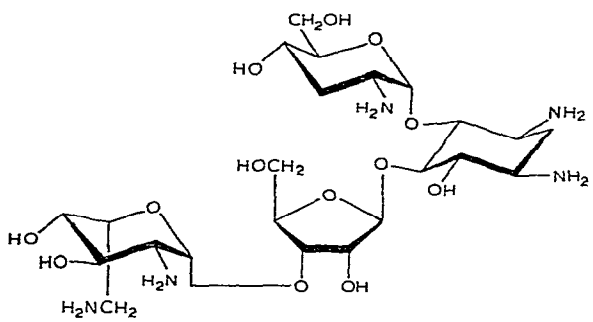
Carbohydrate Research, 45 (1975) 323–326

Note

A facile synthesis of derivatives of lividosamine, a component of lividomycin B*

ELISE JEGOU, JEANINE CLEOPHAX, JEAN LEBOUL, AND S. D. GERO
Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette (France)
(Received June 26th, 1975; accepted for publication, July 7th, 1975)

The antibiotic lividomycin B[1] (**1**), isolated in 1971 from *Streptomyces lividus*[1], is structurally related to neomycin B. However, lividomycin B is less toxic and is not a substrate for certain neomycin B-inactivating enzymes[2,3]. These differences in biological properties are possibly related to the presence in lividomycin B of the amino-sugar component 2-amino-2,3-dideoxy-D-*ribo*-hexose (lividosamine), attached to C-4 of the 2-deoxystreptamine moiety in place of 2,6-diamino-2,6-dideoxy-D-glucose (neosamine) in neomycin B. We now describe a facile, convenient synthesis of lividosamine by a method analogous to that employed previously for the synthesis of the antibiotic sugars tobrosamine[4], purpurosamine[5], and sisosamine[5], namely by way of a 1,4-addition to an α,β-unsaturated carbonyl sugar derivative.

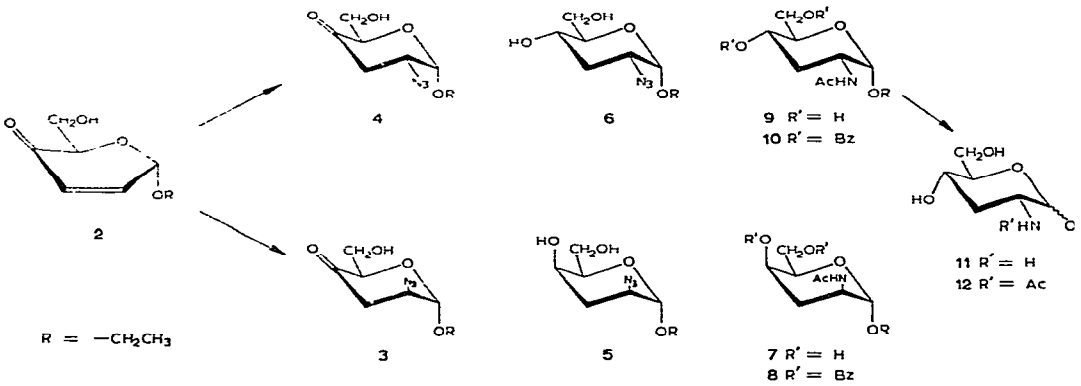


1

Treatment of ethyl 2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose[6] (**2**) with sodium azide in aqueous acetic acid resulted in the addition of the elements of hydrazoic acid to the carbon–carbon double-bond. The progress of the reaction was monitored by p.m.r. spectroscopy. Thus, after 3 min, only the kinetically favored product, ethyl 2-azido-2,3-dideoxy-α-D-*threo*-hexopyranosid-4-ulose (**3**), was observed, as indicated by the signal at δ 5.0 for H-1. Compound **3** was gradually converted into

*Dedicated to the memory of Dr. Hewitt G. Fletcher, Jr.

the thermodynamically more-stable product, ethyl 2-azido-2,3-dideoxy-α-D-*erythro*-hexopyranosid-4-ulose (**4**) (H-1, δ 5.2), and after 4.5 h, the equilibrium mixture contained the D-*erythro* and D-*threo* isomers in the ratio 5.5:4.5.



The mixture of azido-ketones was reduced with sodium borohydride in methanol to give ethyl 2-azido-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**6**) (R_F 0.6) as the preponderant product, together with ethyl 2-azido-2,3-dideoxy-α-D-*lyxo*-hexopyranoside (**5**) (R_F 0.7). These two compounds were isolated by preparative thin-layer chromatography. Hydrogenation of the azides (**5**) and (**6**) in acetic anhydride–methanol over Adams' catalyst afforded ethyl 2-acetamido-2,3-dideoxy-α-D-*lyxo*-hexopyranoside (**7**) and ethyl 2-acetamido-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**9**), respectively. Each of these compounds was characterized as a dibenzoate (**8** and **10**), and the stereochemistry at C-4 was established by p.m.r. spectroscopy. Compound **9** was finally converted into 2-acetamido-2,3-dideoxy-D-*ribo*-hexopyranose (*N*-acetyl-lividosamine) (**12**) by acid-catalyzed hydrolysis, followed by *N*-acetylation of the resulting amine (**11**). The product had physical constants identical to those reported[7] for *N*-acetyl-lividosamine.

EXPERIMENTAL

T.l.c. and preparative-layer chromatography (p.l.c.) were performed with silica gel; compounds were detected by charring with sulphuric acid. Evaporations were carried out at 40° *in vacuo*. All melting points are corrected. New compounds had i.r., n.m.r., and mass spectra consistent with the assigned structures.

Ethyl 2-azido-2,3-dideoxy-α-D-threo-*hexopyranosid-4-ulose* (**3**) *and ethyl 2-azido-2,3-dideoxy*-α-D-erythro-*hexopyranosid-4-ulose* (**4**). — To a solution of ethyl 2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose[6] (**2**) (1 g) in glacial acetic acid (8 ml) was added a solution of sodium azide (1 g) in water (5 ml), and the mixture was kept at room temperature for 5 h with stirring. Ice–water was then added and the mixture was extracted five times with chloroform. The chloroform solution was

washed with water and aqueous sodium hydrogen carbonate, and dried. Evaporation gave a syrupy, crude mixture (1 g, 80%) of azido-ketones (**3** and **4**) in the ratio 4.5:5.5 as determined by n.m.r. spectroscopy. The i.r. spectrum showed the presence of azide and ketone bands at 2100 and 1735 cm^{-1}, respectively.

*Ethyl 2-acetamido-4,6-di-*O*-benzoyl-2,3-dideoxy-α-*D*-ribo-hexopyranoside* (**10**) *and ethyl 2-acetamido-4,6-di-*O*-benzoyl-2,3-dideoxy-α-*D*-lyxo-hexopyranoside* (**8**). — The mixture (1 g) of azido-ketones **3** and **4** was dissolved in methanol (30 ml) and cooled to 0°. Sodium borohydride (4 × 250 mg) was then added during 30 min and the mixture was stirred for an additional 2 h. It was then neutralized with Amberlite IR-120(H^+) ion-exchange resin, filtered, and evaporated under diminished pressure. The residue was fractionated by p.l.c. with chloroform–methanol–hexane (30:20:50 v/v) to give syrupy ethyl 2-azido-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**6**; 224 mg, 22%), R_F 0.6 (t.l.c., chloroform–methanol–hexane, 30:20:50 v/v); and pure ethyl 2-azido-2,3-dideoxy-α-D-*lyxo*-hexopyranoside (**5**; 110 mg, 11%), R_F 0.7.

Compound **6** (224 mg) was dissolved in methanol (30 ml) and acetic anhydride (0.4 ml), and reduced over Adams' catalyst overnight. Filtration and evaporation furnished the crystalline ethyl 2-acetamido-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**9**; 96 mg, 40%), which was recrystallized from ethyl acetate: m.p. 185–187°, $[\alpha]_D$ +149° (*c* 1.05, methanol).

Anal. Calc. for $C_{10}H_{19}NO_5$: C, 51.50; H, 8.20; N, 6.00. Found: C, 51.25; H, 8.10; N, 5.70.

Compound **9** (80 mg) was benzoylated with benzoyl chloride (0.1 ml) in dry pyridine (2 ml) in the usual manner, and the product (24 mg, 16%) crystallized from chloroform–hexane to give ethyl 2-acetamido-4,6-di-*O*-benzoyl-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**10**), m.p. 176–178°, $[\alpha]_D$ +74° (*c* 0.91, chloroform). N.m.r. data (250 MHz, chloroform-*d*): δ 4.78 ($J_{1,2}$ 4 Hz), 5.2 ($J_{4,3e}$ 5 Hz, $J_{4,3a} = J_{4,5} = 11$ Hz).

Anal. Calc. for $C_{24}H_{27}NO_7$: C, 65.30; H, 6.15; N, 3.20. Found: C, 65.05; H, 6.10; N, 3.30.

Compound **5** (110 mg) was reduced using Adams' catalyst, as described above for **6**, to give oily ethyl 2-acetamido-2,3-dideoxy-α-D-*lyxo*-hexopyranoside (**7**; 60 mg, 50%), which was benzoylated with benzoyl chloride in pyridine, in the usual manner, to give ethyl 2-acetamido-4,6-di-*O*-benzoyl-2,3-dideoxy-α-D-*lyxo*-hexopyranoside (**8**), (from ether–hexane) m.p. 75–77°, $[\alpha]_D$ +96° (*c* 0.84, methanol). N.m.r. data (90 MHz, chloroform-*d*): δ 4.7 ($J_{1,2} < 2$ Hz), 5.3 ($J_{4,3a} = J_{4,3e} = J_{4,5} = 2$ Hz).

Anal. Calc. for $C_{24}H_{27}NO_7$: C, 65.30; H, 6.15; N, 3.20. Found: C, 65.05; H, 6.05; N, 3.35.

2-*Acetamido*-2,3-*dideoxy*-D-ribo-*hexopyranose* (**12**) (N-*acetyl-lividosamine*). — Ethyl 2-acetamido-2,3-dideoxy-α-D-*ribo*-hexopyranoside (**9**, 26 mg) was heated under reflux with 0.02M sulphuric acid (15 ml) for 3 h. The solution was then neutralized with 20% aqueous barium hydroxide, the suspension was filtered, and the filtrate was evaporated under diminished pressure. The residue, 2-amino-2,3-dideoxy-D-*ribo*-hexopyranose (**11**; 10 mg, 44%), was treated overnight with methanol (10 ml) and acetic anhydride to furnish crystalline **12**, which, after crystallisation and recrystal-

lisation from ethanol–ether, had m.p. 150–152°, $[\alpha]_D$ +54 (2 h) → +30° (at equilibrium) (*c* 0.6, water); lit.[7] m.p. 151–152°, $[\alpha]_D$ +54 → +26.1° (*c* 1, water).

ACKNOWLEDGMENT

Professor E. Lederer is thanked for this constant encouragement.

REFERENCES

1 T. Mori, T. Ichiyanasi, H. Kondo, K. Tokunasa, T. Oda, and K. Munakata, *J. Antibiot., Ser. A*, 24 (1971) 339–446.
2 H. Umezava, *Advan. Carbohydr. Chem. Biochem.*, 30 (1974) 183–225.
3 K. E. Price, J. C. Goodfrey, and H. Kawaguchi, *Advan. Appl. Microbiol.*, 18 (1974) 191–307.
4 J. Cleophax, S. D. Gero, and J. Leboul, *Chem. Commun.*, (1973) 710–711.
5 J. Cleophax, S. D. Gero, E. Jegou-Aumont, J. Leboul, and D. Mercier, *Chem. Commun.*, (1975) 11–12.
6 B. Fraser-Reid, A. McLean, E. W. Usherwood, and M. Tunker, *Can. J. Chem.*, 48 (1970) 2877–2884.
7 T. Oda, T. Mori, nad Y. Kyotani, *J. Antibiot., Ser. A*, 24 (1971) 503–510.