The Synthesis of *N*-Acetyl-lincosamine (6-Acetamido-6,8-dideoxy-D-*erythro*-D-*galacto*-octose), a Derivative of the Free Carbohydrate Moiety in Lincomycin

By G. B. HOWARTH, W. A. SZAREK,* and J. K. N. JONES
(*Department of Chemistry, Queen's University, Kingston, Ontario, Canada*)

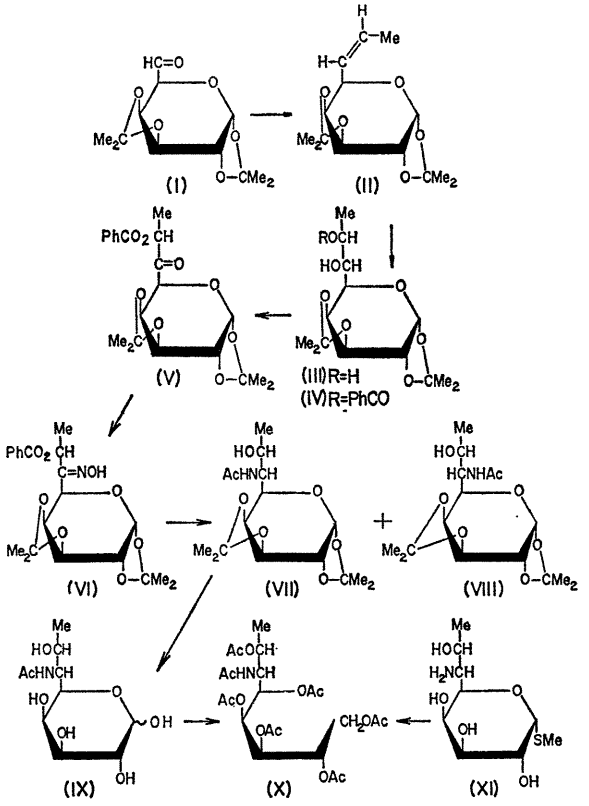
Summary 6-Acetamido-6,8-dideoxy-D-*erythro*-D-*galacto*-octose (*N*-acetyl-lincosamine), the *N*-acetyl derivative of the free carbohydrate moiety in lincomycin, has been synthesised from 1,2 : 3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose by two routes.

LINCOMYCIN is an important antibiotic produced by *Streptomyces lincolnensis* var. *lincolnensis*[1] with activity against Gram-positive organisms. The antibiotic consists of the methyl 1-thioglycoside of an aminodideoxy-octose, methyl 6-amino-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside† (XI),[2] bound to an amino-acid, L-*trans*-4-n-propylhygric acid,[3] by an amide linkage. In a recent publication[4] some syntheses related to the carbohydrate moiety were described. Here we report two syntheses of the *N*-acetyl derivative of the free sugar, 6-acetamido-6,8-dideoxy-D-*erythro*-D-*galacto*-octose (*N*-acetyl-lincosamine) (IX).

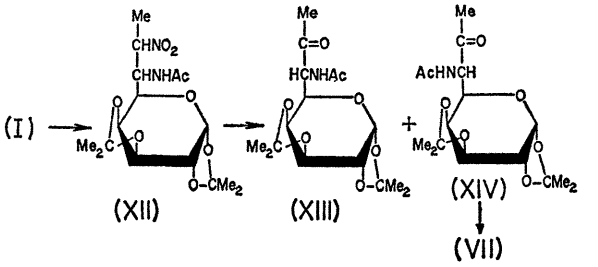
A Wittig reaction[5] between ethylidenetriphenylphosphorane and 1,2 : 3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (I) has been shown[6] to give predominantly *cis*-6,7,8-trideoxy-1,2 : 3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enose (II) (see Scheme 1). Treatment of the Wittig product with aqueous $KMnO_4$ gave a crystalline *vic*-diol, whose structure has been established as 8-deoxy-1,2 : 3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (III).[6] Compound (III) could be selectively benzoylated with benzoyl chloride in pyridine to afford the 7-*O*-benzoyl derivative (IV)‡ in 72% yield, m.p. 141—142°, $[\alpha]_D$ − 82° (*c* 1·2, EtOAc). Oxidation of (IV) with ruthenium tetroxide by an improved procedure[7] gave crystalline 7-*O*-benzoyl-8-deoxy-1,2 : 3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-octos-6-ulose (V) in 78% yield, m.p. 83—84°, $[\alpha]_D$ −135° (*c* 1·3, EtOAc). The appearance, in the n.m.r. spectrum of (V), of the terminal methyl group as a doublet with a spacing of 7 Hz established that the benzoyl group was at C-7. Treatment of compound (V) with hydroxylamine hydrochloride in aqueous EtOH, with pyridine as the acid acceptor and catalyst, afforded both geometrical isomers of the oxime (VI). Reduction of the preponderant isomer (47%), which had m.p. 185—187°, $[\alpha]_D$ − 97° (*c* 1·2, EtOH), with $LiAlH_4$ gave a mixture of stereoisomeric *vic*-amino-alcohols, which on *N*-acetylation yielded two crystalline 6-acetamido-6-deoxy-derivatives. One of these was shown to be 6-acetamido-6,8-dideoxy-1,2 : 3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (VII) (11%), m.p. 166—167°, $[\alpha]_D$ − 53°

† The trivial name methyl thiolincosaminide (MTL) has been given to this compound.
‡ All new compounds gave satisfactory elemental analyses, and gave i.r. and n.m.r. spectra in agreement with the assigned structures.

(*c* 2·5, $CHCl_3$); the other is, therefore, 6-acetamido-6,8-dideoxy-1,2 : 3,4-di-*O*-isopropylidene-D-*threo*-α-D-*galacto*-octopyranose (VIII) (7%), m.p. 173—174°, $[\alpha]_D$ −91° (*c* 1·1, $CHCl_3$). Acid-catalysed hydrolysis of (VII) afforded the free sugar (IX) as an amorphous solid in 80% yield, $[\alpha]_D$ +37° (*c* 0·8, H_2O). Reduction of compound (IX) with $NaBH_4$, and acetylation of the resultant product, gave the crystalline hepta-acetyl derivative (X), m.p. 160—161°. The same compound was obtained from authentic methyl thiolincosaminide§ (XI) by treatment with mercury(II) chloride and cadmium carbonate, followed by reduction of the free sugar with sodium borohydride, and then acetylation of the resultant product, thus establishing that the structure of the sugar (IX) is that of 6-acetamido-6,8-dideoxy-D-*erythro*-D-*galacto*-octose, a derivative of the free carbohydrate moiety in lincomycin.



SCHEME 1



SCHEME 2

The key intermediate (VII) has been prepared also by an alternative synthesis (Scheme 2). During the course of our earlier synthetic studies related to lincomycin,[4] an approximately 1 : 1 mixture of two stereoisomeric 6-acetamido-6,7-dideoxy-7-*C*-nitro derivatives (XII) was obtained from the aldehyde (I). Oxidative denitration with $KMnO_4$[8] of the mixture gave two crystalline 7-ketones, thus establishing that compounds (XII) differ in configuration at C-6. The two ketones are 6-acetamido-6,8-dideoxy-1,2 : 3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-octos-7-ulose (XIII) (66%), m.p. 154—155°, $[\alpha]_D$ − 76° (*c* 1·1, EtOAc), and the D-*glycero*-isomer (XIV) (23%), m.p. 207—208°, $[\alpha]_D$ −55·6° (*c* 0·9, EtOAC). Reduction of (XIV) with $NaBH_4$ gave a mixture of two *vic*-acetamido-alcohols, from which the desired isomer (VII) was isolated in 47% yield by fractional crystallisation.

We thank the National Research Council of Canada for financial support.

(*Received, September 3rd*, 1969; *Com.* 1336.)

§ We are grateful to Dr. G. B. Whitfield, jun., of the Upjohn Company, Kalamazoo, Michigan, for a generous gift of this compound.

[1] D. J. Mason, A. Dietz, and C. DeBoer, "Antimicrobial Agents and Chemotherapy, 1962," American Society for Microbiology, Ann Arbor, Michigan, 1963, p. 554.
[2] W. Schroeder, B. Bannister, and H. Hoeksema, *J. Amer. Chem. Soc.*, 1967, **89**, 2448.
[3] G. Slomp and F. A. MacKellar, *J. Amer. Chem. Soc.*, 1967, **89**, 2454; B. J. Magerlein, R. D. Birkenmeyer, R. R. Herr, and F. Kagan, *ibid.*, p. 2459.
[4] G. B. Howarth, D. G. Lance, W. A. Szarek, and J. K. N. Jones, *Canad. J. Chem.*, 1969, **47**, 75.
[5] D. G. Lance and W. A. Szarek, *Carbohydrate Res.*, 1969, **10**, 306.
[6] D. G. Lance, W. A. Szarek, J. K. N. Jones, and G. B. Howarth, *Canad. J. Chem.*, 1969, **47**, 2871.
[7] G. B. Howarth, W. A. Szarek, and J. K. N. Jones, *Carbohydrate Res.*, 1968, **7**, 284; B. T. Lawton, W. A. Szarek, and J. K. N. Jones, *ibid.*, 1969, **10**, 456.
[8] H. Shechter and F. T. Williams, *J. Org. Chem.*, 1962, **27**, 3699; H. H. Baer and M. C. T. Wang, *Canad. J. Chem.*, 1968, **46**, 2793; E. H. Williams, W. A. Szarek, and J. K. N. Jones, *ibid.*, in the press.