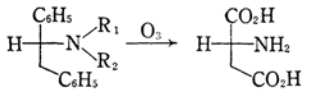
The (R)-configuration of (−)-1, 2-diphenylethylamine (Ia) has been established[1] by the degradation of its (+)-*N*-acetyl derivative Ib to D-aspartic acid (II), and the analgesic property of (−)-*N*, *N*-dimethyl-1, 2-diphenylethylamine (Ic), derived from Ia, has been attributed to its configuration similar to that of (−)-morphine (Fig. 1).



Ia $R_1=R_2=H$ II
b $R_1=Ac$, $R_2=H$
c $R_1=R_2=Me$

Fig. 1

However, this assignment of the absolute configuration to Ia has been found to be inconsistent with the findings of La Manna and his collaborators,[2] who obtained (+)-Ia (the enantiomer of Ia) from (+)-*threo*-1, 2-diphenyl-2-hydroxyethylamine (VIIa) by replacing the hydroxyl group with a chlorine atom with phosphorus pentachloride and by the subsequent hydrogenolysis of the chloro derivative (Fig. 2). The L-configuration* had been assigned to the (+)-*threo* isomer VIIa by Weijlard et al.,[3] who reported that they had converted the *N*-formyl derivative IVb of the D(−)-*erythro* isomer IVa, whose absolute configuration had been proved unambiguously,[4] into the (+)-*threo* isomer VIIa by treating it with thionyl chloride, which is believed to allow only the hydroxyl group to epimerize.[5]

Once this assignment of the L-configuration of the (+)-*threo* isomer VIIa is accepted as correct, it is more than natural that La Manna et al. were led to give the (R)-configuration to (+)-1, 2-diphenylethylamine instead of to the (−)- isomer Ia. However, a very curious situation arose when they found that the D(−)-*erythro* isomer IVa afforded (−)-Ia by the same treatment applied to the (+)-*threo* isomer VIIa.

1) M. Nakazaki, *Chem. & Ind.*, **1962**, 1577; This Bulletin, **36**, 161 (1963).

2) P. Pratesi, A. La Manna and L. Fontanella, *Il Farmaco (Pavia), Ed. Sci.*, **10**, 673 (1955); *Chem. Abstr.*, **50**, 10057 (1956).

* The configurations of the formulations in this paper are in accord with Fischer's convention referring to the asymmetric center at C_2 (Figs. 2 and 3).

3) J. Weijlard, K. Pfister, 3rd, E. F. Swanezy, C. A. Robinson and M. Tishler, *J. Am. Chem. Soc.*, **73**, 1217 (1951).

4) A. McKenzie and D. J. C. Pirie (*Ber.*, **69**, 876 (1936)) correlated the configuration at C_2 of IVa with D(−)-mandelic acid (IIIa) via D(−)-benzoin (IIIb) and D(−)-benzoin oxime (IIIc) (Fig. 2). (Cf. also A. McKenzie and H. Wren, *J. Chem. Soc.*, **93**, 309 (1908).) The erythro configuration of IVa was established by J. Reed and I. G. M. Campbell (ibid., **1930**, 2377) and by A. Weissberger and H. Bach (*Ber.*, **64**, 1094 (1934); **65**, 63 (1935)). On the predominant formation of the erythro derivative IVa by the reduction of benzoin oxime (IIIc), see D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5824 (1952).

5) A mechanism involving the intermediate stages V and VI had been suggested. There is ample evidence to support the idea of the epimerization at the center carrying the hydroxyl group (Cf. D. F. Elliot, *J. Chem. Soc.*, **1950**, 62; G. Fodor, V. Bruckner, J. Kiss and G. Óheggi, *J. Org. Chem.*, **14**, 337 (1949),). Weijlard et al.[3] cites much relevant literature.

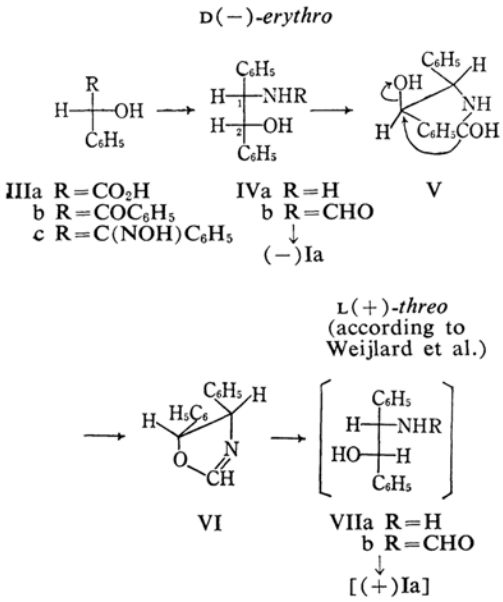


Fig. 2

Since, according to Weijlard et al.,[3] the D(−)-*erythro* isomer IVa and the (+)-*threo* isomer VIIa both have the same configuration at C_1 (the carbon atom carrying amino group) (Fig. 2), both compounds may be expected to give the same optically-active 1,2-diphenylethylamine. To circumvent this difficulty, La Manna and his collaborators suggested that "the replacement of the hydroxyl group (of D(−)-*erythro* isomer IVa) by a chlorine atom by means of phosphorus pentachloride may involve inversion of the configuration at the C_1 center (the carbon atom bearing amino group) which is not directly concerned in the replacement."[2]

Since the absolute configuration of (−)-1,2-diphenylethylamine (Ia) was unambiguously determined[1] by correlating it directly to D-aspartic acid (II), one is forced to assume, contrary to the suggestion of La Manna et al.,[2] that it must not be the D(−)-*erythro* isomer IVa but the (+)-*threo* isomer VIIa which epimerizes at the center of C_1 while the hydroxyl group is replaced at C_2 with phosphorus pentachloride.

However, the awkwardness has still remained, demanding some reasonable mechanism to explain this curious epimerization at C_1; no relevant parallel to which could be found in the literature. This contribution is primarily concerned with the revision of the absolute configuration of *threo*-1,2-diphenyl-2-hydroxyethylamine (VIIa) originally proposed by Weijlard et al.,[3] so as to avoid the awkward circumstance mentioned above.

A survey of the literature reveals that

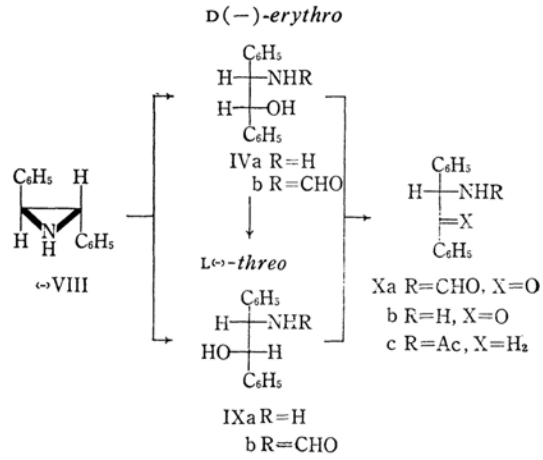


Fig. 3

Weissberger and Bach[6] performed an experiment (Fig. 3) which indicated clearly that (−)-*erythro* isomer IVa and (−)-*threo* isomer IXa have the same configuration at C_1; in this experiment they obtained these two optically-active diastereoisomers from (−)-*trans*-1,2-diphenylethyleneimine (VIII)[7] on hydrolysing it with diluted sulfuric acid. Because the (−)-*erythro* isomer IVa resulted from the *trans*-opening of the (−)-*trans* ethyleneimine, VIII has been shown to have the D-configuration by correlating it with D(−)-mandelic acid IIIa[4] (Fig. 2); the (−)-*threo* isomer which is formed by the cis-opening of the VIII, differing from IVa only at the configuration of C_2 must have the L-configuration, contrary to the conclusion of Weijlard et al., as Fig. 3 shows. This deduction[8] was further supported by the conversion of the *N*-formyl derivatives of both D(−)-*erythro*- (IVb) and L(−)-*threo*- 1,2-diphenyl-2-hydroxyethylamine (IXb) to the same (R)(+)-desylamine hydrochloride (Xb)[9] by sodium

6) A. Weissberger and H. Bach, *Ber.*, **65**, 631 (1932).

7) Since the absolute configuration of D(−)-*erythro*-1,2-diphenyl-2-hydroxyethylamine (IVa) has been established, (−)-*trans*-1,2-diphenylethyleneimine is shown to be 1(S), 2(S)-diphenylethyleneimine (VIII).

8) P. Pratesi, A. La Manna and G. Vitali (*Il Farmaco (Pavia) Ed. Sci.*, **15**, 387 (1960); *Chem. Abstr.*, **54**, 24472 (1960)) reached the same conclusion by obtaining the same optically-active (+)-*N*-acetyl-1,2-diphenylethylamine (Ib) m.p. 164~165°C, $[\alpha]_D$ +14° by hydrogenolysis of the *N*,*O*-diacetyl derivatives of IVa and IXa.

9) This finding also confirms the absolute configuration of (S)(−)-desylamine (the enantiomer of Xb) and the retention of the configuration in the conversion of (S)(−)-desylamine to D(−)-benzoin (IIIb) reported by A. McKenzie and D. J. Cruickshank (*Ber.*, **69**, 876 (1936)), although their deduction of these facts was not complete until the compounds, m.p. 141~142°C ($[\alpha]_D$−10° from (D)-benzoin oxime, $[\alpha]_D$+10.4° from (+)-desylamine)) were shown to be of the erythro form of 1,2-diphenyl-2-hydroxyethylamine.[4] This has been pointed out by C. K. Ingold (1951) in his personal communication to the editor of Beilstein, "Handbuch der Organischen Chemie." (IV Auflage, Bd. 14, zweites Ergänzungswerk, Springer, Berlin (1951), p. 62).

dichromate oxidation, followed by hydrolysis of the resulting *N*-formyldesylamine (Xa).[10]

These results are in harmony with La Manna's finding mentioned above that the (+)-*threo* isomer (now known to be of the D-configuration, the enantiomer of IXa) and the D(−)-*erythro* isomer IVa gave optically-active 1,2-diphenylethylamines with opposite rotations; hence it is not necessary to assume a rather incredible epimerization at C_1 in the replacement reaction of the hydroxyl group at C_2 of the erythro isomer IVa with phosphorus pentachloride.

Let us turn now to the conversion of the *N*-formyl derivative IVb of the D(−)-*erythro* isomer IVa into the (+)-*threo* isomer (now known to have the D-configuration; the enantiomer of IXa) with thionyl chloride reported by Weijlard et al. In order to accommodate their finding to the established absolute configurations (vide supra) of *erythro*- and *threo*-1,2-diphenyl-2-hydroxyethylamine, it seems inevitable, although improbable, to assume the epimerization at C_1 against overwhelming evidence which support the epimerization at the carbon atom C_2 carrying the hydroxyl group under these reaction conditions. On duplicating their isomerization experiment of the *N*-formyl derivative IVb of the D(−)-*erythro* isomer with thionyl chloride, it was found that the *threo* isomer showed, rather surprisingly, $[\alpha]_D -122°$, which has been shown to have the L-configuration IXa (vide supra); this is contrary to the finding of Weijlard et al.

This finding also indicates that the isomerization follows the usual, well-established path, affording an isomer which differs in the configuration of the carbon atoms carrying the hydroxyl groups (V→VI, in Fig. 2).

This error in the measurement of the optical rotation has been responsible for creating a chaos of puzzling phenomena, confusing La Manna and his collaborators in their determination of the absolute configuration of 1,2-diphenylethylamine (Ia).

It may be worthwhile to mention here another attempt to determine the absolute configuration of 1,2-diphenylethylamine (Ia), an attempt which eventually led to a conclusion opposite to ours.[1] Lyle[11] suggested the (R)-configuration for (+)-1,2-diphenylethylamine (the antipode of Ia) because its positive plain rotatory dispersion curve is very close the summation curve of (R)(+)-α-methylbenzylamine and (S)(+)-amphetamine which she considered to be the components of (+)-1,2-diphenylethylamine molecule. The reason why she was led to the wrong conclusion must be sought in her failure to take account of the phenyl-phenyl interaction and of the hydrogen bond between the phenyl groups and the amino groups, as well as the conformational asymmetry emphasized by Brewster.[12]

Experimental

(±)-*erythro*-1,2-Diphenyl-2-hydroxyethylamine ((±)-IVa).—To a solution of 5.7 g. of benzoin-α-oxime in 60 cc. of 90% ethanol was added 0.5 g. of 10% palladium-charcoal catalyst, together with 6 cc. of 5.5 N ethanolic hydrochloric acid; this mixture was then shaken at 40°C in an atmosphere of hydrogen for 6 hr. After the catalyst had been filtered out, the filtrate was concentrated to about 1/3 of the original volume. The crystals (1.1 g.) which were deposited upon the addition of water were recrystallized from benzene to afford hydrobenzoin, m. p. 135~136°C. The aqueous solution was made basic with concentrated aqueous ammonia to yield 3.97 g. of racemic IVa, m. p. 152~158°C. Recrystallization from methanol raised the m. p. to 157~160°C (lit.:[3] m. p. 163°C).

The Hydrochloride.—To a solution of 1 g. of racemic IVa in 10 cc. of ethanol was added 1.2 cc. of 5.5 N ethanolic hydrochloric acid, followed the addition of 10 cc. of ether to precipitate the hydrochloride of IVa (1.1 g.), m. p. 228°C (lit.:[3] m. p. 219~220°C).

***N*-Formyl-(±)-*erythro*-1,2-diphenyl-2-hydroxyethylamine ((±)-IVb).**—One gram of the hydrochloride of racemic IVa was dissolved in 3 cc. of formamide, and the mixture was heated at 150°C for 15~20 min. After being cooled to room temperature, the reaction mixture was diluted with 20 cc. of water to precipitate crystals which were then collected and washed with water to yield 0.61 g. of racemic IVb. Recrystallization from ethanol gave needles which weighed 0.61 g. and which melted at 180~182°C (lit.:[3] m. p. 179~181°C).

(±)-*N*-Formyldesylamine ((±)-Xa) from (±)-IVb.—A solution of 0.21 g. of racemic IVb in 3 cc. of acetic acid was added to a stirred solution of 0.27 g. of sodium dichromate dihydrate in 4 cc. of acetic acid at 10°C over 1/2 hr. The solution was then brought slowly to room temperature (10°C) and allowed to stand overnight. After being heated at 50°C for 20 min., the reaction mixture was diluted with 70 cc. of water and kept in a refrigerator overnight; 76 mg. of prismatic crystals (m. p. 199~120°C) precipitated. Recrystallization from benzene-petroleum ether did not raise the melting point. An infrared spectrum in Nujol indicated major peaks at 3360 (NH), 1685, and 1660 cm^{-1} (CO).

Found: C, 75.2; H, 5.6; N, 6.0. Calcd. for $C_{15}H_{13}O_2N$: C, 75.30; H, 5.48; N, 5.85%.

(±)-Desylamine ((±)-Xb) Hydrochloride from (±)-Xa.—After a mixture of 86 mg. of racemic

10) Optically-active *N*-formyldesylamine could not be obtained in a crystalline state, but the racemic variety was in prism form, m. p. 119~120°C.

11) G. G. Lyle, *J. Org. Chem.*, **25**, 1779 (1960).

12) J. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959).

Xa and 4 cc. of 2 N hydrochloric acid had been refluxed for 2 hr., the solution was evaporated to dryness in a vacuum. The crystalline residure was dissolved in 5 cc. of water and treated with Norit. The filtrate was then concentrated to about 0.5 cc., and 1 cc. of concentrated hydrochloric acid was added. The mixture was allowed to stand in a refrigerator to precipitate fine needles, which were then collected and washed with concentrated hydrochloric acid. The (±)-desylamine hydrochloride, after being dried in a desiccator over sodium hydroxide pellets, decomposed at 220~225°C and weighed 40 mg. (lit.:[3]) the optically active hydrochloride, m. p. 230°C).

(±)-*threo*-1,2-Diphenyl-2-hydroxyethylamine ((±)-IXa).—A mixture of racemic IVb and 3.0 cc. of thionyl chloride was stirred at 0~5°C for 20 min., and the reaction mixture was brought slowly to room temperature over a 1 hr. period. After the excess thionyl chloride had been decomposed with 20 g. of ice, the reaction mixture was refluxed for 2 hr. After being cleared with Norit, the solution was made basic with a 3 N sodium hydroxide solution to precipitate the racemic IXa, which was then washed with water and dried to yield 1.1 g. of crystals, m. p. 128°C. Recrystallization from ethanol gave 0.9 g. of prisms, m. p. 129~130°C (lit.:[3]) m. p. 126~128°C).

The hydrochloride (decomp. p. 205~210°C) was prepared following the procedure described for the erythro isomer IVa. The yield was quantitative (lit.:[3]) decomp. p. 200~201°C).

***N*-Formyl-(±)-*threo*-1,2-diphenyl-2-hydroxyethylamine ((±)-IXb).**—Following the procedure described for the erythro isomer IVb, a mixture of 0.83 g. of the hydrochloride of racemic IXa and 3 cc. of formamide was heated to give 0.65 g. of racemic IXb, m. p. 146~149°C after recrystallization from diluted ethanol (lit.:[3]) m. p. 145~146°C).

(±)-Desylamine ((±)-Xb) Hydrochloride from (±)-IXb.—A solution of 0.60 g. of the racemic IXb in 7 cc. of acetic acid was added gradually to a stirred solution of 0.81 g. of sodium dichromate dihydrate in 12 cc. of acetic acid at 10°C over a 1/2 hr. period. After being allowed to stand over-night at room temperature, the mixture was heated at 50°C for 1/2 hr. This mixture was diluted with 200 cc. of water, saturated with sodium chloride, and then extracted with ether. The ether extract was washed with a dilute sodium hydrogen carbonate solution and then with a saturated sodium chloride solution. The ether extract was dried over anhydrous magnesium sulfate and was concentrated to give 0.42 g. of a viscous residue (the odor of benzaldehyde was noticed) which was then hydrolyzed by boiling it with 10 cc. of 2 N hydrochloric acid for 2 hr. The solution was concentrated under reduced pressure to give a crystalline mass, which was washed with benzene. The residue was dissolved in a small amount of water and concentrated again after treatment with Norit. To the clear solution (about 1 cc.) 3 cc. of concentrated hydrochloric acid was added to precipitate (±)-desylamine hydrochloride, which decomposed at 225~230°C and which weighed 0.12 g.

Found: N, 5.5. Calcd. for $C_{14}H_{14}ONCl$: N, 5.66%.

D(−)-*erythro*-1,2-Diphenyl-2-hydroxyethylamine (IVa).—A mixture of 11.1 g. of racemic IVa and 7.9 g. of L-glutamic acid was dissolved in 330 cc. of 50% ethanol and was kept in a refrigerator to precipitate the L-glutamate of the (−)-amine IVa as fine needles, which were then recrystallized from 50% ethanol. The L-glutamate melted at 213°C with decomposition. $[\alpha]_D^{20}$ −50.0° (*c* 0.42 in water) (lit.:[3]) decomp. p. 215°C, $[\alpha]_D^{25}$ −50.3° (*c* 0.65 in water)). The L-glutamate (6.63 g.) was dissolved in 100 cc. of water, and the D(−)-*erythro* base IVa was precipitated by adding concentrated aqueous ammonia. The base was collected and washed with water to give 3.5 g. of crystals, which melted at 141~144°C after recrystallization from ethanol. $[\alpha]_D^{24}$ −6.4° (*c* 1.25 in ethanol) (lit.:[3]) m. p. 143°C, $[\alpha]_D^{25}$ −10.1° (*c* 0.59 in ethanol)).

The hydrochloride which was prepared following the procedure for the racemic compound decomposed at 215°C, $[\alpha]_D^{21}$ −59.0° (*c* 1.0 in water) (lit.:[3]) decomp. p. 213.5~214.5°C, $[\alpha]_D^{25}$ −69.5° (*c* 0.65 in water)).

Found: N, 5.2. Calcd. for $C_{14}H_{16}ONCl$: N, 5.61%.

***N*-Formyl-D(−)-*erythro*-1,2-diphenyl-2-hydroxyethylamine (IVb).**—The *N*-formyl derivative IVb, which was prepared following the procedure for the racemic erythro amine, melted at 201~202°C after recrystallization from ethanol, $[\alpha]_D^{22}$ +2.6° (*c* 0.45 in ethanol).

Found: C, 74.4; H, 6.3; N, 5.8. Calcd. for $C_{15}H_{15}O_2N$: C, 74.66; H, 6.27; N, 5.81%.

(+)-Desylamine (Xb) Hydrochloride obtained by the Oxidation of IVb.—A solution of 0.411 g. of IVb in 8 cc. of acetic acid was added to a stirred solution of 0.56 g. of sodium dichromate dihydrate in 6 cc. of acetic acid over a 15 min. period at 0°C. After being stirred for 1 hr. at 0°C, the solution was allowed to stand overnight at room temperature. The reaction mixture was then poured into 200 cc. of water and extracted with ether. The ether extract was washed with a dilute sodium hydrogen carbonate solution and then with a saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was removed to give crude *N*-formyl-(+)-desylamine (an oil, $[\alpha]_D^{22}$ +227° (*c* 1.4 in ethanol)), which was hydrolyzed directly by boiling it with 10 cc. of 2N hydrochloric acid for 2 hr. The solution was concentrated under reduced pressure to give a crystalline residue which was dissolved in a small amount of water and treated with Norit. The filtrate freed from Norit was concentrated again to 3 cc., and then 6 cc. of concentrated hydrochloric acid was added to precipitate (+)-desylamine hydrochloride, which decomposed at 225°C and which weighed 60 mg., after drying in a vacuum desiccator over sodium hydroxide pellets., $[\alpha]_D^{21}$ +189° (*c* 1.0 in water) (lit.:[13]) $[\alpha]_D^{16}$ +223.2° (*c* 2.54 in water)).

Found: C, 68.0; H, 5.7. Calcd. for $C_{14}H_{14}ONCl$: C, 67.87; H, 5.69%.

13) A. McKenzie and N. Walker, *J. Chem. Soc.*, **1928**, 646.

The Isomerization of *N*-Formyl-D(−)-*erythro*-1,2-diphenyl-2-hydroxyethylamine (IVb) to L-(−)-*threo* Isomer IXa.—A mixture of 1.5 g. of *N*-formyl-D(−)-*erythro* amine IVb and 3 cc. of thionyl chloride was stirred at 0°C for 5 min., and then the temperature of the mixture was gradually raised to room temperature (15°C) over a 45 min. period. The solution was poured onto 100 g. of ice to decompose the excess thionyl chloride, and the reaction mixture was refluxed for 2 hr. The solution was cleared with Norit and was made basic with a 4 N sodium hydroxide solution to precipitate 1.4 g. of L(−)-*threo* amine IXa, which was collected and washed with water. The amine was recrystallized from ethanol to give needles which melted at 114~116°C, $[\alpha]_D^{22}$ −122° (*c* 1.0 in ethanol) (lit.:[3] m. p. 115.2~115.8°C $[\alpha]_D^{24}$ −123.7° (*c* 1.2 in ethanol) for the "D(−)-*threo*" isomer).

Found: C, 78.8; H, 7.1; N, 6.4. Calcd. for $C_{14}H_{15}ON$: C, 78.84; H, 7.09; N, 6.57%.

The hydrochloride which was prepared following the procedure for the racemic threo compound decomposed at 230°C, $[\alpha]_D^{18}$ −122° (*c* 1.2 in ethanol). (lit.:[3] decomp. p. 220~221°C, $[\alpha]_D^{23}$ +84.7° (*c* 0.01 in water) for the hydrochloride of the "L(+)-*threo*" isomer).

***N*-Formyl-L(−)-*threo*-1,2-diphenyl-2-hydroxyethylamine (IXb).**—The *N*-formyl-L(−)-*threo* isomer IXb which was prepared following the procedure used for the racemic compound melted at 116~119°C after recrystallization from 50% ethanol, $[\alpha]_D^{18}$ +11.3° (*c* 1.2 in ethanol).

Found: C, 74.2; H, 6.2; N, 5.9. Calcd. for $C_{15}H_{15}O_2N$: C, 74.66; H, 6.27; N, 5.81%.

(+)-Desylamine (Xb) Hydrochloride from IXb. Following the procedure used for the oxidation of IVa, 0.469 g. of IXb was oxidized with 0.58 g. of sodium dichromate dihydrate in acetic acid to give 70 mg. of (+)-desylamine hydrochloride, which decomposed at 225°C, $[\alpha]_D^{23}$ +130° (*c* 0.51 in water). Its infrared spectrum was found superimposable on that of (+)-desylamine hydrochloride derived from IVa (in a Nujol mull).

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