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# SYNTHESIS AND STUDY OF THE STABILITY OF 3b,4,4a,5-TETRAHYDROTHIENO[2',3':5,4]-CYCLOPENTA[2,3-b]AZIRIDINE DERIVATIVES

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Abstract — The synthesis of 3b,4,4a,5-tetrahydrothieno[2',3':5,4]cyclopenta[2,3-b]-aziridine derivatives is described. Their stability is studied.

In continuation of our work on the synthesis of new thiophenic compounds[1], we wish to describe herein the first results about the original synthesis and the study of the stability of potential DNA alkylating aziridines, in relation with mitomycin activity[2].

We have recently described the cyclisation of 3-amino-3-(-3 thienyl) propionic acid to 4-amino-4,5-dihydrocyclopenta[b]thiophen-6-one[3]. Halogenation of this latter is the first step of the aziridine synthesis. Bromination, with one equivalent of bromine in chloroform, conducts selectively to a monobromo compound. Nmr data confirm the trans structure 2. When the reaction is run with an excess of bromine, dibromo compound 3 is obtained.

Chlorination of 1, with chlorine in chloroform at room temperature, affords a mixture of chloro compounds. Nmr data of the major compound reveal the cis structure 4. When chlorination is conducted at reflux temperature, it gives the dichloro compound 6.

Obtention of different epimers during the course of halogenations prompts us to investigate these reactions by CG/MS coupling. Bromination is quite simple : selective obtention of trans compound 2, followed by disubstitution in presence of an excess of bromine to give 3. Chlorination is more complex. Following the course of the reaction, by CG/MS coupling, shows that the reaction mixture, at the beginning, is made up of starting material 1, cis and trans monochloro compounds 4 and 5 and dichloro compound 6. After 30 min of reaction, cis chloro compound 4 precipitates. It is isolated by filtration and then the filtrate is composed by cis chloro compound 4 and dichloro compound 6, without trans chloro compound 5.

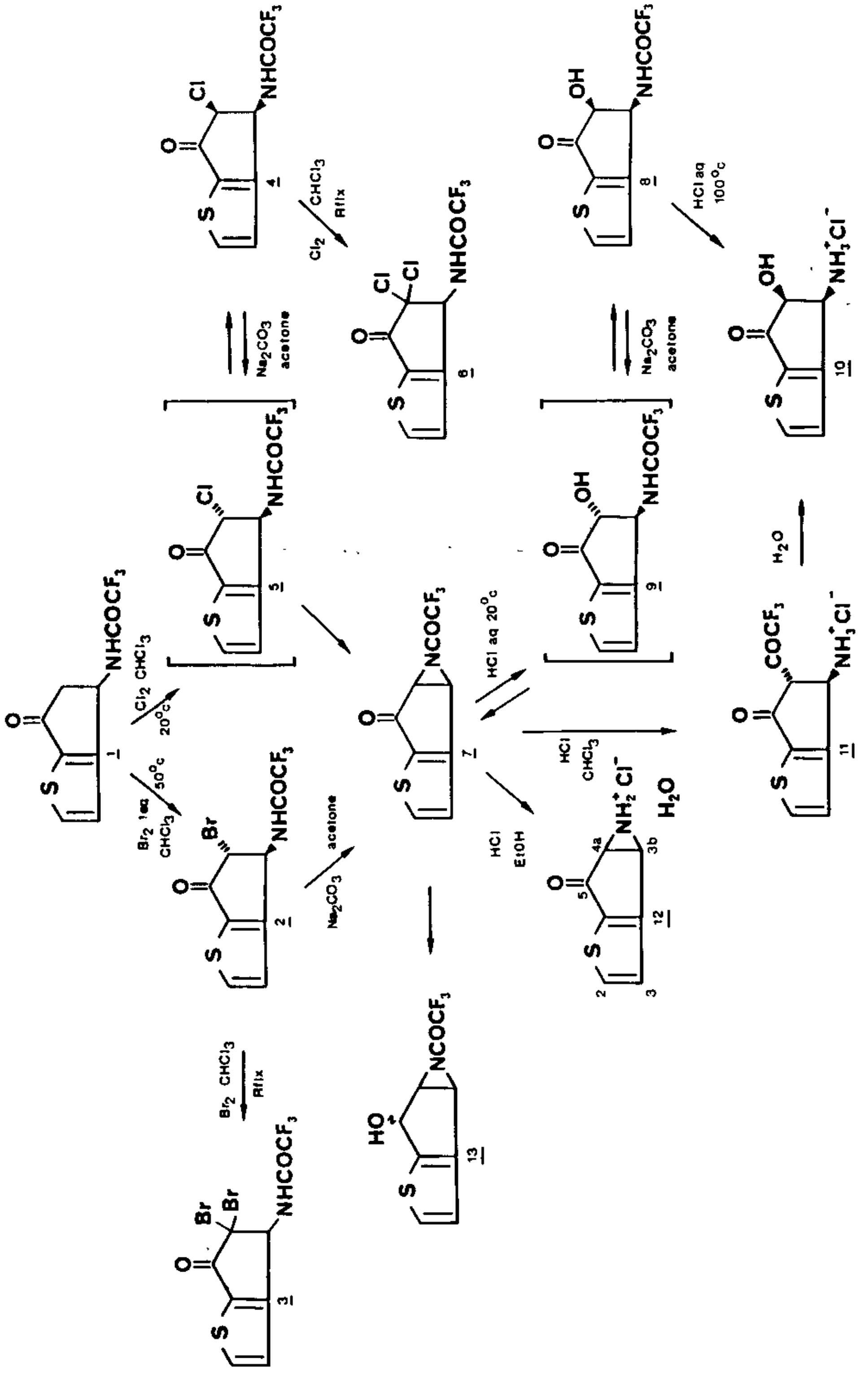
Heating of this filtrate at reflux temperature leads to the disappearance of 4 in favour of dichloro compound 6. This clearly indicates that chlorination process by formation of a trans chloro compound, followed by epimerisation into a cis form, due to the keto-enolic tautomerism. This phenomenon is not observed with bromine probably because of the steric hindrance of the bromine atom.

Treatment of trans bromo compound 2, with sodium carbonate in acetone yields to trifluroacetylaziridine 7. Unexpected cyclisation into 7 is also obtained when cis monochloro compound 4 is treated in the same conditions. In a similar manner as above, we have followed the course of this cyclisation reaction by CG/MS coupling. Results show a reverse epimerisation from the cis to the trans form in alkaline medium. Trans monochloro compound 5, generated in situ, was able to undergo a rear nucleophilic attack.
Further, treatment of 7 by N-hydrochloric acid affords selectively cis hydroxytrifluoroacetamide 8, whose structure is clearly established by nmr data. The synthesis of cis epimer 8 can be explained as above : first formation of intermediate trans compound 9, which undergoes a trans-cis epimerisation in acidic medium. This is supported by ir and nmr study of a mixture of 8 and 9 compounds, obtained from taking at the beginning of the reaction. Furthermore, treatment of 8 by sodium carbonate in refluxed acetone gives aziridine 7. This sequence confirms reverse cis-trans epimerisation in alkaline medium as yet observed in the case of chloro compound 4.

On the other hand, acidic hydrolysis of hydroxy compound 8, by aqueous N-hydrochloric acid solution, gives cis hydroxyammonium chloride 10 which is also obtained by treatment of 7 with hydrochloric acid in chloroform. In this latter reaction, the unstable intermediate trans compound 11 is isolated. Structure of this rearranged compound is supported by ir and nmr spectral data. Compound 11 is quite unstable and, exposure to air, gives, in a few hours, compound 10. Treatment of 7 with hydrochloric acid, in anhydrous protic solvent (ethanol) does not produce the cleavage of the aziridine ring but only leads to the hydrolysis of trifluoroacetyl group, giving the aziridinium chloride 12. This difference of reactivity in protic or aprotic solvents is currently under investigation. In alkaline medium, aziridine 7 is stable. Hydrogenation of 7, with sodium borohydride in methanol, gives the hydroxyaziridine 13 (mixture of epimers) which is very stable in acidic or alkaline medium. This stability confirms the important contribution of the keto-enolic tautomerism in the reactivity of aziridine 7. Further reactions, concerning these compounds and applications to the synthesis of yet unknown corresponding indanoaziridines[4], are in progress.

Ir and Nmr Parameters

| N° | Ir KBr<br>($\nu$ $cm^{-1}$) | δ Nmr/TMS<br>(ppm) | J<br>(Hz) | Solvent |
|---|---|---|---|---|
| 2 | 3280 (NH)<br>1700 (C=O) | 8.08(d,H2) ; 7.63(d,NH) ; 7.11(d,H3) ; 5.56(dd,H4) ; 4.76 (d,H5) | H2/H3=4.88<br>H4/H5 trans=2.70<br>H4/NH=7.50 | $CDCl_3$ |
| 3 | 3250 (NH)<br>1710 (C=O) | 8.10(d,H2) ; 7.08(d,H3) ; 6.96(d,NH) ; 6.08(d,H4) | H4/NH=9.00 | $CDCl_3$ |
| 4 | 3280 (NH)<br>1700 (C=O) | 8.11(d,H2) ; 7.23(d,H3) ; 6.77(broad, NH) ; 5.80(dd,H4) ; 5.08(d,H5) | H4/H5 cis=6.35<br>H4/NH=6.50 | $CDCl_3$ |
| 5 | - | 8.12(d,H2) ; 7.16(d,H3) ; 6.90(broad, NH) ; 5.47(dd,H4) ; 4.72(d,H5) | H4/H5 trans=3.42<br>H4/NH=8.60 | $CDCl_3$ |
| 6 | 3240(NH)<br>1720(C=O) | 8.16(d,H2) ; 7.11(d,H3) ; 6.80(broad, NH) ; 6.01(d,H4) | H4/NH=8.10 | $CDCl_3$ |
| 7 | 1700(C=O) | 8.45(d,H2) ; 7.42(d,H3) ; 5.78(d,H3b or H4a) ; 5.63(d,H3b or H4a) | H3b/H4a=6.83 | $CDCl_3$ |
| 8 | 3480(OH)<br>3300(NH)<br>1700(C=O) | 9.44(d,NH) ; 8.30(d,H2) ; 7.23(d,H3) ; 6.22(broad, OH) ; 5.50(dd,H4) ; 4.71(dd,H5) | H4/H5 cis=6.60<br>H4/NH=6.80<br>H5/OH=4 | DMSO |
| 9 | - | 9.40(d,NH) ; 8.32(d,H2) ; 7.18(d,H3) ; 6.34(d,OH) ; 5.07(dd,H4) ; 4.54(dd,H5) | H4/H5 trans=3.42<br>H4/NH=8<br>H5/OH=7.40 | DMSO |
| 10 | 3280(OH)<br>1675(C=O) | 8.43(broad,$NH_3^+$) ; 8.39(d,H2) ; 7.41(d,H3) ; 7.01(broad, OH) ; 4.80(m,H4 and H5) | H4/H5 cis=6.85 | DMSO |
| 11 | 1800(C=O)<br>1710(C=O) | 8.97(broad, $NH_3^+$) ; 8.48(d,H2) ; 7.50(d,H3)$^3$; 6.35(m,H5) ; 5.12(broad, H4) | H4/H5 trans=3 | DMSO |
| 12 | 1710(C=O) | 8.90(broad, $NH_2^+$) ; 8.46(d,H2) ; 4.52 ; 7.47(d,H3) ; 4.49(d,H3b or H3a) | H3b/H4a=6.80 | DMSO |



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7
8
9
10
11
12
13
NHCOCF3
NCOCF3
COCF3
NH3+Cl−
NH2+Cl−
H2O
Cl2 CHCl3 20°C
Br2 1eq CHCl3 50°C
Br2 CHCl3 Rflx
Cl2 CHCl3 Rflx
Na2CO3 acetone
Na2CO3 acetone
Na2CO3 acetone
HCl aq 20°C
HCl CHCl3
HCl EtOH
HCl aq 100°C
H2O
2
3
3b
4a
5

Elemental analysis

| N° | Molecular formula | Calculated | | | | Found | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | S | F | C | H | S | F |
| 2 | $C_9H_5NO_2SF_3Br$ | 32,95 | 1,54 | 9,77 | 13,37 | 33,14 | 1,65 | 9,91 | 17,15 |
| 3 | $C_9H_4NO_2SF_3Br_2$ | 26,56 | 0,99 | 7,88 | 14,00 | 26,52 | 1,03 | 7,99 | 14,29 |
| 4 | $C_9H_5NO_2SF_3Cl$ | 38,11 | 1,78 | 11,30 | 20,09 | 37,10 | 1,72 | 11,23 | 19,98 |
| 6 | $C_9H_4NO_2SF_3Cl_2$ | 33,98 | 1,27 | 10,08 | 17,92 | 33,27 | 1,31 | 9,82 | 17,30 |
| 7 | $C_9H_4NO_2SF_3$ | 43,73 | 1,63 | 12,97 | 23,06 | 43,43 | 1,89 | 12,82 | 22,73 |
| 8 | $C_9H_6NO_3SF_3$ | 40,76 | 2,28 | 12,09 | 21,49 | 40,88 | 2,29 | 12,20 | 21,75 |
| 10 | $C_7H_8NO_2SCl$ | 40,88 | 3,92 | 15,59 | - | 40,77 | 3,94 | 15,37 | - |
| 12 | $C_7H_8NO_2SCl$ | 40,78 | 3,88 | 15,53 | - | 40,63 | 3,78 | 15,40 | - |

## REFERENCES

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