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Aminocyclitols. XVII. A Facile Synthesis of 2-Deoxystreptamine

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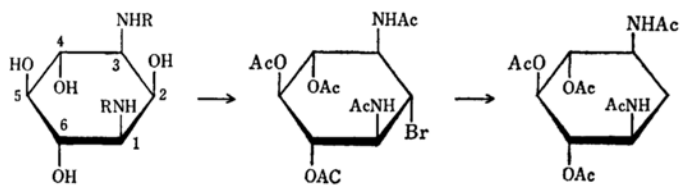
Bromination of *myo*-inosadiamine-1,3 dihydrochloride or its di-*N*-acetyl derivative with acetyl bromide and acetic anhydride yielded pentaacetyl-2-bromo-2-deoxy-*scyllo*-inosadiamine-1,3 (III), which upon reductive debromination afforded pentaacetyl-2-deoxystreptamine (IV). The configurations of the new compounds obtained were established by nuclear magnetic resonance and chemical evidences. A mechanism of the bromination reaction is presented, based on the configuration of the bromo-compound.

2-Deoxystreptamine has been found as a component of the antibiotics neomycin,[1] kanamycin,[2] paromomycin,[3,4] and gentamicin.[5]

The structure and configuration was established to be a 1,3-diamino-4,5,6-cyclohexanetriol with the all-trans configuration, by analogy of the stereochemistry of streptamine,[6] and this has been further confirmed by Lemieux by nuclear magnetic resonance (NMR) spectroscopy.[7]

In the present study we wish to report a two step synthesis of 2-deoxystreptamine from *myo*-inosadiamine-1,3.[8] When *myo*-inosadiamine-1,3 dihydrochloride (I)[9] or its di-*N*-acetyl derivative (II) are heated in a mixture of acetyl bromide and acetic anhydride in a sealed tube at 130—135°C for 6 hr, the identical products (mp 256.5—258°C dec.) are obtained in 48 and 16% yield. The structure and configuration of this product was established to be pentaacetyl-2-bromo-2-deoxy-*scyllo*-inosadiamine-1,3 (III) by elementary analysis, the NMR spectroscopic data and chemical evidence as described below.

The NMR spectrum of III in d_6-dimethylsulfoxide revealed two sharp signals at τ 8.04 (9H) and 8.23 (6H), which can be unequivocally assigned to three equatorial acetoxy groups and two equatorial acetamido groups on the basis of acetyl resonance ranges established for this solvent.[10] An axial acetoxy group, the resonance peak of which would be expected to appear between τ 7.80 and 7.86,[10] is not observed, thus establishing the preferential displacement of the axial hydroxyl group on C-2 by a bromide ion. The configuration of the bromo group, however, could not be deduced from the NMR spectrum, due to the rather complex multiplet patterns of the ring

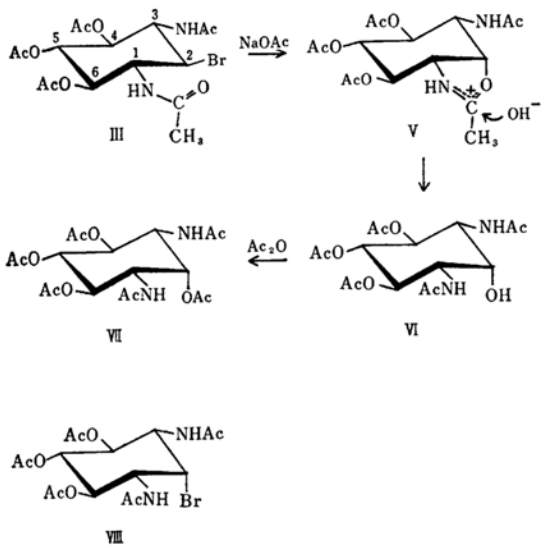


I R=H·HCl
II R=Ac

III IV

Scheme 1

1) F. A. Kuehl, Jr., M. N. Bishop and K. Folkers, *J. Am. Chem. Soc.*, **73**, 881 (1951).
2) H. Umezawa, M. Ueda, K. Maeda, K. Yagishita, S. Kondo, Y. Okami, R. Utahara, Y. Osato, K. Nitta and T. Takeuchi, *J. Antibiotics (Tokyo)*, **10A**, 181 (1957).
3) T. H. Haskell, J. C. French and Q. R. Bartz, *J. Am. Chem. Soc.*, **81**, 3480 (1959).
4) K. L. Rinehart, Jr., M. Hichens, A. D. Argoudelis, W. S. Chilton, H. E. Carter, M. Geordiadis, C. P. Schaffner and R. T. Schillings, *ibid.*, **84**, 3218 (1962).
5) M. J. Weinstein, G. M. Luedemann, E. M. Oden, G. H. Wagman, J. P. Rosselet, J. Marquez, C. T. Coniglio, W. Charney, H. Herzog and J. Black, *J. Med. Chem.*, **6**, 463 (1963).
6) J. R. Dyer, Ph. D. Theses (with H. E. Carter), University of Illinois, 1954.
7) R. U. Lemieux and R. J. Cushley, *Can. J. Chem.*, **41**, 858 (1963).
8) For a preliminary account see T. Suami and S. Ogawa, *Tetrahedron Letters*, **1967**, 2671.
9) S. Ogawa, T. Abe, H. Sano, K. Kotera and T. Suami, This Bulletin, **40**, 2405 (1967).
10) F. W. Lichtenthaler and P. Emig, "Carbohydrate Research," Vol. 6 (1968), in press.



Scheme 2

protons.

Reductive debromination of III with Raney nickel under a hydrogen atmosphere (4 kg/cm²) in aqueous ethanol in the presence of Amberlite IR-4B afforded in 45% yield pentaacetyl-2-deoxystreptamine (IV), which was identified by comparison of mp, IR and NMR spectra with those of an authentic sample.[2]

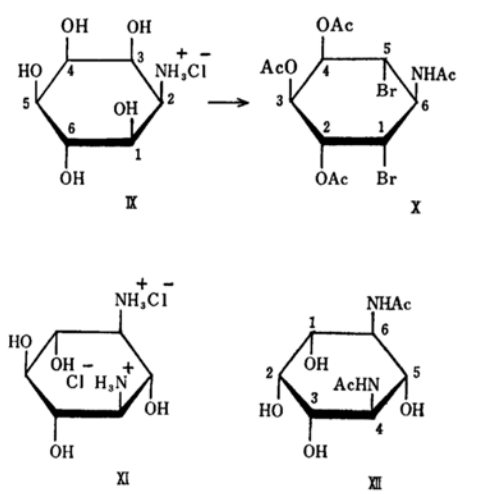
On treatment of III with sodium acetate in aqueous 2-methoxyethanol followed by acetylation, hexaacetyl-*myo*-inosadiamine-1,3 (VII) is obtained in 62% yield. The stereoselectivity of this reaction can only be rationalized by proceeding *via* an oxazolinium intermediate[11,12] with subsequent cis-opening by water (V→VI). The formation of VI however requires an equatorial bromo group as in III, thus establishing its configuration. In the alternate configurational possibility with an axially oriented bromo group (VIII), an anchimeric assistance of the acetamido group is not possible and thus—under the same conditions—should give in a direct S_N2[13] displacement of the bromo group hexaacetyl-streptamine, contrary to the facts.

The mechanism of the bromination reaction is proposed as followings. The results found in the bromination of *myo*-inosadiamine-1,3 and *epi*-inosamine-2 (IX→X)[12] in a mixture of acetyl bromide and acetic anhydride give a strong evidence that the hydroxyl groups vicinal and in cis-position to an amino or acetamido group are preferentially displaced by bromine. Supporting this are the findings that streptamine dihydrochloride (XI) and di-*N*-acetyl-*myo*-inosadiamine-4,6 (XII), both having no *cis* amine-ol arrangement, fail to react with acetyl bromide in acetic anhydride, as evidenced by the isolation of the starting materials in the form of their hexaacetates. On the basis of these results, it seems obvious that any mechanism for the conversion of aminoinositols to bromo- or dibromo-derivatives with acetyl bromide and acetic anhydride must explain: (i) why the acetamido group is necessary for a facile bromination; (ii) why the *trans* amine-ol compounds fail to react and (iii) why an inversion of the configuration attends the replacement process. Of the many mechanisms considered, one involving what Boschan and Winstein[14] termed "front-side participation" seemingly meets the above described requirements.

As exemplified with *myo*-inosadiamine-1,3 or its di-*N*-acetyl derivative, the first step of the reaction is likely to be the formation of an intermediate XIII, generated by partial acetylation, since the axially oriented hydroxyl group on C-2 is less reactive towards acylation than the equatorial ones.[15,16] "Front-side participation" then yields an oxazolidine intermediate (XIV or XV) which is converted to an oxazolinium ion (XVI). Then XVI is opened by S_N2 attack of the bromide ion to give III.

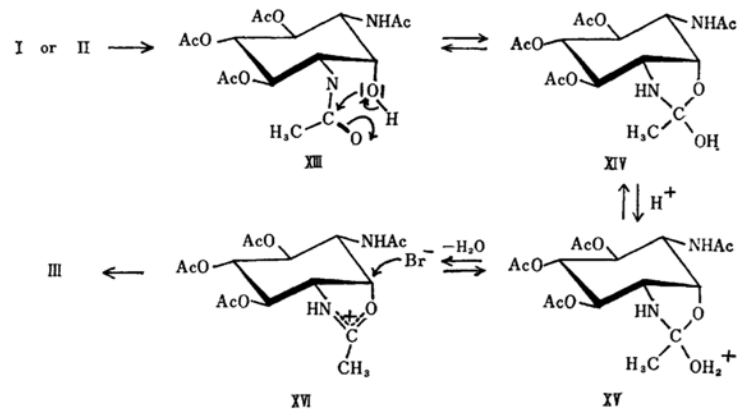
This mechanistic course readily explains the facile formation of tetraacetyl-1,5-dibromo-1,5-dideoxy-*rac*-inosamine-6 (X) from *epi*-inosamine-2 as well as the inertness of *scyllo*-1,3- and *myo*-4,6-inosadiamines (XI and XII) towards this reaction.

A similar mechanistic course, with a participation of an acetoxy group, undoubtedly governs



Scheme 3

11) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *J. Am. Chem. Soc.*, **71**, 637 (1949).
12) T. Suami, S. Ogawa, Y. Nakashima and H. Sano, This Bulletin, **40**, 2958 (1967).
13) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 442 (1963).
14) R. Boschan and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4921 (1956).
15) E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York (1965), p. 72ff.
16) T. Suami, F. W. Lichtenthaler and S. Ogawa, This Bulletin, **39**, 170 (1966).



Scheme 4

the acetyl bromide-acetic anhydride bromination of *myo*- and *epi*-inositols, since it serves to explain the formation of 2-bromo-2-deoxy-*scyllo*-inositol and 1-bromo-1-deoxy-*rac*-inositol from the former[17] and of 5-bromo-5-deoxy-*allo*-inositol from the latter.[18]

Experimental

The melting points were determined in a liquid bath and are corrected. The infrared spectra were determined by pressed potassium bromide disks. The NMR spectra of the samples were determined at a frequency of 60 Mc with a Japan Electron Optics Laboratory JNM-C-60 spectrometer in deuteriochloroform or d_6-dimethylsulfoxide with tetramethylsilane as an internal standard. The peak positions are expressed by τ-values.

Pentaacetyl-2-bromo-2-deoxy-*scyllo*-inosadiamine-1,3 (III). a) A mixture of *myo*-inosadiamine-1,3 dihydrochloride (I) (882 mg),[9] acetyl bromide (1.2 m*l*) and acetic anhydride (2.6 m*l*) was heated in a sealed tube at 130—135°C for 6 hr. After cooling, 1.29 g of the crystalline precipitate was collected by filtration. The crude product was recrystallized from ethanol to give 586 mg of colorless needles melting at 256.5—258.5°C (dec.). The mother liquor was evaporated and the residue was acetylated with acetic anhydride (7.5 m*l*) and pyridine (7.5 m*l*) overnight at room temperature. After an excess amount of acetylating reagent had been removed, the residue was crystallized from ethanol giving 244 mg of colorless needles which was identical with the product in the first crop. The total yield was 48.3% (830 mg).

Found: C, 42.92; H, 5.06; N, 6.24; Br, 17.52%. Calcd for $C_{16}H_{23}N_2O_8Br$: C, 42.58; H, 5.14; N, 6.21; Br, 17.71%.

NMR: (d_6-DMSO) three equatorial acetoxy groups, τ 8.04(9H); two equatorial acetamido groups, τ 8.23 (6H).

b) Di-*N*-acetyl-*myo*-inosadiamine-1,3 (II, 644 mg)[19] was brominated in a mixture of acetyl bromide (0.8 m*l*) and acetic anhydride (1.7 m*l*) similarly as described above, giving 178 mg (16.1%) of III.

Hexaacetyl-*myo*-inosadiamine-1,3 (VII). A mixture of III (190 mg), sodium acetate (197 mg) and 90% aqueous 2-methoxyethanol (10 m*l*) was heated under reflux for 15 hr. Then the solution was evaporated under reduced pressure, and the residue was acetylated with acetic anhydride and pyridine. After an excess acetylating reagent was removed by evaporation, the residue was recrystallized from ethanol to yield 112 mg (61.6%) of colorless plates melting at 282—284°C. This product was identified with an authentic sample of hexaacetyl-*myo*-inosadiamine-1,3[19] by a mixed melting point determination and IR spectra.

Pentaacetyl-2-deoxystreptamine (IV). A 236 mg portion of III was hydrogenated in 50% aqueous ethanol (16 m*l*) with Raney nickel (1.5 spatulas) and Amberlite IR-4B (4 m*l*) under 4 kg/cm² of hydrogen pressure for 20 hr at 30°C. After the catalyst and the ion-exchange resin were removed by filtration, the filtrate was evaporated under reduced pressure. The residue was recrystallized from methanol, giving 87 mg (44.5%) of colorless prisms melting above 300°C. The product was identified with an authentic sample of pentaacetyl-2-deoxystreptamine which had been prepared from kanamycin[2] by IR and NMR spectra.

Bromination of Streptamine Dihydrochloride (XI). Streptamine dihydrochloride (1.00 g)[20] was heated in a mixture of acetyl bromide (1.5 m*l*) and acetic anhydride (2.5 m*l*) in a sealed tube as described above at 150—160°C. Hexaacetyl-streptamine (1.35 g) was recovered in 81.4% recovery, which was identified with an authentic sample[22] by IR spectra and its characteristic transition point at 248°C.

Bromination of Di-*N*-acetyl-*myo*-inosadiamine-4,6 (XII). Finely powdered di-*N*-acetyl-*myo*-inosadiamine-4,6 (1.00 g)[21,22] was heated in an acetyl bromide-acetic anhydride mixture as described above at 130—135°C. Then the reaction mixture was evaporated to dryness and the residue was recrystallized from ethanol

17) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **75**, 4020 (1953).
18) G. E. McCasland, S. Furuta, L. F. Johnson and J. N. Shoolery, *ibid.*, **83**, 2335 (1961).
19) T. Suami and S. Ogawa, This Bulletin, **40**, 1295 (1967).
20) J. Fried, G. A. Boyack and O. Wintersteiner, *J. Biol. Chem.*, **162**, 391 (1946).
21) T. Suami and S. Ogawa, This Bulletin, **38**, 2026 (1965).

to give 1.02 g (62.0%) of the product melting at 270—274°C (dec.). This compound was identified with an authentic sample[22] of hexaacetyl-*myo*-inosadiamine-4,6 by IR spectra.

22) T. Suami and S. Ogawa, *ibid.*, **40**, 1925 (1967).

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