# Studies on Pyrrolizidines and Related Compounds. Part 9.[1] Rearrangement of 7a-Trichloromethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine and Related Compounds: An Alternative Route to 5-Substituted 1-Azabicyclo[3.3.1]nonanes

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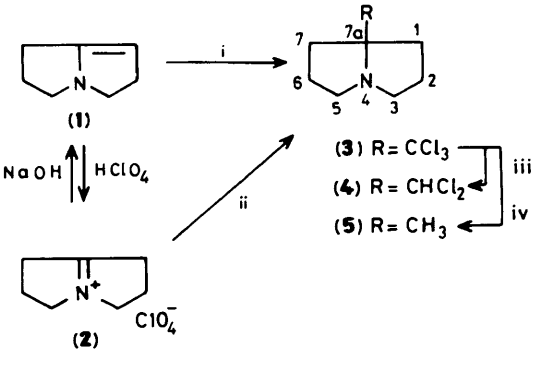
Rearrangement of 7a-trichloromethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine and related compounds provides a new synthesis of 1-azabicyclo[3.3.1]nonanes.

Previous publications in this series have dealt with the preparation and characterization of 2,3,5,6-tetrahydro-1*H*-pyrrolizine (**1**),[2] the synthesis of its analogues,[3] the nature of some of its potential reactivities,[4] and the pharmacological evaluation of the pyrrolizidine analogues.[5] Here, we describe: (i) the preparation of 7a-trichloromethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (**3**), (ii) the rearrangement of compound (**3**) into 1-azabicyclo[3.3.1]nonanes (**7**), and (iii) the characterization of the reaction products. It has been found that treatment of the 1*H*-pyrrolizine (**1**) with trichloroacetic acid in dioxane gives the colourless trichloro derivative (**3**). Compound (**3**) is also obtained by the reaction of the iminium perchlorate (**2**) with sodium trichloroacetate in 1,2-dimethoxyethane. Elemental analysis showed this compound to have the molecular formula $C_{18}H_{12}Cl_3N$ and its mass spectrum (electron impact) suggested that its molecular structure was that of 7a-trichloromethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine. A diagnostically important ion $(M - CCl_3)^+$ was observed as the base ion peak, in addition to $M^+$, and $(M - Cl)^+$. Although the $^1H$ n.m.r. (90 MHz) spectrum of this compound is too complicated for complete analysis, convincing evidence for the structure of (**3**) was supplied by the $^{13}C$-n.m.r. spectrum (Table 1). The $^{13}C$-n.m.r. spectrum of product (**3**) indicates a molecular symmetry and this is also seen in (**4**) and (**5**). Further conclusive evidence for the structure of (**3**) was obtained from its chemical transformation into 7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (**5**)[6] by treatment with excess of lithium aluminium hydride (3.3 equiv) in refluxing ether for 10 h. Interestingly, when the reaction was conducted at room temperature with LAH 1.2 equiv. for 5 h, the major product was 7a-dichloromethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (**4**) (82%) which is also convertible into the 7a-methyl derivative (**5**).




**Scheme 1.** *Reagents:* i, $CCl_3CO_2H$, dioxane, 60 °C; ii, $CCl_3CO_2Na$, 1,2-dimethoxyethane, reflux; iii, LAH(1.2 mol), ether, room temperature; iv, LAH(3.3 mol), ether, reflux.

**Table 1.** $^{13}C$ N.m.r. signals of 7a-substituted (R) 2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizines* (**3**)—(**5**)

| | Carbon atom $\delta_C$/p.p.m. | | | | |
|---|---|---|---|---|---|
| Compound | C-1,7 | C-2,6 | C-3,5 | C-7a | R |
| (**3**) (R=$CCl_3$) | 38.55 | 25.39 | 57.48 | 88.49 | 110.35 |
| (**4**) (R=$CHCl_2$) | 35.57 | 24.91 | 56.34 | 80.95 | 79.80 |
| (**5**) (R=$CH_3$) | 39.59 | 25.53 | 55.56 | 69.87 | 29.67 |

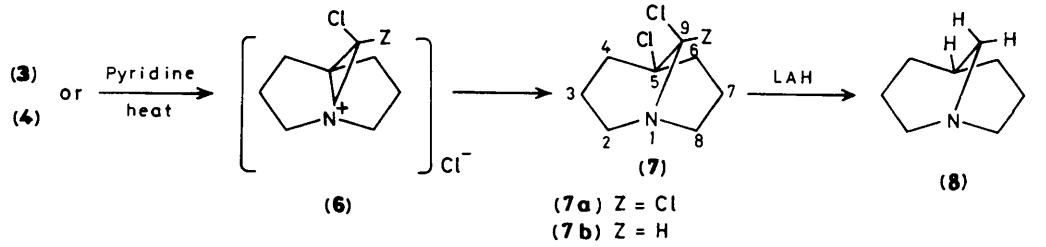
* Determined at 100 MHz in $CDCl_3$ using tetramethylsilane as an internal standard.

Treatment of the trichloromethyl derivative (**3**) with pyridine at 90 °C for 24 h gave 5,9,9-trichloro-1-azabicyclo[3.3.1]nonane (**7a**) in excellent yield, the formation of which can be envisaged as proceeding *via* a rearrangement involving an aziridinium salt intermediate (**6**).[7] Likewise, 7a-dichloromethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (**4**) underwent rearrangement in pyridine to give the corresponding 1-azabicyclo[3.3.1]nonane (**7b**) which is also obtained by the treatment of (**7a**) with LAH 3 equiv. in anhydrous ether at room temperature for 15 h. Surprisingly the rate of rearrangement of compound (**4**) was found to be faster than that of compound (**3**) (checked by $^1H$ n.m.r. monitoring in pyridine).† The structures of products (**7a**) and (**7b**) were confirmed by spectroscopic methods, elemental analysis, and chemical transformation into 1-azabicyclo[3.3.1]nonane (**8**).[8] $^{13}C$-N.m.r. spectroscopy was employed for the structural determination of the products and the starting materials, (Table 2). The fact that six of the observed $^{13}C$ resonances for products (**7a**) and (**8**) coincide, *i.e.*, the chemical shifts of C-2, C-3, and C-4 overlap with those of C-8, C-7, and C-6 respectively, indicates that these molecules are symmetrical. For compound (**7b**), an unsymmetrical molecule, 2D heteronuclear ($^{13}C$–$^1H$) shift correlation spectroscopy (400 MHz) provided evidence that the chemical shifts of C-4 and C-8 carbons coincide at $\delta_C$ 42.70‡ (see Figure 1).

There appears to have been no earlier report of the isolation of a trichloro compound such as (**7a**), which is a proposed intermediate in the reactions of enamines with trichloroacetic acid[7,9] and it is noteworthy that such a compound could be isolated as a stable crystalline product. This stability may be

† The half-lives of (**3**) and (**4**) at 60 °C were >20 h and <1 min, respectively.

‡ The correct assignment of this signal to C-4, and not to C-6 was shown by the 2D-homonuclear ($^1H$–$^1H$) spectrum of this compound, and the chemical shifts for (C-4 and C-8) were $\delta_C$ 42.744 and 42.805 respectively (400 MHz). Conformational analysis of 1-azabicyclo-[3.3.1]nonanes with 2-D n.m.r. spectra will be described in a subsequent paper in detail.




**Scheme 2.**

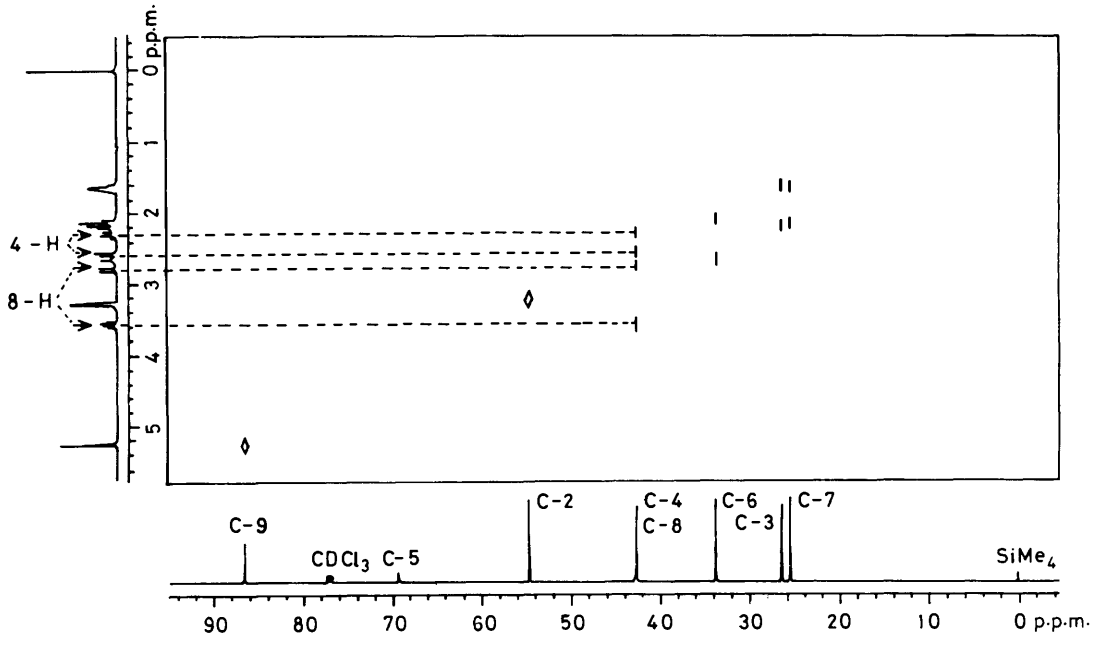
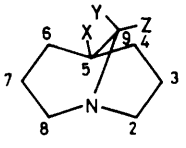



**Figure 1.** The two-dimensional (2D) $^{13}C$–$^{1}H$ chemical shift correlation map (contour plot) for 5,9-dichloro-1-azabicyclo[3.3.1]nonane (**7b**).

**Table 2.** $^{13}C$-N.m.r. signals of 1-azabicyclo[3.3.1]nonanes* (**7a**), (**7b**) and (**8**)




| | Carbon atom $\delta_C$/p.p.m. | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Compound | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-9 |
| (**7a**) (X=Y=Z=Cl) | 50.34 | 24.85 | 39.08 | 74.21 | 39.08 | 24.85 | 50.34 | 114.95 |
| (**7b**) (X=Y=Cl, Z=H) | 54.64 | 26.44 | 42.70 | 69.38 | 33.69 | 25.52 | 42.70 | 86.43 |
| (**8**) (X=Y=Z=H) | 52.75 | 23.51 | 29.97 | 25.77 | 29.97 | 23.51 | 52.75 | 55.31 |

* Determined at 100 MHz in $CDCl_3$ using tetramethylsilane as an internal standard.

attributed to both steric and stereoelectronic effects in the 1-azabicyclo[3.3.1]nonane ring system. Thus, examination of a molecular model of compound (**7a**) shows that $S_N2$ displacement at C-5 would take place only with considerable difficulty because the transition state would require a pentavalent carbon atom. In addition to this, orientation of the nitrogen lone pair towards two chlorine atoms on C-9 (Figure 2) also seems to have an important stabilizing role in that during the elimination process the leaving group (*i.e.* $Cl^-$) prefers anti-periplanar geometry, the so-called 'stereoelectronic effect'.[10] The rigid ring system, however, prevents such an orientation.

Taking account of the difficulties involved in the synthesis of 1-azabicyclo[3.3.1]nonane (**8**) and analogues[8,11] and the ready availability of compound (**1**) and related heterocyclic enamines, the rearrangements described in this paper may provide a new route for the synthesis of such compounds.[3]

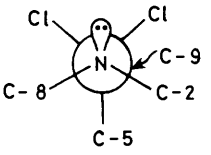



**Figure 2.**

## Experimental

M.p.s are uncorrected. I.r. spectra were recorded with a Hitachi–295 instrument. N.m.r. spectra were measured with Hitachi R–22 (90 MHz) and JEOL JNM-PMX60SI (60 MHz) (both for $^1$H-n.m.r.), and JEOL FX–100 (100 MHz) for $^{13}$C-n.m.r.) spectrometers using tetramethylsilane as an internal standard.

The two-dimensional (2D) heteronuclear ($^{13}$C–$^1$H) shift correlation spectrum of (**7b**) was recorded on a JEOL GX–400 spectrometer with 5-mm probe and tetramethylsilane as an internal standard at 25 °C, equipped with G MHD 80R(JEOL) computer system. 2D Experiments were controlled and the data processed with the standard VCHSHF software package of PLEXUS(JEOL) data system. Time domain matrices S(t1,t2) of 256 × 2 048 points were used, with spectral widths in the f1 and f2 domains of 2 500 and 10 000 Hz respectively. High-resolution mass spectra were obtained with a JEOL JMS–DX300 instrument with a direct inlet system operating at 70 eV.

7a-*Trichloromethyl*-2,3,5,6,7,7a-*hexahydro*-1H-*pyrrolizine* (**3**).—*Method A.* To a mixture of ether (50 ml) and 20% aqueous sodium hydroxide (50 ml) was added 1,2,3,5,6,7-hexahydro-1*H*-pyrrolizinium perchlorate (**2**) (10.47 g, 50 mmol) with stirring. The mixture was stirred at room temperature for 30 min. The resulting mixture was extracted with ether (100 ml). The ether extract was washed with saturated brine, dried ($MgSO_4$) and evaporated. The residue (**1**) was dissolved in dioxane (40 ml) to which a solution of trichloroacetic acid (9.80 g, 60 mmol) in dioxane (20 ml) was added dropwise with stirring and ice cooling. After 30 min, the reaction mixture was stirred and warmed (60 °C) for 3 h. It was then evaporated under reduced pressure and the residue dissolved in ether (100 ml). The resulting mixture was washed with 10% aqueous potassium hydrogen bicarbonate followed by saturated brine, dried ($MgSO_4$) and evaporated to give a solid residue. This was chromatographed on a silica gel column using ether as an eluant to give the product (**3**) (8.69 g, 76%) as colourless prisms, m.p. 77.5—78.5 °C (from acetone–water), $\nu_{max.}$(KBr) 745, 770 and 786 cm$^{-1}$ (C–Cl); *m/z* 227 ($M^+$, 8%, $C_8H_{12}NCl_3$), 192 (70, $M$ − Cl), and 110 (100, $M$ − $CCl_3$); $\delta_H$($CDCl_3$) 1.6—3.6 (complex m, 12 H, all aliphatic H). The $^{13}$C-n.m.r. spectrum of this compound is shown in Table 1 (Found: C, 41.8; H, 5.5; N, 5.85. $C_8H_{12}Cl_3N$ requires C, 42.04; H, 5.29; N, 6.13%).

*Method B.* To a solution of sodium trichloroacetate (70.64 g, 380 mmol) in dimethoxyethane (110 ml) was added iminium perchlorate (II) (19.96 g, 95 mmol), the resulting suspension was stirred and refluxed for 30 min. After filtration, the filtrate was evaporated to the solvent give a solid, which was recrystallized from acetone–water to give compound (**3**) (15.56 g, 71.7%).

7a-*Dichloromethyl*-2,3,5,6,7,7a-*hexahydro*-1H-*pyrrolizine* (**4**).—To a suspension of lithium aluminium hydride (LAH) (0.46 g, 12 mmol) in anhydrous ether (100 ml) was added 7a-trichloromethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (**3**) (2.29 g, 10 mmol) with stirring and ice cooling. The mixture was then stirred at room temperature for 5 h. The remaining LAH was decomposed by dropwise addition of 20% aqueous sodium hydroxide (100 g) with ice cooling, and the resulting mixture was extracted with ether (100 ml). The extract was washed with saturated brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure to afford an oily residue which was chromatographed on a silica gel column using ether as eluant to give the product (**4**) (1.59 g, 82%) yield as a colourless oil, $\nu_{max.}$ (liq. film) 730 and 764 cm$^{-1}$ (C–Cl); *m/z* 193.0332 ($M^+$, $C_8H_{13}Cl_2N$); $\delta_H$($CDCl_3$) 5.50 (s, 1 H, -$CHCl_2$) and 1.4—3.4 (m, 12 H, all aliphatic H). The $^{13}$C-n.m.r. spectrum of this compound is given in Table 1. The picrate of this base melted at 182—183 °C (decomp.), (from methanol) (Found: C, 39.75; H, 3.85; N, 13.05. $C_{14}H_{16}N_4O_7Cl_2$ requires C, 39.73; H, 3.81; N, 13.24%).

7a-*Methyl*-2,3,5,6,7,7a-*hexahydro*-1H-*pyrrolizine* (**5**).—To a suspension of LAH (2.50 g, mmol) in anhydrous ether (150 ml) was added 1*H*-pyrrolizine (**3**) (4.57 g, 20 mmol) with stirring. The mixture was stirred and refluxed for 10 h, after which the remaining LAH was decomposed by addition of 20% aqueous sodium hydroxide (200 ml). The resulting mixture was extracted with ether (200 ml) and the ether extract washed with saturated brine (50 ml), dried ($MgSO_4$), and evaporated; distillation of the residue gave 7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (**5**) (1.53 g, 62%) as a colourless oil, b.p. 100—102 °C/166 mmHg, the picrate of which was identical with that of the authentic sample. The $^{13}$C-n.m.r. spectrum of the free base (**5**) is presented for comparison in Table 1 (Found: C, 47.3; H, 5.15; N, 15.6. $C_{14}H_{18}N_4O_7$ requires C, 47.46; H, 5.12; N, 15.81%).

5,9,9-*Trichloro*-1-*azabicyclo*[3.3.1]*nonane* (**7a**).—A solution of 1*H*-pyrrolizine (**3**) (5.71 g, 25 mmol) in pyridine (50 ml) was stirred and refluxed for 24 h, after which the solvent was evaporated under reduced pressure and the residue dissolved in benzene. The resulting solution was washed with water and saturated brine, dried ($MgSO_4$), evaporated and the residue recrystallized from ethanol to give (**7a**) (5.31 g, 93%) as colourless prisms, m.p. 213—214 °C (decomp.), $\nu_{max.}$(KBr) 792, 820, and 892 cm$^{-1}$ (C–Cl); *m/z* 227.0035 ($M^+$, $C_8H_{12}NCl_3$); $\delta_H$($CDCl_3$) 1.5—3.3 (m, 10 H, aliphatic protons), 3.7—4.3 (m, 2 H, one proton of methylene connected with nitrogen atom × 2). The $^{13}$C-n.m.r. spectrum is shown in Table 2 (Found: C, 41.9; H, 5.55; N, 5.8. $C_8H_{12}Cl_3N$ requires C, 42.04; H, 5.29; N, 6.13%).

5,9-*Dichloro*-1-*azabicyclo*[3.3.1]*nonane* (**7b**).—*Method A.* A solution of 1H-pyrrolizine (**4**) (1 g, mmol) in pyridine (30 ml) was stirred and refluxed for 3 h, after which the solvent was evaporated under reduced pressure and the residue dissolved in ether. The ether solution was washed with 20% aqueous sodium hydroxide and saturated brine, and then dried ($MgSO_4$), evaporated and the residue chromatographed on a silica gel column with ether as eluant to give compound (**7b**) (0.94 g, 94%) as colourless prisms, m.p. 77—80 °C (from hexane), $\nu_{max.}$(KBr) 765, 780, and 817 cm$^{-1}$ (C–Cl); *m/z* 193.0420 ($M^+$, $C_8H_{13}Cl_2N$). The $^{13}$C-n.m.r. spectrum of the product is shown in Table 2, and the 2D heteronuclear ($^{13}$C–$^1$H) shift correlation spectrum (400 MHz) is shown in Figure 1 (Found: C, 49.6; H, 7.05; N, 7.2. $C_8H_{13}Cl_2N$ requires C, 49.50; H, 6.75; N, 7.22%). The picrate of this base melted at 178—180 °C (decomp.), (from ethanol) (Found: C, 40.0; H, 3.95; N, 13.05. $C_{14}H_{16}Cl_2N_4O_7$ requires C, 39.73; H, 3.81; N, 13.24%).

*Method B.* To a suspension of LAH (0.57 g, 15 mmol) in anhydrous ether (100 ml) was added 5,9,9-trichloro-1-azabicyclo[3.3.1]nonane (**7a**) (1.14 g, 5 mmol) with stirring and ice cooling. The mixture was stirred at room temperature for 15 h, after which work-up gave the product (**7b**) (0.42 g, 43%).

1-*Azabicyclo*[3.3.1]*nonane* (**8**).—To a suspension of LAH (1.90 g, 50 mmol) in anhydrous ether (100 ml) was added (**7a**) (1.14 g, 5 mmol) with stirring. The resulting suspension was stirred and refluxed for 16 h after which the remaining LAH was decomposed by addition of 20% aqueous sodium hydroxide

(200 ml). The resulting mixture was extracted with ether (200 ml), and the extract washed with saturated brine (50 ml), dried ($MgSO_4$) and evaporated to give a viscous residue, the sublimation of which (40 °C/17 mm Hg) gave the product (**8**) (0.46 g, 74%) as colourless crystals; *m/z* 125.1197 ($M^+$, $C_8H_{15}N$); $\delta_H(CDCl_3)$ 1.1—3.3 (complicated m, 15 H, all aliphatic H). The $^{13}C$-n.m.r. spectrum is shown in Table 2. The *picrate of this* base had m.p. 282.5—283 °C (decomp.), (from ethanol) [lit.,[8] 283 °C] (Found: C, 47.6; H, 5.1; N, 15.8. $C_{14}H_{18}N_4O_7$ requires C, 47.45; H, 5.12; N, 15.81%).

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