Synthesis of the Indole Nucleoside Antibiotics Neosidomycin and SF-2140: Structural Revision of Neosidomycin

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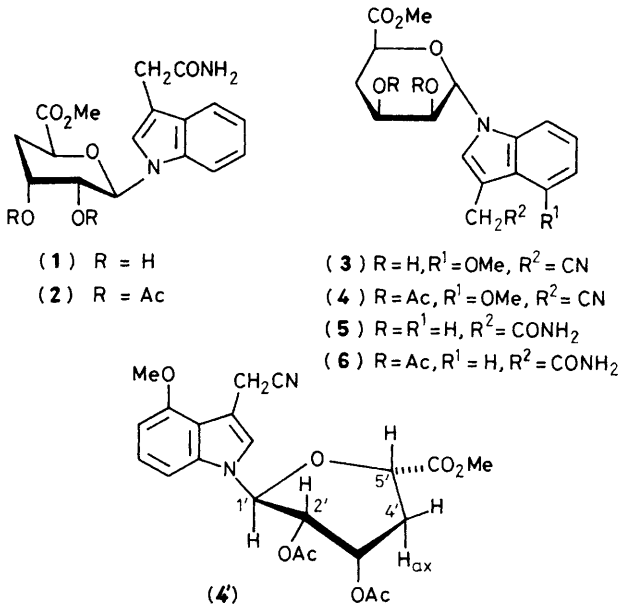
Two structurally related indole nucleoside antibiotics, neosidomycin (**5**) and SF-2140 (**3**) have been synthesised; it is confirmed that the structure initially proposed for neosidomycin must be revised.

In 1979, a novel *N*-glycosyl indole antibiotic, neosidomycin, was isolated from a strain of *Streptomyces hygroscopicus*. The relative stereostructure (**1**) was assigned to neosidomycin, principally on the basis of the n.m.r. data of its di-*O*-acetyl derivative (**2**), with the assumption that both (**1**) and (**2**) adopt $^4C_1$(D) chair conformations in solution.[1] More recently, the antiviral indole nucleoside SF-2140 has been isolated from an *Actinomadura* species, and, on the basis of degradative, spectroscopic, and *X*-ray data, assigned structure (**3**).[2] In order to reconcile the crystallographic and ^{1}H n.m.r. data, which included in particular large coupling constants $J_{1',2'}$ and $J_{4'ax,5'}$, the authors postulated that, in solution, SF-2140 (**3**) and its di-*O*-acetyl derivative (**4**) adopt twist–boat conformations, as illustrated in (**4′**) for the derivative. Since the ^{1}H n.m.r. data for the di-*O*-acetyl derivatives of neosidomycin[1] and SF-2140[2] are virtually identical with regard to the sugar unit, the later workers suggested[2] that the structures of neosidomycin and its di-*O*-acetyl derivative should be revised to (**5**) and (**6**) respectively. We now report the synthesis of (**3**)—(**6**), and confirm the structures of SF-2140 and neosidomycin as (**3**) and (**5**) respectively.

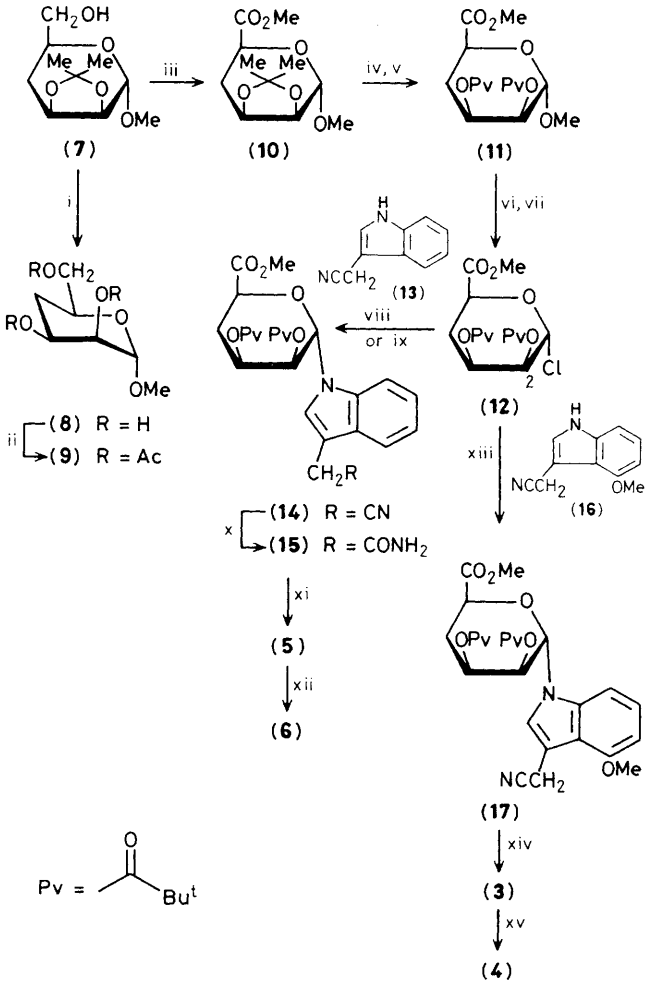
The absolute configuration of SF-2140 was thought to be as shown in (**3**) on the basis of molecular rotation difference data.[2] We confirmed this by conversion (see Scheme 1) of the known 4-deoxy-D-*lyxo*-hexose derivative (**7**)[3] into the triol (**8**), $[\alpha]_D$ + 76°, which had been obtained by degradation of SF-2140, $[\alpha]_D$ + 86°.[2] We further found excellent agreement between the ^{1}H n.m.r. data of synthetic tri-acetyl derivative (**9**) and the data reported[2] for degradative material. Since the $[\alpha]_D$ values for neosidomycin[1] and SF-2140[2] are very similar,



neosidomycin can be assumed to have the same absolute configuration.

To synthesise the antibiotics, (**7**) was converted (see Scheme 1) *via* the uronic ester (**10**) and di-*O*-pivaloyl derivative (**11**) into the glycosyl chloride (**12**). When (**12**) was treated with 3-cyanomethylindole (**13**) in the presence of silver trifluoromethanesulphonate and 2,6-lutidine,[4] *N*-glycosyl indole (**14**) was isolated as a gum in moderate yield after extensive chromatography.† The α-configuration of (**14**) seems assured by the presence of the acyloxy group at C-2 of (**12**), and interestingly (**14**) had similar ^{1}H n.m.r. characteristics to (**4**) and (**6**) (*inter alia*, $J_{1',2'}$ 9.7 Hz, $J_{4'ax,5'}$ 6.9 Hz), indicating a twist–boat conformation. Reaction of (**12**) with the sodium salt[5] of (**13**) gave (**14**) in higher yield after an easier work-up, but contaminated with an inseparable isomer, thought (see below) to be the β-anomer [ratio (**14**): isomer 6 : 1].‡ Nitrile (**14**) (together with isomer) was converted[6] to amide (**15**), and thence (Scheme 1) to (**5**) and (**6**). At no stage was separation of the isomer possible, but the ^{1}H n.m.r. data (chemical shifts and coupling constants) for synthetic (**6**) were virtually identical with those reported[1] for di-*O*-acetylneosidomycin.

Reaction of the sodium salt of 3-cyanomethyl-4-methoxyindole (**16**) with (**12**) gave predominantly α-anomer (**17**),§ which could be separated from the minor β-isomer (ratio 8 : 1) by fractional crystallisation.¶ Deprotection of (**17**) then gave SF-2140 (**3**), which was fully characterised as its di-*O*-acetyl derivative (**4**), $[\alpha]_D$ + 23° (*c* 0.56, MeOH), m.p. 104 °C (lit.[2] 114 °C); the ^{1}H n.m.r. spectrum of synthetic (**4**) was identical with that of a sample of (**4**), m.p. 105 °C, $[\alpha]_D$ + 31° (*c* 0.2, MeOH), prepared by acetylation of natural SF-2140 kindly provided by Dr. T. Mayama.



Scheme 1. i, HOAc, H_2O; ii, Ac_2O, C_5H_5N; iii, $RuCl_3$(cat.), $NaIO_4$, CCl_4/MeCN/H_2O, then CH_2N_2 (72%); iv, 90% CF_3CO_2H, room temp., 15 min (89%); v, pivaloyl chloride, C_5H_5N (81%); vi, Ac_2O, AcOH, H_2SO_4, 0 °C (89%); vii, Cl_2CHOMe, $ZnCl_2$ (96%); viii, (**13**), AgOTf, 2,6-lutidine, CH_2Cl_2, 24 h (36%); ix, (**13**), NaH, MeCN, 0 °C then add (**12**) (44%); x, $Ni(OAc)_2 \cdot 4H_2O$, AcOH, reflux, 24 h (67%); xi, LiOH, MeOH; H^+ resin; CH_2N_2 (72%); xii, as ii (87%); xiii, (**16**), NaH, MeCN, 0 °C (31%); xiv, as xi (76%); xv, as ii (80%). (Tf = CF_3SO_2).

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† Use of the 2,3-di-*O*-acetyl analogue of (**12**) gave the 1,2-*O*-(indol-1-yl)ethylidene derivative; *e.g.* T. N. Solokova, V. E. Shevchenko, and M. N. Preobrazhenskaya, *Carbohydr. Res.*, 1980, **83**, 249.

‡ Use of *O*-acetyl protection gave the *N*-acetyl indole.

§ Reaction of (**12**) and (**16**) in the presence of $AgOSO_2CF_3$ and 2,6-lutidine gave a different product, thought to be a *C*-glycosyl indole.

¶ The minor isomer was not the 5′-epimer of (**17**), since, on treatment with CD_3ONa/CD_3OD, (**17**) was recovered unchanged, but with complete H/D exchange at C-5′.

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