ACETYLATION OF 2-AMINO-2-OXAZOLINES: EVIDENCE OF A RING CLEAVED ACETYLATED COMPOUND

Isabelle Forfar[a], Christian Jarry[a*] and Jean-Michel Leger[b]
[a]Laboratoire de Chimie Physique, [b]Laboratoire de Chimie Analytique, Université *Victor Segalen* Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France

Abstract : Depending on the experimental conditions the reaction of 5-substituted 2-amino-2-oxazolines **1** with acetic anhydridee led to acetylated compounds which exhibit or not an heterocyclic ring. The 5-substituted 3-acetyl-2-oxazolidinones **4** were finally isolated in boiling acetic anhydride.

Introduction

2-Amino-2-oxazolines are five membered heterocyclic compounds subject to amino-imino tautomerism, which present interesting pharmacological properties [1,2]. As a part of our program on oxazolinic structures and in order to develop a derivatization method for analytical purpose, we studied the acylation of pharmacological active 5-substituted 2-amino-2-oxazolines [3]. In the present paper we describe the acetylation of 2-amino-2-oxazolines with acetic anhydride leading to acetylated compounds possessing a heterocyclic ring or to open chain compounds.

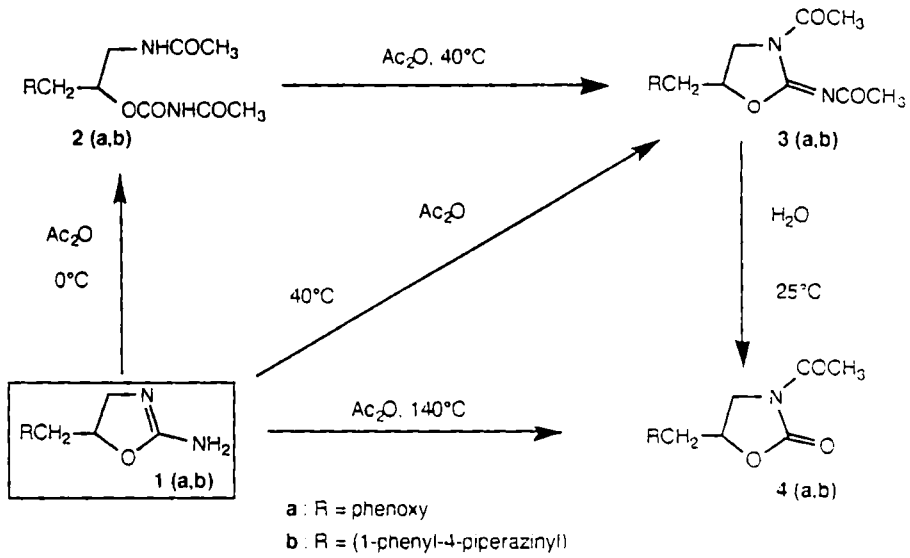
Results

The two nitrogen atoms of 2-amino-2-oxazolines are nucleophilic centres allowing various substitutive reactions which take place either on the endocyclic or on the exocyclic nitrogen atom, depending on the experimental conditions [3,4]. The acetylation of 2-amino-2-oxazolines is a typical example of a reaction between nucleophilic and electrophilic sites [5]. It was first described by Fromm [6], while more recently a few reports have appeared emphasizing the possibility to introduce one or two acyl group [7-9]. With the intention of developing the study of this reaction, we selected different experimental conditions.

The reaction of the 5-phenoxymethyl- **1a** and of the 2-amino-5-(1-phenyl-4-piperazinyl)methyl-2-oxazolines **1b** conducted in acetic anhydride as a solvent at 0 °C led to compounds **2(a,b)**, isolated after precipitation from the mixture by addition of diethyl ether/heptane 30/70 (v/v) (Scheme 1). **2a** was identified by X-ray crystallography as the open-chain 3-acetamido-2-acetylcarbamoyloxy-1-phenoxypropane. Initiation of the reaction could occur with the first acylation of the endocyclic nitrogen atom of the 2-amino-2-oxazoline, followed by the delocalization of the double bond. The key step in the formation of **2** may involve the nucleophilic attack of CH_3COO^- on the C-2 atom inducing the opening of the oxazolidine ring, followed by an

O-N acyl migration [10]. The transient formation of **2** was always suggested by tlc during the described acetylation procedures.

Scheme 1



With regard to the structure of **2 a** (Figure 1) [11] the acetylcarbamoyloxy moiety is found on C(9) whereas the acetamido group is located on C(17).The carbon C(9) is in the sp^3 hybridization state as evidenced by the bond distance C(9)-C(17), C(9)-C(8) and C(9)-O(10) which are 1.51(4) Å, 1.50(4) Å and 1.57(3) Å, respectively. Moreover the bond angles C(8)-C(9)-O(10), C(8)-C(9)-C(17) and O(10)-C(9)-C(17) have the expected values 104(2)°, 110(2)° and 106(2)°, respectively. The acetylcarbamoyloxy chain has a stretched plane conformation. It is described by the torsion angles C(9)-O(10)-C(11)-N(13), O(10)-C(11)-N(13)-C(14) and C(11)-N(13)-C(14)-C(16), which are 171(2)°, 182(2)° and 180(2)°, respectively.

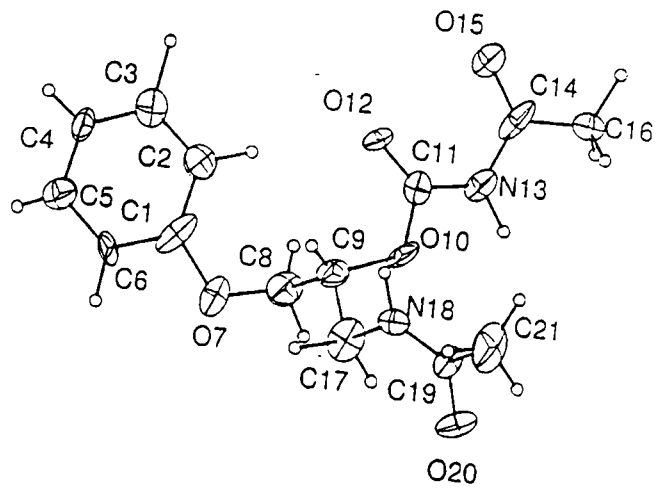


Figure 1 : X-ray crystallographic structure of **2 a**

Both carbonyl groups of the acetylcarbamoyloxy moiety C(11)-O(12) and C(14)-O(15) are in the opposite side with respect to the acetamido chain. This orientation is favoured by two intermolecular hydrogen bonds which occur between O(12) (x, y, z) and N(18) (-x, 1/2+y, 3/2-z) = 2.10(3) Å and between O(15) (x, y, z) and N(18) (-x, 1/2+y, 3/2-z) = 2.89(3) Å. The acetamido moiety is planar with C(17)-N(18)-C(19)-C(21) = 180(2)°. An intermolecular hydrogen bond is found between N(13)(x, y, z) and O(20)(1-x, 1/2+y, 3/2-z) with N(13)...O(20) = 2.80(3)Å and O(20)...H(131)-N(13) = 157(2)°In spite of this opened-ring structure we noticed the stability of **2 a** which may be related to the position of the lateral chains : the acetylcarbamoyloxy chain and the acetamido one are far apart from each other. In the ^{1}H-nmr spectra the C(17) protons are coupled with the one of N(18).

Reaction of **1** in acetic anhydride at 40 °C during two hours afforded the 5-substituted 2,3-diacetyl-2-iminooxazolidines **3**. Lower yields in **3** were obtained if the acetylation was conducted in an acetic anhydride/pyridine mixture, according to the literature [7,8]. The ^{1}H-nmr spectra of **3** confirm the cyclic structure with two ABX system due to C-4, C-5 and CH_2-C-5 protons. The CH_3 singlets were assigned accordingly to **4**.

On the other hand, compounds **3** can be obtained from the corresponding open chain **2**, since we observed that **2** underwent a total transformation to **3** by heating at 40 °C in acetic anhydride, then used as a dehydrating agent [12]. Moreover, the 5-substituted 2,3-diacetyl-2-iminooxazolidines **3** were slightly stable in water, even at ambient temperature. For example, the 3-acetyl-5-(1-phenyl-4-piperazinyl)methyl-2-oxazolidinone **4 b** was obtained in a 20% yield, by hydrolysis of **3 b** at 25 °C for an hour.

Ultimately, the 5-substituted 3-acetyl-2-oxazolidinones **4** were prepared from **1** by heating in acetic anhydride at 140°C for 0.5 hour. For **4** the structural assignment was made on the basis of spectral data. The ir spectra showed two strong absorptions at 1750 and 1685 cm-1 assignable to the carbonyl groups of the cyclic urethane and the acetyl substituent, respectively. Furthermore, the characteristic ABX systems due to the ring protons were observed in the ^{1}H-nmr spectra : the ring C-5 methine was found at about 4.7 ppm. The CH_3 protons appeared as a singlet near 2.55 ppm.

Based on the 13C-nmr spectral data, we observed an obvious deshielding effect for the C-4 in the cyclized compounds **3** and **4** in relation to the corresponding C(17) in **2**.

Experimental

Microanalysis were carried out at the Service central d'analyse CNRS, Vernaison, France. Melting points were determined with a Kofler hot-stage apparatus and were uncorrected.. The ir spectra were obtained with a Beckman Acculab spectrophotometer. Nmr data were recorded with a Bruker AC-200 spectrometer. Chemical shifts (δ in ppm) and coupling constants (J in Hz) were measured using TMS as internal standard.

General procedure for the preparation of 1-substituted 3-acetamido-2-acetylcarbamoyloxypropane (2)

5-Subtituted 2-amino-2-oxazoline (0.02 mole) **1** was dissolved slowly in Ac_2O (0.2 mole) previously cooled at 0 °C. The stirring was prolonged at 0 °C during 2 hours. Then 20 ml of a mixture diethyl ether/heptane 30/70

(v/v) were added, and a white solid precipitated. It was collected by filtration and recrystallized from an appropriate solvent.

3-Acetamido-2-acetylcarbamoyloxy-1-phenoxypropane (2 a)

Yield 94%, mp : 168 °C (toluene) ; ir (KBr): ν NH 3340, OC=O 1755, NHC=O 1640 cm^{-1} ; ^{1}H-nmr (dimethylsulfoxide d_6), δ : 10.56 (s, 1H, CO-N*H*-CO), 8.03 (t, 1H, CH_2-N*H*-CO, J = 5.4 Hz), 7.29 and 6.94 (2m, 5H, Ar-*H*), 5.07 (m, 1H, C*H*), 4.13 (dd ,1H ,OCH_{2a}, J = 11.4, 3.7 Hz), 4.05 (dd ,1H , OCH_{2b}, J = 11.4, 6.2 Hz), 3.50 (m ,1H, CH_{2a}NH), 3.40 (m ,1H, CH_{2b}NH), 2.11 (s, 3H, NHCOCH_3), 1.82 (s, 3H, CONHCOCH_3) ; ^{13}C-nmr, δ: 170.3 (CONH*C* OCH_3), 169.6 (NH*C* OCH_3), 151.1 (O*C* =O), 158.6, 129.4, 120.9, 114.5 (*C* phenyl), 71.8 (*C* H), 66.9 (OCH_2), 38.9 (CH_2N), 24.2 (CONHCOCH_3), 22.4 (NHCOCH_3).

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.13 ; H, 6.16 ; N, 9.52. Found : C, 57.28 ; H, 6.17 ; N, 9.62.

3-Acetamido-2-acetylcarbamoyloxy-1-(1-phenyl-4-piperazinyl)propane (2 b)

Yield 25%, mp : 155°C (toluene) ; yield : 25 % ; ir (KBr): ν NH 3325, OC=O 1765, NHC=O 1640 cm^{-1}; ^{1}H-nmr (dimethylsulfoxide d_6), δ : 10.21 (s, 1H, CO-N*H*-CO), 7.92 (t, 1H, CH_2-N*H*-CO, J = 5.3 Hz), 7.27 and 6.78 (2m, 5H, Ar-*H*), 4.97 (m, 1H, C*H*), 3.57 (m ,2H ,CH_2NH), 3.19 (m , 4H, NCH_2), 2.64 (m ,6H ,NCH_2), 2.12 (s, 3H, NHCOCH_3), 1.81 (s, 3H, CONHCOCH_3) ; ^{13}C-nmr (dimethylsulfoxide d_6), δ : 170.3 (CONH*C* OCH_3), 169.2 (NH*C* OCH_3), 147.9 (O*C*= O), 153.5, 129.3, 119.6, 115.8 (*C* phenyl), 71.4 (*C* H), 58.5 (pip*C* H_2CH), 54.2 and 49.5 (*C*H2pip), 38.7 (CH_2N), 24.5 (CONHCOCH_3), 22.8 (NHCOCH_3).

Anal. Calcd. for $C_{18}H_{26}N_4O_4$: C, 59.65 ; H, 7.23 ; N, 15.46. Found : C, 59.71; H, 7.23 ; N, 15.48.

General procedure for the preparation of 5-substituted 2,3-diacetyl-2-iminooxazolidines (3)

Compound 1 (0.02 mole) was dissolved in acetic anhydride (0.2 mole). After stirring at 40 °C for 2h, the mixture was cooled at 0 °C and diethyl ether (50 ml) was added : a white solid precipitated a few minutes later. It was recrystallized from an appropriate solvent.

2,3-Diacetyl-2-imino-5-phenoxymethyloxazolidine (3 a)

Yield : 27 %, mp : 68 °C (diisopropyl ether) ; ir (KBr): ν C=O 1670, 1725, C=N, 1600 cm^{-1}; ^{1}H-nmr (dimethylsulfoxide d_6), δ : 7.30 and 6.96 (2m, 5H, Ar-*H*), 5.07 (m, 1H, C*H*), 4.29 (dd ,1H ,OCH_{2a}, J = 11.7, 3.2 Hz), 4.21 (dd , 1H, OCH_{2b}, J = 11.7, 4.8 Hz), 4.09 (dd ,1H ,CH_{2a}N, J = 10.9, 8.8 Hz), 3.85 (dd ,1H ,CH_{2b}N, J = 10.9, 6.1 Hz), 2.43 (s, 3H, NCOCH_3), 2.07 (s, 3H, C=NCOCH_3) ; ^{13}C nmr, δ : 180.5 (C=N*C* OCH_3), 169.0 (N*C* OCH_3), 147.1 (*C* =N), 158.0, 129.6, 121.2, 114.6 (*C* phenyl), 74.9 (*C* H), 67.9 (O*C* H_2), 45.0 (CH_2N), 26.3 (C=NCOCH_3), 24.0 (NCOCH_3).

Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53 ; H, 5.16 ; N, 9.58. Found : C, 57.61; H, 5.22 ; N, 9.52.

2,3-Diacetyl-2-imino-5-[(1-phenyl-4-piperazinyl)methyl]oxazolidine (3 b)

Yield : 41 %, mp : 113 °C (ethanol) ; ir (KBr): ν C=O 1730 and 1670 cm^{-1}; ^{1}H-nmr (chloroform d), δ : 7.35 and 6.85 (2m, 5H, Ar-*H*), 4.82 (m, 1H, C*H*), 4.15 and 3.80 (2dd, 1H each, J = 11.2, 6.8Hz, CH_2N), 3.20 (d, 2H, J = 6.8 Hz, NCH_2), 3.15 and 2.75 (2m, 8H, CH_2 piperazine), 2.55 (s, 3H, NCOCH_3), 2.25 (s, 3H, C=NCOCH_3) ; ^{13}C-nmr (chloroform d), δ : 181.2 (C=N*C* OCH_3), 169.7 (N*C* OCH_3), 146.9 (*C*=N), 151.0, 129.0, 119.6, 115.9 (*C* phenyl), 75.4 (*C* H), 60.1 (pip*C* H_2CH), 54.0 and 49.1 (*C*H2pip), 46.9 (*C* H_2N), 26.5 (NCO*C* H_3), 24.2 (C=NCO*C* H_3).

Anal. Calcd. for $C_{18}H_{24}N_4O_3$: C, 62.76 ; H, 7.02 ; N, 16.28. Found : C, 62.84 ; H, 7.00 ; N, 16.46.

General procedure for the preparation of 5-substituted 3-acetyl-2-oxazolidinones (4).

Compound **1** (0.02 mole) was dissolved in acetic anhydride (0.2 mole). The mixture was stirred at 140 °C for 30 min. Then it was evaporated to dryness and the residue was triturated twice with 10 ml of diethyl ether : a white solid precipitated a few minutes later. It was recrystallized from an appropriate solvent.

3-Acetyl-5-phenoxymethyl-2-oxazolidinone (**4 a**)

Yield : 65% mp : 113°C (trichloroethylene); lit. Mp : 115 °C [13] ; ir (KBr) : ν C=O 1750, 1685 cm^{-1}; ^{1}H-nmr (dimethylsulfoxide d_6), δ : 7.34 and 6.96 (2m, 5H, Ar-*H*), 4.99 (m, 1H, C*H*), 4.21 (d ,2H ,OCH_2), 4.07 (m ,1H ,CH_{2a}N), 3.80 (m ,1H ,CH_{2b}N), 2.39 (s, 3H, NCOCH_3) ; ^{13}C-nmr (dimethylsulfoxide d_6), δ : 169.6 (N*C* OCH$_3$), 153.2 (*C* =O), 158.0, 129.6, 121.2, 114.6 (*C* phenyl), 71.8 (*C* H), 68.1 (O*C*H$_2$), 43.9 (*C* H$_2$N), 23.5 (NCO*C* H$_3$).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27 ; H, 5.53 ; N, 5.96. Found : C, 61.33; H, 5.65 ; N, 6.18.

3-Acetyl-5-[(1-phenyl-4-piperazinyl)methyl]-2-oxazolidinone (**4 b**)

Yield : 25% (trichloroethylene), mp : 146°C; ir (potassium bromide): ν C=O 1750 and 1685 cm^{-1}; ^{1}H-nmr (chloroform d), δ : 7.32 and 6.87 (2m, 5H, Ar-*H*), 4.73 (m, 1H, C*H*), 4.10 and 3.70 (2dd, 1H each, J = 10.3, 5.8Hz, C*H*$_2$N), 3.30 and 2.75 (2m, 10H, NC*H*$_2$), 2.55 (s, 3H, NCOC*H*$_3$) ; ^{13}C-nmr (chloroform d), δ : 169.8 (N*C* OCH$_3$), 153.9 (O*C*=O), 151.0, 128.9, 119.6, 115.9 (*C* phenyl), 71.7 (*C* H), 60.0 (pip*C* H$_2$CH), 53.9 and 49.0 (*C*H$_2$pip), 42.4 (*C* H$_2$N), 26.7 (NCO*C* H$_3$).

References and notes

(1) J. A. Frump, Chem. Rev., 71, 483 (1971)

(2) J.J. Bosc, C. Jarry, A. Carpy, E. Panconi and P. Descas, Eur. J. Med. Chem., 27, 437 (1992)

(3) J.J.Bosc, C.Jarry, J.Ouhabi, M.Laguerre and A.Carpy, Can.J.Chem., 74, 1341-1347 (1996)

(4) J.J.Bosc, C.Jarry , Heterocycl.Commun., 2, 355 (1996)

(5) J.Lessel, Pharmac.Acta Hev., 71,109 (1996)

(6) E. Fromm, R. Kapeller, L. Pirk, A. Harn and T. Leipert, Justus Liebigs Ann. Chem.,447, 259 (1926)

(7) G. Poos, J. Carson, J. Rosenau, A. Roszkowski, N. Kelley and J. McGowin, J.MedChem., 6, 266 (1963)

(8) M.R. Harnden and R.R. Rasmussen, J. Med. Chem., 13, 305 (1970)

(9) C. Tanaka, I. Ogata and M. Nishida, Yakugaku Zasshi, 97, 157-164 (1977)Chem. Abst. 87. 39345 (1977)

(10) A.Williams, Acc.Chem.Res., 22, 387 (1989)

(11) X-Ray structure analysis of compound **2 a**

Suitable crystals of **2 a** were obtained by crystallization from MeOH. Initial lattice parameters were obtained from least squares fits to 25 reflexions (θ < 25°). Intensities were collected with an Enraf-Nonius CAD-4 diffractometer using the CuKα radiation and a graphite monochromator up to θ = 65°, scan type 6θ/ω = 3, ω-scan width (0.8 + 0.15 tanθ).

Crystal data for **2a** : C14H18N2O5, Mr = 294.3, monoclinic space group P2$_1$/c, a = 9.295(8), b = 7.324(3), c = 21.717(3)Å, β = 94.63(8)°, V = 1474(3)Å^3, Dx = 1.327 g.cm-3, Z = 4, λ (CuKα) = 1.54178Å, μ (CuKα) = 0.861 mm-1.

Totals of 1886 measured reflections were collected. Data sets were corrected for *Lorentz* and polarization effects but not for absorption. Structure was solved by the direct methods using 738 reflections with $I > 3\sigma(I)$. The final residuals were R = 0.095 and Rw = 0.124. The crystal size and the low number of observed reflexions contribue to explain the R value.

Table 1 : Selected bond lengths (Å) for **2 a**

C(8)-C(9)	1.50 (4)	C(11)-N(13)	1.30 (3)	C(17)-N(18)	1.51 (3)
C(9)-O(10)	1.57 (3)	N(13)-C(14)	1.43 (3)	N(18)-C(19)	1.35 (3)
C(9)-C(17)	1.51 (4)	C(14)-O(15)	1.24 (3)	C(19)-O(20)	1.31(3)
O(10)-C(11)	1.30 (3)	C(14)-C(16)	1.47 (4)	C(19)-C(21)	1.29 (4)
C(11)-O(12)	1.23 (3)				

Table 2 : Selected bond angles (°) for **2 a**

O(7)-C(8)-C(9)	104 (2)	O(10)-C(11)-N(13)	107 (2)	C(9)-C(17)-N(18)	109 (2)
C(8)-C(9)-O(10)	104 (2)	O(12)-C(11)-N(13)	129 (2)	C (17)-N(18)-C(19)	127 (2)
C(8)-C(9)-C(17)	110 (2)	C(11)-N(13)-C(14)	124 (2)	N(18)-C(19)-O(20)	115 (2)
O(10)-C(9)-C(17)	106 (2)	N(13)-C(14)-O(15)	122 (2)	N(18)-C(19)-C(21)	127 (3)
C(9)-O(10)-C(11)	118 (2)	N(13)-C(14)-C(16)	116 (2)	O(20)-C(19)-C(21)	118 (3)
O(10)-C(11)-O(12)	124 (2)	O(15)-C(14)-C(16)	122 (2)		

(12) K. Friedrich and K. Wallenfels, in S.Patai (Ed), The chemistry of the cyano group, Interscience, New-York 1970, p 92

(13) Y. Iwakura, S. Izawa and F. Hayano, Bull. Chem. Soc. Jpn., 39, 2485 (1966)

Received July 10, 1997