Tetrahedron Vol. 38, No. 2, pp. 261 to 266, 1982
Printed in Great Britain.

0040-4020/82/020261-06$03.00/0

AZAPROPELLANES AS PHASE-TRANSFER CATALYSTS—II

A CMR AND PMR STUDY OF THE THREE-DIMENSIONAL STRUCTURE OF 1-AZONIAPROPELLANES CONTAINING 5- AND 6-MEMBERED RINGS

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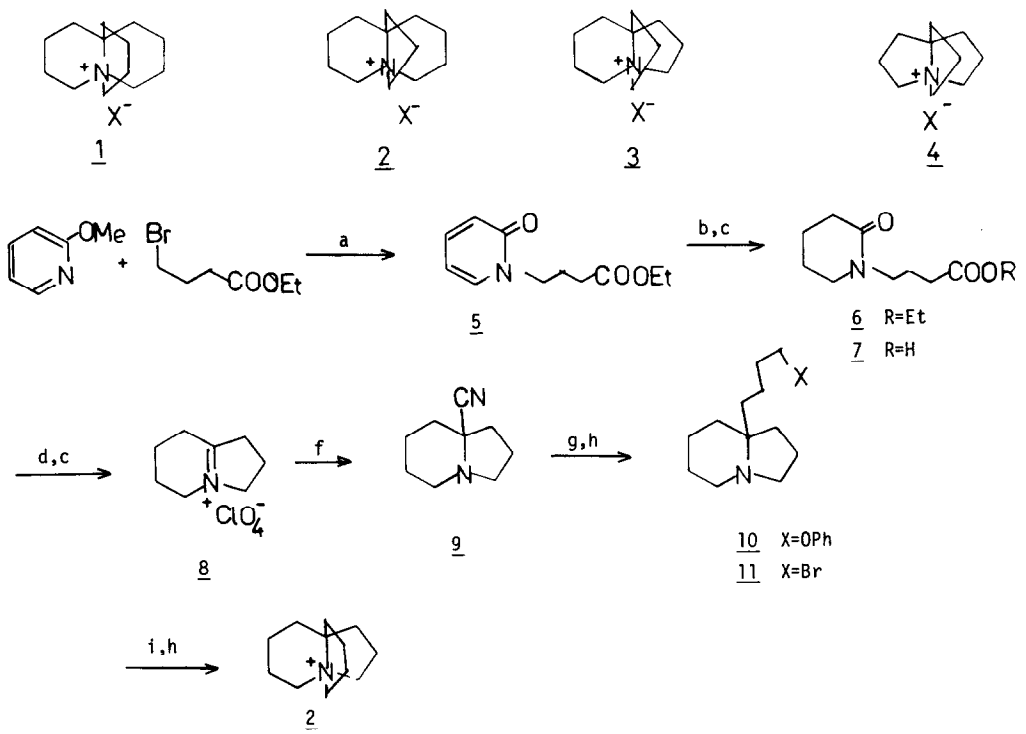
(*Received in U.S.A.* 17 *March* 1981)

Abstract—An improved synthesis of 1-azoniatricyclo[4. 4. 3. $0^{1,6}$] tridecane (**2**) and the preparation of the remaining member of the series, 1-azoniatricyclo[4. 3. 3. $0^{1,6}$] dodecane salts (**3**) have been achieved. Using a combination of ^1H (at 400 MHz) and ^{13}C NMR spectra has allowed the assignment of the signals in the well-resolved ^1H spectra. The results indicate that **1** exists in the all-chair form which undergoes racemization by ring inversion with a rate constant of 0.7 sec^{-1} and further that the counterion in these salts is restricted to associating with only one face of the tetrahedral N atom.

In the first publication in this series,[2] the synthesis of the tricyclic ammonium salts **1** and **2** were reported,[3] and the rationale for considering this type of molecule as the basis for potentially chiral phase-transfer catalysts was outlined. In this report an improved synthesis of **2** and the preparation of the related salt **3** are reported, as well as detailed structure analysis of **1–4**, based on their high-field NMR spectra.

The earlier report of the synthesis of **2** centered on the closing of the 5-membered ring as the final step. Because of poor yields in that sequence, we have modified the route to that shown in Scheme 1. The overall yield of **2** from **9** was improved from 40% to 51%. (Experimental).

For the same methodology to be useful in the preparation of **3**, the cyanoamine **15** was required. This has been most directly prepared[4] by cyclization of **16**. However we have consistently been unable to repeat the reported preparation of **16**.[5] We therefore returned to the use of **9** as a starting point and its transformation into **3** is shown in Scheme 2 (see Experimental). The applicability



[a] 180°; [b] H_2Pt; [c] KOH, EtOH; [d] soda-lime distillation; [e] $HClO_4$, EtOH; [f] KCN, H_2O; [g] $\phi O(CH_2)_4MgBr$, Et_2O; [h] 48% HBr; [i] Ag_2O/H_2O

Scheme 1

of the sequence shown in Scheme 1 to other ring sizes is currently being investigated.

Compound **3** (X = Br) had physical properties entirely consistent with other salts in this series. Thus it melted above 280° and showed only limited water solubility. The trifluoroacetate was completely soluble in halogenated solvents and was thus used in the spectral studies described below.

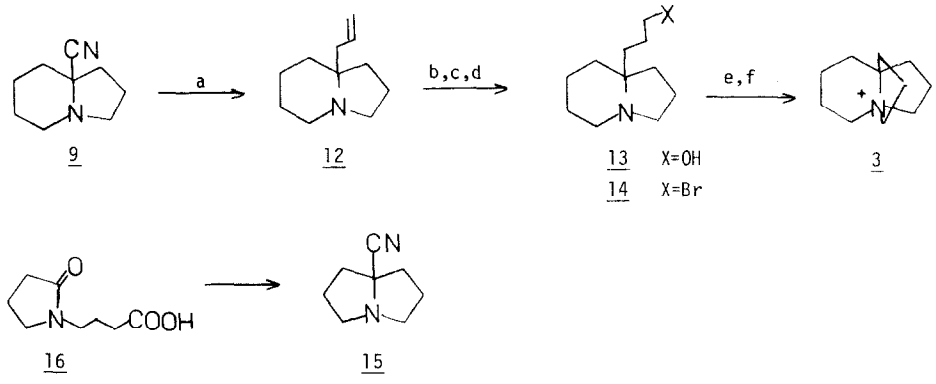
In addition, salt **3**, like **1** and **2**, smoothly catalyzed the test phase-transfer reactions previously described.[2]

The PMR spectra of quinolizidine[6] (**17**) and indolizidine[7] (**18**) have been the subject of several reports. The salient results can be summarized by pointing out that although N inversion is a facile process, the predominant conformation of **17** in solution appears to be the trans-fused isomer. However, in either conformation, the methylene protons adjacent to nitrogen are well separated and that proton situated in an antiperiplanar relationship with the nitrogen lone-pair is substantially shielded relative to its geminal partner. The cause of this shift difference has been the subject of some controversy, but it now seems certain that both the lone pair and the alkyl group on nitrogen play a role.[8] The same observations apply to **18**

Unfortunately we have been unable to find the complete PMR spectral data for the quaternary salts derived from **17** or **18**. Our results using PMR and CMR on the salts **1–4** which bear directly on their structure and particularly on the possibility of resolution of **1** are outlined below.

The CMR data for compounds **1–4** are summarized in Table 1. Also shown is the data for hydrocarbons **19**[9] **20**[10] and **21**.[11] The structural assignments in each case are supported by the small number of lines indicating a highly symmetrical material. The line assignments are based on consideration of the steric interactions, the effect of the positive center, line intensities and the shifts of simple tetraalkyl ammonium salts and are crucial to an interpretation of the PMR spectra discussed later.

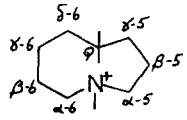
Three interesting points should be noted. The chemical shifts of the quaternary carbons become increasingly more positive as the ring sizes decrease. The shift of 96.1 for **4** is particularly dramatic. This trend may be due, at least in part, to increasing ring-strain. We also prepared



[a] $CH_2=CHCH_2MgBr$, Et_2O; [b] disiamylborane, THF; [c] 30% H_2O_2, NaOH, H_2O; [d] HBr, HOAc; [e] Ag_2O, H_2O; [f] 48% HBr

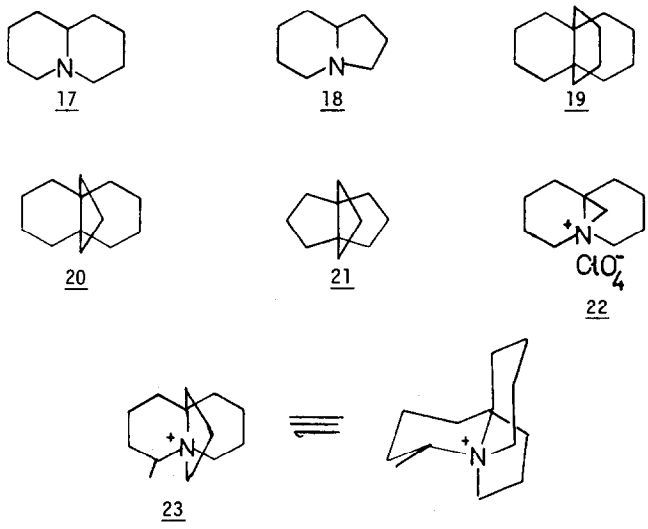
Scheme 2

Table 1. CMR data on 1-azoniapropellanes and some related materials



compound	α-6	β-6	γ-6	δ-6	Q	γ-5	β-5	α-5
1	56.1	19.4	17.1	29.3	65.5			
2	55.9	19.7	17.4	29.4	72.7	31.5	16.9	58.7
3	54.4	19.0	16.7	28.3	80.5	32.6	18.3	60.0
					96.1	36.8	23.0	64.4
19[9]	32.6	21.8	21.8	32.6	35.0			
20[10]	21.6	21.4	21.4	21.6	51.2	37.5	32.0	37.5
21[11]					60.3	40.3	24.6	40.3
22	58.8	20.5	17.0	29.9	56.4		[44.4]	

the position of the carbon relative to the nitrogen atom is indicated in the accompanying drawing.



22[12] and its CMR spectrum is included in Table 1. In this case, the bridgehead carbon resonates that a much higher field. Some of the carbons attached to the positive center appear to show significant C–N couplings, a phenomenon to be expected in highly symmetrical materials. Finally the shifts of the carbons situated on the beta position to the positive nitrogen are shielded relative to their counterparts in the hydrocarbons **19**, **20** and **21**. This type of effect has been commented upon previously.[13]

The proton spectra of **1–4** at 100 MHz or less show all protons adjacent to the positive center as broad multiplets which are clearly second order. However, at 400 MHz, the spectra of **1** and **4** become amenable to first-order analysis. The 400 MHz spectrum of **1** is shown in Fig. 1. The integrated spectrum shows absorptions corresponding to 3, 3, 3, 3, 6, 3 and 3 protons. Such a ratio can only be accommodated by a structure in which the three rings are equivalent and the difference in the chemical shifts of geminal proton pairs is relatively large. Irradiation of the signal at 4.06 caused the collapse of the doublet of doublets at 3.00 to a broadened singlet and altered the pattern in the three-proton multiplet at 2.10 without affecting the signals at 2.52 or 1.29. Conversely, irradiation of the signal at 3.00 eliminated one of the 15 Hz couplings to the signal at 4.06 leaving a doublet of doublets (J = 4, 15 Hz) and also affected the same higher field signals. The chemical shift of 4.06 and 3.00 identifies these protons as being adjacent to the positive center and the coupling constants require that the lower field absorption be the axial proton, the reverse situation to that found in the uncharged quinolizidine. It is perhaps noteworthy that the apparent absence of one coupling constant in the signal for the equatorial proton suggests some deviation from a pure chair form. An X-ray crystallographic structure determination is currently in progress to verify this point.

The presence of a 3-proton doublet at 1.29 immediately suggested that this was one of the two protons adjacent to the carbon bridgehead. Irradiation of this signal removed the 15 Hz coupling from the signal at 2.52, identifying these as geminal protons. Specific proton decoupling of the signals at 1.29 and 2.52 while observing the CMR spectrum confirmed that these were attached to the same carbon and also their position as, in both cases, the absorption at 29.4 ppm was the only one affected.

The chemical shift differences between the axial and equatorial protons adjacent to the bridgeheads (1.06 and 1.23 ppm respectively) are very large for molecules which do not contain lone pairs of electrons. However, the spectrum of the hydrocarbon 19 shows the same large difference (Table 2). Applying the parameters derived by Booth *et al.*[14] for substituted cyclohexanes does predict this difference amazingly well.

Another fact which is of paramount importance emer-

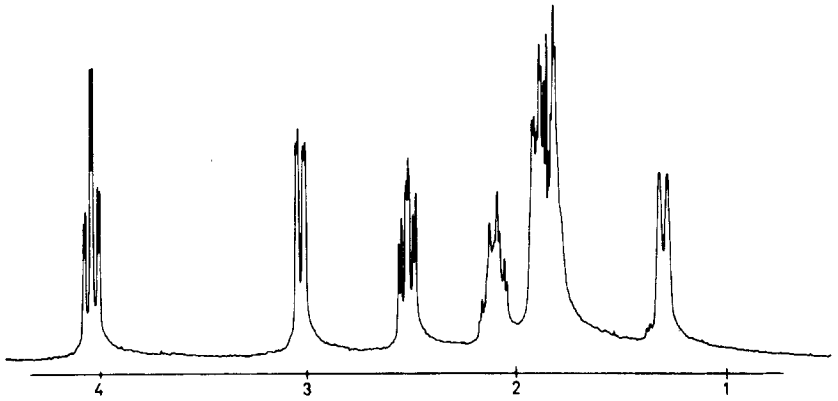


Fig. 1. 400 MHz proton spectrum of 1-azoniatricyclo[4. 4. 4. $0^{1,6}$] tetradecane (1).

Table 2.

compound	
1	4.06 (ddd,3, J=15,15,4 Hz) [N-$\underline{\underline{CH}}_a$-$CH_2$] , 3.00 (dd, 3, J=15,4 Hz) [N-$C\underline{\underline{H}}_e$-$CH_2$] , 2.52 (ddd,3, J=15,13,5 Hz) [N-C(H)-$\underline{\underline{CH}}_a$] , 2.10 (m,3) [N-$CH_2$-$\underline{\underline{CH}}_2$] , 1.89 (m, 6), 1.82 (m,3), 1.20 (bd,3, J=15 Hz) [N-C(H)-$\underline{\underline{CH}}_e$] .
2	3.92 (bs, 2) [N-CH_2 ,5-ring] , 3.67 (m, 2) and 3.56 (m, 2) [N-CH_2 ,6-ring] , 2.35 (m, 2), [N-$CH_2\underline{\underline{CH}}_2$, 5-ring] , 2.18 (bs, 2), 1.96 (bs, 6), 1.78 (bs, 6).
3	3.75 (m, 4) [N-CH_2, 5-ring] , 3.42 (t, 2, J=6Hz) [N-CH_2, 6-ring] , 2.24 (m, 8), 1.86 (m, 4), 1.77 (m, 2).
4	3.49 (t, 6, J=6.2 Hz) [N-CH_2] , 2.12 (m, 6) [N-CH_2-CH_2] , 2.07 (q, 6, J=6.1 Hz) [N-C(H)-CH_2] .
19	2.02 (dt, 6, J=13, 3.5 Hz), 1.45 (m, 12), 0.66 (d, 6, J= 13 Hz).

ged from the decoupling studies. As we have pointed out[2] **1** has C_3 symmetry and is therefore chiral. Racemization of **1** requires the conformational inversion of all three 6-membered rings. When the signal at 4.06 was irradiated, the integrated intensity of its geminal partner at 3.00 decreased noticeably. This spin saturation transfer (Forsen-Hoffman effect)[15] is solid evidence for exchange of these two protons via ring inversion at a rate which is slow on the NMR time scale, but at a rate which clearly precludes the possibility of resolving **1**. Quantitative experiments (see Experimental) led to a value of 0.7 sec^{-1} for the rate constant for inversion at 293°A. The value for the inversion barrier as determined by the coalescence temperature is 17.2 Kcal/mol for **1**[3] and 15.7 Kcal/mol for the 2,2-difluoro derivative of **19**.[16] If the entropy of activation for racemization is assumed to be approx. zero, these numbers are in good agreement.

Finally, the spectrum of the picrate salt of **1** showed the same chemical shifts, with the exception of the signal at 3.00 which had moved to 2.72. This confirms our belief[2] that molecules based on the azapropellane system do restrict association of counterions to the single exposed face of the nitrogen statom.

The proton spectrum of **4** was very simple consisting of a triplet at 3.49 for the six protons adjacent to nitrogen, a 6-proton multiplet at 2.12 for the protons in the beta position and an apparent 6-proton quartet at 2.07 which was not coupled to the signal at 3.49. Models show that all rings are planar and geminal pairs of protons are equivalent.

As might be expected, the spectra of **2** and **3** (Table 2) are considerably more complex than either **1** or **4**. In the case of **2**, the 6 protons adjacent to nitrogen appear as three separate 2-proton signals, the most deshielded of which can be assigned to the 5-membered ring, since decoupling of the signal did not affect the other two. This signal is also coupled to the absorption at 2.35. On the basis of the observed coupling constants, the signals at 3.67 and 3.56 appear to be respectively the axial and equatorial protons on the 6-membered rings. Decoupling of either of these signals led to almost complete disappearance of the other, signifying a much more rapid ring inversion than in **1** and making the examination of the coupling patterns impossible. An X-ray structure determination of this salt is also currently in progress.

In **3**, the protons on the 5-membered rings adjacent to nitrogen appear as a complex 4-proton multiplet at 3.75 while those on the 6-membered ring show a 2-proton triplet at 3.42. Decoupling of the signal at 1.90 collapsed this triplet to a singlet. The equivalency of the axial and equatorial protons may be due to a severe flattening of the ring or to rapid ring inversion.

CONCLUSIONS

The data outlined in this and the previous report can be summarized as follows. The synthesis of salts based on the 1-azapropellane system is straightforward and these salts are active phase transfer catalysts.[2] Although several of these salts are inherently chiral, racemization by ring inversion is rapid and precludes any attempt to utilize the unsubstituted salts as chiral catalysts. NMR does permit the structural analysis of these salts. It confirms that salt **1** exists in a slightly distorted chair form and by using high field spectra, the orientation of protons (and substituents) can be deduced. It also confirms that the counterion is restricted to one face of

the N atom, which is an important point in our analysis of the requirements for effective chiral induction.

While the rate of ring inversion in **1** has been measured, the mechanism of racemization is not clear.[16] This could occur *a priori* by simultaneous inversion of all three rings or, more likely, by sequential inversion. Models indicate that the introduction of a ring substituent will freeze the substituted ring in the conformation possessing an equatorial substituent. Whether this will also stop the inversion of the other two rings is an interesting point which we are now addressing. In any event, molecules such as **26** possess the chiral nitrogen face to which we referred earlier. Our synthetic efforts are now being directed towards preparation of substituted compounds and the results of these investigations will be the subject of future reports.

EXPERIMENTAL

M.ps are corrected; b.ps are uncorrected. IR spectra were run on Beckman IR-12 or Perkin Elmer 297 instruments as films or in dilute $CHCl_3$ solns. PMR spectra were run at 60 or 100 MHz and are reported in ppm downfield from Me_4Si as internal standard; 400 MHz spectra were obtained on a Bruker WP-400 instrument. CMR spectra were run at 22.64 MHz and are referenced to the same standard. Gas chromatographic analyses were performed on SE-30 columns, solvents were removed at reduced pressure and the drying agent was $NaSO_4$.

N-(3-*carbethoxypropyl*)-2-*pyridone* (**5**). Ethyl 4-bromobutyrate (30 g, 0.154 mol) was heated to 180° under N_2 and 20.5 g (0.19 mol) 2-methoxypyridine was added dropwise by syringe over a period of 4 hr. MeBr was evolved. The mixture was heated at 180° for 1 hr after the final addition and the mixture was then distilled. After a forerun consisting largely of N-methyl-2-pyridone, the product **5** was collected (14.0 g, 43%), bp 135–138 (0.1 mm): IR (film) cm^{-1}: 3080, 2980, 1735, 1660, 1590, 1540, 770; PMR ($CDCl_3$): 7.35 (m, 2), 6.56 (dd, 1, J = 1, 9 Hz), 5.18 (dt, 1, J = 1, 6 Hz), 4.15 (q, 2, J = 6 Hz), 4.00 (m, 2), 2.5–1.9 (m, 4), 1.24 (t, 3, J = 6 Hz); CMR ($CDCl_3$): 172.8, 162.7, 140.0, 138,0, 120.8, 106.9, 60.6, 49.2, 31.0, 24.5, 14.2. (Found: C, 63.44; H, 7.12; N, 6.79. Calc for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69).

N-(3-*carbethoxypropyl*)-2-*piperidinone* (**6**). Ester **5** (14 g, 0.067 mol) was dissolved in 150 mL EtOH and hydrogenated over prereduced Pt_2O at an initial pressure of 2.7 atm. Absorption of H_2 was complete in 5 hr. The soln was filtered through Celite and evaporated to afford 14.0 g (100%) of a clear liquid which was pure according to glc analysis: IR (film) cm^{-1}: 2945, 2880, 1740, 1645, 1500; PMR ($CDCl_3$): 4.13 (q, 3, J = 6 Hz), 3.5–3.2 (m, 4), 2.35 (m, 4), 1.80 (m, 6), 1.24 (t, 3, J = 6 Hz); CMR ($CDCl_3$); 173.3, 169.9, 60.4, 48.0, 46.4, 32.3, 31.6, 23.3, 22.4, 21.4, 14.2. (Found: C, 61.31; H, 9.08; N, 6.78. Calc. For $C_{11}H_{19}NO_3$: C, 61. 95; H, 8.98; N, 6. 57).

N-(3-*carboxypropyl*)-2-*piperidinone* (**7**). Ester **6** (14 g, 0.067 mol) was dissolved in 50 mL EtOH and soln of 4.3 g (0.076 mol) KOHaq was added all at once. The mixture was stirred at ambient temp for 16 hr, evaporated to a volume of 10 mL and diluted with 200 ml water. The aqueous soln was extracted once with ether acidified with conc HCl and extracted with 7 × 50 mL $CHCl_3$. The $CHCl_3$ extracts were dried and evaporated, the last traces of solvent being removed at 0.05 mm. The white solid remaining (10.4 g, 86%) had m.p. 98–99°: IR($CHCl_3$) cm^{-1}: 3500–2400, 1720, 1600, 1500, 760; PMR($CDCl_3$): 3.6–3.2 (m, 4), 2.6–2.2 (m, 4), 2.1–1.6 (m, 6); CMR ($CDCl_3$): 176.4, 171.0, 48.0, 46.6, 31.9, 31.5, 23.1, 23.2, 21.1. (Found C, 58.39; H, 8.00; N, 7.53. Calc. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56).

In exactly the same manner, but utilizing ethyl 5-bromovalerate as the alkylating agent, the following homologs of **5** and **6** were prepared:

N-(4-*carbethoxybutyl*)-2-*pyridone*: 44%; b.p. 142–150°(0.10 mm); IR (film) cm^{-1}: 3070, 2980, 2940, 2870, 1730, 1660, 1590, 1540; PMR ($CDCl_3$): 7.36 ($m_{,2}$), 6.56 (dd, 1, J = 1, 9 Hz), 6.11 (dt, 1, J = 1, 6.5 Hz), 4.12 (q, 2, J = 7 Hz), 4.00 (m, 12), 2.34 (t, 2, J = 6 Hz), 2.0–1.5 (m, 4), 1.24 (t, 3, J = 6 Hz); CMR ($CDCl_3$): 173.3, 162.7, 139.6, 137.7, 121.1, 106.4, 60.4, 49.6, 33.8, 28.7, 22.0, 14.2. (Found: C, 64.50; H,7.49; N, 6.10. Calc. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27).

Hydrogenation gave N-(4-carbethoxybutyl)-2-piperidinone (100%), identical to the material previously described.[2]

8*a*-*Cyanoindolizinine* (**9**). Acid **7** (2.4 g, 13 mmol) was ground with 5.0 g of soda lime and placed in a 50 mL r.b. flask fitted with a short-path distillation apparatus. The system was purged with N_2 and distilled using a free flame. Vigorous evolution of CO_2 occurred and the head temp. rose to 144°. The distillate was diluted with pentane and the layers were separated. The aqueous phase was extracted with 10 mL ether and the combined organic phases were dried and evaporated. The residue was dissolved in 30 mL dry EtOH and 70% perchloric acid was added to pH = 1. After storage at −20° for 3 hr, the crystalline salt was isolated by filtration to give **16**[17] in 89% yield. Addition of this to 10 mL sat. NaCNaq followed by ether extraction afforded 89% of **9**[17] which solidified in the freezer.

1-*Azoniatricyclo*[4. 4. 3. $0^{1,6}$] *tridecane bromide* (**2**). In exactly the same manner as previously described for the synthesis of the quinolizidine homolog,[2] the reaction of **9** with the Grignard reagent derived from 4-phenoxybutyl bromide afforded **10** (73%) contaminated with *ca.* 10% of **9**. Pure **10** could be isolated by chromatography: IR (film) cm^{-1}, 3080, 3040, 2930, 2860, 2790, 1600, 1585, 1495, 1470, 1250, 750; PMR ($CDCl_3$): 7.5–6.8 (m, 5), 3.98 (t, 2, J = 6 Hz), 2.81 (m, 4), 2.10–1.00 (m, 16). (Found: C, 79.00; H, 10.01; N, 5.03. Calc. for $C_{17}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12). This material (0.6 g) was dissolved in 6 mL conc HBr and refluxed for 2 hr. The cooled soln was adjusted to pH = 4 with NaOHaq, extracted with ether and then concentrated to dryness to give an hygroscopic orange solid. This material was dissolved in 10 mL water and 2 g Ag_2O was added. The reaction was stirred overnight at ambient temp, filtered through Celite and evaporated at room temp. Slow addition of conc HBr caused the precipitation of **2** as its bromide salt (0.41 g).

This was crystallized from MeOH to give material identical to that previously obtained.[2] The overall yield of **2** from **9** was 51%.

8*a*-(3-*Hydroxypropyl*) *indolizidine* (**13**). A soln of disiamylborane was prepared by slow addition of 2.6 g (0.037 mol) 2-methyl-2-butene to 17 mL of a 1M borane-THF soln at 0°. After 1 hr, a soln of 0.56 g (3.4 mmol) 8a-allylindolizidine[18] in 5 mL dry THF was added at 0°. The mixture was stirred for 1 hr at 0° and 10 hr at ambient temp. Water was added until no more fizzing occurred and then 14 mL 10% NaOHaq was added. The soln was cooled to 0° and 4.5 mL 30% H_2O_2 was added dropwise over 20 min. The soln was stirred at ambient temp for 1 hr after the final addition, saturated with K_2CO_3, the layers were separated and the aqueous phase extracted with ether (4 × 50 mL). The THF was evaporated and the residue combined with the ether extracts and extracted with 4 × 20 mL 10% HClaq. The combined extracts were made basic with 50% NaOHaq and extracted with 4 × 50 mL ether. The ethereal extracts were washed with brine and dried. Evaporation gave 0.38 g (58%) of a clear oil which was pure according to glc analysis. IR(film) cm^{-1}: 3340 (broad), 2910, 2860; PMR ($CDCl_3$): 5.76 (m, 1), 3.58 (bt, 2, J = 4 Hz), 3.17–2.63 (m, 4), 2.00–1.20 (m, 14); CMR ($CDCl_3$): 63.4, 60.9, 49.5, 44.5, 34.5, 33.1, 30.7, 28.3, 20.6, 19.6. (Found: C, 71.95; H, 11.31; N, 7.59. Calc. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64).

1-*Azoniatricyclo*[4. 3. 3. $0^{1,6}$]*dodecane bromide* (**3**). Alcohol **13** (0.2 g, 1.0 mmol) was dissolved in 5 mL 32% HBr in AcOH. The soln was sealed in a tube and heated on the steam-bath overnight. The cooled soln was evaporated to dryness to give 0.33 g of a dark viscous residue. This was dissolved in 5 mL water and 0.4 g Ag_2O was added. The slurry was stirred overnight at ambient temp, filtered through Celite and evaporated at 20° to give a dark oil which was acidified with conc-HBr to pH = 1. The soln was evaporated to dryness, the residue taken up in MeOH and **3** precipitated by the addition of ether. The white crystalline material (134 mg, 51%) did not melt below 280°. It was converted to its trifluoroacetate salt for spectral investigation (see below). (Found: C, 53.12; H, 8.01; N, 5.35; Calc. for $C_{11}H_{20}NBr$: C, 53.66; H, 8.19; N, 5.69) *m/e* (FMDS) = 166.

A portion of the bromide was suspended in 2 mL water and excess Ag_2O was added. The slurry was stirred for 2 hr, filtered

through Celite and evaporated to dryness at 0.1 mm. The residue was treated with excess trifluoroacetic acid and reevaporated at 0.1 mm and 30°. The product was clear liquid which showed the PMR and CMR given in the Tables.

The T_1 measurements were performed by the inversion recovery technique at 400 MHz. The null point for the axial proton adjacent to nitrogen occurred at $\tau = 0.75$ sec. which corresponds to a T_1 of 1.08 sec. The rate constant k for exchange in a two-site equal population system is given by $k = 1/T\ [M(0) - M(\infty)/M(\infty)]$[19,20] where M(0) is the normal equilibrium magnetization of the proton and $M(\infty)$ is the equilibrium magnetization of the proton with saturation of its exchanging partner. Irradiation of the signal at 4.06 caused a decrease of 43% in the integrated intensity of the signal at 3.00. Thus $k = 0.70\ sec^{-1}$. This value is estimated to be accurate to a factor of 2.

The possibility of a perturbation of the integrated intensities due to a Nuclear Overhauser Effect (NOE) was considered. Since the rotational correlation time for molecules of this size is of the order of 10^{-11} sec, any simple NOE will always be positive and the effect of this will be to underestimate the extent of transfer saturation. However, in systems of this type the NOE is likely to be small in any case.

Acknowledgements—The financial assistance for this work was provided by the National Science and Engineering Research Council of Canada. I would like to express my deepest appreciation to the Department of Chemistry, University of Alberta, where much of this work was done during my sabbatical leave. The aid of Dr. T. Nakashima (U. of A.) and Dr. R. Lenkinski (Southwestern Ontario High Field NMR Laboratory) in obtaining the 400 MHz NMR spectra and in aiding the author in the interpretation and defence of the dynamic NMR experiments is particularly appreciated.

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