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Synthesis and Configurational Analysis of 2-Amino-1, 3-cyclohexanediol*

(Received December 20, 1963)

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Abstract

All three diastereomers of 2-amino-1,3-cyclohexanediol are prepared and their configurations are established on the basis of their proton magnetic resonance spectra and the chemical evidences.

Interest in inosadiamine and inosamine has stimulated by their occurrence in certain antibiotics. *scyllo*-Inosadiamine has been isolated from streptomycin.[1] Other antibiotics–neomycin,[2] paromomycin,[3] kanamycin,[4] and zygomycin[5]–contain all-*trans*-2-deoxystreptamine ; *neo*-inosamine-2 was isolated from hygromycin,[6] and *scyllo*-inosamine was found in glebomycin.[7] So it seemed desirable to study the relationship between chemical structure and antibiotic activity with model compounds of simpler structure. For this purpose 2-aminocyclohexyl D-glucosaminides have been synthesized in our laboratory.[8] These previous studies on 2-aminocyclohexanol have stimulated our interest in the synthesis of alicyclic compounds having three neighboring groups. Of the cyclohexane derivatives having two hydroxyl groups and one neighboring amino group, 3-amino-1,2-cyclohexanediols were described,[9] but 2-amino-1,3-cyclohexanediols were unknown.

An attempt to prepare 2-amino-1,3-cyclohexanediol through a corresponding nitrodiol was abandoned by McCasland, Matchett, and Hollander,[10] owing to a poor yield of the nitrodiol obtained by cyclization of glutaraldehyde with nitromethane. Lichtenthaler and Fischer[11] have developed a convenient method for the preparation of 1,4-dideoxy-1,4-dinitro-*neo*-inositol by cyclization of glyoxal with nitromethane, and *neo*-inosadiamine-1,4 was obtained by subsequent hydrogenation of the dinitro compound. Recently Lichtenthaler[12] synthesized two diastereomeric 2-amino-1, 3-cyclohexanediols (trans and DL-isomers) through the corresponding nitrodiol obtained by cyclization of glutaraldehyde with nitromethane. The authors have

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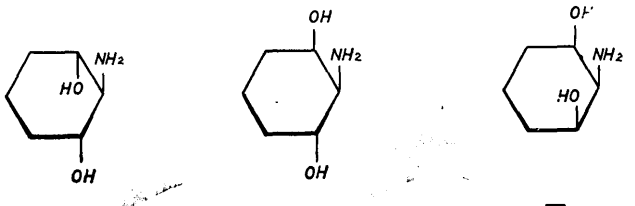
studied the same cyclization independently and all three diastereomers of 2-amino-1,3-cyclohexanediol are prepared.

In the present paper, synthetic routes to three diastereomeric 2-amino-1,3-cyclohexanediols are described and their structures are established by means of the proton magnetic resonance spectra of their acetyl derivatives.

Cyclization of glutaraldehyde with nitromethane in the presence of sodium carbonate gave 2α-nitro-1β,3β-cyclohexanediol (IV) in 60% yield. An attempt was made to reduce IV with hydrogen and platinum oxide at atomospheric pressure, but the expected product was not obtained. However Raney nickel T4[13] gave 2α-amino-1β,3β-cyclohexanediol (Ia) in 63% yield with a theoretical amount of hydrogen uptake.

There are three possible diastereomers of 2-amino-1,3-cyclohexanediol. Both I and III have a plane of symmetry and hence are meso forms, while II is a racemic form.

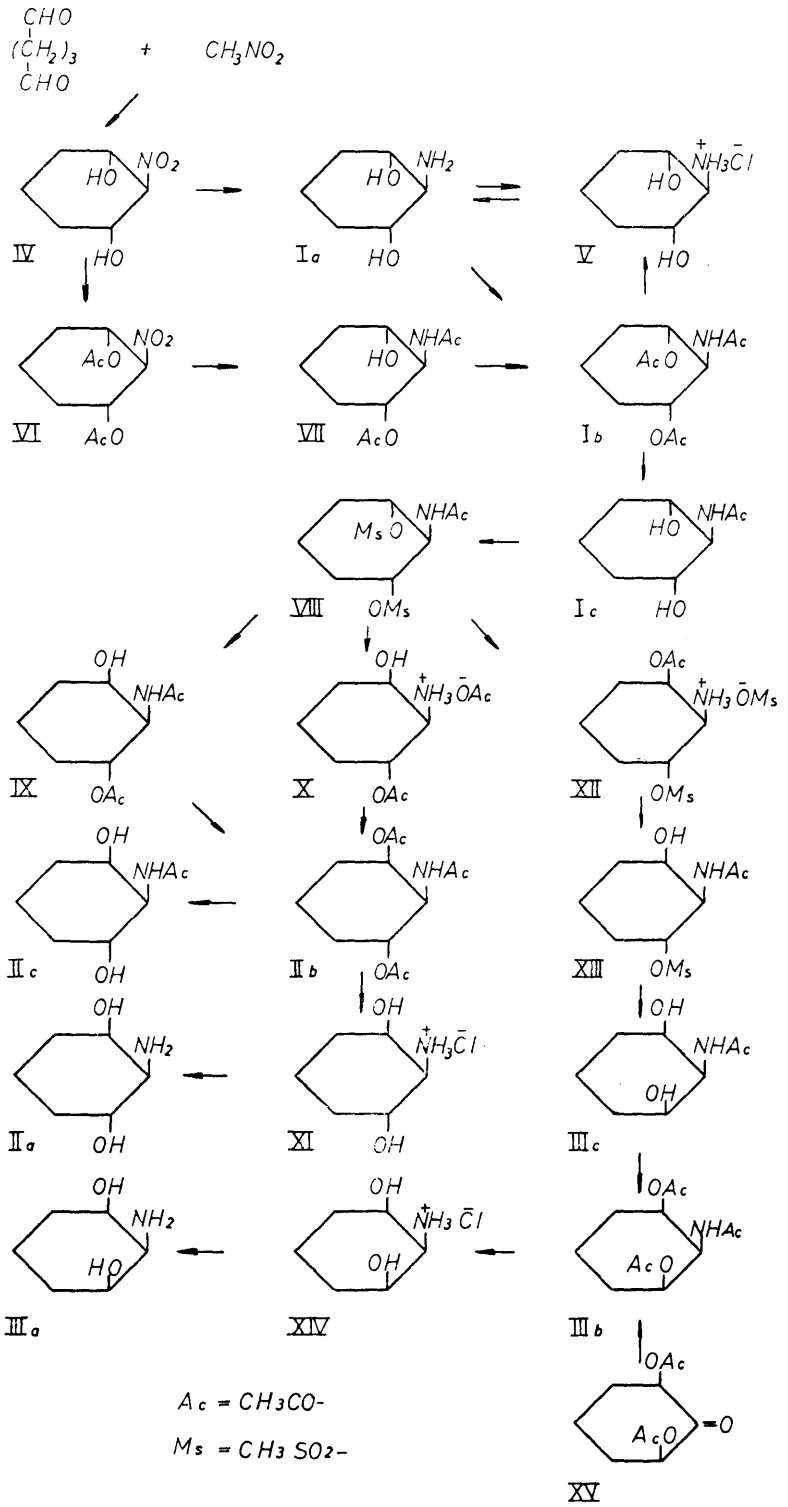


I II III

In order to establish the configurational purity of Ia, paper chromatography was applied. The compound, Ia, consumed 1.91 moles of periodate in aqueous solution in 20 hr., showed a single spot (Rf 0.59) in 1-butanol–ethanol–water (2 : 1 : 3) and also a single spot (Rf 0.45) in 1-butanol–acetic acid–water (4 : 1 : 5). These data provide strong, if not conclusive, evidence that Ia is a single isomer.

Acetylation of Ia with acetic anhydride in pyridine gave a triacetyl derivative (Ib), while IV was acetylated with acetic anhydride and a small amount of concentrated sulfuric acid to obtain di-O-acetyl-2α-nitro-1β,3β-cyclohexanediol (VI). VI was hydrogenated with Raney nickel T4[13] to give 2α-acetamido-O-acetyl-1β,3β-cyclohexanediol (VII) in 53% yield, which might be obtained through O→N migration of an acetyl group[17] during the course of reduction. VII was further acetylated to give Ib in 67% yield.

Under Kunz's condition,[14] Ib was selectively deacetylated showing the presence of two hydroxyl groups. The N-acetyl derivative (Ic) was recovered from the neutralized solution. Ic was prepared also by hydrolysis of Ib with methanol saturated with ammonia in 77% yield. Ic did not consume any periodate in aqueous methanol solution in 50 hr. These data are consistent with a cyclic structure with one acetamido group between two hydroxyl groups. So the assigned structure was obtained for the compound Ia.


CHO
(CH2)3
CHO
+
CH3NO2
HO
NO2
HO
IV
HO
NH2
HO
Ia
HO
+
NH3Cl
HO
V
HO
AcO
NO2
AcO
VI
AcO
HO
NHAc
HO
VII
AcO
AcO
NHAc
AcO
Ib
OAc
MsO
NHAc
OMs
VIII
HO
NHAc
HO
Ic
HO
OH
NHAc
OAc
IX
+
NH3OAc
OAc
X
OAc
OAc
+
NH3OMs
XII
OMs
OH
NHAc
OH
IIc
OAc
NHAc
OAc
IIb
OH
NHAc
OMs
XIII
OH
NH2
OH
IIa
OH
+
NH3Cl
OH
XI
OH
NHAc
OH
IIIc
OH
NH2
HO
IIIa
OH
+
NH3Cl
OH
XIV
OAc
NHAc
AcO
IIIb
OAc
AcO
=O
XV
Ac = CH3CO-
Ms = CH3SO2-

To obtain evidence for the configuration of Ia, an inversion reaction of its mesyl derivative was applied. When a cyclohexane ring containing vicinal mesyloxy and acylamido groups in trans position is treated with sodium acetate in refluxing aqueous 2-methoxyethanol, the replacement of mesyloxy group takes place with Walden inversion through an intermediary oxazolinium ion to give *cis*-acylamido alcohol.[15] When vicinal mesyloxy and acylamido groups are in cis position, the replacement of mesyloxy group takes place at a considerably slower rate.[16]

The compound, Ic, gave 2α-acetamido-di-O-mesyl-1β,3β-cyclohexanediol (VIII) by reaction with mesyl chloride in pyridine. VIII was treated with sodium acetate for 6 hr. in refluxing 95% aqueous 2-methoxyethanol which resulted in the loss of both mesyl groups. But, instead of the expected N-acetyl derivative, a N, O-diacetyl derivative (IX) was obtained. Acetylation of IX with acetic anhydride in pyridine gave a triacetyl derivative (IIb) melting at 146.5°C. A mixed melting point of IIb with Ib was depressed. A selective deacetylation of IIb with methanol saturated with ammonia yielded a N-acetyl derivative (IIc) melting at 142.5°C.

The fact that the replacement of the two mesyloxy groups in VIII took place at a considerably high rate showed that both C-1 and C-3 mesyloxy groups were probably situated in trans position to the C-2 acetamido group.[16] At first the displacement of mesyloxy group occurred with a formation of oxazolinium ion, which was attacked by water to yield *cis*-acetamido alcohol. Then the displacement of another mesyloxy group gave the second oxazolinium ion, which was probably attacked by a liberated acetate ion to yield *trans*-acetamido acetate. Therefore, it seemed probable that IIb had cis-trans configuration.

Also displacement of both mesyloxy groups of VIII gave DL-O-acetyl-2α-amino-1α, 3β-cyclohexanediol acetate (X), when the reaction with two moles of sodium acetate was carried out in boiling water for 1 hr. X gave IIb in 74% over-all yield, after acetylation. Studies on the mechanism of this reaction are in progress.

When IIb was hydrolyzed by refluxing 6 N hydrochloric acid for 7 hr., DL-2α-amino-1α, 3β-cyclohexanediol hydrochloride (XI) melting at 124.5°C was obtained. The free base (IIa) melting at 113°C was recovered from XI by neutralizing XI with sodium hydroxide solution. Paper chromatograms of IIa showed a single spot (Rf 0.39) in 1-butanol–acetic acid–water (4 : 1 : 5).

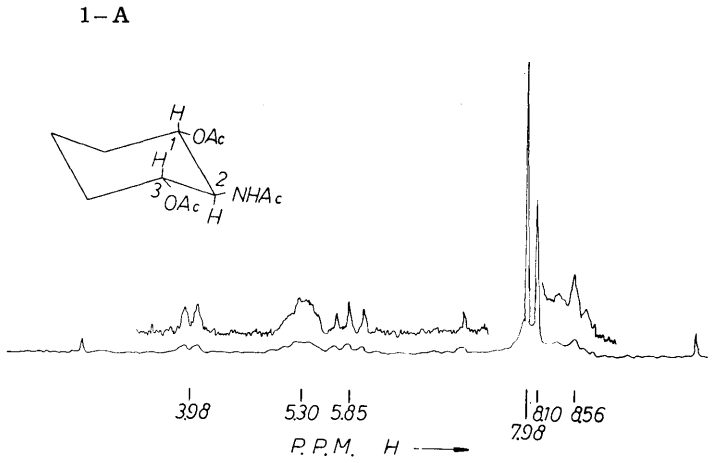
When VIII was refluxed in water for a few minutes without adding any sodium acetate DL-O-acetyl-O-mesyl-2α-amino-1α,3β-cyclohexanediol methanesulfonate (XII) resulted in 74% yield. In this reaction, the replacement of mesyloxy group yielded an oxazolinium ion which was attacked by water to give *cis*-acetamido alcohol as usual. Then the acetyl group could migrate from N to O in an acidic medium to yield XII, which could not undergo a further inversion, owing to a lack of an acetamido group adjacent to mesyloxy group.

On treatment with sodium hydroxide solution, XII gave DL-2α-acetamido-O-mesyl-1α,3β-cyclohexanediol (XIII) in 73% yield. Accordingly, it must involve O→N

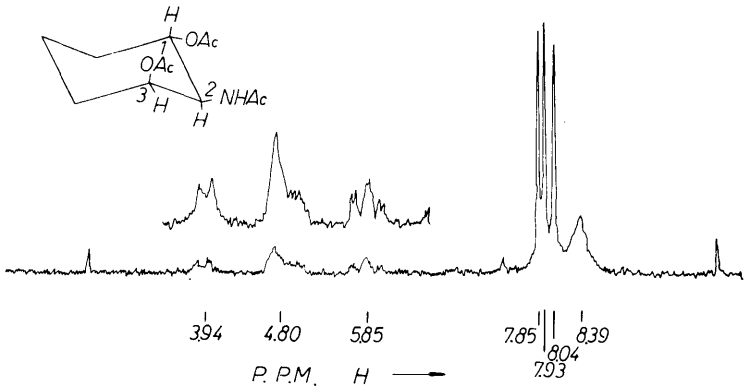
migration of acetyl group.[17] Since XIII had the mesyloxy group situated in trans position to the vicinal acetamido group, a further inversion was expected. XIII was refluxed in 95% aqueous 2-methoxyethanol for 5 hr. to yield the N-acetyl derivative (IIIc) with inversion of configuration. IIIc was acetylated to give triacetyl derivative (IIIb) melting at 179°C. IIIb was hydrolyzed by refluxing 6 N hydrochloric acid to give 2α-amino-1α,3α-cyclohexanediol hydrochloride (XIV) melting at 161,5°C. The free base (IIIa) melting at 128°C was obtained from XIV by an ordinary method. Paper chromatograms of IIIa showed a single spot (Rf 0.37) in 1-butanol–acetic acid–water (4 : 1 : 5).

Now IIIb is different from Ib and IIb, and therefore IIIb must have cis configuration. While IIIb is obtained by a different synthetic route starting from *cis*-2, 6-diacetoxycyclohexanone (XV). XV is prepared by oxidation of cyclohexanone with lead tetra-acetate in boiling benzene.[18] The structure and configuration of XV have been established by converting it to 1α,2α,3α-cyclohexanetriol of known configuration.[19] Anderson and Lardy[20] found that the primary amine obtained from the phenylhydhazone or oxime of *scyllo*-inosose was almost exclusively a single isomer, when glacial acetic acid was used as a solvent and Adams platinum oxide as a catalyst. So the reduction of *cis*-2,6-diacetoxycyclohexanone oxime is carried out by applying the condition of Anderson and Lardy.[20] Then the crude reduction product is treated with acetic anhydride and pyridine to obtain the compound which is identical with IIIb. Since the starting material, XV, has the known configuration, the only point requiring to be clarified is the configuration of a newly introduced amino group. The steric selectivity of the reduction condition employed in this synthesis seems well enough to assign IIIb as all-cis configuration.

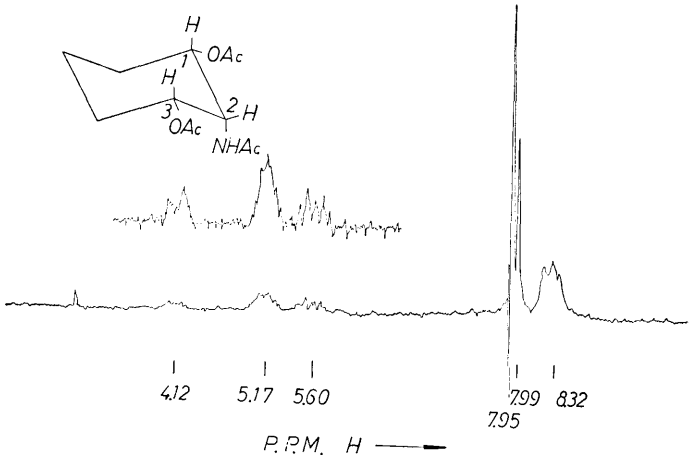
The above considerations regarding the structure of Ib, IIb, and IIIb are fully substantiated by means of their proton magnetic resonance spectra as described below.



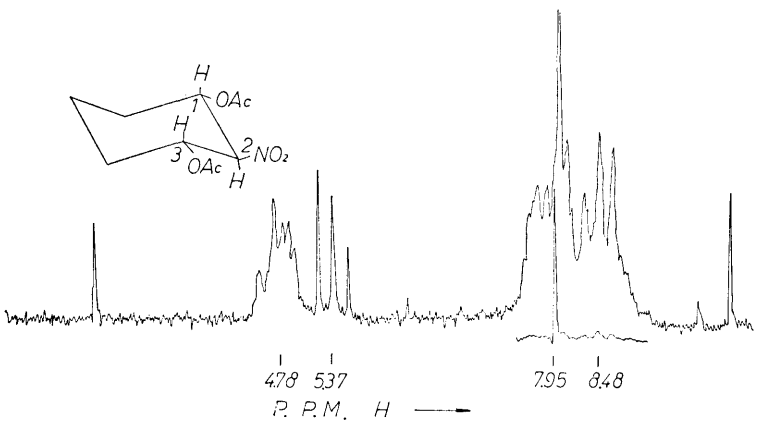
1-B


H
OAc
1
OAc
3
H
2
NHAc
H
3.94
4.80
5.85
7.85
8.04
7.93
8.39
P. P.M. H

1-C


H
OAc
1
H
3
OAc
2
H
NHAc
4.12
5.17
5.60
7.99
7.95
8.32
P. P.M. H

1-D


H
OAc
1
H
3
OAc
2
NO2
H
4.78
5.37
7.95
8.48
P. P.M. H

The usefulness of proton magnetic resonance spectra in configurational and conformational analysis has been well established in cyclohexane derivatives. Lemieux, Kullnig, Bernstein and Schneider[21] have shown on both *myo*- and *l*-inositol hexaacetate that the signals of the protons of an axial acetoxy group appear at lower field than those of an equatorial acetoxy group. Recently Lichtenthaler and Fischer reported the same results on *neo*-inositol derivatives[11] and hexaacetyl-*myo*-inosamine.[22]

In the present studies, an axial acetoxy group could be expected to produce a signal at lower field than an equatorial acetoxy group in triacetyl derivative of 2-amino-1,3-cyclohexanediol, and configurational assignments could be made on the basis of this point. That is, both the structures of I and III had two equatorial acetoxy groups and could be expected to have a sharp signal for the protons in acetoxy groups. While the structure II has only one equatorial acetoxy group and another acetoxy group in an axial position, these protons in acetoxy groups should produce two signals of an equal relative intensity. The spectra obtained for the triacetyl derivatives of three diastereomers of 2-amino-1,3-cyclohexanediol were shown in Fig. 1.

The N M R spectrum of the compound, Ib, as shown in Fig. 1-A revealed two sharp signals of a 2 : 1 relative intensity, as expected from the protons of two equatorial acetoxy groups (observed τ of 7.98) and the equatorial acetamido group (τ of 8.10). IIb (Fig. 1-B) gave the spectrum with three sharp signals of 1 : 1 : 1 relative intensity, which would be expected for the axial acetoxy group (τ of 7.85), the equatorial acetoxy group (τ of 7.93) and the equatorial acetamido group (τ of 8.04). IIIb (Fig. 1-C) gave the spectrum with two sharp signals of a 2 : 1 relative intensity, as expected from the two equatorial acetoxy groups (τ of 7.96) and the axial acetamido group (τ of 8.01).

Also Lemieux, Kullnig, and Moir[23] assigned the configurations of two diastereomeric 2-acetoxy-1,3-dimethoxycyclohexanes on the basis of the fine structure of the signal of an axial proton in their N M R spectra. In the present studies, the axial proton on C-2 of the structure I was coupled with the two axial protons on the neighboring carbon atoms (C-1 and C-3) and the signal for this proton should be a triplet with an intensity of 1 : 2 : 1 ($J_{aa}=8\sim11.5$ c. p. s.).[24] In the case of the structure II, the proton on C-2 was coupled with an axial proton (C-1 or C-3) and an equatorial proton (C-3 or C-1). Since the coupling between an axial proton and an equatorial proton is considerably weaker than that between two axial protons, the signal for the proton on C-2 could be anticipated to be a quartet. Thus, it could be anticipated that the structure I and II could be distinguished on the basis of the fine structures of the signals for the protons on C-2. Also in the case of the structure III, it could be distinguished from the others by a lack of an axial proton on C-2. Obviously, the compound Ib was readily recognized as *trans* isomer by the triplet centered at 5.85 with a 1 : 2 : 1 relative intensity ($J=10.5$ c. p. s.)

in Fig. 1-A. However, the sextuplet at 5.85 in the observed spectrum shown in Fig. 1-B could not be interpreted without counting the spin-spin coupling between the proton on C-2 and the proton on nitrogen atom, but it might be readily understood on the basis of two protons corresponding to hindered rotation around the C-N bond.[25] The spin-spin coupling constant between the proton on C-2 and the proton on nitrogen atom in trans orientation was about 9.0 c. p. s., and this value was close to that of Jaa (10.5 c. p. s.) (the spin-spin coupling constant between two axial protons on adjacent carbon atoms of cyclohexane ring). The axial proton on C-2 was strongly coupled with the axial proton on C-1 and the proton on the nitrogen atom in trans orientation and also coupled weakly with the equatorial proton on C-3 (Jae=3.0 c. p. s.). Therefore, the signal for this proton on C-2 appeared as a sextuplet centered at 5.85 in the fine structure of the signal shown in Fig. 1-B. The same type of sextuplet was observed at 5.63 in the NMR spectrum of hexaacetyl-*myo*-inosamine.[18]

In Fig. 1-C, the signal for the proton on C-2 appeared in lower field (centered at 5.47) and it could be recognized that this proton was in an equatorial position. Since the spin-spin conpling of the equatorial proton on C-2 with the axial protons on C-1 and C-3 was considerably weak (Jae=4 c. p. s.),[24] the signal for the proton on C-2 could be expected to be a narrow triplet. But this triplet was further resolved by the proton on the nitrogen atom as shown in Fig. 1-C. Therefore, IIIb was assigned as cis configuration.

The signal of the protons on C-1 and C-3 was not well resolved, but a width of the signal presented some informations on the configurations. The spin-spin coupling constant is greater between two axial protons than between axial-equatorial or two equatorial protons.[26] So the most narrow peak width observed in Fig. 1-C was consistent with the configuration of IIIb.

The other six ring protons showed a signal at 8.3~8.6, as expected from the ring protons of cyclohexane in chair conformation.[27]

Also the proton on nitrogen atom in an amide group (-NH-) generally showed a signal at 2.0~5.0.[28]

Table 1.

Chemical Shifts Expressed in τ-Values

	Protons (C-1 and C-3)	Peak width c.p.s.
Ib	5.30	30
IIb	4.80	30
IIIb	5.04	17

Table 2.

Chemical Shifts Expressed in τ-Values

	Proton (-NH-)
Ib	3.97
IIb	3.94
IIIb	3.49

The di-O-acetyl nitro compound, VI, gave a triplet for the signal of the proton on C-2 (τ of 5.37)[20] and was readily recognized as a trans isomer with three substituents in equatorial orientations. The triplet arised from an axial proton coupled with two adjacent axial protons (observed Jaa=10.5 c. p. s.). Also VI revealed one sharp signals (τ of 7.95), as expected from the protons of two equatorial acetoxy groups. Only in the trans configuration with the given conformation, the axial proton on C-2 could be adjacent to two other axial protons on C-1 and C-3.

As a result of these considerations on the NMR spectra and the chemical evidences, it might be concluded that the compound, Ib, m. p. 152.5°C, has the trans configuration, IIb, m. p, 146.5°C, has the cis-trans configuration, and IIIb, m. p. 179°C, has the cis configuration.

Experimental

All melting points were corrected, and unless noted otherwise, were measured in capillaries in a liquid bath. Melting points with asterisks were measured on a Mitamura-Riken micro hot stage. The NMR spectra of all the acetyl derivatives were determined in a frequency of 60 Mc. p. s. with a Japan Electron Optics instrument JNM-C-60 in deuteriochloroform containing tetramethylsilane as an internal reference. Peak positions were given in τ-values. Infrared spectra were measured on a Hitachi Model EPI-2 infrared spectrophotometer. The spectra were recorded in potassium bromide pellets.

2α-Nitro-1β,3β-cyclohexanediol (IV). …… A 7.7g. portion of nitromethane was added to a mixture of 50 ml. of commercially available 25% aqueous glutaraldehyde, 90 ml. of methanol and 90 ml. of water. A 50 ml. of aqueous solution of 6.6g. of anhydrous sodium carbonate was added to the mixture in thirty minutes under ice cooling (at 0—5°C) with vigorous agitation. Then the mixture was continuously agitated under ice cooling for 3 hr., and kept in a refregirator overnight. The excess of solvent was evaporated under reduced pressure below 40°C to obtain a pale yellow crystalline residue. The residue was added to 200 ml. of methanol, and an insoluble inorganic salt was removed by filtration. The filtrate was evaporated to dryness under reduced pressure below 40°C. After being dried in a desiccator, the pale yellow product was extracted with ether in a Soxhlet extractor for thirty hr. During a course of extraction, the colorless crystalline product deposited in the solvent vessel of the Soxhlet apparatus. Then the product was collected by filtration to yield 11.8g. (59%) of crystals melting at 155.5—159.5°C. Evaporation of the filtrate yielded 0.2 g. of the second crop of the product. The total yield was 12.0 g. (59.5%). The product was recrystallized from ethyl acetate to yield an analytical sample of fine needles sintering at 140°C and melting at 161.5—163.5°C.

Anal. Calcd. for $C_6H_{11}NO_4$ (161.2) : C, 44.71; H, 6.88; N, 8.69. Found : C, 44.92; H, 6.70; N, 8.71.

The product was soluble in dioxane, ethyl alcohol, water and ethyl acetate, and insoluble in cold ether, benzene and light petroleum ether.

The infrared spectrum of the product showed the absorptions for hydroxyl groups (broad band at 3270 cm.$^{-1}$), nitro group (at 1550 and 1375 cm.$^{-1}$) and cyclohexane ring (at 948 cm.$^{-1}$).

2α-Amino-1β,3β-cyclohexanediol (Ia). …… (a) A mixture of 5.0 g. of IV and 50 ml. of absolute ethanol was hydrogenated at room temperature under 40 p. s. i. g. of initial hydrogen pressure with Raney nickel T4 catalyst[13] obtained from 7.0 g. of Raney nickel alloy in Parr shaker type hydrogenation apparatus for 1 hr. After the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure to obtain a colorless crystalline residue. The residue was recrystallized from absolute ethanol to yield 2.3 g. (56%) of needles melting at 190.5—193.5°C (decompose). The 2nd crop of the product (0.25 g.) was obtained from the mother liquor by evaporating a half volume of the solvent. The total yield was 62.5%. One recrystallization from ethanol gave analytically pure sample melting at 191.5—193.5°C (decompose). (Reported m. p was 190—192°C).[12]

Anal. Calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found : C, 54.77; H, 9.72; N, 10.74.

The infraed spectrum of the product showed the absorptions for hydroxyl groups (broad band at 3350 cm.$^{-1}$), amino group (at 1587 cm.$^{-1}$) and cyclohexane ring (at 929 cm.$^{-1}$).

Paper Chromatography. …… 1-Butanol–ethanol–water (2 : 1 : 3) gave a single spot of Rf of 0. 59 (Rf of glucosamine hydrochloride, 0.33) in ascending development at 23°C. The spot was developed with ninhydrin in pyridine without heating. Both the pure crystals and the crude product gave single spots in the same Rf region and no other spot was observed in a different Rf region. Also an upper layer of 1-butanol–acetic acid–water (4 : 1 : 5) gave only one spot of Rf 0.45 in ascending development at 25°C (Rf of glucosamine hydrochloride, 0.14).

Periodate Oxidation. …… A 100 mg. portion of Ia was treated with 100 ml. of 0.1 M sodium meta periodate solution at 24°C. Iodometric titrations with sodium arsenite[29] revealed that 1.91 moles of periodate was consumed per mole of Ia in 20 hr.

(b) A mixture of 15.0 g. of IV, 75 ml. of ethanol and 75 ml. of water was hydrogenated, as described above for the hydrogenation of IV in absolute ethanol, to yield 5.7 g. (46%) of Ia.

Di-O-acetyl-2α-nitro-1β,3β-cyclohexanediol (IV). …… One gram portion of IV was added slowly to a mixture of 15 ml. of acetic anhydride and 0.25 ml. of concentrated sulfuric acid under water cooling. After the mixture was heated at 50°C for one hour, it was poured into 100 ml. of ice-water with agitation. After standing

for one hour at room temperature, the precipitate was collected by filtration, washed with cold water and dried in a desiccator overnight to obtain 5.2 g. (79%) of the crude product, m. p. 85—89°C. The product was recrystallized twice from 40% aqueous methanol to yield fine needles melting at 88—90°C. (Reported m. p. was 89—90°C).[12]

Anal. Calcd. for $C_{10}H_{15}NO_6$ (245.2) : C, 48.97; H, 6.17; N, 5.71. Found : C, 49.02; H, 6.05; N, 5.60.

The infrared spectrum showed the expected absorptions for ester groups (at 1752 cm^{-1}), nitro group (at 1563 and 1378 cm^{-1}) and cyclohexane (at 955 cm^{-1}).

2α-Amino-1β,3β-cyclohexanediol hydrochloride (V)...... (a) A 135 mg. portion of Ia was dissolved in 10 ml. of 0.1 N hydrochloric acid. The solution was evaporated under reduced pressure, and the evaporation of the residue was repeated with 5 ml. of absolute ethanol. After drying over phosphorus pentoxide in a desiccator, the crystalline residue was dissolved in 2 ml. of absolute ethanol and added with 3.5 ml. of absolute ether until a slight turbid. The mixture was settled in a refrigerator overnight to yield 143 mg. (84%) of the chloride melting at 143.5—145.5°C. Further recrystallization from ethanol and ether gave analytical sample melting at 143.5—145.5°C. (reported m. p. 143—145°C).[12]

Anal. Calcd. for $C_6H_{14}NClO_2$: C, 42.99; H, 8.42; N, 8.36; Cl, 21.15. Found : C, 42.73; H, 8.21; N, 8.52; Cl, 20.85.

The free base Ia was regenerated from the hydrochloride as described below. ..... A 374 mg. portion of V was dissolved in 30 ml. of absolute ethanol and added with a theoretical amount of 0.5 N sodium hydroxide solution. The mixture was evaporated under reduced pressure to dryness, and the residue was repeatedly extracted with absolute ethanol. The combined ethanol extract was evaporated under reduced pressure to yield 217 mg. (74%) of crystals melting at 188.5—190.5°C (decompose), undepressed upon admixture with Ia.

(b) A mixture of 200 mg. of Ib and 10 ml. of 6 N hydrochloric acid was refluxed for 6 hr. The hydrolyzed solution was evaporated under reduced pressure to dryness. After drying over sodium hydroxide pellets in vacuo, the residue was dissolved in 2 ml. of absolute ethanol and added with 6 ml. of absolute ether. The mixture was stored in a refrigerator to yield 100 mg. (77%) of needles melting at 143.5—145.5°C.

N,O-Diacetyl-2α-amino-1β,3β-cyclohexanediol (VII). ..... A mixture of 10 g. of VI and 120 ml. of absolute ethanol was hydrogenated at room temperature for 5 hr. at an initial hydrogen pressure of 47 p. s. i. g. with Raney nickel T4 catalyst,[13] obtained from 10 g. of Raney nickel alloy, in Parr shaker type hydrogenation apparatus. After the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure to yield 6.6 g. (75.2%) of pale yellow crystals. The crude

product was recrystallized from benzene to yield 5.4 g. (61.6%) of colorless needles melting at 126—130°C. An analytical sample was further recrystallized from benzene and melted at 130.5—131.5°C.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found : C, 55.62; H, 8.24; N, 6.63.

The infrared spectrum showed the absorptions at 3420 (OH), 3280, 1626, 1566 (amide), 1745 (ester) and 1025 cm.$^{-1}$ (cyclohexane).

Triacetyl-2α-amino-1β,3β-cyclohexanediol (Ib).····· (a) A 0.8 g. portion of Ia was added to a mixture of 20 ml. of pyridine and 10 ml. of acetic anhydride. The mixture was kept at room temprature for 48 hr. and then evaporated under reduced pressure to dryness. The residue was recrystallized from ethanol to yield 1.4 g. (89%) of the product melting at 150.5—152.5°C. The product was recrystallized again from ethanol to give prisms melting at 151—152.5°C.

Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.02 ; H, 7.44 ; N, 5.44. Found : C, 56.17 ; H, 7.20 ; N, 5.56.

(b) A 2.0 g. portion of the crude product of VII was acetylated with 20 ml. of acetic anhydride and 20 ml. of pridine at room temperature overnight. The mixture was evaporated under reduced pressure to yield a crude product of Ib. The product was recrystallized from ethanol to give 1.98 g. (83.0%) of needles melting at 152—152.5°C.

The product was identified with the triacetyl derivative which was prepared by acetylation of Ia, on the basis of a mixed melting point and infraed spectra.

The infrared spectrum of the product showed the absorptions at 3310, 1662, 1545 (amide), 1732 (ester) and 957 cm.$^{-1}$ (cyclohexane).

2α-Acetamido-1β,3β-cyclohexanediol (Ic).····· (a) Ib (0.6 g.) was added to 25 ml. of methanol saturated with ammonia at 0—5°C. The mixture was kept at room temperature for 24 hr. and evaporated under reduced pressure to obtain a crystalline residue. The residue was recrystallized from 10 ml. of ethanol to yield 0.31 g. (77%) of crystals melting at 208.5—210°C. The product was recrystallized again from ethanol giving needles melting at 209—210°C.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found : C, 55.60; H, 8.64; N, 8.31.

(b) Ib gave 2.15 moles of acetic acid on hydrolysis under Kunz's conditions,[14] as described below : a 250 mg. portion of Ib was dissolved in 25 ml. of acetone and added with 50 ml. of 0.1 N potassium hydroxide solution under ice cooling. The mixture was kept below 0°C for 2 hr. and then an excess of alkali was titrated with 0.2 N hydrochloric acid.

The neutralized solution was evaporated in vacuo and the residue was extracted with acetone. The combined acetone extract was evaporated to yield a crude

product of N-acetyl derivative (Ic). The procuct was recrystallized from ethanol to yield 48 mg. (28.2%) of crystals melting at 208.5—210°C.

The product showed characteristic infrared absorptions at 3300 (OH), 1650, 1570 (amide), and 945 cm.$^{-1}$ (cyclohexane).

The product (200 mg.) did not consume any periodate in 50 hr. in a mixture of 40 ml. of 0.1 M sodium meta periodate solution and 10 ml. of methanol at 26°C.

2α-Acetamido-di-O-mesyl-1β,3β-cyclohexanediol (VIII). ····· To a mixture of 3.5 g. of Ic and 80 ml. of pyridine, 3.5 ml. of methanesulfonyl chloride was added with agitation at 0°C. Then the mixture was agitated at room temperature for 5 hr. The mixture was quenched on ice-water to yield colorless needles. The product was collected by filtration, washed with cold water and dried. The second crop was recovered from the filtrate by evaporation. The total yield was 5.3 g. (80%), m. p. 153—154°C. (Reported m. p. was 152—153°C).[12]

Anal. Calcd. for $C_{10}H_{19}NO_7S_2$: C, 36.46; H, 5.82; N, 4.25; S, 19.47. Found : C, 36.86; H, 5.96; N, 4.27; S, 19.43.

The infrared spectrum of the product showed the absorptions for amide group (at 3240, 1640 and 1562 cm.$^{-1}$), and mesyloxy group (at 1177 and 1346 cm.$^{-1}$)

DL-N,O-Diacetyl-2α-amino-1β,3β-cyclohexanediol (IX). ····· A mixture of 2.0 g. of VIII, and 40 ml. of 95% 2-methoxyethanol was refluxed for 6 hr. After cooling at room temperature, the mixture was filtered to remove insoluble matter. The filtrate was evaporated to dryness under reduced pressure. After drying in a desiccator, the residue was extracted with boiling acetone. The acetone extract was evaporated under reduced pressure to yield an oily residue. The residue was crystallized from a mixture of ethanol and ether to obtain 0.48 g. (36%) of plates melting at 142—147°C. The product was recrystallized from ethanol-ether to yield colorless plates melting at 148—152°C. (Reported m. p. was 149—151°C).[12]

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found : C, 55.96; H, 7.98; N, 6.43.

The infrared spectrum showed the absorptions for hydroxyl group (at 3410 cm.$^{-1}$), amide group (at 3340, 1658 and 1552 cm.$^{-1}$), ester group (at 1714 cm.$^{-1}$), and cyclohexane ring (at 1035 and 962 cm.$^{-1}$).

DL-O-Acetyl-2α-amino-1α,3β-cyclohexanediol acetate (X). ····· A mixture of 5.0 g. of VIII, 2.75 g. of anhydrous sodium acetate and 100 ml. of water was refluxed for 1 hr. Then the mixture was evaporated under reduced pressure to dryness. The residue was extracted with boiling acetone repeatedly. The combined acetone extract was evaporated under reduced pressure to yield a crystalline residue. The residue was washed with a small amount of cold acetone to give 1.3 g. (20%) of colorless needles melting at 104—113°C. One recrystallization from acetone

afforded needles melting at 130.5—132°C, which was shown by infrared spectrum and elemental analysis to be DL-O-acetyl-2α-amino-1α,3β-cyclohexanediol acetate.

Anal. Calcd. for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.01. Found : C, 51.33; H, 8.44; N, 6.14.

The infrared spectrum of the product showed the absorptions for hydroxyl group (at 3200 cm.$^{-1}$), ester group (at 1725 cm.$^{-1}$), NH_3^+ (at 1638 cm.$^{-1}$), COO^- (at 1405 and 1547 cm.$^{-1}$) and cyclohexane ring (at 980 cm.$^{-1}$).

DL-Triacetyl-2α-amino-1α,3β-cyclohexanediol (IIb). ····· A mixture of 5.0 g. of VIII, 2.75 g. of anhydrous sodium acetate, and 100 ml. of water was refluxed for 1 hr. The mixture was evaporated under reduced pressure to dryness at 50°C, and the residue was extracted with 300 ml. of boiling acetone. The acetone extract was evaporated in vacuo. After the addition of 25 ml. of acetic anhydride, the residue was settled at room temperature overnight and then heated at 80°C for 1 hr. The mixture was evaporated under reduced pressure. The residue was dissolved in 100 ml. of chloroform, and the chloroform solution was washed with cold water, dried over anhydrous sodium sulfate and then evaporated in vacuo to dryness. Crystallization of the residue with a mixture of benzene afforded colorless crystals melting at 144.5—146.5°C, which showed melting point depression on admixture with Ib.

Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found : C, 55.81; H, 7.35; N, 5.39.

The infrared spoctrum of the product showed the absorptions for amide group (at 3270, 1643 and 1533 cm.$^{-1}$), ester group (at 1738 cm.$^{-1}$) and cyclohexane ring (at 945 cm.$^{-1}$).

DL-2α-Acetamido-1α,3β-cyclohexanediol (IIc). ····· IIb was selectively hydrolyzed with methanol saturated with dry ammonia as described in Ic to give the crude product melting at 137—140°C in 74% yield. The product was recrystallized from acetone to yield needles melting at 138—141°C. (Reported m. p. was 142—143°C).[12]

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found : C, 55.65; H, 8.37: N, 8.46.

The infrared spectrum showed the absorptions for hydroxyl group (at 3350 cm.$^{-1}$) and amide group (at 1613 and 1558 cm.$^{-1}$).

DL-2α-Amino-1α,3β-cyclohexanediol hydrochloride (XI). ····· A mixture of 0.3 g. of IIb and 15 ml. of 6 N hydrochloric acid was refluxed for 7 hr. The mixture was evaporated under reduced pressure, and the residue was evaporated twice with 5 ml. of absolute ethanol. After drying over sodium hydroxide, the residue was dissolved in 4 ml. of absolute ethanol and added with absolute ether. The mixture was kept in a refrigerator to yield 0.13 g. (67%) of crystals melting at 111—117°C. The product was recrystallized from absolute ethanol-absolute ether to yield fine

needles melting at 115—117°C after sintering at 110°C.

Anal. Caled. for $C_6H_{14}NClO_2$: C, 42.99; H, 8.42; N, 8.36; Cl, 21.15. Found : C, 42.89; H, 8.40; N, 8.18; Cl, 21.33.

The infrared spectrum showed the absorptions for hydroxyl group (at 3320 cm.$^{-1}$), NH_3^+ (at 1590 and 1493 cm.$^{-1}$) and cyclohexane ring (a 983 cm.$^{-1}$).

DL-2α-Amino-1α,3β-cyclohexanediol (IIa). ····· A 517 mg. portion of XI was dissolved in 50 ml. of ethanol and added with 6.2 ml. of 0.5 N sodium hydroxide solution. The mixture was evaporated under reduced pressure to dryness. The residue was extracted three times with 10 ml. of absolute ethanol. The combined ethanol extract was evaporated under reduced pressure to yield 400 mg. (98%) of a crude product which crystallized gradually in a vacuum desiccator. The crude product melting at 109—110°C was recrystallized from absolute ethanol–absolute ether to give hygroscopic crystals melting at 112—113°C.

Anal. Calcd. for $C_6H_{13}NO_2$: C, 54.93; H, 9.99; N, 10.68. Found : C, 54.81; H, 10.01; N, 10.89.

Paper Chromatography. ····· An upper layer of 1-butanol–acetic acid–water (4 : 1 : 5) gave a single spot of Rf 0.49 in ascending development at 25°C.

The infrared spectrum showed the absorptions at 3320 (OH), 1567 (amino), 980 cm.$^{-1}$ (cyclohexane).

DL-O-Acetyl-O-mesyl-2α-amino-1α,3β-cyclohexanediol methanesulfonate (XII). ····· A mixture of 5.0 g. of VIII and 70 ml. of water was refluxed for a few minutes to give a clear acidic solution (pH 1.0). After settled at room temperature overnight, the solution was evaporated under reduced pressure. The residue was recrystallized from absolute ethanol to yield 3.6 g. (68%) of crystals melting at 173—174°C. The second crop of the product (0.3 g.) was recovered from the mother liquor. The total yield of the crude product was 74%. The product was recrystallized from ethanol to yield needles melting at 174.5—175°C.

Anal. Calcd. for $C_{10}H_{21}NO_8S_2$: C, 34.57; H, 6.09; N, 4.03; S, 18.46. Found : C, 34.80; H, 6.23; N, 3.97; S, 18.11.

The infrared spectrum showed the characteristic absorptions for ester (at 1740 cm.$^{-1}$), NH_3^+ (at 1622 and 5538 cm.$^{-1}$), and mesyloxy group (at 1355 and 1170 cm.$^{-1}$).

DL-2α-Acetamido-O-mesyl-1α,3β-cyclohexanediol (XIII). ····· A 2.0 g. portion of XII was dissolved in 6 ml. of water, and adjusted with 10% potassium hydroxide solution to pH 11. Then the solution was cooled in an ice bath to give white crystalline precipitate. After cooling at 0°C for 1 hr., the product was collected by filtration, washed with a small amount of ethanol and dried in a vacuum desiccator overnight to yield 1.05 g. (72.5%) of crystals melting at 118—119°C. A sample

was recrystallized from ethanol for analysis to show its melting point at 118—118.5°C.

Anal. Calcd. for $C_9H_{17}NO_5S$: C, 43.01; H, 6.82; N, 5.58; S, 12.78. Found: C, 43.17; H, 7.07; N, 5.61; S, 12.69.

The infrared spectrum of the product showed characteristic absorptions at 3540 (OH), 3320, 1643, 1542 (amide), 1340, 1175 (mesyloxy) and 960 cm.$^{-1}$ (cyclohexane).

2α-Acetamido-1α,3α-cyclohexanediol (IIIc). …… (a) A mixture of 0.55 g. of XIII, 0.6 g. of anhydrous sodium acetate, 0.5 ml. of water and 10 ml. of 2-methoxyethanol was refluxed for 5 hr. The mixture was evaporated under reduced pressure to dryness. After drying in a vacuum desiccator, the residue was extracted with 10 ml. of boiling acetone five times, and the combined acetone extract was evaporated under reduced pressure to give an oily residue. Trituration of the residue with a mixture of ethanol and ether gave 0.30 g. (79%) of crystals melting at 118—120°C. Twice recrystallization from acetone afforded colorless needles melting at 120—123°C.

Anal. Calcd. for $C_8H_{19}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found : C, 55.21; H, 8.97; N, 8.31.

The infrared spectrum showed the absorptions at 3365 (OH), 3305, 1675, 1555 (amide) and 1045 cm.$^{-1}$ (cyclohexane).

b) A 203 mg. portion of IIIb was added to 10 ml. of methanol previously saturated with ammonia. The mixture was kept at room temperature overnight and evaporated under reduced pressure to obtain a crystalline residue. The product was recrystallized from ethanol to yield 117 mg. (85.6%) of crystals melting at 119—123°C.

Triacetyl-2α-amino-1α,3α-cyclohexanediol (IIIb). …… (a) A mixture of 2.2 g. of XIII, 2.4 g. of anhydrous sodium acetate, and 42 ml. of 95% aqueous 2-methoxyethanol was refluxed for 5 hr. After cooling at room temperature, the mixture was filtered to remove an insoluble precipitate. The filtrate was evaporated to dryness under reduced pressure. The residue was dried in a desiccator overnight and extracted with 20 ml. of boiling acetone four times. The combined acetone extracts were evaporated under reduced pressure. The residue was acetylated with a mixture of 20 ml. of acetic anhydride and 20 ml. of pyridine at room temperature for 24 hr. The mixture was evaporated in vacuo to yield a crystalline residue, which was crystallized from benzene to give 1.6 g. (71%) of colorless needles melting at 175.5—177.5°C. Analytical sample was obtained by recrystallization from benzene, m. p. 177.5—179°C.

Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found : C, 56.23; H, 7.56; N, 5.35,

The infrared spectrum of the product showed the absorptions at 3320, 1653, 1557

(amide), 1750 (ester) and 983 cm.$^{-1}$ (cyclohexane).

(b) A starting material, cis-2,6-diacetoxycyclohexanone (XV), was prepared by the method of Cavill and Solomon.[18] A mixture of 2.97 g. of XV and 70 ml. of methanol was added to a mixture of 1.49 g. of hydroxylamine hydrochloride, 2.58 g. of sodium hydroxide and 13 ml. of water under ice cooling. The mixture was kept in a refrigerator overnight and then evaporated under reduced pressure below 40°C. The residue was added to 40 ml. of absolute ethanol and an insoluble salt was removed by filtration. The filtrate was evaporated in vacuo to yield the oxime. The oxime could not be isolated from the residue as crystals. The crude oxime was dissolved in 50 ml. of glacial acetic acid. By employing the method of Anderson and Lardy,[20] the mixture was reduced with 0.57 g. of Adams platinum catalyst and atomospheric pressure of hydrogen. After shaking for 130 min. at room temperature, the mixture was filtered to remove the catalyst. The filtrate was evaporated in vacuo to leave a crude amine acetate. The crude product was acetylated with 12.5 ml. of acetic anhydride and 12.5 ml. of pyridine for 3 hr. at 100°C. The mixture was evaporated in vacuo and the residue was dissolved in 50 ml. of ethyl acetate. The solution was washed with water, dried over anhydrous sodium sulfate and evaporated in vacuo to yield a crystalline residue. The crude product was recrystallized twice from ethanol-ether to yield 0.33 g. (9.3%) of needles melting at 176.5—178°C.

A mixed melting point with the sample of (a) was undepressed.

2α-Amino-1α,3α-cyclohexanediol hydrochloride (XIV). …… A mixture of 2.0 g. of IIIb and 100 ml. of 6 N hydrochloric acid was refluxed for 6 hr. The mixture was evaporated under reduced pressure and evaporation of the residue was repeated with 5 ml. of absolute ethanol. The residue was kept in a dessicator to give 1.21 g. (93%) of crystals melting at 156.5—160°C. The crude product was recrystallized from absolute ethanol–absolute ether to give needles melting at 160.5—161.5°C.

Anal. Calcd. for $C_6H_{14}NClO_2$: C, 42.99; H, 8.42; N, 8.36; Cl, 21.15. Found : C, 42.67; H, 8.46; N, 8.41; Cl, 21.38.

The infrared spectrum showed the absorptions for hydroxyl group (at 3200 cm.$^{-1}$), NH_3^+ (at 1622 and 1542 cm.$^{-1}$) and cyclohexane (at 973 cm.$^{-1}$).

2α-Amino-1α,3α-cyclohexanediol (IIIa). …… A 1.02 g. portion of the crude product of XIV was dissolved in 70 ml. of ethanol and added with 12.2 ml. of 0.5 N sodium hydroxide solution. The mixture was evaporated in vacuo and the residue was extracted with absolute ethanol. The combined ethanol extract was evaporated in vacuo to yield 743 mg. (93%) of crystals melting at 78—83°C. The product was recrystallized from absolute ethanol–absolute ether to yield 322 mg. (40.5%) of crystals melting at 126—128°C.

Anal. Calcd. for $C_6H_{13}NO_2$: C, 54.93; H, 9.99; N, 10.68. Found : C, 54.65; H, 9.97; N, 10.84.

The infrared spectrum showed the absorptions for amino group (at 1585 cm.$^{-1}$), hydroxyl group (at 3300 cm.$^{-1}$) and cyclohexane (at 968 cm.$^{-1}$).

Paper Chromatography. ····· An upper layer of 1-butanol–acetic acid–water (4 : 1 : 5) gave a single spot of Rf 0.44 in ascending development at 25°C.

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