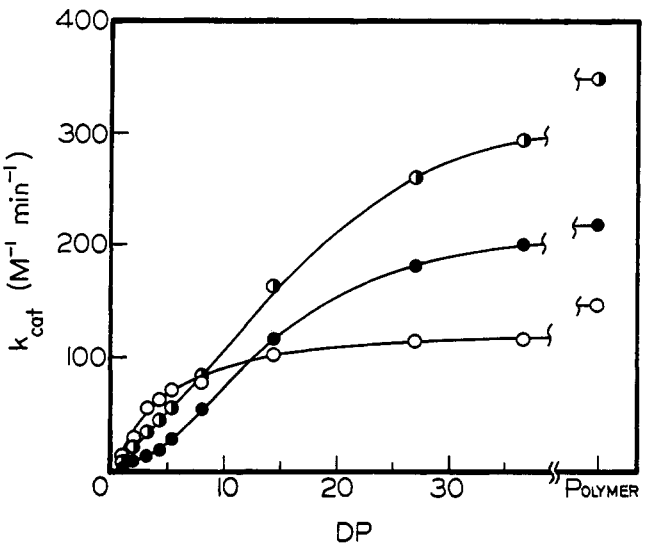

Figure 7. Plot of second-order rate constants *vs.* degree of polymerization of oligo(4(5)-vinylimidazole): (●) pH 5.5, (◑) pH 7.1, (○) pH 9.1.

highest pK_1 value, which is attributed to the inductive effect of the ethyl group. This compound may be expected to be the most active catalyst based on the Brönsted relationship.[17] However, the catalytic activity (k_{cat}/α_1) was much less than that of imidazole. The same phenomenon has been found in the catalyses of 2-methylimidazole and imidazole.[18] The reason for this may be that 2-ethylimidazole and 2-methylimidazole are sterically hindered in the hydrolysis of the ester, but not in the addition of a proton. The most sterically hindered compounds, **4b** and **4c**, had the smallest pK_1 values and no catalytic activity, indicating that these bulky groups exhibit a steric effect even for a proton.

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(17) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 170.
(18) T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **80**, 148 (1968).

Synthesis and Resolution of *cis*- and *trans*-5-Methylproline

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ABSTRACT: The synthesis and resolution of *cis*- and *trans*-5-methylproline are described. *cis*-5-Methylproline was synthesized by catalytic hydrogenation of Δ^1-2-methylpyrroline-5-carboxylic acid. The structural assignment was made by conversion of *cis*-5-methylproline to *cis*-2,5-dimethylpyrrolidine. A mixture of *cis*- and *trans*-5-methylproline was obtained by sodium borohydride reduction of Δ^1-2-methylpyrroline-5-carboxylic acid. The methylproline isomers can be separated by reaction with *p*-toluenesulfonyl chloride because the trans isomer only reacts slowly. The *cis*- and *trans*-5-methylproline enantiomeric pairs were resolved with tartaric acid. The absolute configurations of the diastereomers were determined by optical rotatory dispersion.

The biochemical and metabolic roles played by metabolites, analogs, homologs, and novel derivatives of proline have recently been the focus of many investigations. As a result, the synthetic routes to a wide variety of these compounds have been developed.[1]

Among the compounds described are the simple monomethyl derivatives of proline. Up to the time this work was undertaken, only the *cis*- and *trans*-3- and -4-methylprolines had been separated, resolved, and unequivocally characterized.[1] We wished to investigate the effect of a methyl group in the 5 position of proline on the conformational behavior of the polypeptides derived from this amino acid.[2]

5-Methylproline has been synthesized by ammonolysis of methyl 2,5-dibromocaproate,[3] by decarboxylation of diethyl Δ^1-2-methylpyrroline-5,5-dicarboxylate,[4] and by catalytic hydrogenation of Δ^1-2-methylpyrroline-5-carboxylic acid[5] or its ethyl ester.[4] The isomer of 5-methylproline obtained by catalytic hydrogenation is reported to have mp 188°,[4,5] while for the isomer synthesized by the two other methods, mp 207°[3,4] has been reported. The cis configuration has been assigned to the former and the trans configuration to the latter 5-methylproline by comparing the pK_a' values of the derived 1,5-dimethyl-2-pyrrolidine methanols.[6] In this paper this assignment is considered in more detail. Furthermore, we report a new synthesis, the separation of *cis*- and *trans*-5-methylproline, and the resolution of both isomers to give the optically active amino acids.

Synthesis and Separation of *cis*- and *trans*-5-Methylproline (Figure 1). The hydrochloride of Δ^1-2-methylpyrroline-5-carboxylic acid (II) was prepared by cyclization of ethyl 2-acetamido-2-carbethoxy-5-oxohexanoate (I) with hydrochloric acid. A variation of the method described in the literature[5] resulted in higher yields and a purer product. Catalytic hydrogenation gave predominantly one isomer of 5-methylproline hydrochloride (IIIa) as shown by the nmr spectrum and vapor-phase chromatography (vpc). The small amount of the other isomer present could be removed by recrystallization. The free amino acid (IVa) had mp 185–189° dec, which

(1) A. B. Mauger and B. Witkop, *Chem. Rev.*, **66**, 47 (1966), and references cited therein.
(2) C. G. Overberger and K.-H. David, *Macromolecules*, **5**, 373 (1972).
(3) K. Winterfeld and H. E. Rönsberg, *Arch. Pharm.*, **274**, 40 (1936).
(4) Y. Sanno, *Yakugaku Zasshi*, **78**, 1113 (1958).
(5) H. Gershon and A. Scala, *J. Org. Chem.*, **26**, 2347 (1961).
(6) T. Mizoguchi and I. Iijima, *Yakugaku Zasshi*, **85**, 641 (1965).

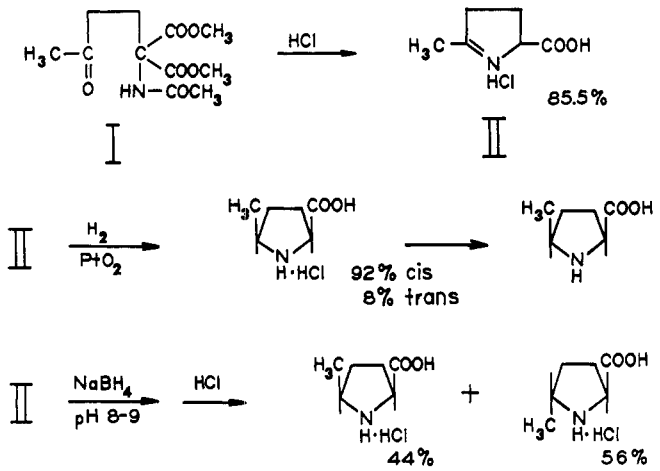


Figure 1. Synthesis of *cis*- and *trans*-5-methylproline.

is in good agreement with the reported value of 188°.[4,5] To determine its configuration, IVa was converted to *N*-benzyl-2,5-dimethylpyrrolidine (VIIIa) (Figure 2). Its nmr spectrum[7] identified VIIIa as the cis isomer. Therefore, IVa can be assigned as *cis*-5-methylproline, in accordance with the earlier assignment.[5]

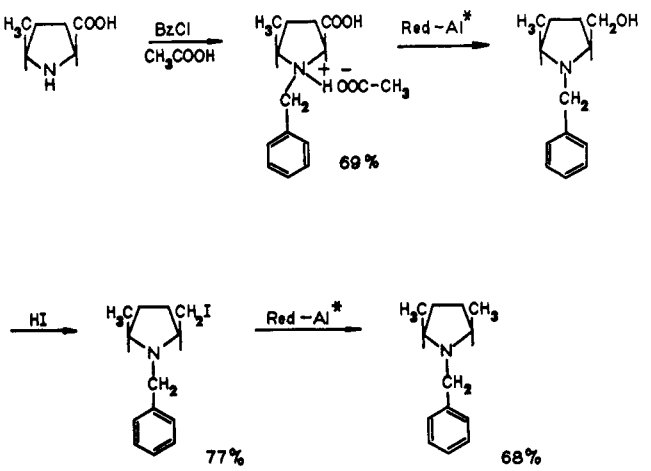
Reduction of II with sodium borohydride gave a mixture of *cis*- and *trans*-5-methylproline hydrochloride (IIIa and IIIb), as shown by nmr and vpc. We have found that the cis isomer forms a sulfonamide readily, while the trans isomer reacts very slowly, resulting in hydrolysis of the sulfonyl chloride in the aqueous system. This difference in reactivity was utilized to separate the isomers. Similar selective reactivity had been used to obtain the pure diastereomers of 3-methylproline.[8] The mixture of *cis*- and *trans*-5-methylproline was stirred with an equimolar amount of *p*-toluenesulfonyl chloride in a water–acetone solution for 24 hr (Figure 3). The sulfonamide IXa containing predominantly the cis isomer was extracted with ethyl acetate. The aqueous solution contained the *p*-toluenesulfonate salt of *trans*-5-methylproline (Xb). The free amino acid IVb was prepared by passing this salt over a weakly basic ion-exchange resin; recrystallized IVb had mp 218.5–219°. Vpc showed the complete absence of the cis isomer.

Since, in a recent paper,[6] the trans configuration has been assigned to 5-methylproline with mp 207° as obtained by decarboxylation of Δ^1-2-methylpyrroline-5,5-dicarboxylate[4] or ammonolysis of 2,5-dibromocaproate,[3] these syntheses were repeated. Nmr and vpc showed that in both reactions a mixture of cis and trans isomers is formed. The 5-methylproline of mp 207° to which the trans configuration had been assigned is a mixture of cis and trans isomers.

The sulfonamide IXa was hydrolyzed with hydrochloric acid to give a mixture of 77% *cis*- and 23% *trans*-5-methylproline.

Determination of the Cis–Trans Ratio. Vpc was used to determine the cis–trans ratio of various samples. The methyl esters of *cis*- and *trans*-5-methylproline could be separated on a 20-ft Carbowax 20M column at 200°. Under these conditions, however, the trans isomer decomposed partly while the cis isomer was stable. Therefore, the analytical samples were converted to *cis*- or *trans*-*N*-methyl-5-methylproline by reductive alkylation with formaldehyde and hydrogen over Pd/C.[9] Reaction with diazomethane gave the corresponding methyl esters, which could be separated on the

(7) R. K. Hill and T.-H. Chan, *Tetrahedron*, **21**, 2015 (1965).
(8) F. Irreverre, A. B. Mauger, and B. Witkop, *J. Amer. Chem. Soc.*, 87, 4975 (1965).
(9) R. E. Bowman and H. H. Stroud, *J. Chem. Soc.*, 1342 (1950).



*Red-Al = 70% solution of Na bis (2-methoxyethoxy) -Al hydride in benzene

Figure 2. Structure assignment for *cis*-5-methylproline.

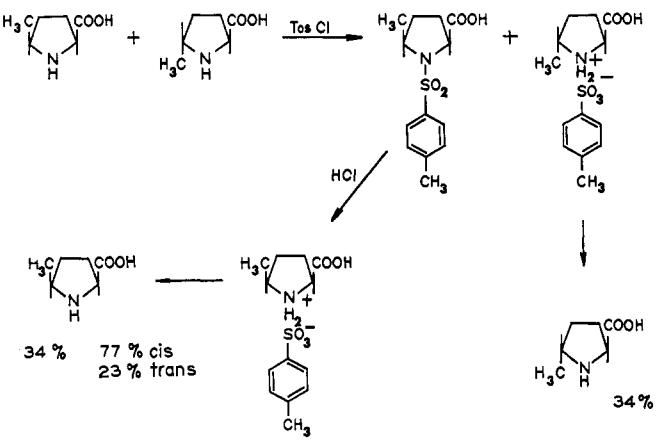


Figure 3. Separation of *cis*- and *trans*-5-methylproline.

same column at 145°. Vpc of samples prepared in this way showed that 5-methylproline obtained by catalytic hydrogenation contained 92% cis and 8% trans isomers. The recrystallized product was pure cis isomer. 5-Methylproline prepared by reduction with sodium borohydride contained 44% cis and 56% trans isomer. Pure *trans*-5-methylproline was obtained after separation with *p*-toluenesulfonyl chloride and recrystallization. The sulfonamide from the cis–trans separation gave, after hydrolysis, a mixture of 77% cis and 23% trans isomers.

Optical Resolution (Figure 4). The diastereomeric 5-methylprolines were resolved with L(+)-tartaric acid, in analogy with the resolution of pipecolic acid.[10] The 1:1 salt of *cis*-5-methylproline methyl ester and tartaric acid was formed in absolute methanol. The less soluble salt crystallized and was purified by four recrystallizations from absolute methanol. The specific rotation ([α]D) of this salt in water was +32.2° and the yield was 65% of the theoretical value for one enantiomer. Addition of potassium chloride to the aqueous solution of this salt caused precipitation of potassium tartrate. After hydrolysis of the ester group, (+)-*cis*-5-methyl-L-proline hydrochloride with [α]D +34.1° in water was obtained. The free amino acid had [α]D +69° in water. The levorotary salt was recrystallized five times from ace-

(10) F. Mende, *Ber.*, **29**, 2887 (1896).

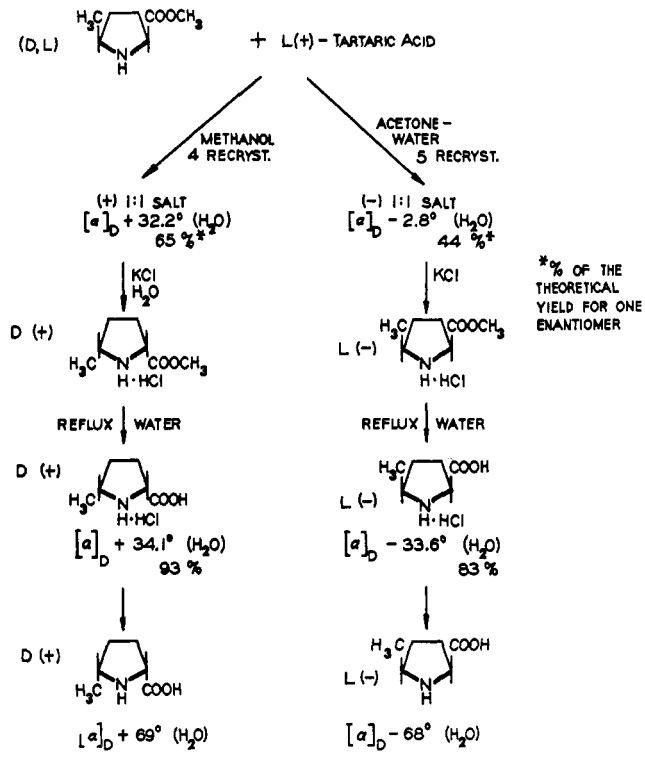


Figure 4. Resolution of *cis*-5-methylproline.

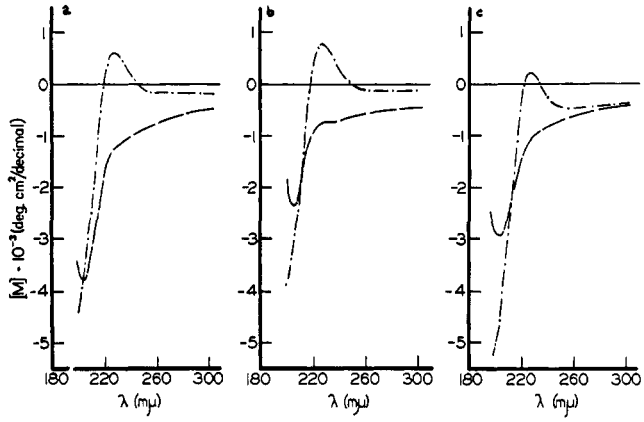


Figure 5. ORD spectra of (a) L-proline; (b) (−)-*cis*-5-methyl-L-proline; (c) (−)-*trans*-5-methyl-L-proline (--) and their hydrochlorides (-··-) in 95% ethanol.

tone–water solution and was obtained in 44% of the theoretical yield for one enantiomer, $[\alpha]_D$ −2.8° in water. (−)-*cis*-5-Methyl-L-proline hydrochloride and the free amino acid had $[\alpha]_D$ −33.6° and −68°, respectively. The 1:1 salt of *trans*-5-methylproline methyl ester and tartaric acid was formed in a methanol–acetone mixture. In this case, the levorotary salt was less soluble. Six recrystallizations from methanol–acetone were necessary to achieve a constant value of $[\alpha]_D$ −11.7° in water, in a yield of 20% of the theoretical value for one enantiomer. (−)-*trans*-5-Methyl-L-proline hydrochloride and the free amino acid have $[\alpha]_D$ −57.1° and −86.2° in water. Partially resolved (−)-*trans*-5-methylproline was recovered from the filtrates of the fractional crystallizations. The dextrorotary salt could not be obtained in crystalline form. Partially resolved (+)-*trans*-5-methylproline with $[\alpha]_D$ +50° was recovered in 51% of the theoretical yield for one enantiomer.

Determination of Absolute Configuration. Optical rotatory dispersion (ORD) can be used for a rapid assignment of the absolute configuration of α-amino acids.[11,12] L α-amino acids and their hydrochlorides show a trough near 200 mμ and a shoulder or a peak at higher wavelength. The ORD spectra of the D α-amino acids are symmetrically opposite to those of the L series.

Figure 5 describes the ORD spectra of L-proline, (−)-*cis*-5-methylproline, and (−)-*trans*-5-methylproline and their hydrochlorides. It can clearly be seen that all these amino acids belong to the L series. The ORD spectra of (+)-*cis*-5-methylproline and its hydrochloride were also recorded. They were symmetrically opposite to the spectra of the L compounds.

At this juncture, it is of interest to note the trend of values obtained for the positive extrema of the L series of amino acid hydrochlorides in question (taken from Figure 5).

Amino Acid	*cis*-Methyl	Proline	*trans*-Methyl
$[M]_\lambda \times 10^{-3}$	800_{220}	625_{218}[13]	200_{222}

Jorgensen[14] has recently proposed a sector rule for relating optical rotatory dispersion with the conformation and absolute configuration of α-anino acids. He attributes the low rotation for proline to a balancing of substituents among negative, null, and positive sectors, in relation to a presumed preferred conformation of proline. Jorgensen, in his discussion, concentrates upon substituents at the α or 2 position, since from his sector diagram such substitutions should give rise to the most perturbative interactions in a positive sector for the α-amino acids. In the proline case, it can be seen that the δ or 5 position is also critically substituted for maximum interaction with a *negative* sector. Preliminary considerations of molecular models of *cis*- and *trans*-5-methylproline and the above results appear to bear out this conjecture. Since the net result of interactions in proline is approximately balanced, deviations from the value of extreme rotation for proline observed upon simple substitution *must* reflect changes in the net balance. Thus the fact that, for *cis*- and *trans*-5-methylproline with respect to proline, the changes are in *opposite* directions supplies information on either the geometry of these molecules or the sectors. Since the cis isomer is more positive than proline, the methyl group must reside very near, or in, a null sector. Alternatively stated, the substitution of a methyl group in cis relationship disturbs the balance extant in proline toward a more positive value by decreasing the negative contributions to the net rotation. Similarly, since the trans isomer is less positive than proline, the methyl group must reside in or near a negative sector.

We cannot, at this point, make a definitive statement that the conformations of the molecules are changed by substitution or that the sectors are in fact curved. We are currently attempting to design experiments which will clarify this point.

Experimental Section

Δ¹-2-Methylpyrroline-5-carboxylic Acid Hydrochloride[5] (II). Ethyl 2-acetamido-2-carbethoxy-5-oxohexanoate[5] (481 g, 1.68 mol) was dissolved in 600 ml of methylene chloride. The solution was added dropwise over 4 hr to 1 l. of refluxing 6 *N* hydrochloric acid while methylene chloride was continuously distilled. After the addition, the solution was evaporated to dryness. The residue was repeatedly dissolved in water and evaporated to dryness to remove

(11) J. C. Craig and S. K. Roy, *Tetrahedron*, **21**, 391 (1965).
(12) E. Iizuka and J. T. Yang, *Biochemistry*, **3**, 1519 (1964).
(13) The value given here is higher than that reported previously[11] ($[\phi]_{225}$ = +410) and is blue shifted. These effects are presumably due to the solvent, *i.e.*, 95% ethanol was used in this work, while the quoted value was obtained in water.
(14) E. C. Jorgensen, *Tetrahedron Lett.*, 863 (1971).

hydrochloric acid. The crystalline residue was dissolved in water, decolorized with charcoal, and again evaporated to dryness. It was dissolved in 700 ml of methanol, precipitated with ether, and cooled: 211.5 g of II (77%), mp 191–193° dec. A second crop of 23 g of I (8.5%), mp 140–150°, was obtained from the filtrate. Recrystallization from methanol–ether gave II with mp 192–194° dec (lit.[5] 193° dec); nmr (D_2O) 2.58 (d, J = 1.5 Hz, CH_3), 3.22 (m, CH_2) 5.22 ppm (m, CH).

Anal. Calcd for $C_6H_{10}NO_2Cl$ (mol wt 163.61): C, 44.05; H, 6.16; N, 8.56; Cl, 21.67. Found: C, 44.13; H, 6.12; N, 8.42; Cl, 21.65.

***cis*-5-Methylproline Hydrochloride (IIIa).** II (211.5 g, 1.29 mol) was dissolved in 800 ml of water and hydrogenated over 1 g of platinum oxide for 12 hr at 35 psi. The catalyst was removed by filtration and the solution was evaporated to dryness. Vpc after conversion to the appropriate derivative (*vide infra*) showed a mixture of 92% cis and 8% trans isomer. Recrystallization from a 1-l. methanol–ether 1:1 solution gave 123.5 g of pure IIIa (58%), mp 185–188°; after a second recrystallization, mp 189–190° (lit.[5] 184–188°). A second crop of 59 g (28%), mp 183–185°, and a third crop of 30 g (14%), of sticky material were obtained from the filtrate: nmr (D_2O) 1.44 (d, J = 6.6 Hz, CH_3), 2.32 (m, CH_2), 3.87 (m, α-CH), 4.50 ppm (m, δ-CH).

Anal. Calcd for $C_6H_{12}NO_2Cl$ (mol wt 165.63): C, 43.51; H, 7.30; N, 8.46; Cl, 21.41. Found: C, 43.56; H, 7.26; N, 8.52; Cl, 21.29.

***cis*-5-Methylproline (IVa).** IIIa was dissolved in water and passed through a column of Amberlite IR-45, a weakly basic ion-exchange resin in the hydroxyl form. The free amino acid was eluted with water. After two recrystallizations from methanol–ether (1:1), mp 185–189° dec (lit.[5] 188–189°) was obtained.

Anal. Calcd for $C_6H_{11}NO_2$ (mol wt 129.16): C, 55.79; H, 8.59; N, 10.85. Found: C, 55.83; H, 8.48; N, 10.94.

***N*-Benzyl-*cis*-5-methylproline Acetate (Va).** IVa (8.5 g, 0.066 mol) was dissolved in a mixture of 6.5 g of potassium hydroxide, 40 ml of water, 50 ml of ethanol, and 30 ml of benzyl chloride and stirred overnight at room temperature.[15] The solution was refluxed for 1 hr, evaporated to dryness, made alkaline, neutralized with acetic acid, and again evaporated to dryness. The residue was extracted with hot acetone. The combined acetone fractions were evaporated and the residue was twice crystallized from acetone–ether to give 12.7 g of Va (69%), mp 120–123°; nmr ($CDCl_3$) 1.39 (d, J = 6.4 Hz, 5-CH_3), 2.13 (m, ring CH_2), 3.33 and 3.97 (m, CH), 4.30 (s, benzylic CH_2), 7.37 (s, aromatic H), 2.0 (s, acetate), 10.85 ppm (2 H, s, COOH, NH).

Anal. Calcd for $C_{15}H_{21}NO_4$ (mol wt 279.34): C, 64.50; H, 7.58; N, 5.01. Found: C, 64.54; H, 7.59; N, 5.16.

***N*-Benzyl-*cis*-2-methyl-5-hydroxymethylpyrrolidine (VIa).** Va (1 g, 3.6 mmol) suspended in 20 ml of dry benzene was reduced with 2.5 g (8 mmol) of a 70% solution of sodium bis(2-methoxyethoxy)-aluminum hydride in benzene (Red-Al, Aldrich Chemical Co.). After stirring for 2 hr at room temperature, excess hydride was destroyed with 1 N sodium hydroxide, and benzene was evaporated to give crude VIa. Its structure was confirmed by nmr ($CDCl_3$): 1.04 (3 H, d, J = 6 Hz, CH_3), 1.73 (4 H, m, ring CH_2), 2.84 (2 H, m, CH), 3.25 (2 H, d, J = 3.3 Hz, α-CH_2), 3.73 (2 H, d, J = 3 Hz, benzyl CH_2), 7.28 (5 H, s, phenyl H), 2.81 ppm (1 H, s, OH).

***N*-Benzyl-*cis*-2-methyl-5-iodomethylpyrrolidine (VIIa).** Crude VIa was refluxed for 24 hr with 20 ml of 47% hydroiodic acid. The solution was evaporated to dryness and the residue was crystallized from acetone. VIIa was obtained (868 mg, 77% of theory based on Va) as a white powder which became colored during drying at room temperature *in vacuo*. The ir spectrum showed the absence of an OH band.

***N*-Benzyl-*cis*-2,5-dimethylpyrrolidine (VIIIa).** VIIa (558 mg, 1.8 mmol) was suspended in 20 ml of benzene and reduced with 500 mg (1.8 mmol) of a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene at room temperature. The solution was refluxed overnight and then hydrolyzed with 1 N NaOH. The benzene solution was dried over magnesium sulfate and evaporated to dryness. VIIIa, 228 mg (68%), was obtained as a colorless liquid which darkened on exposure to air. The structure was confirmed by nmr to be *cis*-VIII. The nmr spectrum of *cis*-VIII shows a singlet for the benzylic protons at τ 6.30 (3.70 ppm), while *trans*-VIII shows an AB quartet at τ 6.37 (3.63 ppm);[7] nmr (CCl_4) 0.95 (6 H, d, J = 6 Hz, CH_3), 1.55 (4 H, m, ring CH_2), 2.55 (2 H, m, CH), 3.60 (2 H, s, benzylic CH_2), 7.10 ppm (5 H, s, phenyl H).

***cis*- and *trans*-5-Methylproline Hydrochloride (IIIa and IIIb) by Sodium Borohydride Reduction.** II (229 g, 1.4 mol) and 215 g (1.56 mol) of potassium carbonate were dissolved in 700 ml of water. A solution of 54 g (1.43 mol) of sodium borohydride and 27 g (0.195 mol) of potassium carbonate in 400 ml of water was added dropwise at 0–5°. The solution was stirred overnight, acidified with hydrochloric acid, and evaporated to dryness. The residue, a mixture of IIIa and IIIb, was extracted with absolute ethanol.

The nmr spectrum showed two doublets for the methyl group at 1.42 (trans) and 1.44 ppm (cis) in D_2O and at 1.33 (cis) and 1.36 ppm (trans) in DMSO-d_6, of approximately equal intensity. Vpc showed a mixture of 44% cis and 56% trans isomer.

Separation of the Isomers. The crude mixture of IIIa and IIIb was dissolved in 700 ml of water containing 380 g (4.5 mol) of sodium bicarbonate. *p*-Toluenesulfonyl chloride, 275 g (1.45 mol), in 350 ml of acetone was added over 2 hr. The solution was stirred overnight, the acetone was evaporated, and the aqueous solution was acidified with hydrochloric acid. The sulfonamide IXa was extracted with ethyl acetate. The aqueous solution was evaporated to dryness and the *p*-toluenesulfonate salt of *trans*-5-methylproline was extracted with acetone. It was dissolved in water, decolorized with charcoal, poured on a column of Amberlite IR-45 (hydroxyl form), and eluted with water. Crude IVb was dissolved in chloroform and the water was removed by azeotropic distillation. The solution was then concentrated to 150 ml and the amino acid was precipitated with ether to yield 62 g of IVb (34%), mp 190–194° dec. Vpc after conversion to the appropriate derivative showed less than 1% of the cis isomer. Two recrystallizations from methanol–ether gave mp 218.5–219° for the pure trans isomer.

Anal. Calcd for $C_6H_{11}NO_2$ (mol wt 129.16): C, 55.79; H, 8.59; N, 10.85. Found: C, 55.63; H, 8.61; N, 10.87.

***trans*-5-Methylproline hydrochloride (IIIb)** had mp 152–153° dec after recrystallization from methanol–ether; nmr (D_2O) 1.42 (d, J = 6.8 Hz, CH_3), 2.25 (m, CH_2), 3.80 (m, α-CH), 4.50 ppm (m, δ-CH).

Anal. Calcd for $C_6H_{12}NO_2Cl$ (mol wt 165.63): C, 43.51; H, 7.30; N, 8.46; Cl 21.41. Found: C, 43.72; H, 7.38; N, 8.38; Cl, 21.50.

***N*-Tosyl-*cis*-5-methylproline (IXa).** A small portion of crude IXa from the separation of the isomers was crystallized from methanol–water. Two recrystallizations gave IXa with mp 157–159°. The sample melted at 158–160° after sublimation at 100° [(0.5 mm); nmr ($CDCl_3$) 1.37 (d, J = 6.4 Hz, 5-CH_3), 1.80 (m, CH_2), 2.43 (m, aromatic CH_3), 3.80 and 4.23 (m, CH), 7.55 (q, aromatic H), 10.65 ppm (s, COOH).

Anal. Calcd for $C_{13}H_{17}NO_4S$ (283.35): C, 55.10%; H, 6.05%; N, 4.94%; S, 11.32%. Found: C, 55.01%; H, 6.06%; N, 4.82%; S, 11.27%.

Hydrolysis of Sulfonamide IXa. Crude IXa was refluxed for 48 hr with 6 N hydrochloric acid. The solution was evaporated to dryness and the residue was dissolved in water and evaporated to dryness several times to remove excess hydrochloric acid. After decolorizing with charcoal, the solution was passed through a column of Amberlite IR-45 (hydroxyl form) and eluted with water. Crude 5-methylproline, 61 g (34%), was obtained. Vpc after conversion to the appropriate derivative showed a mixture of 77% cis and 23% trans isomer.

***cis*-5-Methylproline Methyl Ester Hydrochloride (XIa).** IIIa was dissolved in absolute methanol and the solution was saturated with gaseous hydrochloric acid. After 24 hr, the solvent was evaporated *in vacuo* and the residue was repeatedly dissolved in methanol and evaporated to dryness to remove excess hydrochloric

(15) L. Velluz, G. Amiard, and R. Heymes, *Bull. Soc. Chim. Fr.*, 201 (1955).

acid. The yield of XIa, mp 176° dec after recrystallization from methanol–ether, was quantitative; nmr (D_2O) 1.44 (d, J = 6.8 Hz, CH_3), 2.33 (m, CH_2), 3.85 ppm (s, OCH_3), CH obscured by OCH_3 and water.

Anal. Calcd for $C_7H_{14}NO_2Cl$ (mol wt 179.65): C, 46.80; H, 7.85; N, 7.80; Cl, 19.74. Found: C, 46.95; H, 7.74; N, 7.73; Cl, 19.84.

***trans*-5-Methylproline Methyl Ester Hydrochloride (XIb).** XIb was prepared from IVb analogously to XIa, mp 135.5–136.5° dec.

Anal. Calcd for $C_7H_{14}NO_2Cl$ (mol wt 179.65): C, 46.80; H, 7.86; N, 7.80; Cl, 19.74. Found: C, 46.90; H, 7.97; N, 7.73, Cl, 19.84.

Resolution of *cis*-5-Methylproline. Finely powdered XIa (211.5 g, 1.18 mol) was suspended in 1 l. of absolute ether. Triethylamine (119 g, 1.18 mol) was added over 1 hr with vigorous stirring. After 2 hr, the solution was cooled in an ice bath and filtered from triethylamine hydrochloride. The triethylamine hydrochloride was suspended in 1 l. of ether, refluxed for 30 min, cooled, and filtered. The combined filtrates were concentrated at reduced pressure at a bath temperature not exceeding 30°. Liquid *cis*-5-methylproline methyl ester (XIIa) (158.8 g, 1.11 mol, 94%) remained. To XIIa, dissolved in 1 l. of absolute methanol, was added 166.5 g (1.11 mol) of tartaric acid in 1 l. of absolute methanol. The solution was heated almost to boiling. Upon cooling, 152 g of a dextrorotary salt with $[\alpha]_D$ +30° crystallized. After three recrystallizations from absolute methanol, 105.5 g of (XIII), mp 159–161° dec (65% of the theoretical yield for one enantiomer), with $[\alpha]_D$ +32.2° remained.

Anal. Calcd for $C_{11}H_{19}NO_8$ (mol wt 293.28): C, 45.05; H, 6.53; N, 4.78. Found: C, 45.14; H, 6.59; N, 4.57.

The filtrate from the first crystallization was evaporated to dryness. The oily residue was stirred with a refluxing mixture of 50 ml of methanol and 500 ml of acetone. The oil crystallized on cooling. An additional 250-ml increment of acetone was added. A salt (161.5 g) with $[\alpha]_D$ +3.14° was collected after cooling for several hours. Five recrystallizations from a mixture of acetone–water (9:1) gave 72 g of a levorotary salt (XIV), mp 72–73°, with $[\alpha]_D$ −2.8°. This is 44% of the theoretical yield for one enantiomer.

(+)-*cis*-5-Methyl-D-proline Hydrochloride (XV) and (+)-*cis*-5-Methyl-D-proline (XVI). Potassium chloride (27 g, 0.36 mol) in 100 ml of hot water was added to XIII (105.3 g, 0.36 mol) in 200 ml of hot water. Acetone (300 ml) was added and the solution was cooled overnight. The potassium tartrate was filtered and the filtrate was evaporated to dryness. The residue was redissolved in 300 ml of water and was refluxed for 1 hr to hydrolyze the methyl ester completely. The residue was crystallized from methanol–ether after evaporation to dryness to yield 42.3 g of XV (71.2%), mp 190.5–192°, $[\alpha]_D$ +34.1°.

The filtrate from the crystallization was evaporated to dryness and the residue was dissolved in water and passed through an Amberlite IR-45 column (hydroxyl form). Crude XVI, 11.5 g (24.7%), was obtained, bringing the total yield of amino acid and hydrochloride to 95.9%.

Two recrystallizations gave the free amino acid with mp 202–203°, $[\alpha]_D$ +69.5°.

Anal. Calcd for $C_6H_{11}NO_2$ (mol wt 129.16): C, 55.79; H, 8.59; N, 10.85. Found: C, 55.95; H, 8.56; N, 10.90.

(−)-*cis*-5-Methyl-L-proline Hydrochloride (XVII) and (−)-*cis*-5-Methyl-L-proline (XVIII). The liberation of the amino acid from the levorotary salt was performed in the same way as described for the dextrorotary salt: from 69.5 g of XIV was obtained 21 g of XVII, mp 190–191°, $[\alpha]_D$ −33.6°, and 9 g of XVIII, mp 200–200.5° dec, $[\alpha]_D$ −68°. The total yield was 83%.

Resolution of *trans*-5-Methylproline. The resolution was performed analogously to the resolution of the cis isomer. The salt from 43.5 g of *trans*-5-methylproline methyl ester and 45.5 g of tartic acid was formed in 120 ml of acetone containing 15% methanol. A salt, 43 g, with $[\alpha]_D$ +3.35°, crystallized. A constant $[\alpha]_D$ −11.7° was reached after six recrystallizations from acetone–methanol. The yield of levorotary salt was 9.0 g, *i.e.*, 20% of the theoretical yield for one enantiomer, mp 132–136.5°.

The dextrorotary salt could not be obtained in crystalline form. Partially resolved *trans*-5-methylproline, 10 g, with $[\alpha]_D$ +50°, was recovered from the first filtrate.

(−)-*trans*-5-Methyl-L-proline Hydrochloride (XIX) and (−)-*trans*-5-Methyl-L-proline (XX). The free amino acid and its hydrochloride were recovered from the tartaric acid salt in the same way as described for the cis isomer: 9 g of the levorotary salt gave 4.2 g of XIX (86%), mp 180°, $[\alpha]_D$ −57.1°. XX had mp 227° and $[\alpha]_D$ −86.2°.

Anal. Calcd for $C_6H_{11}NO_2$ (XX, mol wt 129.16): C, 55.79; H, 8.59; N, 10.85. Found: C, 55.95; H, 8.64; N, 10.78.

***cis*-*N*-Methyl-5-methylproline (XXIa).** *cis*-5-Methylproline (3 g, 0.023 mol) in 50 ml of water containing 6 ml of 40% formaldehyde solution and 1 g of 5% Pd/C was hydrogenated for 24 hr at 60 psi. The solution was filtered through Celite, evaporated to dryness, and repeatedly redissolved and evaporated to remove unreacted formaldehyde. Two crystallizations from acetone–ether gave XXIa, 3.5 g (61.5%), mp 105–109°. Sublimation at 80° (0.5 mm) raised the melting point to 109–110°; nmr ($CDCl_3$) 1.54 (d, J = 6.4 Hz, 5-CH_3), 2.1 (m, CH_2), 2.83 (s, N-CH_3), 3.1 and 3.6 ppm (m, CH).

Anal. Calcd for $C_7H_{13}NO_2$ (mol wt 143.19): C, 58.72; H, 9.15; N, 9.78. Found: C, 58.69; H, 9.14; N, 9.82.

***cis*-*N*-Methyl-5-methylproline Methyl Ester (XXIIa).** The methyl esters was prepared by adding diazomethane to a solution of XXIa in absolute methanol until a yellow color persisted. The excess diazomethane was removed *in vacuo:* nmr ($CDCl_3$) 1.39 (d, J = 6.6 Hz, 5-CH_3), 2.94 (s, N-CH_3), 3.38 (s, 5-CH_3), 2.34 (m, CH_2), 3.5–4.4 ppm (m, CH).

***trans*-*N*-Methyl-5-methylproline Methyl Ester (XXIb).** This compound was prepared analogously to XXIa, mp 153–156° from acetone. The melting point was unchanged after sublimation at 120° (0.5 mm); nmr ($CDCl_3$) 1.31 (d, J = 6.8 Hz, 5-CH_3), 2.77 (s, N-CH_3), 2.25 (m, CH_2), 3.6–4.4 ppm (m, 5-CH_3).

Anal. Calcd for $C_7H_{13}NO_2$ (mol wt 143.19): C, 58.72; H, 9.15; N, 9.78. Found: C, 58.57; H, 9.08; N, 9.88.

***trans*-*N*-Methyl-5-methylproline Methyl Ester (XXIIb).** This compound was prepared analogously to XXIIa: nmr ($CDCl_3$) 1.05 (d, J = 6.4 Hz, 5-CH_3), 2.38 (s, N-CH_3), 3.70 (s, OCH_3), 2.0 (m, CH_2), 3.0–3.7 ppm (m, CH).

Vapor-Phase Chromatography. Methylproline (100 mg) or its hydrochloride was dissolved in 20 ml of water containing 0.5 ml of 40% formaldehyde solution and 100 mg of 5% palladium on charcoal. The mixture was hydrogenated for 24 hr at 50 psi and room temperature. The catalyst was filtered and the solution was repeatedly evaporated to dryness and redissolved in water to remove excess formaldehyde. Finally, the residue was dissolved in absolute methanol and diazomethane in ether was added until a yellow color persisted. The excess diazomethane was removed *in vacuo* at room temperature.

cis- and *trans*-*N*-Methyl-5-methylproline methyl esters could be separated on a 20 ft × 0.25 in. column of 10% Carbowax 20M on Chromosorb W at 145° with a helium flow rate of 150 ml/min. The retention times were 9.5 min for the trans isomer and 10.5 min for the cis isomer. The percentages of cis and trans isomers were calculated from the heights of the peaks. For a test mixture of 50% *cis*- and 50% *trans*-5-methylproline treated as described above, 49.7% trans isomer and 50.3% cis isomer were found.

Optical Rotation Measurements. Optical rotations were measured with a Bendix automatic polarimeter, Model 143A, at room temperature using a 0.2-dm cell. Concentrations were 2 g/100 ml in water

ORD measurements were made with a Durrum-Jasco ORD-UV 5 spectrophotometer at room temperature using a 0.1-mm fused-silica cell. Concentrations for the amino acids or their hydrochlorides were about 10 mg/ml.

Nmr. Nmr spectra were taken with a Varian Model T-60 spectrophotometer at 35°. TMS or sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used as an internal standard.

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