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Studies on Dimethoxyphenylaminoalcohols.[1] III. The Enantiomers of 1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butanol

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(±)-*erythro*-1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butanol was resolved with *d*- and *l*-10-camphorsulfonic acid to (+)- and (−)-enantiomers. The optically active *threo*-enantiomers were synthesized from the optically active *erythro*-enantiomers. Their absolute configurations were determined by chemical interrelation.

Keywords——β-aminoalcohols; antitussives; resolution; absolute configuration; 1,3-asymmetric induction

As described in the previous paper,[1] we have studied on the stereochemistry of 1-dimethoxyphenyl-3-alkylamino-*n*-butanols (I).

These aminoalcohols were synthesized by reduction of the β-aminoketones with metal hydride, and the diastereomers were isolated as styphnates. Their relative configurations were determined by the nuclear magnetic resonance. It was proved by the intramolecular nuclear Overhauser effect (NOE) that the predominant diastereomer is *erythro* type. Although the minor diastereomer did not exhibit the NOE, it was estimated to be *threo* type. These diastereomers exhibited the antitussive action, and potentiated that of codein. It is known that optical isomers exhibit the different physiological activity from that of the optically inactive substance. Then we tried to isolate the four enantiomers.

This paper deals with resolution of *erythro*-1-(2,5-dimethoxyphenyl)-3-diethylamino-*n*-butanol, and the synthesis of (+)- and (−)- *threo*-enantiomers.

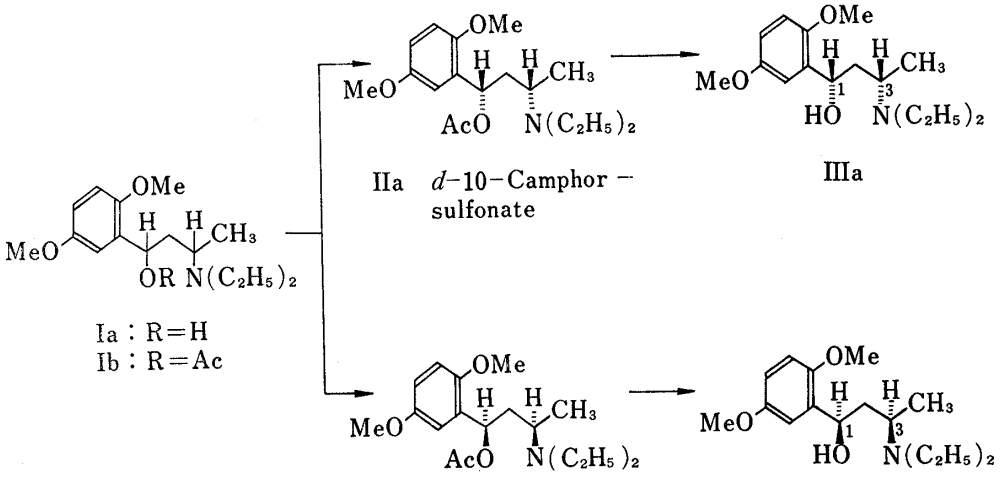


Chart 1

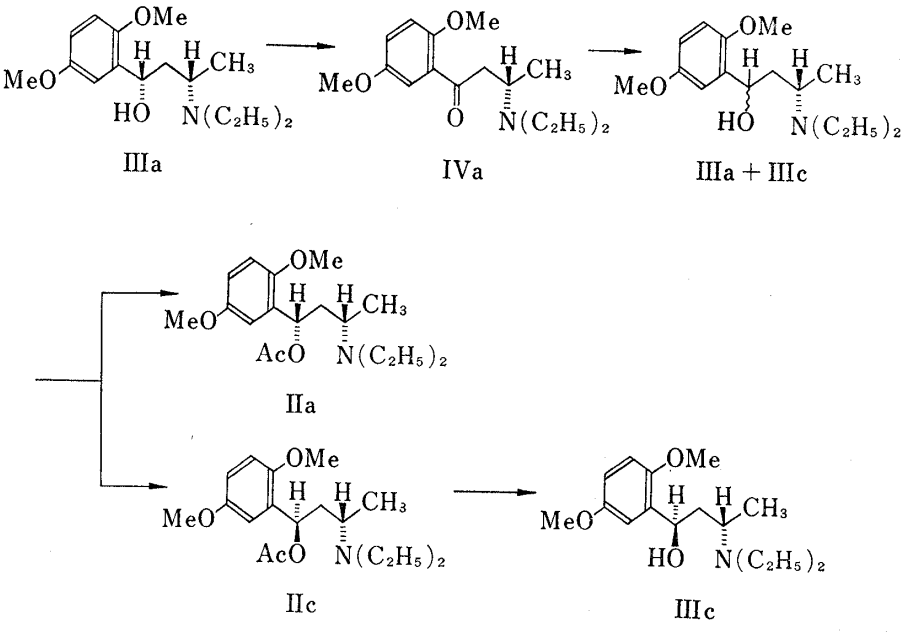
1) Part II: H. Hamano and S. Okuda: *Chem. Pharm. Bull.* (Tokyo), **22**, 1348 (1974).
2) Location: *a) 3-31, Shimo-cho, Kita-ku, Tokyo 115, Japan; b) 1-1-1, Yayoi, Bunkyo-ku, Tokyo 113, Japan.*

(A) Resolution of *erythro*-*l*-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butanol

Attempts to resolve the *erythro*-aminoalcohol (Ia) with *d*-10-camphorsulfonic acid, *d*-tartaric acid, O,O′-diacetyltartaric acid, O,O′-dibenzoyltartaric acid, *l*-mandelic acid, and various substituted tartranilic acid[3] were all unsuccessful because all the salts did not crystallize. However, it was found that the acetate (Ib) reacted with *d*-10-camphorsulfonic acid to give the crystalline salt. After the repeated recrystallizations from ethyl acetate, the optically pure salt (IIa) was obtained. The acetate obtained by decomposing the salt was reduced with lithium aluminum hydride to give (−)-*erythro*-aminoalcohol (IIIa), $[\alpha]_D^{25}$ −44.02° (c=5.52, EtOH). Although the (+)-salt did not crystallize from the mother liquor, the (+)-enriched base which isolated from the sirupy residue reacted with *l*-10-camphorsulfonic acid to give the crystalline salt (IIb), which was treated similarly to afford (+)-*erythro*-aminoalcohol(IIIb), $[\alpha]_D^{25}$ +44.06° (c=5.50, EtOH).

(B) The Synthesis of (+)- and (−)-*threo*-1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butanol

The resolution of the *erythro*-diastereomer was achieved successfully as described above, but the *threo*-diastereomer was not resolved by the similar manner. The acetate of the *threo*-diastereomer reacted with *d*-10-camphorsulfonic acid to give crystalline salt, which did not afford the optically active base in spite of cautiously repeated recrystallizations. Attempts using the other resolving agents such as O,O′-dibenzoyltartaric acid and the various substituted tartranilic acids[3] were all unsuccessful. And the ester of I with D-phenylalanine N-phthalide was crystalline, but the optically active diastereomer could not be isolated in spite of the careful recrystallizations, Thus the *threo*-diastereomer was not resolved by the usual methods. Then we tried to synthesize the optically active *threo*-diastereomers from the optically active *erythro* diastereomers utilizing the effect of 1,3-asymmetric induction as shown in Chart 2.



IIIa IVa IIIa + IIIc

IIa

IIc IIIc

Chart 2

The (−)-*erythro*-aminoalcohol (IIIa) was oxidized with Collins' reagents followed by reduction with sodium bis-(2-methoxyethoxy)-aluminum hydride to give a mixture of oily (−)-*erythro*- and (+)-*threo*-aminoalcohol (IIIa and IIIc) in the ratio of 65 to 35, respectively. The

3) T.A. Montzka, T.L. Pindell, and J.D. Matiskella, *J. Org. Chem.*, 33, 3993 (1968).

isolation of pure (+)-*threo*-aminoalcohol from this mixture was not easy. Although the styphnate of the aminoalcohol did not crystallize, the acetate reacted with *d*-10-camphorsulfonic acid to crystallize the salt of *erythro*-acetate, and then the base which was isolated from the mother liquor, reacted with *l*-10-camphorsulfonic acid to give the crystalline salt of *threo*-acetate. After the repeated purifications, isolation of the base and ester-cleavage, (+)-*threo*-aminoalcohol (IIIc), $[\alpha]_D^{25}$ +27.53° (c=3.10, EtOH), was obtained. Similarly (−)-*threo*-aminoalcohol (IIId) was obtained from IIIb, $[\alpha]_D^{25}$ −27.58° (c=3.20, EtOH).

The absolute configuration of IIIc which is the diastereomer IIIa is 1*R* and 3*S*, because that of IIa hydrobromide was determined by X-ray crystallographic analysis to be 1*S* and 3*S*.[4] And the absolute configuration of IIId is 1*S* and 3*R*, because that of IIIb which is the enantiomer of IIIa is 1*R* and 3*R* (see Table I).

The *erythro*-diastereomer lowered the effective antitussive dose of codein in guinea pigs. ED_{50} of this substance and codein phosphate was 22.1 and 16.2 mg/kg, respectively, and a dose of the 1/7 effective dose of this substance reduced the effective dose of codein to below 1/4.5.[5] The pharmacological activities of the *threo*-diastereomer and the four enantiomers will be reported elsewhere.

Table I. The Absolute Configurations of 1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butanols

Streoisomers	mp (°C) of camphorsulfonate	Optical rotation $[\alpha]_D^{25}$ (EtOH)		Absolute configuration	
		Acetate	Free base	C_1	C_3
IIIa	*d*-, 128—129°	−64.32° (c=2.50)	−44.02° (c=5.52)	*S*	*S*
IIIb	*l*-, 131—132°	+64.27° (c=2.48)	+44.06° (c=5.50)	*R*	*R*
IIIc	*l*-, 132—134°	+56.34° (c=0.80)	+27.53° (c=3.10)	*R*	*S*
IIId	*d*-, 130—132°	−56.29° (c=0.84)	−27.58° (c=3.20)	*S*	*R*

Experimental

Melting points were determined in a Mitamura micromelting point apparatus and uncorrected. Infrared (IR) spectra were taken with JASCO IR-G spectrophotometer. Optical activities were measured on Perkin Elmer Model 141 polarimeter. All the gas chromatograms were measured with a Shimadzu GC-5APTF (hydrogen flame ionization detector). The chromatographic column consisted of glass tubing (2 m×3 mm i.d.) prepacked with Chromosorb W-HP (80—100 mesh) coated with 3% silicon OV-17. The column was maintained isothermally at 200° with both the detector and injection port at 220°.

Resolution of *erythro*-1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butyl Acetate (1a)——The solution of Ib (10.4 g), prepared from Ia as usual method, and *d*-10-camphorsulfonic acid (7.5 g) in ethyl acetate (20 ml) was kept in a refrigerator for 24 hr. A precipitate was filtered, and recrystallized 4 times from ethyl acetate (25 ml) to give needles (1.812 g), mp 128—129°. *Anal.* Calcd. for $C_{28}H_{45}NO_8S$: C, 60.51; H, 8.16; N, 2.52. Found: C, 60.59; H, 8.08; N, 2.66.

The above salt was dissolved in 15 ml of H_2O and basified with aq. NH_3 (3 ml), and the separated oil was extracted with ether (15 ml×3). The extract was washed with H_2O (10 ml×3) and dried over Na_2SO_4. Ether was evaporated to give oily acetate (IIa) (1.002 g). $[\alpha]_D^{25}$ −64.32° (c=2.50, EtOH), IR ν_{max}^{film} cm^{-1} 1740 (C=O).

(−)-*erythro*-1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butanol (IIIa)——To a suspension of $LiAlH_4$ (150 mg) in ether (10 ml) was added dropwise the solution of above acetate (850 mg) in ether (10 ml). The reaction mixture was heated with stirring for 3 hr, and poured onto ice-water. The ethereal solution was separated and the aqueous layer was extracted with ether (10 ml×3). The combined ethereal solution was

4) Y. Masuda, Y. Iitaka, and H. Hamano, *Bull. Chem. Soc. Japan*, **47**, 825 (1974).
5) Y. Kasuya, M. Watanabe, K. Miyasaka, and Y. Ishii, *Arzneim.-Forsch.*, **27**, 1450 (1977).

washed with water (10 ml×2), and dried over Na_2SO_4. Ether was evaporated to give an oil (700 mg). IR and GLC of the oil was consistent with those of Ia. $[\alpha]_D^{25}$ −44.02° (c=5.52, EtOH).

(+)-*erythro*-1-(2,5-Dimethoxyphenyl)-3-diethylaminobutyl Acetate (IIb)——The sirupy salt obtained from the above mother liquor was dissolved in 2 N NH_4OH, and the separated oil was extracted with ether. The ethereal solution was washed with water, and dried over Na_2SO_4. Ether was evaporated to give an oil (6.871 g). $[\alpha]_D^{25}$ +22.8° (c=2.38, EtOH). This base and *l*-10-camphorsulfonic acid (4.800 g) was disolved in ethyl acetate (25 ml), and the solution was kept in a refrigerator for 24 hr. The crystalline salt was taken by filtration, and recrystallized twice from ethyl acetate (20 ml) to give needles (4.350 g), mp 131—132°. *Anal.* Calcd. for $C_{28}H_{45}NO_8S$: C, 60.51; H, 8.16; N, 2.52. Found: C, 60.48; H, 8.21; N, 2.34.

The salt was dissolved in 2 N NH_4OH, and the separated base was extracted with ether. The extract was treated as usual to give an oil (1.553 g). $[\alpha]_D^{25}$ +64.27° (c=2.48, EtOH). IR and GLC of this oil was consistent with those of Ib.

(+)-*erythro*-1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butanol (IIIb)——To a suspension of $LiAlH_4$ (200 mg) in ether (15 ml) was added dropwise a solution of above acetate (1.300 g) in ether (15 ml). The reaction mixture was heated under reflux with stirring for 3 hr, and treated as usual work to give an oil (1.216 g). IR and GLC of this oil were consistent with those of Ia. $[\alpha]_D^{25}$ +44.06° (c=5.50, EtOH).

Oxidation of IIIa——A solution of IIIa (1.012 g) in CH_2Cl_2 (10 ml) added dropwise to a solution of CrO_3-pyridine complex (4.7 g) in CH_2Cl_2 (100 ml) at −10°. After the addition was over, the reaction mixture was stirred at −10—0° for 3 hr, poured onto ice-water (100 g). The aqueous layer was basified with 2 N NaOH (5 ml), and extracted with CH_2Cl_2 (20 ml×3). The combined extract was treated as usual work to give pale yellow oil (0.987 g). IR ($\nu_{C=O}$ 1675 cm^{-1}) and TLC was identical with the racemic ketone. This ketone (IVa) was immediately used for the next step without further purification.

Reduction of IVa——A solution of the above ketone in dry ether (5 ml) was added dropwise to a solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (70% solution in benzene, 2 g) in dry ether at −10°. After the addition was over, the reaction mixture was stirred at −10° for 1 hr, and poured onto ice-water (5 g). The ethereal solution was decanted, and residue was washed with ether (10 ml×3). The combined ethereal solution was treated as usual work to give an oil (575 mg, *threo*/*erythro* ratio=35/65). This oil was used for the next step without further purification.

(+)-*threo*-1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butanol (IIIc)——A solution of *d*-10-camphorsulfonic acid (440 mg) and the acetate (613 mg) prepared from the above aminoalcohol in ethyl acetate (2 ml) was allowed to stand in a refrigerator for 24 hr. The crystalline salt (mp 128—129°, 520 mg) filtered off, and the base (*threo*/*erythro*=70/30, 278 mg) was isolated from the mother liquor. This base and *l*-10-camphorsulfonic acid (193 mg) were dissolved in ethyl acetate (1 ml), and allowed to stand in a refrigerator for 24 hr. The fine needles was separated by filtration, and recrystallized twice from ethyl acetate to give the pure salt, mp 132—133°. *Anal.* Calcd. for $C_{28}H_{45}NO_8S$: C, 60.51; H, 8.16; N, 2.52. Found: C, 60.41; H, 8.20; N, 2.50.

The free base ($[\alpha]_D^{25}$ +56.34° (c=0.80, EtOH), 120 mg) obtained by the usual work dissolved in 5 ml of EtOH containing 2 N NaOH (1 ml), and the reaction mixture was warmed at 50° for 2 hr. After the treatment by the usual work the aminoalcohol (IIIc, 70 mg) was obtained, $[\alpha]_D^{25}$ +27.53° (c=3.10, EtOH). IR and GLC of IIIc were identical with those of the racemic *threo*-aminoalcohol.

Oxidation of IIIb——A solution of IIIb (1.960 g) in CH_2Cl_2 (10 ml) was added dropwise to a solution of CrO_3-pyridine complex (6.7 g) in CH_2Cl_2 (100 ml) at −10°. The reaction mixture was treated in the similar manner as described for the preparation of IVa to give aminoketone (IVb, 1.280 g). IVb was immediately used for the next step without purification.

Reduction of IVb——The reaction of 1.250 g of IVb with 3 g of $NaAlH_2(OCH_2CH_2OCH_3)_2$ under conditions similar to those for the preparation of a mixture of IIIa and IIIc gave a mixture of IIIb and IIId (*threo*/*erythro*=40/60, 1.153 g). This alcohol was used for the next step without purification.

(−)-*threo*-1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butyl Acetate (IId)——The acetate (1.216 g) prepared from the above alcohol by the usual method reacted with *l*-10-camphorsulfonic acid (875 mg) in ethyl acetate (5 ml) to give the crystalline salt of IIb (940 mg), mp 131—132°. The free base (629 mg) obtained from the mother liquor reacted with *d*-10-camphorsulfonic acid (424 mg) in ethyl acetate (3 ml) to give crystalline salt, which was recrystallized twice from ethyl acetate to give pure salt, mp 130—131°. *Anal.* Calcd. for $C_{28}H_{45}NO_8S$: C, 60.51; H, 8.16; N, 2.52. Found: C, 60.42; H, 8.16; N, 2.20.

The structure of the free base ($[\alpha]_D^{25}$ −56.29°, (c=0.84, EtOH) isolated from the above salt was confirmed by comparing its IR and GLC with those of the racemic *threo*-acetate.

(−)-*threo*-1-(2,5-Dimethoxyphenyl)-3-diethylamino-*n*-butanol (IIId)——The above acetate (175 mg) was treated with 2 N NaOH in the similar manner as described for the preparation of IIIc to give IIId (120 mg) IR and GLC of IIId were identical with those of the racemic *threo*-aminoalcohol. $[\alpha]_D^{25}$ −27.58° (c=3.20, EtOH).

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