Aminocyclitols. VI.* The Synthesis and Configurational Analysis of *trans*-2, 3-Diaminocyclohexanol

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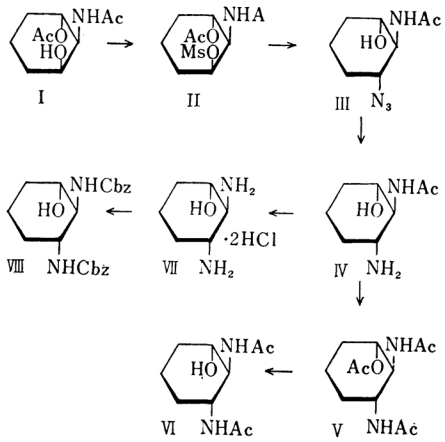
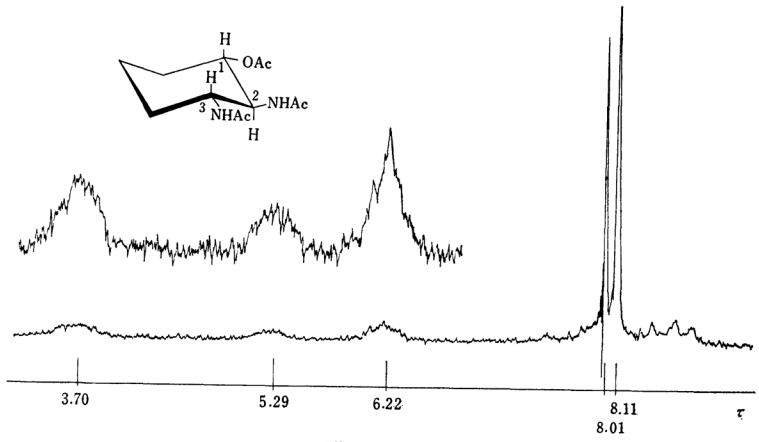
In connection with the previous papers of this series,[1] the synthesis of DL-*trans*-2, 3-diaminocyclohexanol and a study of its structure by means of the proton magnetic resonance spectrum of the acetyl derivative will be described in the present paper.



Starting from 1-*O*-acetyl-DL-2α-acetamido-1β, 3α-cyclohexanediol (I),[2] 1-*O*-acetyl-3-*O*-mesyl-DL-2α-acetamido-1β, 3α-cyclohexanediol (II) is obtained in 58% yield by treating I with methanesulfonyl chloride in pyridine.

Compound II is treated with sodium azide in boiling 90% aqueous 2-methoxyethanol to give DL-2α-acetamido-3β-azido-1β-cyclohexanol (III) as colorless crystals in 73% yield. Then III is hydrogenated with a platinum catalyst in a hydrogen stream to give DL-2α-acetamido-3β-amino-1β-cyclohexanol (IV) in 87% yield. On acetylating IV with acetic anhydride and pyridine, the triacetyl derivative (V) is obtained in 83% yield. When V is refluxed with 6 N hydrochloric acid, deacetylation takes place, giving the dihydrochloride (VII) in 92% yield. By an ordinary method, di-*N*-carbobenzyloxy derivative (VIII) is prepared in 96% yield. By deacetylating V with ammonia in methanol, diacetamidocyclohexanol (VI) is prepared in 89% yield.

The mesyloxy group is located in a cis position to the vicinal acetamido group in II; therefore, the replacement of the mesyloxy group by an azide ion should take place through a direct S_N2 mechanism.[3] As a result, the inversion of the configuration at C-3 must occur, and the product should be DL-2α-acetamido-3β-azido-1β-cyclohexanol. This configuration is also supported by the NMR spectrum of V; as is shown in Fig. 1, the spectrum



H, p. p. m.

Fig. 1

1) * Part IV: T. Suami and S. Ogawa, This Bulletin, 37, 733 (1964).

2) T. Suami and S. Ogawa, ibid., 37, 194 (1964)

3) T. Suami, F. W. Lichtenthaler and S. Ogawa, ibid., 38, 754 (1965).

reveals two sharp signals of a 1 : 2 relative intensity, as is to be expected from one equatorial acetoxy group (of 8.01 τ) and two equatorial acetamido groups (of 8.11 τ).[2,4] 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 protons than between axial-equatorial protons or two equatorial protons,[5] 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.[6]

Experimental

All the melting points have been corrected. The NMR spectrum was determined at a frequency of 60 Mc. p. s. with a Japan Electron Optics JNM-C-60 spectrometer in deuteriochloroform. Tetramethylsilane was used as an internal reference in the sample. Peak positions are given in τ-values.

1-*O*-Acetyl-3-*O*-mesyl-DL-2α-acetamido-1β, 3α-cyclohexanediol (II). — To a mixture of 3.5 g. of 1-*O*-acetyl-DL-2-acetamido-1,3-cyclohexanediol[2,7] 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-2α-Acetamido-3β-azido-1β-cyclohexanol (III). —A mixture of 2.2 g. of II, 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-2α-Acetamido-3β-amino-1β-cyclohexanol (IV). —A 1.05 g. portion of III 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-2α, 3β-Diacetamido-1β-cyclohexanol Acetate (V).—A mixture of 156 mg. of IV, 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-2α, 3β-Diamino-1β-cyclohexanol Dihydrochloride (VII).—A mixture of 455 mg. of IV and 25 ml. of 6 N hydrochloric acid was refluxed for 3 hr. and then evaporated to dryness in vacuo. The residue was recrystallized from 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[12] gave a single spot of R_f/R_fglucosamine: 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 R_f 0.19 at 23°C (R_f of glucosamine hydrochloride: 0.19).

DL-2α, 3β-Diacetamido-1β-cyclohexanol (VI).—A 136 mg. portion of V 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 with 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-2α,3β-diamino-1β-cyclohexanol (VIII).—To a mixture of 100 mg. of VII, 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%.

4) F. W. Lichtenthaler, *Chem. Ber.*, **96**, 2047 (1963).
5) S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).
6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London (1962), p. 73.
7) F. W. Lichtenthaler, *Chem. Ber.*, **96**, 845 (1964).

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