Structure of products of the reaction of 2-cyanoaziridine with carbonyl compounds

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The structure of azimexone (**3**), the product of the reaction of 2-cyanoaziridine with acetone, was confirmed on the basis of ^1H and ^{13}C NMR spectra. The formation of this product is accounted for by the α-aziridinoalkylating action of an intermediate containing a good leaving iminoyloxy group. Similar reactions were observed for 1-chloromethylaziridine and a 1-aziridinylmethylammonium salt (**6**), but not for 1-methoxymethylaziridine (**7**) and 1-aziridinemethanol.

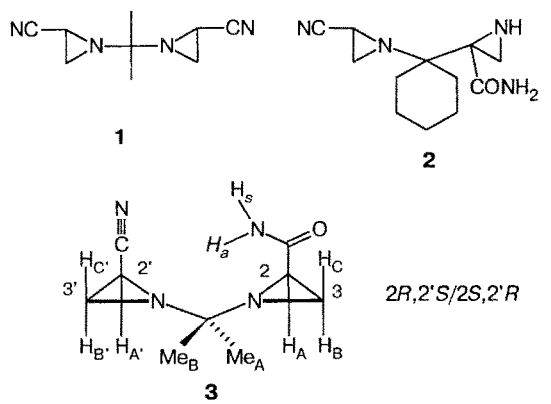
Key words: 2-(2-cyanoaziridino)-2-(2-carbamoylaziridino)propane; 1-*tert*-butyl-2-carbamoylaziridine; α-1-aziridinoalkylation; ^1H and ^{13}C NMR spectra.

The products of the reaction of 2-cyanoaziridine with carbonyl compounds, specifically with acetone (azimexone), are of great interest and are being studied intensely in view of their immunostimulating, antitumor, and radioprotective activity, azimexone being an antidote against sulfur[1] and nitrogen mustard (cyclophosphamide, *etc.*).[2—4]

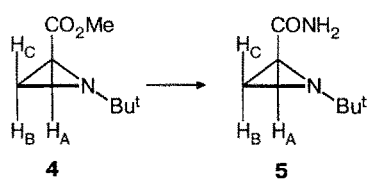
However, unambiguous data on the structure of these products are still lacking. For instance, earlier structure **1** was postulated[5]. Structure **2** was suggested for the adduct of 2-cyanoaziridine with cyclohexanone[6] on the basis of the fact that the $^1J_{CH}$ coupling constant for one carbon atom of the 2-carbamoylaziridine moiety was absent in the ^{13}C NMR spectrum. The type **3** structure was assigned[7] to this adduct, as well as to azimexone, since 2-cyano- and 2-carbamoylaziridines are formed on hydrolysis. However, the experimental procedures were not described, the ^1H NMR spectra for the products recorded at 60 MHz are not informative, while the ^{13}C NMR spectra were totally proton decoupled, *i.e.*, these spectra were not in conflict with the conclusions presented in Ref. 6.

On the basis of ^1H (Table 1) and ^{13}C NMR spectra, we unambiguously confirmed structure **3** for azimexone prepared by the procedure reported in Ref. 7. Compound **3** was isolated as described previously[6,7] as one diastereomer. The signals for the atoms of the cycles in the ^1H and ^{13}C NMR spectra were assigned by comparing them with the spectra of model compounds, namely, 1-*tert*-butyl-2-carbamoylaziridine **5**, prepared by ammonolysis of ester **4** (Scheme 1),[8,9] 1-isopropyl- and 1-*tert*-butyl-2-cyanoaziridines,[10] as well as with the use of double homonuclear and selective heteronuclear resonance.

Thus, when $H_{A'}$ was decoupled, the multiplet signals $H_{B'}$ and $H_{C'}$ were transformed into doublets



Scheme 1



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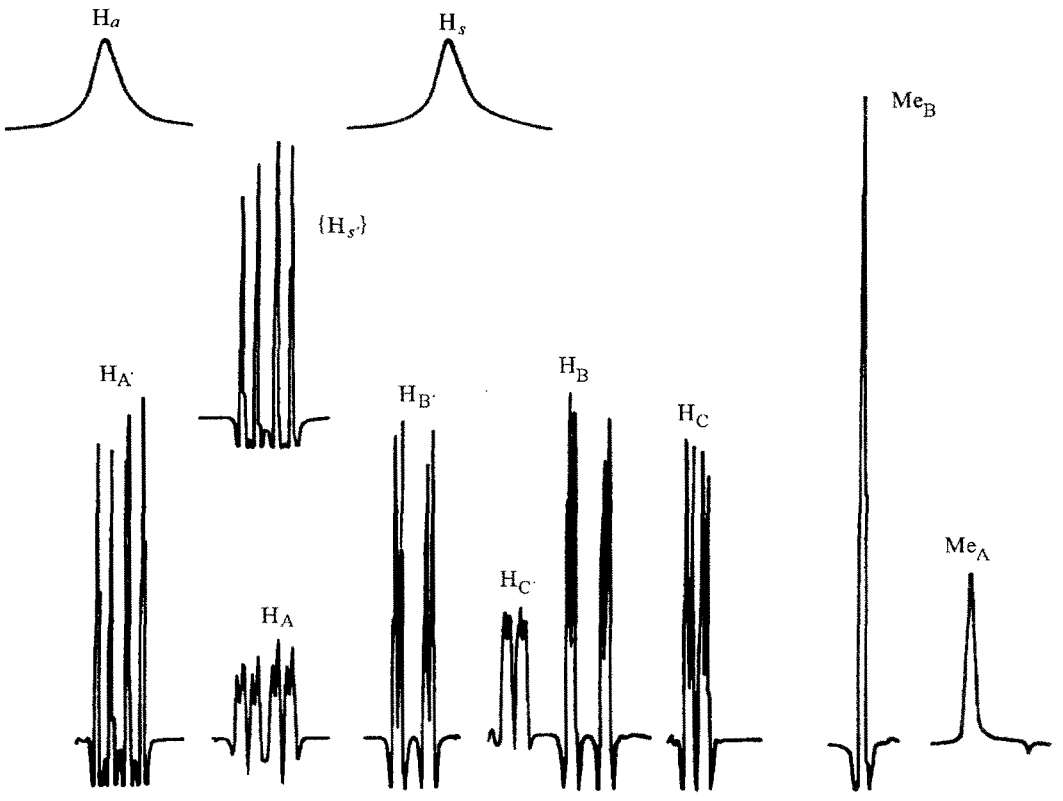


Fig. 1. ^{1}H NMR spectrum of azimexone **3** in CD_2Cl_2 at 20 °C. Proton signals of the cycle and the Me_2C group were recorded in the line narrowing mode, signals for the Me_2C and NH_2 groups with different amplification, for the NH_2 group with different scanning.

($^2J_{BC}$ = 1.2 Hz), and the ^2J coupling constants for atoms C≡N and C-3′ disappeared in the ^{13}C NMR spectrum. The correspondence between the ^{13}C and ^{1}H signals was confirmed by the two-dimensional COSY spectrum. Note that the ^{13}C chemical shifts obtained in the present work almost coincide with those given in Ref. 7. Obviously, the low-field line of the doublet has been taken previously[6] for the singlet of the C-2 atom. The signals for the NH_2 protons, *syn (s)* and *anti (a)* with respect to the CO group, were assigned on the basis of the fact that the ^4J coupling constant for H_A is only possible with the H_s proton (the planar zigzag conformation). Hence, the H_s proton corresponds to the high-field signal of NH_2, as in the case of formamide.[11]

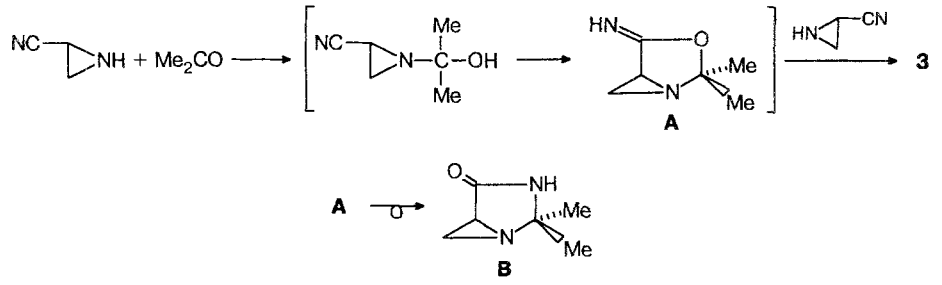
In the ^{1}H NMR spectrum of azimexone (in CD_2Cl_2), significant broadening of the Me_A signal (Fig. 1) was observed; this broadening disappeared in polar solvents (MeOH, MeCN) and on heating to 50 °C, which was accompanied by a significant upfield shift of the H_s signal (see Table 1). These changes in the spectrum are attributable to the breaking of hydrogen bonds. Analysis of molecular models demonstrates that the intramolecular hydrogen bond is only possible with the participation of the H_a proton and the C≡N group with the inversion of the cyanoaziridine N atom. However, previously we found that in the case of 1-*tert*-butyl-2-cyanoaziridine the ^{1}H NMR spectrum showed no signals for the *cis*-isomer, and, according to the above data, it is the H_s

Table 1. Parameters of the ^{1}H NMR spectra of azimexone **3** and amide **5** (CD_2Cl_2, δ, *J*/Hz)

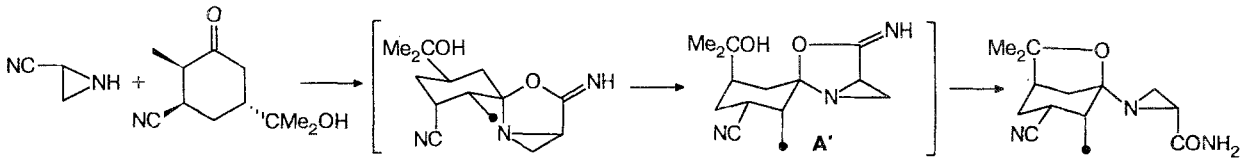
Compound	H_A ($H_{A'}$)	H_B ($H_{B'}$)	H_C ($H_{C'}$)	Me_A (Me_3C)	Me_B	H_s*	H_a*	$^3J_{AB}$ ($^3J_{A'B'}$)	$^3J_{AC}$ ($^3J_{A'C'}$)	$^2J_{BC}$ ($^2J_{B'C'}$)	$^4J_{AH_s}$
3	2.31 (2.58)	2.03 (2.19)	1.76 (2.07)	1.07	1.18	5.71	6.11	7.0 (6.4)	3.1 (2.8)	1.2 (1.2)	1.2
5	2.17	1.86	1.70	(1.00)	—	5.31	6.52	6.7	2.8	1.2	0.9

* On heating from 20 °C to 50 °C the signals were shifted to higher fields: H_s by 0.22 ppm (**3**) and 0.14 ppm (**5**); H_A by 0.04 ppm (**3** and **5**).

Scheme 2



Scheme 3



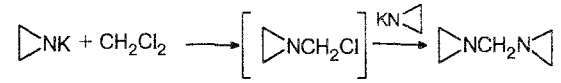
proton that is involved in the hydrogen bonding. Therefore, the model of a dimer formed by two hydrogen bonds —C≡N ··· H with the same orientation of the C≡N and $CONH_2$ groups as in structure **3** (the hydrogen bond with the participation of the C≡N group is sufficiently strong[12]), is the most adequate. In this case, the rotation of the Me_A group, which adopts the bisecting orientation with respect to both cycles, is hindered (unlike the Me_B group). The breaking of the mentioned hydrogen bonds by heating or as a result of competitive interactions with polar solvents leaves the conformation of the molecule unchanged, and the Me_A and Me_B groups occupy positions in which the rotation of these groups is not hindered. In the framework of this model, the configuration of diastereomer **3** can only be *2R,2'S/2S,2'R*.

Previously,[13] we substantiated the rule of prohibition of α-aminoalkylation for three-membered nitrogen heterocycles. In the present work we demonstrated that the prohibition is extended to 1-methoxymethylaziridine,[14] which, unlike ordinary alkoxymethylamines, shows no reaction on prolonged boiling with ethylene imine and morpholine. Therefore, the formation of compound **3** cannot proceed *via* intermediate 2-(2-cyanoaziridino)-2-propanol. This can be thought of as aziridinomethylation *via* an intermediate **A** with a good leaving iminoyloxy group (Scheme 2).

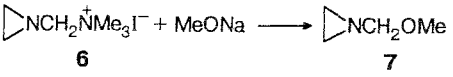
The formation of intermediate **B** in this reaction[7] catalyzed by MeONa is attributable to the Chapman rearrangement of intermediate **A**.

Recently, the highly enantioselective hydration of 2-cyanoaziridine under the action of a chiral substituted cyclohexanone[15] was carried out to yield the product of the intramolecular nucleophilic substitution of the iminoyloxy group in the intermediate **A'** (Scheme 3). Unchanged 2-cyanoaziridine became enriched with the *S*-(−)-enantiomer with optical purity > 99 %.

We first demonstrated the possibility of aziridinomethylation in the presence of a good leaving α-substituent using the synthesis of 1,1-methylenediaziridine[16] as an example.



In the present work, this was demonstrated for 1-aziridinylmethyltrimethylammonium iodide (**6**) prepared as described previously.[17,18]



Compound **7** was identified by comparing it with that described in Ref. 14. Previously, the formation of **7** in this reaction has been detected only from the mass spectrum.[17]

Experimental

NMR spectra were recorded on a Bruker WM-400 spectrometer operating at 400.13 MHz (^1H) and 100.62 MHz (^{13}C) with TMS as the internal standard. Melting points were measured on a Boetius RNMK-0.5 instrument.

2-(2-Cyano-1-aziridinyl)-2-(2-carbamoyl-1-aziridinyl)propane (3) was prepared according to the procedure in Ref. 7, m.p. 157—158 °C. ^{13}C NMR (CD_3OD), δ: 18.15 (C-2', ^1J = 183.5 Hz); 22.44 (Me_A, ^1J = 127.1 Hz, ^3J = 3.7 Hz); 25.01 (Me_B, ^1J = 127.1 Hz, ^3J = 3.7 Hz); 28.60 (C-3', $^1J_{CHB'}$ = 170.8 Hz, $^1J_{CHC'}$ = 180.6 Hz, $^2J_{CHA'}$ = 1.8 Hz); 29.94 (C-3, $^1J_{CHB}$ = 167.1 Hz, $^1J_{CHC}$ = 178.0 Hz); 32.89 (C-2, ^1J = 170.7 Hz); 73.75 (NCN, ^2J = 4.4 Hz); 120.62 (CN, $^2J_{CHA'}$ = 2.2 Hz, $^3J_{CHC'}$ = 3.6 Hz, $^3J_{CHB'}$ = 2.9 Hz); 175.75 (CO).

1-*tert*-Butyl-2-methoxycarbonylaziridine (4) was prepared according to the procedure in Ref. 8, b.p. 36 °C (1 Torr). The mass spectrum is identical with that described previously.[13] ^{1}H NMR ($CDCl_3$), δ: 0.66 (s, Me_3C); 1.48 (dd, H_B, $^3J_{AB}$ = 6.4 Hz, $^2J_{BC}$ = 1.5 Hz); 1.60 (dd, H_C, $^3J_{AC}$ = 2.8 Hz); 1.93 (dd, H_A); 3.36 (s, MeOH). ^{13}C NMR ($CDCl_3$), δ: 25.32 (Me_3C, ^1J = 125.0 Hz); 26.98 (C-3, $^1J_{CHB}$ = 164.2 Hz, $^1J_{CHC}$ = 178.8 Hz); 29.93 (C-2, ^1J = 170.0 Hz); 51.09 (MeO, ^1J = 146.8 Hz); 52.78 (CMe_3); 170.98 (CO, ^3J = 3.7 Hz).

1-*tert*-Butyl-2-carbamoylaziridine (5). A solution of 0.8 g (5 mmol) of ester **4** in 10 mL of anhydrous MeOH saturated with NH_3 was kept for 24 h at 20 °C and evaporated. The residue was recrystallized from a 10:1 hexane—benzene mixture and sublimed at 60 °C (1 Torr). The yield of **5** was 0.5 g (70 %), m.p. 90—92 °C. Found: N, 19.85 %. $C_7H_{14}N_2O$. Calculated: N, 19.7 %. ^{13}C NMR: (CD_3OD), δ: 26.48 (Me_3C, ^1J = 126.4 Hz, ^3J = 4.4 Hz); 28.75 (C-3, $^1J_{CHB}$ = 165.7 Hz, $^1J_{CHC}$ = 177.3 Hz); 32.90 (C-2, ^1J = 168.6 Hz); 54.32 ($\underline{C}Me_3$, ^2J = 4.4 Hz); 176.52 (CO).

1-Aziridinylmethyltrimethylammonium iodide (6) was prepared according to the procedure in Ref. 18, m.p. 178—179 °C, the ^{1}H NMR spectrum was identical to that described in Refs. 17, 18.

1-Methoxymethylaziridine (7). A solution of 12.1 g (50 mmol) of 1-aziridinylmethyltrimethylammonium iodide **6** in 10 mL of MeOH was added to a solution of sodium methoxide (from 1.15 g (50 mmol) of metallic Na). The mixture was kept for 24 h at 20 °C, then evaporated; the product was extracted with ether. After removal of the ether, the residue was distilled over metallic Na. The yield of compound **7** (b.p. 100—102 °C) was 1.3 g (30 %); compound **7** was identified with the compound described previously[16] by its ^{1}H NMR and mass spectra. Product **7** was unchanged after boiling with an equimolar amount of ethylene imine, morpholine, or nitromethane for 10 h (monitoring by ^{1}H NMR spectra).

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