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Preliminary communication

7-*O*-(3-Azido-2,3,6-trideoxy-α- and -β-L-*ribo*-hexopyranosyl)carminomycinone: novel analogues of anthracycline antibiotics

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Daunomycin (**1**), adriamycin (**2**), and carminomycin (**3**) are clinically useful anticancer agents, but they possess undesirable side-effects[1]. The carbohydrate component of **1**–**3** is daunosamine (**4**). Analogues, in which the daunosamine moiety has been replaced by other aminodeoxy[2–4] and neutral sugars[5,6], have been described and we now report on a derivative of carminomycin, containing a 3-azido-2,3,6-trideoxy-L-*ribo*-hexopyranose (**5**) unit.

Treatment of the readily available[7] methyl 3-azido-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (**6**) with *p*-nitrobenzoyl chloride (pyridine, 20°, 3 h) gave the 4-*p*-nitrobenzoate **7** (85%), m.p. 116–117° (from ethanol–water), $[\alpha]_D^{21}$ −98° (*c* 0.41, methanol)*. Hydrolysis of **7** with M hydrochloric acid (100°, 30 min) or, more suitably, 50% acetic acid (100°, 4 h) gave 3-azido-2,3,6-trideoxy-4-*O*-*p*-nitrobenzoyl-L-*ribo*-hexopyranose (**8**, 50%), m.p. 147–149° (from water), $[\alpha]_D^{21}$ +62→+64° (after 1 h; *c* 0.4, methanol). The 1,4-di-*p*-nitrobenzoate **9** had m.p. 169–170° (from chloroform–light petroleum), and the 1-acetate **10** (acetic anhydride–pyridine, 20°, 24 h) had m.p. 124–125° (from ethanol).

In contrast to earlier results[3], acetolysis of **8** gave **10** in low yield (~20%). Saturation of a solution of **9** in dichloromethane with dry hydrogen chloride and the reaction of carminomycinone with the resulting, crude glycosyl chloride [Koenigs–Knorr conditions; dichloromethane, mercuric bromide, mercuric cyanide, and molecular sieve (3 Å), 24–28 h, 20°] gave a 3:1 mixture (~32%) of **12** and **13** which was fractionated by p.l.c. [Kieselgel 60F_{254} (Merck), 99:1 dichloromethane–methanol]. Compound **12** had m.p. 233–235°, $[\alpha]_D^{23}$ +335° (*c* 0.56, chloroform), R_F 0.72; ν_{max}^{KBr} 2100 (N_3), 1738 (ester C=O), 1720 (acetyl C=O), 1612 (quinone), 1532 (NO_2), and 1353 cm^{-1} (NO_2); $\lambda_{max}^{CHCl_3}$ 255, 466, 480, 492, 515, and 528 nm. ^{13}C-N.m.r. data ($CDCl_3$, 25.16 MHz): δ 98.38 (C-1′), 34.02 and 33.92 (C-2′), 56.94 (C-3′), 62.98 (C-4′), 75.55 (C-5′), and 17.46 (C-6′). Compound **13** had m.p. 112–115°,

*All new compounds gave satisfactory elemental analyses.

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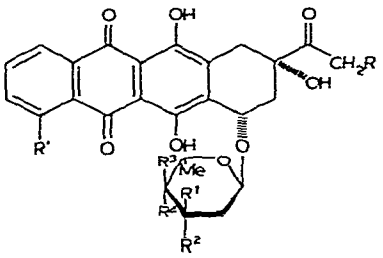
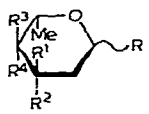
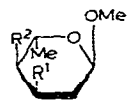


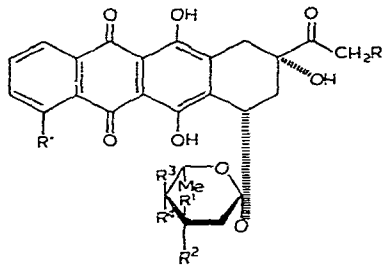
1 R = H, R' = OMe, $R^1 = R^3 = H$, $R^2 = NH_2$, $R^4 = OH$
2 R = R^4 = OH, R' = OMe, $R^1 = R^3 = H$, $R^2 = NH_2$
3 R = $R^1 = R^3 = H$, $R^2 = NH_2$, R' = R^4 = OH
12 R = $R^2 = R^4 = H$, R' = OH, $R^1 = N_3$, $R^3 = OBz\text{-}pNO_2$
14 R = $R^2 = R^4 = H$, R' = R^3 = OH, $R^1 = N_3$



4 R = R^4 = OH, $R^1 = R^3 = H$, $R^2 = NH_2$
5 R = R^3 = OH, $R^1 = N_3$, $R^2 = R^4 = H$
8 R = OH, $R^1 = N_3$, $R^2 = R^4 = H$, $R^3 = OBz\text{-}pNO_2$
9 R = $R^3 = OBz\text{-}pNO_2$, $R^1 = N_3$, $R^2 = R^4 = H$
10 R = OAc, $R^1 = N_3$, $R^2 = R^4 = H$, $R^3 = OBz\text{-}pNO_2$
11 R = Cl, $R^1 = N_3$, $R^2 = R^4 = H$, $R^3 = OBz\text{-}pNO_2$



6 R' = N_3, R^2 = OH
7 R' = N_3, $R^2 = OBz\text{-}pNO_2$



13 R = $R^2 = R^4 = H$, R' = OH, $R^1 = N_3$, $R^3 = OBz\text{-}pNO_2$
15 R = $R^2 = R^4 = H$, R' = R^3 = OH, $R^1 = N_3$

$[\alpha]_D^{25}$ +143° (*c* 0.86, chloroform), R_F 0.62; ν_{max}^{KBr} 2120 (N_3), 1740 (ester C=O), 1720 (acetyl C=O), 1615 (quinone), 1536 (NO_2), and 1355 cm^{-1} (NO_2); $\lambda_{max}^{CHCl_3}$ 255, 464, 480, 493, 514, and 529 nm. ^{13}C-N.m.r. data: δ 97.10 (C-1'), 34.17 and 34.49 (C-2'), 58.45 (C-3'), 67.96 (C-4'), 75.37 (C-5'), and 17.67 (C-6').

Comparison of the chemical shifts of the carbons of the L-*ribo*-pyranosyl ring with those of **7** indicated **12** and **13** to be α and β isomers, respectively. Zemplén de-esterification of **12** and **13** gave 7-*O*-(3-azido-2,3,6-trideoxy-α- (**14**) and -β-L-*ribo*-hexopyranosyl)carminomycinone (**15**) which were purified by p.l.c. as described above. Compound **14** had m.p. 226–229° (from chloroform containing 5% of 1-propanol), $[\alpha]_D^{20}$ +367° (*c* 0.49, chloroform), R_F 0.36; ν_{max}^{KBr} 2110 (N_3), 1715 (acetyl C=O), and 1612 cm^{-1} (quinone); $\lambda_{max}^{CHCl_3}$ 255, 466, 483, 490, 515, and 527 nm. Compound **15** had m.p. 193–196°, $[\alpha]_D^{20}$ +180° (*c* 0.9, chloroform), R_F 0.17; ν_{max}^{KBr} 2145 (N_3), 1730 (acetyl C=O), and 1620 cm^{-1} (quinone); $\lambda_{max}^{CHCl_3}$ 255, 466, 482, 493, 514, and 530 nm.

Compounds **14** and **15** are potential prodrugs, since the azido group may be reduced *in vivo*. An investigation of the biological action of these compounds is in progress.

ACKNOWLEDGMENTS

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