# Facile Synthesis of the 4-Azatricyclo[2.2.1.0$^{2,6}$]heptane System

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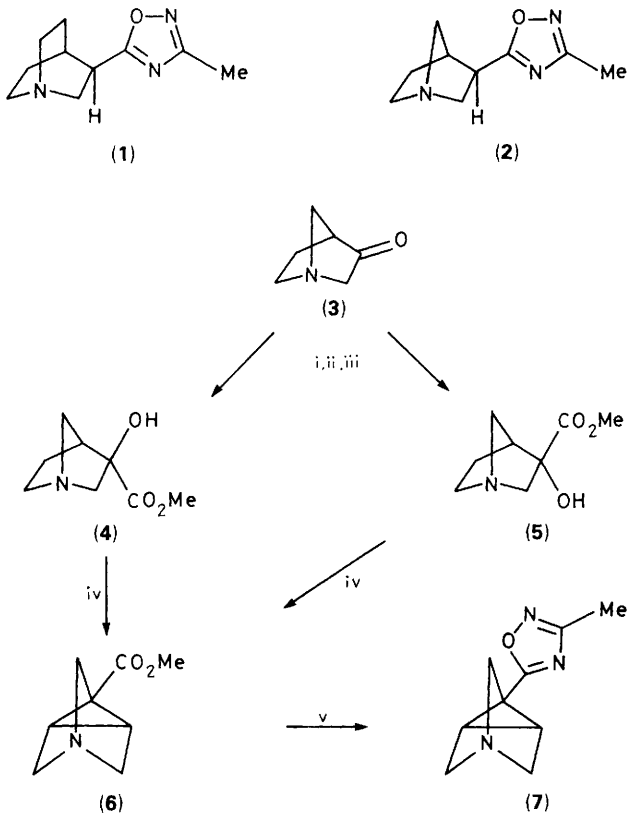
1-Methoxycarbonyl-4-azatricyclo[2.2.1.0$^{2,6}$]heptane has been prepared by an efficient carbonium ion mediated rearrangement and shown to have a relatively low p$K_a$; the crystal structure of the hydrochloride salt has been determined.

We have described[1,2] the synthesis and biochemical properties of 1,2,4-oxadiazoles substituted onto quinuclidine (**1**) and 1-azanorbornane (**2**) which are potent, high efficacy agonists at muscarinic acetylcholine receptors. For amine containing drugs targeted at receptors in the central nervous system the p$K_a$ at the basic nitrogen has an important bearing on the observed activity *in vivo*. In the absence of an active transport system such compounds must penetrate the blood–brain barrier by passive diffusion of the free base whereas the active form at the receptor is the charged, protonated species. The relative proportion of these two forms at physiological pH can be manipulated by altering the p$K_a$ at the basic nitrogen. To investigate the effect on efficacy of varying p$K_a$ we wished to make analogues of (**2**) with reduced basicity. One important constraint placed on the choice of compound was that a significant increase in steric bulk should be avoided since this

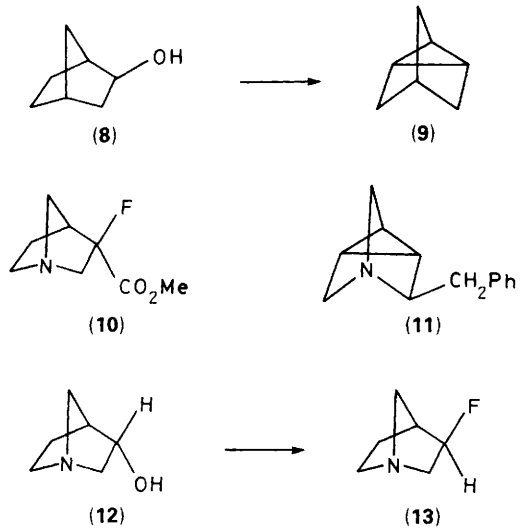
**Table 1.** Comparison of basicity in known and novel compounds (at 20 °C).

| Compound | p$K_a$ |
|---|---|
| (**1**) | 8.7 |
| (**2**) | 8.0 |
| (**7**) | 6.0 |
| 3-Methoxycarbonylquinuclidine | 9.5 |
| 3-Methoxycarbonyl-1-azanorbornane | 8.7 |
| (**6**) | 6.8 |
| Quinuclidine | 10.8 |
| 1-Azanorbornane[a] | 10.5 |
| (**15**) | 9.0 |

[a] At 35 °C, see ref. 8.



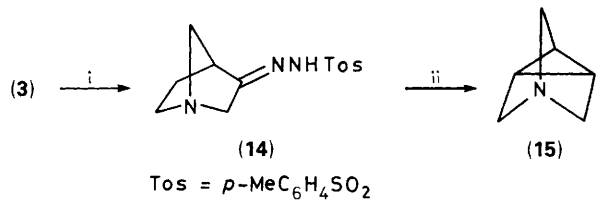

**Scheme 1.** *Reagents*: i, NaCN, $H_2O$; ii, conc. HCl; iii, MeOH, HCl; iv, DAST, $CH_2Cl_2$; v, $MeC(NH_2)$=NOH, NaOEt, EtOH.




is known to lead towards antagonist activity.[2] Our objective was achieved by introducing an additional bridging C–C bond into the azabicycles resulting in a substantial reduction in $pK_a$ through increased ring strain.[3]

The azanortricyclene ester (**6**) was prepared by an efficient Wagner–Meerwin rearrangement of *exo*-3-hydroxy-*endo*-3-methoxycarbonyl-1-azabicyclo[2.2.1]heptane (**4**) which itself is readily available† from the cyanohydrin prepared from

† The stereoselective syntheses of hydroxy-esters (**4**) and (**5**) form part of a manuscript in preparation.




**Scheme 2.** *Reagents*: i, $TosNHNH_2$, EtOH, $H_2O$, reflux; ii, $HOCH_2$-$CH_2OH$, Na, reflux.

1-azabicyclo[2.2.1]heptan-3-one (**3**).[4] It is known[5] that the stable norbornyl cation, generated from norborneol (**8**) using $SbF_5$–$SO_2$, gives nortricyclene (**9**) as the only identifiable product (80%) on quenching with pyridine. By analogy with this reaction, treating (**4**) with diethylaminosulphur trifluoride (DAST) at −78 °C in $CH_2Cl_2$ gave 1-methoxycarbonyl-4-azatricyclo[2.2.1.$0^{2,6}$]heptane (**6**) in 76% yield. The isomeric hydroxy-ester (**5**) treated similarly with DAST gave (**6**) in 40% yield reflecting the less favourable *endo* configuration of the hydroxy group for this bond forming process. In this latter preparation a small amount (3%) of the α-fluoro ester (**10**) was isolated with fluorine, predictably, in the *exo* configuration as judged by NMR.

The structure of (**6**), whose simple tricyclic skeleton has one previous note in the literature[6] for compound (**11**), was confirmed by an *X*-ray crystal structure determination on the hydrochloride salt (Figure 1).‡ In the crystal the molecule has a plane of symmetry containing atoms N(1), C(5), C(4), C(6), O(9), O(7), and C(8) (numbering used in crystallography). The C–N–C and N–C–C bond angles are 103 and 97° respectively compared to 110 and 110° for the equivalent angles in the less strained quinuclidine bicycle.[7] Using the standard procedure the crystalline 1,2,4-oxadiazole (**7**) was prepared from (**6**) in 60% yield. Both the $pK_a$'s of (**6**) and (**7**) were measured to be around 2.0 and 2.7 units lower than those of the analogous 1-azanorbornanes and quinuclidines respectively (see Table 1). Since the electron withdrawing effect of the substituents may vary between the ring systems because of variation in the distance between the point of substitution and the nitrogen atom we were interested to find out what the $pK_a$ for the unknown parent tricycle (**15**) would be in comparison with bicyclic and non-cyclic analogues.

The obvious first approach to (**15**) was to treat 1-azabicyclo[2.2.1]heptan-3-ol (**12**)[4]† with DAST as above.

‡ *Crystal data*: $C_8H_{12}ClNO_2$, $M$ = 189.64, monoclinic, $P2_1/m$, $a$ = 5.788(2), $b$ = 6.804(1), $c$ = 11.513(3) Å, β = 92.02(2)°, $U$ = 453.1 Å$^3$, $Z$ = 2, $D_c$ = 1.390 g cm$^{-3}$, μ = 34.71 cm$^{-1}$, $F(000)$ = 200. 738 Unique reflections were measured with a CAD4 diffractometer using Cu-$K_\alpha$ radiation, λ = 1.54184 Å, $T$ = 23 °C, data 2θ limit = 120°, data index range $+h$, $+k$, $\pm l$. Data were corrected for: Lorentz effect, polarisation, background, linear decay, and absorption. The structure was solved by random-solution direct methods (SHELXS) and refined (full-matrix least squares refinement using $F$ magnitudes for 94 parameters varied) using 718 reflections with $I > 3\sigma(I)$. The final residuals were $R$ = 0.058; $R_w$ = 0.078. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1. This structure was also refined in the $P2_1$, space group. The refinement converged with the following statistics: $R$ = 0.047, $R_w$ = 0.066, $S$ = 8.6, $(\Delta/\sigma)_{max}$ = 0.2. Maximum peak in final difference Fourier is 0.30(5) e Å$^{-3}$. The number of variables in this structure was 110, with 92 in the centrosymmetric structure. There was no significant deviation from the point group symmetry in the molecular dimensions of the acentric structure.

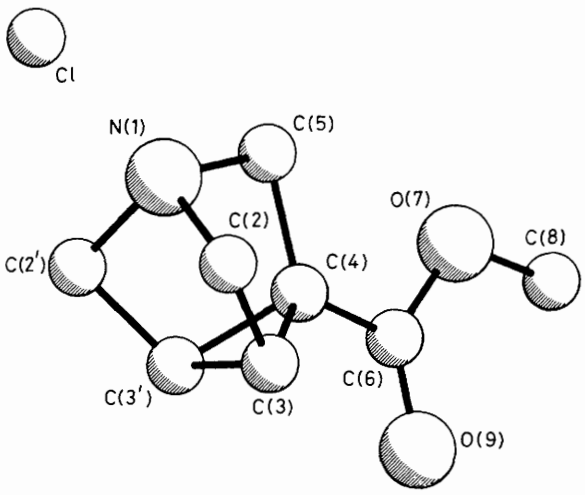



**Figure 1.** Crystal structure of the hydrochloride salt of (**6**) with numbering system used in the determination.

However, in the absence of the destabilising effect of the ester group [in (**4**)] on the intermediate carbonium ion, fluorination predominated over rearrangement giving (**13**) as the major product with no (**15**) detected. A successful approach was found easily in the base catalysed decomposition of the tosyl hydrazone derived from (**3**) which gave (**15**), the tricyclic analogue of triethylamine, in 42% yield isolated as the hydrochloride salt. This compound again showed a much lower p$K_a$ than 1-azanorbornane or quinuclidine indicating a similar degree of substituent effect in the three ring systems studied. This work demonstrates that the p$K_a$ in biologically active amines can be modified without resorting to the addition of electron withdrawing substituents which may have other effects at the active site of a receptor. The biology of (**7**) and related compounds will be presented in due course.

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