BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 1843—1846 (1970)

Aminocyclitols. XXII. A Synthesis of Actinamine and Hyosamine[1]

Tetsuo SUAMI, Seiichiro OGAWA and Hiroshi SANO

Department of Applied Chemistry, Faculty of Engineering, Keio University, Koganei-shi, Tokyo

(Received December 16, 1969)

Hydrazinolysis of 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol, followed by catalytic hydrogenation afforded *myo*-inosadiamine-1,3 *via* an intermediary 6,7-diazabicyclo[3.2.1]-octane-2,3,4,8-tetrol. In this reaction, the use of *N,N'*-dimethylhydrazine and *N*-methylhydrazine, instead of hydrazine, gave actinamine: a component of an antibiotic spectinomycin, and *N*-methyl-*myo*-inosadiamine-1,3: an important intermediary compound for a synthesis of DL-hyosamine, respectively. Details of the convenient syntheses of actinamine and DL-hyosamine are described.

Actinamine has been found in the antibiotic spectinomycin[2,3] as its component and its structure has been established to be *N,N'*-dimethyl-*myo*-inosadiamine-1,3.[4-6] The synthesis has been done by several authors[7-10] in laborious procedures.

While hyosamine has been discovered in the antibiotic hyosamine B[11] and later in destomycin A[12] as their components. The structure has been established to be *N*-methyl-2-deoxy-streptamine[11,12] and the synthesis has been described by Nakajima and his coworkers.[13]

In the present papers, the authors wish to report

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a detail of a convenient synthesis of actinamine and DL-hyosamine.

myo-Inosadiamine-1,3 has been readily prepared from 1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (I)[14] by the reaction with hydrazine,[15] and hence, actinamine and DL-*N*-methyl-*myo*-inosadiamine-1,3 could be prepared from I by the reactions with *N*,*N*′-dimethylhydrazine and *N*-methylhydrazine.

From the latter compound, DL-hyosamine could be prepared by analogous reaction procedures in which 2-deoxystreptamine had been successfully synthesized from *myo*-inosadiamine-1,3.[16,17]

When I was heated under reflux in a mixture of *N*,*N*′-di-methylhydrazine and 2-methoxyethanol for 19 hr, an oily product was obtained upon evaporation of the solvent, which was hydrogenated in the presence of the Raney nickel catalyst under 3.4 kg/cm² of an initial hydrogen pressure for 22 hr at 40°C. The reduction product was acylated with acetic anhydride in pyridine to give crystalline hexaacetyl-actinamine (II) in a yield of 36%, which was identified with an authentic sample[18] by a mixed melting point determination and a comparison of IR spectra.

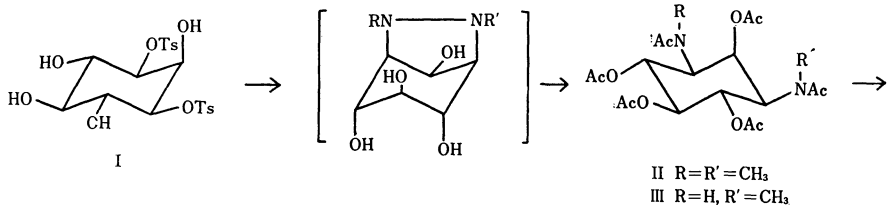
While I was heated under reflux in a mixture of *N*-methylhydrazine and 2-methoxyethanol for 20 hr and the product was hydrogenated in the presence of Raney nickel, followed by a conventional acetylation, hexaacetyl DL-*N*-methyl-*myo*-inosadiamine-1,3 (III) was obtained in 43% yield. A selective de-*O*-acetylation of III afforded di-*N*,*N*′-acetyl-DL-*N*-methyl-*myo*-inosadiamine-1,3 (IV) in 98% yield, and a hydrolysis of III in 6N hydrochloric acid gave DL-*N*-methyl-*myo*-inosadiamine-1,3 dihydrochloride (V) in 86% yield.

The hydroxyl groups vicinal and in a *cis* position to an amino or acetamido group in aminocyclitols are preferentially displaced by halogen in a mixture of acetyl halide and acetic anhydride.[17,19] Since there is an axial hydroxyl group on C-2 in a *cis*-disposition to the vicinal amino groups in the compound V, the hydroxyl group should be displaced by halogen in a mixture of acetyl halide and acetic anhydride with an inversion of the configuration on C-2.

When V was heated in the mixture of acetyl bromide and acetic anhydride in a sealed tube at 130—135°C for 13 hr, the bromination product was obtained in 22% yield, which was identified to be pentaacetyl-DL-2-bromo-2-deoxy-*N*-methyl-*scyllo*-inosadiamine-1,3 (VI) by analogy with a bromination product of *myo*-inosadiamine-1,3 dihydrochloride in an analogous reaction condition.

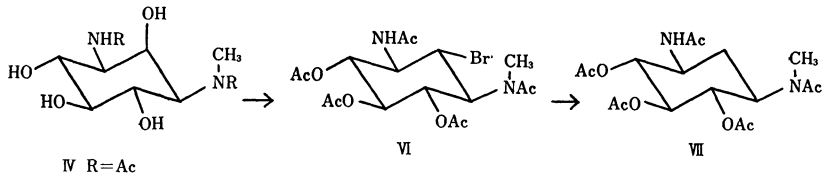
Catalytic debromination of VI with Raney nickel and Amberlite IR-4B (OH^-) under a hydrogen stream of 3.4 kg/cm² for 20 hr afforded pentaacetyl DL-hyosamine (VII) in a yield of 87%, which was identified with an authentic sample obtained from antibiotic destomycin A[12] with an exception of an optical activity.

To elucidate the reaction mechanism of the present hydrazinolysis, an attempt to isolate an inter-



I

II R=R′=CH₃
III R=H, R′=CH₃



IV R=Ac
V R=H 2HCl

VI

VII

14) T. Suami, F. W. Lichtenthaler and S. Ogawa, This Bulletin, **40**, 1488 (1967).

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16) T. Suami, S. Ogawa and H. Sano, *Tetrahedron Lett.*, **1967**, 2671.

17) T. Suami, F. W. Lichtenthaler, S. Ogawa, Y. Nakashima and H. Sano, This Bulletin, **41**, 1014 (1968).

18) The authors thank Dr. P. F. Wiley (Upjohn Co., Kalamazoo, Mich., U. S. A.) for supplying an authentic sample of hexaacetyl-actinamine.

19) T. Suami, S. Ogawa, Y. Nakashima and H. Sano, This Bulletin, **40**, 2958 (1967).

mediate in a crystalline state failed. But it seemed quite sure that these hydrazinolyses might proceed through intermediary bicyclic compounds, because II or III was obtained in a considerably good yield as a sole product, and formations of II and III were reasonably explained only by assuming an existence of bicyclic intermediates.

Experimental

The melting points reported were determined on a Mitamura Riken micro hot stage and uncorrected. The PMR spectra of the samples were measured on Varian Associate A-60D spectrometer at the frequency of 60 MHz at a concentration of 10% in deuteriochloroform, deuteriodimethylsulfoxide (d_6-DMSO) or deuterium oxide with tetramethylsilane or sodium trimethylsilylpropanesulfonate as an internal standard. The peak positions are given in τ-values.

Hexaacetyl Actinamine (II). A suspension of 2.18 g of *N,N'*-dimethylhydrazine sulfate in 50 m*l* of 2-methoxyethanol was treated with 1.31 g of sodium hydroxide in 1.5 m*l* of water. A 1.48 g portion of 1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (I) was added to the resulting solution and refluxed for 20 hr. An insoluble material was filtered off and the filtrate was evaporated *in vacuo* to give an oily residue. A solution of the residue in 35 m*l* of water was hydrogenated in the presence of Raney nickel catalyst (two spatula) in a Parr shaker type apparatus at room temperature in the initial hydrogen pressure of 3.4 kg/cm^2. After shaking for 22 hr, the reaction mixture was filtered to remove the catalyst and evaporated to dryness. The glassy residue was treated with a mixture of 15 m*l* of acetic anhydride and 15 m*l* of pyridine at room temperature overnight. Evaporation of excess reagent *in vacuo* gave an oily product, which was chromatographed on active aluminum oxide and eluted with chloroform to afford 507 mg of colorless plates (36.3%), mp 202—203°C. One recrystallization from methanol gave a pure sample of II, mp 205—206°C, which was identified with the authentic sample derived from antibiotic spectinomycin by mixed melting point determination and comparing with IR spectra.

Hexaacetyl DL-*N*-Methyl-*myo*-inosadiamine-1,3 (III). A suspension of 6.63 g of *N*-methylhydrazine sulfate in 50 m*l* of 2-methoxyethanol was treated with 3.69 g of sodium hydroxide in 5 m*l* of water and a precipitated sodium sulfate was removed by filtration. An 1.50 g portion of I was added to the filtrate and the mixture was refluxed for 20 hr under nitrogen. The reaction mixture was evaporated *in vacuo* to dryness and a solution of the residue in 20 m*l* of water was hydrogenated in the presence of Raney nickel catalyst (two spatula) in a Parr shaker type apparatus at 40—50°C in the initial hydrogen pressure of 3.4 kg/cm^2 for 22 hr. Filtering off the catalyst, the solution was evaporated *in vacuo* to dryness. Then the oily product was treated with a mixture of 15 m*l* of acetic anhydride and 15 m*l* of pyridine at room temperature overnight. The reaction mixture was evaporated *in vacuo* to remove excess reagent and the residue was chromatographed on active aluminum oxide. Elution with chloroform gave a colorless oil which crystallized upon addition of ethanol and ether. Recrystallization from ethanol gave colorless rhombic crystals weighing 582 mg (42.7%), mp 229—230°C. IR (KBr): 1750 (OAc), 1694, 1642 and 1525 cm^{-1} (amide). PMR ($CDCl_3$): τ 7.12 (NCH_3), 7.79 (3), 7.95 (6), 7.99 (6) and 8.12 (3)*1 (OAc and NAc).

Found: C, 51.39; H, 6.85; N, 6.17%. Calcd for $C_{19}H_{28}N_2O_{10}$: C, 51.34; H, 6.35; N, 6.30%.

Di-*N,N'*-acetyl-DL-*N*-methyl-*myo*-inosadiamine-1,3 (IV). A 203 mg portion of III was treated with 20 m*l* of methanol saturated with ammonia (at 5°C) overnight at room temperature. The solution was evaporated *in vacuo* to yield an oily residue which crystallized upon trituration by ethyl acetate. Crude crystals were recrystallized from 80% methanol to afford 113 mg of colorless needles (89.3%), mp 253—254°C. PMR (D_2O): τ 6.95, 7.00 (NCH_3), 7.82 (3) and 7.95 (3) (NAc).

Found: C, 48.16; H, 7.82; N, 9.77%. Calcd for $C_{11}H_{20}N_2O_6$: C, 47.82; H, 7.30; N, 10.14%.

DL-*N*-Methyl-*myo*-inosadiamine-1,3 Dihydrochloride (V). A 239 mg portion of III was refluxed with 10 m*l* of 6N hydrochloric acid for 2 hr. The reaction mixture was evaporated *in vacuo* and the crystallization was induced by addition of aqueous ethanol. Colorless needles were obtained by recrystallization from aqueous ethanol, 122 mg (85.5%), mp 300°C (dec.). PMR (D_2O): τ 7.16 (NCH_3).

Found: C, 31.64; H, 6.98; N, 10.45; Cl, 26.52%. Calcd for $C_7H_{16}N_2O_4 \cdot 2HCl$: C, 31.71; H, 6.84; N, 10.56; Cl, 26.75%.

Pentaacetyl-DL-2-bromo-2-deoxy-*N*-methyl-*scyllo*-inosadiamine-1,3 (VI). A mixture of 359 mg of powdered V (dried *in vacuo* P_2O_5 at 100°C), 0.43 m*l* of acetyl bromide and 0.94 m*l* of acetic anhydride was heated in a sealed tube at 130—135°C for 13 hr. After cooling to room temperature, the sealed tube was opened carefully, to which 25 m*l* of ethanol was added dropwise under ice cooling. The reaction mixture was allowed to stand in a refrigerator overnight, and then treated with 20 m*l* of Amberlite IRA-400 (OH^-). The solution was evaporated *in vacuo* to drynesss and the residue was acetylated with a mixture of 25 m*l* of acetic anhydride and 25 m*l* of pyridine at room temperature overnight. The mixture was evaporated *in vacuo* to remove excess reagent and the residue was dissolved in a small amount of chloroform. The solution was chromatographed on active aluminum oxide and eluted with chloroform afforded an oil which crystallized upon trituration by a mixture of ethanol and ether. Crude crystals (233 mg) showed mp 165—175°C and a small amount of III was shown to be contained by TLC (silica gel, chloroform-ethanol=8 : 2). Fractional crystallization from ethanol and ether afforded 80 mg of III and 120 mg of VI, mp 168—180°C (dec.). The yield of VI was 22.0% based on V consumed. Recrystallization from ethanol and ether gave analytical pure crystals of VI, mp 179—183°C (dec.). PMR ($CDCl_3$): τ 6.85, 7.10, 7.20 (NCH_3), 7.79, 7.88, 7.92 and 7.98 (OAc and NAc).

Found: C, 44.19; H, 5.52; N, 6.03; Br, 16.76%. Calcd for $C_{17}H_{25}N_2O_8Br$; C, 43.88; H, 5.42; N, 6.02; Br, 17.18%.

Pentaacetyl-DL-hyosamine (VII). A solution of 106 mg of VI in 8 ml of 50% aqueous ethanol was

*1 In parentheses, proton numbers are indicated.

hydrogenated in the presence of Raney nickel catalyst (one spatula) and 1.2 m*l* of Amberlite IR-4B (OH^-) in a Parr shaker type apparatus in the initial pressure of 3.4 kg/cm^2 at room temperature. After shaking for 20 hr, the catalyst and resin were filtered off and the filtrate was evaporated *in vacuo* to give a colorless oil. Trituration by chloroform and ether gave 76 mg of colorless crystals (86.6%), mp 201—202.5°C (with transition at 143—165°C). Recrystallization from chloroform and ether afforded colorless crystals, mp 202—203°C after melting and resolidified at 162—165°C. This product was identified with an authentic active material derived from antibiotic destomycin A by comparing with IR (in chloroform) and PMR (in $CDCl_3$) spectra.

Found: C, 52.50; H, 7.00; N, 7.37%. Calcd for $C_{17}H_{26}N_2O_8$: C, 52.84; H, 6.78; N, 7.25%.

The authors are grateful to Professor Sumio Umezawa for his kind advice, to Mr. Saburo Nakada for his elementary analyses and to Mr. Naoyuki Kato for his assistance in the preparative experiments. The financial support from the Ministry of Education for this work is gratefully acknowledged.