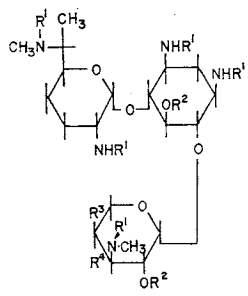
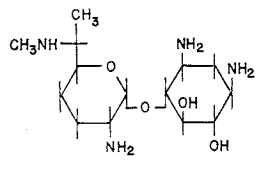
Communications to the editor

THE SYNTHESIS OF 4″-DEOXYGENTAMICIN C_1

Sir:

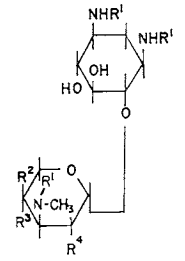
During recent years a considerable effort has been directed towards the elucidation of the resistance mechanisms whereby resistant bacterial strains inactivate many clinically useful aminocyclitol antibiotics[1]. As a result of these studies it has become possible to make rational modifications to these antibiotics either at the site of inactivation[2~6], or at a group remote from the site of inactivation[7] to produce in many instances new semisynthetic aminocyclitol antibiotics with greatly improved antibacterial activity against resistant organisms. Although the 4″-hydroxyl group in gentamicin C_1 (**1**) is not directly modified by any of the known resistant organisms, it was removed to give 4″-deoxygentamicin C_1 (**2**) in order to determine what changes could be induced in the antibacterial spectrum of the compound.

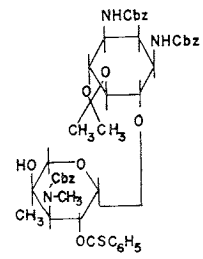




(5)

(1) $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = CH_3$
(2) $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$
(3) $R^1 = Cbz$, $R^2 = H$, $R^3 = OH$, $R^4 = CH_3$
(4) $R^1 = Cbz$, $R^2 = Ac$, $R^3 = OAc$, $R^4 = CH_3$
(6) $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$





(7) $R^1 = Cbz$, $R^2 = OAc$, $R^3 = CH_3$, $R^4 = OH$
(8) $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4 = OH$
(9) $R^1 = R^3 = H$, $R^2 = CH_3$, $R^4 = OH$
(10) $R^1 = Cbz$, $R^2 = OH$, $R^3 = CH_3$, $R^4 = OAc$
(12) $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = CH_3$

(11)

Gentamicin C_1 (**1**) was converted to the penta-N-carbobenzoxy derivative (**3**) which on treatment with acetic anhydride containing concentrated hydrochloric acid (10% v/v) at room temperature for seventeen hours, gave the per-O-acetyl derivative (**4**)*. The protected gentamicin C_1 (**4**) was reduced with sodium in liquid ammonia to give, after chromatography on silica gel using the lower phase of a chloroform - methanol - ammonium hydroxide system (1 : 1 : 1) as the eluent, 4″-deoxygentamicin C_1 (**2**) (11%), gentamicin C_1 (**1**) (18%) and gentamine C_1 (**5**) (6%). The latter must have been formed by base catalysed hydrolysis of the garosamine unit.

4″-Deoxygentamicin C_1 (**2**) showed the expected molecular ion at *m/e* 461 corresponding to a molecular formula $C_{21}H_{43}N_5O_6$, with peaks at *m/e* 334, 316, 306, 288 due to the disaccharide ions containing the 4″-deoxygarosamine unit[8] and a peak at *m/e* 144 due to the glycosyl cleavage of that sugar. The 100 MHz n. m. r. spectrum of **2** in D_2O exhibited two doublets at δ 0.78 (J 6.5 Hz, 4″-CH_3) and 0.95 (J 6.5 Hz, 6′-CH_3) and two singlets at δ 2.23 and 2.25 due to the two N-CH_3 groups. The anomeric protons gave rise to doublets at δ 4.97 (J 4 Hz, H_1″) and 5.02 (J 4 Hz, H_1′). Small amounts of the 4″-axial compound (**6**) (<5%) could be detected in the n. m. r. spectrum of **2** giving rise to a doublet due to the 4″-CH_3 group at δ 0.62 (J 6.5 Hz). The c. d. spectrum of **2** in TACu showed $[\theta]_{285}$—14,000.

4″-Deoxygentamicin C_1 (**2**) exhibited only very weak antibacterial activity against some sensitive gram-positive bacteria and was otherwise inactive. It may therefore be concluded that the 4″-hydroxy group is essential for biological activity in these compounds.

When 4′-O-acetyl-1, 3, 3′-tri-N-carbobenzoxy garamine (**7**) was similarly treated a mixture of

* All compounds gave satisfactory microanalyses and spectral data were in accord with the proposed structures.

the 4′-deoxygaramines (**8**) and **9** was formed in a ratio of *ca.* 7 : 3. Although **8** and **9** could not be separated chromatographically they could readily be distinguished in the n. m. r. spectrum of the mixture in D_2O (100 MHz) which showed doublets due to the 4′-axial and 4′-equatorial methyl groups at δ 0.69 (J 6.5 Hz) and 0.86 (J 6.5 Hz) respectively. The 3′-N-CH_3 and H_1' signals occurred at δ 2.32 and 5.02 (d, J 3.5 Hz) in **8**, and at 2.63 and 5.08 (d, J 3.5 Hz) in **9** respectively. The H_3' signal in **8** occurred at 2.57 (dd, $J_{2',3'}=J_{3',4'}=10$ Hz).

Application of the reaction to the 2′-acetyl and 2′-thiono-benzoyl garamine derivatives **10** and **11** respectively followed by removal of the isopropylidene group in the case of **11**, gave only traces of the 2′-deoxygaramine (**12**), which showed an $M^+ + 1$ ion at *m/e* 306 in the mass spectrum consistent with the proposed structure. Thus the reaction is not generally applicable to the synthesis of 2″-deoxygentamicin derivatives.

The reaction is thought to proceed by way of a tertiary radical intermediate.

We thank Messrs. J.B. MORTON and J. MCGLOTTEN and their staffs for spectral data.

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(Received October 2, 1973)

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