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CONFORMATIONAL ANALYSIS USING TORSION ANGLE NOTATION : ATTEMPTED PREDICTION AND INTERPRETATION OF THE STERIC COURSE OF THE CLEAVAGE REACTION BETWEEN BICYCLIC AZIRIDINES AND HYDROGEN FLUORIDE IN PYRIDINE SOLUTION

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ABSTRACT - Dynamic conformational analysis of the cleavage of methyl-substituted 7-aza bicyclo [4.1.0] heptanes by Olah's reagent (30 wt % of pyridine in hydrogen fluoride), using the torsion angle notation, allows structural and conformational prediction of the 2-fluoro cyclohexylamine products. Consequently, a mechanism for the cleavage is proposed.

From the first work of Bucourt[1], in 1963, on the notion of torsional angles in the problem of transmission of conformational deformation, Dynamic Conformational Analysis (D.C.A.), elaborated by Toromanoff[2,3], proved successful in interpretation and prediction of several types of reaction ; e.g. addition to cyclanones and α,β unsaturated cyclenones[3,4], sensitized photooxydation of alkenes[5], syn-addition to alkenes and dienes[3,6], 1,4-conjugate elimination reactions[7] and cleavage of bicyclic oxiranes[8].

In spite of the interest taken in the comparison of ring cleavage reactions of the 3-membered rings of the oxiranes and aziridines[9,10], the stereoselectivity of aziridine ring-opening in polycyclic structures has received little attention[11] in comparison to the oxiranes[12-15].

Although, the mechanistic study of aziridine ring opening with Olah's reagent (hydrogen fluoride in pyridine solution)[16] has given rise to some controversy[17-19], we aimed to predict the structure and conformation of the products of aziridines 1-4 cleavage (scheme 1) using D.C.A. and SN_2-type-reaction on the aziridinium ion and to compare these predictions with our experimental results[20].

Scheme 1

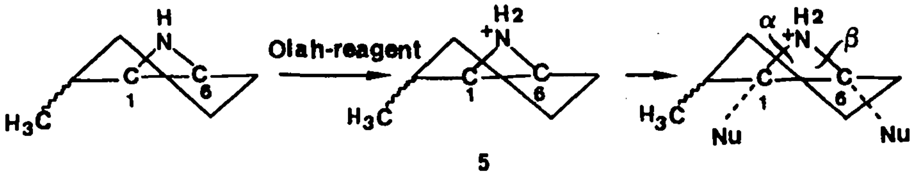
*In trans isomers, the methyl group in position 2 and the aziridine ring are on opposite sides of the mean plane, in cis isomers, they are on the same side of the mean plane.

I - BASIC ASSUMPTIONS

The use of D.C.A. requires a good knowledge of the rules linked to this theory. These rules were developed in detail by Toromanoff[4], so we don't intend to review them here. However, in the view of an application to aziridine and for the sake of clarity, we state the main basic hypotheses :

(1) - The preliminary formation of aziridinium ion 5 [21] occurs (scheme 2).

(2) - The backside approach of the nucleophilic species occurs along the axis of the C_1-N (attack α) or C_6-N (attack β) bonds[8c,22] (scheme 2).



Scheme 2

(3) - The Principle of Least Conformational Distortion developed by Toromanoff[8a,22].

(4) - The investigation of all possible initial conformations of bicyclic aziridines[2] and selection of the most energetically favourable i.e. those of lowest energy[8c].

(5) - Among the selected initial conformers, only those with the C_1-C_6-N ring perpendicular to the mean 6-membered ring plane are considered[22].

II - DISCUSSION

A - Prediction of cleavage products

Taking into account these hypotheses and applying them to the unmethylated 7-aza bicyclo [4.1.0] heptane, we start from the conformational equilibrium between 1.2, 1.3 and 1.4-diplanar (boats) forms of the aziridinium ion, which are analogous to the case of cyclohexene[8b] (scheme 3).

Among the ten initial reactive forms, the energy increases from the 1.2- to 1.3-diplanar forms up to 1.4-diplanar forms, so, we will only consider the lowest energy 1.2-diplanar forms (according to hypotheses n° 4).

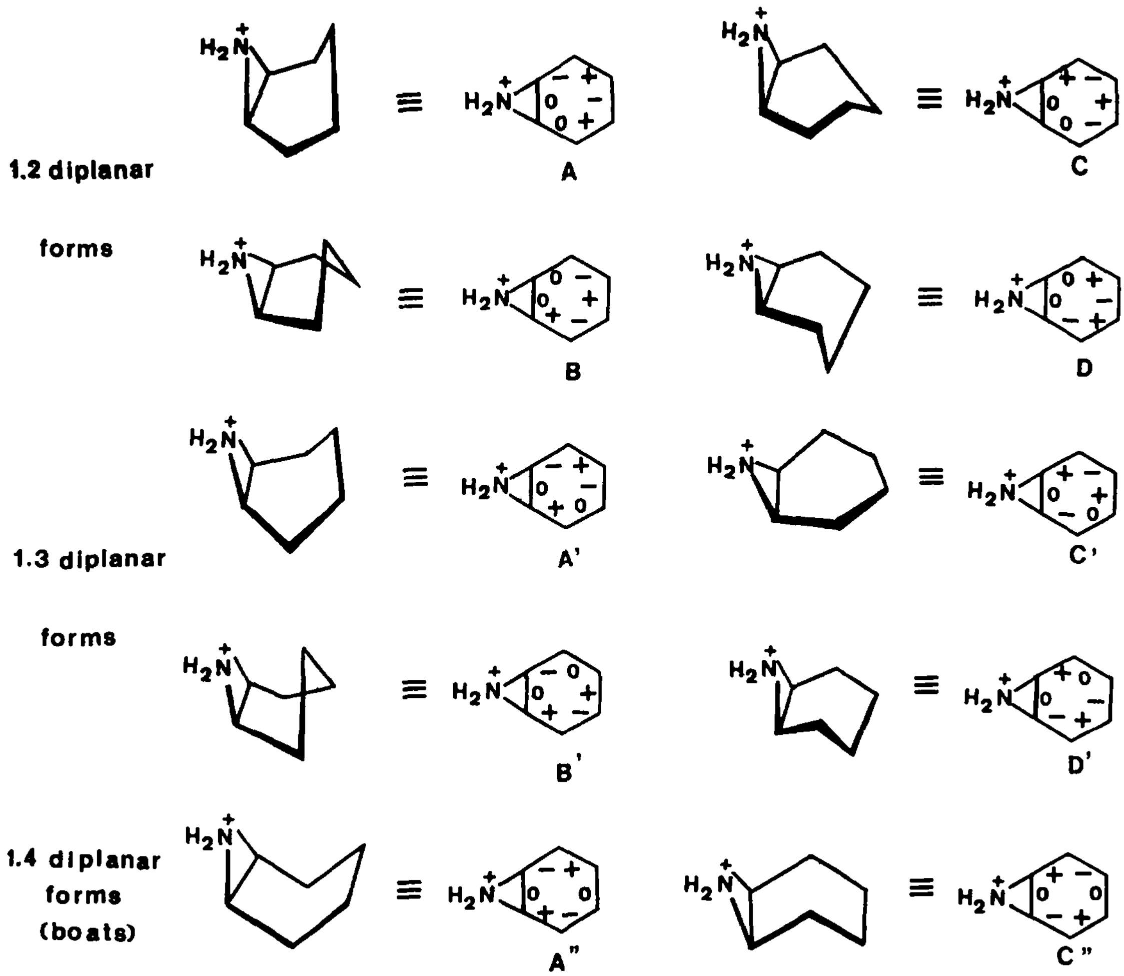
The position of the bonds involved in anti-elimination requires that the reactive conformations of aziridinium ion (chosen from 1.2-diplanar forms) are the axial forms (A and B). The bisectional conformations (C and D) have to undergo a conformational change to become axial before any reaction[8b] will occur (according to the hypothesis n° 5).

In the absence of strong steric hindrance or strong polar effects, starting from A or B the "initial reactive forms" of the aziridinium ion up to the corresponding kinetic products (primary final forms of fluoro compounds), the reaction will occur preferentially with the transition state of least energy, leading to the primary final form of lowest energy[2].

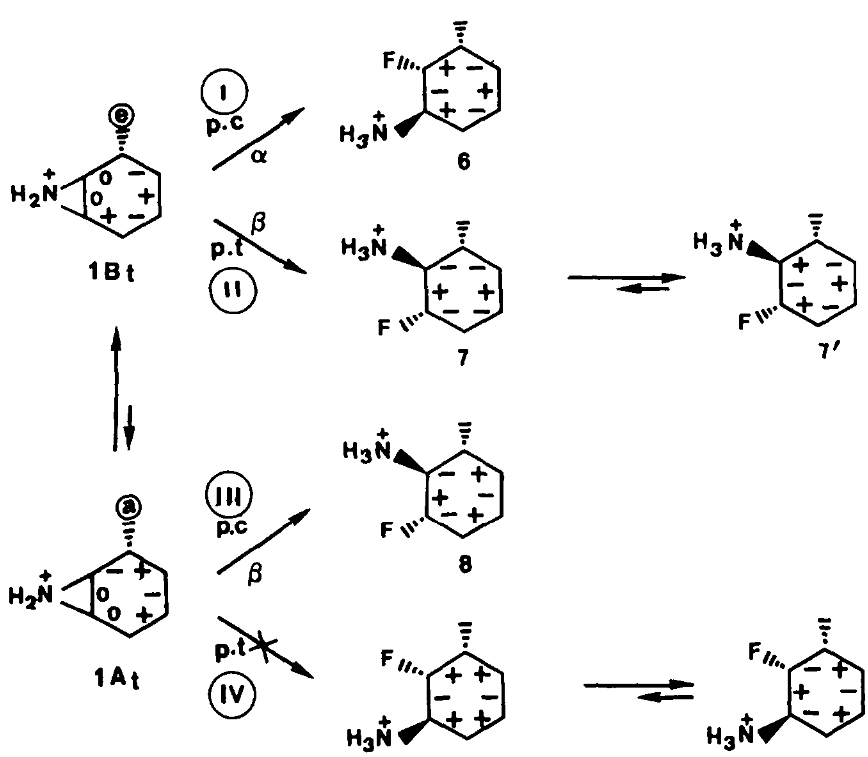
In the case of 1 (sceheme 4), the 1.2-diplanar conformers $1A_t$ and $1B_t$ have the axial aziridinium ion ring above the mean plane with the 2-methyl group in an equatorial position (the sign sequence clockwise is 0,-) in the case of $1B_t$ and the 2-methyl group in an axial position (the sign sequence clockwise is -, +) in the other conformer A_t. From each 1.2-diplanar form, $1A_t$ or $1B_t$, two pathways are possible, one corresponding to a transition state leading to a chair form ("pre-chair transition state"), pathway I from $1B_t$ and pathway III from $1A_t$), the other leading to a twist form ("pre-twist transition state" pathway II from $1B_t$ and pathway IV from $1A_t$).

From $1B_t$, pathway I is slightly destabilized by a gauche interaction between the equatorial 2-Me and the incoming fluoro group. Thereby, as there is no such steric effect in the "pre-twist" state, we can predict a minor participation of pathway II.

From $1A_t$, the axial 2-Me prevents any "pre-twist" approach in pathway IV (1.2-syn diplanar steric interaction between the axial methyl and the fluoro group approaching the adjacent carbon) and delays "the pre-chair" approach corresponding to pathway III.



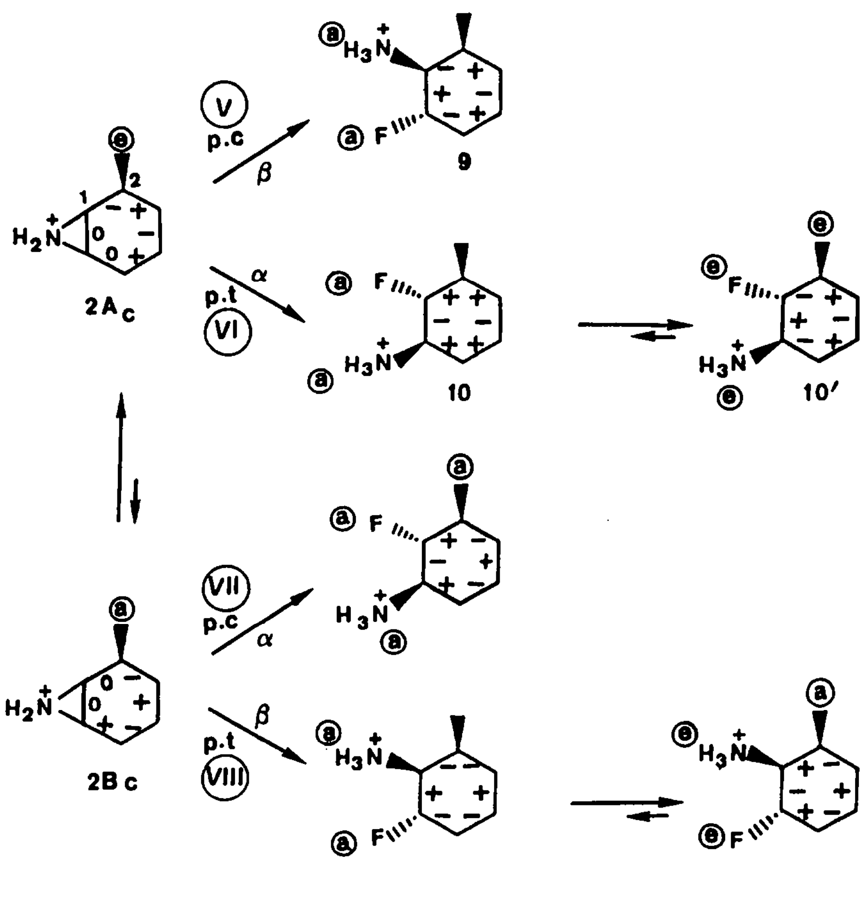
Scheme 3



Scheme 4

Now, with respect to scheme 4, it can be concluded that, the cleavage of 1 with Olah's reagent should give a mixture of fluoro compounds. The α cleavage, through the "pre-chair" transition state (pathway I), ought to be the main pathway giving the primary final form 6. The β cleavage also occurs, mainly from $1B_t$ (pathway II) giving the primary final form 7, and to a lesser extend from $1A_t$ (pathway III) giving the primary final form 8.

The same type of reasoning applies to cis 2 (scheme 5). We have to evaluate the relative transition state levels of pathways V - VIII, 2 A_c and 2 B_c being the initial reactive 1.2-diplanar forms with the aziridinium ion in the axial orientation.



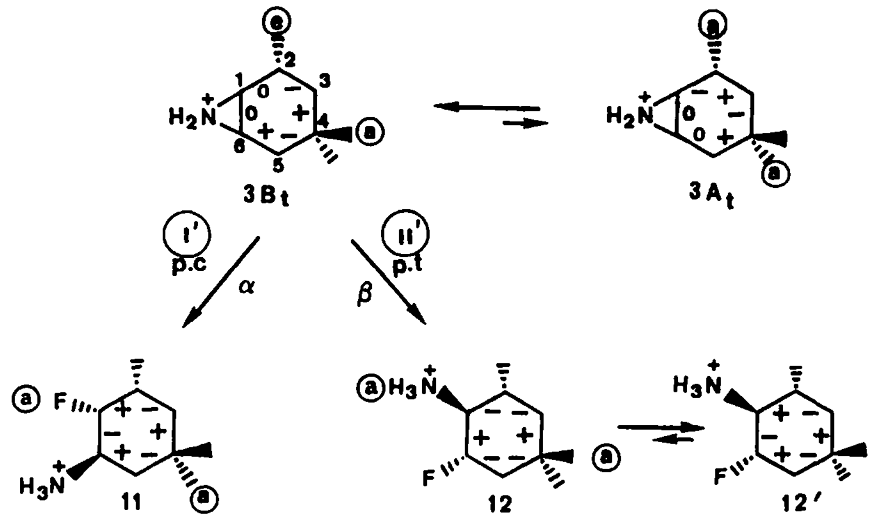
Scheme 5

From the more stable form 2 A_c and subsequent transition states, there is no hindrance for the incoming fluoro group approaching at the rear of the C-$\overset{+}{N}H_2$ bond. The two pathways V and VI are possible but, with regard to the "pre-twist" transition state, which gives the primary final form 10, the lower energy of the "pre-chair" transition state implies that pathway V, giving the primary final form 9, is the main, if not the only pathway.

The transition states from the less stable 1.2-diplanar conformer 2 B_c, are obviously of higher energy, so we may discard pathways VII and VIII. Consequently, conformational factors drive the cleavage of aziridinium ion to be highly β stereoselective. Thus, the main product should correspond to the more stable primary final form 9, with the methyl group in the equatorial position.

Turning now the case of 3 and 4, we have to evaluate the steric effects of gemdimethylation and their effect on the transition state level, with respect to the monomethylated aziridinium ions corresponding to initial aziridines 1 and 2.

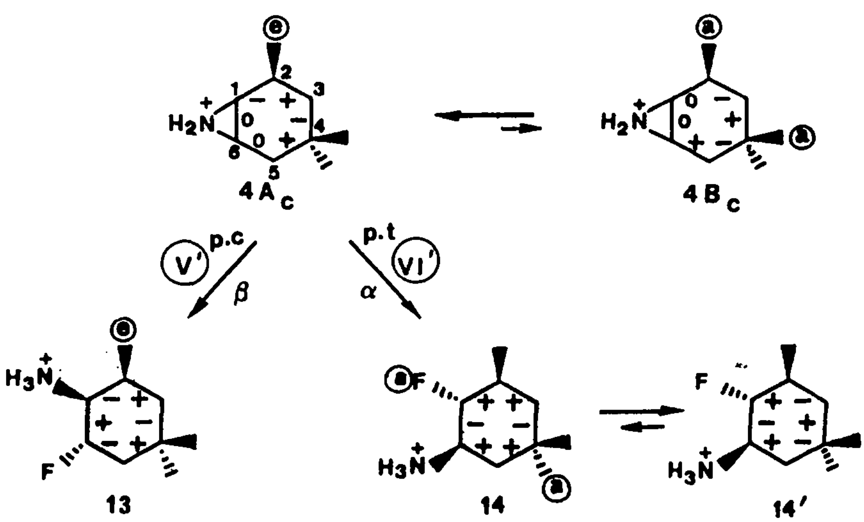
For 3 (scheme 6), we take in account the two possible initial primary reactive forms A_t and B_t, previously retained for 1. As the result of 1.3-syn axial interaction between the methyl groups in the 2 and 4 positions, the initial reactive 1.2-diplanar form 3 A_t is highly unlikely, so we can neglect it and start from the 1.2-diplanar form 3 B_t.



Scheme 6

In comparison with the "pre-chair" transition state level of aziridinium ion of 1, that of 3, with an axial 4-methyl and an axial ammonium group in 1.3-position in the primary final form 11, is of higher energy. However, as a result of the strong 1.4-steric interaction between the axial 4-Me (of gemdimethyl group) and the axial ammonium group in the primary final form 12, pathway II' involves a transition state of distinctly higher energy. So the main contribution is expected to be from pathway I' (α cleavage giving the primary final form 11) with a minor contribution from pathway II' (β cleavage giving the primary final form 12).

Similarly in the case of 4 (scheme 7), only one 1.2-diplanar form 4 A_c has to be considered

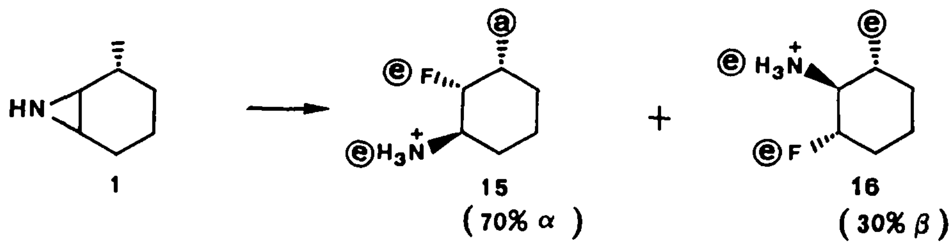


Scheme 7

since a contribution from 4 B_c is excluded for steric reasons (1.3-syn-axial interaction between 2-Me and 4-Me). From 4 A_c, the "pre-chair" transition state leads to primary final form 13 which has a 1.3-diaxial interaction between 4-Me and fluoro group. In the pathway VI', there is a strong steric 1.4-interaction between the axial-Me (of the gemdimethyl group) and the axial fluoro group in the primary final form 14. Thus, it may be concluded that the main, if not the only product, comes from pathway V' via the primary final form 13.

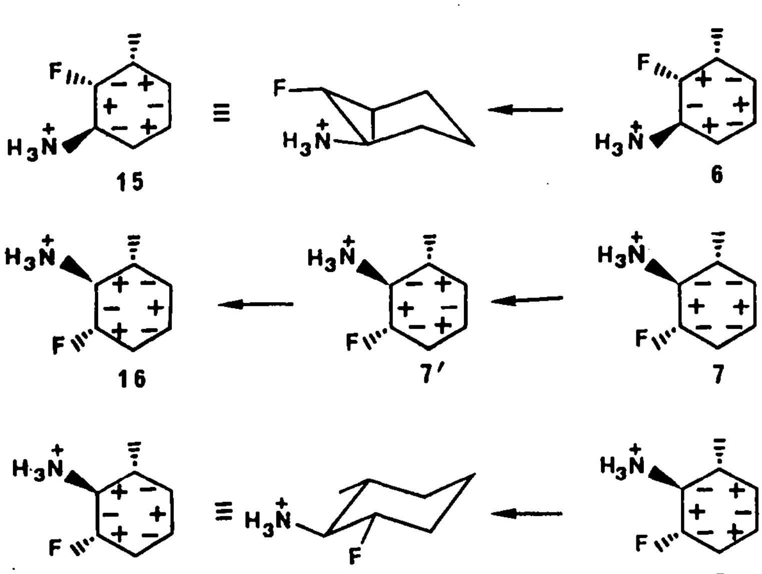
B - Comparison with experimental results

To be effective, the reaction of aziridines 1-4 with Olah's reagent requires a temperature of 70°C and produces only trans addition products [20]. Thus, reaction with trans aziridine 1 yields a mixture of isomeric fluoro-2 amines obtained by neutralisation of the two initial ammonium ions 15 and 16. The major isomer (70%) 15 corresponds to α cleavage and the minor isomer 16 to β cleavage (scheme 8).



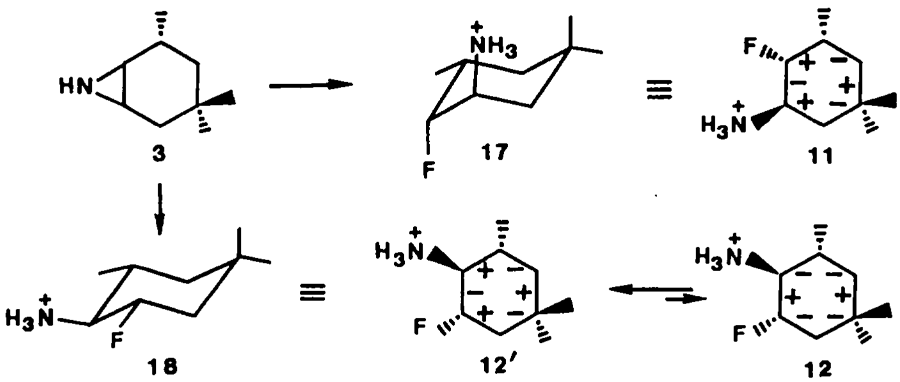
Scheme 8

In both products, the ammonium group and fluoro group are in the equatorial orientation. Now, if we compare these experimental results with those predicted by the conformational analysis, the observed regioselectivity and cleavage type are in good agreement with this prediction. The 15 and 16 conformations arise from the interconversion of primary final forms 6-8. These are the kinetic products of the reaction in which at least two groups are in axial orientation (scheme 9).



Scheme 9

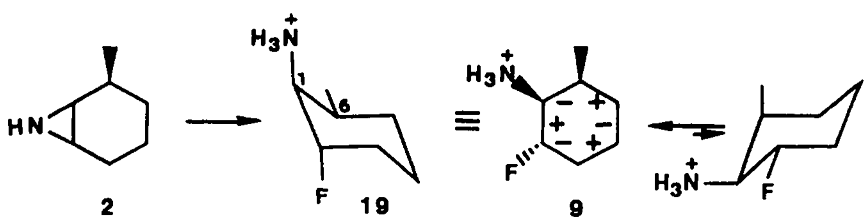
As expected, gemdimethylation results in an increase of the regioselectivity, as a result of steric interaction. Thus, cleavage of the aziridine 3 gives two products 17 and 18 (90/10). (scheme 10)



Scheme 10

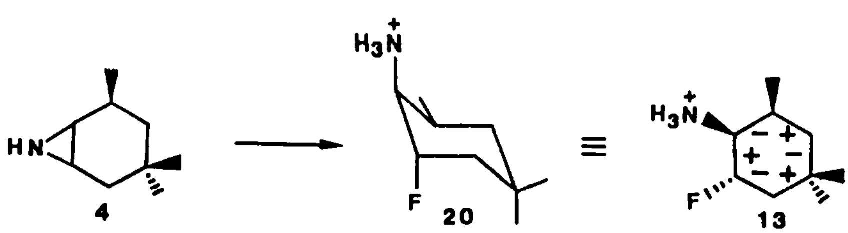
The major product 17 corresponds to the primary final form 11 (11≡17), whereas the compound 15 (obtained from 1) has arisen from a conformational change of primary final form 6.

The reaction of cis aziridine 2 leads to a single fluoro compound 19 by β cleavage (scheme 11). The exclusive product has the same conformation as the primary final form 9, as predicted by D.C.A. The strong Van der Waals type repulsion in 9 (≡19) between the ammonium and 6-methyl groups, restricts a later chair inversion.



Scheme 11

In comparison to 2, the gem dimethylation in compound 4 (scheme 12) bears no particular effect on the steric course of the reaction. Indeed, the experimental results also show the stereospecificity of the reaction affording 20, and in a conformationaly mobile cyclohexane system, the same argument may be used to explain the configuration of the unique reaction product.



Scheme 12

III - CONCLUSION

The dynamic method of conformational analysis using the torsion angle notation allows the prediction of the experimental results when 3-methyl 7-aza bicyclo-[4.1.0] heptanes and 3,5,5-trimethyl 7- aza-bicyclo-[4.1.0] heptanes are cleaved by hydrogen fluoride in pyridine. In many cases, the presence of methyl groups on the cyclohexane structure prevents an interconversion of the primary final forms in the more stable conformers, allowing the trans diaxial orientation of the remaining C-N bond and the newly formed C-F bond. Moreover, whilst not a definitive proof, this result is an unquestionable argument for the intervention of a SN_2 mechanism in the opening of aryl-unsubstituted aziridines, under the experimental conditions used.

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