The Synthesis and Configurational Analysis of 2,3-Diaminocyclohexanol

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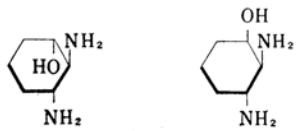
The previous studies on 2-amino-1,3-cyclohexanediol[1] have stimulated our interest in the synthesis of an alicyclic compound with two amino groups and one hydroxyl group. In the present paper, the synthesis of 2,3-diaminocyclohexanol is described, and its structure is established by means of the proton magnetic resonance spectra of the acetyl derivatives. Di-*O*-mesyl-*trans*-2-acetamido-1,3-cyclohexanediol (I)[2] is used as a starting material for this preparation. 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 III or compound IV is hydrolyzed by 6 N hydrochloric acid, giving 2,3-diaminocyclohexanol dihydrochloride (VI). The picrate is prepared from compound VI.

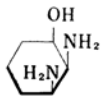
1) T. Suami and S. Ogawa, This Bulletin, **37**, 194 (1964).
2) F. W. Lichtenthaler *Chem. Ber.*, **96**, 845 (1963).

There are four predicted diastereomers of 2,3-diaminocyclohexanol (IX, X, XI and XII), but they are wholly unknown:

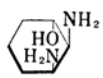


IX

X



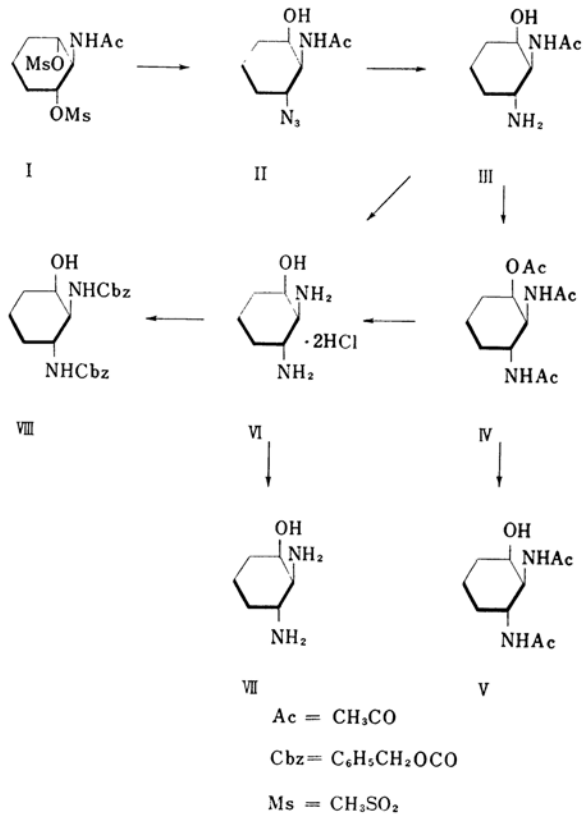
XI



XII

None of them has a plane of symmetry; hence, they are racemic forms.

In the present experiment, the starting material I 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.

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 X, but if it occurs with an inversion, the product should have the structure XI.

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 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 inosadiamine 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, shown in Fig. 1-B, shows only one sharp signal at 7.97 τ, as is to be expected from two acetamido

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

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. Kujomoto and E. L. Rollins, ibid., **85**, 3061 (1963).

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

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

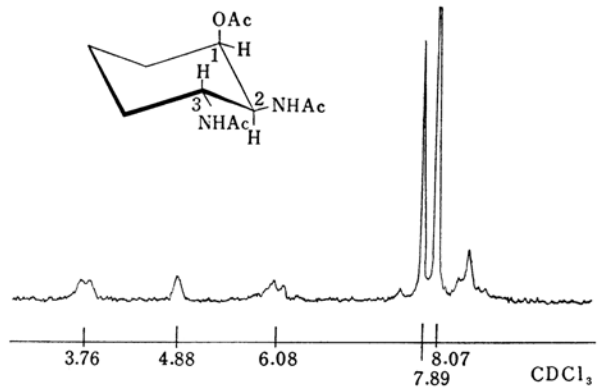


Fig. 1-A

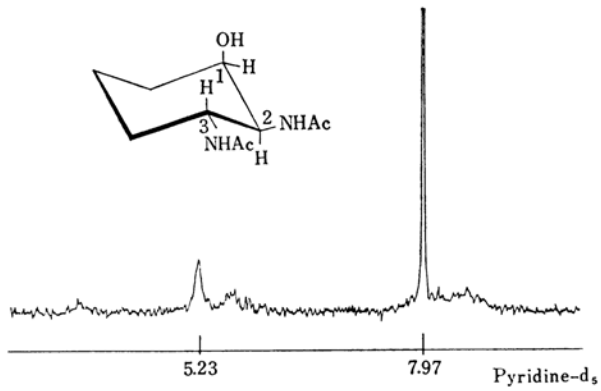


Fig. 1-B

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 may be assigned as $2\alpha, 3\beta$-diacetamido-1α-cyclohexyl acetate and that, accordingly, the attack of azide ions occurs anchimerically, with a retention of the configuration.

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 position are given in τ-values.

DL-2α-Acetamido-3β-amino-1α-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 100 ml. 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) and 1653, 1544 cm^{-1} (amide).

A solution of the sirup in 40 ml. of ethanol was hydrogenated with Raney nickel T4,[7] 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 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-2α, 3β-Diacetamido-1α-cyclohexyl Acetate (IV).—A mixture of 1.0 g. of compound III, 50 ml.

7) S. Nishimura, This Bulletin, 32, 61 (1959).

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 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-2α, 3β-Diacetamido-1α-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 (with decomposition). The sample for analysis obtained from ethanol-ether had an m. p. of 258~259°C (with 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-2α, 3β-Diamino-1α-cyclohexanol Dihydrochloride (VI). — a) A mixture of 0.5 g. of compound IV and 30 ml. of 6 N 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 (with decomposition). The analytical sample was obtained from methanol-ether as colorless plates, which started turning brown at 280°C and which melted at 301~303°C with 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 6 N hydrochloric acid was treated as described in a) to obtain 0.58 g. (82%) of the product, m. p. 290~293°C (with decomposition.)

DL-2α, 3β-Diamino-1α-cyclohexanol (VII). — A 8 ml. portion of a 0.5 N 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 (with 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*-carbobenzoxy-DL-2α, 3β-diamino-1α-cyclohexanol (VIII). — A 0.3 ml. portion of carbobenzoxy 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%.

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