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2-AZATRICYCLO[2.2.1.0^{1,6}]HEPTANE: SYNTHESIS AND CONVERSION TO 2-AZABICYCLO[2.2.1]HEPTANES

P. S. PORTOGHESE* and D. T. SEPP
Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

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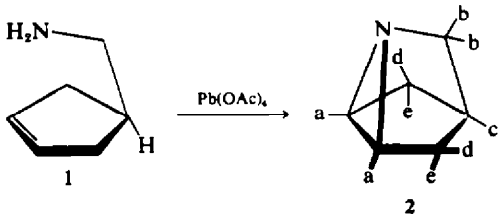
Abstract—A facile route to 6-substituted 2-azabicyclo[2.2.1]heptanes via the novel tricyclic system, 2-azatricyclo[2.2.1.0^{1,6}]heptane (**2**), is described. The key intermediate (**2**) was prepared by oxidation of 4-aminomethylcyclopentene with lead tetra-acetate, and the bicyclic system was obtained by reaction of acetate with **2**.MeI. Equilibration of *exo*- and *endo*-6-hydroxy-1-methyl-2-azabicyclo-[2.2.1]heptane afforded an *exo–endo* isomeric ratio close to that of norborneol, and on this basis it is suggested that the steric requirements of the nitrogen lone pair are similar to that of CH.

During the course of an investigation aimed at elucidating the stereochemical requirements of ligands acting at cholinergic receptors, it was necessary to develop a convenient synthesis of 2-azabicyclo[2.2.1]heptane containing functionality at C-6. Although we have reported[1] the preparation of this bicyclic system, the synthesis was not of sufficient versatility for use as a general procedure. We now wish to report a facile synthesis of this system using 2-azatricyclo[2.2.1.0^{1,6}]heptane (**2**) as the key intermediate.

It has been reported by Nagata *et al.*[2] that 4-aminomethylcyclohexene and its derivatives can be oxidized to bridged aziridines. We decided to investigate the utility of this reaction in converting 4-aminomethylcyclopentene (**1**) to aziridine **2**, since nucleophilic opening of **2** or its quaternary derivative (**3**) should afford the desired 6-substituted bicyclic system.

The amine **1** was prepared from 4-carboxycyclopentene by the procedure described in the experimental section. Oxidation of **1** was carried out in refluxing benzene with excess lead tetra-acetate. Isolation of bridged aziridine **2** was difficult, as extensive decomposition occurred on distillation or using preparative GLC. Small samples of pure **2** were obtained by column chromatography and it was possible to minimize polymerization by working with dilute solutions.

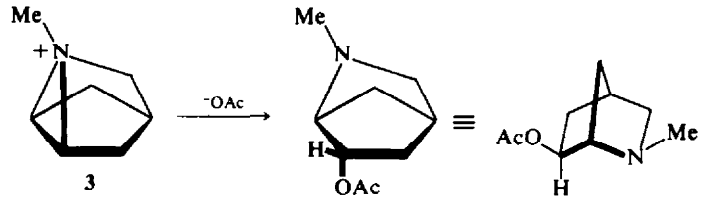
But virtue of its molecular symmetry, the NMR spectrum of **2** ($CDCl_3$) was predictably very simple. The highest field signal centered at δ 1·28 integrated for four protons and consequently was assigned to two equivalent pairs of methylene protons (H_d, H_e). Due to coupling with other protons and near-identical chemical shifts of H_d and H_e, the absorption was seen as a broadened singlet ($W_{1/2}$ = 5 Hz) with satellite peaks indicative of a tight AB pattern (J_{gem} ~ 13 Hz). Bridgehead proton H_c appears at δ 2·12 ($W_{1/2}$ ~ 7 Hz). The remainder of the spectrum consists of two sharp singlets, $W_{1/2}$ = 2·5 Hz, and δ 2·20 and 2·25, each integrating for two protons. An assignment of these signals to either H_a or H_b could not be made.



1 2

Because of the instability of **2**, it was not purified after our initial characterization studies, but rather was converted without isolation to the methiodide salt **3** in an overall yield of 52% (based upon **1**). This salt was quite stable in the crystalline state and could be stored without decomposition. The unusual stability of **3** was also noted in aqueous solution, as no difference in its NMR spectrum was observed after standing in D_2O for nine days at ambient temperature. The NMR spectrum of **3** was similar to that of **2** except that the absorptions were shifted to lower field. The signals for H_d and H_e appear as an AB pattern (J_{de} = 13 Hz) with doublets centered at δ 1·78 and 2·13. The bridgehead proton, H_c, absorbs at δ 2·77 ($W_{1/2}$ = 6 Hz), and the signals for H_a and H_b appear at δ 3·07 ($W_{1/2}$ = 2·5 Hz) and 3·82 ($W_{1/2}$ = 3 Hz); the specific assignment of these resonances to H_a or H_b was not determined. The singlet at δ 3·20 was attributed to the Me group.

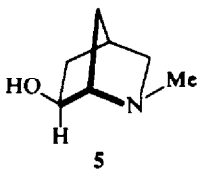
Reaction of **3** with potassium acetate in refluxing ethanol yielded the desired bicyclic system **4** in good yield. GLC analysis of the reaction mixture indicated that only one diastereomer was formed, and NMR analysis verified the product to be the



3 4

stereochemically expected *exo* isomer. The alcohol **5**, was obtained by reduction of **4** with LAH.

Equilibration of the *exo* alcohol **5** with aluminum isopropoxide[3] was investigated as a means of obtaining the *endo* isomer **6**. The composition at equilibrium was 83% *exo* and 17% *endo*, which is quite close to the *exo–endo* ratio (80:20) for norborneol[3] under identical conditions. The similar isomer composition is not surprising in view of the comparable steric requirement of the nitrogen lone pair and NH in piperidine systems.[4]



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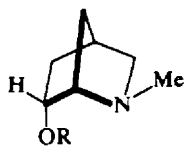
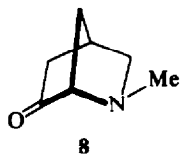


6: R = H
7: R = OAc



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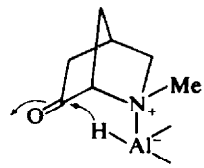
As an alternative procedure, **4** was oxidized with Jones reagent, and the resulting ketone **8** was reduced with LAH to afford alcohols **6** and **5** in a 82:18 ratio. It is noteworthy that under similar conditions N-tosyl-5-keto-2-azabicyclo[2.2.1]-heptane afforded a higher *endo–exo* ratio (93:7),[5] and norbornanone yielded ~92% of the *endo* isomer.[6,7] The lower *endo–exo* ratio in the reduction of **8** suggests that the delivery of hydride to the *endo* face of the molecule might be facilitated by the formation of **9**, which would arise by the displacement of an alkoxy group of the aluminum alkoxyhydride species by the amine function.



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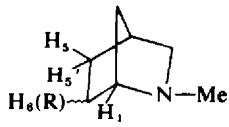
It is of interest that the epimeric alcohols possessed considerably different GLC retention times (55·7 min for **5**; 12·7 min for **6**); this is very likely due to the lower polarity of **6** as a consequence of intramolecular O—H · · · · N bonding.

The NMR spectra of the esters (**4**, **7**) and alcohols (**5**, **6**) corroborates the stereochemistry of these compounds (Table 1). The H_6 proton invariably absorbed at lowest field by virtue of the inductive deshielding effect of the oxygen function. The signal for H_1 was distinguishable as the next lowest field absorption. The chemical shift of H_6 does not differ appreciably between the *exo* and *endo* alcohols ($\delta \approx 4$) or between *exo* and *endo* esters ($\delta \approx 5$). However, the multiplicity and general

Table 1. NMR data for 2-azabicyclo[2.2.1]heptanes



		Chemical Shifts (δ)			Coupling Constants (Hz)		
Compd	R	*endo* H_6	*exo* H_6	H_1	J_{5-6}	$J_{5'-6}$	J_{6-1}
4	OAc	4·95	—	3·12	3	7	0
5	OH	4·00	—	3·07	2	7	0
6	OH	—	3·97	[a]	9	3	3
7	OAc	—	4·90	3·50	10	4	4

[a]Exact assignment could not be made due to overlapping signals.

appearance of the H_6 signal is characteristic of its orientation. In the *endo* isomers (**6**, **7**) H_6 exhibits a six line pattern resembling a pair of closely spaced triplets, and this is consistent with $J_{5-6} = 9-10$ Hz and $J_{5'-6}J_{1-6} = 3-4$ Hz. For H_6 in the *exo* isomers (**4**, **5**) the pattern is a pair of doublets ($J_{5'-6} = 7$ Hz; $J_{5-6} = 2-3$ Hz; $J_{1-6} \sim 0$). There is ample data[8-14] from other NMR studies of bicyclo[2.2.1]heptanes which show that these coupling constants are consistent with the assigned stereochemistries. For example, it has been shown that the coupling between two *exo* protons is larger than that between two *endo* protons, and this is in harmony with the *endo*-H_6 resonances (**5**, **6**) having greater values of J_{5-6} than the *exo*-H_6 absorptions (**6**, **7**). The fact the H_6 exhibits little or no coupling with H_1 in **5**, **6** is also consistent with the assigned *exo* oxygen function, since the dihedral angle between these protons is ~90°.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were measured with a Perkin-Elmer 237B grating spectrometer. NMR spectra were obtained on a Varian XL-100 spectrometer in $CDCl_3$ solvent using TMS as internal standard. GLC analyses were carried out on a Perkin-Elmer 900 or a Varian Aerograph Model 700. Elemental analyses were performed by M.H.W. Laboratories, Garden City, Michigan.

3-Cyclopentene-1-carboxamide. Excess liquid NH_3 was cautiously added with stirring to an Et_2O soln (1·1.) of Δ^3-cyclopentenecarbonyl chloride[15] (24·9 g, 0·17 mole). The solvent then was removed by evaporation and the residual solid was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ phase was separated, dried ($MgSO_4$), and after removal of solvent the product (16·1 g, 88%) was recrystallized (Et_2O): m.p. 158–159°; I.R. (KBr) 3348 and 3169 cm^{-1} (NH_2), 1629 cm^{-1} (C =O). (Found: C, 64·93; H, 8·26; N, 12·78. C_6H_9NO requires; C, 64·84; H, 8·16; N, 12·60%).

3-Cyclopenteneaminomethane (**1**). A hot THF soln (300 ml) of 3-cyclopentene-1-carboxamide (15·5 g, 0·14 mole) was rapidly added to a slurry of LAH (5·7 g, 0·15 mole) in THF (50 ml) and the mixture was stirred at reflux for 18 hr. The mixture was cooled, acidified with 10% HCl (100 ml), and the THF removed *in vacuo*. The aqueous residue was washed with Et_2O, made alkaline with NaOH, and extracted with 5 × 100 ml of Et_2O. The combined Et_2O extracts were dried ($MgSO_4$), the Et_2O removed, and the residue distilled to yield 6·2 g (46%) of **1**, b.p. 85–87° (128 mm) [lit[16] b.p. 87–88° (134 mm)]. As an alternate procedure, the combined extracts were treated with anhydrous HCl to yield 11·0 g (61%) of **1**·**HCl**, m.p. 180° dec, and the free base regenerated by treatment of base and extraction with Et_2O.

2-Azatricyclo[2.2.1.0^{1,6}]*heptane methiodide* (**3**). A soln of **1** (11·6 g, 0·049 mole) in anhyd benzene (10 ml) was quickly added to a stirred mixture containing $Pb(OAc)_4$ (35 g, 0·079 mole; recrystallized from HOAc and dried *in vacuo* over KOH), anhyd K_2CO_3 (42 g, 0·304 mole), and dry benzene (100 ml) maintained at 60°. The mixture was stirred at reflux for one hr, cooled to 20°, Et_2O (250 ml) added, and the supernatent decanted from the solid residue which then was extracted with Et_2O (3 × 50 ml) after treatment with 10% NaOH (50 ml). The Et_2O extract was combined with the decanted Et_2O soln, washed with 50% NaOH (10 ml), and dried ($MgSO_4$). GLC (7′ × ¼″ column; 15% carbowax 4000/chromosorb W, 45/60 mesh; 100°; He flow, 185 cc/min) analysis of this soln indicated a R_t of 5·6 min for **2**. TLC (silica gel; $CHCL_3$-MeOH, 20:1) showed a single spot (R_f, 0·45) when visualized with I_2 vapor. A very small amount of **2** was collected by distillation (40–45°, 77 mm) before extensive decomposition occurred. The IR spectrum (neat) showed bands at 3060, 2996, and 1266 cm^{-1}, characteristic of the aziridine ring.[2] A sample of **2** was purified by column chromatography (alumina-$CHCl_3$).

Since **2** readily polymerized in the neat form, the Et_2O soln of **2** was treated with MeI (72 g, 0·5 mole) and allowed to stand at 20° for 24 hr. The product was collected by filtration, washed with Et_2O, and recrystallized (EtOH-Et_2O) to afford 6·06 g (52%) **3**, m.p. 195–205° (dec). (Found: C, 35·47; H, 5·06; N, 5·73. $C_7H_{12}NI$ requires: C, 35·46; H, 5·10; N, 5·91%).

N-Methyl-exo-6-acetoxy-2-azabicyclo[2.2.1]*heptane* (**4**). An ethanolic soln (200 ml) containing **3** (4·5 g, 0·019 mole) and KOAc (18·6 g, 0·190 mole) was refluxed for 18 hr. After cooling most of the EtOH was removed *in vacuo*, the residue taken up into H_2O (100 ml) and extracted with Et_2O (5 × 100 ml). The Et_2O extract was dried ($MgSO_4$), the solvent removed, and the residue fractionally distilled to yield 2·05 g (63% of **4**, b.p. 97–98° (13 mm); IR (neat) 1736 cm^{-1} (OAc); R_t, 4 min on a 3′ × ¼″ column of 5% carbowax 4000 on chromosorb W (45/60 mesh) at 100° with He flow rate of 120 cc/min. (Found: C, 63·70; H, 9·21; N, 8·52. $C_9H_{15}NO_2$ requires: C, 63·88; H, 8·93; N, 8·28%).

N-Methyl-exo-6-hydroxy-2-azabicyclo[2.2.1]*heptane* (**5**). An Et_2O soln (10 ml) of **4** (2·03 g, 0·012 mole) was added to a slurry of LAH (0·72 g, 0·019 mole) in Et_2O (100 ml). The mixture was stirred at 25° for 24 hr and then quenched with sequential addition of H_2O (1 ml), 15% KOH (1 ml) and H_2O (1 ml). The mixture was filtered, the solids washed with Et_2O, and the combined Et_2O solns dried ($MgSO_4$). Removal of solvent afforded 1·51 g (99%) of **5** b.p. 101–102° (0·4 mm): R_t, 7·5 min (using GLC conditions described for **4**). (Found: C, 65·84; H, 10·32; N, 10·92. $C_7H_{13}NO$ requires: C, 66·11; H, 10·30; N, 11·01%).

N-Methyl-2-azabicyclo[2.2.1]*heptane-6-one* (**8**). Compound **5** (4·25 g, 0·031 mole) was dissolved in 1M H_2SO_4 (40 ml) and mixed with 30 ml (0·08 mole) standard Jones reagent.[17] The soln was heated at 60° for 15 min and then immediately cooled in an ice-bath. After making the mixture alkaline (30% NaOH) it was saturated with NaCl and extracted with Et_2O (5 × 200 ml). The combined extracts were dried ($MgSO_4$) and the Et_2O removed *in vacuo* to afford 2·78 g (70% mass recovery) of an oil which was composed of 17% **5** and 83% **8** (Rt, 3·3 min under GLC conditions described for **4**). A pure sample of **8** was obtained by preparative GLC (⅜″ × 5′ column; 10% carbowax 4000 on chromosorb W, 45/60 mesh; 100°; He flow rate, 125 cc/min), R_t = 23·5 min. IR 1739 cm^{-1} (C=O). (Found: C, 66·93; H, 8·94; N, 11·41. $C_7H_{11}NO$ requires: C, 67·17; H, 8·86; N, 11·19%).

N-Methyl-endo-6-hydroxy-2-azabicyclo[2.2.1]*heptane* (**6**). A mixture of **5** and **8** (2·5 g) obtained from the previous oxidation procedure was reduced with LAH and worked up as described in the preparation of **5**. After removal of solvent, a residual oil (1·65 g) was obtained which was comprised of 63% **6** and 37% **5**. The mixture of alcohols was separated by preparative GLC using conditions

described for the collection of **8**. The Rt for **6** was 12·7 min and that for **5** was 55·7 min. GLC analysis of the products derived from LAH reduction of pure **8** indicated the isomeric ratio, **5**:**6** = 18:82. (Found: C, 66·11; H, 10·51, N, 11·25. $C_7H_{13}NO$ requires: C, 66·11; H, 10·30; N, 11·01%).

N-*Methyl*-endo-6-*acetoxy*-2-*azabicyclo*[2.2.1]*heptane* (**7**). A mixture of **6** (0·164 g, 0·0012 mole) and acetyl chloride (1·287 g, 0·0165 mole) in Et_2O was stirred for 18 hr at 25°. The Et_2O was decanted, the solid washed with Et_2O, and extracted into Et_2O after addition of NaOH aq (1 ml). The Et_2O extracted was separated from the aqueous phase, dried ($MgSO_4$), and the solvent removed *in vacuo* to yield crude **7** (0·152 g, 75%) as an oil. Pure **7**, Rt = 7·5 min, was obtained by preparative GLC ($\frac{3}{4}'' \times 5'$ column; 5% carbowax 4000 on chromosorb W, 45/60 mesh; 100°; He flow rate of 165 cc/min). (Found: C, 63·62; H, 8·87; N, 8·15; $C_9H_{15}NO_2$ requires: C, 63·88; H, 8·93; N, 8·28%).

Equilibration study. The procedure was identical to that reported by Wilcox *et al.*[3] and was carried out over a period of 8 days. The equilibration was terminated after the isomeric composition had been static for 3 days. The composition at equilibrium, as measured by GLC, was 82% **5** and 18% **6**. Both **5** and **6** gave identical isomeric ratios.

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