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Author	須網, 哲夫(Suami, Tetsuo) 小川, 誠一郎(Ogawa, Seiichiro)
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Synthesis and High Resolution NMR Analysis of 2,3-Diaminocyclohexanol*

(Received June 2, 1965)

Tetsuo SUAMI**

Seiichiro OGAWA***

Abstract

Two of the four possible diastereomers of 2,3-diaminocyclohexanol have been prepared and their configurations are established by means of their proton magnetic resonance spectra.

The previous studies on 2-amino-1,3-cyclohexanediol¹⁾ have stimulated our interest in the synthesis of an alicyclic compound having two amino groups and one hydroxyl group.

In the present paper, the syntheses of two diastereoisomeric 2,3-diaminocyclohexanol and their structures established by means of the proton magnetic resonance spectra are described. At first di-O-mesyl-trans-2-acetamido-1,3-cyclohexanediol (I)²⁾ is used as a starting material. By treating compound I with sodium azide in boiling aqueous 2-methoxyethanol, DL-2-acetamido-3-azidocyclohexanol (II) is obtained. This compound is hydrogenated by Raney nickel in a hydrogen stream to give DL-2-acetamido-3-aminocyclohexanol (III) in 48.8 % yield from compound I. Compound III is treated with acetic anhydride and pyridine, giving the triacetyl derivative (IV), melting at 206.5°C, in 77.0 % yield. Compound IV is selectively deacetylated by methanol saturated with dry ammonia to give 2,3-diacetamidocyclohexanol (V). Also compound IV is hydrolyzed by 6N hydrochloric acid, giving 2,3-diaminocyclohexanol dihydrochloride (VI). The picrate is prepared from compound VI.

There are four predicted diastereomers of 2,3-diaminocyclohexanol (XVI, XVII, XVIII and XIX), but they are wholly unknown: None of them has a plane of symmetry; hence, they are racemic forms.

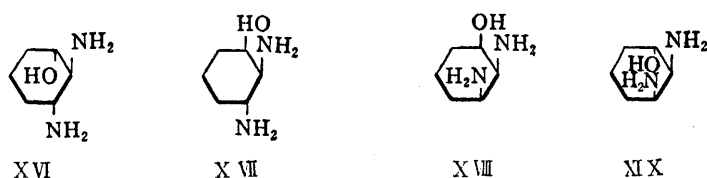
* This work has been contributed to the Bulletin of the Chemical Society of Japan (December 28, 1963; September 22, 1964).

** 須網 哲夫, 教授 Ph. D., Professor of Organic Chemistry, Keio University.

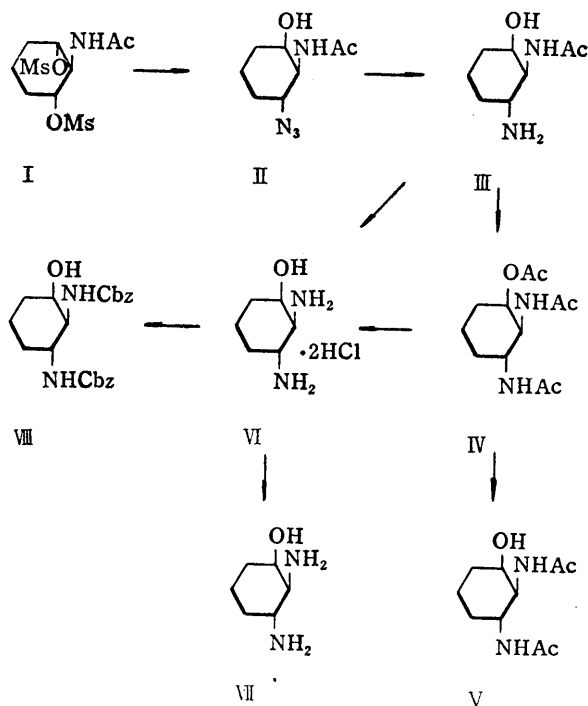
*** 小川 誠一郎, 大学院学生 Graduate Student, Keio University.

1) T. Suami and S. Ogawa, Bull. Chem. Soc. Japan, **37**, 194 (1964).

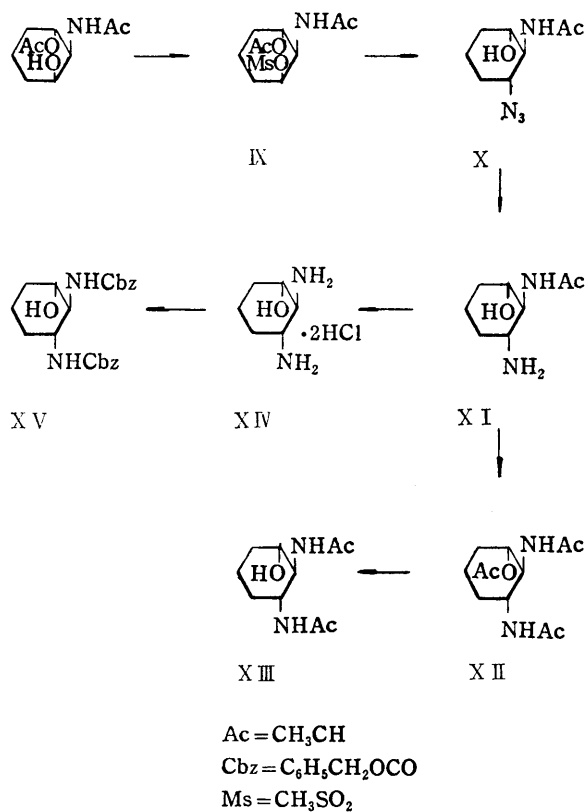
2) F. W. Lichtenthaler Chem. Ber., **96**, 845 (1963).



In the present experiment, the starting material has the trans configuration.^{1) 2)} The loss of both the mesyloxy groups takes place when compound I is treated with sodium azide in boiling aqueous 2-methoxyethanol, but azido alcohol II is obtained instead of the diazido derivative. An analogous phenomenon has been described in the solvolysis of compound I with sodium acetate.²⁾ This fact might be explained as follows: the displacement of mesyloxy group occurs with formation of oxazolinium ions,³⁾ which are attacked by water to give the cis-acetamido alcohol. Then the displacement of another mesyloxy group would take place via an anchimeric reaction or a direct S_N2 mechanism.



3) S. Winstein, E. Grunwald, R. E. Buckles and C. Hanson, J. Am. Chem. Soc., **70**, 816 (1948).



Recently the displacement of a secondary sulphonate group in sugar derivatives with sodium azide has been described by several authors,⁴⁾ but that in alicyclic compounds has never been described.

In the present experiment, if an attack by an azide ion occurs at C-3 (or C-1), with a retention of the configuration, the product should have the structure XVII, but if it occurs with an inversion, the product should have the structure XVIII.

The NMR spectrum of the triacetyl derivative, IV, gives an equivocal answer on this point. An acetoxy group produces a signal at a different field than does an acetamido group; moreover, an axial acetamido group gives a signal at a lower

4) E. J. Reist, R. R. Spencer, B. R. Baker and L. Goodman, *Chem. & Ind.*, 1962, 1794; B. R. Baker and A. H. Haines, *J. Org. Chem.*, 28, 442 (1963); C. L. Stevens P. Blumbergs and F. A. Daniher, *J. Am. Chem. Soc.*, 85, 1552 (1963); C. L. Stevens, P. Blumbergs, F. A. Daniher, R. W. Wheat, A. Kujimoto and E. L. Rollins, *ibid*, 85, 3061 (1963).

field than does an equatorial acetamido group in cyclohexane derivatives.^{1) 5)} Therefore, the structure could be assigned on the basis of this point. The NMR spectrum of compound IV, as is shown in Fig. 1-A, reveals two sharp signals of a 1:2 relative intensity, as is to be expected from one axial acetoxy group (τ of 7.89)⁵⁾ and two equatorial acetamido groups (τ of 8.07). The doublet produced by the proton on a nitrogen atom in the acetamido group with a coupling constant of 10 c.p.s. (τ of 3.76) corresponds to two protons and gives further evidence that the two acetamido groups may be expected to have an identical conformation, since inosadamine hexaacetate with one axial and one equatorial acetamido groups reveals two doublets.⁶⁾ The ring protons show a peak at 4.88 τ , as is to be expected from one equatorial proton at C-1, and a peak at 6.08 τ , as is to be expected from two axial protons at C-2 and C-3.

The NMR spectrum of compound V, as is shown in Fig. 1-B, shows only one sharp signal at 7.97 τ , as is to be expected from two acetamido groups; this means that the two acetamido groups are equivalent.

As a result of the consideration of the NMR spectra, it might be concluded that compound IV can be assigned as 2 α ,3 β -diacetamido-1 α -cyclohexyl acetate and that, accordingly, the attack of azide ions occurs anchimerically with a retention of the configuration.

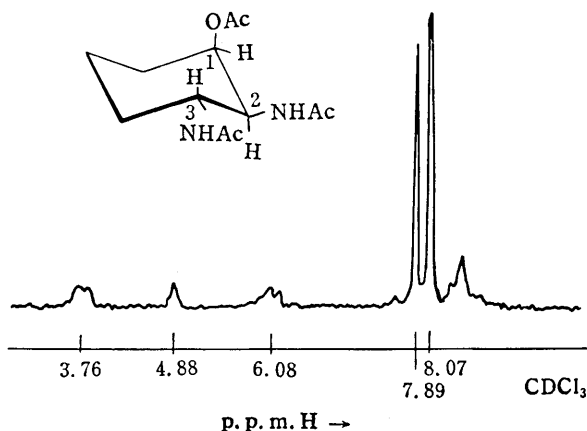
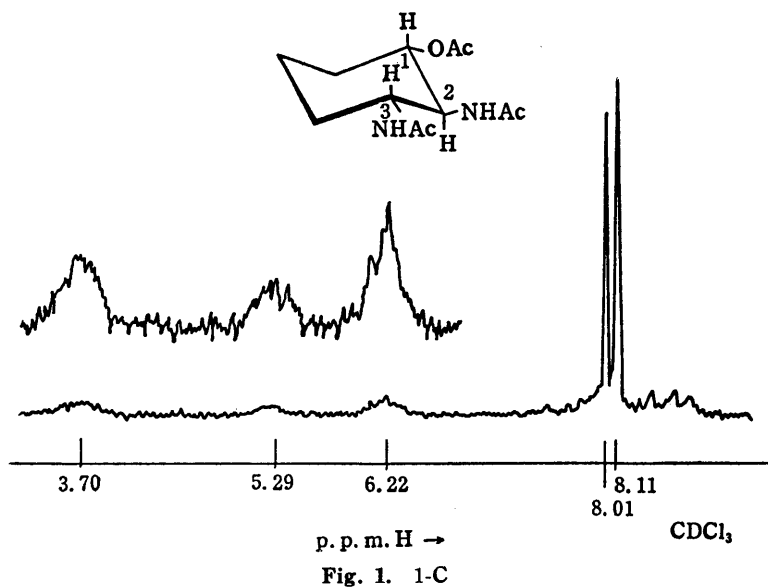
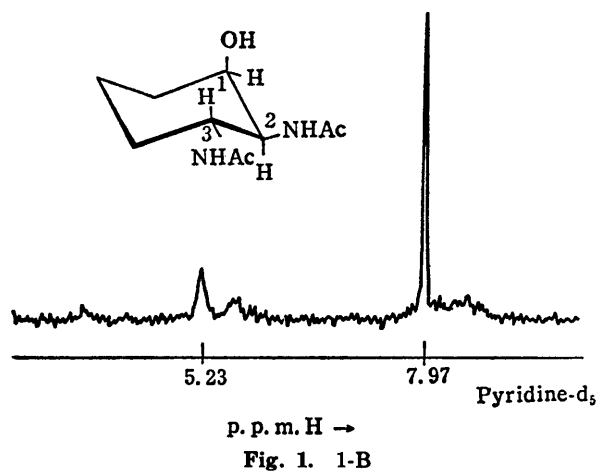


Fig. 1. 1-A.

5) F. W. Lichtenthaler, Chem. Ber., **96**, 2047 (1963).

6) M. Nakajima, A. Hasegawa and F. W. Lichtenthaler, Ann., **669**, 75 (1963).



While an analogous reaction is started from 1-O-acetyl-DL-2 α -acetamido-1 β ,3 α -cyclohexanediol,¹⁾ one of the other three diastereomers, DL-trans-2,3-diaminocyclohexanol is obtained. 1-O-Acetyl-3-O-mesyl-DL-2 α -acetamido-1 β ,3 α -cyclohexanediol (IX) is obtained in 58 % yield by treating 1-O-acetyl-DL-2 α -acetamido-1 β ,3 α -cyclohexanediol with methanesulfonyl chloride in pyridine.

Compound IX is treated with sodium azide in boiling 90 % aqueous 2-methoxyethanol to give DL-2 α -acetamido-3 β -azido-1 β -cyclohexanol (X) as colorless crystals in 73 % yield. Then X is hydrogenated with a platinum catalyst in a hydrogen stream to give DL-2 α -acetamido-3 β -amino-1 β -cyclohexanol (XI) in 87 % yield.

On acetylating XI with acetic anhydride and pyridine, the triacetyl derivative (XII) is obtained in 83 % yield. When XII is refluxed with 6N hydrochloric acid, deacetylation takes place, giving the dihydrochloride (XIV) in 92 % yield. By an ordinary method, di-N-carbobenzyloxy derivative (XV) is prepared in 96 % yield. By deacetylating XII with ammonia in methanol, diacetamidocyclohexanol (XIII) is obtained in 89 % yield.

The mesyloxy group is located in a *cis* position to the vicinal acetamido group in IX; therefore, the replacement of the mesyloxy group by an azide ion should take place through a direct S_N2 mechanism.⁷⁾ As a result, the inversion of the configuration at C-3 must occur, and the product should be DL-2 α -acetamido-3 β -azido-1 β -cyclohexanol. This configuration is also supported by the NMR spectrum of XII; as is shown in Fig. 1-C, the spectrum reveals two sharp signals of a 1:2 relative intensity, as is to be expected from one equatorial acetoxo group (of 8.01 τ) and two equatorial acetamido groups (of 8.11 τ).^{1) 5)} The two axial ring protons on C-2 and C-3 show the broad signal (peak width: 25 c.p.s.) at 6.22 τ , while the one axial ring proton on C-1 reveals an unresolved broad signal (peak width: 27 c.p.s.) at 5.29 τ . Since the vicinal spin-spin coupling constant is greater between two axial-equatorial protons than between axial-equatorial protons or two equatorial protons, the broad peak widths of the ring protons correspond to the assigned configuration.

The protons on the nitrogen atoms in amide groups show the signal at 3.70 τ .

Experimental

All melting points have been corrected. The NMR spectrum was determined at a frequency of 60 Mc.p.s. with a Varian Associates A-60 spectrometer. Tetramethylsilane was used as an internal reference in the samples. The peak positions are given in τ -values.

DL-2 α -Acetamido-3 β -amino-1 α -cyclohexanol (III). A mixture of 4.0 g. of di-O-mesyl-*trans*-2-acetamido-1,3-cyclohexanediol (I), 3.3 g. of sodium azide and 100ml. of 75 % aqueous 2-methoxyethanol was heated under reflux for 2 hr. The mixture was then evaporated to dryness under reduced pressure. The residue was repeatedly extracted with hot acetone. The combined acetone extract was evaporated to give a brownish sirup, which showed infrared absorptions at 3300 (broad) (OH), 2090 (N_3) 1653, and 1544 cm^{-1} (amide).

A solution of the sirup in 40 ml. of ethanol was hydrogenated with Raney nickel T4,⁸⁾ obtained from 10 g. of Raney nickel alloy, in a hydrogen stream of an initial pressure of 50 p.s.i.g. for 4 hr. Then the mixture was filtered to remove the catalyst, and the filtrate was evaporated in vacuo. The crystalline residue was

7) T. Suami, F. W. Lichtenthaler and S. Ogawa, Bull. Chem. Soc. Japan, 38, 754 (1965).

8) S. Nishimura, Bull. Chem. Soc. Japan, 32, 61 (1959).

recrystallized from ethanol-ether to yield 0.79 g. of compound III, m.p. 174~177°C. The second crop of the product (0.26 g.) was obtained from the mother liquor. The total yield was 48.8 % from compound I. The product was recrystallized from the same solvent to give an analytical sample in the form of colorless needles, m.p. 182.5~184°C.

Found: C, 55.63; H, 9.21; N, 16.47. Calcd. for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27 %.

The infrared spectrum of the product (KBr disk) showed the expected absorptions at 3150 (broad) (OH and NH_2), 3290, 1550 (amide) and 1585 cm^{-1} (NH_2).

DL-2 α ,3 β -Diacetamido-1 α -cyclohexyl Acetate (IV). A mixture of 1.0 g. of compound III, 50 ml. of pyridine and 50 ml. of acetic anhydride was heated at 80°C for 1 hr. and then allowed to stand overnight at room temperature. The mixture was evaporated under reduced pressure. The crystalline residue was recrystallized from ethanol-ether to yield 1.15 g. (77%) of plates, m.p. 203~206.5°C. A sample recrystallized from ethanol-ether (m.p. 205~206.5°C) was subjected to an elemental analysis.

Found: C, 56.38; H, 7.78; N, 10.87. Calcd for $C_{12}H_{20}N_2O_4$: C, 56.23; H, 7.87; N, 10.93 %.

DL-2 α ,3 β -Diacetamido-1 α -cyclohexanol (V). A solution of 0.21 g. of compound IV in 20 ml. of methanol previously saturated with ammonia at 5°C was allowed to stand at room temperature overnight. The solution was then evaporated in vacuo. The residue was crystallized from ethanol-ether to yield 0.14 g. (82 %) of compound V, m.p. 237~241°C (decomposition). The sample for analysis obtained from ethanol-ether had an m.p. of 258~259°C (decomposition).

Found: C, 56.33; H, 8.60; N, 13.09. Calcd for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08 %.

DL-2 α ,3 β -Diamino-1 α -cyclohexanol Dihydrochloride (VI). a) A mixture of 0.5 g. of compound IV and 30 ml. of 6N hydrochloric acid was refluxed for 6 hr. and then evaporated under reduced pressure to dryness, giving 0.31 g. (84.5 %) of white crystals, m. p. 289~293°C (decomposition). The analytical sample was obtained from methanol-ether as colorless plates, which started turning brown at 280°C and melted at 301~303°C (decomposition).

Found: C, 35.62; H, 7.61; N, 14.26; Cl, 35.45. Calcd. for $C_6H_{14}N_2O \cdot 2HCl$: C, 35.48; H, 7.94; N, 13.79; Cl, 34.91 %.

Paper Chromatography. An upper layer of 1-butanol-acetic acid-water (4:1:5) gave a single spot of R_f 0.18 in ascending development at 17°C (R_f of glucosamine hydrochloride, 0.15).

b) A mixture of 0.60 g. of compound III and 60 ml. of 6N hydrochloric acid was treated as described in a) to obtain 0.58 g. (82 %) of the product, m.p. 290~293°C (decomposition.)

DL-2 α ,3 β -Diamino-1 α -cyclohexanol (VII). A 8 ml. portion of a 0.5N sodium hydroxide solution was added to a mixture of 406 mg. of compound VI and 20 ml. of methanol. The mixture was evaporated in vacuo, and the residue was extracted with absolute ethanol. The ethanol extract was evaporated to yield 260 mg. of an oily product.

The picrate was obtained by an ordinary method as yellow crystals, m.p. 255°C (decomposition).

Found: C, 37.06; H, 3.62; N, 19.22. Calcd. for $C_6H_{14}N_2O \cdot 2C_6H_3N_3O_7$: C, 36.74; H, 3.43; N, 19.04 %.

Di-N-carbobenzyloxy-DL-2 α ,3 β -diamino-1 α -cyclohexanol(VIII). A 0.3 ml. portion of carbobenzyloxy chloride in toluene (85 % solution) was added to a mixture of 100 mg. of compound VI, 340 mg. of sodium bicarbonate and 3 ml. of water under agitation. After the mixture had been stirred for 6 hr., 157 mg. (79 %) of the crude product was obtained as a white powder, m.p. 161.5~164.5°C. The analytical sample was obtained from ethanol as needles, m.p. 163.5~164.5°C.

Found: C, 66.48; H, 6.55; N, 7.07. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03 %.

1-O-Acetyl-3-O-mesyl-DL-2 α -acetamido-1 β ,3 α -cyclohexanediol (IX). To a mixture of 3.5 g. of 1-O-acetyl-DL-2-acetamido-1,3-cyclohexanediol^{1) 2)} and 40 ml. of pyridine, 2.4 g. of methanesulfonyl chloride was added drop by drop under ice cooling with agitation. After it had stood overnight in a refrigerator, the reaction mixture was poured into ice and water. The mixture was then evaporated under reduced pressure until a precipitate appeared; this was collected by filtration and washed with cold water. The crude product (2.75 g.) melted at 159~163°C. The analytical sample was recrystallized from ethanol and melted at 161.5~162°C.

Found: C, 45.00; H, 6.42; N, 4.94; S, 10.70. Calcd. for $C_{11}H_{19}NO_6S$: C, 45.04; H, 6.53; N, 4.78; S, 10.93 %.

DL-2 α -Acetamido-3 β -azido-1 β -cyclohexanol (X). A mixture of 2.2 g. of IX, 1.5 g. of sodium azide and 65 ml. of 90 % aqueous 2-methoxyethanol was refluxed for 20 hr. The reaction mixture was then evaporated under reduced pressure to dryness, and the residue was extracted repeatedly with boiling acetone. The combined acetone extract was evaporated to yield 1.4 g. of the crystalline residue. The residue was recrystallized from acetone-ether to give 1.09 g. of crystals (73 %) melting at 134~137°C. Recrystallization from the same mixed solvent raised the

melting point to 137~139°C.

Found: C, 48.57; H, 7.07; N, 28.15. Calcd. for $C_8H_{14}N_4O_2$: C, 48.47; H, 7.12; N, 28.27 %.

IR: 3350 ($-OH$), 2110 ($-N_3$), 3280, 1650, 1628 and 1555 cm^{-1} (amide).

DL-2 α -Acetamido-3 β -amino-1 β -cyclohexanol (XI). A 1.05 g. portion of X was hydrogenated in 60 ml. of ethanol over 0.2 g. of platinum oxide at room temperature for 10 hr. The catalyst was then removed by filtration, and the filtrate was evaporated to give the crystalline residue. The residue was recrystallized from ethanol-ether to give 0.8 g. of the product (87 %) melting at 176~177°C. The analytical sample was recrystallized from ethanol-ether and melted at 180~181°C after having sintered at 178°C.

Found: C, 55.38; H, 9.12; N, 16.02. Calcd. for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27 %.

DL-2 α ,3 β -Diacetamido-1 β -cyclohexanol acetate (XII). A mixture of 156 mg. of XI, 5 ml. of acetic anhydride and 5 ml. of pyridine was allowed to stand overnight at room temperature; then it was evaporated under reduced pressure to yield a crystalline residue. The residue was recrystallized from ethanol-ether to give 102 mg. (83 %) of needles melting at 223.5~224.5°C. Further recrystallizations did not raise its melting point.

Found: C, 56.38; H, 7.68; N, 10.86. Calcd. for $C_{12}H_{20}N_2O_4$: C, 56.23; H, 7.87; N, 10.93 %.

DL-2 α ,3 β -Diamino-1 β -cyclohexanol Dihydrochloride (XIV). A mixture of 455 mg. of XI and 25 ml. of 6N hydrochloric acid was refluxed for 3 hr. and then evaporated to dryness in vacuo. The residue was recrystallized for ethanol giving 491 mg. (92 %) of crystals which melted at 263°C with decomposition, after having turned brown at 250°C. Further recrystallization from methanol-ether did not raise the melting point.

Found: C, 35.66; H, 8.02; N, 13.40; Cl, 34.65. Calcd. for $C_6H_{14}N_2O \cdot 2HCl$: C, 35.48; H, 7.94; N, 13.79; Cl, 34.91 %.

Paper Chromatography. An ethyl acetate-pyridine-acetic acid-water (5 : 5 : 3 : 1) system gave a single spot of Rf/Rf glucosamine : 1.14 in ascending development at 24°C with Toyo filter paper No. 51. An upper layer of 1-butanol-acetic acid-water (4 : 1 : 5) gave a single spot of Rf 0.19 at 23°C (Rf of glucosamine hydrochloride : 0.19).

DL-2 α ,3 β -Diacetamido-1 β -cyclohexanol (XIII). A 136 mg. portion of XII was added to 20 ml. of methanol which had previously been saturated with ammonia, and the mixture was allowed to stand overnight at room temperature.

Then the mixture was evaporated in vacuo. The residue was recrystallized from ethanol-ether to give 101 mg. (89 %) of crystals melting at 240~241°C (decomposition).

Found: C, 55.81; H, 8.48; N, 12.72. Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08 %.

Di-N-carbobenzyloxy-DL-2 α ,3 β -diamino-1 β -cyclohexanol (XV). To a mixture of 100 mg. of XIV, 336 mg. of sodium bicarbonate and 3 ml. of water, 0.3 ml. of carbobenzyloxy chloride (a 85 % toluene solution) was added under agitation. After the mixture had been allowed to stand overnight, the precipitate was collected by filtration and washed with cold water and toluene, giving 188 mg. (96 %) of the product. The crude product was recrystallized from ethanol to give needles melting at 157~159°C.

Found: C, 66.59; H, 6.45; N, 7.01. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03 %.

The authors are indebted to professor Sumio Umezawa for his helpful advice, to Dr. Frieder W. Lichtenthaler (Technische Hochschule Darmstadt, Germany) for measurements of the NMR spectra and his stimulating discussions on the NMR spectra, and to Mr. Saburo Nakada for his microanalysis. This research has been supported in part by a grant from the Ministry of Education, to which the authors' thanks are due.