# Chemistry of 2-Azabicyclo[2.2.1]heptan-3-one Derivatives: Role of the Nitrogen Atom in Determining the Stereochemistry of Products Isolated after Formation of an Incipient Carbocation at C-6

**Christopher F. Palmer,[a] Keith P. Parry,[b] Stanley M. Roberts[a] and Vladimir Sik[a]**
[a] *Department of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK*
[b] *ICI Agrochemicals, Jealotts Hill Research Station, Bracknell, Berkshire RG12 6EY, UK*

The nitrogen atom of the amide group is responsible for retention of stereochemistry for the products obtained when the alcohol **6** is allowed to react under Mitsunobu conditions and when **6** is treated with diethylaminosulphur trifluoride.

2-Azabicyclo[2.2.1]hept-5-en-3-one **1** has been shown to be a versatile starting material for the synthesis of carbocyclic nucleosides.[1] In work aimed at the synthesis of the anti-tumour agent neplanocin A,[2] Snider and co-workers[3] showed that bromination of the *N*-benzyllactam **2** gave the dibromide **4**. We have recently shown that similar results are obtained with the 4-methoxybenzyl lactam **3**.[4] Here we report results which provide further evidence that the nitrogen atom of the amide group plays an important rôle in the stereochemical outcome of reactions involving 2-azabicyclo[2.2.1]heptan-3-ones.

Treatment of the lactam **2** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in glacial acetic acid at room temperature for 2 h gave the dibromide **4** and bromoacetate **5** in 3.4 and 81% yield respectively. The structure of the bromoacetate was confirmed from nOe studies in deuteriated benzene: particularly informative was the observed enhancement of the signal due to 6-H upon irradiation at the field strength due to the benzylic protons. This clearly showed 6-H to be on the *endo*-face of the molecule. In addition hydrodebromination and saponification gave 2-benzyl-6*exo*-hydroxy-2-azabicyclo[2.2.1]heptan-3-one identical with an authentic sample (m.p., NMR).[5] Thus the first formed *exo*-bromonium ion[3,4] is intercepted by the transannular nitrogen atom and the attendent nucleophile attacks the resultant carbocation **A** (Fig. 1).

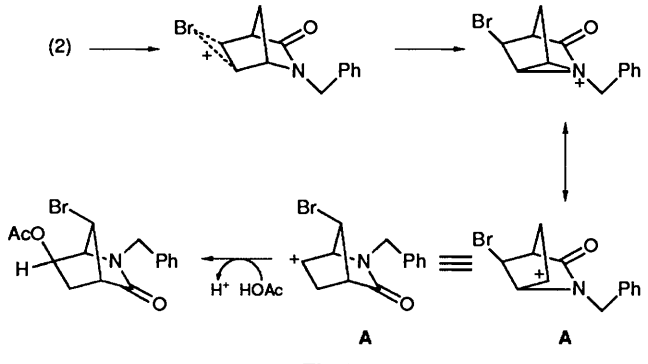
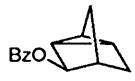



**Fig. 1**

The acetate **5** was saponified to give the alcohol **6**. Treatment of the alcohol **6** (0.33 mmol) with triphenylphosphine (0.5 mmol) and diethyl azodicarboxylate (0.5 mmol) and benzoic acid (0.5 mmol) in dry THF (1 ml)[6] gave, after chromatography, the *exo*-benzoate as the sole product. Once again an nOe study was useful since irradiation at the field strength due to 6-H produced enhancement of the signal due to a benzylic CH (3.3%). It is postulated that, in the Mitsunobu reaction, the activated hydroxy group is displaced by the nitrogen atom to regenerate the aziridinium species shown in Fig. 1 which is subject to nucleophilic attack by benzoic acid. This reaction pathway is reminiscent to that taken by *exo*-norbornenol which, on being subjected to a Mitsunobu reaction, gave the tricyclic benzoate **8**.[7]




**8**

Similarly, treatment of the alcohol **6** with DAST (3 equiv.) in dry dichloromethane at 0 °C gave the *exo*-fluoride **9**. The same dihalogeno compound was formed as the major product (43% yield) on treatment of the unsaturated lactam **2** with *N*-bromosuccinimide and triethylamine tris(hydrogen fluoride).[8] Compound **4** was produced concurrently (14% yield). Hydrodebromination of **9** (using tributyltin hydride and azoisobutyronitrile in refluxing benzene) furnished the fluoride **10**. The structure of the latter compound was determined by 2D COSY and nOe measurements. Once again it is envisaged that lone pair participation results in the activated intermediate being intercepted to give an aziridinium ion which is susceptible to nucleophilic attack to give the observed product. Retention of configuration has previously been observed in other DAST reactions, involving the participation of a neighbouring group.[9] It is noteworthy that the stereocontrolled sequence of reactions **2** ⟶ **5** ⟶ **6** ⟶ **9** ⟶ **10** (overall yield 50%) gives improved access to a potentially valuable precursor of 2′-fluoro-2′,3′-dideoxy carbocyclic nucleosides.[4]

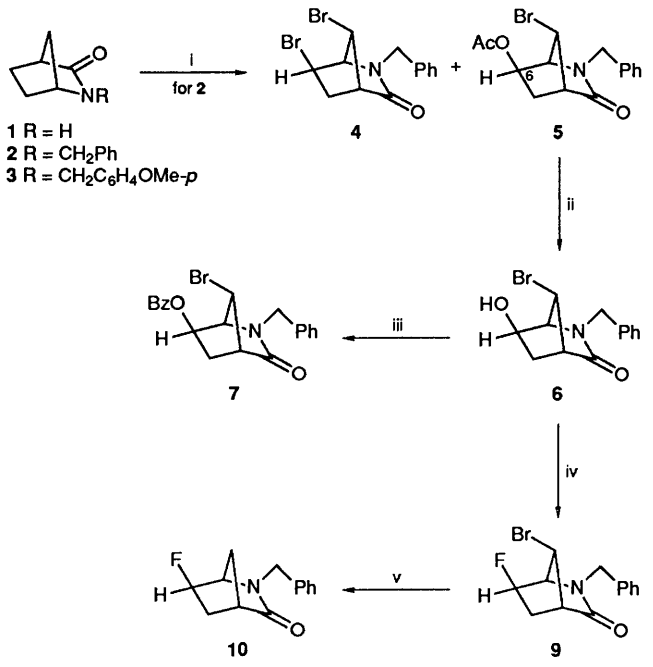
In conclusion, we have shown that, for 2-azabicyclo-[2.2.1]heptan-3-ones, the stereochemical outcome of reactions involving the transient formation of a carbocation at C-6 is profoundly influenced by the presence of the transannular nitrogen atom.

## Experimental

The physical data for compounds **7** and **9** are as follows. *J* Values in Hz.

2-*Benzyl*-6exo-*benzoyloxy*-7anti-*bromo*-2-*azabicyclo*[2.2.1]-*heptan*-3-*one* **7**. M.p. 119–121 °C (Found: $[M + H]^+$ 400.0548. $C_{20}H_{18}{}^{79}BrNO_3$ requires $[M + H]^+$ 400.0548); $\nu_{max}$(KBr)/cm$^{-1}$ 3065, 3031, 2949, 2856 (CH), 1715 (CO), 1599 and 1493 (C=CAr); $\delta_H$($CDCl_3$) 8.10 (2 H, m, ArH), 7.40 (8 H, m, ArH), 5.10 (H, m, 6-H), 4.84 (H, d, *J* 15, $CH_2Ph$), 4.26 (H, m, 7-H), 4.03 (H, d, *J* 15, $CH_2Ph$), 3.97 (H, dd, *J* 3, 1.5, 1-H), 3.02 (H, m, 4-H) and 2.50 (2 H, m, 2 × 5-H); $\delta_C$($CDCl_3$) 173.0 (CO), 166.0 (CO), 135.9, 135.3, 129.8, 129.6, 129.0, 128.5, 128.4, 128.2 (ArC), 72.7 (C-6), 64.6 (C-1), 50.7 (C-4), 48.5 (C-7), 44.6 ($CH_2Ph$) and 30.4 (C-5).

2-*Benzyl*-6exo-*fluoro*-7anti-*bromo*-2-*azabicyclo*[2.2.1]*heptan*-3-*one* **9**. M.p. 116–117 °C (Found: C, 52.1; H, 4.3; Br, 27.0; N, 4.3. $C_{13}H_{13}BrFNO$ requires C, 52.4; H, 4.4; Br, 26.8; N, 4.7%); $\nu_{max}$($CHCl_3$)/cm$^{-1}$ 3011 and 1700 (CO); $\delta_H$($CDCl_3$) 7.40




**Scheme 1** *Reagents and conditions:* i, 1,3-Dibromo-5,5-dimethylhydantoin, acetic acid (glacial), room temp., 24 h (82%); ii, $K_2CO_3$, MeOH, room temp., 2 h (98%); iii, diethyl azodicarboxylate, $Ph_3P$, benzoic acid, tetrahydrofuran, room temp., 18 h; iv, diethylaminosulphur trifluoride, $CH_2Cl_2$, 0 °C, 2 h (62%); v, $Bu_3SnH$, AIBN (cat.), benzene, reflux, 24 h (91%)

(5 H, m, ArH), 4.68 (2 H, m, 6-H, CHPh), 4.23 (1 H, m, 7-H), 4.08 (1 H, d, *J* 15, CHPh), 3.91 (1 H, m, 1-H) and 2.94 (1 H, m, 4-H); $\delta_C(CDCl_3)$ 172.7 (CO), 135.6 (aryl C), 129.1, 128.3, 128.2 (aryl CH), 90.6 (d, *J* 200, C-6), 64.6 (d, *J* 23, C-1), 50.3 (C-4), 48.5 (C-7), 47.9 ($CH_2Ph$) and 31.0 (d, *J* 22, C-5).

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