Electrophilic Substitution of a 2-Azabicyclo[2.2.1]hept-5-en-3-one as a Potential Route to 3-Deoxycarbocyclic Nucleosides

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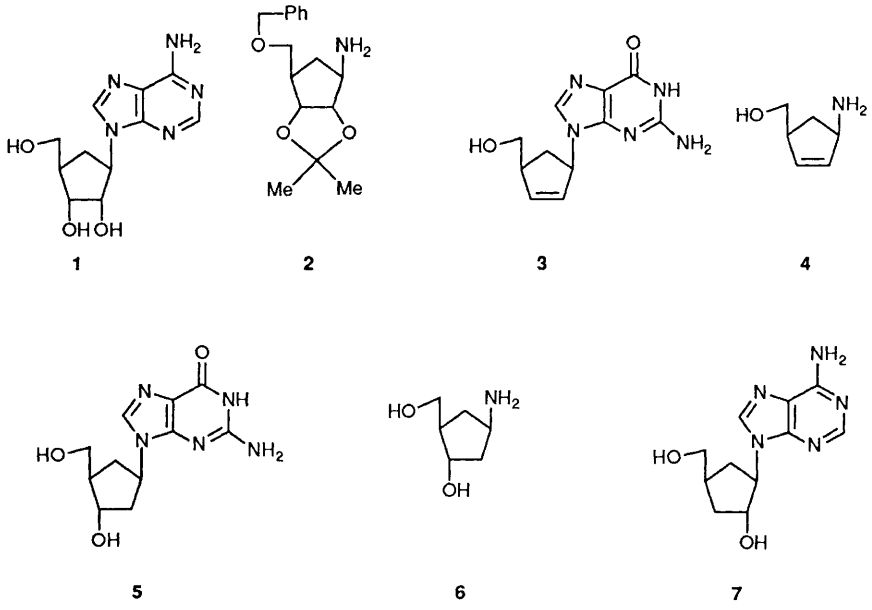
The γ-lactam **9** reacted with bromine in the presence of acetic acid or fluoride ion to give the 6,7-substituted 2-azanorbornan-3-ones **10** or **15** respectively. The latter compounds were converted into the cyclopentylamine derivatives **14** and **16** which represent potentially useful precursors for carbocyclic 3-deoxyribonucleosides.

The interesting biological activity associated with carbocyclic nucleosides[1] has led to considerable effort being directed at the preparation of selected cyclopentylamine derivatives as key intermediates. For example aristeromycin **1** is prepared from



1 2 3 4

5 6 7

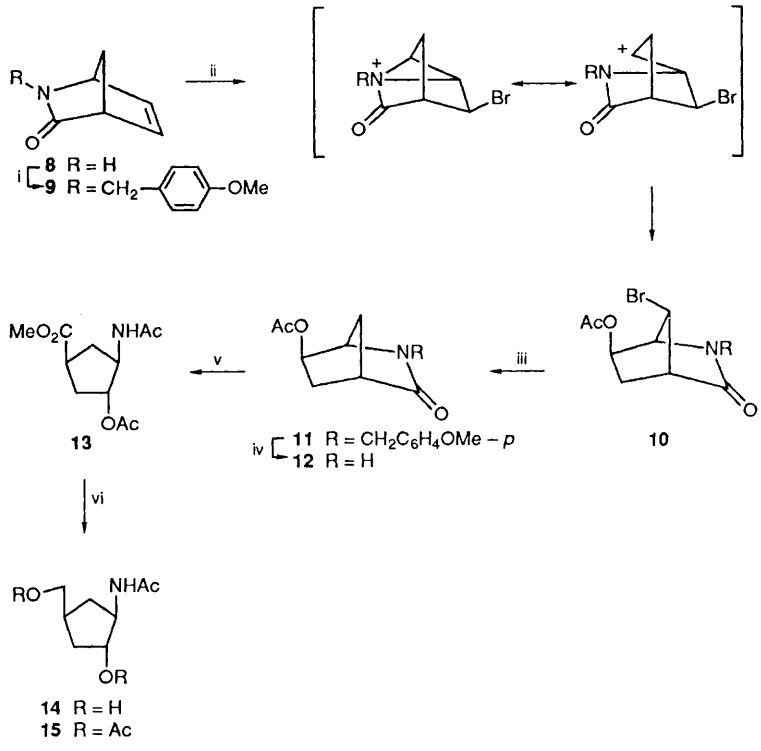
the amine **2**,[2] carbovir **3** is synthesised from hydroxymethylcyclopentenylamine **4**[3] and the carbocyclic 2-deoxyribonucleoside **5** is available from the amino diol **6**.[4] We report that an interesting synthon for carbocyclic 3-deoxyribonucleosides (*e.g.* carbocyclic cordycepin **7**[5]) is available by electrophilic substitution and concomitant rearrangement of an *N*-substituted azabicyclo[2.2.1]heptenone.

2-Azabicyclo[2.2.1]hept-5-en-3-one **8**[6] is readily converted into the *N*-(4-methoxybenzyl) derivative **9**. Reaction of the latter compound with dibromodimethylhydantoin in acetic acid gave the bromo compound **10** (70%), which was hydrodebrominated to give the acetate **11**. The stereochemistry of the product **11** was unequivocally defined by NMR spectroscopy (including NOE experiments) and is in accord with the proposed mechanism (Scheme).[7] *N*-Deprotection afforded the amide **12** (71%) which was efficiently ring-opened to provide the ester **13** (65%). Reduction gave the diol **14** which was fully characterised as the triacetate **15** (74% yield from **13**).

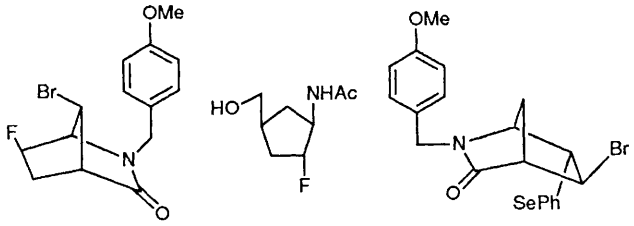
Similarly the *N*-substituted amide **9** reacted with *N*-bromosuccinimide and triethylamine tris(hydrogen fluoride)[8] to give the dihalogeno compound **16** (43%) as the major product. A similar sequence of reactions to that described in Scheme 1 converted the amide **16** into the fluoro alcohol **17** (61% overall yield).

The ready availability of the two enantiomers of the lactam **8**[9] enhances the potential utility of this synthetic method.

Further development of the chemistry to establish a novel route to neplanocin analogues was thwarted by the fact that



Scheme 1 *Reagents*: i, Lithium hexamethylsilyl azide/*p*-methoxybenzyl chloride–tetrabutylammonium iodide/THF/DMF, −78 °C ⟶ room temp. 66%; ii, 1,3-dibromo-5,5-dimethylhydantoin/AcOH, 70%; iii, Bu_3SnH/AIBN/benzene, 86%; iv, ceric ammonium nitrate/MeCN/H_2O, 83%; v, (a) 1M HCl (aq.); (b) $(MeO)_2CMe_2$/MeOH/H^+; (c) Ac_2O/ pyridine/CH_2Cl_2, 65%; vi, (a) $Ca(BH_4)$/ultrasound; (b) Ac_2O/pyridine, 74%.



16 17 18

addition of benzeneselenenyl bromide to the amide **8** did not give 6*exo*-bromo-7*anti*-phenylselenenyl-2-azabicyclo[2.2.1]-heptan-3-one* as expected, but instead furnished the isomeric compound **18** indicating preferential approach of the phenylselenenyl cation from the ostensibly more-hindered *endo*-face of the molecule. An energetically favourable π-stacking interaction between the aromatic rings of the incoming electrophile and the *N*-protecting group (Fig. 1) may account for this anomalous result. Further studies are being carried out to try to clarify the situation.[10]

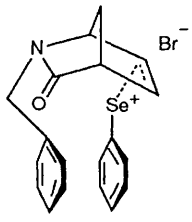


Fig. 1

Experimental

J Values are given in Hz.

Bromoacetoxylation of 2-(4-*Methoxybenzyl*)-2-*azabicyclo*-[2.2.1]*hept*-5-*en*-3-*one* **9**.—1,3-Dibromo-5,5-dimethylhydantoin (0.965 g, 3.38 mmol) was added portionwise to a stirred solution of 2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one **9** (1.539 g, 6.72 mmol) in glacial acetic acid (15 ml) and the resulting solution stirred at room temperature for 18 h. The solution was diluted with dichloromethane (250 ml) and washed with water (3 × 50 ml), 10% aqueous sodium sulphite (3 × 50 ml), and saturated aqueous sodium hydrogen carbonate (3 × 50 ml). The aqueous layers were combined and extracted with dichloromethane (2 × 100 ml). The combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography over silica using petroleum–ethyl acetate (3:1) as eluent to give 6*exo*,7*anti*-dibromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (0.095 g, 4%), m.p. 117–118 °C (dichloromethane–hexane) (Found: C, 42.9; H, 3.7; N, 3.6. $C_{14}H_{15}Br_2NO_2$ requires C, 43.2; H, 3.9; N, 3.6%). Further elution gave 6*exo*-acetoxy-7*anti*-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one **10** (1.723 g, 70%) as a clear oil (Found: $[M + H]^+$ 368.0497. $C_{16}Y_{18}{}^{79}BrNO_4$ requires $[M + H]$ 368.0497); $\nu_{max}(CHCl_3)/cm^{-1}$ 2997, 2839, 1706 (CO), 1609 and 1507; $\delta_H(CDCl_3)$ 7.20 (2 H, m, 2 × ArH), 6.90 (2 H, m, 2 × ArH), 4.69 (2 H, m, 6-H, CHAr), 4.15 (H, m, 7-H), 3.93 (H, d, *J* 15, CHAr), 3.79 (3 H, s, CH_3O), 2.90 (H, m, 4-H), 2.32 (2 H, m, 2 × 5-H) and 2.03 (3 H, s, CH_3); $\delta_C(CDCl_3)$ 172.8, 170.6, 159.5, 129.8, 127.8, 114.4, 72.7, 63.8, 55.3, 50.6, 48.4, 44.0, 29.9 and 20.0.

Bromofluorination of 2-(4-*Methoxybenzyl*)-2-*azabicyclo*-[2.2.1]*hept*-5-*en*-3-*one* **9**.—Triethylamine tris(hydrogen fluoride) (12 ml) was added dropwise to a stirred solution of 2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one **9** (3.400 g, 14.80 mmol) and *N*-bromosuccinimide (4.22 g, 23.7 mmol, 1.6 equiv.) in dichloromethane (150 ml) in the dark at 0 °C and the resulting solution was stirred at 4 °C for 4 days. It was then diluted with dichloromethane (500 ml), washed with water (2 × 50 ml), 10% aqueous sodium sulphite (4 × 50 ml) and saturated aqueous sodium hydrogen carbonate (4 × 50 ml). The aqueous layers were combined and extracted with dichloromethane (2 × 100 ml). The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography over silica using petroleum–ethyl acetate (3:1) as eluent to give 6-*exo*,7*anti*-dibromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (1.26 g, 22%). Further elution gave 7*anti*-bromo-6*exo*-fluoro-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one **15** (2.09 g, 43%), m.p. 95–97 °C (ethanol–water) (Found: C, 51.1; H, 4.9; N, 4.1. $C_{14}H_{15}BrFNO_2$ requires C, 51.2; H, 4.6; N, 4.3%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2958, 2840, 1706 (CO), 1610 and 1507; $\delta_H(CDCl_3)$ 7.20 (2 H, m, 2 × ArH), 6.80 (2 H, m, 2 × ArH), 4.62 (2 H, m, 6-H and CHAr), 4.21 (H, br s, 7-H), 4.07 (H, d, *J* 14.5, CHAr), 3.90 (H, br s, 1-H), 3.81 (3 H, s, CH_3), 2.93 (H, m, 4-H) and 2.40 (2 H, m, 2 × 5-H); $\delta_C(CDCl_3)$ 172.6, 159.6, 129.6, 127.7, 114.5, 90.6 (d, J_{CF} 200.1), 64.4 (d, J_{CF} 22.9), 55.3, 50.4, 47.9, 44.3, 30.9, (d, J_{CF} 21.5); $\delta_F(CDCl_3)$ 11.3 (ddd, *J* 54, 27, 12, 6-H).

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* The positions *syn*- and *anti*- refer to the orientation of the substituent at the apex relative to the carbonyl group. *exo*- and *endo*- Refer to the orientation of the substituent on the C-2 bridge relative to the amide unit.