Aminocyclitols. V. A New Synthesis of 2-Amino-1, 3-cyclohexanediol*

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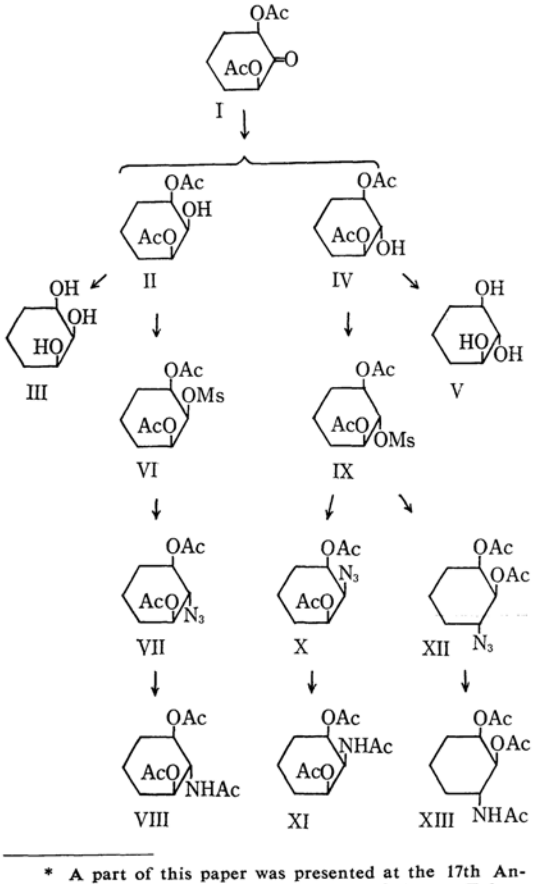
(Received September 5, 1964)

In the previous paper,(1) it has been described how the mesyloxy group of di-*O*-mesyl-*trans*-2-acetamido-1, 3-cyclohexanediol can be displaced by an azide group in an anchimeric reaction to DL-2-acetamido-3-azidocyclohexanol. In the present paper, the displacement of the mesyloxy group of 1, 3-di-*O*-acetyl-2-*O*-mesylcyclohexanetriol by a highly nucleophilic azide ion is the main subject.

As a starting material, 2, 6-diacetoxycyclohexanone (I)(2) is used, because its configuration has been shown to be cis by Cavill and Solomon.(2) The cis-configuration of I is, furthermore, confirmed by the NMR spectrum, which reveals one sharp signal at 7.79 τ for the methyl protons of the two acetoxy groups. Subsequently, they must be conformationally equivalent.(3)



When I is hydrogenated in a hydrogen stream with platinum oxide, a mixture of 1, 3-di-*O*-acetyl-*cis*-cyclohexanetriol (II) and 1, 3-di-*O*-acetyl-*trans*-cyclohexanetriol (IV) is obtained. Fractional crystallizations of the mixture from ethanol give only II as crystals in 40% yield. The configuration of II is confirmed by converting it to *cis*-1, 2, 3-cyclohexanetriol.(4) Several attempts have been made to obtain IV as crystals, but no satisfactory result has been achieved.

The deacetylation of the crude oily product of IV gives *trans*-1, 2, 3-cyclohexanetriol(4) (V) in 50% yield; this fact indicates that the oily product consists mainly of the trans-derivative.

Therefore, the above-mentioned, intact mixture is treated with methanesulfonyl chloride and pyridine to yield a mixture of mesyl derivatives VI and IX. When this mixture is then fractionated from ethanol, both VI and IX are obtained in pure crystalline states in 50 and 17% yields respectively. Also, VI is obtained almost quantitatively from II by treating it with methanesulfonyl chloride and pyridine, while IX is prepared from crude IV in 73% yield.

The configurations of VI and IX are substantiated by means of their proton magnetic resonance spectra. The NMR spectrum of VI, as shown in Fig. 1-A, shows signals for the two equatorial acetoxy groups at 7.93 τ, and for the axial mesyloxy group at 6.92 τ. The two axial ring protons show the signal at around 5.20τ, while the equatorial proton (C-2) reveals a 1 : 2 : 1-triplet at 4.90 τ of J_{ab} 2.5 c.p.s.,(5) proving the cis-configuration. The

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* A part of this paper was presented at the 17th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1964.

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

2) G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, **1955**, 4427.

3) In inositol derivatives, axial acetoxy groups usually absorb within the range of 7.78—7.87 τ [F. W. Lichtenthaler, *Chem. Ber.*, **96**, 2047 (1963)]. In view of the signal obtained (7.79 τ), this might indicate a diaxial orientation of the acetoxy groups in I. However, there are not sufficient NMR-data available for us to exclude an diequatorial orientation, for the shift to a lower field might also be caused by the neighboring carbonyl group. Thus, the configuration of I can be unequivocally deduced from the NMR spectrum, but not the exact orientation of the acetoxy groups.

4) T. Posternak and F. Ravenna, *Helv. Chim. Acta*, **80** 441 (1947).

5) S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).

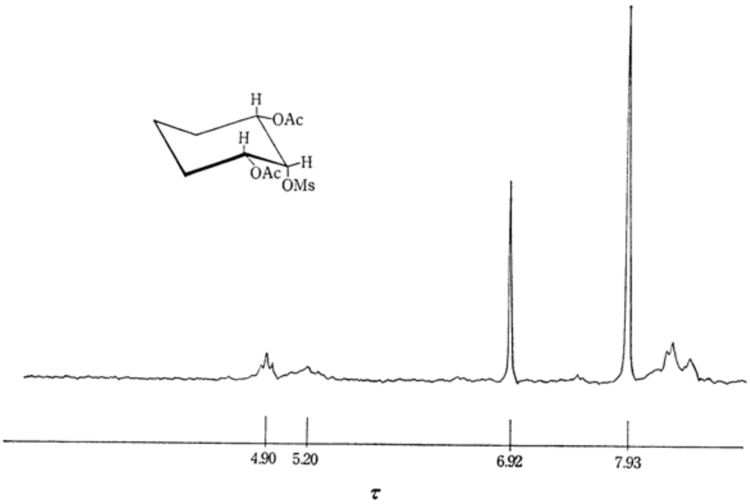

Fig. 1-A

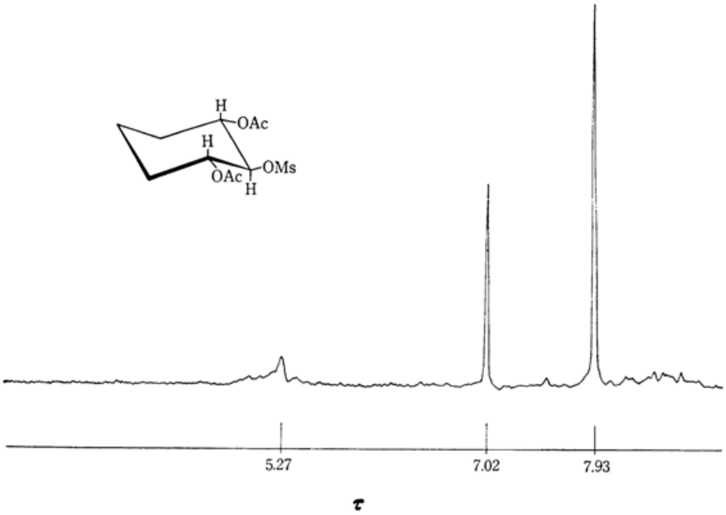

Fig. 1-B

NMR spectrum of IX, as shown in Fig. 1-B, gives signals at 7.93 τ, corresponding to the two equatorial acetoxy groups, and at 7.02 τ, corresponding to the equatorial mesyloxy group. The three axial ring protons are centered around 5.27 τ as an unresolved broad peaks.

This is the first interesting example of how the protons of mesyloxy groups appear at quite a different field from these of acetoxy groups; and the expected 0.1 p.p.m. difference is obtained between an axial and an equatorial mesyloxy group. Thus, the configuration of VI is established to be 1,3-di-*O*-acetyl-2-*O*-mesyl-*cis*-1,2,3-cyclohexanetriol. The configuration of the other mesylate obtained is probably that of 1,3-di-*O*-acetyl-2-*O*-mesyl-*trans*-1,2,3-cyclohexanetriol (IX). Since no acyl migration has been observed during the course of the reactions in the cis-isomer, there is more certainly no acyl migration⁽⁶⁾ in the case of the trans-isomer.

The treatment of VI with sodium azide in boiling aqueous 2-methoxyethanol or in boiling aqueous dimethylformamide yields an oily product (VII), which shows a strong characteristic azide absorption at 2090 cm^{-1}.⁽⁷⁾ The reduction of VII with a catalyst in a hydrogen stream and subsequent acetylation with acetic anhydride and pyridine give *trans*-2-acetamido-1,3-cyclohexanediol diacetate (VIII)⁽⁸,⁹⁾ in 41% yield.

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6) J. M. Sugihara, "Advances in Carbohydrate Chem.," Vol. 8, Academic Press Inc., New York (1953), p. 6.

7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, New York (1958), pp. 273—274.

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

9) T. Suami and S. Ogawa, This Bulletin, **37**, 194 (1964).

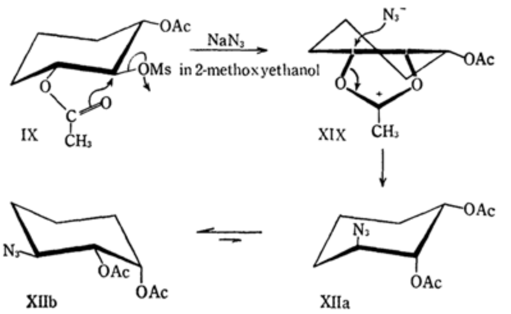
When a cyclohexane ring containing vicinal sulfonyloxy and acetoxy groups in the trans position is treated with sodium acetate in an appropriate solvent, the replacement of the sulfonate group takes place with Walden inversion through an intermediary acetoxonium ion, giving *cis*-acetate alcohol.[10] When they are in the cis position, the replacement occurs at a considerably slower rate,[11] because of an anchimerically-unassisted conformation.[12] A mechanism analogous to that of the reaction with sodium azide has been proposed.[1,13]

In the present experiment, the mesyloxy group of VI is located in the cis orientation to the vicinal acetoxy group; the fact that the *trans*-2-amino-1, 3-cyclohexanediol derivative is obtained as a main product indicates that the introduction of an azide group is operated predominantly by an S_N2 mechanism.

The demesylation of the *trans*-mesylate, IX, by an azide ion in boiling aqueous dimethylformamide is also dominated by a direct S_N2 reaction, since, upon the catalytic hydrogenation of the azido derivative (X) and the subsequent acetylation, the *cis*-triacetyl derivative (XI)[9] is obtained in 43% yield.

The same reaction, however, proceeds via quite a different stereochemical course when carried out in 2-methoxyethanol. Upon hydrogenation and acetylation *cis*-2-acetamido-1, 3-cyclohexanediol diacetate is obtained in only a 3% yield, whereas DL-3β-acetamido-1α, 2α-cyclohexanediol diacetate (XIII)[14,15] can be isolated in 25% yield.

The formation of XIII from IX can only be rationalized by assuming neighboring-group participation from the acetoxy group in the course of the reaction; the mesyloxy group is eliminated with the formation of an acetoxonium ion intermediate (XIX), in which the nucleophilic attack occurs predominantly at the quasi-equatorial C-O bond. Thus the diaxial product (XIIa) is primarily obtained, which product then switches over to the other more stable chair conformation (XIIb). This stereochemical course of the reaction has analogies in the opening of the acetoxonium ring by the acetate ion[12] and also in the nucleophilic oxirane-ring fission.[16,17]



The solvent-dependence of the course of the (IX → XIII) reaction—mainly a direct S_N2 reaction in dimethylformamide, and predominantly an anchimeric reaction in 2-methoxyethanol—can be explained by saying that the relative strengths of the two competing nucleophiles—an azide ion and an anchimeric acetoxy group respectively—are different in their solvents. Similar effects have been discussed in the demesylation of hexitol derivatives.[18]

Experimental

All melting points were measured on a Mitamura-Riken micro hot stage. The NMR spectra were determined at a frequency of 60 Mc.p.s. with Varian Associates A-60 and Japan Electron Optics JNM-C-60 spectrometers in deuteriochloroform. Tetramethylsilane was used as an internal reference. Peak positions were given in τ-values. The infrared spectra were recorded in potassium bromide pellets.

1, 3-Di-*O*-acetyl-*cis*-1,2,3-cyclohexanetriol (II).—The starting material, *cis*-2,6-diacetoxycyclohexanone (I), was prepared by the method of Cavill and Solomon.[2] A mixture of 5.0 g. of I and 150 ml. of ethanol was hydrogenated with 0.3 g. of platinum oxide in Parr shaker-type apparatus at 40°C for 23 hr. under 50 p.s.i.g. of an initial pressure of hydrogen. After the catalyst had been removed by filtration, the filtrate was evaporated under reduced pressure to yield 5.0 g. of a colorless semicrystalline residue. The residue was purified by crystallization from ethyl acetate to give 2.2 g. (44%) of needles melting at 103—104°C.

Found: C, 55.71; H, 7.55. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46%.

A solution of 81 mg. of II in 30 ml. of methanol previously saturated with ammonia was allowed to stand at room temperature overnight. The solution was then evaporated in vacuo to yield a crystalline residue, which was recrystallized from ethyl acetate to give 37 mg. of analytically-pure *cis*-1, 2, 3-cyclohexanetriol (III) melting at 146.5—147.5°C (lit.[3] m. p. 147—148°C). (Found: C, 54.52; H, 8.96%).

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[10] S. Winstein, H. V. Hess and R. E. Buckles, *J. Am. Chem. Soc.*, **64**, 2796 (1942); S. Winstein, C. Hanson and E. Grundwald, ibid., **70**, 812 (1948).

[11] S. Winstein, E. Grunwald, R. E. Buckles and C. Hanson, ibid., **70**, 816 (1948).

[12] E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York (1962), pp. 565—566.

[13] B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 442 (1963).

[14] R. A. B. Bannard and L. R. Hawkins, *Can. J. Chem.*, **36**, 1241 (1958).

[15] The infrared spectrum of an authentic sample of DL-3β-acetamido-1α, 2α-cyclohexanediol diacetate was kindly presented by Dr. R. A. B. Bannard of the Defence Research Chemical Lab., Ottawa, Canada.

[16] D. H. R. Barton, *J. Chem. Soc.*, **1953**, 1027; E. Eliel, in M. S. Newman, "Steric Effects in Organic Chemistry," J. Wiley & Sons, New York (1956), pp. 130—134.

[17] M. Nakajima, A. Hasegawa and F. W. Lichtenthaler, *Ann. Chem.*, **669**, 75 (1963).

[18] B. R. Baker and H. S. Sachdev, *J. Org. Chem.*, **28**, 2132 (1963).

The remaining oily product (450 mg.), obtained by evaporating the mother liquor of II, was treated in the manner which has been described for III to yield 200 mg. of crude *trans*-1,2,3-cyclohexanetriol (V). Recrystallization from ethyl acetate gave 135 mg. of analytically-pure V melting at 107—108°C (lit.[3] m. p. 108°C). (Found: C, 54.67; H, 9.15%).

1,3-Di-*O*-acetyl-2-*O*-mesyl-*cis*-1,2,3-cyclohexanetriol (VI).—A 0.6 ml. portion of methanesulfonyl chloride was added to a mixture of 1.0 g. of II and 15 ml. of pyridine under ice cooling, and the mixture was allowed to stand overnight in a refrigerator. Then the mixture was poured into ice-water. The precipitate was collected by filtration, washed with cold water, and dried to yield 1.3 g. (95%) of the crude product melting at 150—151°C. When recrystallized from ethanol, it melted at 152—152.5°C.

Found: C, 45.18; H, 6.23; S, 10.67. Calcd. for $C_{11}H_{18}O_7S$: C, 44.89; H, 6.16; S, 10.90%.

1,3-Di-*O*-acetyl-2-*O*-mesyl-*trans*-1,2,3-cyclohexanetriol (IX).—The crude oily product of IV (220 mg.) was treated in the manner described for VI. The reaction mixture was poured into ice water, and the solution was evaporated in vacuo to a half volume to yield the crude product. Recrystallization from ethanol gave 210 mg. (73%) of needles melting at 136—137°C.

Found: C, 45.33; H, 6.12; S, 10.37. Calcd. for $C_{11}H_{18}O_7S$: C, 44.89; H, 6.16; S, 10.90%.

The Mesylation of the Mixture of II and IV.—A 3.8 g. portion of the mixture of II and IV obtained by the hydrogenation of 5 g. of I was treated overnight with 3.0 ml. of methanesulfonyl chloride and 50 ml. of pyridine. The mixture was then treated in the manner described for IX to yield 4.2 g. (82%) of a mixture of VI and IX melting at 124—150°C. The mixture was fractionally recrystallized from ethanol to give 2.56 g. (50%) of VI melting at 150—152°C and 0.88 g. (17%) of IX melting at 136—137°C.

***trans*-2-Acetamido-1,3-cyclohexanediol Diacetate (VIII).**—a) A mixture of 0.50 g. of VI, 0.60 g. of sodium azide, and 20 ml. of 85% aqueous 2-methoxyethanol was refluxed for 14 hr. The solvent was then removed by evaporation in vacuo. The residue was repeatedly extracted with hot acetone, and the combined extracts were evaporated to give 480 mg. of a brown oil, showing a strong infrared absorption of an azide group at 2090 cm^{-1}. The crude VII dissolved in 8 ml. of ethanol was hydrogenated in an initial hydrogen pressure of 50 p.s.i.g. with Raney nickel. After the catalyst had been removed by filtration, the filtrate was evaporated to yield 415 mg. of an oil. This was acetylated overnight with 10 ml. of acetic anhydride and 10 ml. of pyridine. The mixture was then evaporated in vacuo to dryness, and the residue was triturated with ether to give 180 mg. (41%) of a product which, after recrystallization from ethanol - ether, gave crystals melting at 150—152°C. The melting point showed no depression upon admixture with an authentic sample.[9] b) When the same reaction was carried out in aqueous dimethylformamide, the same results as in a) was obtained.

DL-3β-Acetamido-1α,2α-cyclohexanediol Diacetate (XIII).—A mixture of 1.4 g. of IX, 1.5 g. of sodium azide, and 60 ml. of 85% aqueous 2-methoxyethanol was refluxed for 30 hr. Then the mixture was treated in a manner similar to that described for VIII to give 0.30 g. (25%) of a product melting at 146.5—147°C. The product was recrystallized from benzene to yield plates melting at 147—148.5°C (lit.[9] m. p. 148—149.5°C). (Found: C, 56.17; H, 7.40; N, 5.48%).

The infrared spectrum was superimposable on that of an authentic sample.[15]

The mother liquor of XIII was kept in a refrigerator for a long time to give 0.04 g. (3%) of crystals melting at 175°C. The crystals were recrystallized from benzene to give needles melting at 175—178°C. The product was identified as *cis*-2-acetamido-1,3-cyclohexanediol diacetate[9] on the basis of a mixed melting point determination and its infrared spectrum.

***cis*-2-Acetamido-1,3-cyclohexanediol Diacetate (XI).**—A mixture of 502 mg. of IX, 550 mg. of sodium azide, and 20 ml. of 85% aqueous dimethylformamide was refluxed for 14 hr. The mixture was treated in a manner similar to that described above to give 190 mg. (43%) of the product melting at 175.5—177°C. The product was recrystallized from ethanol - ether to give needles melting at 175—176°C. A mixed melting point determination with an authentic sample[9] was undepressed.

The authors are indebted to Professor Sumio Umezawa for his helpful advice, to Mr. Saburo Nakada for his microanalysis, to Mr. Masahiko Kitajima and Mr. Yasumasa Ishida for their assistance in the analytical experiments, and to Miss Sunao Ohata for the measurement of the infrared spectra. This research has been supported in part by the Asahi Glass Foundation for Contributions to Industrial Technology and by the Deutsche Forschungs Gemeinschaft.

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