# Synthesis of 5,9,9-Trisubstituted 1-Azabicyclo[3.3.1]nonanes and their Conformational Analyses[1]

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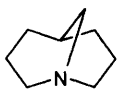
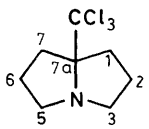
A new route for the preparation of 1-azabicyclo[3.3.1]nonane (**1**) and related compounds, consisting of the reactions similar to the skeletal rearrangement of 2,3,5,6,7,7a-hexahydro-7a-trichloromethylpyrrolizine (**2**) into 5,9,9-trichloro-1-azabicyclo[3.3.1]nonane (**3**), is described. The conformational analysis and some chemical properties of the products are also mentioned.

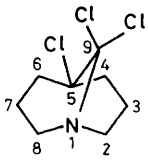
1-Azabicyclo[3.3.1]nonane (**1**) and related heterocycles have attracted considerable attention[2,3] because of their chemical and theoretical interest. It is also of great interest to compare these chemical properties with those of bicyclo[3.3.1]-nonanes.[4] In order to elaborate the new skeletal rearrangement [2,3,5,6,7,7a-hexahydro-7a-trichloromethylpyrrolizine (**2**) ⟶ 5,9,9-trichloro-1-azabicyclo[3.3.1]nonane (**3**)],[5] hopefully as a strategy for the preparation of such heterocycles, we have now examined some reactions relating to this rearrangement.



(**1**)



(**2**)



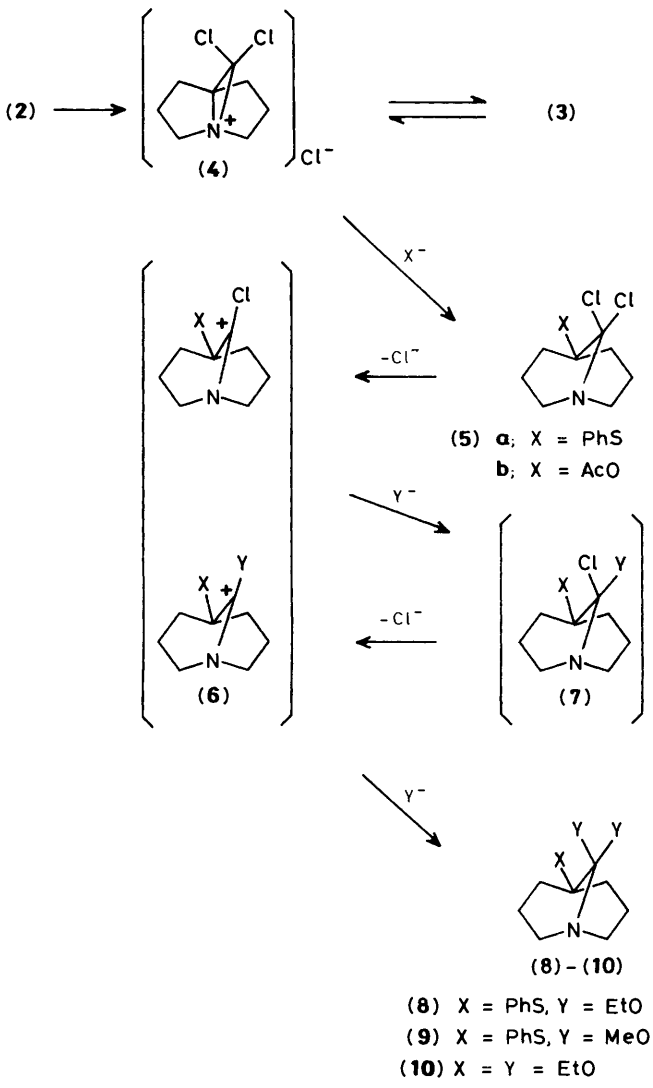
(**3**)

In this paper, the preparation and the conformational analysis of 5,9,9-trisubstituted 1-azabicyclo[3.3.1]nonanes, as well as some of their chemical properties, are described.

*Synthesis and Chemical Properties of* 5,9,9-*Trisubstituted* 1-*Azabicyclo*[3.3.1]*nonanes.*—The new method for 5-substituted 9,9-dichloro derivatives (**3**), (**5a**), and (**5b**) listed in Table 1 can be rationalized as the ring-opening reaction of an intermediate aziridinium ion (**4**) by the nucleophilic attack of an anion ($X^-$) to the electron-deficient bridgehead carbon corresponding to C-5 in the molecule of 1-azabicyclo[3.3.1]nonane (see Scheme 1).

Thus, treatment of the 7a-trichloromethyl compound (**2**) with a slight excess of thiophenol (1.2 mol equiv.) under reflux in pyridine in the presence of potassium t-butoxide (1.2 mol equiv.) gave 9,9-dichloro-5-phenylthio-1-azabicyclo[3.3.1]nonane (**5a**) in 64% yield. Compound (**5a**) was also obtained, in 60% yield, from the reaction employing 5,9,9-trichloro-1-azabicyclo-[3.3.1]nonane (**3**) as the starting material instead of (**2**). These results confirm that the chloro substituent on the bridgehead carbon (C-5) of 1-azabicyclo[3.3.1]nonane ring can easily undergo nucleophilic substitution. Such ionic cleavage of the Cl–C(5) bond leading to the intermediate (**4**) should be accelerated by the nucleophilic participation of the bridgehead nitrogen atom (N-1).

On the other hand, the reaction with a nucleophile such as the acetate anion resulted in the formation of considerable amounts of compound (**3**) in addition to the desired product (**5b**) (see Experimental section), which clearly indicates that




**Scheme 1.**

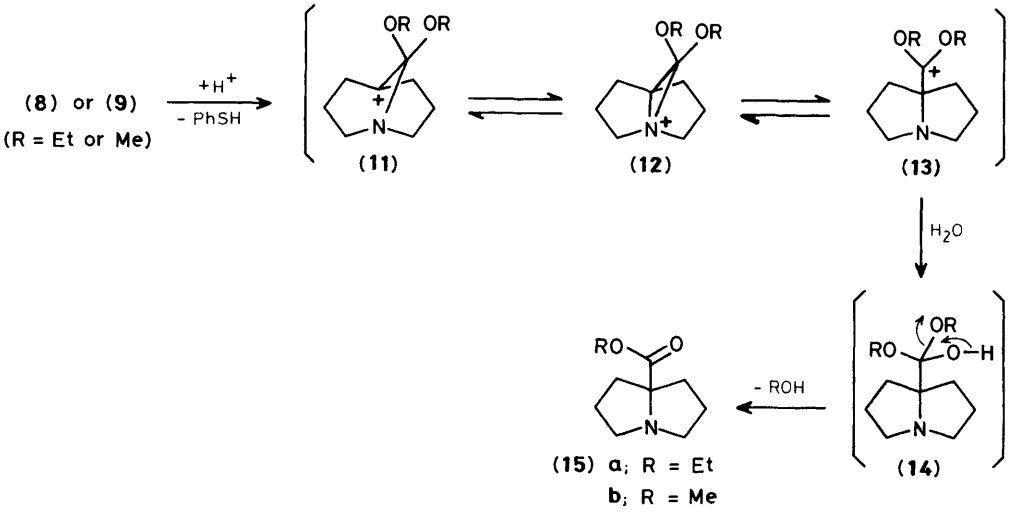
the two nucleophiles ($Cl^-$ and $AcO^-$) in the medium attack the intermediate aziridinium ion (**4**) competitively.

5-Substituted 9,9-dichloro derivatives (**5a**) and (**5b**) could be isolated as stable crystals at room temperature. The stability of the products which have an α,α-dichloromethylamine moiety may be attributed to both steric and stereoelectronic effects in

**Table 1.** $^{13}C$ N.m.r. signals of 1-azabicyclo[3.3.1]nonanes[a]

| Compound | Carbon atom $\delta_C$ C-2,-8 | C-3,-7 | C-4,-6 | C-5 | C-9 | Substituents |
|---|---|---|---|---|---|---|
| (3) | 50.2 | 24.8 | 39.0 | 74.2 | 115.1 | |
| (5a) (X = PhS) | 50.6 | 23.6 | 36.3 | 58.6 | 118.0 | 128.3, 129.2, 130.3, 138.4 (Ph) |
| (5b) (X = AcO) | 50.5 | 22.9 | 31.8 | 81.9 | 114.0 | 22.2 (Me), 169.4 (C=O) |
| (8) (X = PhS, Y = EtO) | 48.8 | 24.5 | 36.1 | 55.1 | 106.6 | 15.5 (Me × 2), 58.1 ($CH_2$ × 2),127.9, 128.3, 132.1, 138.1 (Ph) |
| (9) (X = PhS, Y = MeO) | 48.7 | 24.2 | 36.0 | 55.0 | 106.7 | 50.7 (Me × 2), 128.0, 128.4, 131.2, 138.2 (Ph) |
| (10) (X = Y = EtO) | 48.6 | 24.2 | 32.4 | 76.0 | 106.5 | 15.5 (Me × 2), 16.4 (Me), 56.7 ($CH_2$ × 2), 56.9 ($CH_2$) |
| (1) | 52.5 | 24.3 | 29.8 | 25.7 | 55.1 | |

[a] Determined at 90 MHz in $CDCl_3$ with $SiMe_4$ as internal standard.




**Scheme 2.**

the 1-azabicyclo[3.3.1]nonane ring system, as mentioned in our previous paper.[5]

Both chlorine atoms on C-9 of these products (**5**), however, could be displaced by further treatment upon heating with a strong nucleophile ($Y^-$) such as alkoxide anion, without destroying the 1-azabicyclo[3.3.1]nonane ring system. For example, when the 9,9-dichloro derivative (**5a**) was treated with sodium ethoxide (2.2 mol equiv.) in absolute ethanol under reflux for 16 h it afforded the 9,9-diethoxy derivative (**8**) in 65% yield. Compounds (**9**) and (**10**) obtained from nucleophilic substitution of 9,9-dichloro or 5,9,9-trichloro derivatives are also listed in Table 1.

From these results, we consider that these reactions, coupled with the rearrangement (**2**) ⟶ (**3**) in the presence of nucleophiles, may proceed by a mechanism involving the intermediates (**6**) and (**7**), as shown in Scheme 1, providing a new synthetic pathway for the preparation of 5,9-disubstituted 1-azabicyclo-[3.3.1]nonanes.

Among the chemical properties of these products, of particular interest is the fact that the 9,9-dialkoxy-5-phenylthio derivatives (**8**) and (**9**) readily undergo the skeletal reconversion into 7a-alkoxycarbonylhexahydropyrrolizines (**15**) by refluxing in alcohol containing two molar equivalents of hydrochloric acid. The products [(**15a**; R = Et) and (**15b**; R = Me)] were identical with samples prepared from 7a-cyanohexahydropyrrolizine according to the method described previously.[6,7] A mechanistic rationalization may involve the assumption that (**8**) or (**9**) is first converted into carbocation (**11**), which is in equilibrium with the carbocation (**13**) through the aziridinium ion (**12**). The carbocation (**13**) reacts with water and then eliminates an alcohol molecule [see (**14**)] to give rise to the final product (**15**) (see Scheme 2).

*Conformation of 5,9,9-Trisubstituted 1-Azabicyclo*[3.3.1]-*nonanes.*—For the 1-azabicyclo[3.3.1]nonane system three groups of conformational features [3] should be envisaged: (a) the rigid double-chair [CC], (b) the rigid boat-chairs [BC], and (c) the flexible double-boat [BB]* conformations as shown in Figure 1. $^{13}C$ N.m.r. data (90 MHz) of 5,9,9-trisubstituted 1-aza-

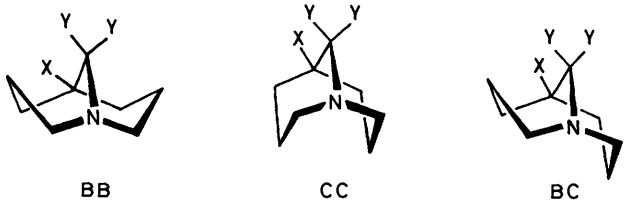



**Figure 1.**

* This eclipsed BB conformation is not an energy minimum, and corresponds to the transition state between the two twist-BB conformations (see, *e.g.*, J. A. Peters, J. M. A. Baas, B. van de Graaf, J. M. van der Toorn, and H. van Bekkum, *Tetrahedron*, 1978, **34**, 3313).

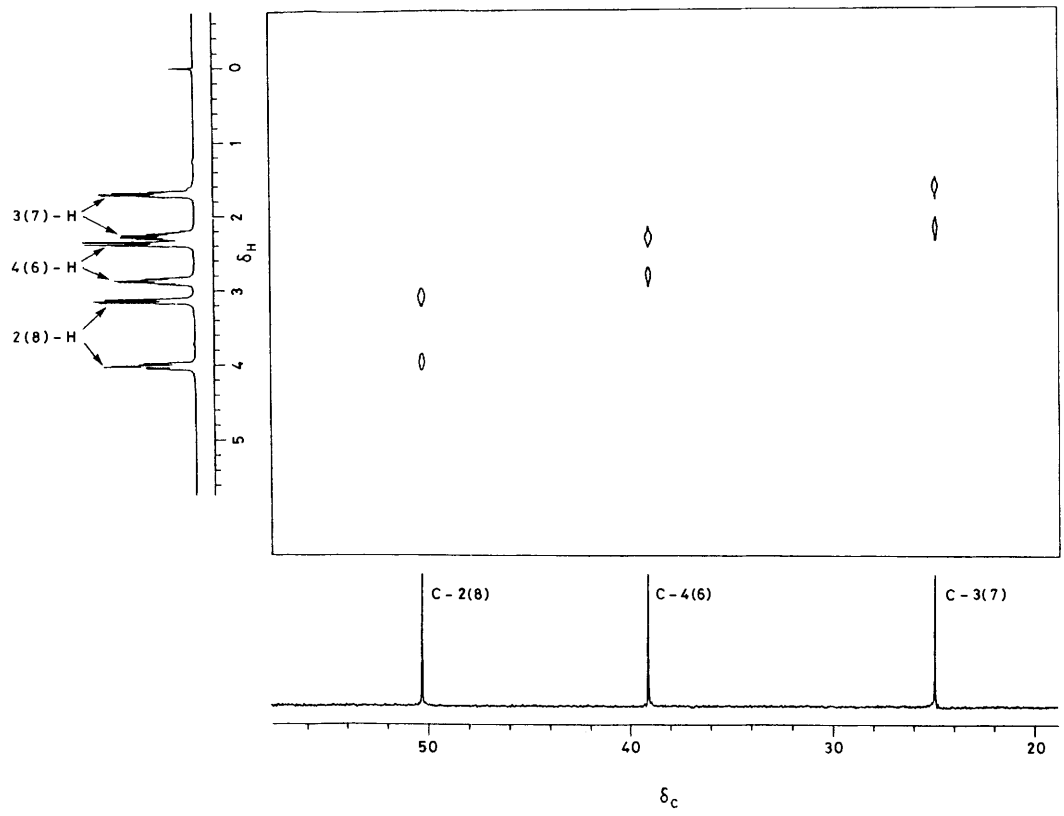



**Figure 2.** The $^1H$–$^{13}C$ heteronuclear shift-correlated 2D n.m.r. spectrum (contour plot) for 5,9,9-trichloro-1-azabicyclo[3.3.1]nonane (**3**)

**Table 2.** Vicinal coupling constants (Hz) in 5,9,9-trichloro-1-azabicyclo-[3.3.1]nonane (**3**)[a]

| | | | |
|---|---|---|---|
| $J_{2(8),3(7)}$ (β β) | 6.0 | $J_{3(7),4(6)}$ (β–β) | 7.0 |
| $J_{2(8),3(7)}$ (β–α) | 13.5 | $J_{3(7),4(6)}$ (β–α) | 1.0 |
| $J_{2(8),3(7)}$ (α β) | <1.0 | $J_{3(7),4(6)}$ (α–β) | 13.5 |
| $J_{2(8),3(7)}$ (α–α) | 7.0 | $J_{3(7),4(6)}$ (α–α) | 7.0 |

[a] Determined by decoupling method at 400 MHz in $CDCl_3$. Geminal coupling constants [$J_{2(8),2(8)}$, $J_{3(7),3(7)}$, and $J_{4(6),4(6)}$] and a long-range coupling constant [$J_{2(8),4(6)}$ (α–α)] were 14.0, 13.5, 14.0, and 1.5 Hz, respectively.

bicyclo[3.3.1]nonanes (**3**), (**5**), (**8**), (**9**), and (**10**), together with compound (**1**), are summarized in Table 1. The data clearly show that the unsymmetrical fixed BC conformation for these products should be excluded, because the chemical shifts of C-2, C-3, and C-4 coincide with those of C-8, C-7, and C-6 respectively. Such overlap of $^{13}C$ resonances for the ring carbons evidently shows a symmetrical molecular feature: *i.e.*, either a single fixed CC or BB conformation, or otherwise a time-averaged conformationally mobile BC ⇌ CB equilibria.

The magnitudes of vicinal coupling constants ($^1H$ n.m.r.) excluded the possibility of time-averaged, conformationally mobile BC ⇌ CB equilibria. Thus, for instance, the magnitudes of four vicinal coupling constants between C-2 (or C-8) and C-3 (or C-7) protons in compound (**3**) were 13.5, 7.0, 6.0, and <1.0 Hz respectively.* The vicinal *J*-values summarized in Table 2 obviously indicate that the compound exists in only one fixed conformation in solution.[8]

* In a conformationally mobile ring system, these values would be time-averaged to intermediate values.[8]

The $^1H$–$^{13}C$ heteronuclear and $^1H$–$^1H$ homonuclear shift-correlated two-dimensional (2D) n.m.r. spectra[9] of compound (**3**) are shown in Figures 2 and 3 respectively. These spectroscopic data, together with n.O.e. difference spectrum[9] of (**3**),† permit two types of assignment for $^1H$ resonances: *i.e.*, one is the assignment for CC conformation as shown in Figure 3 and the other possibility is a complete reversal ($H_\alpha \longrightarrow H_\beta$; $H_\beta \longrightarrow H_\alpha$) leading to the BB conformation.

Our final determination of the molecular conformation in solution was based on an *X*-ray examination combined with a solid-state $^{13}C$ n.m.r. spectroscopic study[10] of compound (**3**). In the solid-state $^{13}C$ n.m.r. spectrum, three peaks assignable to the ring carbons [C-2(8), C-3(7), and C-4(6)] were found to be virtually identical with those in solution (see Experimental section), providing a 'bridge' between crystal-structure information and solution data. The *X*-ray analysis[11,12] of compound (**3**) confirmed that it adopts the CC conformation‡ in the solid state as shown in Figure 4. The average values of dihedral angles for the ring protons (positioned in tetrahedral sites and then refined) in the crystal structure of compound (**3**) are shown in Table 3, the data in which are compatible with the assignment of $^1H$ resonances (1D) including *J*-values (Table 2).

† For example, irradiation of the proton ($\delta_H$ 1.69) and measurement of the n.O.e. difference spectrum[9] (400 MHz) easily confirmed that this proton has a larger n.O.e. effect on the ring protons with $\delta_H$ 4.01 and 2.87 than on those protons with $\delta_H$ 3.13 and 2.35. Thus, the set of three protons ($\delta_H$ 1.69, 2.87, and 4.01) and the set of the other protons ($\delta_H$ 2.25, 2.35, and 3.13) can apparently be distinguished by their relative spatial orientations ($H_\alpha$ and $H_\beta$).

‡ Although the term 'chair-chair (CC)' has been used in the text (where applicable to bicyclo[3.3.1]nonane ring systems[3,4]), the bond angles in the crystal structure are slightly removed from those of the classical chair form.

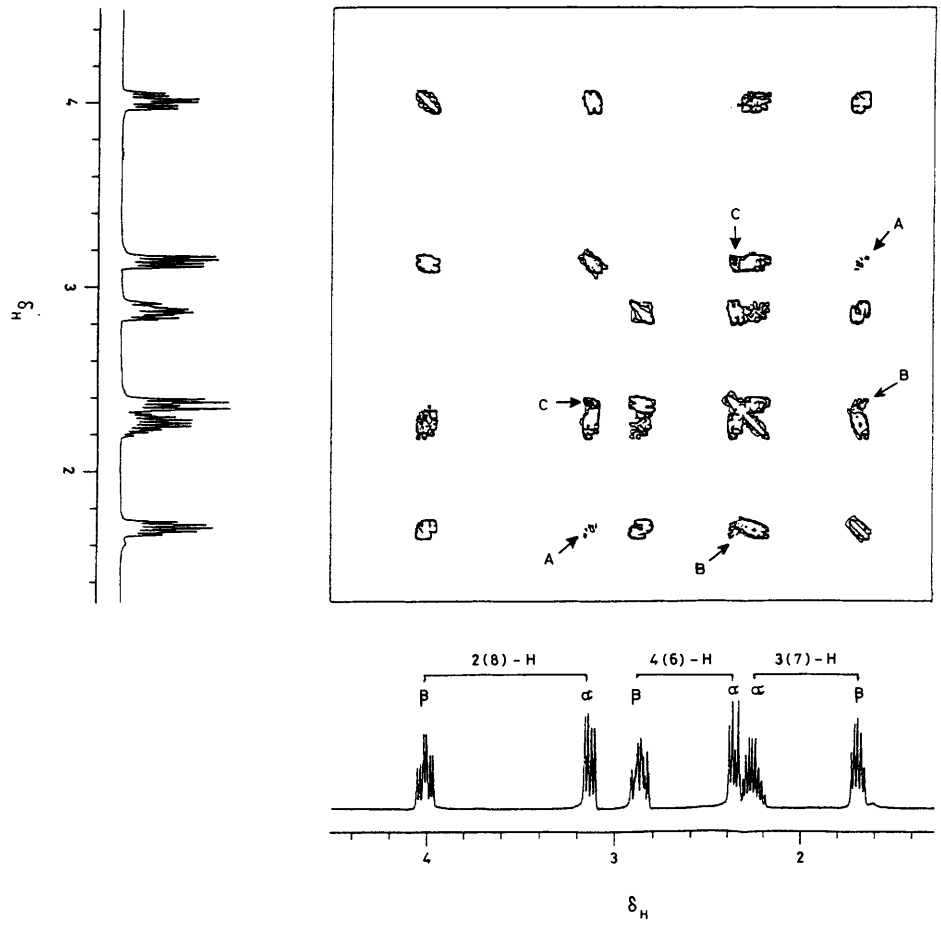



**Figure 3.** The $^1H$–$^1H$ shift-correlated 2D n.m.r. spectrum of 5,9,9-trichloro-1-azabicyclo[3.3.1]nonane (**3**)

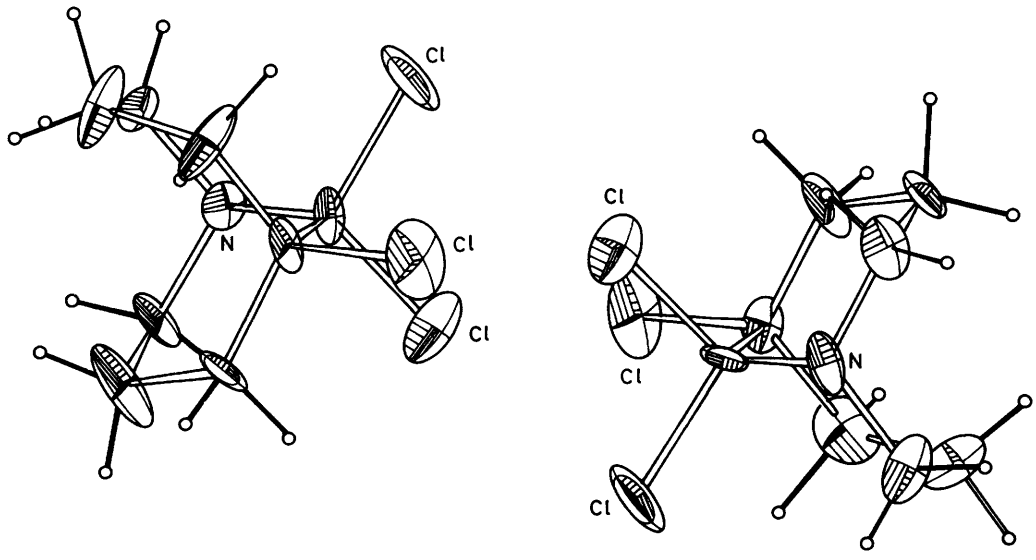



**Figure 4.** Perspective ORTEP drawing of 5,9,9-trichloro-1-azabicyclo[3.3.1]nonane in the unit cell

In the $^1H$–$^1H$ homonuclear shift-correlated 2D n.m.r. spectrum of compound (**3**) (Figure 3), the fact that two cross-peaks, **A** between **a** [$H_\alpha$ on C-2 (or C-8)] and **d** [$H_\beta$ on C-3 (or C-7)] and **B** between **d** [$H_\beta$ on C-3 (or C-7)] and **e** [$H_\alpha$ on C-4 (or C-6)], have quite weak intensities is well interpreted with the values of the corresponding dihedral angles (77° and 74°). In fact, the observed *J*-values between these protons were $< 1.0$ Hz and 1.0 Hz, respectively (Table 2). In addition, the significant

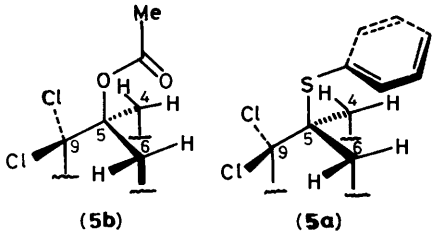
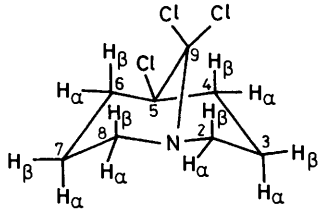



**Figure 5.**

**Table 3.** Averaged dihedral angles (°) of 5,9,9-trichloro-1-azabicyclo-[3.3.1]nonane




| | |
|---|---|
| $H_\beta$–C-2(8)–C-3(7)–$H_\beta$ | 40 |
| $H_\beta$–C-2(8)–C-3(7)–$H_\alpha$ | 146 |
| $H_\alpha$–C-2(8)–C-3(7)–$H_\beta$ | 77 |
| $H_\alpha$–C-2(8)–C-3(7)–$H_\alpha$ | 29 |
| $H_\beta$–C-4(6)–C-3(7)–$H_\beta$ | 42 |
| $H_\beta$–C-4(6)–C-3(7)–$H_\alpha$ | 152 |
| $H_\alpha$–C-4(6)–C-3(7)–$H_\beta$ | 74 |
| $H_\alpha$–C-4(6)–C-3(7)–$H_\alpha$ | 36 |

cross-peak **C** between **a** [$H_\alpha$ on C-2 (or C-8)] and **e** [$H_\alpha$ on C-4 (or C-6)] can be ascribed to the long-range coupling ($J$ 1.5 Hz) for 'W-configuration' arrangement of these protons in the CC conformation.

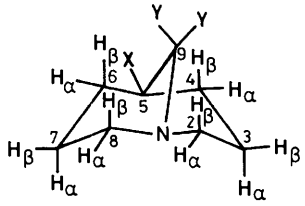
Similar splitting ($^1$H 1D n.m.r.) and correlation ($^1$H–$^1$H 2D n.m.r.) patterns were observed in all compounds and they were successfully resolved as those for the fixed CC conformation, the results of which are summarized in Table 4.

In the case of compounds (**9**) and (**10**), from the fact that no significant cross-peak between the protons **a** [$H_\alpha$ on C-2 (or C-8)] and **d** [$H_\beta$ on C-3 (and C-7)] could be observed, even at a low threshold level including noise, it is inferred that the dihedral angle $H_\alpha$–C-2(8)–C-3(7)–$H_\beta$ in such compounds is nearly 90° in solution. Concerning the chemical shifts of $H_\alpha$ (**e**) on C-4 (and C-6), compared with that of (**3**), compounds (**5a**) and (**5b**) showed shielding (0.40 p.p.m.) and deshielding (0.67 p.p.m.) respectively. The reason for this anomaly can be explained by considering two types of spatial orientation of C-5 substituents bisecting the C-4 (and C-6) protons in the CC conformation, as shown in Figure 5.* Such spatial orientations of these planar functional groups (phenyl and carbonyl) would be expected to cause anisotropic effects especially to the two $H_\alpha$ protons on C-4 (and C-6) which are favourably situated in the space exerting the shielding (**5a**) and deshielding effect (**5b**), respectively.

Regarding the unsubstituted 1-azabicyclo[3.3.1] nonane (**1**), the predominant contribution of the CC conformation is readily

* Taking into account the steric interactions between the substituents and ring components, molecular model studies bear out these molecular features as being the most favourable ones.

**Table 4.** $^1$H–$^1$H Shift-correlated 2D n.m.r. results and chemical shifts ($\delta_H$)[a,b]




| | C-2 (and C-8) | | C-3 (and C-7) | | C-4 (and C-6) | | |
|---|---|---|---|---|---|---|---|
| Compound | $H_\alpha$(**a**) | $H_\beta$(**b**) | $H_\alpha$(**c**) | $H_\beta$(**d**) | $H_\alpha$(**e**) | $H_\beta$(**f**) | Other ring protons |
| (**3**) | b,c,d,e | a,c,d | a,b,d,e,f | a,b,c,e,f | a,c,d,f | c,d,e | |
| | (3.13) | (4.01) | (2.25) | (1.69) | (2.35) | (2.87) | |
| (**5a**) | b,c,d,e, | a,c,d | a,b,d,e,f | a.b.c.e.f | a,c,d,f | c,d,e | |
| | (3.10) | (3.99) | (2.08) | (1.57) | (1.95) | (2.56) | |
| (**5b**) | b,c,d,e | a,c,d | a,b,d,e,f | a,b,c,e,f | a,c,d,f | c.d.e | |
| | (3.11) | (3.97) | (2.19) | (1.67) | (3.02) | (2.38) | |
| (**8**) | b,c,d,e | a,c,d | a,b,d,e,f | a,b,c,e,f | a,c,d,f | c,d,e | |
| | (2.80) | (3.33) | (1.97) | (1.43) | (1.77) | (2.31) | |
| (**9**) | b,c,e | a,c,d | a,b,d,e,f | b,c,e,f | a,c,d,f | c,d,e | |
| | (2.80) | (3.29) | (1.92) | (1.42) | (1.76) | (2.36) | |
| (**10**) | b,c,e | a,c,d | a,b,d,e,f | b,c,e,f | a,c,d,f | c,d,e | |
| | (2.77) | (3.33) | (2.05) | (1.59) | (1.81) | (2.18) | |
| (1) | b,c,d,e,h | a,c,d | a,b,d,e,f | a,b,c,e,f | a,c,d,f,g,h | c,d,e,g | e,f,h |
| | (3.08) | (3.15) | (2.04) | (1.49) | (1.86) | (1.90) | (1.62) [H on C-5(**g**)] a,e,g (2.93) [H on C-9(**h**)] |

[a] Determined with Hitachi GX-400 (400 MHz) in $CDCl_3$ with TMS as internal standard at 25 °C. The correlation of two methylene protons to the corresponding ring carbon was established from the $^1$H–$^{13}$C 2D n.m.r. spectrum of the product. [b] Other protons on substituents were observed: $\delta_H$ 7.26—7.61 (5 H, m, Ph) (**5a**); 2.07 (3 H, s, Me) (**5b**); 1.25 (6 H, t, $J$ 7.0 Hz, Me × 2), 3.79—4.00 (4 H, m, $OCH_2$ × 2), and 7.25—7.62 (5 H, m, Ph) (**8**); 3.55 (6 H, s, Me × 2) and 7.27—7.58 (5 H, m, Ph) (**9**); 1.10 (3 H, t $J$ 7.5 Hz, Me), 1.21 (6 H, t, $J$ 7.5 Hz, Me × 2), 3.63 (2 H, q, $J$ 7.5 Hz, $OCH_2$), and 3.68—3.81 (4 H, m, $OCH_2$ × 2) (**10**).

revealed only from the data of the $^1H$–$^1H$ homonuclear shift correlated 2D n.m.r. spectrum shown in Table 4. Thus, proton **e** [$H_\alpha$ on C-4 (and C-6)] showed two characteristic cross-peaks, which are obviously due to the 'W-configuration' long-range couplings with the proton **a** [$H_\alpha$ on C-2 (and C-8)] and a proton (**h**) on C-9 respectively. A molecular model examination easily confirms that such a configuration is acceptable only when the molecule acquires the CC conformation.* The protonation-induced $^{13}C$ shift ($\Delta\delta$)[13] of the C-3 (and C-7) carbons of compound (**1**) also supported the CC conformation.†

It is recognized that the conformational preference of bicyclo-[3.3.1]nonanes[4] and their 1-aza analogues[3] depends on the steric requirement of substituents on the ring carbons. So far, it is well documented that the introduction of two bulky α-substituents at C-3 and C-7 in such ring systems shifts the equilibrium toward the BB conformation. From our conformational analysis described in this paper, we consider that two bulky substituents introduced on C-9 may force the ring concerned into the CC conformation.

## Experimental

M.p.s were determined with a Yanaco micro-melting point apparatus, and uncorrected. I.r. spectra were obtained on a Hitachi 250 spectrometer. $^1H$ and $^{13}C$ N.m.r. spectra were recorded on a Hitachi R-90H instrument (90 MHz), with tetramethylsilane as internal standard.

The $^1H$–$^1H$ shift-correlated 2D n.m.r. data were obtained with a JEOL GX-400 spectrometer with 5 mm probe, and tetramethylsilane as internal standard at 25 °C in $CDCl_3$, and equipped with a G MHD 80R(JEOL) computer system. 2D Experiments were controlled by, and the data processed with, the standard VCOSYN ($^1H$–$^1H$ homonuclear shift-correlation spectra) and VCHSHF ($^1H$–$^{13}C$ heteronuclear shift-correlation spectra) software packages of a PLEXUS (JEOL) data system. Time-domain matrices $S(t1,t2)$ of 512 × 1 024 points ($^1H$–$^1H$ shift-correlation) and 256 × 2 048 points ($^1H$–$^{13}C$ shift-correlation) were used, with spectral widths in the $f1$ and $f2$ domains of 3 750 and 3 750 Hz ($^1H$–$^1H$ shift-correlation) and 2 500 and 10 000 Hz ($^1H$–$^{13}C$ shift-correlation) respectively. Figures 2 and 3 show the results for the compound (**3**). The $^1H$–$^1H$ 2D n.m.r. data are summarized in Table 4.

The $^{13}C$ CPMAS (cross-polarization and magic-angle spinning) solid-state n.m.r. spectrum of compound (**3**) was obtained at 25.0 MHz on a JNM-FX100 NM-SH100 (CPMAS unit) with magic-angle spinning at a rate of 3.5 kHz. The $^{13}C$ chemical shifts were referenced with respect to internal Si gum, which has a shift of 1.57 p.p.m. with respect to tetramethylsilane. The chemical shifts for C-2(8), C-3(7), and C-4(6) were 50.8, 24.9, and 40.1 p.p.m., respectively. The chemical shifts for C-5 and C-9 could not be determined, because these signals were substantially broadened by the chlorine substituent having a large quadrupole coupling constant.[14]

High-resolution mass spectra were obtained with a JEOL JMS-DX300 instrument.

1-Azabicyclo[3.3.1]nonane (**1**), 2,3,5,6,7,7a-hexhydro-7a-trichloromethylpyrrolizine (**2**), and 5,9,9-trichloro-1-azabicyclo-[3.3.1]nonane (**3**) were prepared by the method described previously.[5]

9,9-*Dichloro*-5-*phenylthio*-1-*azabicyclo*[3.3.1]*nonane* (**5a**).—A solution of compound (**2**) (10.00 g, 44 mmol), thiophenol (5.817 g, 52.8 mmol), and potassium t-butoxide (5.925 g, 52.8 mmol) in pyridine (50 ml) was stirred and refluxed for 19 h, after which the solvent was evaporated off under reduced pressure and the residue was dissolved in chloroform (350 ml). The solution was washed with saturated brine, dried over anhydrous magnesium sulphate, and evaporated to give a solid residue. This was chromatographed on a silica gel column with diethyl ether as eluant to give the *product* (**5a**) (8.526 g, 64%) as crystals, m.p. 100—105 °C (from ethanol), *m/z* 301.045 76 ($M^+$, $C_{14}H_{17}Cl_2NS$). The n.m.r. data of this compound are shown in Tables 1 and 4 (Found: C, 55.8; H, 5.8; N, 4.7. $C_{14}H_{17}Cl_2NS$ requires C, 55.63; H, 5.67; N, 4.63%). Similar treatment of compound (**3**) also gave (**5a**), in 60% yield.

5-*Acetoxy*-9,9-*dichloro*-1-*azabicyclo*[3.3.1]*nonane* (**5b**).—A mixture of compound (**2**) (1.00 g, 4.4 mmol) and sodium acetate (3.59 g, 44 mmol) in pyridine (20 ml) was stirred and refluxed for 23 h. After removal of the solvent under reduced pressure, the residue was chromatographed on a column [Lobar Fertigsäule Größe B (310-25) Lichroprep Si60 (40—63 μm)] with chloroform as eluant to give *compound* (**5b**) (166 mg, 16%) as crystals, m.p. 136—136.5 °C and compound (**3**) (162 mg, 15%). The n.m.r. data of the product (**5b**) are shown in Tables 1 and 4 (Found: C, 47.5; H, 6.2; N, 5.5. $C_{10}H_{15}Cl_2NO_2$ requires C, 47.63; H, 6.00; N, 5.56%).

When the above reaction was carried out in ethanol (refluxing for 17 h), three products (**3**), (**5b**), and (**10**) were isolated in 1, 4, and 10% yield respectively.

9,9-*Diethoxy*-5-*phenylthio*-1-*azabicyclo*[3.3.1]*nonane* (**8**).—To a solution of compound (**5a**) (4.366 g, 14.5 mmol) in absolute ethanol (230 ml) was added sodium ethoxide (2.170 g, 30.9 mmol). The mixture was refluxed for 16 h under nitrogen. After evaporation of the solvent under reduced pressure, the residue was treated with chloroform (300 ml). The resulting solution was washed successively with water and saturated brine, and then dried over anhydrous magnesium sulphate. After evaporation of the solvent under reduced pressure, the residue was purified on a silica gel column with chloroform as eluant to give the product (**8**) (2.908 g, 65%). Recrystallization from ethanol gave *crystals*, which were sublimed at 91—99 °C; *m/z* 321.176 79 ($M^+$, $C_{18}H_{27}NO_2S$). The n.m.r. data are shown in Tables 1 and 4 (Found: C, 67.2; H, 8.2; N, 4.3. $C_{18}H_{27}NO_2S$ requires C, 67.25; H, 8.47; N, 4.36%).

9,9-*Dimethoxy*-5-*phenylthio*-1-*azabicyclo*[3.3.1]*nonane* (**9**).—A mixture of compound (**5a**) (2.00 g, 6.6 mmol) and sodium methoxide (0.788 g, 14.6 mmol) in absolute methanol (50 ml) was refluxed for 19 h under nitrogen. The precipitate which separated on cooling was filtered off, the solvent was removed under reduced pressure, and the residual mass was recrystallised from ethanol to afford *compound* (**9**) (1.702 g, 88%) as crystals, m.p. 122—123 °C, *m/z* 293.146 38 ($M^+$, $C_{16}H_{23}NO_2S$). The n.m.r. data are shown in Tables 1 and 4 (Found: C, 65.3; H, 8.15; N, 5.0. $C_{16}H_{23}NO_2S$ requires C, 65.49; H, 7.90; N, 4.77%).

5,9,9-*Triethoxy*-1-*azabicyclo*[3.3.1]*nonane* (**10**).—A mixture of compound (**3**) (1.00 g, 4.4 mmol) and sodium ethoxide (0.95 g, 14 mmol) in absolute ethanol (150 ml) was refluxed for 16.5 h. After removal of the solvent, the residue was treated with chloroform (200 ml), and the resulting solution was washed with saturated brine and dried over anhydrous magnesium sulphate. After evaporation of the solvent, the residue was chromatographed on a silica gel column [Lobar Fertigsäule Größe B(310-25) Lichroprep Si 60 (40—63 μm)] to afford the *product* (**10**) (202 mg, 18%) as a pale yellow oil, *m/z* 257.198 57 ($M^+$,

* In the BB conformation, molecular model examination reveals that such long-range couplings from the protons **a** and **h** would occur to protons $H_\beta$(**f**) and $H_\alpha$(**e**) on C-4 and C-6, respectively.

† The $\Delta\delta$ [$\Delta\delta = \delta_C(CDCl_3 + CF_3CO_2H) - \delta_C(CDCl_3)$] value was appreciably larger (+3.7 p.p.m.). If compound (**1**) had the BB conformation, a small $\Delta\delta$ value would be expected because the dihedral angle of H–$N^+$–C2(8)–C3(7) in such a conformation is nearly 120° (molecular model examination) (see ref. 13).

$C_{14}H_{27}NO_3$). The n.m.r. data are shown in Tables 1 and 4 (Found: C, 65.6; H, 10.7; N, 5.1. $C_{14}H_{27}NO_3$ requires C, 65.33; H, 10.57; N, 5.44%).

*Ethyl* 2,3,5,6,7,7a-*Hexahydropyrrolizine*-7a-*carboxylate* (**15a**).—A mixture of compound (**8**) (1.00 g, 3.1 mmol) and 1M-HCl (6 ml) in ethanol (40 ml) was refluxed for 2.5 h. After evaporation of the solvent, the residue was treated with saturated aqueous sodium carbonate, then extracted with chloroform (300 ml), and the extract washed with saturated brine and dried over anhydrous magnesium sulphate. After removal of the solvent, the residue was chromatographed on a silica gel column with chloroform–methanol (80:1) as eluant to give compound (**15a**) (209 mg, 37%) as an oil, *m/z* 183.126 74 ($M^+$, $C_{10}H_{17}NO_2$). This compound was identical with an authentic sample.[6,7]

*Methyl* 2,3,5,6,7,7a-*Hexahydropyrrolizine*-7a-*carboxylate* (**15b**).—By a similar procedure to that described above, compound (**15b**) (118 mg, 41%), *m/z* 169.109 06 ($M^+$, $C_9H_{15}NO_2$), was obtained as an oil from the reaction of compound (**9**) (500 mg) in methanol (50 ml) in the presence of 1M-HCl (3.4 ml). The $^1H$ and $^{13}C$ n.m.r. data were identical with those of an authentic sample prepared from 2,3,5,6,7,7a-hexahydropyrrolizine-7a-carbonitrile according to the previous method.[6,7]

*Crystal Data for Compound* (**3**).—Compound (**3**), $C_8H_{12}Cl_3N$, crystallizes from ethanol in the monoclinic space group $P2_1$; $a = 7.315(2)$, $b = 21.401(7)$, $c = 6.949(2)$ Å; $\beta = 116.73(2)$, $D_c = 1.56$ g cm$^{-3}$; $Z = 4$. The structure was solved by direct methods (MULTAN84)[11] using 2 045 independent reflections. An *E* map revealed all chemically reasonable positions among 24 non-hydrogen atoms; refinement on *F* was by successive Fourier synthesis and block-diagonal least-squares; H-atoms were positioned in tetrahedral sites, then refined by block-diagonal least-squares; anisotropic temperature factors were used for non-hydrogen atoms, and isotropic ones for H atoms; the final cycle of least-squares analysis gave *R* 0.043. Both crystallographically independent molecules observed in the unit cell had the CC conformation. A perspective ORTEP drawing of the crystallographic structure in the unit cell is shown in Figure 4. The atomic co-ordinates for this work will be published.[12] The averaged values for dihedral angles obtained from this *X*-ray study are summarized in Table 3.*

* Full details of the crystallographic analysis have been published.[12]

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