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A CONVENIENT METHOD FOR THE ASSIGNMENT OF THE ABSOLUTE CONFIGURATION TO CYCLIC AMINES

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Abstract—We have assigned the absolute configuration to *trans*-2,5-dimethylpyrrolidine and *trans*-2,6-dimethylpiperidine through radical chlorination in ω-1 position of optically active amines, **2** and **5**, of known absolute configuration, followed by cyclization. CD curves of **1f** and **4g** derivatives indicate that the reaction is stereospecific. The absolute configuration of *trans*-2,5-dimethyl-Δ^3-pyrroline has also been determined.

We have previously been interested in studies concerning the assignment of the absolute configuration to amino compounds by means of CD curves of the corresponding pyridyl-N-oxide derivatives. Correlations of the chiroptical properties of these derivatives and the absolute configuration of starting amines not containing the nitrogen atom in a cyclic structure[1] have been recently extended to mono-substituted cyclic amines.[2]

Going on in these studies, our present main interest is the determinations of absolute configuration of disubstituted cyclic amines. It has been noted, unfortunately, that the 2,6-disubstituted piperidines are much less reactive than the analogous 5-membered ring toward 2-fluoropyridine-N-oxide. The impossibility to introduce this thoroughly studied chromophore, led us to find different ways to determine the absolute configuration of disubstituted cyclic amines. We therefore applied radical chlorination in ω-1 position of optically inactive aliphatic amines, followed by cyclization.[3] With optically active long chain amines we obtained mixtures of *cis-trans* cyclic isomers in which the absolute configuration of the asymmetric centre is preserved.

Synthesis of (−)-2,5-dimethylpyrrolidine (**1a**) from R-(−)-1-methylpenthylamine (**2**) proved that the reaction is stereospecific; in fact the CD curve of the pyridyl-N-oxide derivative of the so obtained pyrrolidine (**1a**) is comparable with those showed by pyridyl-N-oxide derivatives of α-monosubstituted cyclic amines with R configuration[2] (Fig. 1). In this case it is not necessary to separate *cis* and *trans* compounds since the *cis* isomer is achiral.

This synthetic method, owing to the more favorable *cis-trans* ratio, is a valid alternative to the N-acyl-lactam rearrangement of Mundy that has recently been applied[4] to optical active N-acyl-6-methyl-2-piperidones which give prevalently *cis* cyclic amines.

In this paper 2,5-dimethylpyrroline (**3a**), 2,5-dimethylpyrrolidine (**1a**) and 2,6-dimethylpiperidine (**4a**) are examined (Scheme 1).

These compounds are of unknown configuration except **4a** that has been related to *S*-(+)-heptanol.[5]

Optical active **1a** and **4a** were obtained, with the above mentioned method,[3] in a *cis–trans* mixture (ratio 1:1, determined by NMR and GLC measurements). R-(−)-1-methylpenthylamine[6] (**2**) and R-(−)-1-methylhexylamine[7] (**5**) gave 2*R*, 5*RS*-(−)-2,5-dimethylpyrrolidine (**1a**) and 2*R*,6*RS*-(−)-2,6-dimethylpiperidine (**4a**) respectively. The *cis* isomers were not separated from *trans* isomers for the former are achiral.

To compare CD pattern showed by mono and disubstituted cyclic amines having a chromophoric group other than pyridyl-N-oxide, we prepared the N-chloro derivative of (−)-**4a** and its CD curve has similar behaviour, but an opposite sign (Fig. 1), compared with the one showed by N-chloro-derivative of the corresponding mono-substituted amine, *S*-N-chloro-2-methylpiperidine,[8] as expected from the absolute configuration of the starting amine.

The compound (−)-**1a** was also obtained by reduction of *trans*-(−)-2,5-dimethyl-Δ^3-pyrroline hydrochloride (**3c**); the latter, therefore, has 2*R*,5*R* configuration. CD curves of pyridyl-N-oxide derivatives of **3a** and of the corresponding saturated compound, **1a**, have the same sign (Fig. 1).

Trans-(−)-**3c** was isolated from the commercial mixture, constituted by *cis*, *trans* and Δ^1 isomers, by fractional crystallization of the corresponding tosylates, *cis*-**3b** and *trans*-**3b**. The N-tosyl-isomers were hydrolyzed and the *cis* and *trans* amines were identified by NMR spectra of the corresponding N-benzyl-derivatives,[9] *cis*-**3e** and *trans*-**3e**. Resolution of the *trans* optical isomers, (−)-and (+)-**3a**, were obtained by means of diacetonyl-2-keto-L-(−)-gulonic-acid.

EXPERIMENTAL

General. Microanalyses were conducted by Dr. R. De Leonardis, Istituto di Chimica Farmaceutica Bari, with a Hewlett-Packard 185 C,H,N analyzer. All m.ps and b.ps are uncorrected. The specific rotations were measured with a Perkin-Elmer 241 MC Polarimeter, concentrations are expressed in g/100 ml. CD and UV spectra were recorded with Cary 61 dichrograph and with Cary 15 spectrophotometer, respectively; cells of 10 mm pathlength were used; concentrations are expressed in g/l. NMR spectra were determined with a Varian HA-100 spectrometer, using TMS as internal standard; signals are reported in ppm (δ); in the NMR data the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. GLC was effected on a Hewlett-Packard 5750 G instrument fitted with a 6-ft column packed with 10% silicone gum rubber UCC-W-982 on chromosorb W 60–80 mesh.

General procedure[1] *for the preparation of N-[2-pyridyl-N-oxide]-amino-derivatives*

The amino compound (1 mmole) was reacted with 2-fluoropyridine-N-oxide (1.2 mmole); in the presence of $NaHCO_3$ (1 mmole) in a mixture (1:1) of H_2O–EtOH (5 ml) at room temp. for 3 days. For amines hydrochloride, $NaHCO_3$ was replaced by an equimolar amount of NaOH.

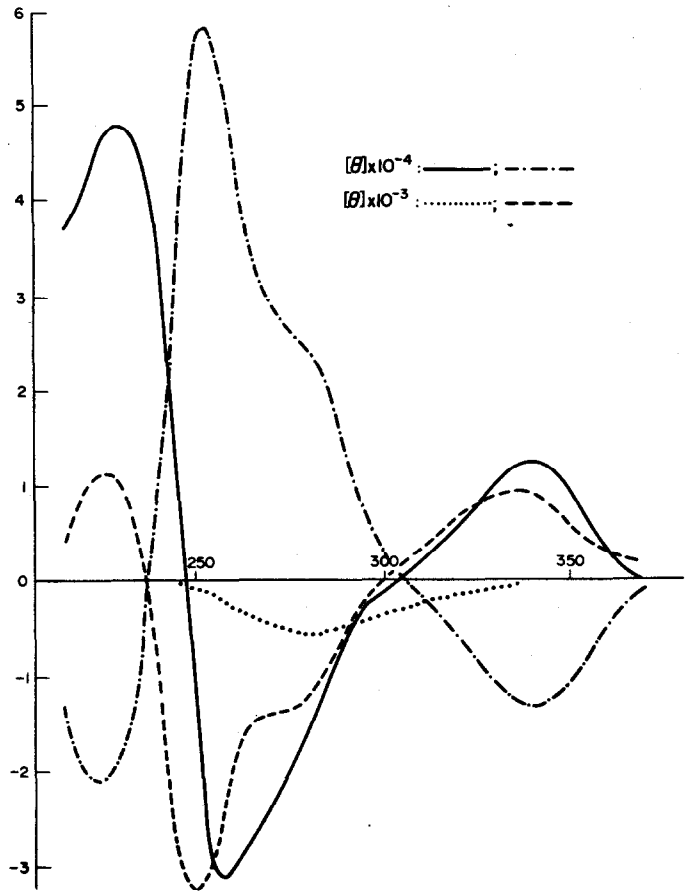
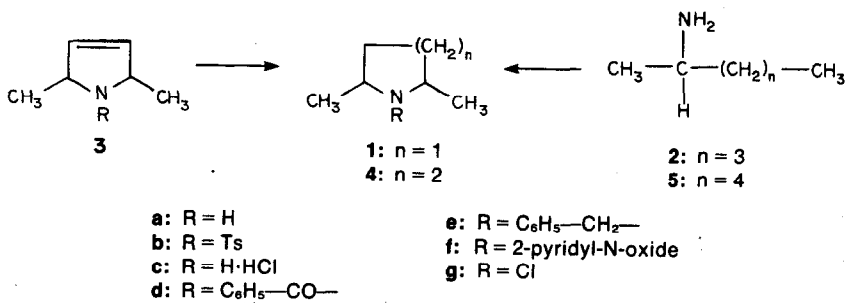


Fig. 1. CD curves: (+)-**3f** ——; (−)-**1f**, from (−)-**3c**, -.-.-.-; (+)-**1f**, from (+)-**2** – – – –; (−)-**4g**.....



Scheme 1.

The reaction mixture was then concentrated under vacuum and extracted with CH_2Cl_2. The residue obtained from evaporation of the organic solvent was distilled under vacuum.

General procedure[3] *for the selective halogenation in ω-1 position and cyclization of saturated aliphatic amines*

To a stirred soln of aliphatic amine (0.1 mol) and N-chlorodimethylamine (0.2 mol) in 100 ml conc. H_2SO_4, was added $FeSO_4 \cdot 7H_2O$ (0.03 mol). Temperature goes up from 5 to 36°C in 6 min. After standing for 15 min at room temp., the mixture was made alkaline with NaOH, 30%, (the temp. must not exceed more than 20°) and extracted with ether.

The solvent was removed *in vacuo* and to the crude chloroamino compound obtained was added NaOH (0.2 mol) in methanol. The mixture was heated to reflux for 6h and then made acid with HCl.

After removing methanol under reduced pressure, the soln was made alkaline with NaOH and extracted with ether. The residue obtained from evaporation of the organic solvent was distilled.

Cis,trans-*N-tosyl*-2,5-*dimethyl*-Δ^3-*pyrroline*

To a stirred soln of 2,5-dimethyl-Δ^3-pyrroline (Aldrich) (composition: 75% isomer Δ^3, 25% isomer Δ^1; 40g) in 200 ml dry pyridine was added dropwise at 0° a soln of tosyl chloride (70g) in 100 ml dry pyridine. After standing for 0.5h at 0° and for 2 days at room temp., the mixture was poured into 500 ml ice-water. The resulting ppt was filtered off, washed with HCl 2N and H_2O. A fractional crystallization of the crude compound (63g) from CH_2Cl_2–hexane, allowed the separation of *cis*-**3b** and *trans*-**3b**. This separation was analyzed by GLC. Compound *cis*-**3b** showed m.p. 112–113°, *trans*-**3b** m.p. 79–81°. (Found: C, 61.82; H, 6.91; N, 5.55. $C_{13}H_{17}NSO_2$ requires: C, 62.14; H, 6.82; N, 5.57%) NMR ($CDCl_3$) (of *cis*-**3b**) δ: 7.66 (d, 2 Harom, J = 8 Hz); 7.22 (d, 2 Harom, J = 8 Hz); 5.42 (s, 2H, H-C=C-H); 4.36 (q, 2H, CH-N-CH); 2.38 (s, 3H, CH_3-Ar); 1.40 (d, 6H, 2CH_3, J = 6 Hz). NMR ($CDCl_3$) (of trans-**3b**) δ: 7.74 (d, 2 Harom, J = 8 Hz); 7.24 (d, 2 Harom, J = 8 Hz); 5.54 (s, 2H, H-C=C-H); 4.60 (m, 2H, CH-N-CH); 2.40 (s, 3H, CH_3-Ar); 1.36 (d, 6H, 2CH_3, J = 6 Hz).

Trans-(±)-2,5-*dimethyl*-Δ³-*pyrroline hydrochloride*[(±)-*trans*-**3c**]

To a refluxing soln of 25g of compound, (±)-*trans*-**3b**, in 300 ml of n-amyl alcohol was added 30g of sodium in 1g portions. The portions of sodium were added after the preceding portion had completely reacted with the solvent. After the addition the solution was cooled and 300 ml of water was added. The layers were separated, the acqueous layer was extracted 6 times with ether and this was then washed with 2N HCl, the organic layer was extracted with 2N HCl. The combined acid extracts were evaporated under vacuum and residue obtained (10g) of (±)-*trans*-**3c** was crystallized from dry-EtOH-dray ether: m.p. 90–92° (hygroscopic). NMR (CD_3OD) δ: 5.88 (s, 2H, H-C=C-H); 4.60 (m, 2H, CH-N-CH); 1.44 (d, 6H, $2CH_3$, J = 6 Hz).

Cis-2,5-*dimethyl*-Δ³-*pyrroline hydrochloride*[cis-**3c**]

In the same way as *trans*-**3b**, the compound *cis*-**3b** was detosylated. The amine hydrochloride (cis-**3c**) obtained, was crystallized from EtOH–ether, m.p. 141–143°. NMR (CD_3OD) δ: 5.86 (s, 2H, H-C=C-H); 4.48 (q, 2H, CH-N-CH); 1.48 (d, 6H, $2CH_3$, J = 6 Hz).

Trans-(±)-*N*-*benzoyl*-2,5-*dimethyl*-Δ³-*pyrroline*[(±)-trans-**3d**]

The compound *trans*-**3c** was reacted with benzoyl chloride under Schotten–Baumann reaction conditions. The N-benzoyl-derivative obtained, *trans*-**3d**, was crystallized from petroleum ether, m.p. 68–70° (Found: C, 77.21; H, 7.39; N, 6.73. $C_{13}H_{15}NO$ requires: C, 77.58; H, 7.51; N, 6.96%). NMR ($CDCl_3$) δ: 7.40 (m, 5 Harom); 5.60 (m, 2H, H-C=C-H); 5.10–4.70 (br, 2H, CH-N-CH); 1.46 (d, 3H, CH_3, J = 6 Hz); 0.82 (d, 3H, CH_3, J = 6 Hz).

Cis-*N*-*benzoyl*-2,5-*dimethyl*-Δ³-*pyrroline*[cis-**3d**]

The compound *cis*-**3c** was reacted with benzoyl chloride under Schotten–Baumann reaction conditions. The N-benzoyl-derivative obtained, *cis*-**3d**, was an oil, b.p. 123°/0.03 mmHg. NMR ($CDCl_3$) δ: 7.38 (s, 5 Harom); 5.70 (s, 2H, H-C=C-H); 5.10–4.20 (br, 2H, CH-N-CH); 1.60–0.80 (br, 6H, $2CH_3$).

Trans-(±)-*N*-*benzyl*-2,5-*dimethyl*-Δ³-*pyrroline*[(±)-trans-**3e**]

By reduction, with $LiAlH_4$ in dry THF, of the compound *trans*-**3b**, was obtained a oil, trans-**3e**, b.p. 88°/3 mmHg (Found: C, 83.68; H, 9.26; N, 7.31. $C_{13}H_{17}N$ requires: C, 83.37; H, 9.15; N, 7.48%). NMR ($CDCl_3$) δ: 6.30 (m, 5 Harom); 5.66 (s, 2H, H-C=C-H); 3.80 (q, 2H, CH_2-Ar, J_{AB} = 14 Hz)[9]; 3.80 (m, 2H, CH-N-CH); 1.04 (d, 6H, $2CH_3$, J = 6 Hz).

Cis-*N*-*benzyl*-2,5-*dimethyl*-Δ³-*pyrroline*[cis-**3e**]

By reduction, with $LiAlH_4$ in dry THF, of the compound *cis*-**3d**, was obtained a oil, *cis*-**3e**, b.p. 100°/9 mmHg, NMR ($CDCl_3$) δ: 6.20 (m, 5 Harom); 5.48 (s, 2H, H-C=C-H); 3.80 (s, 2H, CH_2-Ar)[9]; 3.64 (m, 2H, CH-N-CH); 1.02 (d, 6H, $2CH_3$, J = 6 Hz).

Trans-[-(−)-2*R*,5*R*]-2,5-*dimethyl*-Δ³-*pyrroline hydrochloride*[(−)-**3c**]

The compound *trans*-**3c**, 10g, was dissolved in water (20 ml), containing sodium hydroxide, 4g. The free amine was extracted 5 times with ether. To combined etheral extracts was added a soln of diaceton-2-keto-L-(−)-gulonic-acid, 20g, in MeOH (20 ml). The resulting salt was filtered off, 27g, and crystallized from MeOH–ether, m.p. 170–173°. After three crystallizations†, the salt, $[\alpha]_D^{20}$ − 65° (c, 1.5% in MeOH), 10g, was dissolved in water, 20 ml, containing sodium hydroxide, 2g. The free amine was extracted with ether, 5 times. The ethereal extracts were washed with HC12N and then evaporated under vacuum. The residue obtained, 3g, of (−)-**3c**, was crystallized from dry EtOH–dry ether, m.p. 90–92° (hygroscopic), $[\alpha]_D^{20}$ − 143° (c, 1% in CH_3OH).

Trans-[-(−)-2*R*,5*R*]-2,5-*dimethylpyrrolidine hydrochloride*[(−)-**1c**] *from* [(−)-**3c**].

Hydrogenation of compound (−)-**3c**, 1.2g, was carried out at approx. 3 atm pressure and room temp., for 2 days, over Adams catalyst, 0.1g, in dry EtOH (70 ml). The resulting ppt, 1.2g, (−)-**1c**, was crystallized from EtOH–ether, m.p. 187–189°; $[\alpha]_D^{20}$ − 1.1 (c, 3.9% in CH_3OH); $[\alpha]_{340}^{20}$ − 15.7 (c, 5% in 1N HCl). (Found: C, 53.43; H, 10.56; N, 10.41. $C_6H_{14}NCl$ requires: C, 53.13; H, 10.40; N, 10.33%) NMR (CD_3OD) δ: 3.80 (m, 2H, CH-N-CH); 2.40–1.60 (br, 4H, CH_2-CH_2); 1.46 (d, 6H, $2CH_3$, J = 6 Hz).

[-(−)-2*R*,5*RS*]-2,5-*dimethylpyrrolidine*[(−)-cis,trans-**1a**] *from* [(−)-**2**]

Starting from *R*-(−)-1-methylpenthylamine, (−)-**2**, 5g, $[\alpha]_D^{20}$ − 3.2 (neat; d^{20} = 0.75) [Reported[6] $[\alpha]_D^{20}$ − 4.3 (neat)] (obtained from salt with L-(+)-tartaric acid), the 2,5-dimethylpyrrolidine was prepared by a known method.[3] The *cis,trans*-**1a**, 2g, was obtained, b.p. 107°/760 mmHg; $[\alpha]_D^{20}$ − 6.5 (neat, d^{20} = 0.82). The picrate exhibited m.p. 108–110° (benzene) (Found: C, 43.83; H, 4.88; N, 16.68. $C_{12}H_{16}N_4O_7$ requires: C, 43.91; H, 4.91; N, 17.07%).

The ratio 1:1 of the two *cis* and *trans* isomers was estimated by GLC analysis. The same ratio was also estimated by NMR spectra (in CD_3OD) of (−)-*cis,trans*-**1c** obtained in this reaction in comparison with (−)-*trans*-**1c** obtained from (−)-**3c** [δ: 1.46 (d, 6H, $2CH_3$, trans isomer); 1.46 (d, 6H, $2CH_3$, cis isomer)].

The optical purity of (−)-cis, trans-**1a** is low for the presence of the *cis* achiral isomer and because the optical purity of the starting product, (−)-**2**, is not maximum. The highest value of specific rotation, in 1N HCl is at 340 mm, $[\alpha]_{340}^{20}$ − 1.7 (c, 7%). At same wavelength, the product (−)-**1c**, obtained from (−)-**3c**, has $[\alpha]_{340}^{20}$ − 15.7 (c, 5% in HCl 1N).

Trans-[-(−)-2*R*,5*R*]-*N*-[2-*pyridyl*-*N*-*oxide*]-2,5-*dimethyl*-Δ³-*pyrroline*[(−)-**3f**]

The compound (−)-**3c** was reacted with 2-fluoropyridine-N-oxide in the usual way.[1] After purification an oil was obtained. B.p. 100°/0.1 mmHg; $[\alpha]_D^{20}$ − 65 (c, 0.7% in CH_3OH). The picrate exhibited m.p. 188–192° (EtOH) (Found: C, 48.34; H, 3.81; N, 16.27. $C_{17}H_{17}N_5O_8$ requires: C, 48.69; H, 4.09; N, 16.70%). NMR ($CDCl_3$) δ: 8.10 (m, 1 Harom, N-CH=); 7.30–6.60 (m, 3 Harom); 5.70 (s, 2H, H-C=C-H); 5.40 (br, 2H, CH-N-CH); 1.10 (d, 6H, $2CH_3$, J = 6 Hz). UV (c, 0.0138 in CH_3OH): λ_{max} 245 nm (log ε = 4.25); λ_{max} 275 (log ε = 3.86); λ_{max} 335 (log ε = 3.54). CD (c, 0.0142 in CH_3OH): $[\theta]_{375} \pm 0$; $[\theta]_{340} \pm 13000$; $[\theta]_{300} \pm 0$; $[\theta]_{257}$ + 31100; $[\theta]_{245} \pm 0$; $[\theta]_{225}$ − 48500.

Trans-[-(−)-2*R*,5*R*]-*N*-[2-*pyridyl*-*N*-*oxide*]-2,5-*dimethylpyrrolidine*[(−)-trans-**1f**]

The compound (−)-**1c**, obtained by reduction of (−)-**3c**, was reacted with 2-fluoropyridine-N-oxide in the usual way.[1] After purification an oil was obtained. B.p. 110°/0.1 mmHg; $[\alpha]_D^{20}$-107 (c, 1.4% in CH_3OH). NMR ($CDCl_3$) δ: 8.10 (*m*, 1 Harom, N-CH=); 7.24–6.60 (m, 3 Harom); 4.60–4.30 (br, 2H, CH-N-CH); 2.40–1.40 (br, 4H, CH_2-CH_2); 1.06 (d, 6H, $2CH_3$, J = 6 Hz). UV (c, 0.0138 in CH_3OH): λ_{max} 245 nm (log ε = 4.32); λ_{max} 277 (log ε = 3.90); λ_{max} 335 (log ε = 3.58). CD (c, 0.0138 in CH_3OH): $[\theta]_{375} \pm 0°$; $[\theta]_{340}$ − 13150; $[\theta]_{305} \pm 0$; $[\theta]_{280}$ + 24100; $[\theta]_{250}$ + 58200; $[\theta]_{237} \pm 0$; $[\theta]_{225}$ − 21400.

(−)-2*R*,5*RS*-*N*-[2-*pyridyl*-*N*-*oxide*]-2,5-*dimethylpyrrolidine*[(−)-cis,trans-**1f**]

The compound (−)-*cis,trans*-**1a**, obtained from *R*-(−)-1-*methylpenthylamine* (**2**), was reacted with 2-fluoropyridine-N-oxide in the usual way.[1] After purification an oil was obtained. B.p. 110°/0.1 mmHg; $[\alpha]_D^{20}$ − 11.6° (c, 1.4% in CH_3OH). NMR ($CDCl_3$) δ: 8.10 (m, 1 Harom, N-CH=); 7.24–6.60 (m, 3 Harom); 4.60–4.30 (br, 2H, CH-N-CH); 2.40–1.40 (br, 4H, CH_2-CH_2); 1.35 (d, 6H, $2CH_3$ of *cis*, J = 6 Hz); 1.06 (d, 6H, $2CH_3$ of *trans*, J = 6 Hz). UV (c, 0.0104 in CH_3OH): λ_{max} 245 (log ε = 4.29); λ_{max} 275 (log ε = 3.85); λ_{max} 337 (log ε = 3.62). CD in CH_3OH (c, 0.0624): $[\theta]_{380} \pm 0$; $[\theta]_{335}$ − 1160; $[\theta]_{300} \pm 0$; (c, 0.0208): $[\theta]_{275}$ + 1700; $[\theta]_{250}$ + 4200; $[\theta]_{240} \pm 0$; $[\theta]_{225}$ − 1400.

(−)-2*R*,6*RS*-2,6-*dimethylpiperidine*[(−)-cis,trans-**4a**]

Starting from R-(−)-1-methylhexylamine, (−)-**5**, 5g, $[\alpha]_D^{20}$ − 5.5 (neat; d^{20} = 0.76) [Reported[7] $[\alpha]_D^{20}$ − 6.7 (neat)] (obtained from salt

†The attempted resolution by means of L-(+)-dibenzoyltartaric acid gave no better results and, only after several crystallizations, we obtained in low yields an amine hydrochloride with $[\alpha]_D^{20}$ + 143 (c, 1% in CH_3OH).

with L-(+)-tartaric acid), the 2,6-dimethylpiperidine was prepared by a known method.[3] The *cis,trans*-**4a**, **2g**, was obtained, b.p. 128°/760 mmHg; $[\alpha]_D^{20} - 5.0$ (neat, $d^{20} = 0.84$), [Reported[5] $[\alpha]_D^{20} - 13.8$ (neat)]. NMR ($CDCl_3$) δ: 3.20–2.70 (br, 2H, CH-N-CH); 1.80–1.20 (7H, NH,CH_2-CH_2-CH_2); 1.10 (6H, $2CH_3$ of *trans*, J = 6 Hz); 1.08 (6H, $2CH_3$ of *cis*, J = 6 Hz). The picrate exhibited m.p. 151–153° (benzene). (Found: C, 46.01; H, 5.16; N, 16.50. $C_{13}H_{18}N_4O_7$ requires: C, 45.61; H, 5.30; N, 16.37%).

The ratio, 1:1, of the two *cis* and *trans* isomers was estimated by GLC analysis. The same ratio was also estimated by NMR spectra of product obtained in this reaction in comparison with the commercial *cis*-2,6-dimethylpiperidine. The optical purity of (−)-*cis,trans*-**4a** is low for the presence of the *cis* achiral isomer and because the optical purity of the starting product, (−)-5, is not maximum.

(−)-2*R*,6*RS*-*N*-*chloro*-2,6-*dimethylpiperidine*[(−)-cis,trans-**4g**]

The compound (−)-*cis*, *trans*-**4a**, $[\alpha]_D^{20} - 5.0$ (neat), was reacted with N-chlorosuccinamide as reported.[8] After purification an oil was obtained, $[\alpha]_D^{20} - 23.3°$ (c, 1.7% in dioxane). UV (c, 0.170 in dioxane): λ_{max} 275 (log $\epsilon = 2.57$). CD (c, 0.860 in dioxane): $[\theta]_{340} \pm 0$; $[\theta]_{275} - 510$; $[\theta]_{235} \pm 0$.

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