Pergamon

Tetrahedron, Vol. 52, No. 48, pp. 15157-15170, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00952-0

Imidazo[1,5-g][1,4]diazepines, TIBO Analogues Lacking the Phenyl Ring : Synthesis and Evaluation as Anti-HIV Agents.

Yves L. Janin,[a] Anne-Marie Aubertin,[b] Angèle Chiaroni,[a] Claude Riche,[a]
Claude Monneret,[c*] Emile Bisagni,[d*] David S. Grierson*[a]

[a]Institut de Chimie des Substances Naturelles CNRS, Av. de la Terrasse, F-91198 Gif-sur-Yvette.
[b]INSERM U74, Institut de Virologie, 3 rue Koeberlé, F-67000 Strasbourg.
[c]CNRS, URA 1387, Institut Curie, Section de Biologie, 26 rue d'Ulm, F-75005 Paris.
[d]CNRS, URA 1387, Institut Curie, Section de Biologie, Université de Paris Sud, F-91405 Orsay.

Abstract : The imidazo[1,5-g][1,4]diazepine derivatives **7a** and **7b**, analogues of TIBO lacking the aromatic ring, were prepared as part of a research program to find compounds displaying antiviral activity against HIV-2 and resistant strains of HIV-1. Condensation of N-trityl and N-tosyl 4-(2-chloroethyl)-imidazole with the appropriate amino alcohols gave compounds 10a-c and 16a-e. The hydroxyl group in these intermediates was activated toward closure of the [1,4]diazepine ring by either conversion to the corresponding chloro derivative, or by N → O transfer of the tosyl group. However, only cyclization to compounds **13a** and **13b** proved efficient. These products were converted to the target molecules **7** by reaction of their C-2 anion with S8. In vitro evaluation of compounds **7a,b** and **13a,b** in cell culture (CEM SS/HIV-1-LAI and CEM SS/HIV 1 nevirapine resistant cells) revealed that only **13b** displayed minimal activity. Copyright © 1996 Elsevier Science Ltd

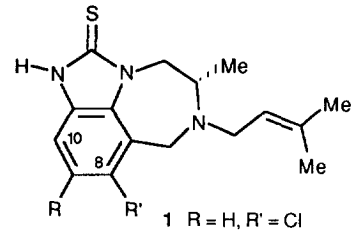
INTRODUCTION

The 4,5,6,7-tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1H)-thione (TIBO) **1**[1] was the first member of a series of seemingly structurally unrelated heterocycles to be discovered which are potent selective, non competitive inhibitors of HIV-1 reverse transcriptase (RT). This group of non nucleoside RT inhibitors (NNRTI's)[2-11] interferes with the function the viral polymerase through interaction at a common "allosteric" binding site which is in close proximity to the catalytic site of DNA synthesis.[11-14] Early X ray diffraction[15-19] and photo-affinity labelling[20,21] experiments showed that some 30 amino acids make-up this hydrophobic pocket. Further results from mutagenesis studies and clinical trials[22,23] showed that through point mutation[24-26] of certain of these amino acids, HIV strains resistant to TIBO and the other NNRTI's arise quickly. Within the TIBO family, a number of structural modifications have been made in the search for new compounds which block the replication of both wild type HIV-1 and the different resistant strains.

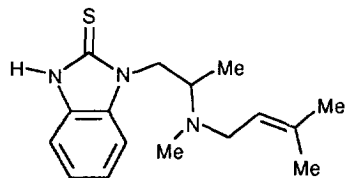
From SAR studies, the importance of the thioimidazolone system[27-29], the N-dimethylallyl side chain[27,28] and the seven membered diazepine ring[30,31] in TIBO, on biological activity, was established. Thus acyclic analogues such as benzimidazole **2** are either weak inhibitors of RT_1 or inactive.[31,32] However, certain urea and thiourea derivatives such as **3** which possess some conformational rigidity display potent anti HIV-1 activity.[33] Replacement of the diazepine tertiary nitrogen as in the racemic "carba" analogues **4** has also shown to be possible,[34] as is the exchange of the phenyl ring by a pyridine moiety.[35] However, the corresponding change for

Fax : (33) 01-6907-7247
e-mail : grierson@icsn.cnrs-gif.fr

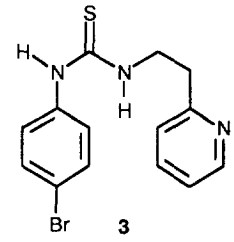
a pyrimidine ring failed to give active compounds.[36] The influence of a 8-Cl substitution of the aromatic ring in potentiating the activity of the TIBO system is also remarkable,[35] as is the recent finding that shifting the position of the chloro group from C-8 to C-9 (cf. **5**) restores activity (EC_{50} = 0.13 μM) against the HIV-1 strain resistant to compound **1**.[37]



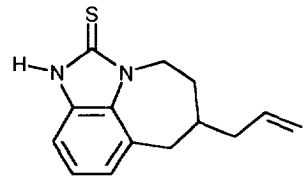
1 R = H, R' = Cl
5 R = Cl, R' = H



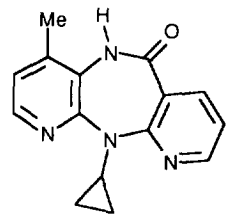
2



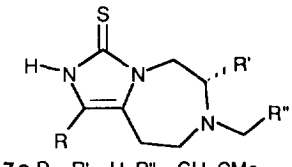
3



4



6



7a R = R' = H, R" = $CH{=}CMe_2$
7b R = R' = H, R" = Ph
7c R = H, R' = Me, R" = $CH{=}CMe_2$

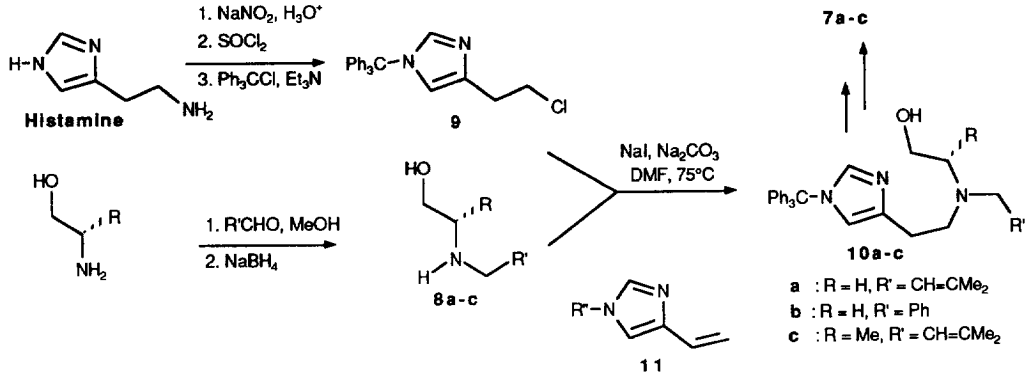
Our project in which a further modification of the TIBO skeleton is studied, has its foundation in the observations that many NNRTI's, including **1** and nevirapine **6**, display essentially no activity against the (Tyr-181→ Cys) HIV-1 mutant strain.[26,38-40] For compound **6** it has been shown that π-stacking with Tyr-181 plays an essential role in its binding within the allosteric pocket.[18] It can thus be concluded that replacement of this aromatic amino acid residue by Cys disrupts this highly favourable interaction. Taking into consideration that a similar loss of π-stacking capability may be at the origin of the lack of activity of TIBO toward the same mutant strain,[41] a project was initiated to prepare analogues **7** in which the phenyl ring is either removed (R = H) or replaced by a more conformationally mobile alkyl chain or aryl substituent (R = alkyl, Ar). In this way a possible "mismatch" involving the rigid phenyl ring in TIBO and the flexible hydrocarbon like chain in the Cys-181 residue in the allosteric pocket of the mutated RT which may lead to a loss of binding affinity could potentially be avoided. In this paper we describe the preparation and biological evaluation of compounds **7a** and **7b**, as well as efforts to construct compound **7c** bearing a (*S*)-methyl substituent on carbon 5.

RESULTS AND DISCUSSION

Of the many strategies which can be envisaged for the construction of the imidazo[1,5-*g*][1,4]diazepine ring system of **7a-c** we opted for the route in which the β-aminoalcohols **8** are condensed with an appropriately protected 4-chloroethylimidazole derivative, followed by a S_N2 ring closure step (Scheme 1). This choice was in many respects determined by the possibility that (*S*)-(+)-alaninol could be used for the preparation of optically active analogue **7c**.

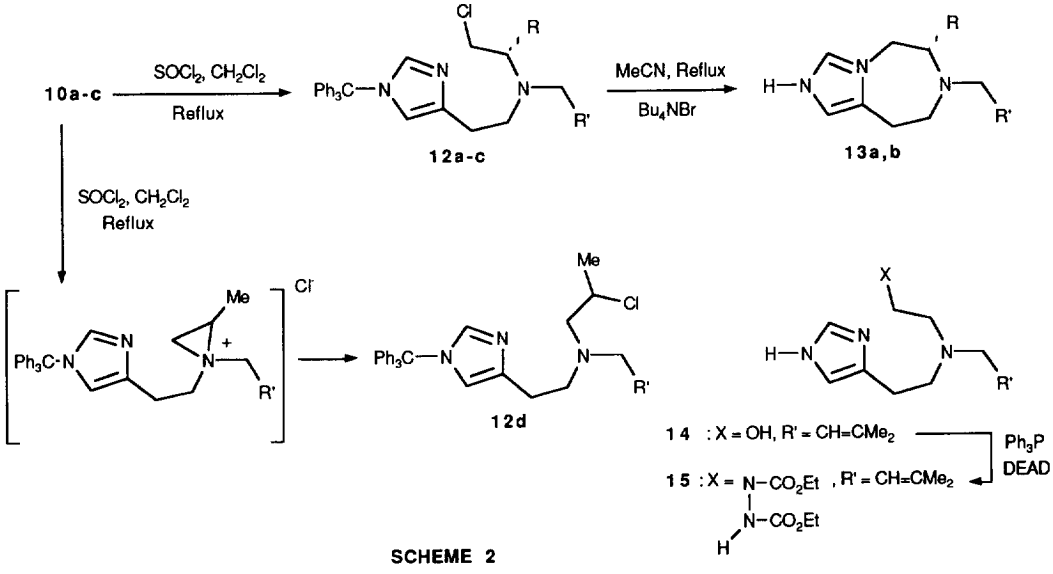
Initially, the N-tritylated chloroethylimidazole **9** was used as the imidazole component, since it is available in two simple steps from histamine, and is soluble in most common solvents.[42] The secondary amines **8a,b** were obtained by reaction of 2-aminoethanol with 3-methylcrotonaldehyde and benzaldehyde, respectively, and reduction of the *in situ* generated imines (oxazolidines) with $NaBH_4$. In an identical fashion intermediate **8c** was prepared from (*S*)-(+)-alaninol and 3-methylcrotonaldehyde in 46% yield. N-alkylation of amines **8a-c** with the chloroimidazole **9** was effected by heating at 75°C in DMF containing an excess of sodium iodide and sodium carbonate. When these conditions were respected competing formation of vinyl imidazole **11** (R" = Ph_3C) (ABC

system : δ 6.76, 5.82 and 5.1 ppm) was almost completely suppressed,[43] and compounds **10a** and **10b** were obtained in yields ranging from 56% to 60%. For the branched amine **8c**, conversion to **10c** was somewhat less efficient (26%).



SCHEME 1

To activate the hydroxyl group in **10a** toward reaction with the free imidazole nitrogen and consequent ring closure, it was treated with methane sulfonyl chloride in pyridine (1 hour at 0°C). However, the expected mesylate product proved to be labile, undergoing transformation to β-chloroamine **12a**. A higher yield of this compound and β-chloroamine **12b** was obtained by reaction of alcohols **10a,b** with thionyl chloride in refluxing CH_2Cl_2 (Scheme 2). Compounds **12a,b** were sufficiently stable to permit separation from minor impurities by silica-gel column chromatography (50 -70% isolated yields), but in general, they were used immediately in the next step without purification.



SCHEME 2

Heating of **12a** in acetonitrile gave **13a** in 25% yield (from **10a**) along with decomposition products. No reaction occurred in DMF, and in toluene and THF predominant formation of highly polar material was observed. Taking into consideration that an intermediate imidazolinium salt may initially be formed in this cyclization reaction, which in turn is converted to **13a** through displacement of the trityl group by the Cl^- counter ion, we figured that we could enhance both steps by addition of tetrabutylammonium bromide to the reaction medium. Indeed, by heating **12a** in boiling acetonitrile in the presence of TBAB for 36 hours the yield of **13a** was raised to 46% (from **10a**).[44,45]

Other attempts to activate compound **10a** with respect to ring closure include reaction with the triphenyl phosphine-bromine complex, and with triflic anhydride. Under the first set of conditions no reaction occurred, whereas with the triflating reagent decomposition products were formed. Starting material was also recovered upon reaction of the detritylated derivative **14** under Mitsunobu reaction conditions, using tetrafluoroboric acid as the proton source. Interestingly, in the absence of HBF_4 the hydrazine adduct **15** was formed.[46]

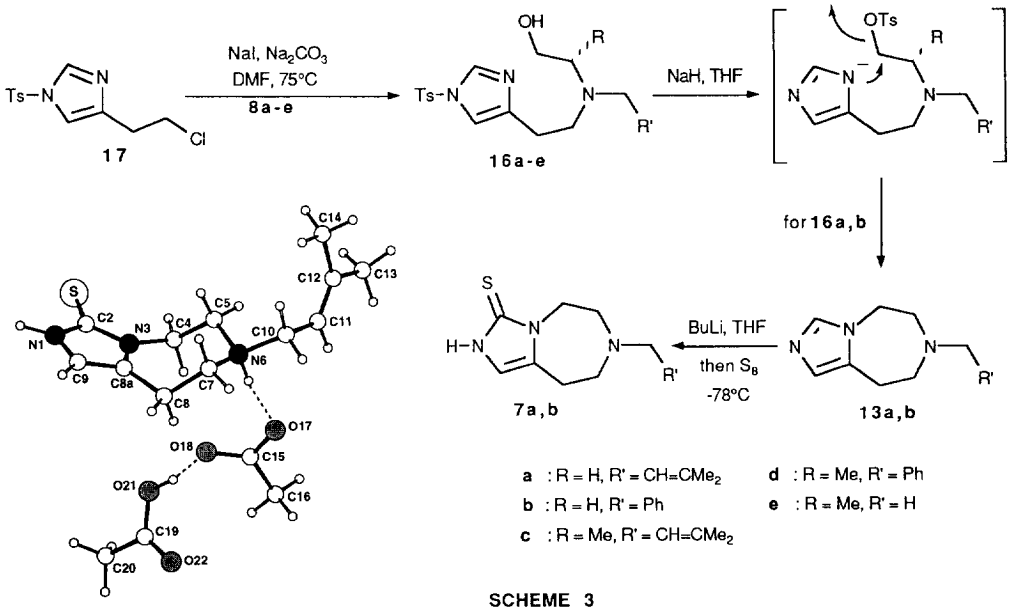
The formation of compound **15** and the direct conversion of **10a** to the corresponding chloro derivative on treatment with mesyl chloride hinted that an aziridinium salt is generated upon activation of the primary alcohol function, and that in fact, this species may also be involved in both the diazepine ring forming reaction, and the side reactions which give rise to decomposition products. The possibility that an equilibrium may exit between such an aziridinium intermediate and the imidazolinium salt initially formed in the desired ring closure process cannot be ignored. Such a situation would explain the low yield observed in the cyclization of **12a** into **13a**, and our failure to obtain significant amounts of **13b** from **12b**. Firmer evidence for aziridinium intermediate formation was obtained by the observation that chlorination of **10c** gave the rearranged β-chloroamine **12d** rather than compound **12c**.[47,48] The structure of this rearrangement product was deduced from the presence of a tertiary ClC-H signal (δ = 3.99 ppm) in the ^1H NMR spectrum, the absence of an absorption corresponding to a CH_2Cl carbon in the ^{13}C NMR, and by the results of a carbon-carbon long distance correlation experiment through the tertiary nitrogen. As in the case of **12b**, attempted cyclization of **12d** led only to highly polar material.

To render our [1,4]diazepine construction strategy more efficient, the idea was formulated to employ the N-protected imidazole intermediates **16** as precursors to diazepines **13**, since N -> O tosyl migration would effect both OH activation and imidazole deprotection (Scheme 3).[49,50] An important advantage of this approach is that the imidazole anion liberated in this process is a good nucleophile, and tosylate displacement leads directly to the target molecule. N-Tosylation of 4-(2-chloroethyl)imidazole[51] gave crystalline **17** in 86% yield, and alkylation of amines **8a-d** and **8e**[52] with this intermediate provided alcohols **16a-e** [along with variable small amounts of the elimination product **11**(R" = Ts)]. As planned, simple treatment of alcohols **16a** and **16b** with an excess of sodium hydride in dry THF led to direct formation of the cyclized compounds **13a** and **13b** in 39 and 67% yield, respectively.

However, even under these conditions alcohol **16c** and its N-benzyl or N-methyl counterparts **16d** and **16e** failed to cyclize in the desired manner. For **16c**, changing the solvant (DMF), and/or the base (BuLi, 1 equivalent at low temperature), as well as other modifications in the reaction conditions (KOH, CH_2Cl_2, n-Oct_4NBr) led only to the formation of highly polar products. Unfortunately, none of these reaction components could be properly isolated and characterised, which would have perhaps provided evidence for the intermediacy of an aziridinium salt in their formation.

Having obtained diazepines **13a** and **13b**, their conversion to the TIBO analogues **7a** and **7b** was achieved by C-2 deprotonation using BuLi, and treatment of the derived anions with elemental sulfur (68% yield). To complete structural studies on these new compounds the X-ray crystal structure of the di-HOAc salt of compound **7a** was obtained. Torsion angle measurements show that the imidazole ring in this molecule is perfectly planar

and that the benzodiazepine ring adopts the chair conformation with atoms N3 and C8a above by 0.925 (2) and 1.007 (2) Å and atom N6 below by -0.704 (2) Å the mean plane of the other four atoms C4, C5, C7 and C8. In addition, the N6 dimethylallyl side chain is in an equatorial position (torsion angles C7-N6-C10-C11 = 178.0 (2), N6-C10-C11-C12 =116.4 (2)°).



SCHEME 3

Compounds **7a,b**, and their precursors **13a,b** were tested for their antiviral activity on CEM-SS cells infected with wild type HIV-1 and the (Tyr-181→Cys) HIV-1 mutant strain resistant to nevirapine **6**. Compound **13b** blocked virus replication at 165 μM (wild type) and 225 μM (nevirapine resistant) concentrations with selectivity indexes [EC_{50}/CC_{50}] of 5.8 and 4.3, respectively. The other compounds tested were not soluble in the culture medium at this concentration range, and at the highest concentration tested (100 μM) they had no effect either on virus multiplication, or on cell metabolism.

Recent X-ray crystal studies on 8 and 9-chloro TIBO bound to HIV-1 RT have clearly shown that, contrary to the solid state structures, both the N-6 substituent and the adjacent C-5 (*S*)-methyl group are axially oriented in the bound active conformation.[53-55] Part of the reason for the large difference in activities between TIBO's **1** and **5** and our analogs toward the wild type HIV-1 may thus reside in the absence of any structural "pressure" for compounds **7** to populate the conformation in which the N6 side chain is positioned axially such that it can interact optimally with Tyr181. With respect to our initial working hypothesis, a further, and unexpected revelation from the X-ray studies is the finding that it is the dimethylallyl side chain, and not with the phenyl ring, in TIBO which interacts with the Tyr181 residue in RT.[56]

EXPERIMENTAL

Melting points were determined using a Reichert Thermovar apparatus and are uncorrected. Mass spectra were obtained on an MS-50 AEI (EI, 70 eV) or an MS-9 AEI (CI, isobutane) spectrometer. ^1H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (except where noted) on a Brüker spectrometer (200 or 250 M Hz), using tetramethylsilane as an internal standard. Chemical shift data are reported in parts per million (δ in ppm) where s, d, dd, t, q and m designate singlet, doublet, doublet of doublets, triplet, quartet and multiplet

respectively. ^{13}C NMR spectra where recorded in $CDCl_3$ on the same instruments. Flash column chromatography was performed using Merck silica gel 60 (Art. 9385). In all cases the solvent system used for the chromatographic separations was chosen such that on TLC an Rf of 0.25-0.30 was observed for the compound to be isolated. All microanalytical results for C, H, and N are within ± 0.4% of the theoretical value.

Antiviral Test.

The capacity of compounds **7a,b** and **13a,b** to block HIV-1 replication was measured in CEM-SS cells acutely infected with HIV-1 as previously described. Briefly, HIV-1 LA1 and HIV-1 nevirapine resistant strain virus production was measured by quantification of the reverse transcriptase activity associated with the virus particules released in the culture supernatant,[57] except that 100 $TCID_{50}$ of virus was used for infection. In control experiments, uninfected cell cytotoxicity was determined after five days of incubation using the colorimetric MTT test based on the property of mitochondrial dehydrogenases to reduce 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) into formazan.[58] The 50% cytotoxic concentration (CC_{50} = concentration at which OD_{540} was reduced by half) were derived from the computer-generated[59] median effect plot of the dose-effect data. CEM-SS cells and the HIV nevirapine resistant strain were obtained from Peter Nara and D. Richman through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH.

Preparations of β-aminoalcohols **8a-e**

The appropriate β-aminoalcohol (2-aminoethanol, (*S*)-(+)-alaninol) (0.035 mol) and either benzaldehyde or 3-methylcrotonaldehyde (0.035 mol) were dissolved in MeOH (150 ml), and stirred at room temperature for 30 min. The solution was then cooled to 0°C and $NaBH_4$ (2.02 g, 53 mmol) was added in small portions. The reaction mixture was stirred for 1 h, after which time HCl (1N, 30 ml) was cautiously added. The solvent was then removed under reduced pressure, and the residue was taken up in aqueous K_2CO_3 (0.5N, 100 ml) and extracted with CH_2Cl_2. The combined organic layers were dried over K_2CO_3, and concentrated. Compounds **8a-c** were isolated pure by distillation of the crude product mixture at low pressure, and **8b** was isolated by recrystallization. Compound **8e** was prepared according literature[52] and isolated as its HCl salt.

2-(3-methyl-2-butenyl-1-amino)ethanol **8a** : Yield : 43%. $E_{13\ mm}$ = 114-116°C. ^1H NMR ($CDCl_3$): 1.65 (s, 3H, CH_3 cis), 1.72 (s, 3H, CH_3 trans), 2.77 (t, 2H, J = 5.1, CH_2-2), 3.22 (d, 2H, J = 6.7, CH_2-1'), 3.64 (t, 2H, J = 5.1, CH_2-1), 5.24 (m, 1H, CH-2'). ^{13}C: 18.0 (CH_3 cis), 25.8 (CH_3 trans), 46.9 (CH_2-1'), 50.8 (CH_2-2), 61.0 (CH_2-1), 122.9 (CH-2'), 134.6 (C-3').

2-benzylaminoethanol **8b**. Yield : 65%. $E_{0,2\ mm}$ = 114-116°C. ^1H NMR ($CDCl_3$): 2.3 (s(br), 2H, NH and OH), 2.76 (t, 2H, J = 5.2, CH_2-2), 3.62 (t, 2H, J = 5.2 CH_2-1), 3.77 (s, 2H, CH_2 benzyl), 7.28 (m, 5H, Ar). ^{13}C: 50.7 (CH_2-1), 53.6 (CH_2 benzyl), 61.0 (CH_2-1), 127.1, 128.1, 128.5, 140.29 (Ar).

2-(3-methyl-2-butenyl-1-amino)-2-methylethanol **8c**. Yield : 46%. $E_{15\ mm}$ = 114-117°C. ^1H NMR ($CDCl_3$): 1.06 (d, 3H, J = 6.4, CH_3), 1.65 (s, 3H, CH_3 cis), 1.72 (s, 3H, CH_3 trans), 2.79 (m, 1H, CH-2), 3.21 (m, 3H, CH_2-1' and CH-1), 3.58 (dd, 1H, J = 4.1 and 10.5, CH-1), 5.23 (m, 1H, CH_2-2'). ^{13}C: 17.2 (CH_3), 17.9 (CH_3 cis), 25.8 (CH_3 trans), 44.5 (CH_2-1'), 53.9 (CH_2-2), 65.5 (CH_2-1), 123.1 (CH-2'), 134.4 (C-3').

2-benzylamino-2-methylethanol **8d**. Yield : 84%. m. p. = 68 °C (heptane). ^1H NMR ($CDCl_3$): 1.07 (d, 3H, J = 6.3, CH_3), 2.3 (s(br), 2H, NH and OH), 2.83 (m, 1H, CH-2), 3.28 (dd, 1H, J = 7.1 and 10.5, CH-1), 3.56 (dd, 1H, J = 4.04 and 10.5, CH-1), 3.72 (d, 1H, J = 12.9, CH benzyl), 3.85 (d, 1H, J = 12.9, CH benzyl), 7.28 (m, 5H, Ar). ^{13}C: 17.1 (CH_3), 51.1 (CH_2 benzyl), 53.8 (CH-2), 65.5 (CH_2-1), 127.1, 128.1, 128.5, 140.29 (Ar). *Anal.* Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.32; H, 8.85; N, 8.31.

2-methylamino-2-methylethanol **8e**. (Hydrochloride salt) ^{1}H NMR (MeOH): 1.27 (d, 3H, J = 6.7, CH_3), 2.67 (s, 3H, N-CH_3), 3.24 (m, 1H, CH-2), 3.51 (dd, 1H, J = 6.2 and 11.9, CH-1), 3.81 (dd, 1H, J = 3.7 and 11.9, CH-1). ^{13}C: 13.2 (CH_3), 30.6 (N-CH_3), 57.8 (CH-1), 62.3 (CH_2-2).

General Protocol for the Preparation of Compounds **10a-c**

A suspension of compound **9** (0.14 g, 0.37 mmol),[42] the appropriate β-aminoalcohol **8a-c** (0.37 mmol), dry NaI (0.28g, 1.9 mmol), dry Na_2CO_3 (0.15g; 1.5 mmol) in dry DMF (10 ml) was heated under argon at 75°C for 72 hours. The reaction mixture was then concentrated, and the residue was dispersed in water and extracted with Et_2O. The combined organic phases were dried over K_2CO_3, and concentrated. Compounds **10a-c** were obtained pure after silica-gel flash column chromatography (CH_2Cl_2/MeOH; 95/5). In general, small quantities of starting material (5%) and varying amounts of the vinyl imidazole **11a**[43] were also isolated (at reaction temperatures > 80°C compound **11a** was the major reaction component).

2-{2-(3-Methyl-but-2-enyl)-[2-(1-trityl-1H-imidazol-4-yl)-ethyl]-amino}-ethanol **10a** :
Colorless gummy solid; Yield : 60%; m.p. = 80-90°C (dec); NMR data ($CDCl_3$): (see Table 1); *Anal.* Calcd. for $C_{31}H_{35}N_3O$ + 1.5 H_2O: C, 75.58; H, 7.77; N, 8.53. Found: C, 75.81; H, 7.47; N, 8.43.

2-{2-Benzyl-[2-(1-trityl-1H-imidazol-4-yl)-ethyl]-amino}-ethanol **10b**. Colorless gummy solid; Yield : 56%; m.p. = 118°C; NMR data ($CDCl_3$): (see Table 1); *Anal.* Calcd. for $C_{33}H_{33}N_3O$ + 1/2 H_2O: C, 79.81; H, 6.90; N, 8.46. Found: C, 80.01; H, 6.74; N, 8.71.

2-{2-(3-Methyl-but-2-enyl)-[2-(1-trityl-1H-imidazol-4-yl)-ethyl]-amino}-propan-1-ol **10c**. Colorless gummy solid; Yield : 26%; m.p. = 70°C (dec); NMR data ($CDCl_3$): (see Table 1); *Anal.* Calcd. for $C_{32}H_{37}N_3O$ + H_2O: C, 77.23; H, 7.90; N, 8.44. Found: C, 77.47; H, 7.61; N, 8.67.

General Protocol for the Preparation of Compounds **12a,b** *and* **12d**

To a solution of **10a-c** (1.0 mmol) in CH_2Cl_2 (200 ml; distilled over P_2O_5) was added thionyl chloride (5 mmol), and the mixture was refluxed for 1 h, evaporated to dryness, and redissolved in methanol free CH_2Cl_2. The resultant solution was washed with a $NaHCO_3$ (0.5 M), dried over K_2CO_3, and concentrated to dryness. For characterization purposes, products **12a**, **12b**, and **12d** were separated from minor impurities by silica-gel flash column chromatography (CH_2Cl_2/MeOH; 97/3). However, generally, these compounds were taken immediately through to the next step.

(2-Chloro-ethyl)-(3-methyl-but-2-enyl)-[2-(1-trityl-1H-imidazol-4-yl)-ethyl]-amine **12a**. Colorless oil; Yield : 45%; NMR data ($CDCl_3$) (see Table 1); MS : *m/z* (EI) = 483 (M^+).

(2-Chloro-ethyl)-benzyl-[2-(1-trityl-1H-imidazol-4-yl)-ethyl]-amine **12b.** Colorless oil; yield : 76%; NMR data ($CDCl_3$) (see Table 1); MS : *m/z* (CI) = 506 (MH^+).

(2-Chloro-prop-1-yl)-(3-methyl-but-2-enyl)-[[2-(1-trityl-1H-imidazol-4-yl)-ethyl]-amine **12d**. Colorless oil; yield : 52%; NMR data ($CDCl_3$) (see Table 1); MS : *m/z* (CI) = 520 (MH^+).

6-(3-methyl-2-buten-1-yl)-4,5,7,8-tetrahydroimidazo[1,5-g][1,4]diazepine **13a** *by cyclization of* **12a.** A solution of chloramine **12a** [obtained from **10a** (0.04 g; 0.083 mmol)] in dry acetonitrile (30 ml; distilled over CaH_2) containing n-Bu_4NBr (0.027g; 0.086 mmol) was refluxed for 36 hours. The mixture was then evaporated to dryness, and the residue was silica-gel flash column chromatographed (CH_2Cl_2/MeOH 95-5). Diazepine **13a**, obtained as a colorless oil, was crystallized as its bismesylate salt in dry acetone (0.016 g; 46%, from 10a) : m.p. (mesylate salt) = 265°C (acetone); ^{1}H NMR ($CDCl_3$) (free base): 1.64 (s, 3H, CH_3 cis), 1.75 (d, 3H, J = 0.75, CH_3 trans), 2.66 (m, 4H, CH_2-8, CH_2-5), 2.86 (m, 2H, CH_2-7), 3.12 (d, 2H, J = 7.0, CH_2-1'),

4.07 (m, 2H, CH_2-4), 5.27 (dq, 1H, J = 0.75 and 7.0, CH-2'), 6.76 (d, 1H, J = 0.5, H-9), 7.32 (d, 1H, J = 0.5, H-2). ^{13}C NMR: 18.1 (CH_3 cis), 26.0 (CH_3 trans and CH_2-8), 47.8 (CH_2-4), 55.5 (CH_2-1'), 56.0 (CH_2-5), 56.7 (CH_2-7), 121.2 (CH-2'), 127.4 (CH-9), 129.5 (C-8a), 136.0 (C-3'), 136.8 (CH-2). MS : *m/z* (CI) = 206 (MH^+); *Anal.* Calcd. for $C_{12}H_{19}N_3$ + 2 CH_3SO_3H: C, 42.30; H, 6.85; N, 10.57. Found : C, 42.11; H, 6.64; N, 10.34.

2-[[2-(1H-Imidazol-4-yl)-ethyl]-(3-methyl-2-buten-1-yl)-amino]-ethanol **14.** Alcohol **10a** (0.1 g; 0.215 mmol) was heated at 80°C in HCl (2N, 30 ml) for 2 h. The mixture was then filtered and the filtrate concentrated to dryness. The residue was basified with solid K_2CO_3 in MeOH, adsorbed onto silica-gel (0.25 g), and the solvent was removed under reduced pressure. Silica-gel column chromatography was performed eluting first with MeOH/CH_2Cl_2 (5/95) and then with NH_3satd-MeOH/CH2Cl2 (5/95). Compound **14** was obtained as a colorless oil (0.040 g; 83 %): NMR data ($CDCl_3$): (see Table 1); MS : *m/z* (CI) = 224 (MH^+).

Hydrazine adduct **15**

Triphenyl phosphine (0.47 g; 1.8 mmol) and diethyldiazodicarboxylate (0.24 ml; 1.5 mmol) were added sequentially to a cooled (0°C) solution of alcohol **14** (0.073 g; 0.32 mmol) in dry THF (20 ml), and the mixture was stirred for 1 h. The solvent was then removed, and the residue was silica-gel flash column chromatographed (CH_2Cl_2/MeOH; 9/1). Compound **15** was obtained as a colorless oil (0.022 g; 17%): Signal attribution for the N,N-dicarboethoxy component of **15** follows, for the remainder of the NMR data see Table 1. ^1H NMR ($CDCl_3$): 1.22 (m, 6H, CH_3 ester); 4.16 (m, 4H, CH_2 ester), 7.78 (s(br), 2H, NH). ^{13}C NMR: 14.6 (CH_3 ester); 62.7 (CH_2 ester); 156.5 and 156.7 (C=O). MS : m/z (CI) = 382 (MH^+).

1-Tosyl-4-(2-chloroethyl)-imidazole **17**

Tosyl chloride (1.04 g; 5.4 mmol) followed by Et_3N (1.33 ml; 9.5 mmol) were added to a suspension of 4-(2-chloroethy)-imidazole hydrochloride[51] (0.76 g; 4.5 mmol) in CH_2Cl_2 (100 ml, distilled over P_2O_5). The mixture was stirred for 30 min at room temperature, then washed with aqueous K_2CO_3 (0.5 M), dried over solid K_2CO_3 and concentrated. Recrystallization of the residue using heptane afforded compound **17** as colorless crystals (1.1 g; 86%): m.p. = 125°C (heptane); ^1H NMR ($CDCl_3$): 2.43 (s, 3H, CH_3), 2.86 (t, 2H, J = 6.8, CH_2-1'), 3.86 (t, 2H, J = 6.8, CH_2-2'), 7.13 (s, 1H, H-5), 7.36 (d, 2H, J = 8.2, H-tosyl), 7.81 (d, 2H, J = 8.2, H-tosyl), 7.93 (s, 1H, H-2); ^{13}C NMR: 21.7 (CH_3), 31.7 (CH_2-1'), 42.8 (CH_2-2'), 114.5 (CH-5), 127.5 and 130.5 (CH-tosyl), 135.1 (C-3), 136.4 (CH-2'), 141.5 and 146.3 (C-tosyl); Anal. Calcd. for $C_{12}H_{13}ClN_2O_2S$: C, 50.62; H, 4.60; N, 9.84; S, 11.26; Cl, 12.45. Found: C, 50.57; H, 4.77; N, 9.85; S, 11.33; Cl, 12.58.

Preparation of Compounds **16a-e**

A suspension of compound **17** (0.44 g; 1.5 mmol), the appropriate β-aminoalcohol **8a-e** (1.5 mmol) (**8e** as its HCl salt), dry NaI (1.3 g; 8.2 mmol), and dry Na_2CO_3 (0.72g; 6.6 mmol) in dry DMF (40 ml) was heated under argon at 75°C during 72 hours. The mixture was then evaporated to dryness, and the residue was dispersed in water and extracted with ether (CH_2Cl_2. The combined organic phases were dried over K_2CO_3, and then concentrated. Compounds **16a-e** were obtained pure after silica-gel column chromatography (CH_2Cl_2/MeOH 95/5). In general, small quantities of starting material (5%) and varying amounts of the vinyl imidazole **11b** were also isolated (at reaction temperatures > 75°C compound **11b** was the major reaction component).

2-((3-Methyl-but-2-enyl)-{2-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl]-ethyl}-amino)-ethanol **16a.** Colorless oil; Yield : 55%; NMR data ($CDCl_3$) (see Table 1); MS : *m/z* (EI) = 377 (M^+).

2-(Benzyl-{2-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl]-ethyl}-amino)-ethanol **16b.** Colorless oil, Yield : 44%; NMR data ($CDCl_3$) (see Table 1); MS : *m/z* (IC) = 400 (MH^+).

2-((3-Methyl-but-2-enyl)-{2-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl]-ethyl}-amino)-propan-1-ol **16c**. Colorless oil; Yield : 40%; NMR data ($CDCl_3$) (see Table 1); MS : *m/z* (EI) = 391 (M^+).

2-(Benzyl-{2-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl]-ethyl}-amino)-propan-1-ol **16d**. Colorless oil; Yield : 20%; NMR data ($CDCl_3$) (see Table 1); MS : *m/z* (IC) = 414 (MH^+).

2-(Methyl-{2-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl]-ethyl}-amino)-ethanol **16e**. Colorless oil; Yield : 46%; NMR data ($CDCl_3$) (see Table 1) MS : *m/z* (IC) = 338 (MH^+).

1-Tosyl-4-vinylimidazole **11b**

Colorless crystals; m.p. (heptane) = 105°C; ^1H NMR ($CDCl_3$) : 2.43 (s, 3H, CH_3), 5.25 (dd, 1H, J = 1.8, and 10.9, CH-trans), 5.92 (dd, 1H, J = 1.8, and 17.3, CH-cis), 6.49 (dd, 1H, J = 10.9, and 17.3, CH-Im), 7.16 (s, 1H, H-5), 7.34 (d, 2H, J = 7.9, H-tosyl), 7.81 (d, 2H, J = 7.9, H-tosyl), 7.95 (s, 1H, H-2); ^{13}C NMR: 21.8 (CH_3), 113.9 (CH-5), 115.9 (CH_2), 127.0 (CH-vinyl), 127.4 and 130.5 (CH-tosyl), 134.9 (C-4), 136.8 (CH-2), 142.8 and 146.4 (C-tosyl); MS : *m/z* (EI) = 248 (M^+). *Anal.* Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; S, 12.91. Found: C, 58.02; H, 4.94; N, 11.18; S, 12.87.

Preparation of Imidazo-1,4-diazepine **13a** *by Cyclization of* **16a**

To a solution of alcohol **16a** (0.1 g, 0.26 mmol) in THF (10 ml) was added an excess of NaH (10 mmol), and the reaction was stirred at room temperature under argon for 3 h. The mixture was then evaporated to dryness, and the residue was silica-gel column chromatographed (CH_2Cl_2/MeOH; 95/5). Diazepine **13a**, obtained as a colorless oil, was crystallized as its bismesylate salt in dry acetone (0.042 g; 39%). A somewhat higher yield (47%) was obtained using DMF as reaction solvent.

Preparation of 6-Benzyl-4,5,7,8-tetrahydroimidazo[1,5-g][1,4]diazepine **13b** *by cyclization of* **16b**

Following the procedure for the preparation of **13a** from **16a**, alcohol **16b** (0.1 g, 0.25 mmol) was reacted with an excess of NaH (2 mmol) in THF (10 ml). Diazepine **13b** was isolated as its bismesylate salt by recrystallization in dry acetone (0.039 g, 67%): m.p. (bismesylate salt) = 262°C; ^1H NMR ($CDCl_3$) (free base): 2.66 (m, 4H, CH_2-8, CH_2-5), 2.86 (m, 2H, CH_2-7), 3.68 (s, 2H, CH_2-Bn), 4.07 (m, 2H, CH_2-4), 6.75 (s, 1H, H-9), 7.33 (m, 6H, H-2 and Ar); ^{13}C NMR: 25.9 (CH_2-8), 47.6 (CH_2-4), 55.5 (CH_2-5), 55.9 (CH_2-7), 63.1 (CH_2-Bn), 126.7 (CH Ar), 127.3 (CH-9), 128.4 and 128.9 (CH Ar), 132.8 (C-8a), 136.8 (CH-2), 138.4 (C Ar); MS : *m/z* (CI) = 228 (MH^+); *Anal.* Calcd. for $C_{14}H_{17}N_3$ + 2 CH_3SO_3H: C, 45.81; H, 6.01; N, 10.02; S, 15.28. Found: C, 46.05; H, 5.89; N, 10.01; S, 15.21.

6-(3-Methyl-2-buten-1-yl)-4,5,7,8-tetrahydroimidazo[1,5-g][1,4]diazepin-2(1H)-thione **7a**

Butyllithium (1.6 M solution in hexane; 0.5 ml; 0.8 mmol) was added to a cold (-78°C) solution of imidazodiazepine **7a** (0.014 g, 0.068 mmol) in dry THF (15 ml) (Ar atmosphere). After 30 minutes stirring solid sulfur (32 mg, 1 mmol;) was added. The mixture was then warmed slowly to room temperature and evaporated to dryness. The residue was silica-gel column chromatographed (CH_2Cl_2/MeOH; 98/2). The di-HOAc salt of **7a** (0.012 g, 67%) was obtained by dissolving the free base in a minimum of CH_2Cl_2 and adding this solution to 10 ml of hexane containing two drops of acetic acid, followed by slow solvent evaporation over two days: m.p. (di-HOAc salt) = 80-90°C (dec.); I.R. : ν (diacetic salt/KBr)/cm^{-1} : 1714, 1271; ^1H NMR ($CDCl_3$) (free base): 1.62 (s, 3H, CH_3 cis), 1.74 (s, 3H, CH_3 trans), 2.74 (m, 6H, CH_2-8, CH_2-7, CH_2-5), 3.09 (d, 2H, J = 7.0, CH_2-1'), 4.36 (m, 2H, CH_2-4), 5.24 (m, 1H, CH-2'), 6.42 (s, 1H, H-9), 11.35 (s(br), 1H, H-1). ^{13}C NMR: 18.1 (CH_3 cis), 26.1 (CH_3 trans), 26.4 (CH_2-8), 46.6 (CH_2-4), 55.16 (CH_2-5), 55.27 (CH_2-1'), 56.6 (CH_2-4), 109.7 (CH-9), 120.6 (CH-2'), 132.6 (C-8a), 136.6 (C-3'), 160.1 (C-2); MS : *m/z* (IE) = 237 (M^+); *Anal.* Calcd. for $C_{12}H_{19}N_3S$ + 2 CH_3COOH: C, 53.76; H, 7.61; N, 11.75; S, 8.97. Found: C, 53.71; H, 7.41; N, 11.71; S, 8.91.

Table 1: ^{1}H and ^{13}C signals attribution for compounds **10a-c, 12a-b, 12d, 14, 15** and **16a-e**.

Cp.	Imidazole[a]	Protec.[b]	Side chain	Main chain
10a	7.4 (s) ; 6.56 (s)	Trityl	5.20 (m); 3.19 (d, J = 6.5); 1.77; 1.66	2.65 (m, 3H) 3.58 (m)
	138.5; 118.5; 139.4		136.2; 120.1; 51.6; 26.0; 18.1	26.1; 55.3; 53.4; 58.7
10b	7.40 (s); 6.50 (s)	Trityl	7.14 (m); 3.64	2.67 (m, 3H); 3.57 (t; J = 4.9)
	138.3; 118.4; 139.6		140.0; 128.9; 128.2; 126.9; 55.6	26.3; 59.1; 53.5; 59.6
10c	7.36 (s); 6.57 (s)	Trityl	5.10 (m); 3.13 (m); 1.67; 1.61	2.66 (m, 2H); 3.08 (m); 3.13 (m); 0.91 (d, J = 6.6, CH_3)
	138.6; 118.6; 139.4		128.0; 121.8; 47.4; 27.1; 18.1	27.1; 48.4; 56.3; 62.8; 9.6
12a	7.4 (s); 6.61 (s)	Trityl	5.22 (m); 3.15 (d, J = 6.7); 1.71; 1.62	2.80 (m, 3H); 3.47 (m)
	138.2; 118.4; 139.6		135.2; 121.2; 52.0; 25.9; 18.0	26.7; 55.5; 54.1; 41.9
12b	7.35 (s); 6.61 (s)	Trityl	7.14 (m); 3.64	2.79 (m); 2.88 (m); 2.80 (m); 3.37 (t; J = 7.0)
	138.3; 118.5; 139.6		139.7; 128.7; 127.0; 55.6	26.8; 59.0; 54.4; 42.0
12d	7.33 (d); 6.60 (d, J = 1.0)	Trityl	5.17 (m); 3.11 (d, J = 6.7); 1.69; 1.60	2.71 (m); 2.80 (m); 2.55 (dd, J = 13.3, 7.7) and 2.78 (m); 3.99 (m); 1.41 (d, J = 6.5, CH_3)
	138.3; 118.4; 140.0		134.7; 121.7; 52.4; 26.0; 18.1	26.8; 54.7; 62.5; 56.3; 18.1
14	7.56 (s); 6.80 (s)	-	5.22 (m); 3.86 (d, J = 7.0); 1.74; 1.66	2.86 (m); 2.99 (m); 2.87 (m); 3.75 (t; J = 4.0)
	138.4; 117.9; 134.6		134.1; 118.1; 51.4; 26.1; 18.3	26.1; 55.1; 53.4; 58.3
15	7.51 (s); 6.76 (s)	-	5.17 (m); 3.15 (d, J = 6.2); 1.71; 1.63	2.76 (m, 3H); 3.63 (m)
	136.6; 119.9; 133.7		134.5; 119.5; 51.3; 26.0; 18.2	26.0; 53.6; 51.1; 47.72
16a	7.92 (d) ; 7.02 (d, J = 0.9)	Tosyl	5.10 (m); 3.11 (d, J = 6.8); 1.69; 1.60	2.74 (m, 3H); 3.52 (m)
	136.3; 113,6 ;135.7		135.3; 120.7; 51.4; 26.0; 18.1	26.4; 55.2; 52.8; 58.7
16b	7.91 (d) ; 6.91 (d, J = 0.7)	Tosyl	7.15 (m); 3.58	2.73 (m, 3H); 3.54 (m)
	136.0; 113.6; 135.2		139.1; 128.7; 128.2; 127.1; 55.7	26.1; 58.8; 52.9; 59.2
16c	7.90 (s); 7.00 (s)	Tosyl	4.95 (m); 2.98 (m); 1.63; 1.57	2.61 (m); 2.61 (m); 2.75 (m); 3.15 (m); 0.83 (d, J = 6.6, CH_3)
	135.6; 112.9; 134.6		133.8; 122.0; 47.3; 25.2; 17.3	27.0; 55.3; 46.3; 62.3; 8.8
16d	7.89 (d) ; 6.88 (d, J = 0.5)	Tosyl	7.13 (m); 3.34 (d) and 3.83 (d, J = 13.6)	2.62 (m); 2.76 (m); 2.99 (m); 3.39 (m); 0.91 (d, J = 6.9, CH_3)
	136.2; 113.6; 135.2		139.6; 128.3; 127.1; 53.6	27.2; 48.0; 53.6; 63.2; 9.1
16e	7.93 (s); 7.04 (s)	Tosyl	2.23; 36.0	2.70 (m, 2H); 2.89 (m); 3.36 (m); 0.86 (d, J = 6.6, CH_3)
	136.4; 113.0; 135.2			26.9; 52.1; 59.7; 62.9; 8.8

a : Chemical shift assignment : C(H)-2; C-4: C(H)-5

b : Chemical shift values Trityl : δ 7.4-7.26 (± 0.1 ppm) (m) / 142.6; 129.9; 128.1; 75.2 (± 0.1 ppm). Tosyl : δ 7.81 and 7;35 (d, J = 8.1); 2.44 / 146.2; 143.7; 130.5; 127.5; 21.8 (± 0.1 ppm).

6-Benzyl-4,5,7,8-tetrahydroimidazo[1,5-g][1,4]diazepin-2(1H)-thione **7b**

Following the procedure for **7a**, imidazodiazepine **7b** (0.081 g, 0.31 mmol) was reacted at -78°C with BuLi (1.6M in hexane; 0.89 ml; 1.2 mmol), and the resultant anion was treated with sulfur (0.064 g, 2 mmol). Compound **7b** was obtained as a gum (0.063 g, 68%) after silica-gel column chromatography (CH_2Cl_2/MeOH; 98/2): I.R.: ν (KBr)/cm^{-1} : 1244; ^1H NMR ($CDCl_3$): 2.67 (m, 2H, CH_2-8), 2.74 (m, 4H, CH_2-7, CH_2-5), 3.67 (s, 2H, CH_2-Bn), 4.37 (m, 2H, CH_2-4), 6.41 (d, 1H, J = 1.9; H-9), 7.30 (m, 5H Ar), 10.90 (s(br), 1H, NH); ^{13}C NMR: 26.5 (CH_2-8), 46.8 (CH_2-4), 55.2 (CH_2-5), 55.5 (CH_2-7), 63.2 (CH_2-Bn), 109.6 (CH-9), 127.4 (CH Ar), 128.5 and 129.0 (CH Ar), 132.2 (C-8a), 138.2 (C Ar), 160.3 (C-2); MS : *m/z* (CI) = 260 (MH^+).

X-ray crystallographic analysis of compound **7a**

Crystal data : $[C_{12}\ H_{20}\ N_3\ S]^+$, $[C_2\ H_3\ O_2\ ]^-$, $C_2\ H_4\ O_2$, M_W = 357.47, crystal of 0.20 x 0.28 x 0.28 mm, triclinic, space group P -1, Z = 2, a = 7.610 (4), b = 9.490 (5), c = 14.910 (8) Å, α = 106.96 (3), β = 88.03 (3), γ = 113.56 (3)°, V= 939.9 (8) $Å^3$, d_{calc} = 1.26 g cm^{-3}, F(000) = 384, λ (Cu Kα) = 1.5418 Å, μ = 1.69 mm^{-1}.

Intensity data were measured on a Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Cu Kα radiation and the (θ-2θ) scan technique up to θ = 66°. Of the 3903 collected reflexions (-8 ≤ h ≤ 8, -11≤ k ≤ 10, -10 ≤ l ≤ 17), 3161were unique (R_{int} = 0.011) of which 2977 were considered as observed having I ≥ 3 σ(I). Cell parameters were refined from 25 well centered reflexions with 12 ≤ θ ≤ 24.5°. The structure was solved by direct methods using *SHELXS*86 [60] and refined by full-matrix least-squares with *SHELX*76 [61], minimizing the function $\sum w(Fo-|Fc|)^2$. The hydrogen atoms, located in difference Fourier maps, were fitted at theoretical positions (d(C-H) = 1.00 Å) except those fixed at N6 and O21, kept experimental. They were assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.057 and R_w = 0.072 (with $R_w = [\sum w(Fo-|Fc|)^2 / \sum wFo^2]^{1/2}$ and $w = 1/[\sigma^2(Fo) + 0.0001\ Fo^2]$. The residual electron density in the final difference map was located between -0.27 and 0.42 e $Å^3$.It is interesting to note that each molecule of compound **7a** crystallizes with two molecules of acetic acid, strongly hydrogen-bonded through atoms O21-H and O18 (O21...O18 = 2.569 (3), H_{O21}...O18 = 1.54 Å, angle O-H...O = 167.5°), one of these molecules being deprotonated in O17 and so, the nitrogen N6 appearing positively charged. In the crystal packing, each molecule is linked to two groups of solvent molecules by means of hydrogen bonds established between the nitrogen atoms N6 and N1 of the molecule and the oxygen atoms O17 of acetic acid according to the schemes : N6-H ...$O17_{(x, y, z)}$ (N6...O17 = 2.705 (2), H_{N6}...O17= 1.78 Å, angle N-H...O = 172.5°) and N1-H ...$O17_{(x, y -1, z)}$ (N1...O17 = 2.814 (3), H_{N1}...O17= 1.82 Å, angle N-H...O = 170.6°). Atomic coordinates, thermal parameters, bond lengths, bond and torsion angles have been deposited at the Cambridge Crystallographic Data Centre and can be obtained, on request from the Director, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Acknowledgements

The Agence National de Recherche sur le SIDA (A.N.R.S.) is gratefully acknowledged for its financial support and for a post-doctoral fellowship for one of us (Y.L.J.).

REFERENCES AND FOOTNOTES

1 Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M.J.; Breslin, H.J.; Raeymaeckers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Janssen, M.A.C.; De Clercq, E.; Janssen, P.A. *Nature* **1990**, *343*, 470-474.

2 Hargrave, K.D.; Proudfoot, J.R.; Grozinger, K.G.; Cullen, E.; Kapadia, S.R.; Patel, U.R.; Fuchs, V.U.; Mauldin, S.C.; Vitous, J.; Behnke, M.L.; Klunder, J.M.; Pal, K.; Skiles, J.W.; McNeill, D.W.; Rose, J.M.; Chow, G.C.; Skoog, M.T.; Wu, J.C.; Schmidt, G.; Engel, W.W.; Eberlein, W.G.; Saboe, T.D.; Campbell, S.J.; Rosenthal, A.S.; Adams, J. *J. Med. Chem.* **1991**, *34*, 2231-2241.

3 Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R.T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 2507-2509.

4 Saari, W.S.; Wai, J.S.; Fisher, T.E.; Thomas, C.M.; Hoffman, J.M.; Rooney, C.S.; Smith, A.M.; Jones, J.H.; Bamberger, D.L.; Goldman, M.E.; O'Brien, J.A.; Nunberg, J.H.; Quintero, J.C.; Schleif, W.A.; Emini, E.A.; Anderson, P.S. *J. Med. Chem.* **1992**, *35*, 3792-3802.

5 Romero, D.L.; Morge, R.A.; Biles, C.; Berrios-Pena, N.; May, P.D.; Palmer, J.R.; Johnson, P.D.; Smith, H.W.; Busso, M.; Tan, C.H.; Voorman, R.L.; Reuser, F.; Althaus, I.W.; Downey, K.M.; So, A.G.; Resnick, L.; Tarpley, W.G.; Aristoff, P.A. *J. Med. Chem.* **1994**, *37*, 999-1014; and references therein.

6 Livermore, D.G.H.; Bethell, R.C.; Cammack, N.; Hancock, A.P.; Hann, M.M.; Green, D.V.S.; Lamont, R.B.; Noble, S.A.; Orr, D.C.; Payne, J.J.; Ramsay, MV.J.; Shingler, A.H.; Smith, C.; Storer, R.; Williamson, C.; Willson, T. *J. Med. Chem.* **1993**, *36*, 3784-3794.

7 Tucker, T.J.; Lyle, T.A.; Wiscount, C.M.; Britcher, S.F.; Young, S.D.; Sanders W.M.; Lumma, W.C.; Goldman, M.E.; O'Brien, J.A.; Ball, R.J.; Scheilf, W.A.; Emini, E.A.; Huff, J.R.; Anderson, P.S. *J. Med. Chem.* **1994**, *37*, 2437-2444.

8 Massa, S.; Mai, A.; Artico, M.; Sbardella, G.; Tramontano, E.; Loi, A.G.; Scano, P.; La Colla, P. *Antiviral Chem. Chemother.* **1995**, *6*, 1-8.

9 Williams, T.M.; Ciccarone, T.M.; MacTough, S.C.; Rooney, C.S.; Balani, S.K.; Condra, J.H.; Emini, E.A.; Goldman, M.E.; Greenlee, W.J.; Kaufman, L.R.; O'Brien, J.A.; Sardana, V.V.; Schleif, W.A.; Theoharides, A.D.; Anderson, P.S. *J. Med. Chem.* **1993**, *36*, 1291-1294.

10 Pauwels, R.; Andries, K.; Debyser, Z.; Daele, P.V.; Schols, D.; Stoffels, P.; DeVreese K.; Woestenborghs, R.; Vandamme, A-M.; Janssen, C.G.M.; Anne, J.; Cauwenbergh, G.; Desmyter, J.; Heykants, J.; Janssen, M.; De Clercq, E.; Janssen, P.A. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 1711-1715.

11 De Clercq, E. *Med. Res. Rev.* **1993**, *13*, 229-258.

12 Young, S.D. *Perspectives in Drug Discovery and Design* **1993**, *1*, 181-192.

13 Nanni, R.G.; Ding, J.; Jacobo-Molina, A.; Hughes, S.H.; Arnold, E. *Perspectives in Drug Discovery and Design* **1993**, *1*, 129-150.

14 Tantillo, C.; Ding, J.; Jacobo-Molina, A.; Nanni, R.; Boyer, P.L.; Hughes, S.H.; Pauwels, R.; Andries, K.; Janssen, P.A.; Arnold, E. *J. Mol. Biol.* **1994**, *243*, 369-387.

15 Kohlstaedt, L.A.; Wang, J.; Friedman, J.M.; Rice, P.A.; Steitz, T.A. *Science* **1992**, *256*, 1783-1790.

16 Jacobo-Molina, A.; Ding, J.; Nanni, R.G.; Clark, A.D.; Lu, X.; Tantillo, C.; Williams, R.L.; Kamer, G.; Ferris, A.L.; Clark, P. Hizi, A.; Hughes, S.H.; Arnold, E. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6320-6324.

17 Jager, J.; Smerdon, S.J.; Wang, J.; Boisvert, D.C.; Steitz, T.A. *Structure*, **1994**, *2*, 869-876.

18 Smerdon, S.J.; Jäger, J.; Wang, J.; Kohlstaedt, L.A.; Chirino, A.J.; Friedman, J.M.; Rice, P.A.; Steitz, T.A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3911-3915.

19 Stammers, D.K.; Somers, D.O'N.; Ross, C.K.; Kirby, I.; Ray, P.H.; Wilson, J.E.; Normann, M.; Ren, J.S.; Esnouf, R.M.; Garman, E.F.; Jones, E.Y.; Stuart, D.I.; *J. Mol. Biol.* **1994**, *242*, 586-588.

20 Cohen, K.A.; Hopkins, J.; Ingraham, R.H.; Pargellis, C.; Wu, J.C.; Palladino, D.E.H.; Kinkade, P.; Warren, T.C.; Rogers, S.; Adams, J.; Farina, P.R.; Grob, P.M. *J. Biol. Chem.* **1991**, *266*, 14670-14674.

21 Wu, J.C.; Warren, T.C.; Adams, J.; Proudfoot, J.; Skiles, J.; Raghavan, P.; Perry, C.; Potocki, I.; Farina, P.R.; Grob, P.M. *Biochemistry* **1991**, *30*, 2022-2026.

22 Saunders, J. *Drug Des. Discovery* **1992**, *8*, 255-263.

23 Richman, D.D.; Havlir, D.; Corbeil, J.; Looney, D.; Ignacio, C.; Spector, S.A.; Sullivan, J.; Cheeseman, S.; Barringer, K.; Pauletti, D.; Shih, C.K.; Myers, M.; Griffin, L. *J. Virol* **1994**, *68*, 1660-1666.

24 Mellors, J.W.; Im, G.J.; Tramontano, E.; Winkler, S.R.; Medina, D.J.; Dutschman, G.E.; Bazmi, H.Z.; Piras, G.; Gonzalez, C.J.; Cheng, Y C. *Mol. Pharmacol.* **1993**, *43*, 11-16.

25 De Clercq, E. *Biochem. Pharmacol.* **1994**, *47*, 155-169.

26 De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491-2517.

27 Kukla, M.J.; Breslin, H.J.; Pauwels, R.; Fedde, C.L.; Miranda, M.; Scott, M.K.; Sherrill, R.G.; Raeymaeckers, A.; Gelder, J.; Andries, K.; Janssen, M.A.C.; De Clercq, E.; Janssen, P.A. *J. Med. Chem.* **1991**, *34*, 746-751.

28 Kukla, M.J.; Breslin, H.J.; Diamond, C.J.; Grous, P.P.; Ho, C.Y.; Miranda, M.; Rodgers, J.D.; Sherrill, R.G.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L.J.; Janssen, M.A.C.; Janssen, P.A. *J. Med. Chem.* **1991**, *34*, 3187-3197.

29 Liu, J.; Dodd, R.H. *J. Heterocyclic Chem.* **1995**, *32*, 523-528.

30 Breslin, H.J.; Kukla, M.J.; Ludovici, W.D.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, J.D.; Hitchens, T.K.; Leo, G.; Gauthier, D.A.; Ho, C.Y.; Scott, M.K.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M.A.C.; Janssen, P.A. *J. Med. Chem.* **1995**, *38*, 771-793.

31 Swayze, E.E.; Peiris, S.M.; Kucera, L.S.; White, E.L.; Wise, D.S.; Drach; J.C.; Townsend, L.B. *Biorg. Med. Chem. Lett.* **1993**, *3*, 543-546.

32 Gardiner, J.M.; Loyns, C.R.; Burke, A.; Khan, A.; Mahmood, N. *Biorg. Med. Chem. Lett.* **1995**, *5*, 1251-1254.

33 Bell, F.W.; Cantrell, A.S.; Högberg, M.; Jaskunas, S.R.; Johansson, N.G.; Jordan, C.L.; Kinnick, M.D.; Lind, P.; Morin, J.M.; Noréen, R.; Öberg, B.; Palkowitz, J.A.; Parrish, C.A.; Pranc, P.; Sahlberg, C.; Ternansky, R.J.; Vasileff, R.T.; Vrang, L.; West, S.J.; Zhang, H.; Zhou, X-X. *J. Med. Chem.* **1995**, *38*, 4929-4936.

34 Salaski, E.J. *Tetrahedron Lett.* **1995**, *36*, 1387.

35 Ho, W.; Kukla, M.J.; Breslin, H.J.; Ludovici, W.D.; Grous, P.P.; Diamond, C.J.; Miranda, M.; Rodgers, J.D.; Ho, C.Y.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M.A.C.; Janssen, P.A. *J. Med. Chem.* **1995**, *38*, 794-802.

36 Ho, C.Y.; Kukla, M.J. *Biorg. Med. Chem. Lett.* **1991**, 1(10), 531-534.

37 Pauwels, R.; Andries, K.; Debyser, Z.; Kukla, M.J.; Schols, D.; Breslin, H.J.; Woestenborghs, R.; Desmyter, J.; Janssen, M.A.C.; De Clercq, E.; Janssen, P.A. *Antimicrob. Agents Chemother.* **1994**, *38*, 2863-2870.

38 Richman, D.; Shih, C K.; Lowy, I.; Rose, J.; Prodanovich, P.; Gogg, S.; Griffin, J. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 11241-11245.

39 Balzarini, J.; Karlsson, A.; Perez-Perez, M J.; Vrang, L.; Walbers, J.; Zhang, H.; Oeberg, B.; Vandamme, A M.; Camarasa, M J.; De Clercq, E. *Virology* **1992**, *192*, 246-253.

40 Mellors, J.W.; Dutschman, G.E.; Im, G.J.; Tramontano, E.; Winkler, S.R.; Cheng, Y C. *Mol. Pharmacol.* **1992**, *41*, 446-451.

41 Mui, P.W.; Jacober, S.P.; Hargrave, K.D.; Adams, J. *J. Med. Chem.* **1992**, *35*, 201-202.

42 Cordi, A.A.; Snyers, M.P.; Giraud-Mangin, D.; Van der Maesen, C.; Van Hoeck, J.P.; Beuze, S.; Ellens, E.; Napora, F.; Gillet, C.; Gorissen, H.; Calderon, P.; Remacle, M.D.; Janssen de Varebeke, P.; Van Dorsser, W.; Roba, J. *Eur. J. Med. Chem.* **1990**, *25*, 557-568.

43 Altman, J.; Wilchek, M. *J. Heterocyclic. Chem.* **1988**, *25*, 915-916.

44 Compernolle, F.; Ashty Saleh, M.; Toppet, S.; Hoornaert, G. *J. Org. Chem.* **1991**, *56*, 5192-5196.

45 In contrast, addition of NaI to the reaction medium had no effect on reaction rate or product yield.

46 Sammes, P.G.; Smith, S. *J. Chem. Soc. Perkin I* **1984**, 2415-2419.

47 Ross, S.D. *J. Am. Chem. Soc.*, **1947**, *69*, 2982-2983.

48 Huh, N.; Thompson, C.M. *Tetrahedron*, **1995**, *21*, 5935-5950.

49 Rubialta, M.; Diez, A.; Vila, C. *Tetrahedron* **1990**, *46*, 4443-4456.

50 Cink, R.D.; Forsyth, C.J. *J. Org. Chem.* **1995**, *60*, 8122-8123.

51 Overberger, C.G.; Vorchheimer, N. *J. Am. Chem. Soc.* **1963**, *85*, 951-955.

52 Minoura, Y.; Takebayashi, M.; Price, C.C. *J. Am. Chem. Soc.* **1959**, *81*, 4689-4692.

53 Ding, J.; Das, K.; Moereels, H.; Koymans, L.; Andries, K.; Janssens, P.A.J.; Hughes, S.H.; Arnold, E. *Stuctural Biology* **1995**, *2*, 407-415.

54 Ren, J.; Esnouf, R.; Hopkins, A.; Ross, C.; Jones, Y.; Stammers, D.; Stuart, D. *Structure*, **1995**, 3, 915-926.

55 Considerable differences exist between the solid state conformation adopted by TIBO with and without association with RT; see also: Liaw, Y.-C.; Gao, Y.-G.; Robinson, H.; Wang, A. H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 1857-1859.

56 Schafer, W.; Freibe, W-G.; Leinert, H.; Mertens, A.; Poll, T.; von der Saal, W.; Zilch, H.; Nuber, B.; Ziegler, M.L. *J. Med. Chem.* **1993**, *36*, 726-732.

57 Moog, C.; Wick, A.; Le Ber, P.; Kim, A.; Aubertin, A.M. *Antiviral Research* **1994**, *24*, 275-288.

58 Mosmann, T. J. *Immunol. Methods* **1983**, *65*, 55-63.

59 Chou, J.; Chou, T-C. Dose-effect analysis with microcomputers: quantitation of ED_{50}, LD_{50}, synergism, antagonism, low-dose risk, receptor binding and enzyme kinetics. Computer software for Apple II Series and IBM-PC and instruction manual. Elsevier-Biosoft, Elsevier Science Publishers, Cambridge, U.K. **1985**, 19-28.

60 Sheldrick, G.M. (1986).SHELXS86. Program for the solution of crystal structures. Univ. of Göttingen, Germany

61 Sheldrick, G. M. (1976). SHELX76. Program for crystal structure determination. Univ. of Cambridge, England

(*Received in Belgium* 8 *July* 1996; *accepted* 17 *October* 1996)