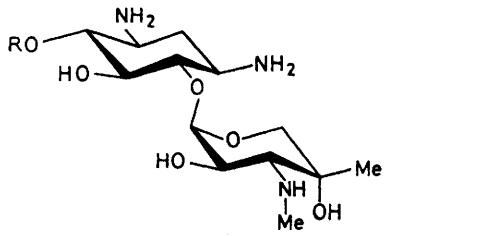
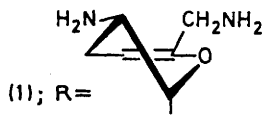
Synthesis of Derivatives of Sisosamine and Purpurosamine C: Confirmation of the Structure of Sisomicin

By J. CLEOPHAX, S. D. GERO,* E. JEGOU-AUMONT, J. LEBOUL, and D. MERCIER
(*Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France*)
and A. FORCHIONI
(*Service de Chimie Physique, B.P. n° 2, CEA, 91190 Gif-sur-Yvette, France*)

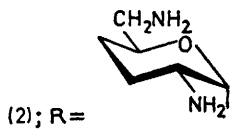
Summary The synthesis of derivatives of sisosamine (**12**) and purpurosamine C (**16**), components of the aminoglycoside antibiotics, sisomicin (**1**) and gentamicin C_{1a} (**2**) is described; one key intermediate, 2-azido-2,3-dideoxy-6-*O*-toluene-*p*-sulphonyl-α-D-*erythro*-hexopyranosid-4-ulose (**5**) being used for both reaction sequences.

SISOMICIN[1] (**1**) and gentamicin C_{1a}[2] (**2**) are important aminoglycoside antibiotics[3] whose structures have been proposed on the basis of physical properties and chemical studies. Both contain the branched chain amino-sugar garosamine, and deoxystreptamine but are distinguished by a third component belonging to a new class of 2,6-diamino-2,3,4,6-tetradeoxyhexoses. These components have been named sisosamine and purpurosamine C from sisomicin (**1**) and gentamicin C_{1a} (**2**), respectively.

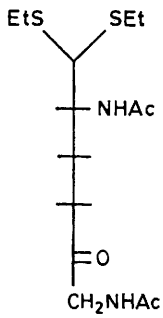




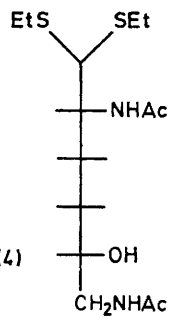
(1); R=



(2); R=

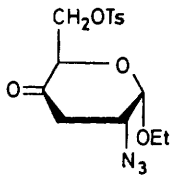


(3)

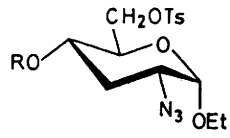


(4)

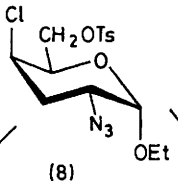
We now describe the synthesis of derivatives of sisosamine and purpurosamine C, and their identification using the diethyl dithioacetals (**3**) and (**4**) which can be obtained by mercaptolysis of the per-*N*-acetylated derivatives of sisomicin (**1**) and gentamicin C_{1a} (**2**). Compounds (**3**) and (**4**) were also synthesised from ethyl 2-azido-2,3-dideoxy-6-*O*-toluene-*p*-sulphonyl-α-D-*erythro*-hexopyranosid-4-ulose (**5**), an intermediate used recently for the preparation[4] of nebrosamine a component of another important aminoglycoside antibiotic, tobramycine.



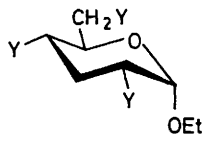
(5)



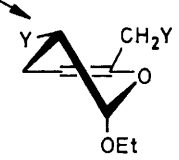
(6); R = H
(7); R = Ms



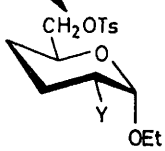
(8)



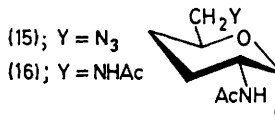
(9); Y = N_3
(10); Y = NHAc



(11); Y = N_3
(12); Y = NHAc



(13); Y = NH_2
(14); Y = NHAc



(15); Y = N_3
(16); Y = NHAc

The ketone (**5**) was reduced with sodium borohydride in methanol to the syrupy ethyl 2-azido-2,3-dideoxy-6-*O*-toluene-*p*-sulphonyl-α-D-*ribo*-hexopyranoside (**6**) [characterised as its *O*-mesylate (**7**)]. The alcohol (**6**) on treatment with sulphuryl chloride in pyridine solution was smoothly converted into the oily ethyl 2-azido-4-chloro-2,3,4-trideoxy-6-*O*-toluene-*p*-sulphonyl-α-D-*xylo*-hexopyranoside (**8**), in 66% yield. The antiperiplanar arrangement of the chloride group at C-4 and the hydrogen atom at C-5, very suitable for an elimination reaction, was inferred from the ^1H n.m.r. spectrum ($J_{4,5}$ 3 Hz).

Treatment of chloride (**8**) with azide anion in hexamethylphosphoric triamide at 100° for 2 h, followed by selective hydrogenation and *N*-acetylation of the resultant azides (**9**) and (**11**), gave two crystalline products (A) and (B) in yields of 9% and 30% respectively. The minor product (A) m.p. 232—233° $[\alpha]_D$ + 131° (c = 0·98 in EtOH) gave analytical and spectroscopic data corresponding to ethyl 2,4,6-triacetamido-2,3,4,6-tetradeoxy-α-D-*ribo*-

hexopyranoside (**10**). The latter clearly arose by a displacement of the chloride and tosyloxy groups in (**8**) by azide ion.

The major product (B), m.p. 159—160°, $[\alpha]_D$ + 115° (c = 1·0 in $CHCl_3$) was found to be ethyl 2,6-diacetamido-2,3,4,6-tetradeoxy-D-*glycero*-hex-4-enopyranoside (**12**). Compound (**12**) is a rare and interesting example[5] of a nitrogen-containing endocyclic enolacetal glycoside. The structure was unequivocally assigned on the basis of ^1H, ^{13}C and mass spectral data, and also by chemical correlation.

Mercaptolysis of the unsaturated glycoside (**12**) with ethanethiol and concentrated hydrochloric acid followed by *N*-acetylation gave the highly crystalline 2,6-diacetamino-2,3,4,6-tetradeoxy-α-D-*glycero*-5-hexulose-diethyl dithioacetal (**3**), m.p. 152—153°, $[\alpha]_D$ + 33° (c = 0·33 in $CHCl_3$) M^+ 334, identical with (**3**) obtained by mercaptolysis of the per-*N*-acetyl-sisomicin [Lit.[2]: M^+ 334, m.p., 153—154°, $[\alpha]_D$ + 33·7° (c = 0·3 in $CHCl_3$)].

Derivatives of purpurosamine C could also be made from the chloride (**8**). Thus dechlorination of (**8**) with Raney nickel in the presence of hydrazine hydrate in ethanolic solution at 100° over 2 h, followed by *N*-acetylation of the resultant amine (**13**) gave the crystalline ethyl 2-acetamido-2,3,4-trideoxy-6-*O*-toluene-*p*-sulphonyl-α-D-*erythro*-hexopyranoside (**14**) in 35%, overall yield from the chloride (**8**); m.p. 100—101°, $[\alpha]_D$ + 88° (c = 1·0 in EtOH).

Treatment of (**14**) with sodium azide in dimethylformamide at 90° for 2 h, followed by hydrogenation of the resultant azido derivative (**15**) in acetic anhydride–methanol afforded ethyl-α-D-diacetamido-purpurosaminide C, (**16**), m.p. 201—202°, $[\alpha]_D$ + 159° (c = 1·07 in EtOH).

Mercaptolysis of the glycoside (**16**) with ethanethiol in concentrated hydrochloric acid followed by *N*-acetylation, gave the crystalline 2,6-diacetamido-2,3,4,6-tetradeoxy-α-D-*erythro*-hexose diethyl dithioacetal (**4**); m.p. 110—112°, $[\alpha]_D$ + 27° (c = 0·46 in MeOH): identical with (**4**) prepared[5] by mercaptolysis of the per-*N*-acetyl gentamicin C_{1a}.

Satisfactory spectroscopic and analytical data have been obtained for all compounds.

We thank Dr. P. J. L. Daniels (Schering Corporation) and Professor R. D. Guthrie (Griffith University) for discussion, P. J. L. Daniels for the authentic sample of purpurosamine C, and Professor E. Lederer for constant encouragement.

(*Received, 28th August* 1974; *Com.* 1100.)

[1] H. Reimann, D. J. Cooper, A. K. Mallams, R. S. Jaret, A. Yehaskel, M. Kugelman, H. F. Vernay, and D. Schumacher, *J. Org. Chem.*, 1974, **39**, 1451; H. Reimann, R. S. Jaret, and D. J. Cooper, *Chem. Comm.*, 1971, 924; M. Kugelman, A. K. Mallams, and H. F. Vernay, *J. Antibiotics*, 1973, **26**, 394.

[2] D. J. Cooper, M. D. Yudis, H. M. Marigliano, and Th. Traubel, *J. Chem. Soc.* (*C*), 1971, 2876; R. D. Guthrie and G. J. Williams, *J.C.S. Perkin I*, 1972, 2619; J. B. Morton, R. C. Long, P. J. L. Daniels, R. W. Tkach, and J. H. Goldstein, *J. Amer. Chem. Soc.*, 1973, **95**, 7464.

[3] Ch. C. Crowe and E. Sanders, *Antimicrobial Agents Chemotherapy*, 1971, 285.

[4] J. Cleophax, S. D. Gero, J. Leboul, and A. Forchioni, *J.C.S. Chem. Comm.*, 1973, 710.

[5] J. Kiss, *Adv. Carbohydrate Chem. Biochem.*, 1974, **29**, 229.