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Synthetic Reactions of Aliphatic Nitro-Compounds. III. The Synthesis and Configurational Analysis of 2-Hydroxymethyl-2-aminocyclohexanediol

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In a previous communication,[1] the synthesis of a cyclic amino acid, 1-amino-2,6-dihydroxycyclohexane-1-carboxylic acid (**1**), by the base-catalyzed cyclization of glutaraldehyde with ethyl nitroacetate was described. The structure of **1**, as determined by interpreting the NMR spectrum of its derivative, was designated as 2β-carboxyl-2α-aminocyclohexane-1β,3β-diol.

In order to obtain further evidence to support the above configuration, we have now synthesized the tetraacetyl derivative (**4**), mp 149—150.5°C, of 2-hydroxymethyl-2-aminocyclohexanediol-1,3 (**3**), mp 150.5—151.5°C. We prepared in the steps shown in Chart 1, and then established its configuration by means of NMR spectroscopy. The NMR spectrum*2 of **4** shown in Fig. 1, shows three sharp singlets (3 : 6 : 3 in relative intensity) resulting from one equatorial acetamido group[2] (τ 8.06), one axial acetoxy group (τ 7.92) of a acetoxymethyl*1 at the C-2 position, and two equatorial acetoxy groups[2] (τ 7.96), suggesting that these two *O*-acetyl groups have the same orientation, a *cis*-configuration. The two axial ring protons on C-1 and C-3 appear as a broad signal at about τ 4.36, while the methylene protons on C-2 appear as a singlet at τ 5.36. The proton on nitrogen in the amide group shows its signal at 4.19 τ.

As a result of the consideration of the NMR spectrum of **4**, it can be concluded that the structure of **1** takes the same configuration as that described in our previous studies.

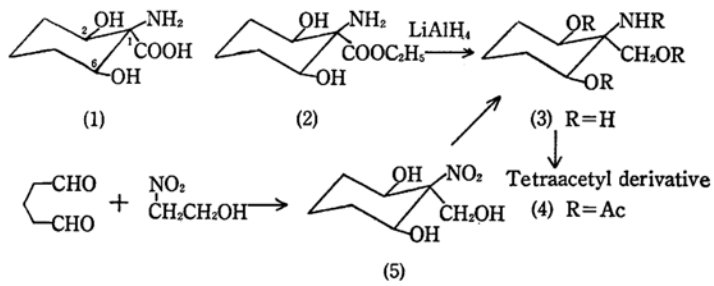

Chart. 1

1) S. Zen, Y. Takeda, A. Yasuda and S. Umezawa, This Bulletin, **40**, 431 (1967).

2) F. W. Lichtenthaler and P. Emig, *Tetrahedron Letters*, **1967**, 557.

*1 This group corresponds to the carboxyl group of **1**.

*2 These data agree well with those of F. W. Lichtenthaler (private communication).

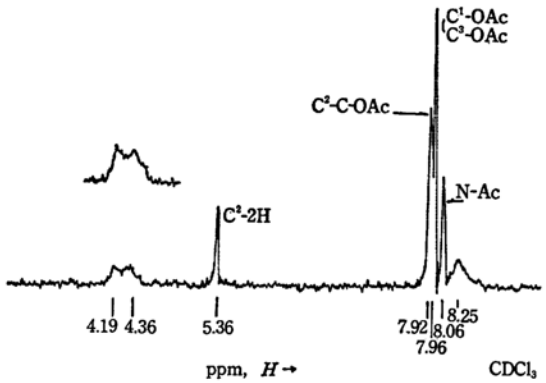

Fig. 1. NMR spectrum of tetraacetyl derivative (**4**).

Furthermore, we obtained the identical compounds, (**3** and **4**), through different steps; *i. e.*, we prepared then from 2-hydroxymethyl-2-nitrocyclo hexane-1,3-diol (**5**), mp 167—169°C, which had itself been synthesized by a cyclization of glutaraldehyde with nitroethanol under non-aqueous conditions. This fact leads to the conclusion that this cyclization proceeds in fashion analogous to Lichtenthaler's nitromethane-dialdehyde cyclization, in which the corresponding product has the *trans*-configuration.[3-5]

Experimental

2-Hydroxymethyl-2-aminocyclohexanediol-1,3 (3).—Procedure-A *Prepared from 2-Ethoxycarbonyl-2-aminocyclohexanediol-1,3* (*2*). To a mixture of lithium aluminium hydride (333 mg) and dioxane (60 m*l*), 600 mg of **2**[1] was added; then the mixture was heated for 9 hr with occasional shaking under reflux, guarded by a tube containing calcium chloride, and subsequently allowed to stand overnight. Then 30 m*l* of water was added slowly, and the mixture was stirred for one hour. The precipitate thus formed was collected by filtration, and the filtrate was concentrated to dryness *in vacuo*. A yellow solid, 384 mg, was obtained in a yield of about 80%; it was crystallized from ethanol to give colorless needles, mp 150.5—151.5°C: ν(KBr), 3500, 3220 (OH) 1540 (NH), 1093 and 1050 cm^{-1} (OH). Found: C, 52.19; H, 9.35; N, 8.49%. Calcd. for $C_7H_{15}O_3N$: C, 52.17; H, 9.31; N, 8.69%.

Procedure-B *Prepared by the Reduction of 2-Hydroxymethyl-2-nitrocyclohexanediol-1,3* (*5*). 500 mg of the nitro-alcohol (**5**) was hydrogenated for 1 hr with 3m*l* of the Raney Nickel T-1[6] catalyst in 30 m*l* of ethanol at about 40°C under 55 psi of hydrogen*3. The filtrate from the nickel was evaporated *in vacuo* to dryness to give the crude product, light green-yellow crystals (377 mg), mp 144—146°C in a 90% yield. The sample, consisting of colorless needles for analysis obtained from ethanol, had a mp of 150—151°C.

This product was found to be identical with the above sample prepared from **2** (by procedure A) by a mixed-melting-point determination and by a comparison of their infrared spectra.

Tetraacetyl Derivative (*4*) *of* *3*. To a solution of 50mg of **3** (prepared by Procedure A), in acetic anhydride (5 m*l*), 5 m*l* of pyridine was added, and then the mixture was allowed to stand overnight at room temperature. After the mixture was then treated as usual, an amorphous powder was obtained in a yield of 96%; it was then recrystallized from ethyl acetate-ligroin as colorless needles (mp 149—150.5°C), ν(KBr): 1740 (CO), 1640, 1560, 1250 and 1225 cm^{-1}(amide). The NMR spectrum*4 of this compound is shown in Fig. 1.

Found: C, 54.81; H, 7.11; N, 4.34%. Calcd for $C_{15}H_{23}O_7N$: C, 54.71; H, 6.99; N, 4.25%.

The tetraacetyl derivative obtained by "procedure B" was found to be the same product (**4**) by an examination of its mp, the results of its elementary analysis, and its IR and NMR spectra.

2-Hydroxymethyl-2-nitrocyclohexanediol-1,3 (5). Freshly-distilled glutaraldehyde (3.0 g) and equimolar nitroethanol[7] (2.73 g) were dissolved in 10 m*l* of methanol. 1.5 m*l* of 3 N potassium hydroxide in methanol was then added to the mixture, which was agitated continuously at room temperature. The reaction mixture was made alkaline (pH 8.0—8.2). After two hours, it was acidified to pH 4 using a sulfuric acid. The salt thus precipitated was separated by filtration and then the filtrate was evaporated to dryness under reduced pressure.

The crystalline residue was washed with ethyl acetate to yield 1.40 g of the crude product, mp 150—160°C. After recrystallization from acetone, the analytical sample, mp 167—169°C was obtained as colorless needles. ν(KBr): 3260 (OH), 1542, 1355 cm^{-1} ($C-NO_2$).

Found: C, 43.79; H, 7.17; N, 7.16%. Calcd for $C_7H_{13}O_5N$: C, 43.98; H, 6.85; N, 7.33%.

The authors are indebted to Dr. Hamao Umezawa, the head of Institute of Microbial Chemistry, for his kindness for the measurements of NMR spectra.

3) F. W. Lichtenthaler, *Angew. Chem.*, **76**, 84 (1964).
4) F. W. Lichtenthaler, *Chem. Ber.*, **96**, 845 (1963).
5) T. Suami and S. Ogawa, This Bulletin, **37**, 194 (1964).
6) X. A. Dominguez, I. C. Lopez and P. Franco, *J. Org. Chem.*, **26**, 1625 (1961).
*3 Parr low-pressure hydrogenator (Parr Instrument Co.).
*4 The NMR spectrum (in $CDCl_3$) was determined by means of a Varian A-60 spectrometer. Tetramethylsilane was used as the internal reference.
7) W. E. Noland, "Organic Syntheses," Vol. 41, p. 67 (1961).