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Medicinal Chemical Studies on Antiplasmin Drugs. II.[1] Separation of Stereoisomers of 4-Aminomethylcyclohexanecarboxylic Acid and Assignment of Their Configuration[2]

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The stereoisomers of 4-aminomethylcyclohexanecarboxylic acid (I) and (II) were completely separated from their mixture, respectively, and it is proved that lower-melting isomer has the *cis*-configuration and higher-melting isomer whose antiplasmin activity is much potent has the *trans*-configuration.

The preceding paper[1] reported the assay method for antiplasmin activity of various ω-aminoacids, showing that the activity of *trans*-4-aminomethylcyclohexanecarboxylic acid was most potent. It was estimated to be about 50 times more potent than that of *cis*-isomer and 5—7 times more than that of ε-aminocaproic acid. The present paper deals with the separation of two forms of 4-aminomethylcyclohexanecarboxylic acid (AMCHA), the assignment of their configurations, and the syntheses thereof.

The reduction of *p*-aminomethylbenzoic acid with sodium and amyl alcohol[4] afforded AMCHA which was also prepared by the catalytic hydrogenation with platinum[5,6] or rhodium[7] of *p*-aminomethylbenzoic acid or *p*-cyanobenzoic acid.[8] The stereoisomers of AMCHA, however, have been little studied except by Einhorn[4] who obtained two forms of isomers, designated α and β, whose configurations have remained speculative.

Since the preliminary experiment of the high pressure catalytic hydrogenation of *p*-aminomethylbenzoic acid over Raney nickel did not afford AMCHA, the same catalytic hydrogenation was applied to N-acetylated *p*-aminomethylbenzoic acid and its ester. The hydrogenated products were hydrolyzed to AMCHA, whose physical properties were in agreement with the data described by S. Okamoto, *et al.*[9] and Mangyo.[10] Boiling of AMCHA with cupric carbonate in aqueous solution gave the sparingly soluble and deep-blue precipitates which were presumably a complex salt of copper with AMCHA. After decomposition of the precipitated copper salt with ionic exchange resin in diluted aqueous ammonia, the lower-melting compound I, mp 236—238° (decomp.) was obtained by recrystallization. On the other hand, crystallization of resulting mixture obtained from the mother liquor of the above copper salt gave the higher-melting compound II, mp 386—392° (decomp.). Recrystallization had to be repeated many times to get pure compound II because of the difficulty in removing a

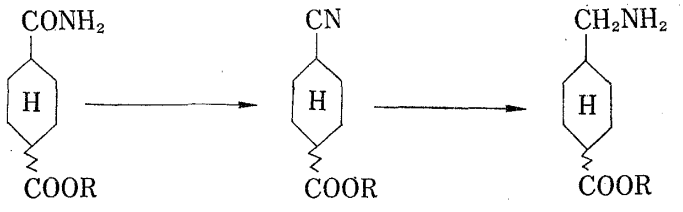
1) Part I: *Chem. Pharm. Bull.* (Tokyo), **16**, 357 (1968).
2) Preliminary communication of this work appeared in *Chem. Pharm. Bull.* (Tokyo), M. Shimizu, T. Naito, A. Okano, and T. Aoyagi, **13**, 1012 (1965).
3) Location: *Minamifunaboricho, Edogawa-ku, Tokyo.*
4) A. Einhorn, and C. Ladisch, *Ann.* **310**, 194 (1900).
5) E. Takagi, M. Yokoi, and M. Mangyo, Japan. Patent 242664 (1957).
6) M. Levine and R. Sedlecky, *J. Org. Chem.*, **24**, 115 (1957).
7) M.N. Bogdanov, G.I. Kudryavisev, F.M. Mandosova, I.A. Spirina, and D.E. Ostromogolskii, *Vysomolekul. Sodin.*, **3**, 1326 (1961).
8) E. Takagi, M. Yokoi, and M. Mangyo, Japan. Patent 240611 (1958).
9) S. Okamoto and U. Okamoto, *Keio J. Med.*, **11**, 105 (1962).
10) M. Mangyo, *J. Japan. Biochem. Soc.*, **36**, 735 (1964).

small amount of I from impure crystals of II. Subsequently the authors found it very convenient to use *p*-toluenesulfonic acid in separation, because the salts of I and II showed a great difference in solubility. The purities of I and II were established by thin-layer chromatography and gas chromatography.[11] The compounds I and II showed the same analytical value and the same *Rf* values on paper chromatography, but the infrared spectra of them were not identical. Melting points of their several derivatives are shown in Table I.

The comparison of the following physical properties between I and II led to suggestion that I and II would be assigned to *cis*- and *trans*-forms, respectively. (1) The difference of the acidic pK_a values between I (pK_{a1} 4.51) and II (pK_{a1} 4.33) were in correspondence with the difference of the ionization constants between *cis*- and *trans*-4-methylcyclohexanecarboxylic acids.[12] (2) *Rf* value of I was larger than that of II on thin-layer chromatography. This difference is assumed to depend on different affinity for adsorbents between equatorial and axial group at cyclohexane ring.[13] II was more strongly adsorbed on silica-gel than I, presumably bacause the aminomethyl and the carboxyl groups in II with their affinities for the adsorbent were more exposed in diequatorial form. (3) In the nuclear magnetic resonance spectra of I and II it was confirmed that the half-intensity width of the resonance absorption peak attributed to the ring protons was considerably greater in II than in I.This relation was in agreement with the observation of stereoisomers of various 1,4-disubstituted cyclohexane derivatives.[14]

Chemical experiments, on the other hand, were conducted to note the difference in chemical behavior between I and II. The isomerization of I with alkaline aqueous solution at 200° gave the equilibrium mixutre in which II was predominantly contained, and then II was easily isolated by fractional crystallization. The potassium permanganate oxidation of I and II in the solution of 0.26 N sodium carbonate at room temperature afforded *cis*- and *trans*-hexahydroterephthalic acids,[15] respectively. These facts also supported the assignment presumed from the physical properties described above.

The syntheses of I and II were performed to obtain additional evidence confirming their configuration as shown in Chart 1. Reaction of *cis*- or *trans*-4-carbamoylcyclohexanecarboxylic acid (III or IV)[16] with thionyl chloride gave *cis*- or *trans*-4-cyanocyclohexanecarboxylic acid (VII or VIII).[17] Hydrogenation of the cyano compounds in the presence of Raney nickel



	cis	*trans*	*cis*	*trans*	*cis*	*trans*
R: H	III	IV	VII	VIII	I	II
R: CH_3	V	VI	IX	X	XI	XII

Chart 1. Syntheses of Stereoisomers of 4-Aminomethylcyclohexanecarboxylic acid

11) Gas chromatographic analysis of AMCHA will be reported in future.
12) J.F.J. Dippy, S.R.C. Hughes, and J.W. Laxton, *J. Chem. Soc.*, **1954**, 4102.
13) H. Feltkamp and F. Koch, *J. Chromatog.*, **15**, 314 (1964).
14) S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).
15) R. Malachowski and J. Jankiewiczówna, *Ber.*, **67**, 1783 (1934).
16) J. Siegel and J.M. Komarmy, *J. Am. Chem. Soc.*, **82**, 2547 (1960).
17) B. Rickborn, *et al.*[18] confirmed by gas chromatographic analysis that thionyl chloride did not raise any change of configuration in dehydration of carboxamido group to cyano group in substituted cyclohexane compounds.
18) B. Rickborn and F.R. Jensen, *J. Org. Chem.*, **27**, 4608 (1962).

gave readily aminomethyl compounds which were identified with I and II, respectively, by the comparison of melting point, infrared spectrum, nuclear magnetic resonance spectrum, thin-layer chromatography, *etc.* It became clear that lower-melting compound I was synthesized from *cis*-isomer, III and higher-melting compound II was from *trans*-isomer IV. The reactions carried out in the above syntheses can be definitely accepted to take place without any change of configuration at the cyclohexane ring. Thus it follows that I has to be *cis*-configuration[19] and II the *trans*-configuration. These all results of physical and chemical experiments drew the same conclusion.

The crystal structures of hydrohalides of both isomers were also determined by X-ray diffraction method.[20]

Table I. Melting Points of AMCHA and Its Derivatives (mp °C)

Compounds	*cis*-isomer	*trans*-isomer
AMCHA	236—238 (decomp.)	386—392 (decomp.)
Hydrochloride	195—197 (decomp.)	238—242 (decomp.)
Hydrobromide	205—208 (decomp.)	227—229 (decomp.)
Tosylate	177—178	262—264
HCl-$PtCl_4$	233 (decomp.)	254—255 (decomp.)
HCl-$AuCl_3$	178—180 (decomp.)	205—206 (decomp.)
N-Acetate	189—190	154—155
N-Benzoate	157—158	177—178

Experimental[21]

Methyl *p*-Acetamidomethylbenzoate——A suspension of 4 g (0.02 mole) of *p*-acetamidomethylbenzoic acid in 40 ml of MeOH containing 4 g (0.11 mole) of dry HCl was refluxed for 45 min until the solid had dissolved. The reaction mixture was then concentrated to syrup *in vacuo*, 50 ml of $CHCl_3$ was added, and the chloroform solution was washed with H_2O, 2% NaOH and H_2O, respectively. After drying with Na_2SO_4, the chloroform solution was evaporated to dryness. The dry residue was washed with *n*-hexane; yield, 3.5 g (82% of theory); mp 110—112°. *Anal.* Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.89; H, 6.33; N, 7.01.

Ethyl *p*-Acetamidomethylbenzoate——Ethyl ester was prepared in the same manner described above; mp 98—99. *Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.78; H, 6.73; N, 6.40.

4-Aminomethylcyclohexanecarboxylic Acid (AMCHA)

a) From ethyl *p*-acetamidomethylbenzoate: A solution of 5 g (0.023 mole) of ethyl *p*-acetamidomethylbenzoate in 35 ml of ethanol was hydrogenated over 4 g of Raney nickel in autoclave at 180° for 3 hr. The initial pressure of hydrogen was 65 atm/cm². The reaction mixture was filtered, and the filtrate was condensed. The sirup was refluxed with 25 ml of 20% HCl for 3 hr and the reaction mixture was freed from HCl by passage down a column of "Amberlite IR 4B (OH^-)." The deionized solution was evaporated to dryness *in vacuo*, the residue was crystallized from H_2O-Me_2CO: yield, 1.84 g (52% of theory) mp 228—231° (decomp.) *Anal.* Calcd. for $C_8H_{15}O_2N$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.97; H, 9.45; N, 8.79.

b) From *p*-acetamidomethylbenzoic acid: A solution of 3.9 g (0.02 mole) of *p*-acetamidomethylbenzoic acid and 0.8 g (0.02 mole) of NaOH in 15 ml of H_2O was hydrogenated in the presence of 3 ml of Raney nickel in autoclave (100 ml) at 170°. Th initial pressure of hydrogen was 82 atm/cm² and the hydrogeantion was taken place completely in about 2 hr. The catalyst was filtered off, the filtrate was acidified with 4 N H_2SO_4, and precipitated crude 4-acetamidomethylcyclohexanecarboxylic acid (2.5 g mp 130—160°) was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in Me_2CO, insoluble materials were filtered off and the filtrate was concentrated to dryness, and oily sirup (1.4 g) was obtained.

19) It was reported by W.E. Meyer that the configuration of *cis*-isomer could be established by conversion of *cis*-4-aminomethylcyclohexanecarboxylic acid into 4-aminomethylcyclohexanecarboxylic acid lactam (*J. Med. Chem.*, 9, 641 (1966)).

20) One of the authors cooperated with Dr. Iitaka in this work. S. Kadoya, F. Hanazaki, and Y. Iitaka, *Acta Cryst.*, 21, 38 (1966).

21) Melting points are uncorrected. IR spectra were measured on a Hitachi EPI-2 spectrophotometer.

Total 3.9 g of the crude 4-acetamidomethylcyclohexanecarboxylic acid was refluxed in 20 ml of 20% HCl for 3 hr in oil bath (at 150°). The reaction mixture was evapoarated to dryness *in vacuo* and the reisude dissolved in 50 ml of H_2O. The water solution was freed from HCl by passage down a column of "Abmerlite IR-4B (OH^-)" (15 ml) and washed with water. The eluted water was evaporated and crystallization of the residue gave 2.24 g of 4-aminomethylcyclohexanecarboxylic acid, mp 232—236° (decomp.). *Anal.* for $C_8H_{15}O_2N$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.23; H, 9.56; N, 8.80.

Separation of *cis*- and *trans*-4-Aminomethylcyclohexanecarboxylic Acids——4-Aminomethylcyclohexanecarboxylic acid (10 g, 0.064 mole) was refluxed with 9.15 g (0.038 mole) of cupric carbonate in 100 ml of H_2O for 60 min and the mixture was gradually changed into deep-blue. The mixture was cooled and the deep-blue precipitates were separated. The precipitates were dissolved into 100 ml of 8% aqueous ammonia and insoluble substance was filtered off. The filtrate was passed through a column of "Diaion SK#1 (NH_4^+)" and the column was washed with water. The eluted solution was then passed through a column of "Amberlite IR-4B (OH^-)" and the effluent was concentrated to dryness. The residue was crystallized from H_2O–Me_2CO; mp 221—223° (decomp.), yield 6.75 g. Repeated recrystallization gave (I), mp 236—238° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 2940, 2660, 1639, 1560, 1509, 1408, 1305, 930, 904. pK_{a1} 4.51, pK_{a2} 10.72. *Anal.* Calcd. for $C_8H_{15}O_2N \cdot 1/2\ H_2O$: C, 57.80; H, 9.70; N, 8.43. Found: C, 57.96; H, 9.67; N, 8.26.

The filtrate was similarly deionized by a column of exchange resin as described above. The deionized solution was evaporated to dryness *in vacuo* and the residue was crystallized from H_2O–Me_2CO; yield 3.37 g. By the repeated crystallization from H_2O–EtOH–Me_2CO II, mp 386—392° (decomp.), was obtained. IR ν_{max}^{KBr} cm^{-1}: 2940, 2610, 1637, 1535, 1383, 920. pK_{a1} 4.51, pK_{a2} 10.72. *Anal.* Calcd. for $C_8H_{15}O_2N$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.08; H, 9.65; N, 8.96.

Thin-layer Chromatography——A thin-layer was made on a glass plate, 20×5 cm, with silica-Rider[22] or Silica gel G (Merck). Solvent used for development was *n*-PrOH–H_2O (65:35) and the plate was developed by the ascending method in a closed vessel saturated with the developing solvent. The amino acid was detected with ninhydrin spray followed by heating. *Rf* value of (I) was 1.2 times as large as that of (II).

Salts of *cis*- and *trans*-4-Aminomethylcyclohexanecarboxylic Acids

The following salts were all prepared in conventional way.

i) Hydrochlorides: The hydrochloride of I, recrystallized from H_2O–Me_2CO as prisms, melts at 195—197° (decomp.). *Anal.* Calcd. for $C_8H_{16}O_2NCl$: C, 49.61; H, 8.33; N, 7.23; Cl, 18.31. Found: C, 49.76; H, 8.28; N, 7.22; Cl, 18.51.

The hydrochloride of II, recrystallized from H_2O–Me_2CO as needles, melts at 238—241.5° (decomp.). *Anal.* Calcd. for $C_8H_{16}O_2NCl$: C, 49.61; H, 8.33; N, 7.23; Cl, 18.31. Found: C, 49.39; H, 8.39; N, 7.32; Cl, 18.35.

ii) Hydrobromides: The hydrobromide of I, recrystallized from Me_2CO as plates, melts at 205—208° (decomp.). *Anal.* Calcd. for $C_8H_{16}O_2NBr$: C, 40.35; H, 6.77; N, 5.88; Br, 33.56. Found: C, 40.46; H, 6.90; N, 6.03; Br, 33.59.

The hydrobromide of II, recrystallized from H_2O as plates, melts 227—229° (decomp.). *Anal.* Calcd. for $C_8H_{16}O_2NBr$: C, 40.35; H, 6.77; N, 5.88; Br, 33.56. Found: C, 40.50; H, 6.65; N, 5.95; Br, 33.66.

iii) *p*-Toluenesulfonates: The *p*-toluenesulfonic acid salt of I, recrystallized from *n*-propyl alcohol–ether, melts at 177—178°. *Anal.* Calcd. for $C_{15}H_{23}O_5NS$: C, 54.69; H, 7.04; N, 4.25. Found: C, 54.95; H, 7.06; N, 4.24.

The same salt of II, recrystallized from H_2O, melts at 262—264°. *Anal.* Calcd. for $C_{15}H_{23}O_5NS$: C, 54.69; H, 7.04; N, 4.25. Found: C, 54.50; H, 7.00; N, 4.38.

iv) Hydrochloride trichloroaurates: The aurate of I, recrystallized from H_2O as yellow needles, melts at 178—180° (decomp.). *Anal.* Calcd. for $C_8H_{16}O_2NAuCl_4$: C, 19.32; H, 3.22; N, 2.82; Au, 39.66. Found: C, 19.32; H, 3.30; N, 2.86; Au, 39.81.

The aurate of II, recrystallized from H_2O as yellow prisms, melts at 204—206° (decomp.). *Anal.* Calcd. for $C_8H_{16}O_2NAuCl_4$: C, 19.32; H, 3.22; N, 2.82; Au, 39.66. Found: C, 19.55; H, 3.21; N, 2.74; Au, 39.41.

v) Hydrochloride tetraplatinates: The platinate of I, recrystallized from H_2O as yellow needles, melts at 233° (decomp.). *Anal.* Calcd. for $C_{16}H_{32}O_4N_2Cl_6Pt$: C, 26.53; H, 4.45; N, 3.87; Pt, 26.95. Found: C, 26.86; H, 4.26; N, 3.78; Pt, 26.72.

The platinate of II, recrystallized from H_2O as yellowish orange plates melts at 254—255° (decomp.). *Anal.* Calcd. for $C_{16}H_{32}O_4N_2Cl_6Pt$: C, 26.53; H, 4.45; N, 3.87; Pt, 26.95. Found: C, 26.79; H, 4.74; N, 3.72; Pt, 27.16.

4-Acetamidomethylcyclohexanecarboxylic Aicds

a) *cis*-4-Acetamido derivative: To a solution of I (1.0 g) in 11.5 ml of chilled 2 N NaOH, 13.0 g of Ac_2O was added with stirring. The mixture was stirred for 30 min at room temperature and was brought to pH 2 with dil. HCl. The precipitated acetyl derivative was filtered and recrystallized from EtOH to give acetamido derivative, prisms, mp 189—190°. IR ν_{max}^{KBr} cm^{-1}: 3340, 1694, 1613, 1563, 1228. *Anal.* Calcd. for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.34; H, 8.39; N, 6.84.

b) *trans*-4-Acetamido derivative: To a solution of II (1.00 g) in 2 N NaOH, Ac_2O was added and treated

22) Silica gel for thin-layer chromatography, Daiichi Pure Chemicals, Co., Ltd.

in the same method described above. Recrystallization from Me_2CO afforded acetamido derivative, prisms, mp 154—155°. IR ν_{max}^{KBr} cm^{-1}: 3310, 1692, 1598, 1555, 1194. *Anal.* Calcd. for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.50; H, 8.48; N, 6.86.

4-Benzamidomethylcyclohexanecarboxylic Acids

a) *cis*-4-Benzamido derivative: To a solution of I (1.00 g) in 13.5 ml of chilled 2 N NaOH, were added alternately benzoylchloride (1.79 g) and 2 N NaOH at 0—5° to maintain pH 8—8.5. After addition of HCl, the precipitates were filtered off. Recrystallization from EtOH–benzene to give the benzamido derivative as plates (1.27 g), mp 157—158°. IR ν_{max}^{KBr} cm^{-1}: 3350, 1688, 1630, 1550, 1305, 1213, 1198. *Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.25; H, 7.12; N, 5.35.

b) *trans*-4-Benzamido derivative: II (1.00 g) was treated in the same manner described above and recrystallization from EtOH–H_2O to afford the benzamido derivative as needles (1.48 g), mp 177—178°. IR ν_{max}^{KBr} cm^{-1}: 3320, 1696, 1630, 1552, 1313, 1193. *Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.89; H, 7.43; N, 5.53.

Isomerization of *cis*-4-Aminomethylcyclohexanecarboxylic Acid (I)——A solution of I (2 g) in 26 ml of 0.5 N NaOH was heated in silver vessel of autoclave at 200° for 6 hr. The resulting solution was passed through a column of "Amberlite IR-120 (NH_4^+)" and the column was washed with H_2O. The eluted was evaporated *in vacuo* and the residue was recrystallized from H_2O–MeOH four times to give 0.8 g of II, mp 384—390° (decomp.). This was identified with a sample by IR spectrum and thin-layer chromatography. *Anal.* Calcd. for $C_8H_{15}O_2N$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.20; H, 9.54; N, 9.00.

Oxidation of *cis*- and *trans*-4-Aminomethylcyclohexanecarboxylic Acids (I) and (II) with Potassium Permanganate

a) Oxidation of I: To a stirred solution of I (0.5 g) in 100 ml of 0.26 N Na_2CO_3 was added potassium permanganate (0.67 g) and the mixture was allowed to stand for 15 hr at room temperature. The precipitated manganese dioxide was filtered off and colorless filtrate was passed through a column of "Diaion SK#1(H^+)" (25 ml). The column was washed with H_2O. The eluted solution was evaporated *in vacuo* below 50° and the dried residue was washed with *n*-hexane and benzene. Insoluble material was recrystallized from H_2O three times to give crystals, mp 167—170°; yield, 0.2 g. These crystals were identified with *cis*-hexahydroterephthalic acid[20] by IR spectrum and mixed fusion.

b) Oxidation of II: To a solution of II (0.8 g) in 160 ml of 0.26 N Na_2CO_3 was added potassium permanganate (1.08 g), and the mixture was stirred occasionally at room temperature and allowed to stand for 15 hr. The reaction mixture was treated in the same method described above. Recrystallization from H_2O afforded crystals, mp 293—300°; yield, 0.3 g. The crystals were identified with *trans*-hexahydroterephthalic acid by IR spectrum and mixed fusion.

4-Cyanohexanecarboxylic Acids (VII) and (VIII)

a) *cis*-4-Cyanohexanecarboxylic acid (VII): A solution of *cis*-4-carbamoylcyclohexanecarboxylic acid (mp 210—212°; 0.13 g) (III) in thionyl chloride was refluxed for 15 min and thionyl chloride was distilled off *in vacuo*. The residue was dissolved in H_2O and extracted with chloroform. The extract was washed with H_2O, dried with Na_2SO_4 and evaporated. The residue was crystallized from *n*-hexane to give *cis*-4-cyanocyclohexanecarboxylic acid, mp 105—107°; Yield, 0.07 g. IR ν_{max}^{KBr} cm^{-1}: 2220, 1690, 1446, 1434, 1251, 1203. *Anal.* Calcd. for $C_8H_{11}O_2N$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.77; H, 7.15; N, 9.23.

b) *trans*-4-Cyanocyclohexanecarboxylic acid (VIII): A suspension of *trans*-4-carbamoylcyclohexanecarboxylic acid (mp 270° (decomp.); 0.11 g) (IV) and thionyl chloride was refluxed and treated in the same manner described above. Recrystallization from chloroform–*n*-hexane to afford *trans*-4-cyanocyclohexanecarboxylic acid, mp 149.5—151°; yield, 0.06 g. IR ν_{max}^{KBr} cm^{-1}: 2235, 1683, 1453, 1415, 1269, 1212. *Anal.* Calcd. for $C_8H_{11}O_2N$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.54; H, 7.38; N, 9.02.

Methyl 4-Cyanocyclohexanecarboxylatse (IX) and (X)

a) Methyl *cis*-4-Cyanocyclohexanecarboxylate (IX): A solution of methyl *cis*-4-carbamoylcyclohexanecarboxylate (mp 124—126°; 0.8 g) (V) in 1.7 ml of thionyl chloride was refluxed for 30 min. The reaction mixture was evaporated *in vacuo* to oily syrup. The syrup was dissolved in benzene and the benzene solution was washed with H_2O, 0.5 N NaOH and H_2O, dried over Na_2SO_4 and evaporated. The oily residue was obtained; yield 0.7 g. IR $\nu_{max}^{liq\ film}$ cm^{-1}: 2220, 1728, 1226, 1194, 1166, 1032.

b) Methyl *trans*-4-cyanocyclohexanecarboxylate (X): A solution of methyl *trans*-4-carbamoylcyclohexanecarboxylate (mp 194—195°; 3.0 g) (VI) in 5.8 ml of thionyl chloride was refluxed about 20 min. The reaction mixture was treated in the same method described above. The ester was obtained by distillation, bp 135° (11mmHg); yield, 2.32 g. IR $\nu_{max}^{liq\ film}$ cm^{-1}: 2230, 1729, 1260, 1193, 1172, 1048. *Anal.* Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.84; N, 8.37. Found: C, 64.56; H, 7.82; N, 8.41.

4-Aminomethylcyclohexanecarboxylic Acids

i) *cis*-4-Aminomethylcyclohexanecarboxylic acid from (VII): A solutionof 1.0 g of VII in 30 ml of 3% aqueous ammonia was hydrogenated in the presence of 0.3 ml of Raney nickel. The required quantity of hydrogen was absorbed for 3 hr. The catalyst was subsequently filtered off and the filtrate was passed

through a column of "Amberlite IRC–50 (H^+)." The column was washed with water. The eluted solution was evaporated to dryness *in vacuo*, and residue was crystallized from H_2O–Me_2CO to afford needles, mp 236—238° (decomp.) yield, 0.92 g. The crystals were identified with a sample of the above mentioned, by IR spectrum and thin–layer chromatography. *Anal.* Calcd. for $C_8H_{15}O_2N \cdot \frac{1}{2}H_2O$: C, 57.80; H, 9.70; N, 8.43. Found: C, 57.86; H, 9.68; N, 8.30.

ii) *cis*–4–Aminomethylcyclohexanecarboxylic acid from IX: A solution of (IX) (0.7 g) in a mixture of MeOH (7.5 ml) and aqueous ammonia (0.5 ml) was hydrogenated in the autoclave at room temperature in the presence of Raney nickel. The initial pressure of hydrogen was 50 atm/cm². The catalyst was filtered off and the filtrate was evaporated. The oily sirup (XI) hydrolyzed with 10 % BCl and the reaction mixture was passed through a column of "Amberlite IR–4B (OH^-)" and the column was washed with water. The eluted solution was evaporated and the residue was crystallized from H_2O–Me_2CO as needles (0.5 g), mp 234—236° (decomp.), which was identical with I by a comparison of IR spectra and thin–layer chromatography. *Anal.* Calcd. for $C_8H_{15}O_2N \cdot \frac{1}{2}H_2O$: C, 57.80; H, 9.70; N, 8.43. Found: C, 57.96; H, 9.67; N, 8.26.

iii) *trans*–4–Aminomethylcyclohexanecarboxylic acid from VIII: A solution of 1 g of VIII in 30 ml of 3% aqueous ammonia was hydrogenated in the presence of 0.3 ml of Raney nickel and the reaction mixture was treated in the same manner as written above. Recrystallization from H_2O–Me_2CO gave needles (0.94 g), mp 386—392° (decomp.). Identity with a sample of II was established by IR spectrum and *Rf* value on thin–layer chromatograhy. *Anal.* Calcd. for $C_8H_{15}O_2N$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.30; H, 9.51; N, 8.83.

iv) *trans*–4–Aminomethylcyclohexanecarboxylic acid from X: Hydrogenation of X (0.5 g) was taken place in the same method described above. The resulting solution of hydrolysis was deionized by exchange resin. The effluent was evaporated to dryness *in vacuo*, The residue was crystallized from H_2O–Me_2CO to give needles (0.36 g) mp 384—389° (decomp.), which was identified with a sample obtained in iii) by a comparison of IR spectra and thin–layer chromatography.

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