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SYNTHESIS OF MEDIUM-RING BICYCLIC DIAMINES BY THE ALKYLATION AND CLEAVAGE OF CYCLIC AMIDINES

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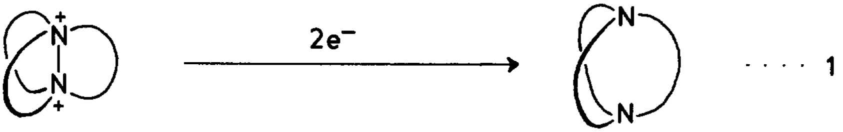
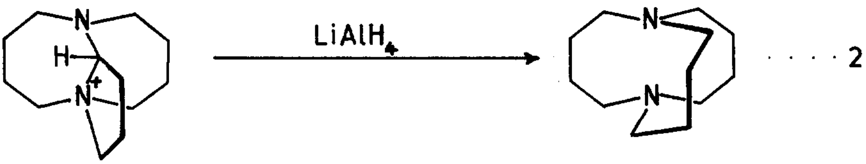
Summary: 1,6-Diazabicyclo[4.3.3]dodecane (**7**), 1,6-diazabicyclo[4.3.2]undecane (**8**) and 1,8-diazabicyclo[6.3.3]tridecane (**9**) have been made by reduction of tricyclic α-aminoammonium salts with $LiAlH_4$; the protonation and oxidation of **8** and **9** are discussed.

Our continuing interest in the unusual chemistry of medium-ring bicyclic diamines possessing bridgehead nitrogen atoms[1,2] has prompted us to seek new routes to other members of this group. We have shown that reductive cleavage of propellane hydrazinium dications is an efficient route to a number of these diamines[2] (equation 1). However, the method is limited by the usual problems of constructing rings other than 5- or 6-membered in the propellane. The observation that the tricyclic α-aminoammonium salt **1** is cleaved by lithium aluminium hydride to the bicyclic diamine **2**[2] (equation 2) provides the opportunity for an alternative route to the diamines which retains the efficacious strategy of ring cleavage. We show here that tricyclic α-aminoammonium salts can be prepared which give diamines with both longer and shorter bridges than are accessible *via* the propellane dications, hence the two methods are complementary.

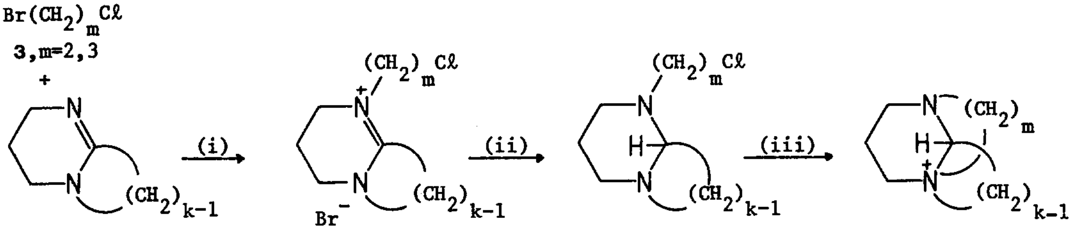




1 **2**

Scheme 1 shows how three tricyclic α-aminoammonium salts (**6a-c**) were constructed from the commercially available amidines 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). Various reaction conditions were tried for the alkylation of the amidines. It was found that reaction at room temperature in dry ether gave the best ratio of substitution to elimination products. For example, a solution of DBN and 1 equivalent of 3-bromo-1-chloropropane in ether deposited crystals of **4a** over a period of a week in good yield and purity. Similar reaction of DBN with 2-bromo-1-chloroethane and DBU with 3-bromo-1-chloropropane gave good yields of **4b** and **4c** respectively, but these were contaminated with 10-20% of the corresponding amidine hydrobromide salts arising from eliminations. Reaction of DBU with 2-bromo-1-chloroethane gave exclusively DBU·HBr. Reduction of the amidinium salts **4a** and **4c** with lithium aluminium hydride afforded the aminals **5a** and **5c** as unstable liquids, **5c** required purification by rapid chromatography (alumina/Et_2O). Cyclisation was carried out immediately under medium dilution conditions, which were achieved by dropwise addition of a solution of the aminal (∿ 4g/100 ml CH_3CN) to dry refluxing acetonitrile (400 ml) during 4h. Both **6a**·$C\ell^-$ and **6c**·$C\ell^-$ were deliquescent, but were conveniently purified and stored as the moisture-stable perchlorate salts (prepared by ion exchange over Dowex

Scheme 1



k-1=3,DBN
k-1=5,DBU

4a k-1=3,m=3
4b k-1=3,m=2
4c k-1=5,m=3

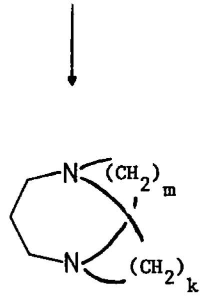
5a k-1=3,m=3
5b k-1=3,m=2
5c k-1=5,m=3

6a k-1=3,m=3
6b k-1=3,m=2
6c k-1=5,m=3

Preparation of **7**: (i) DBN + 1 eq. **3** (m=3)/Et_2O, RT, 1 week, 87%; (ii) $LiA\ell H_4$/THF, RT, 2h, 68%; (iii) CH_3CN, reflux (medium dilution), 4h, 62%; (iv) $LiA\ell H_4$/DME, RT, 24h, 62%.

Preparation of **8**: (i) DBN + 1 eq. **3** (m=2)/Et_2O, RT, 1 week, 70%; (ii + iii) $LiA\ell H_4$/THF, RT, 2h, cyclisation to **6b** occurs on work up (see text) 43%; (iv) $LiA\ell H_4$/DME, RT, 24h, 78%.

Preparation of **9**: (i) DBU + 4 fold excess **3** (m=3)/Et_2O, RT, 1 week 97%; (ii) $LiA\ell H_4$/THF, RT, 2h, 49%; (iii) CH_3CN reflux, (medium dilution), 4h, 68%, (iv) $LiA\ell H_4$/DME, RT, 24h, 80%.



7 k=4,m=3
8 k=4,m=2
9 k=6,m=3

1-8 resin). The aminal **5b** apparently cyclises spontaneously and was not isolated. Thus work up of the lithium aluminium hydride reduction of **4b** by addition of sodium hydroxide followed by trifluoromethanesulphonic acid (to pH9) and continuous extraction with methylene chloride gave a moderate yield of **6b**$\cdot CF_3SO_3^-$. This salt is a liquid, and attempts to crystallise the iodide, chloride, tosylate, perchlorate and trifluoroacetate salts of **6b** were equally unsuccessful. However, the crude **6b**$\cdot CF_3SO_3^-$ is sufficiently pure (NMR) to be used directly for the next reaction. Indeed, all three salts, **6a**$\cdot C\ell O_4^-$, **6b**$\cdot CF_3SO_3^-$ and **6c**$\cdot C\ell O_4^-$ reacted smoothly with lithium aluminium hydride in DME to the corresponding diamines 1,6-diazabicyclo[4.3.3]dodecane (**7**), 1,6-diazabicyclo[4.3.2]undecane (**8**) and 1,8-diazabicyclo[6.3.3]tetradecane (**9**). Diamine **7** is identical with a sample prepared via the dication route.^{2} Sublimation of **8** (10 Torr, 100°) gave air stable white crystals (m.p. 119-20°, sealed tube). Compound **9** proved to be very sensitive towards atmospheric oxidation and was handled under nitrogen, sublimation (1 Torr/100°) onto a cold finger condenser (0°) gave colourless crystals (m.p. 63-8°, sealed tube).

One of the remarkable properties of **2** is its ready oxidation to an exceptionally long lived radical cation. Neither **8** nor **9** gave persistent radical cations on the laboratory time scale at room temperature when chemically oxidised in solution (Ag^+/CH_3CN, $pBrPh_3N^{+\cdot}/CH_3CN$ or $CH_2C\ell_2$). Of the two diamines only **9** reduces the oxidised dication of **2** ($\mathbf{2}^{\ddagger}$) to the corresponding radical cation $\mathbf{2}^{+\cdot}$ (63% yield assuming a one electron transfer; $\mathbf{2}^{+\cdot}$ was the only persistent radical species produced in this reaction (UV, ESR)). While **9** is oxidised as easily as **2** , at least in the gas-phase[†], its radical ion is transient, suggesting that there is no simple relationship between stability and persistence for 3-electron σ-bonded radical cations. Both diamines show strong absorptions in the UV (**8**, λ_{max} 238 nm, ε 6500; **9**, λ_{max} 210 nm, ε 7600, shoulders at 235 nm ε 6300 and 265 nm, ε 2300) which is either due to lone pair orbital mixing or flattening at nitrogen^3 or, most likely, both.

The pK$_a$s of **8** were determined approximately by following the evolution of the ($>NCH_2CH_2N<$) proton chemical shifts with pD (I = 0.01 - 0.1). Values of 9.8 and 5.2[‡] were obtained which are quite typical for a diamine of structure $R_2NCH_2CH_2NR_2$. The first pK$_a$ of **9** has not yet been determined because it is extremely insoluble in water. An outside monoprotonated ion ($\mathbf{9}o^+$) is observed in dilute aqueous acid by ^1H and ^{13}C nmr and an outside diprotonated ion ($\mathbf{9}o^+o^+$) is formed in trifluoromethanesulphonic acid. When **9** is dissolved in trifluoroacetic acid about equal amounts of $\mathbf{9}o^+$ and $\mathbf{9}o^+o^+$ are formed hence the second pKa is around -3 showing that the bicyclic structure strongly resists outward pyramidalisation of both bridgeheads, this behaviour is similar to that of the structural isomer $\mathbf{2}^4$. When a solution of **9** in trifluoroacetic acid is refluxed overnight the spectrum of a new compound appears, this is assigned as the inside monoprotonated ion ($\mathbf{9}i^+$) on the basis of the low field $\overset{+}{N}$-H signal at 17.25 δ, indicative of a very strongly hydrogen bonded proton. An inside proton is also found when the reaction is carried out in deuterated trifluoroacetic acid. Inspection of the ^2H nmr spectrum of this reaction product

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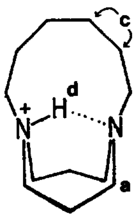
[†] The photoelectron spectrum of **9** shows a first band at I_1^v, = 6.78 eV, similar to that of **2** (I_1^v, = 6.75 eV). PE spectra of **8** and **9** were measured by Professor E. Heilbronner and coworkers and will be discussed in detail elsewhere.

[‡] corrected for the deuterium isotope effect by adding 0.4 to the values measured.

shows the incorporation of about one deuterium per molecule* distributed as shown in Figure 1.

Figure 1



	% ^{2}H	
	reaction in TFA-D	reaction in D_2SO_4
a	30	53
b	50	47
c	10	<1
d	10	<1

Presumably inside "protonation" occurs by a mechanism similar to that proposed for inside "protonation" of **2**[4], namely a radical chain process involving hydrogen atom abstraction from a bridge $-CH_2-$ by a bridgehead aminium radical cation followed by transfer of a solvent D· to the carbon radical. The presence of 10% deuterium in the $\overset{+}{N}$-H position is most likely due to competitive proton transfer from the solvent into the cavity. Warming a solution of **9** and $K_2S_2O_8$ in 50% H_2SO_4/H_2O also generates **9i**$^+$. When this reaction is carried out in 50% D_2SO_4/D_2O no internal $\overset{+}{N}$-D is found and the substitution pattern in the methylene bridges is altered (see Figure 1). It is hoped that a thorough study of the reactions giving **9i**$^+$ and **2i**$^+$ will reveal the details of the mechanism of this intriguing process. The chemical shift difference ($\delta\ 9i^+H - \delta\ 9i^+D$) = + 0.76 ppm indicates that the inside proton is in a deep, symmetrical, double minimum potential energy well[5]. **9i**$^+$ is protonated in trifluoromethanesulphonic acid forming **9i**$^+$o$^+$.

Reductive cleavage of tricyclic α-aminoammonium ions promises to be a good method of preparing many medium-ring bicyclic diamines and we are currently developing new ways of constructing these systems.

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*determined by integration against a known amount of an internal standard (d^6 benzene).

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