THIENOCYCLOPENTA[2,3- *b*]AZIRIDIN-5-ONE : CLEAVAGE IN ACIDIC MEDIUM

Patrick Dallemagne, Juan Carlos Pilo, Sylvain Rault, and Max Robba*
Laboratoire de Chimie Thérapeutique U.F.R. des Sciences Pharmaceutiques
1 rue Vaubénard - 14032 CAEN cedex, France

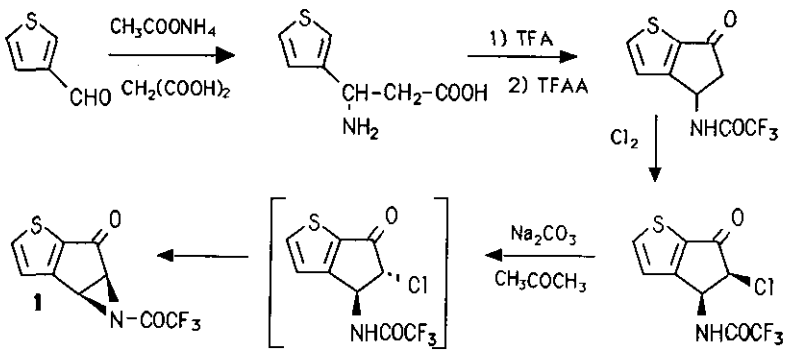
Michel Saux, and Alain Carpy
SDI 6315 CNRS Faculté de Pharmacie
3,place de la Victoire - 33076 BORDEAUX cedex, France

Abstract - Cleavage of thienocyclopenta[2,3-*b*]aziridin-5-one leads to *cis* and *trans* isomers of hydroxyoxocyclopenta[*b*]thienylammonium chlorides whose structures are established by X-ray analysis and unequivocal synthesis. The mechanism of cleavage is studied.

In continuation of our works concerning the formation of new heterocyclic systems with potential therapeutic interest, we recently described the synthesis of thienocyclopenta[2,3- *b*]aziridines[1] and indano[1,2-*b*]aziridines.[2] We have studied their reactivity and particularly the conditions of formation and cleavage of the indano[1,2-*b*]aziridines.[3]

We wish to establish clearly, by X-ray analysis and unequivocal synthesis, the structure of some products issued of the cleavage of 5-oxo-4-trifluoroacetyl-3b,4,4a,5-tetrahydrothieno[2',3' : 5,4]cyclopenta[2,3- *b*]aziridine (**1**) in acidic medium and to reinvestigate the synthetic route to their formation, previously mentioned in a preliminary paper.[1]

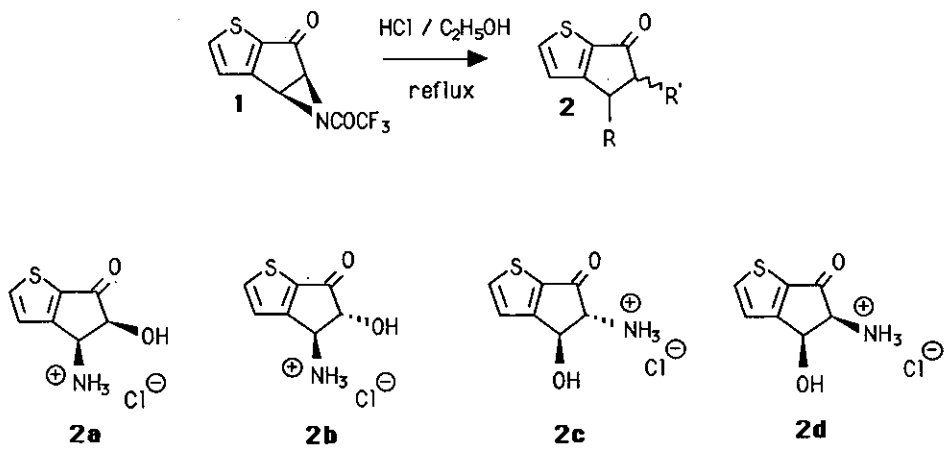
5-Oxo-4-trifluoroacetyl-3b,4,4a,5-tetrahydrothieno[2',3' : 5,4]cyclopenta[2,3- *b*]aziridine (**1**) was obtained in 4 steps starting from 3-thiophenecarboxaldehyde as previously described [4,1] (Scheme 1).



Scheme 1

1 was stable in alkaline medium, but, by treatment with gaseous hydrochloric acid in refluxing ethanol, it led to the formation, in equal parts, of two compounds which could be isolated by fractionnal crystallizations in ethanol.
Ir, ^{1}H-and ^{13}C-nmr data revealed that these compounds were two isomers of ketohydroxyammonium chlorides, formed by cleavage of aziridine ring and trifluoroacetamido group.

However, in this study we could not determine the position of amino and hydroxyl groups on the cyclopentane ring nor the cis or trans structure of these compounds (2) (Scheme 2).



Scheme 2

One of these derivatives was subjected to X-ray analysis. Small single crystals were obtained by slow evaporation of a 2-propanol solution. One of them, a 0.17 x 0.15 x 0.05 mm platelet was chosen. The symmetry was orthorombic, spatial group $P2_12_12_1$, with a = 5.250 (1), b = 6.402 (1), c = 27.011 (9) Å, V = 908.0(1) Å^3, z = 4, d_{calc} = 1.504.

The structure, so revealed, corresponded to the formula (2a) with hydroxyl group (C(6) - O(10) = 1.47(3) Å) in α position to cyclopentane carbonyl and in *cis* position to amino group (N(9) - C(6) - O(10) = -1(2)°) (Figure1). The non-hydrogen atoms are listed in Table 1.

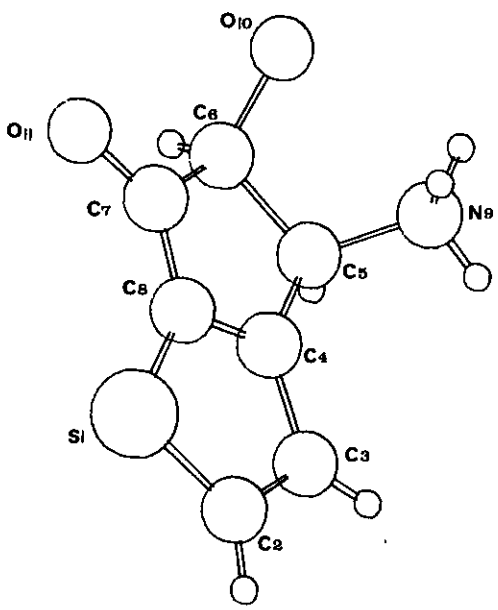
The coupling constant $^{3}J_{H\text{-}4\,H\text{-}5}$, measured at 6.35 Hz on the ^{1}H-nmr spectrum of 2a, was equal to that of the cyclopentane protons of aziridine (1), which are necesseraly in *cis* position. This confirms the value to be *cis* coupling constant in this system.
On the other hand, the ^{1}H-nmr spectrum of the second derivative (2) revealed a coupling constant, measured at 3.17 Hz which indicated a *trans* structure. However, none of the spectrometric data was clearly in favor of 2b or 2c.

Table 1

Atom	x	y	z	B (Å²)
S1	0.472(1)	0.104(1)	0.5255(2)	4.6(1)
O10	0.359(3)	0.513(2)	0.6834(5)	16.2(5)
O11	0.210(3)	0.536(3)	0.5823(5)	15.5(5)
N9	0.696(3)	0.221(2)	0.6987(5)	5.3(4)
C2	0.724(4)	-0.049(4)	0.5430(7)	4.3(5)
C3	0.836(5)	0.012(3)	0.5879(7)	4.1(5)
C4	0.701(5)	0.196(3)	0.6059(7)	3.6(4)
C5	0.735(4)	0.331(3)	0.6502(6)	3.4(4)
C6	0.537(5)	0.506(4)	0.6414(6)	4.0(5)
C7	0.401(4)	0.430(4)	0.5976(8)	5.3(6)
C8	0.505(4)	0.252(3)	0.5767(6)	3.0(4)
C112	0.309(1)	0.0463(9)	0.2010(2)	4..3(1)

Fractional coordinates of non-hydrogen atoms and equivalent isotropic thermal parameters defined by the relation
$4/3\ [a^2\beta_{11} + b^2\beta_{22} + c^2\beta_{33} + ab\cos\gamma\ \beta_{12} + ac\cos\beta\ \beta_{13} + bc\cos\alpha\ \beta_{23}]$
Estimated standard deviations are in parentheses.

Figure 1

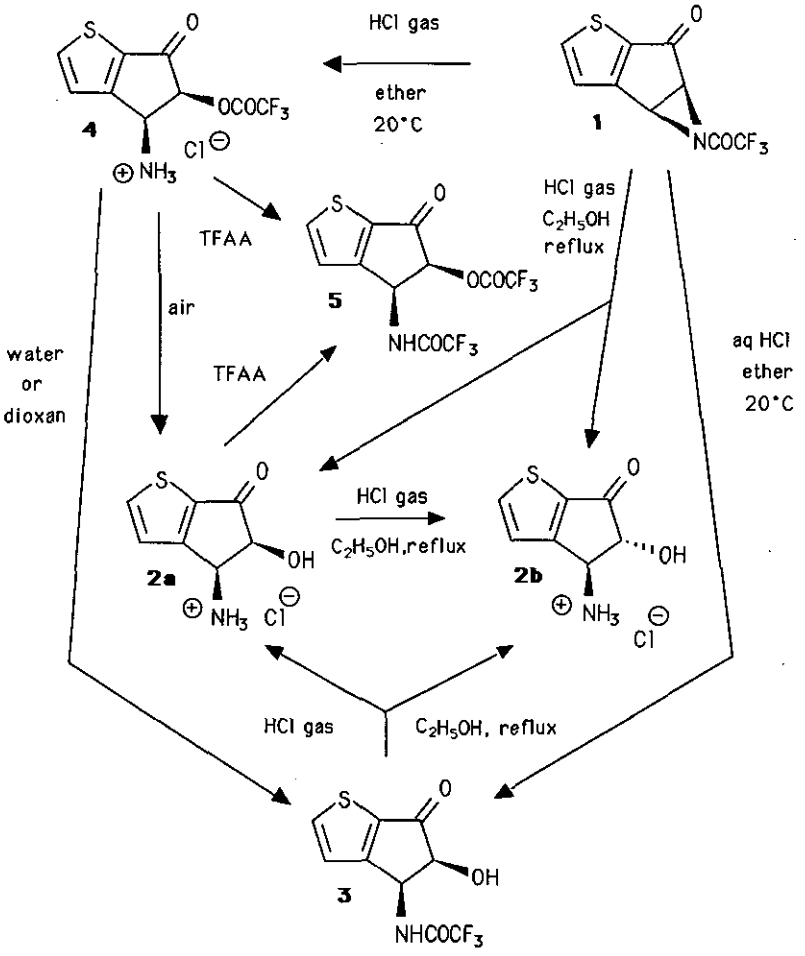


Perspective view of the molecule (**2a**) showing respectives positions of hydroxyl group (non localised hydrogen) and amino group.

The final positions of hydroxyl and amino groups of this latter compound were at last determinated by the epimerisation of **2a**, realized in refluxing ethanol, previously saturated with gaseous hydrochloric acid.This reaction led to a mixture, in equal parts, of the *cis* and *trans* isomers : starting material **(2a)** and **(2b)**. Comparison of the spectrometric data shown clearly that the second product of the cleavage of aziridine **(1)** was **2b.**

This result confirms the selective cleavage of the aziridine ring of **1**, between carbon C-2 and nitrogen, in acidic medium, which led to the selective formation of the α-hydroxy-β-aminocyclopentathiophenones result of the following sequence : cleavage of the aziridine ring, fixation of the hydroxyl group, hydrolysis of the trifluoroacetamido group and partial epimerisation.

With a view to put into order these different steps, we investigated various treatments of the aziridine **(1)** in acidic medium (Scheme 3).

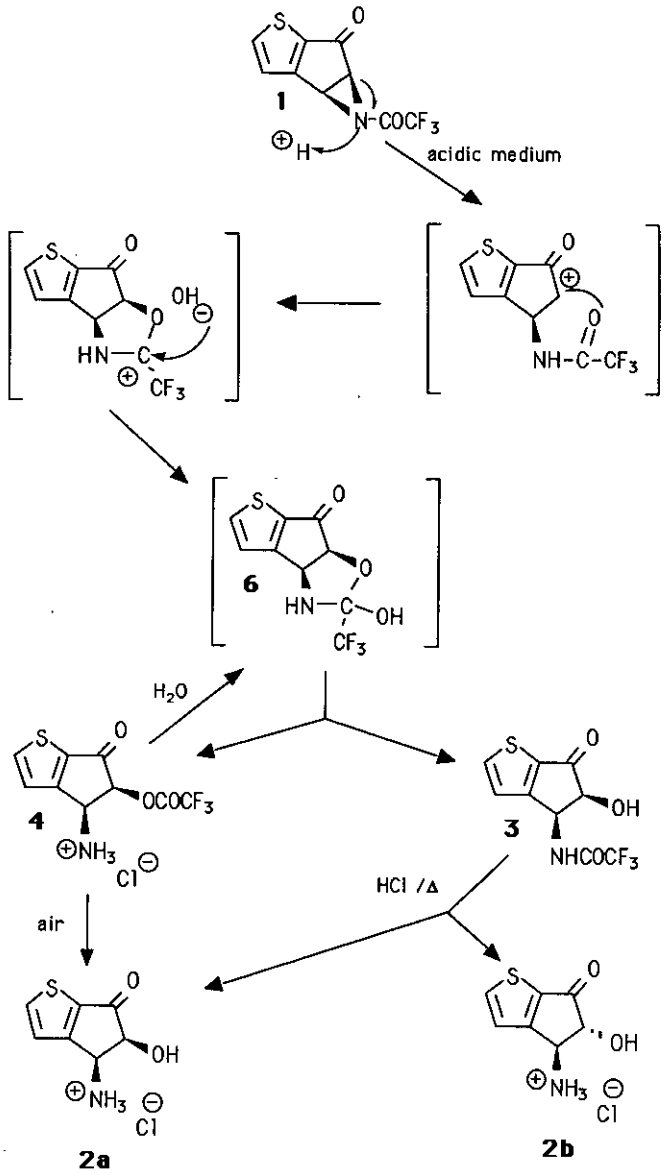


Scheme 3

Thus, an etheral solution of **1** was treated at room temperature with a 6 N aqueous solution of hydrochloric acid under vigourous stirring. After evaporation of ether, the reaction gave hydroxytrifluoroacetamido derivative **(3)** in quantitative yield. ^{1}H-Nmr spectrum revealed a *cis* structure. Then, **3** was refluxed in 6N aqueous hydrochloric acid to give a mixture, in equal parts, of the hydroxyammoniun chlorides **(2a)** and **(2b)**.
This reaction shows first that cleavage of the aziridine ring had preceded hydrolysis of the trifluoroacetamido group and secondly that fixation of hydroxyl group was realized in *cis* position to amino group. The epimerisation finally took place by heating in an acidic medium.
We can explain this surprising selective addition of the hydroxyl group on the most bulky *cis* position by an anchimeric assistance mechanism deduced from the following reaction. An etheral solution of aziridine **(1)** was treated, at room temperature, by a gaseous hydrochloric acid flow. When air was admitted in the reaction mixture, a precipitate **(4)** appeared. It was separated and the filtrate was removed under reduced pressure. The major residual solid was the *cis* hydroxytrifluoroacetamido compound **(3)**.
4 was identified to the *cis* trifluoroacetoxyammonium chloride and not to the trifluoroacetyl derivative as proposed in a previous paper.[1] Structure of **4** was established by ir spectrum analysis which revealed two carbonyl absorptions at 1805 and 1715 cm^{-1} and by the following reactions.
(4), in solid state, was exposed to air for 12 h to give the *cis*-hydroxyammonium chloride **(2a)** already described. Further, treatment of compounds **(4)** and **(2a)** by trifluoroacetic anhydride (TFAA) led to the same result : formation of the trifluoroacetoxytrifluoroacetamido compound **(5)**. At last, we have demonstrated that **4**, by dissolution in water or dioxane was able to rearrange into compound **(3)**.

In order to explain these results, we propose a pathway involving an anchimeric assistance reaction of trifluoroacetamido group.This route leads to the formation of the intermediate **(6)** whose rearrangement is able to give either trifluoroacetoxyammonium chloride **(4)** by cleavage of the C-N bond, or hydroxytrifluoroacetamide **(3)** by cleavage of the C-O bond (Scheme 4).
This mechanism implicates the participation of an hydroxyl anion produced by air moisture admitted in the reaction mixture. The fact that **4** was easily transformed into **3** by dissolution can be explained considering **4** as the kinetic product of the cleavage of the intermediate **(6)**. In solution, **4** is in equilibrium with **6** which finally leads to the thermodynamic product **(3)**. The isolation of **4** was due to its insolubility in ether and this explains that in all others solvents such as water or ethanol, the only products isolated after cleavage of aziridine are hydroxy derivatives with or without hydrolysis of trifluoroacetamido group. The anchimeric assistance of the trifluoroacetamido group is the only way to explain the conservation of the *cis* structure all along the sequence preceding the final epimerisation. This complicated mechanism is in agreement with a similar rearrangement described by Verdine [5] during the treatment of mitomycin with trifluoroacetic acid and our previous work concerning the indanoaziridines.[3]

These results will permit to initialize synthesis of new compounds which will be studied as potent enzyme inhibitors in relation with the recently described properties of some related indane derivatives.[6]


1
N-COCF3
⊕H
acidic medium
NH-C-CF3
HN—C
OH
CF3
6
H2O
4
OCOCF3
⊕NH3 Cl⊖
3
NHCOCF3
air
HCl /Δ
2a
2b

Scheme 4

EXPERIMENTAL

General Methods. Melting points were taken on a Köfler bank and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. Nmr spectra were recorded on a Jeol FX 200 in DMSO-d_6 solution using TMS as an internal standard. Chemical shift are reported in ppm downfield (δ) from TMS.

5-Hydroxy-6-oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thienyl-4-ammonium chlorides (2a) and (2b).

Method A : Aziridine (1) (2.5 g, 0.01 mol) was dissolved in a solution of ethanol (100 ml), previously saturated by gaseous hydrochloric acid. The reaction mixture was refluxed for 15 min and then the solvent was removed under reduced pressure. The residual solid (1.9 g, 97%) was constituted, in equal parts,by a mixture of **2a** and **2b**.

Method B : *cis*-Hydroxyammonium chloride (2a) (2 g, 0.01 mol) was treated in a similar way as method A. The residual solid (1.9 g, 9 7%) was constituted, in equal parts,by the same mixture of **2a** and **2b**.

Separation of *cis* and *trans* isomers :The previous mixture was dissolved in 2-propanol (50 ml). The insoluble solid was filtered to give the *trans* isomer (2b) as white crystals (0.85 g, 40%) : mp > 260°C (ethanol) ; ir (KBr) 3180 (OH), 3100 - 2800 (NH_3^+), 1715 (CO); ^{1}H-nmr 9.14 (broad, NH_3^+), 8.46 (d, $J_{H\text{-}2\,H\text{-}3}$ = 4.88 Hz, H-2), 7.60 (d, $J_{H\text{-}3\,H\text{-}2}$ = 4.88 Hz, H-3), 6.65 (broad, OH), 4.61 (d, $J_{H\text{-}5\,H\text{-}4}$ = 3.17 Hz, H-5), 4.51 (d, $J_{H\text{-}4\,H\text{-}5}$ = 3.17 Hz, H-4); ^{13}C-nmr 191.43 (C-6), 158.38 (C-6a), 143.19 (C-2), 139.26 (C-3a), 124.27 (C-3), 80.65 (C-5), 53.49 (C-4); Anal. Calcd for $C_7H_8NO_2ClS$: C, 40.88; H, 3.92; N, 6.81, S, 15.59. Found : C, 40.63; H, 3.78; N, 6.68; S, 15.40.

The filtrate was removed under reduced pressure. Residual crystals were recrystallized from 2-propanol to give **2a** as white crystals (0.75 g, 36%): mp > 260°C (2-propanol); ir (KBr) 3280 (OH), 3100 - 2540 (NH_3^+), 1675 (CO); ^{1}H-nmr 8.43 (broad, NH_3^+), 8.39 (d, $J_{H\text{-}2\,H\text{-}3}$ = 4.88 Hz, H-2), 7.41 (d, $J_{H\text{-}3\,H\text{-}2}$ = 4.88 Hz, H-3), 7.01 (broad, OH), 4.82 (d, $J_{H\text{-}5\,H\text{-}4}$ = 6.35 Hz, H-5), 4.78 (d, $J_{H\text{-}4\,H\text{-}5}$ = 6.35 Hz, H-4); ^{13}C-nmr 193.59 (C-6), 159.84 (C-6a), 142.55 (C-2), 140.62 (C-3a), 125.38 (C-3), 74.98 (C-5), 47.83 (C-4); Anal. Calcd for $C_7H_8NO_2ClS$: C, 40.88; H, 3.92; N, 6.81, S, 15.59. Found : C, 40.77; H, 3.94; N, 6.94; S, 15.37.

cis-5-Hydroxy-4-trifluoroacetylamino-4,5-dihydrocyclopenta[*b*]thiophen-6-one (3). A solution of aziridine (1) (2.5 g, 0.01 mol) in ether (150 ml) was stirred for 10 min, at room temperature, with a 6N aqueous hydrochloric acid solution (50 ml). The organic layer was separated, dried over calcium sulfate and the solvent was evaporated under vacuum. The solid residue was recrystallized from ethyl acetate to give 3 as white crystals (2.52 g, 95%): mp 205°C (ethyl acetate); ir (KBr) 3300 (NH), 3480 (OH), 1700 (CO); ^{1}H-nmr 9.44 (d, $J_{NH\,H\text{-}4}$ = 8.30 Hz, NH), 8.30 (d, $J_{H\text{-}2\,H\text{-}3}$ = 4.88 Hz, H-2), 7.23 (d, $J_{H\text{-}3\,H\text{-}2}$ = 4.88 Hz, H-3), 6.22 (broad, OH), 5.50 (dd, $J_{H\text{-}4NH}$ = 8.30 Hz , $J_{H\text{-}4\,H\text{-}5}$ = 6.34 Hz, H-4), 4.71 (d, $J_{H\text{-}5\,H\text{-}4}$ = 6.34 Hz, H-5); Anal. Calcd for $C_9H_6NO_3F_3S$: C, 40.76; H, 2.28; S, 12.09. Found : C, 40.88; H, 2.29; S, 12.20.

cis-6-Oxo-5-trifluoroacetoxy-5,6-dihydro-4*H*-cyclopenta[*b*]thienyl-4-ammonium chloride (4). A solution of aziridine (1) (2.5 g, 0.01 mol) in ether (100 ml) was bubbled at room temperature for 45 min by a gaseous hydrochloric acid flow. The precipitate formed was filtered and washed with ether to give 4 as white crystals (2.2 g, 73%) : mp > 260°C (ethanol); ir (KBr) 3100 - 2520 (NH_3^+), 1805 and 1715 (CO); ^{1}H-nmr 8.97 (broad, NH_3^+), 8.48 (d, $J_{H\text{-}2\,H\text{-}3}$ = 4.88 Hz, H-2), 7.50 (d, $J_{H\text{-}3\,H\text{-}2}$ = 4.88 Hz, H-3), 6.35 (d, $J_{H\text{-}5\,H\text{-}4}$ = 6.29 Hz, H-5), 5.12 (d, $J_{H\text{-}4\,H\text{-}5}$ = 6.29 Hz, H-4).

cis -5-Trifluoroacetoxy-4-trifluoroacetylamino-4,5-dihydrocyclopenta[*b*]thiophen-6-one (5): A solution of trifluoroacetoxyammonium chloride (4) (3.00 g, 0.01 mol) in trifluoroacetic anhydride (25 ml) was heated at 60°C for 15 min. The excess of anhydride was removed under reduced pressure and the oily residue was triturated with water to give 5 which was recrystallized from ether (3.4 g, 94%) : mp 127°C; ir (KBr) 3280 (NH), 1790 and 1710 (CO); ^{1}H-nmr 10.00 (d, $J_{NH\,H-4}$ = 8.50 Hz, NH), 8.42 (d, $J_{H-2\,H-3}$ = 4.88 Hz, H-2), 7.36 (d, $J_{H-3\,H-2}$ = 4.88 Hz, H-3), 6.24 (d, $J_{H-5\,H-4}$ = 6.30 Hz, H-5), 5.79 (dd, $J_{H-4\,H-5}$ = 6.30 Hz, $J_{H-4\,NH}$ = 8.50 Hz, H-4); Anal. Calcd for $C_{11}H_5NO_4F_6S$: C, 36.57; H, 1.39; N, 3.88. Found : C, 36.64; H, 1.41; N, 3.71.
cis -Hydroxyammonium chloride (2a) (2.00 g, 0.01 mol)was treated with trifluoroacetic anhydride as above to give (5) (3.3 g, 92%).

X-ray structure determination of (2a). 832 independent reflections were recorded at room temperature on an automated Enraf-Nonius CAD4 diffractometer using CuK_α radiation (λ = 1.54178 Å) monochromated by a graphite plate untill θ = 60°C. The intensities were corrected for Lorentz, polarization but not for absorption (υ = 56.0 cm $^{-1}$). 688 reflections with $F_0 > 3\,\sigma\,(F_0)$ have been considered as observed and used for refinement.The structure was solved by direct methods with MULTAN program implanted in MolEn [7] and was refined by the block-diagonal least-squares method. Hydrogen atoms were placed in theoretical positions (excepted for hydroxyl group) and refined by an isotropic manner.In spite of its important value, the final reliability factor R = 0.11 (small platelet, 137 parameters refined for only 668 reflections used) is unequivocal towards availability of result.

REFERENCES

1. P. Dallemagne, S. Rault, D. Maume, and M. Robba, Heterocycles , 1987, 26, 1449.

2. S. Rault, J. C. Pilo, P. Dallemagne, M. P. Foloppe, and M. Robba, Bull. Soc. Chim. Fr., 1990, 316.

3. J. C. Pilo, S. Rault, P. Dallemagne, and M. Robba, Bull. Soc. Chim. Fr., 1991, 207.

4. P. Dallemagne, S. Rault, M. Cugnon de Sévricourt, Kh. M. Hassan, and M. Robba, Tetrahedron Lett., 1986, 27, 2607.

5. G. L. Verdine, B. F. McGuiness, and K. Nakanishi, Heterocycles, 1987, 25, 577.

6. T. A. Lyle, C. M. Wiscount, J. P. Guare, W. J. Thompson, P. S. Anderson, P. L. Darke, J. A. Zugay, E. A. Emini,W. A.Schleif, J. C. Quintero, R. A. F. Dixon, I. S. Sigal, and J. R. Huff, J. Med. Chem., 1991, 34, 1222.

7. MolEN, An interactive Structure Solution Procedure, Enraf-Nonius, Delft, Pays-Bas, 1990.

Received, 30th January, 1992