Bis-aziridinomethanes: synthesis, structure and properties

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Bis-aziridinomethanes were prepared by the reaction of $Me_2NCH(OMe)_2$ with aziridines and characterised by X-ray diffraction analysis and NMR spectroscopy.

The incorporation of a nitrogen atom into a three-membered ring excludes (a) the α-aminoalkylation reaction[1] and (b) amide conjugation.[2] These basic rules result from decreasing the *p*-character of the nitrogen lone pair (lp) and hence its electron-donating properties.[1(*e*)–(*f*),2(*a*),(*d*),(*e*),(*g*)–(*i*),3] Limitations (a) and (b) are most pronounced in the chemistry of bis-aziridinomethanes (BAMs). These compounds cannot be prepared by typical syntheses of usual aminales,[4] such as reactions of aziridine with aldehydes, as well as 1-aziridinocarbinol or 1-alkoxymethylaziridines.[1] Bis-aziridinomethoxymethane also does not react with aziridine even under severe conditions[1(*e*)] [limitation (a)].

In accordance with limitation (b), the first BAMs were obtained by a mild addition of aziridine to activated acetylenes (bis-adducts **A**),[5] whereas usual amines give only mono-adducts, which are amide vinylogs with deactivated double bonds. The simplest BAM **B**,[6(*a*)] as well as aziridinoform **C**[6(*b*)–(*d*)] and derivatives **D**,[6(*e*)] was synthesised by the alkylation of aziridine under the action of CH_2Cl_2, $CHCl_3$ and a corresponding *gem*-dichloroalkane either in the presence of bases[6(*c*)–(*e*)] or through potassium ethyleneamide.[6(*a*),(*b*)] The first and second steps of alkylation are determined by the presence of the easier leaving group Cl^- (as compared with X^- = OH, OR). In addition, the synthesis of diazaquadricyclane **E** containing a BAM fragment was reported.[7] Finally, it was found that 5,5-dimethoxytetrachlorocyclopenta-1,3-diene reacts with aziridine under mild conditions with formation of BAM **F**.[8] This reaction results from the allylic activation of MeO groups at both steps of the reaction.

The reaction of 2-cyanoaziridine with ketones[9] (Scheme 1) is inconsistent with rule (a). There are contradictory data[9] on the structure of the products which possess a high biological activity; they were described as bis-cyanoaziridinoalkanes.[9(*c*)] The structure of **1** was strictly confirmed; however, data on the relative configuration are ambiguous. It can be suggested that the key intermediates in the synthesis of **1** are the structures $\mathbf{I}_1$ and $\mathbf{I}_2$. The latter is a product of the transformation of $\mathbf{I}_1$ by Pinner reaction. The aziridinomethylating action of $\mathbf{I}_2$ is determined by the presence of the easily leaving iminoyloxy group as in the case of the above intermediate 1-chloromethylaziridines. The Chapman rearrangement of $\mathbf{I}_2$ into a corresponding lactam,[9(*b*)] as well as the transformation of the adduct of 2-cyanoaziridine ($\mathbf{I}_2$-type) with substituted cyclohexanone into compound **G** by intramolecular aziridinomethylation at the OH group, is well known.[11]

On the basis of the above analysis, we proposed a new efficient way for the preparation of BAM **2**. It consists in the dimethylaminomethylenation of aziridine with dimethylformamide dimethylacetal (Scheme 1).† This reaction is a result of strong electron donation of Me_2N, which increases the mobility of MeO groups (like allyl activation of MeO groups in the synthesis of BAM **F**). A special feature of the NMR spectra of **2** is that all protons and carbons of the aziridine ring are non-equivalent† [*cf.* ref. 1(*e*)].

BAM **1** was extensively studied as a biologically active compound[10] for examining the nitrogen inversion and dynamic effects in BAMs, as well as for determining the relative configuration. Compound **1** was found to crystallise in two modifications, with mp 157.5 (from acetone) and 172.5 °C (from MeOH–Et_2O), both having identical NMR spectra, which correspond to one diastereomer. Thus, BAM **1** is formed diastereoselectively. In the ^{1}H NMR spectrum in an aprotic solvent ($CDCl_3$, 18 °C), a considerable broadening of the upfield signal from the A-Me group and signals from all aziridine ring protons (particularly, H_a, H_b and $H_{a'}$) are observed. In contrast, at 60 °C, the broadening disappeared and the signals due to amide protons H_a, H_s shifted upfield (0.1 and 0.3 ppm). This temperature dependence of the spectrum points to the presence of hindered rotation, nitrogen inversion in the 2-cyanoaziridine moiety, as well as an intramolecular H-bond in the 2-carbamoylaziridine fragment of **1**.

The monocrystals suitable for an X-ray study‡ were grown only from the higher melting modification of **1** (not described earlier). According to the X-ray analysis, compound **1** is crystallised as a racemate (space group $P\bar{1}$), and asymmetric centres in **1** [C(2) and C(7)] have identical configurations in contrast to published data[9(*a*)] [Figure 1(*a*).]

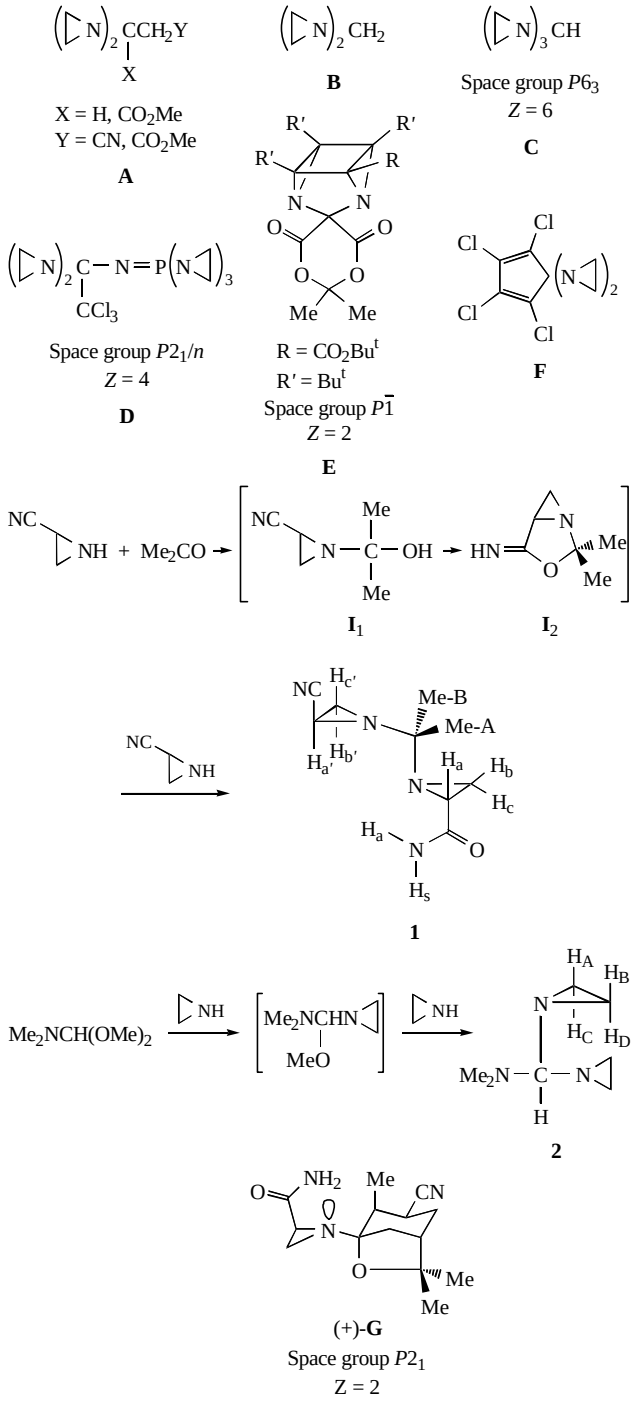
In the crystal of **1**, shortened contacts are observed. Namely, H···H contacts (2.16 and 2.22 Å) formed by the methyl group $H_3C(5)$ with H(7) and H(8B) atoms, and H(2)···N(3) (2.38 Å)

† *Characteristics and spectroscopic data*. ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.61 MHz, respectively.

1:[9(*b*)] mp 172.5 °C (MeOH–Et_2O) and 157.5 °C (acetone) [*cf.* refs. 9(*a*),(*b*)]. ^{1}H NMR ($CDCl_3$ at 50 °C) δ: 1.11 (br. s, 3H, A-Me), 1.19 (s, 3H, B-Me), 1.80 (dd, 1H, H_C, $^3J^{trans}$ 2.9 Hz, $^2J^{gem}$ 1.2 Hz), 2.06 (dd, 1H, H_B, $^3J^{cis}$ 6.8 Hz, $^2J^{gem}$ 1.2 Hz), 2.11 (dd, 1H, $H_{C'}$, $^3J^{cis}$ 2.9 Hz, $^2J^{gem}$ 1.3 Hz), 2.15 (dd, 1H, $H_{B'}$, $^3J^{cis}$ 6.3 Hz, $^2J^{gem}$ 1.3 Hz), 2.40 (ddd, 1H, H_A, $^3J^{cis}$ 6.8 Hz, $^3J^{trans}$ 2.9 Hz, $^4J_{As}$ 0.9 Hz), 2.52 (dd, $H_{A'}$, $^3J^{cis}$ 6.8 Hz, $^3J^{trans}$ 2.9 Hz), 5.32 (br. s, 1H, H_s), 6.08 (br. s, 1H, H_a).

2: A mixture of aziridine and dimethylformamide dimethylacetal in a molar ratio of 2:1 was kept at 20 °C for 10–12 h, evaporated and distilled over sodium metal *in vacuo*, bp 36.5–37 °C (1 torr), yield 65–75%. ^{1}H NMR (C_6D_6) δ: 1.10, 1.19, 1.47 and 1.64 (m, 8H, ring protons, ABCD spectrum, $\Delta\nu_{AB}$ 43.0 Hz, ν_{CD} 35.5 Hz, $^3J^{cis}_{AB}$ 5.4 Hz, $^3J^{cis}_{CD}$ 7.1 Hz, $^3J^{trans}_{AD} = {}^3J^{trans}_{BC}$ = 3.8 Hz, $^2J^{gem}_{AC} = {}^2J^{gem}_{BD}$ = 0.7 Hz), 1.77 (s, 1H, HC), 2.55 (s, 6H, Me_2N). ^{13}C NMR (C_6D_6) δ: 22.0 (ddm) and 24.6 (ddm) (ring carbons, ^1J 165.0 Hz, ^1J 175.0 Hz), 39.9 (qq, MeN, ^1J 133.3 Hz, ^3J 4.0 Hz), 105.2 (dm, CH, ^1J 153.0 Hz).

‡ *Crystallographic data for* **1**: at 293 K, crystals of $C_9H_{14}N_4O$ are triclinic, space group $P\bar{1}$, a = 6.309(2) Å, b = 6.791(2) Å, c = 13.082(2) Å, α = 75.27(2)°, β = 89.20(2)°, γ = 83.34(2)°, V = 538.3(2) Å^3, Z = 2, d = = 1.198 g cm^{-3}, μ = 0.83 cm^{-1}, $F(000)$ = 208. Intensities of 3384 reflections were measured with an Enraf Nonius CAD-4 diffractometer at 293 K [λ(MoKα) = 0.710712 Å, graphite monochromator, $\theta/2\theta$-scans, $2\theta < 60°$], and 3117 independent reflections (R_{int} = 0.0290) were used in a further refinement. The structure was solved by the direct method and refined by full-matrix least squares against F^2 in the anisotropic approximation for non-hydrogen atoms. All the hydrogen atoms were located from the electron density difference synthesis and included in the refinement in an isotropic approximation. The refinement converged to wR_2 = 0.1316 and GOF = 1.008 for all independent reflection [R_1 = = 0.0433 was calculated against F for 2300 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0 program. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/92.



Scheme 1

[Figure 1(a)]. Note that these protons exhibited the most broadened signals in the ^{1}H NMR spectrum [A-Me, H_a, H_b, $H_{a'}$ (Scheme 1)]. In the crystal of **1**, molecules take part in the formation of intermolecular hydrogen bonds. Being bonded by the inversion centre in the crystal, the molecules of **1** form dimers due to the amide H-bonds. These dimers are combined into chains directed along the axis *c* by the H-bonds involving the nitrile group CN···H–N [Figure 1(*b*)].

The mutual arrangements of aziridine rings in relation to the fragment $Me_2C(4)$ are different. The angles between the ring planes N(2)C(2)C(3) and N(3)C(7)C(8) relative to the plane C(5)C(4)C(6) are 4.3 and 67.4°, respectively. Evidently, the above shortened contacts are responsible for increasing the angle N(3)C(4)C(5) up to 115.7(1)° [the other CCN angles at C(4) are in a range of 105.6–106.2°], as well as for flattening the N(3) atom as compared with N(2) (the sums of bond angles are 301.4 and 297.6°, respectively).

The observed steric hindrance in **1** is probably caused by the stabilization of a conformation with the antiperiplanar orientation of lp of the N(2) atom in relation to the C(4)–N(3) bond [pseudotorsion angle lp–N(2)–C(4)–N(3) is 173°], *i.e.*, by the anomeric effect $n_{N(2)} \rightarrow \sigma^*_{C(4)N(3)}$. The pseudotorsion angle lp-N(3)–C(4)–N(2) is equal to 45°; this excludes its participation in the anomeric interaction with the C(4)–N(2) bond. The simultaneous antiperiplanar orientations of lp-N(2) and lp-N(3) in relation to the corresponding CN bonds are sterically hindered and result in more shortened contacts H···H.

In spite of anomeric interaction, the C(4)–N(2) and C(4)–N(3) bond lengths are practically the same. Such a situation is typical of aziridines[1(*g*),6(*d*)] and it is in agreement with recent high level calculations.[12] The best indicator of anomeric effects is the NCN angles, which are quite close to each other in **1** [110.6(1)°] and $CH_2(NH_2)_2$ (113°).[12]

It should be noted that anomeric effects in aziridines were confirmed by theoretical and experimental investigations in gas, liquid and solid states. For tris-aziridinomethane, the calculated and experimental (GED) lp-NCN, NCN angles are 166.3°, 112.6° and 172.6°, 114°, respectively.[6(*d*)] For 1-methoxymethylaziridine, the lp-NCO, NCO angles are 174.2°, 113.2° and 161°, 113.4°, respectively.[1(*g*)] In the latter case, the anomeric effect reveals itself in a considerable decrease in the nitrogen inversion barrier due to stabilization of the planar transition state.[1(*g*)] It can be demonstrated by comparing 1-dimethylaminomethylaziridine and its 2,2-dimethyl analogue.[13] The transformation of the former compound into methyl iodide leads to a great decrease in the nitrogen inversion barrier (by 3.5 kcal mol^{-1}) due to the anomeric effect $n(N) \rightarrow \sigma^*(C–N^+)$, whereas upon a similar transformation of the latter compound the inversion barrier remained unchanged due to steric hindrances for the anomeric effect. Finally, according to an X-ray database, the anomeric effect is also observed in 1-alkoxyaziridine (+)-**G**[11] where it is strengthened by steric strain which is favourable to lengthening the C–O bond [bond lengths: N(1)–C(3) 1.418 Å, C(3)–O(1) 1.458 Å; bond angles: lp-N(1)–C(3)–O(1) 178°, N(1)–C(3)–O(1) 112°].

Apparently, the properties of (+)-**G** and its precursor, an intermediate of the $\mathbf{I}_2$ type, are responsible for the enantioselectivity of 2-cyanoaziridine hydration catalysed by a chiral substituted cyclohexanone (ee > 99%).[11]

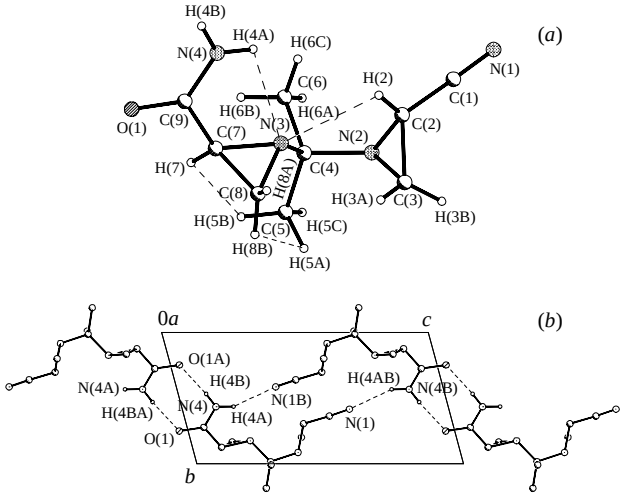


Figure 1 (*a*) The general view of **1**. Selected bond lengths (Å): C(1)–N(1) 1.140(2), C(1)–C(2) 1.442(2), N(2)–C(3) 1.446(2), N(2)–C(2) 1.459(2), N(2)–C(4) 1.479(1), C(2)–C(3) 1.483(2), N(3)–C(7) 1.454(1), N(3)–C(8) 1.463(2), N(3)–C(4) 1.473(1), N(4)–C(9) 1.318(2); selected bond angles (°): N(3)–C(4)–N(2) 110.6(1), N(3)–C(4)–C(5) 115.7(1), N(2)–C(4)–C(5) 105.6(1), N(3)–C(4)–C(6) 106.1(1), N(2)–C(4)–C(6) 106.0(1), C(5)–C(4)–C(6) 112.5(1). The parameters of intramolecular H-bonds: N(3)···H(2) 2.38 Å, N(3)···C(2) 2.752(1) Å, C(2)–H(2)–N(3) 99°, N(3)–H(4A) 2.40 Å, N(3)···N(4) 2.800(1) Å, N(4)–H(4A)–N(3) 109°. (*b*) The formation of H-bonded chains directed along crystallographic axis *c*. The parameters of H-bonds: O(1)···H(4B) 2.04 Å, N(4)···O(1) 2.908(2) Å, O(1)–H(4B)–N(4) 172(2)°; N(1)···H(4A) 2.52 Å, N(1)···N(4) 3.268(2) Å, N(1)–H(4A)–N(4) 146(1)°.

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