Tetrahedron Vol. 42, No. 1, pp. 71 to 80, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00

UNUSUAL RING OPENING OF A CYCLOPROPYLIDENEAMINE DERIVATIVE DURING A FAVORSKII-TYPE REARRANGEMENT OF α-CHLOROKETIMINES

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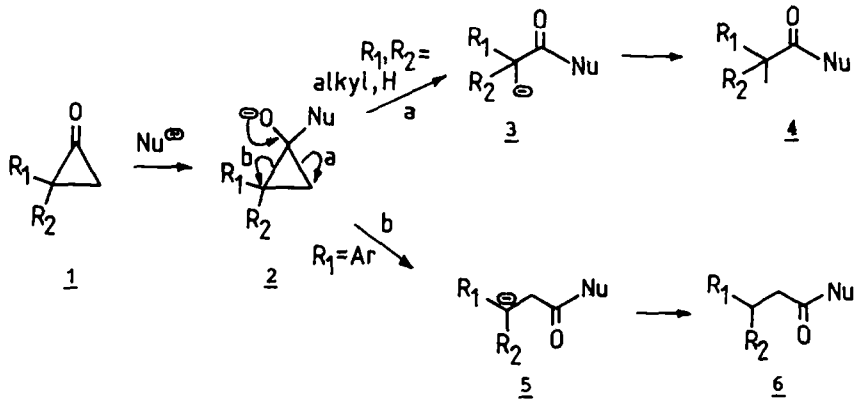
(*Received in UK* 14 *May* 1985)

Abstract : The reaction of N-(3-chloro-3-methyl-2-butylidene)amines (i.e. α-chloroketimines) with lithium diisopropylamide in tetrahydrofuran gave rise to an unexpected reaction leading to 2-(N-alkylimino)-3,3-dimethyl-1-isopropyl-5-(2-methylpropylidene)pyrrolidines in good yields. The reaction mechanism is interpreted in terms of a Favorskii-type 1,3-dehydrochlorination affording intermediate cyclopropylideneamines (N-analogues of cyclopropanones), which "dimerize" in an unusual way. This mechanism entails a "normal" opening as well as an "abnormal" opening of incipient cyclopropylideneamine adducts. This rearrangement represents an example of the scarcely reported abnormal opening of functionalized cyclopropylamines.

Introduction

The Favorskii rearrangement is the well-known base-induced skeletal rearrangement of α-halogenated ketones to afford carboxylic acid derivatives (acids s.s., esters, amides).[1,2] It is now well-established that this reaction either proceeds via a cyclopropanone intermediate (1) or via a less frequently encountered so-called semi-benzilic type rearrangement. The regiochemistry of the opening of cyclopropanone adducts 2 during the more abundant type of the Favorskii rearrangement is in accord with the relative stabilities of the putative carbanions (3 and 5) which are generated by cleavage of the carbon-carbon bonds (Scheme I). However, in a few cases of the Favorskii rearrangement of isomeric α-haloketones it was noted that a larger group than a methyl in the intermediate cyclopropanone increased the amount of carboxylic acid derivative derived from the incipient less stable carbanion.[3] This is still a puzzling result (on the assumption that free carbanions are involved as intermediates) why the propyl substituted carbanion should be less stable than the methyl substituted species. The most pertinent exception to the normally expected ring cleavage of cyclopropanones was observed during the methoxide induced ring opening of 2,2-di-t-butylcyclopropanone 1 (R_1=R_2=t-Bu) which



SCHEME I

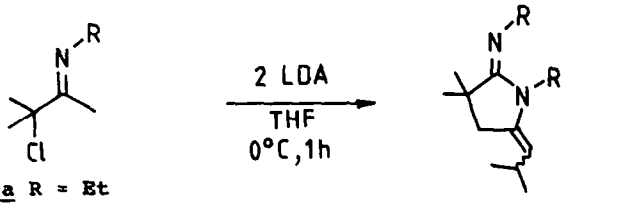
afforded only 25% of the "normal" ring opening product 4 (R_1=R_2=t-Bu; Nu=OMe), but gave rise to predominantly (75%) the "abnormal" opening product 6 (R_1=R_2=t-Bu; Nu=OMe).[4] These experiments demonstrated that steric factors, in addition to carbanion stability, determine the direction of the base-catalyzed ring opening of cyclopropanones.[3]

α-Halogenated ketimines, i.e. the N-analogues of α-halogenated ketones, have also been shown to rearrange with bases via a Favorskii-type mechanism, which entails the intermediacy of cyclopropylidenamines.[5-10] Also in these cases, the direction of ring opening of the N-analogues of cyclopropanones has been shown to follow considerations of carbanion stabilities.[10]

We would like to report now an unusual ring opening of an intermediate cyclopropylidenamine derivative during a Favorskii-type rearrangement of α-chloroketimines.

Results and Discussion

The reaction of N-(3-chloro-3-methyl-2-butylidene)amines 7a,b,c, easily prepared from 3-chloro-3-methyl-2-butanone and the corresponding primary amine in the presence of titanium(IV)chloride,[11] with two equivalents of lithium diisopropylamide in tetrahydrofuran (0°C/2 h) afforded 2-(N-alkylimino)-3,3-dimethyl-1-isopropyl-5-(2-methylpropylidene)pyrrolidines 8a,b,c in 65-80% yield (Scheme II). Compounds 8 occurred as one stereoisomer but a definitive stereochemical assignment could not be established. Compound 8b was investigated by 2D-NOE NMR experiments which revealed some interaction between the substituent on the 1 position (N-atom) and the adjacent isopropyl groups. However a decission regarding the stereochemistry could not be taken because of overlap of the signals (360 MHz, ^{1}H NMR) of the allylic methylene function (4-position) and the vinylic hydrogen on the exocyclic double bond.



7a R = Et
7b R = i-Pr
7c R = Me

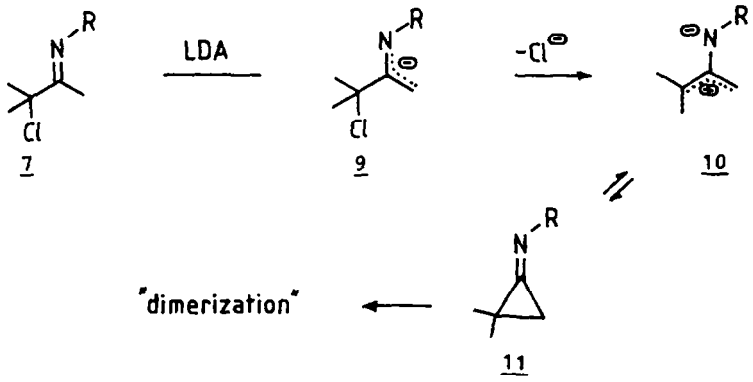
8a R = Et
8b R = i-Pr
8c R = Me

SCHEME II

However, inspecting these molecules by Dreiding models indicated a large sterical congestion when the molecule had the Z-stereochemistry at the olefinic double bond. This sterical hindrance is totally absent in the E-stereoisomer and this might be an indication that this is the actual stereochemistry involved in the isolated compounds 8.

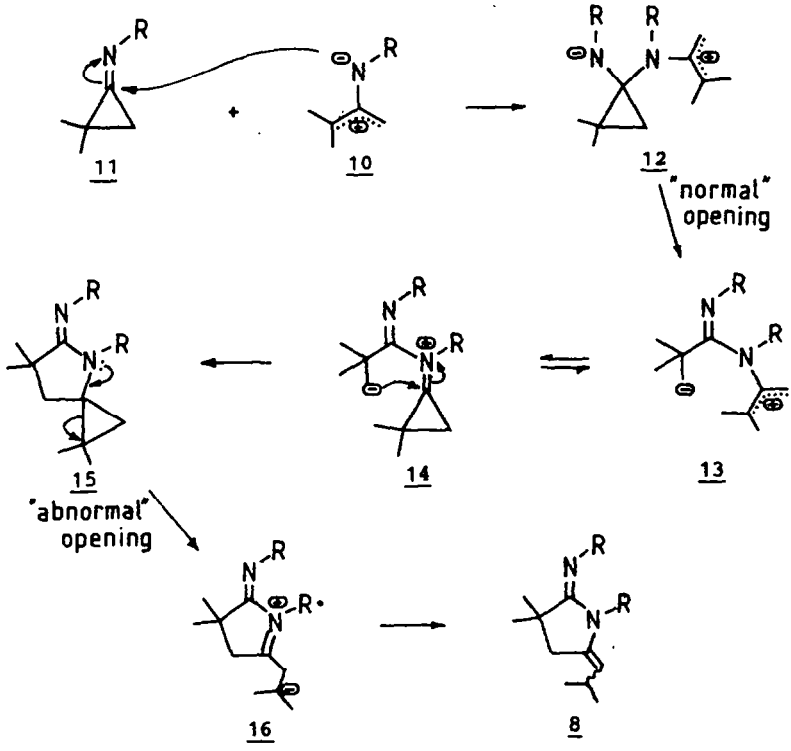
Compounds 8 are characterized by a strong stretching vibration at 1640-1650 cm^{-1} and by a complex resonance pattern in the ^1H NMR spectra. Important structural features could be deduced from the 360 MHz ^1H NMR spectrum, as exemplified for heterocycle 7b. Three doublets, each integrating for six protons, are situated at 0.92, 1.07 and 1.27 ppm while the six proton singlet at 1.28 ppm is attributed to a geminal dimethyl function on a quaternary carbon atom. The methine septets of the isopropyl groups linked to nitrogen resonate at 4.07 and 4.49 ppm, but the third methine signal is a very broad multiplet (δ 2.2 ppm) covered by the doublet (allylic coupling, J=1.8Hz) of the methylene group. The olefinic hydrogen is situated at 4.29 ppm as a broadened doublet (J=9Hz). Of major importance for the structural elucidation were the typical ^{13}C NMR signals at 103.30 ppm (d, β-carbon of the enamine moiety), 137.10 ppm (s,quaternary α-carbon of the enamine moiety) and 160.56 ppm (s, imino carbon). Putting all structural units together suggest compounds 8 to have a heterocyclic five membered ring structure with an exocyclic olefinic double bond. From the mass spectrum (molecular ion) and the elemental analysis it was concluded that the reaction products originated from a dehydrochlorination step followed by a dimerization process. In view of the known chemistry of α-haloimines[12] and its potential for base-induced 1,3-dehydrochlorinations, it is reasonable to propose a mechanistic rationale starting with a base-induced Favorskii-type ring contraction affording cyclopropylideneamines 11 (Scheme III). The final molecules 8 contain two such entities 11 and, therefore, a "dimerization" process involving a mechanism as outlined below is suggested.

The dimerization reaction might be envisioned as an addition of zwitter-ion 10 across the reactive imino bond of the cyclopropylideneamine 11 and subsequent



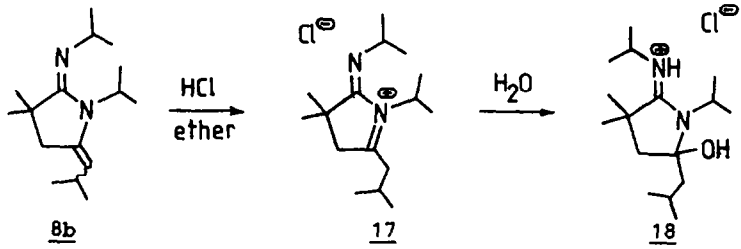
SCHEME III

"normal" opening (i.e. generating the most stable carbanion) of the resulting aminal anion 12. 2-Azaallylic carbenium ions are the nitrogen analogues of the well-known oxyallylic carbenium ions, which have received considerable interest in recent years.[13] The equilibrium between 2-azaallylic carbenium ions and their ring closed isomeric species, i.e. cyclopropylideniminium ions, has been discussed recently.[14] Applying this equilibrium to 13 provides 14 which suffers nucleophilic addition to afford bicyclic intermediate 15. In order to produce amidines 8 this bicyclic substrate has to undergo an "abnormal" ring opening by which the least stable carbanionic species 16 is formed.[15] Protonation of this carbanion and conversion (by deprotonation) of the iminium moiety into the corresponding enamine



SCHEME IV

yields the functionalized amidines 8. The enamine has the exocyclic structure which is clearly understood in terms of the formation of the less sterically hindered olefinic double bond (Scheme IV). As discussed already above the ^{1}H NMR spectra of compounds 8 are very complex due to overlap of several signals (for instance compound 8b contains three isopropyl groups). Therefore it was tried to grow a single crystal of compound 8b but any effort in various solvent systems remained unsuccessful. Derivatization proved also to be difficult. Compound 8b was resistent to boiling aqueous mineral acids (12N HCl, 50% H_2SO_4) and was not reduced by lithium aluminium hydride in ether (reflux). However, treatment of 8b with dry hydrogen chloride in ether gave a solid hydrochloride 17, which on crystallization from water produced nice crystalls of the water addition product 18 (Scheme V).



8b 17 18

SCHEME V

The stability of carbinolamines such as 18 is not surprising in view of the stabilizing properties of the electron-withdrawing imidoyl substituent on nitrogen.

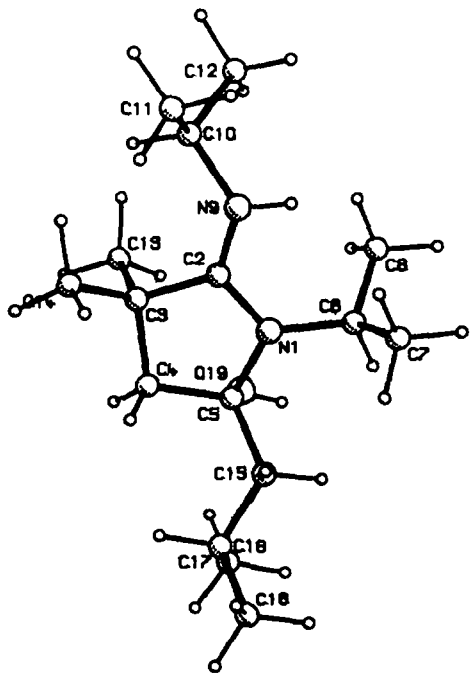


Figure 1 : Stereoscopic view of carbinolamine salt 18.

Carbinolamine 18 was subjected to X-ray crystallographic analysis, which clearly established its structure. The principal crystallographic parameters are : monoclinic, $P2_1$, a=8.532(1), b=11.157(2), c=9.735(2)Å, β=90.42(2)°, V=926.7(3)Å^3, Z=2, Dx=1.09 g.cm^{-3}, MoKα, λ=0.71069Å, μ=2.1 cm^{-1}, F(000)=336, T=291K, R=0.034 for 1352 observed reflections. The atomic parameters are given in Table 1. Figure 1 gives a stereoscopic view of the molecule showing the numbering of the atoms. Bond distances and angles are given in Tables 2 and 3 while torsion angles are compiled in Table 4. In addition, the following hydrogen bonds can be described : O_{19}-H...Cl (x,y,z-1) 3.13 Å and N_9-H...Cl (-x, 1/2 + y, 1-z) 3.34 Å.

TABLE 1

Atomic coordinates(X10^4) and equivalent temperature factors(Å^2)

$B_{eq}=(8/3)\pi^2\Sigma_i\Sigma_j U_{ij}a^*_i a^*_j a_i a_j$

	x/a	y/b	z/c	Beq
N1	2205(3)	1803(3)	1093(3)	2.69(4)
C2	2304(4)	1873(3)	2452(3)	2.54(5)
C3	3529(4)	1009(3)	3011(3)	2.97(5)
C4	4450(4)	723(4)	1695(3)	3.26(6)
C5	3344(4)	930(3)	481(3)	2.65(5)
C6	911(4)	2261(3)	199(4)	3.47(6)
C7	1160(5)	3571(4)	-193(4)	4.43(7)
C8	-710(4)	2002(4)	776(5)	4.62(8)
N9	1447(3)	2601(3)	3194(3)	2.85(5)
C10	1198(5)	2558(4)	4697(3)	3.89(7)
C11	1796(7)	3700(5)	5355(4)	5.85(10)
C12	-543(5)	2368(5)	4946(6)	5.72(10)
C13	2711(5)	-123(4)	3557(4)	4.62(7)
C14	4660(5)	1549(5)	4088(4)	4.65(8)
C15	4155(4)	1488(3)	-751(3)	2.89(5)
C16	5598(4)	815(4)	-1288(4)	3.36(6)
C17	5211(5)	-368(4)	-1981(5)	5.10(9)
C18	6482(5)	1631(5)	-2263(4)	5.00(8)
O19	2567(3)	-139(2)	170(2)	3.37(4)
CL	818(1)	0	7335(1)	4.07(2)

TABLE 2

Bond distances(Å)

C2 -N1	1.328(4)	C5 -N1	1.502(4)
C6 -N1	1.490(4)	C3 -C2	1.519(5)
N9 -C2	1.313(4)	C4 -C3	1.541(4)
C13 -C3	1.539(5)	C14 -C3	1.542(5)
C5 -C4	1.524(4)	C15 -C5	1.522(5)
O19 -C5	1.397(4)	C7 -C6	1.527(6)
C8 -C6	1.524(5)	C10 -N9	1.481(4)
C11 -C10	1.513(6)	C12 -C10	1.522(6)
C16 -C15	1.537(5)	C17 -C16	1.517(6)
C18 -C16	1.520(6)		

TABLE 3

Bond angles(°)

C5	-N1	-C2	113.3(2)	C6	-N1	-C2	127.1(3)
C6	-N1	-C5	118.0(2)	C3	-C2	-N1	111.0(3)
N9	-C2	-N1	123.5(3)	N9	-C2	-C3	125.5(3)
C4	-C3	-C2	100.8(2)	C13	-C3	-C2	109.4(3)
C13	-C3	-C4	110.6(3)	C14	-C3	-C2	114.9(3)
C14	-C3	-C4	109.0(3)	C14	-C3	-C13	111.6(3)
C5	-C4	-C3	107.3(3)	C4	-C5	-N1	100.9(2)
C15	-C5	-N1	110.3(3)	C15	-C5	-C4	113.0(3)
O19	-C5	-N1	109.4(2)	O19	-C5	-C4	109.2(3)
O19	-C5	-C15	113.3(3)	C7	-C6	-N1	111.7(3)
C8	-C6	-N1	113.0(3)	C8	-C6	-C7	113.7(3)
C10	-N9	-C2	127.4(3)	C11	-C10	-N9	109.9(3)
C12	-C10	-N9	108.0(3)	C12	-C10	-C11	112.1(4)
C16	-C15	-C5	116.0(3)	C17	-C16	-C15	113.8(3)
C18	-C16	-C15	108.8(3)	C18	-C16	-C17	110.6(3)

TABLE 4

Torsion angles(°) (σ=0.6)

C5	-N1	-C2	-C3	-1.7
C5	-N1	-C2	-N9	178.2
C6	-N1	-C2	-C3	163.6
C6	-N1	-C2	-N9	-16.5
C2	-N1	-C5	-C4	-14.3
C2	-N1	-C5	-C15	-134.0
C2	-N1	-C5	-O19	100.7
C6	-N1	-C5	-C4	179.0
C6	-N1	-C5	-C15	59.2
C6	-N1	-C5	-O19	-66.0
C2	-N1	-C6	-C7	87.1
C2	-N1	-C6	-C8	-42.6
C5	-N1	-C6	-C7	-108.2
C5	-N1	-C6	-C8	122.1
N1	-C2	-C3	-C4	16.7
N1	-C2	-C3	-C13	-99.9
N1	-C2	-C3	-C14	133.7
N9	-C2	-C3	-C4	-163.2
N9	-C2	-C3	-C13	80.2
N9	-C2	-C3	-C14	-46.2
N1	-C2	-N9	-C10	164.8
C3	-C2	-N9	-C10	-15.4
C2	-C3	-C4	-C5	-25.1
C13	-C3	-C4	-C5	90.5
C14	-C3	-C4	-C5	-146.4
C3	-C4	-C5	-N1	24.2
C3	-C4	-C5	-C15	141.9
C3	-C4	-C5	-O19	-91.0
N1	-C5	-C15	-C16	167.1
C4	-C5	-C15	-C16	55.0
O19	-C5	-C15	-C16	-69.9
C2	-N9	-C10	-C11	118.7
C2	-N9	-C10	-C12	-118.7
C5	-C15	-C16	-C17	70.0
C5	-C15	-C16	-C18	-166.2

Experimental Section

Infrared spectra were recorded with a Perkin Elmer model 1310 spectrophotometer while ^{1}H NMR spectra were measured with Varian T-60 (60 MHz) or Bruker WH-360 FT (360 MHz) spectrometers. ^{13}C NMR spectra were taken on Varian FT 80 (20 MHz) or Bruker WH-360 FT (50 MHz) spectrometers. Mass spectra were obtained from a Varian MAT 112 mass spectrometer (direct inlet system; 70 eV). Dry tetrahydrofuran was prepared from benzophenone ketyl and lithium diisopropylamide was prepared

in THF from diisopropylamine and butyllithium (in hexane) or methyllithium (in ether). α-Chloroketimines 7a, 7b, 7c were synthesized by our previously published method.[11,16]

Reaction of α-Chloroketimines 7 with Lithium Diisopropylamide in Tetrahydrofuran

A solution of 8.88 g (0.088 mol) of diisopropylamine in 40 ml of freshly distilled dry tetrahydrofuran was placed in an ice bath and treated with 41 ml n-butyllithium in hexane (1.95 M; 0.08 mol). After stirring for 15 minutes at the ice bath temperature, this solution was treated dropwise with a solution of 6.46 g (0.04 mol) of N-(3-chloro-3-methyl-2-butylidene)isopropylamine 7b in 6 ml of dry tetrahydrofuran. The homogeneous solution was stirred one our at the same temperature after which the reaction mixture was poured into aqueous sodium hydroxide (0.5 N), extracted with ether and dried (K_2CO_3). After evaporation of the solvent, the residual oil was distilled to afford 7.3 g (73%) of heterocycle 8b, bp 121-130°C/15 mmHg or 63-66°C/0.01 mmHg, mp 49°C (MeOH).
IR (KBr) : 1640 cm^{-1} (strong).
^1H NMR (360 MHz, $CDCl_3$) : δ 0.92 (6H, d, J=6.5Hz, $\underline{Me}_2CH$); 1.07 (6H, d, J=6.0Hz, $\underline{Me}_2CH$); 1.27 (6H, d, J=6.5Hz, $\underline{Me}_2CH$); 1.28 (6H, s, $\underline{Me}_2C$-C=N); 2.3 (1H, m, C$\underline{H}$-C=C); 2.3 (2H, d, J=1.8Hz, CH_2); 4.49 (1H, septet, J=6.5Hz, N=C-N-C$\underline{H}$); 4.06 (1H, septet, J=6.0Hz, C=N-C$\underline{H}$); 4.29 (1H, broad d, J=9Hz, C$\underline{H}$=C).
^{13}C NMR (20 MHz, $CDCl_3$) : δ 17.93 (q, Me_2); 24.44 (q, Me_2); 25.49 (q, Me_2); 26.77 (q, Me_2); 27.63 (d, $\underline{C}$H-C=C); 39.30 (s, $\underline{C}$-C=N); 43.19 (t, CH_2); 43.19 (d, N$\underline{C}$H); 46.64 (d, N$\underline{C}$H); 103.73 (d, N-C=C$\underline{H}$); 136.32 (s, N-$\underline{C}$=C); 160.74 (s, $\underline{C}$=N).
Mass spectrum m/e (%) : 250 (M^+; 38); 235 (52); 207 (100); 194 (14); 193 (76); 166 (19); 165 (33); 151 (48); 150 (14); 111 (19); 109 (21); 83 (19); 82 (29); 69 (38); 68 (29); 55 (19); 43 (39); 42 (28); 41 (66).
Elemental analysis : C (calcd) : 76.74 %, C (found) : 76.59 %; H (calcd) : 12.08 %, C (found) : 12.19 %; N (calcd) : 11.19 %, N (found) : 11.25 %.
Compounds 8a (R=Et) and 8c (R=Me) were obtained in similar way as described for compound 8b.

Compound 8a (R=Et), bp 53-57°C/0.01 mmHg, yield 65 %.
IR (NaCl) : 1640 cm^{-1} (br, s).
^1H NMR (60MHz, $CDCl_3$) : δ 0.9-1.3 (12H, overlapping signals, 4 Me); 1.32 (6H, s, $\underline{Me}_2C$-C=N); 2.2 (1H, m, C$\underline{H}$-C=C); 2.40 (2H, d, J=1.7Hz, $\underline{CH}_2$-C=C); 3.54 and 3.48 (each 2H, each q, J=7.5Hz and J=7Hz resp., $\underline{CH}_2$-N=C-N-$\underline{CH}_2$); 4.20 (1H, dxt, J=9Hz, J=1.7Hz, C$\underline{H}$=C).
Mass spectrum m/e (%) : 222 (M^+; 9); 207 (44); 179 (12); 152 (8); 110 (12); 97 (12); 96 (23); 91 (14); 82 (34); 81 (9); 70 (10); 69 (27); 68 (52); 67 (14); 65 (8); 57 (13); 56 (31); 55 (39); 54 (14); 53 (17); 44 (20); 43 (27); 42 (39); 41 (100); 40 (14); 39 (27).
Elemental analysis : C (calcd) : 75.62 %, C (found) : 75.51 %; H (calcd) : 11.79 %, H (found) : 11.64 %; N (calcd) : 12.60 %, N (found) : 12.69 %.

Compound 8c (R=Me); bp 117-120°C/12 mmHg, yield 80 %.
IR (NaCl) : 1650 cm^{-1} (br, s).
^1H NMR (60MHz, $CDCl_3$) : δ 0.98 (6H, d, J=6.5Hz, $\underline{Me}_2CH$); 1.34 (6H, s, Me_2); 2.4 (2H, d, J=2Hz, CH_2); 2.86 (3H, s, CH_3N); 3.26 (3H, s, C=NCH_3); 2.4 (1H, m, C$\underline{H}Me_2$); 4.16 (1H, dxt, J=7Hz, J=2Hz, C$\underline{H}$=C).

Mass spectrum m/e (%) : 194 (M^+; 23); 179 (93); 138 (20); 95 (23); 82 (55); 56 (14); 55 (17); 42 (32); 41 (25); 40 (100).
Elemental analysis : C (calcd) : 74.17 %, C (found) : 74.29 %; H (calcd) : 11.41 %, H (found) : 11.48 %; N (calcd) : 14.42 %, N (found) : 14.29 %.

Synthesis of amidinium salt 18

The reaction of cyclic amidine 8b (R=i-Pr) with excess dry hydrogen chloride in dry ether (room temperature) produced a salt (mp 161°), which was dissolved in water. On standing for two weeks, nice crystals separated (mp 158°C) which were shown by X-ray analysis to be carbinol amine salt 18 (see Figure 1).
IR (KBr) : 3130 cm^{-1} (s) and 1630 cm^{-1} (s).
^1H NMR (60MHz, DMSO-d_6/$CDCl_3$ 1:1) : δ 1.03 (6H, d, J=6Hz, Me_2CH); 1.41 (6H, d, J≈6Hz, partially covered, Me_2CH); 1.47 (6H, s, Me_2); 2-2.7 (3H, m, CH_2CH); 3.36 (1H, br s, OH); 4.3 (1H, m, NCH); 5.1 (1H, m, NCH); 9.8 (1H, br, C=NH-).

X-Ray crystallographic analysis

A parallelepiped crystal of 18 with dimensions 0.2x0.2x0.4 mm was used. Lattice parameters were refined using 15 reflections in the range 4° < 2θ < 20°. Syntex $P2_1$, graphite monochromatized MoK_α radiation.
1453 hk±l independent reflections with $\sin\theta/\lambda < 0.561$ $Å^{-1}$, 1352 with $I > 2.5\sigma$. The standard reflection (2, 2, -1) was checked every 50 reflections : no significant deviation was observed. The structure was solved by SHELX84. Anisotropic least squares refinement (SHELX76) using F; H isotropic with common refined temperature factor (B = 6.2 $Å^2$). $w = 1/(\sigma^2 + 0.00046F^2)$, R = 0.034, R_w = 0.038, S = 2.1 for 1352 observed reflections. Final maximum shift to error = 0.12. Maximum and minimum heights in final difference fourier synthesis = 0.18 and -0.14 e.Å-3.

Acknowledgements : We are greateful to the "Commissariaat-Generaal voor de Internationale Culturele Samenwerking" (Belgium) for a post-doctoral research grant for one of us (Mariana Palamareva) and to the Belgian National Fund for Scientific Research for financial support to the laboratory. We are also indebted to Prof. M.J.O. Anteunis, Dr. F. Borremans and Mr. Weiguo Zhang (Laboratory of Organic Chemistry, NMR Spectrometric Unit, Faculty of Sciences, State University of Gent) for recording the 360 MHz ^1H NMR spectrum and carrying out the 2D-NOE experiments.

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N. De Kimpe and J.-P. Declercq are Senior Research Associates of the Belgian National Fund for Scientific Research.
This paper was presented at the "10th International Congress of Heterocyclic Chemistry" (Waterloo, Canada) (1985).

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