Tetrahedron Letters No.8, pp. 839-846, 1966. Pergamon Press Ltd.
Printed in Great Britain.

ALDGAROSE, A CYCLIC CARBONATE SUGAR OF NATURAL ORIGIN

M. P. Kunstmann, L. A. Mitscher and N. Bohonos

Biochemical Research Section, Lederle Laboratories
A Division of American Cyanamid Company, Pearl River, New York

(Received 2 December 1965)

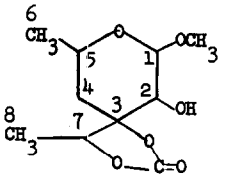
The infrared spectra of some of the neutral macrolide antibiotics contain an unusual absorption band at 1800 cm^{-1}. Megacidin (1), bandamycin A (2) and aldgamycin E (3) are typical examples. Despite its unusually high frequency, there has been no comment in the literature as to the molecular meaning of this band. We would like to present evidence that it is a reflection of the presence of an unusual sugar containing a cyclic carbonate function.

Treatment of aldgamycin E ($C_{37}H_{58}O_{15}$, M = 742 ± 0*) with barium hydroxide at room temperature leads to the rapid precipitation of one mole of barium carbonate and the production of a new crystalline antibiotic**, aldgamycin C ($C_{36}H_{60}O_{14}$, M = 716 ± 0*; Found: C, 60.62; H, 8.50; O, 31.14), m.p. 150-153°; $[\alpha]_D^{25}$ -70° (c 0.670, MeOH), λ_{max}^{MeOH} 217 mμ (log ε 4.13). Aldgamycin C, which has also been isolated from the same culture filtrate as had been E (Streptomyces lavendulae, Lederle soil isolate AL471), no longer contains the 1800 cm^{-1} band. The difference in molecular formulae is consistent with the hypothetical base-labile cyclic carbonate function (4).

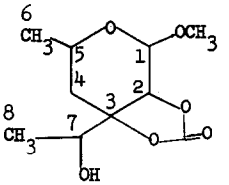
Methanolysis of aldgamycin E liberates three sugars, isolated as

*Direct inlet mass spectroscopy (Atlas CH4).
**Treatment of bandamycin A under the same conditions gives a similar result.

their methyl glycosides. These are methyl mycinoside (present also in chalcomycin (5) and neutramycin (6)), methyl aldgaroside A (I) and methyl aldgaroside B (II), the latter two being isomeric. Methyl aldgaroside A (I) contains the 1800 cm^{-1} band and is probably the isomer present in aldgamycin E. Methyl aldgaroside B (II), which exhibits the carbonate band at 1770 cm^{-1}, probably arises from methyl aldgaroside A by an O to O acyl migration (7) during the methanolysis and isolation process.



(I)



(II)

Removal of the carbonate function from methyl aldgaroside B [m.p. 175-177°, $[\alpha]_D^{25}$ -41° (c 1.004, MeOH), Found for $C_{10}H_{16}O_6$: C, 51.49; H, 7.05; O-methyl, 7.89; C-methyl, 6.09; M = 232 ± 0*7] with dilute barium hydroxide followed by periodate oxidation gave one mole each of acetaldehyde and glyoxal, isolated as their dinitrophenylhydrazone derivatives. The nmr spectrum of II (Fig. 1) is consistent with the assigned structure, revealing one O-methyl group (6.52τ), two C-methyl groups (8.48τ and 8.77τ, doublets) and one deuterium exchangeable secondary hydroxyl group. In addition, H_1 (5.52τ) and H_2 (5.73τ) are coupled only to one another (J = 5.5 cps) indicating no hydrogen at C_3. The three hydrogens at C_8 are coupled (7 cps) to H_7 (6.55τ) which is in turn coupled to the C_8 hydrogens and a hydroxyl proton (4.72τ) by 5 cps. The H_7 signal is simplified and the hydroxyl proton peak is lost upon deuterium exchange. Lack of additional coupling

*Direct inlet mass spectroscopy (Atlas CH4).

confirms the lack of hydrogen at C_3. H_{4a} (8.40τ) and H_{4e} (8.10τ) are coupled to one another (12 cps) and H_{4e} to a single hydrogen at H_5 (6.15τ). Apparently the dihedral angle between H_{4a} and H_5 is such that there is very little observable coupling between them. The methyl hydrogens at C_6 are coupled (6 cps) with a single hydrogen at C_5. The coupling constants for the ring hydrogens are intermediate in magnitude and do not allow assignment of the relative stereochemistry with confidence. This may be due to steric constraint imposed upon the ring by the cyclic carbonate function.

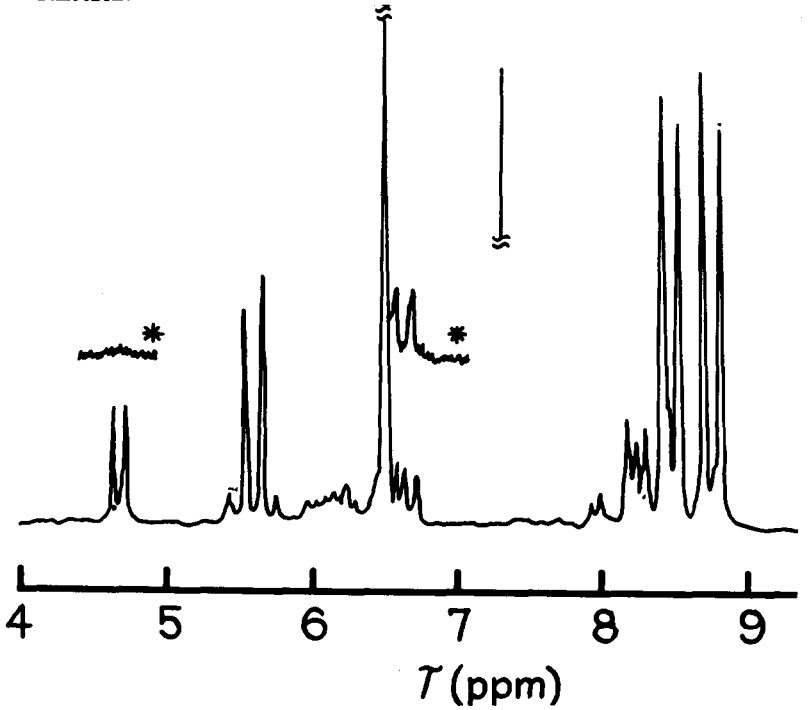
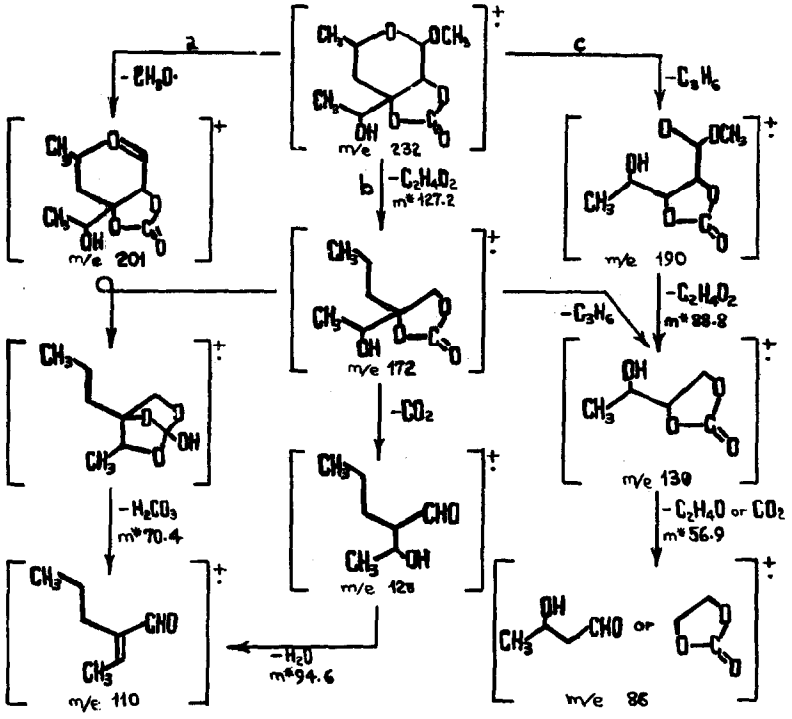


FIG. 1 NMR Spectrum of Methyl Aldgaroside B (II)**

*After active hydrogen exchange with CD_3OD.
**Spectrum determined at 60 Mc in $CDCl_3$ containing d_6-DMSO.

The mass spectrum (Fig. 2) is also consistent with structure II and the principal fragmentation processes can be deduced partly with the aid of several important metastable ions. The three most important processes involve initial loss of a) the anomeric methoxyl, b) methyl formate followed by propene, and c) propene followed by methyl formate. Paths b and c converge at m/e 130 which then loses mass 44 to produce the base peak at m/e 86. This could correspond to either loss of CO_2 or C_2H_4O, and further fragmentations of m/e 86 did not differentiate between the possibilities. The other fragmentations are largely self explanatory.



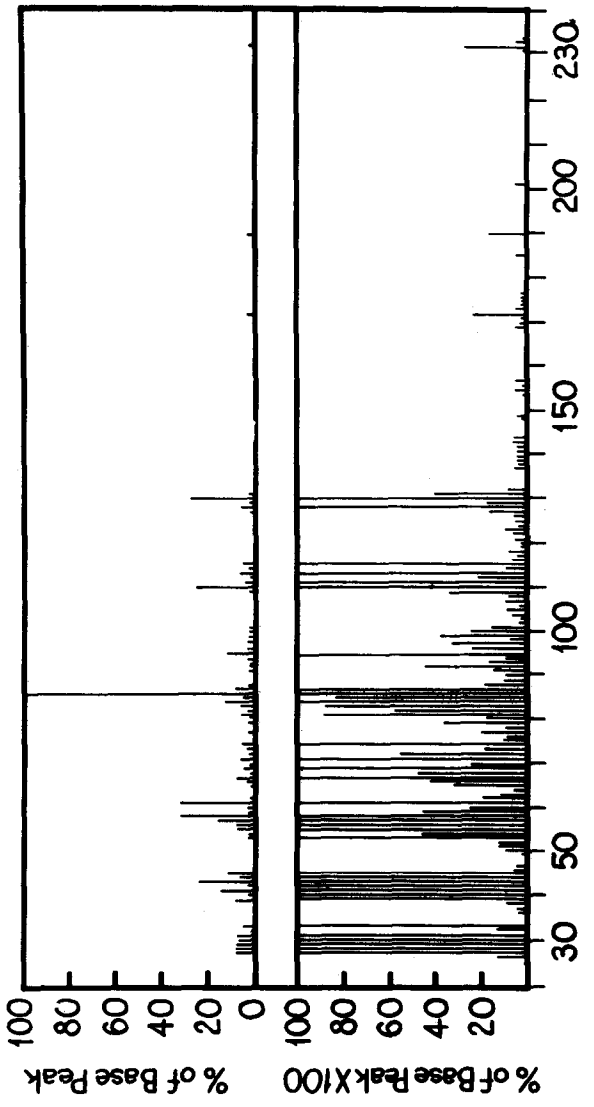


FIG. 2 Mass Spectrum of Methyl Aldgaroside B (II) (Atlas CH_4, Direct Inlet)

The structure of methyl aldgaroside A (I), m.p. 91-94°, may be deduced from its nmr spectrum (Fig. 3). The spectrum is very similar to that of methyl aldgaroside B (II) except that H_2 is shifted to higher field (6.33τ), and in addition to being coupled (4.5 cps) with H_1 (5.32τ), is coupled (9 cps) to a hydroxyl hydrogen (5.48τ) as shown by deuterium exchange. H_7 now occurs at lower field (5.65τ) and is only coupled with the methyl hydrogens at C_8. It is well known that acylation of a hydroxyl group results in a downfield shift for the hydrogen attached to the oxygen-bearing carbon. Thus, in the case where the hydroxyl at C_7 is acylated by the carbonate function (I), H_7 is shifted downfield, whereas when the hydroxyl at C_2 is acylated (II), H_2 is shifted downfield.

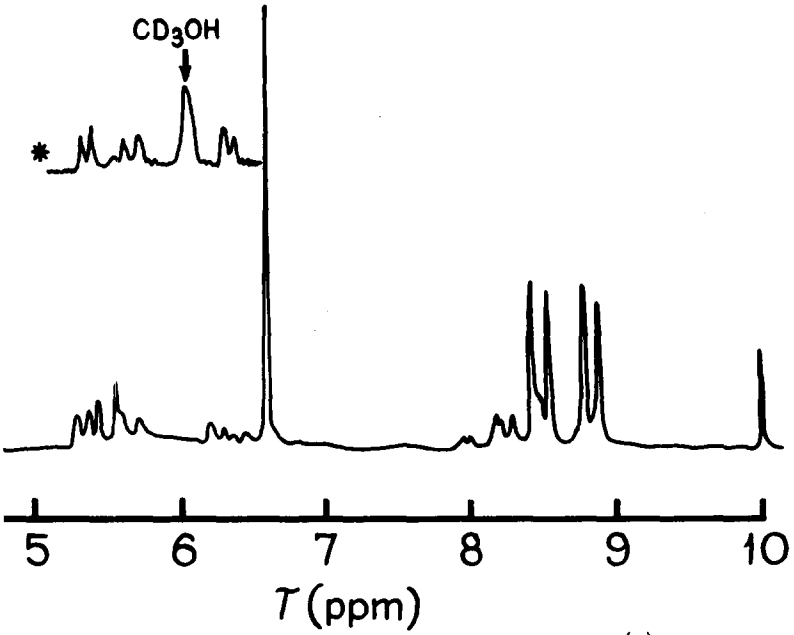


FIG. 3 NMR Spectrum of Methyl Aldgaroside A (I)**

*After active hydrogen exchange with CD_3OD.
**Spectrum determined at 60 Mc in $CDCl_3$ containing d_6-DMSO.

The mass spectra of aldgamycin E and C provide additional evidence for the presence of the sugars. "E" has M=742 followed by m/e 567 (loss of mycinosyl), m/e 551 (loss of mycinosyloxy), m/e 540 (loss of aldgarosyl), m/e 524 (loss of aldgarosyloxy) and peaks at m/e 365, 349 and 333 corresponding to various combinations of losses of both sugars with and without their connecting oxygens. The m/e 333 peak, corresponding to loss of both sugars and their connecting oxygens, is the strongest peak above m/e 150. "C" has M = 716 followed by m/e 542 (loss of either sugar) and m/e 524 (loss of either sugar and its connecting oxygen) and with additional peaks at m/e 368, 367, 351, 350 and 333 (again corresponding to loss of both sugars with and without their connecting oxygens).

The isolation of aldgarose represents the first recorded observation of a cyclic carbonate sugar from an antibiotic. It is interesting from a biogenetic viewpoint to emphasize the fact that aldgarose and chalcose, the companion sugar to mycinose in chalcomycin and neutramycin, are both 4,6-didesoxy sugars. As all three antibiotics contain mycinose, the altered substitution pattern of aldgarose may be a reflection of an evolutionary change or a biochemical error in that the sugar which was to have been chalcose was further elaborated at an intermediate stage.

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