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Preliminary communication

Anthracycline chemistry: direct conversion of daunorubicin into the L-*arabino*, L-*ribo*, and L-*xylo* analogues, and selective deoxygenation at C-4′

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The antitumour activity of doxorubicin (**1**) and daunorubicin (**2**) has stimulated interest in the synthesis of analogues having altered sugar moieties. Among the large number of new anthracyclines of this type, 4′-*epi*doxorubicin (**3**), which was shown to have the same antitumour activity as **1**, but a diminished toxicity[1], and 4′-deoxydoxorubicin (**4**), which has significant antitumour activity against human-colon carcinomas transplanted in nude mice[2], have been selected for clinical trials. Compounds **3** and **4**, as well as other configurational analogues, have hitherto been obtained following a general scheme which included the synthesis of the desired amino sugars and their coupling with daunomycinone[3]. We now report on a straightforward method for conversion of the *N*-trifluoroacetyl derivative **5** (L-*lyxo* configuration) into analogues having the L-*arabino* (**6**), L-*ribo* (**7**), and L-*xylo* (**8**) configurations of the sugar moiety. Moreover, in order to deoxygenate the glycoside moiety of daunorubicin to give **9**, the possibility of iodide displacement of the trifluoromethanesulfonates[4] **10** and **11** was investigated.

Treatment of **5** with methyl sulfoxide–trifluoroacetic anhydride–triethylamine[5] at −70° oxidized HO-4′, to give the L-*threo* ketone **12**** (80%), m.p. 205–210°. P.m.r. data (acetone-d_6): *inter alia*, δ 5.46 (d, 1 H, $J_{1',2'a}$ 5.3, $J_{1',2'b}$ <1 Hz, H-1′). Treatment of **12** with buffered silica gel (phosphate buffer, pH 7) inverted the configuration at C-3′, affording a mixture of **12** and the L-*erythro* ketone **13**, from which the latter (50%) crystallized and had m.p. 235°. P.m.r. data (acetone-d_6): *inter alia*, δ 5.90 (d, 1 H, $J_{1',2'a} = J_{1',2'b} = 7$ Hz, H-1′), indicating a change of conformation of the sugar moiety after epimerization at C-3′. The corresponding methyl glycosides **16** and **17** (the latter obtained by epimerization of **16**), each of which gave a p.m.r. signal ($CDCl_3$) for H-1 at δ 4.92 (W_H 5 Hz), and *N*-trifluoroacetyl derivatives **6** and **7**, which gave signals for H-1′ at δ 5.45 and 5.43, respectively (W_H 6 Hz), possess the usual $^1C_4$ conformation observed for daunosamine derivatives and stereoisomers[6].

Treatment of **12** with 1 equiv. of $NaBH_4$ at −70° (MeOH–CH_2Cl_2) afforded

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**All compounds gave mass, i.r., and p.m.r. spectra consistent with the assigned structures.

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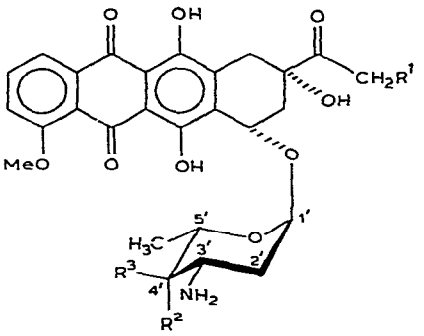
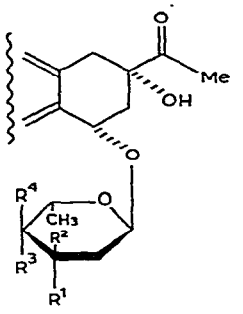
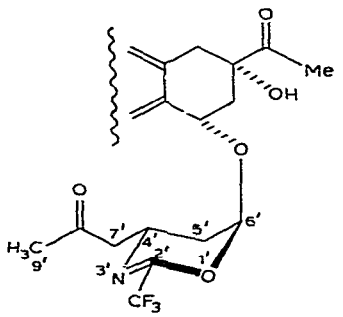


1 $R^1 = R^2 = OH, R^3 = H$
2 $R^1 = R^3 = H, R^2 = OH$
3 $R^1 = R^3 = OH, R^2 = H$
4 $R^1 = OH, R^2 = R^3 = H$



5 $R^1 = NHCOCF_3, R^2 = R^4 = H, R^3 = OH$
6 $R^1 = NHCOCF_3, R^2 = R^3 = H, R^4 = OH$
7 $R^1 = R^3 = H, R^2 = NHCOCF_3, R^4 = OH$
8 $R^1 = R^4 = H, R^2 = NHCOCF_3, R^3 = OH$
9 $R^1 = NHCOCF_3, R^2 = R^3 = R^4 = H$
10 $R^1 = NHCOCF_3, R^2 = R^4 = H, R^3 = OSO_2CF_3$
11 $R^1 = NHCOCF_3, R^2 = R^3 = H, R^4 = OSO_2CF_3$
12 $R^1 = NHCOCF_3, R^2 = H, R^3 = R^4 = O$
13 $R^1 = H, R^2 = NHCOCF_3, R^3 = R^4 = O$
14 $R^1 = NHCOCF_3, R^2 = R^4 = H, R^3 = I$



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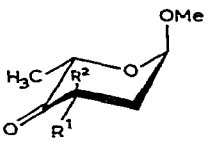

16 $R^1 = NHCOCF_3, R^2 = H$
17 $R^1 = H, R^2 = NHCOCF_3$

an almost quantitative yield of known[3] *N*-trifluoroacetyl-**6**. At higher temperature, with tetrahydrofuran as solvent, a small proportion of the L-*lyxo* isomer was also formed. In contrast, the reduction of **13** gave the L-*ribo* (**7**) and the L-*xylo* (**8**) isomers in the ratio ~1:1.

In seeking to deoxygenate position 4′, the 4′-triflate (**10**) of *N*-trifluoroacetyl-daunorubicin was treated with tetrabutylammonium iodide. However, as unusual rearrangement occurred, to give mainly **15**, m.p. 170° (dec.); field-desorption mass spectrum: *m/z* 705 ($M^{+\cdot}$). The structure of **15** was deduced as follows. The p.m.r. spectrum (250 MHz, $CDCl_3$) showed, *inter alia*, a methyl singlet at δ 2.14 [*cf.* the doublet at δ 1.32 (J 6.5 Hz) for Me-5′ of daunosamine] and spin-decoupling experiments were in agreement with the proton sequence H-4′,5′,6′ of the dihydro-oxazine ring. Furthermore, the proton-decoupled, ^{13}C-n.m.r. spectrum contained two CO signals at δ 206.3 and 207.8 (singlets), excluding the presence of $COCF_3$. Therefore

the new acetyl group (C-8',9') originates *via* a *trans*-diaxial elimination of the 4'-triflate and H-5' of **10**, to give an enolic system which subsequently undergoes opening of the pyranoid ring. A new 6-membered ring is formed by a rearrangement involving the $NHCOCF_3$ group in the enolic form. The undesired elimination has been overcome by using the 4'-triflate (**11**) of 4'-*epi*-*N*-trifluoroacetyldaunorubicin, which, by reaction with Bu_4NI at 30°, readily gave the iodo derivative **14** (75%), m.p. 112–114°; field-desorption mass spectrum: *m/z* 733 ($M^{+\cdot}$). Finally, the reaction of **14** with Bu_3SnH in refluxing toluene, with the addition of α,α'-azoisobutyronitrile as initiator[7], gave known[3] 4'-deoxy-*N*-trifluoroacetyldaunorubicin **9** (75%).

Studies aimed at extending this reaction sequence to anthracyclines having other carbohydrate systems are in progress.

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