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First Stable α-Diols and Hemiketals from the α-Halo Pyruvamide Series

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Abstract: The addition of water or alcohol to 3-halopyruvamides, having a special interest in enzymology, permitted us to isolate stable α-diols and hemiketals, until then detected only by spectroscopic means. The reaction is not diastereoselective, but selective precipitation of only one diastereoisomer shifts the equilibrium between the two isomers. Isolated compounds were fully characterised and results discussed. © 1997 Elsevier Science Ltd.

INTRODUCTION

The addition of water or alcohol to ketone, giving respectively hydrate or hemiketal, is an equilibrium which generally favours the starting materials. The unstable tetrahedral adducts can only be, in some particular cases, either spectroscopically detected or sometimes isolated. This is essentially the case when :

- addition of ROH relieves some strain, for example during the formation of the hydrate of cyclopropanone by assuming sp^2 to sp^3 rehybridation ;[1,2]
- some strong electron withdrawing atoms in the α-position stabilize the hemiketal as it is the case with perfluoro and perchloro compounds ;[2,3]
- carbonyl function is adjacent to the position to be attacked, what is related to important enzymatic transformations of pyruvic acid and pyruvamide.

These last two compounds and some derivatives have been the focus of great interest, in particular to clarify enzyme-substrate interaction and also to develop inhibitors of pyruvate dependent enzymes.[5,6] However, no stable hemiketal has ever been isolated up to now in this class of chemicals. In the present article we report the diastereoselective synthesis and full characterisation of the first stable hydrate and hemiketals obtained starting from original α-halopyruvamides that we have recently described.[7]

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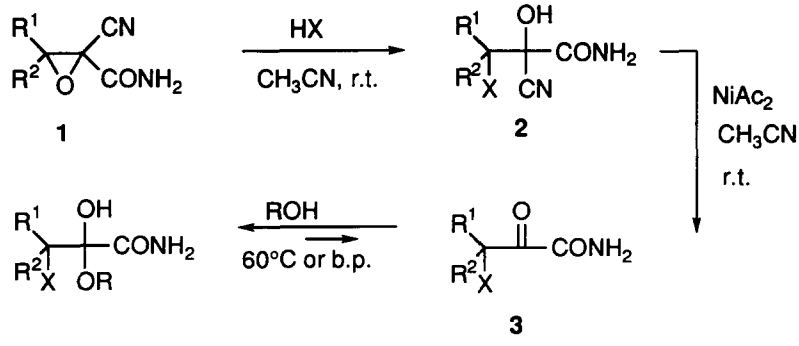
RESULTS AND DISCUSSION

The title compounds are easily obtained by refluxing the starting pyruvamide in the appropriate solvent for one hour (except for water for which temperature must not exceed 60°C) (**Scheme 1**). During cooling a white microcrystalline powder of high purity is formed. Yields of the first purified fraction are spread between 48 to 74% depending on the substituents (**Table 1**).



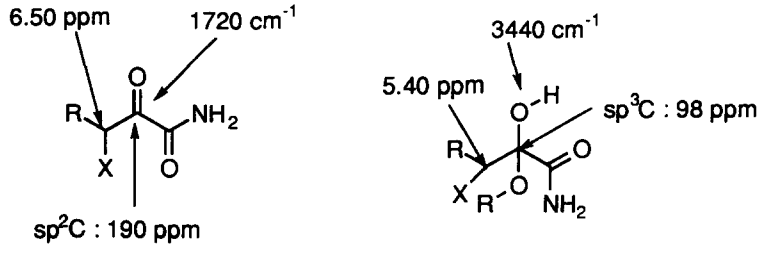
X = Cl, Br

4 R = H ; **5** R = CH_3 ; **6** R = CH_2CH_3 ; **7** R = $CH(CH_3)_2$.

a : R^1 = $pClC_6H_4$, R^2 = H, X = Cl ; **b** : R^1 = C_6H_5, R^2 = H, X = Cl ; **c** : R^1 = $pNO_2C_6H_4$, R^2 = H, X = Cl ;
d : R^1 = $pCH_3C_6H_4$, R^2 = H, X = Cl ; **e** :R^1, R^2 = -$(CH_2)_4$-, X = Cl ; **f** : R^1 = C_6H_5, R^2 = H, X = Br ;
g : R^1 = $pClC_6H_4$, R^2 = H, X = Br ; **h** : R^1 = $pNO_2C_6H_4$, R^2 = H, X = Br ; **i** : R^1 = R^2 = C_6H_5, X = Cl ;
j : R^1 = $pCH_3C_6H_4$, R^2 = H, X = Br ; **k** : R^1 = C_6H_5, R^2 = H, R = CD_3, X = Cl.

Scheme 1

Microanalysis indicates a one to one stoichiometry ROH / pyruvamide. IR and NMR data confirm that the nucleophile is covalently bonded to the central carbonyl. **Scheme 2** illustrates the main spectroscopic modifications observed for hemiketal with respect to pyruvamide:



Scheme 2

- the ketone IR vibration at 1720 cm^{-1} disappears while 1670 cm^{-1} amide absorption remains nearly unchanged ; a new sharp OH vibration appears at about 3440 cm^{-1};
- sp^2 ketone carbon at 190 ppm is replaced by a low field sp^3 quaternary signal at 98 ppm ;
- CH signal is shifted upfield for more than one ppm (from 6.50 to 5.40) due to disappearance of the deshelding effect by the neighbouring carbonyl ;
- the chemical shift of the new hydroxylic proton at about 6.40 ppm (identified by deuterium exchange) proved to be independant from concentration which indicates that it should be hydrogen bonded to the carbonyl, increasing the stability of hemiketals ;
- E.I.Mass spectra of both pyruvamid and hemiketal are strictly identical because of a rapid elimination of alcohols during sublimation of the sample.

In all studied cases only one diastereoisomer is obtained. The first collected fraction represents generally about 50% yield in hemiketal and is clean enough to be directly microanalysed as it arises from crystallisation (The formed powder had to be rapidly washed with the alcohol employed and dried). However, if the remaining solution is kept standing, it delivers gradually new fractions of the same diastereoisomer that can be successively collected. To investigate this interesting stereochemical aspect, we ran some NMR experiments in CD_3OD, which have given the following indications : a) when a pyruvamide **3b** is dissolved in CD_3OD, an equilibrium takes place in about an hour giving about 10 % of **3b** and the two diastereoisomeric hemiketals **5k** in similar proportions ; b) dissolution of diastereoisomericaly pure hemiketal **6b** in CD_3OD leads to the same mixture through trans-hemiketalisation ; c) both diastereoisomers have exactly the same ^1H NMR, but are easily distinguished by ^{13}C NMR, giving two sets of signals for each carbon.

From this experiment it is clear that the obtention of only one diastereoisomer by simple filtration results from a gradual and selective crystallisation which displaces continuously the equilibrium towards the formation of this diastereoisomer. We succeeded in isolating only one diastereoisomer so that we have not sufficient information to establish its stereochemistry.

Table 1. Yields of Hemiketals **5**, **6** and **7** .

N° of compound	R^1	R^2	X	R	Yields [%]*
5a	$pClC_6H_4$	H	Cl	CH_3	50
5c	$pNO_2C_6H_4$	H	Cl	CH_3	74
5g	$pClC_6H_4$	H	Br	CH_3	50
6a	$pClC_6H_4$	H	Cl	CH_2CH_3	56
6b	C_6H_5	H	Cl	CH_2CH_3	55
6d	$pCH_3C_6H_4$	H	Cl	CH_2CH_3	51
6e	$-(CH_2)_4-$	$-(CH_2)_4-$	Cl	CH_2CH_3	52
7a	$pClC_6H_4$	H	Cl	$CH(CH_3)_2$	52
7c	$pNO_2C_6H_4$	H	Cl	$CH(CH_3)_2$	48

* This yield corresponds to the first collected fraction by filtration representing only one diastereoisomer. The stereochemistry of the two asymetric carbons was not established.

CONCLUSION

Despite being tetrahedric compounds, diols and hemiketals obtained from α-substituted α-halopyruvamides are quite stable compounds in the solid state. Their rapid formation starting from racemic pyruvamide is not diastereoselective as we proved it by NMR experiments. However the equilibrated reaction delivers exclusively one diastereoisomer by selective crystallisation. Title compounds can be considered as a protected form of very reactive α-halopyruvamides, showing a special interest in enzymology and also interesting as starting material for the synthesis of potentially biologically active compounds.

EXPERIMENTAL

General. ^{1}H NMR spectra were recorded at 80 MHz on a Bruker WP 80 spectrometer or at 300 MHz on a Bruker AM 300 spectrometer and ^{13}C NMR spectra at 75 MHz on a Bruker AM 300 spectrometer using tetramethylsilane as internal reference. High resolution mass spectra were obtained with a Varian Mat 311 mass spectrometer. IR spectra were determined with a Perkin-Elmer 225 or 1420 spectrometer. Melting points were taken with a Kofler hot stage apparatus.

All NMR spectra of hemiketals **5**,**6** and **7** were realised starting from the first isolated fraction, which corresponds to one isomer. A low solubility of these hemiketals forced us to record our spectra in DMSO. Because of the transformation of hemiketals in this solvent to pyruvamide and later to other unidentified products, spectra must be recorded immediately. As indicated in discussion, we have realised a study in deuterated methanol, starting first from pyruvamide **3b** and then from a pure hemiketal **6b**. NMR data of both diastereoisomers are indicated under **5k**.

General Procedure for the Preparation of Oxiranes 1.

The starting oxiranes **1** were easily prepared by treating the corresponding cyano ester oxiranes[8] with ammonia according to a described procedure .[8]

General Procedure for the Preparation of Cyanohydrines 2.

Hydrochloric acid (12 mol/L or 37 %; 10 mL and 7 mL for R^1, R^2 = - $(CH_2)_4$ -) or hydrobromic acid respectively (18 mol/L or 47.0 % ; 10 mL) was added to the solution of the oxirane **1** (5.3 mmol) dissolved in MeCN (20 mL and 11mL for R^1,R^2 = - $(CH_2)_4$ -) and left at room temperature for 12h . The reaction mixture was diluted with water (100 ml) and extracted with diethylether (100 ml x 3). The combined extracts were dried (Na_2SO_4) and evaporated to give **2** as a solid after diethylether workup. Sometimes cyanhydrines **2** crystallised in situ after 2 to 4 days at room temperature. The product was removed by filtration, washed with water (to pH = 7), dried in vacuo (50°C) and recrystallised in MeCN. The crude product is pure enough for the preparation of pyruvamides **3**.

2a (R^1 = $pClC_6H_4$, R^2 = H, X = Cl) : (63% yield) ; m.p. 206°C (MeCN) ; IR (Nujol) 3460, 3340, 2240, 1675 cm^{-1} ; ^1H NMR (CD_3CN) δ_H 5.50 (s, 1H, CHCl), 6.30 (br, 1H, OH), 6.50 (br, 1H) and 6.80 (br, 1H)($CONH_2$), 7.37(m, 4H, C_6H_4) ; ^{13}C NMR (CD_3CN) δ_C 65.03 (d, ^1J = 157, CHCl), 77.35 (d, ^2J =6.74, COH), 118.23 (CN), 129.30, 131.98, 134.04, 136.00 ($pClC_6H_4$), 167.34 ($CONH_2$) ; HRMS : Found 232.9836. Calc. for $C_9H_7NO_2Cl_2$ (M^+ - HCN) : 232.9824 ; Anal. calc. for $C_{10}H_8N_2O_2Cl_2$: C, 46.36 ; H, 3.11 ; N, 10.82 ; Cl, 27.37 ; Found : C, 46.56, H, 3.05 ; N, 10.91 ; Cl, 27.41.

2b (R^1 = C_6H_5, R^2 = H, X = Cl) : (75% yield) ; m.p. 203°C (MeCN) ; IR (Nujol) 3460, 3340, 2240, 1680 cm^{-1} ; ^1H NMR (CD_3CN) δ_H 5.65 (s, 1H, CHCl), 6.20 (br, 1H, OH), 6.40 (br, 1H) and 6.90 (br, 1H)($CONH_2$), 7.50(m, 5H, C_6H_5) ; ^{13}C NMR (CD_3CN) δ_C 65.83 (d, ^1J = 157, CHCl),77.55 (d, COH), 118.46 (CN), 129.26, 130.12, 130.16, 135.16 (C_6H_5), 167.37 ($CONH_2$) ; HRMS : Found 197.0251. Calc. for $C_9H_8NO_2Cl$ (M^+ - HCN) : 197.0244 ; Anal. calc. for $C_{10}H_9N_2O_2Cl$ C, 53.46 ; H, 4.04 ; N, 12.47 ; Found : C, 53.44, H, 4.10 ; N, 12.51.

2c (R^1 = $pNO_2C_6H_4$, R^2 = H, X = Cl) : (48% yield) ; m.p. 178°C (MeCN) ; IR (Nujol) 3420, 3310, 2239, 1670 cm^{-1} ; ^1H NMR ($CDCl_3$,CF_3COOH) δ_H 5.60 (s, 1H, CHCl), 7.10 (br, 1H,) and 7.20 (br, 1H)($CONH_2$), 7.90(m, 4H, $pNO_2C_6H_4$) ; ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 63.85 (d, ^1J = 157, CHCl), 76.66 (d, ^2J = 5.27, COH), 115.47 (d, ^3J=2.18, CN), 124.53, 131.22, 140.51, 149.27 (C_6H_4), 169.19 (s, $CONH_2$) ; HRMS : Found 242.0090. Calc. for $C_9H_7N_2O_4Cl$ (M^+ - HCN) : 242.0094 ; Anal. calc. for $C_{10}H_8N_3O_4Cl$: C, 44.54 ; H, 2.99 ; N, 15.58 ; Found : C, 44.47, H, 3.27 ; N, 15.33.

2d (R^1 = $pCH_3C_6H_4$, R^2 = H, X = Cl) : (80% yield) ; m.p. 200°C (MeCN) ; IR (Nujol) 3460, 3340, 2240, 1675 cm^{-1} ; ^1H NMR ($CDCl_3$, CF_3COOH) δ_H 2.32 (s, 3H, CH3), 5.45 (s, 1H, CHCl), 6.90 (br, 1H,) and 7.20 (br, 1H)($CONH_2$), 7.20 (m, 4H, C_6H_4) ; ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 21.29 (q, ^1J=127, pCH3), 65.46 (d, ^1J = 157, CHCl), 77.02 (COH), 115.90 (CN), 129.26, 129.45, 129.97, 141.56 (C_6H_4), 169.47 ($CONH_2$) ; HRMS : Found 211.0399. Calc. for $C_{10}H_{10}NO_2Cl$ (M^+ - HCN) : 211.0399 ; Anal. calc. for $C_{11}H_{11}N_2O_2Cl$: C, 55.35 ; H, 4.65 ; N, 11.74; Found : C, 55.31, H, 4.58 ; N, 12.02.

2e (R^1, R^2 = - $(CH_2)4$ -, X = Cl) : (54 % yield) ; m.p. 118°C (MeCN) ; IR (Nujol) 3450, 3340, 3100, 2240, 1680 cm^{-1} ; ^1H NMR ($CDCl_3$, CF_3COOH) δ_H 2.10 (m, 8H, - $(CH_2)4$ -), 7.30 (br, 1H), 7.65 (br, 1H) ($CONH_2$); ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 23.10 (t, ^1J = 135), 23.49 (t, ^1J = 132), 38.42 (t, ^1J = 132), 37.94 (t, ^1J = 132) (- (CH_2) -)4, 76.66 (d, COH), 82.61 (m, CCl), 169.40 (s, $CONH_2$) ; HRMS : Found 159.0440. Calc. for C_7H_9NOCl (M^+ - $CONH_2$) : 159.04509; Anal. calc. for $C_8H_{11}N_2O_2Cl$: C, 47.41; H, 5,47; N, 13.83; Cl, 17.49; Found C, 47.32; H, 5.41; N, 13.81; Cl, 17.55.

2f (R^1 = C_6H_5, R^2 = H, X = Br) : (63% yield) ; m.p. 209°C (MeCN) ; IR (Nujol) 3450, 3320, 2238, 1680 cm^{-1} ; ^1H NMR ($CDCl_3$, CF_3COOH) δ_H 5.55 (s, 1H, CHBr), 6.95 (br, 1H) and 7.20 (br, 1H) ($CONH_2$), 7.30 to 7.50 (m, 5H, C_6H_5) ; ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 55.61 (d, ^1J = 157, CHBr), 76.44 (d, ^2J = 6.24, COH), 115.45 (d, ^3J=2.13, CN) 128.66, 129.19, 130.38, 132.48 (C_6H_5), 168.31 ($CONH_2$) ; HRMS : Found 240.9730. Calc. for $C_9H_8NO_2Br$ (M^+ - HCN) : 240.9738 ; Anal. calc. for $C_{10}H_9N_2O_2Br$: C, 44.63 ; H, 3.37 ; N, 10.41 ; Br, 29.70 . Found : C, 44.73, H, 3.46 ; N, 10.85 ; Br, 30.00.

2g (R^1 = $pClC_6H_4$, R^2 = H, X = Br) : (80% yield) ; m.p. 190°C (MeCN) ; IR (Nujol) 3450, 3320, 2240, 1665 cm^{-1} ; ^1H NMR ($CDCl_3$, CF_3COOH) δ_H 5.60 (s, 1H, CHBr), 7.00 (br, 1H,) and 7.25 (br, 1H)

($CONH_2$), 7.25 to 7.60 (m, 4H, $pClC_6H_4$) ; ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 53.78 (d, ^1J = 157, CHBr), 76.43 (d, ^2J = 6.52, COH), 116.00 (d, ^3J=2.10, CN), 129.72, 131.29, 131.94, 137.42, ($pClC_6H_4$), 168.31 ($CONH_2$) ; HRMS : Found 274.9339. Calc. for $C_9H_7NO_2BrCl$ (M^+ - HCN) : 274.9349 ; Anal. calc. for $C_{10}H_8N_2O_2BrCl$: C, 39.57 ; H, 2.66 ; N, 9.23; Cl, 11.68. Found : C, 39.57, H, 2.64 ; N, 9.36; Cl, 11.51.

2h (R^1 = $pNO_2C_6H_4$, R^2 = H, X = Br) : (68% yield) ; m.p. 174°C (MeCN) ; IR (Nujol) 3415, 3310, 2250, 1670 cm^{-1} ; ^1H NMR ($CDCl_3$, CF_3COOH) δ_H 5.70 (s, 1H, CHBr), 7.20 (br, 1H) and 7.30 (br, 1H) ($CONH_2$) 7.70 to 8.20 (m, 4H, $pNO_2C_6H_4$) ; ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 52.72 (d, ^1J = 158, CHBr), 75.90 (d, ^2J = 6.25, COH), 114.00 (d, ^3J=1.77, CN), 123.47, 130.79, 140.60, 148.21 ($pNO_2C_6H_4$), 168.03 (s, $CONH_2$) ; HRMS : Found 285.9580. Calc. for $C_9H_7N_2O_4Br$ (M^+ - HCN) : 285.9589 ; Anal. calc. for $C_{10}H_8N_3O_4Br$: C, 38.24 ; H, 2.57 ; N, 13.38 ; Found : C, 37.61, H, 2.77 ; N, 13.09.

2i (R^1 = R^2 = C_6H_5, X = Cl) : (78% yield) ; m.p. 200°C (MeCN) ; IR (Nujol) 3410, 3320, 3270, 3180, 2250, 1680 cm^{-1} ; ^1H NMR ($CDCl_3$, CF_3COOH) δ_H 7.15 to 7.90 (m, 12H) (C_6H_5 and $CONH_2$) ; ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 77.50 (m, CCl), 77.13 (d, ^2J = 7.21, COH), 116.33 (s, CN) 127.98 to140.28 (C_6H_5), 168.46 ($CONH_2$) ; HRMS : Found 256.0548. Calc. for $C_{15}H_{11}NOCl$ (M^+ - $CONH_2$) : 256.0529 ; Anal. calc. for $C_{16}H_{13}N_2O_2Cl$ C, 63.90 ; H, 4.36 ; N, 9.32 ; Cl, 11.79 ; Found : C, 64.34, H, 4.38 ; N, 9.46 ; Cl, 11.17.

General Procedure for the Preparation of Pyruvamides 3.

Nickel acetate (1.25 g, 7 mmol) was added to a stirred solution of chlorohydrin **2** (2.2 mmol) dissolved in MeCN (12,5 mL). After 1h at room temperature the mixture was diluted with water (20 mL) and extracted with diethylether (20 mL x 3). The organic layer was dried over Na_2SO_4 and evaporated. The solid **3** obtained was purified by sublimation and characterized by its spectroscopic spectra.

3a (R^1 = $pClC_6H_4$, R^2= H, X = Cl) : (90 % yield), m.p. 152°C (MeCN) ; IR (Nujol) 3370, 3300, 3180, 1720, 1660 cm^{-1} ; ^1H NMR (CD_3CN) δ_H 6.65 (s, 1H, CHCl), 6.60 (br, 1H) and 7.30 (br, 1H) ($CONH_2$), 7.50 (m, 4H, C_6H_4) ; ^{13}C NMR (CD_3CN) δ_C 60.82 (CHCl), 129.9, 130.50, 130.57, 135.6 (C_6H_4), 161.75 ($CONH_2$), 189.95 (CO) ; HRMS : Found 232.9859. Calc. for $C_9H_7Cl_2NO_2$: M^+ 232.9854. Anal. calc.for $C_9H_7Cl_2NO_2$: C, 46.58 ; H, 3.04; N, 6.04; Cl, 30.56. Found : C, 46.94, H, 2.99 ; N, 6.10 ; Cl, 29.89.

3b (R^1 = C_6H_5, R^2= H, X = Cl) : (85 % yield), m.p. 121°C (MeCN) ; IR (Nujol) 3380, 3300, 3180, 1725, 1655 cm^{-1} ; ^1H NMR (CD_3CN) δ_H 6.75 (s, 1H, CHCl), 6.60 (br, 1H) and 7.3 (br, 1H) ($CONH_2$), 7.6 (m, 5H, C_6H_5) ; ^{13}C NMR (CD_3CN) δ_C 62.07 (CHCl), 129.90, 130.49, 130.56, 130.62 (C_6H_5), 162.00 ($CONH_2$), 190.00 (CO) ; HRMS : Found 197.023. Calc. for $C_9H_8ClNO_2$: M^+ 197.0243. Anal. calc. for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09; Cl, 17.94. Found : C, 54.79, H, 4.14 ; N, 7.27 ; Cl, 17.85.

3c (R^1 = $pN0_2C_6H_4$, R^2=H, X = Cl) : (82 % yield) ; m.p. 130°C (MeCN) ; IR (Nujol) 3371, 3300, 3180, 1731, 1697 cm^{-1} ; ^1H NMR ($CDCl_3$, CF_3COOH) δ_H 6.50 (s, 1H, CHCl), 7.30 (br, 1H) and 7.40 (br, 1H) ($CONH_2$), 8.00 (m, 4H, C_6H_4) ; ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 57.75 (d, ^1J=156, CHCl), 123.93, 130.50, 130.54, 140.32, 148.54 (C_6H_4), 161.91 ($CONH_2$), 187.25 (CO) ; HRMS : Found 242.00943. Calc.for $C_9H_7ClN_2O_4$: M^+ 242.00941.

3d (R^1= $pMeC_6H_4$, R^2= H, X = Cl) : (80 % yield) ; m.p. 114°C (MeCN) ; IR (Nujol) 3380, 3300, 3170, 1725, 1650 cm^{-1} ; ^1H NMR ($CDCl_3$, CF_3COOH) δ_H 2.35 (s, 3H, CH_3) 6,40 (s, 1H, CHCl), 7.25 (br, 2H, $CONH_2$), 7.25 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 21.14(q, ^1J=127, CH_3) 59.66 (d, ^1J = 155, CHCl), 128.75, 129.49, 130.05, 140.30 (C_6H_4), 162.40 ($CONH_2$), 187.91 (CO) ; HRMS : Found 211.0400 . Calc. for $C_{10}H_{10}ClNO_2$: M^+ 211.0390. Anal. calc. for $C_{10}H_{10}ClNO_2$: C, 55.35; H, 4.65; N, 6.62; Found : C, 55.31; H, 4.58 ; N, 6.34.

3e (R^1, R^2 = - $(CH_2)4$ -, X = Cl) : (40 % yield) ; m.p. 53°C (MeCN) ; IR (Nujol) 3380, 3270, 3170, 1645 cm^{-1} ; ^1H NMR ($CDCl_3$, CF_3COOH) δ_H 1.75 to 2.50 (m, 8H, -$(CH_2)4$ -), 7.30 (br, 1H), 7.50 (br, 1H) ($CONH_2$,); ^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 23.70 (2t, ^1J = 131, - $(CH_2)4$ -), 39.61 (2t, ^1J = 134, -$(CH_2)4$-), 77.17 (m, CCl), 164.27 ($CONH_2$), 190.00 (CO) ; HRMS : Found 139.06240. Calc. for $C_7H_9NO_2$ (M^+-HCl):139.06332.

3f (R^1 = C_6H_5, R^2 = H, X = Br) : (70 % yield) ; m.p. 150°C (MeCN) ; IR (Nujol) 3390, 3300, 3180, 1715, 1655 cm^{-1}; ^1H NMR (CD_3CN) δ_H 6.70 (s, 1H, CHBr) ; 6.55 (br, 1H) and 7.3 (br, 1H) ($CONH_2$), 7.5 (m, 5H, C_6H_5) ;^{13}C NMR (CD_3CN) δ_C 49.49 (d, ^1J = 157, CHBr), 126.58, 129.47, 131.58 and 139.72, (C_6H_5), 161.72 ($CONH_2$), 189.80 (CO) ; HRMS : Found 240.9734. Calc. for $C_9H_8NO_2Br$: M^+-HCl 240.9737. Anal. calc. for $C_9H_8NO_2Br$: C, 44.66 ; H, 3.33 ; N, 5.79 ; Br, 33.02 . Found : C, 44.46 ; H, 3.34 ; N, 6.09 ; Br, 32.59.

3g (R^1 = $pClC_6H_4$, R^2= H, X = Br) : (74 % yield) ; m.p. 148°C (MeCN) ; IR (Nujol) 3380, 3300, 3180, 1715, 1655 cm^{-1}; ^1H NMR (CD_3CN) δ_H 6.25 (br, 1H, CONH2), 6.55 (s, 1H, CHBr), 7.10 (br, 1H, $CONH_2$), 7.45 (m, 4H, $pClC_6H_4$) ; HRMS : Found 274.9349. Calc. for $C_9H_7ClBrNO_2$: M^+ 274.9339. Anal. calc. for $C_9H_7ClBrNO_2$: C, 39.09; H, 2.55; N, 5.07. Found : C, 38.86, H, 2.60 ; N, 4.69.

3h (R^1 = $pNO_2C_6H_4$, R^2 = H, X = Br) : (65 % yield) ; m.p. 134°C (MeCN) ; IR (Nujol) 3320, 3110, 1725, 1650 cm^{-1}; ^1H NMR (CD_3CN) δ_H 6.60 (br, 1H, $CONH_2$), 6.65 (s, 1H, CHBr), 7.30 (br, 1H, $CONH_2$), 7.90 (m, 4H, C_6H_4) ;.^{13}C NMR (CD_3CN) δ_C 46.55 (d, ^1J = 158, CHBr), 123.50, 124.34, 131.80, 142.77 ($pNO_2C_6H_4$), 161.52 ($CONH_2$), 189.14 (CO) ; HRMS : Found 285.9589. Calc. for $C_9H_7BrN_2O_4$: M^+ 285.9593.

3j (R^1 = $pCH_3C_6H_4$, R^2= H, X = Br) : (81 % yield) ; m.p. 150°C (MeCN) ; IR (Nujol) 3380, 3300, 3180, 1720, 1655 cm^{-1} ; ^1H NMR (CD_3CN) δ_H 2.35 (s, 3H, CH_3), 6.40 (br, 1H, $CONH_2$), 6.54 (s, 1H, CHBr), 7.30 (br, 1H, $CONH_2$), 7.50 (m, 4H, C_6H_4) ;^{13}C NMR ($CDCl_3$, CF_3COOH) δ_C 20.32 (q, CH_3) 48.71 (d, ^1J = 157, CHBr), 126.59, 129.47, 131.57, 139.71 (C_6H_4), 160.75 ($CONH_2$), 188.76 (CO) ; HRMS : Found 254.9895. Calc. for $C_{10}H_{10}BrNO_2$: M^+ 254.9887. Anal. calc. for $C_{10}H_{10}BrNO_2$ C, 46.90 ; H, 3.94 ; N, 5.47 ;. Found : C, 47.50 ; H, 4.26 ; N, 5.62.

General Procedure for the Preparation of α-Diols 4.

A stirred solution of pyruvamide **3** (1 mmol) in water (10 mL) was heated (60 °C) for 45 minutes. After cooling the solvent was partially removed in vacuo to give the crude solid product which was filtered off, washed with water and dried.

4a (R^1 = $pClC_6H_4$, R^2 = H, X = Cl) : (49% yield) ; m.p. 151°C (H_2O) ; IR (Nujol) 3465, 3356, 1667, 1648 cm^{-1} ; ^1H NMR (DMSO) δ_H 5.30 (s, 1H, CHCl), 6.49 (br, 1H, OH) and 6.66 (br, 1H, OH), 7.38 to

7.53 (m, 6H, $pClC_6H_4$ and $CONH_2$). Anal. calc. for $C_9H_9NO_3Cl_2$: C, 43.22 ; H, 3.60 ; N, 5.60 : Cl. 28.35. Found : C, 43.50 ; H, 3.43 ; N, 5.97 ; Cl, 28.13.

4b ($R^1 = C_6H_5$, R^2 = H, X = Cl) : (55 % yield) ; m.p. 120°C (H_2O) ; IR (Nujol) 3467, 3356, 1667. 1645 cm^{-1} ; ^1H NMR (DMSO) δ_H 5.20 (s, 1H, CHCl), 6.34 (br, 1H, OH), 6.48 (s, 1H, OH), 7.21 to 7.43 (m, 7H, C_6H_5 and $CONH_2$) ; Anal. calc. for $C_9H_{10}NO_3Cl$: C, 50.13 ; H, 4.64 ; N, 6.50 ; Found : C, 49.70 ; H, 4.64 ; N, 6.66.

General Procedure for the Preparation of Hemiketals 5, 6, 7.

A stirred solution of pyruvamide **3** (1 mmol) in the corresponding alcohol (10 mL) was heated under reflux for 1 hour. After cooling the first fraction of crystals was removed to give the crude product which was generaly pure enough for microanalysis after washing with alkohol and drying.

5a ($R^1 = pClC_6H_4$, R^2= H, R = CH_3, X = Cl) : (50 % yield) ; m.p. 145°C (CH_3OH) ; IR (Nujol) 3465, 3351, 1668, cm^{-1} ; ^1H NMR (DMSO) δ_H 3.03 (s, 1H, OCH_3), 5.35 (s, 1H, CHCl), 6.69 (br, 1H, OH), 7.45 (m, 4H, $pClC_6H_4$), 7.85 (s, 1H) and 7.90 (s, 1H) ($CONH_2$) ; ^{13}C NMR (DMSO) δ_C 49.89 (q, ^1J = 143.80, OCH_3), 65.03 (d, ^1J = 154.85, CHCl), 97.83 (s, COH), 127.77, 130.99, 133.06, 135.94, ($pClC_6H_4$), 169.44 (CO) ; Anal. calc. for $C_{10}H_{11}NO_3Cl_2$: C, 45.48 ; H, 4.20 ; N, 5.30 ; Cl, 26.85. Found : C, 45.84 ; H, 4.18 ; N, 5.03 ; Cl, 26.83.

5c ($R^1 = pNO_2C_6H_4$, R^2= H, R = CH_3, X = Cl) : (74 % yield) ; m.p. 148°C (CH_3OH) ; IR (Nujol) 3419, 3304, 1668, cm^{-1} ; ^1H NMR (DMSO) δ_H 3.03 (s, 3H, OCH_3), 5.54 (s, 1H, CHCl), 6.60 (br, 1H, OH), 7.87 (s, 1H) and 7.89 (s, 1H) ($CONH_2$), 7.99 (m, 4H, $pNO_2C_6H_4$) ; ^{13}C NMR (DMSO) δ_C 51.28 (q, ^1J = 143.26, OCH_3), 63.00 (d, ^1J = 155.07, CHCl), 98.92 (s, COH),123.74, 131.81, 144.80, 148.13 ($pNO_2C_6H_4$) 170.88 (CO) ; Anal. calc. for $C_{10}H_{11}N_2O_5Cl$: C, 43.70 ; H, 4.05 ; N, 10.20 ; Cl, 12.91. Found: C, 43.65; H, 4.06 ; N, 10.10 ; Cl, 12.80.

5g ($R^1 = pClC_6H_4$, R^2= H, R = CH_3, X = Br) : (50 % yield) ; m.p. 155°C (CH_3OH) ; IR (Nujol) 3415, 3308, 1658, cm^{-1} ; ^1H NMR (DMSO) δ_H 3.03 (s, 1H, OCH_3), 5.44 (s, 1H, CHBr), 6.69 (br, 1H, OH), 7.45 (m, 4H, $pClC_6H_4$), 7.85 (s, 1H) and 7.80 (s, 1H) ($CONH_2$) ; ^{13}C NMR (DMSO) δ_C 46.74 (q, ^1J = 143.00, OCH_3), 47.89 (d, ^1J = 156.35, CHBr), 91.05 (s, COH), 128.64, 130.52, 131.36, 133.76, ($pClC_6H_4$), 161.34 (CO) ; Anal. calc. for $C_{10}H_{11}NO_3Cl_2$: C, 45.48 ;Anal. calc. for $C_{10}H_{11}NO_3ClBr$: C, 38.93 ; H, 3.59 ; N, 4.54. Found : C, 40.90 ; H, 3.97 ; N, 4.61.

5k ($R^1 = C_6H_5$, R^2 = H, R = CD_3, X = Cl,) : ^1H NMR (CD_3OD) δ_H , 5.2 (s, 1H, CHCl), 7.3-7.6 (m, 7H, C_6H_5 and $CONH_2$).; ^{13}C NMR (CD_3OD) δ_C 48.00 (OCD_3, signals mixed with CD_3OD), 65.16 (CHCl), 100.07 (COD), 128.59 129.33, 130.87, 137.51 (C_6H_5), 173.08 (CO), and for other diastereoisomer δ_C 48.00 (OCD_3, signals mixed with CD_3OD), 67.71 (CHCl), 100.12 (COH), 128.87, 129.59, 130.47, 138.15 (C_6H_5), 173.95 (s, CO).

6a ($R^1 = pClC_6H_4$, R^2 = H, R = CH_2CH_3, X = Cl) : (56 % yield) ; m.p. 150°C (EtOH) ; IR (Nujol) 3444, 3334, 1662, cm^{-1} ; ^1H NMR (DMSO) δ_H 1.06 (t, 3H, CH_3), 3.22 (q, 1H) and 3.60 (q, 1H) (CH_2), 5.35 (s, 1H, CHCl), 6.65 (br, 1H, OH), 7.45 (m, 6H, $pClC_6H_4$ and $CONH_2$); ^{13}C NMR (DMSO) C 15.13 (q,^1J=125.92, CH3), 57.86 (t, ^1J=144, CH_2), 65.09 (d, ^1J=153.68, CHCl), 97.49 (s, COH), 127.72.

130.62, 131.00, 135.98 (m, $pClC_6H_4$), 169.90 ($CONH_2$). Anal. calc. for $C_{11}H_{13}NO_3Cl_2$: C, 47.50 : H. 4.71 ; N, 5.04 ; Cl, 25.49. Found : C, 47.31 ; H, 4.79 ; N, 5.06 ; Cl, 25.64.

6b ($R^1 = C_6H_5$, R^2= H, R = CH_2CH_3, X = Cl) : (55 % yield) ; m.p. 142°C (EtOH) ; IR (Nujol) 3442. 3323, 1667, cm^{-1} ; ^1H NMR (DMSO) δ_H 1.18 (t, 3H, ^1J=7.00, CH_3), 3.28 (q, 1H, ^1J=8.18, CH_2). 3.65 (q, 1H, ^1J=8.20, CH_2), 5.39 (s, 1H, CHCl), 6.56 (br, 1H, OH), 7.47 (m, 7H, C_6H_5 and $CONH_2$); ^{13}C NMR (DMSO) δC 15.13 (q, 1J=126.10, CH_3), 57.73 (t, ^1J=142, CH_2), 66.04 (d, ^1J=153.03, CHCl). 97.55 (s, COH), 127.65, 128.25, 129.19, 136.95 (m, C_6H_5), 170.01 ($CONH_2$); Anal. calc. for $C_{11}H_{14}NO_3Cl$: C, 54.21 ; H, 5.75 ; N, 5.75 ; Cl, 14.58. Found : C, 54.26 ; H, 5.84 ; N, 5.56 ; Cl, 14.74.

6d (R^1= $pCH_3C_6H_4$, R^2= H, R = CH_2CH_3, X = Cl) : (51 % yield) ; m.p. 170°C (EtOH) ; IR (Nujol) 3446, 3335, 1661, cm^{-1} ; ^1H NMR (DMSO) δ_H 1.07 (t, 3H, ^1J=2.0, CH_3), 2.26 (s, 3H, pCH_3) 3.24 (q, 1H) and 3.61 (q, 1H) (CH_2), 5.32 (s, 1H, CHCl), 6.62 (br, 1H, OH), 7.22 (m, 6H, C_6H_4 and $CONH_2$). ^{13}C NMR (DMSO) C 15.11 (q, ^1J=126.00, CH_3), 21.30 (q, pMe), 57.70 (t, ^1J=143, CH_2), 65.74 (d, ^1J=153.05, CHCl), 97.58 (s, COH), 129.32, 129.44, 130.50, 135.22 (m, C_6H_4), 179.05 ($CONH_2$). Anal. calc. for $C_{12}H_{16}NO_3Cl$: : C, 55.92 ; H, 6.26 ; N, 5.44 ; Cl. 13.76. Found : C, 55.55 ; H, 6.34 ; N, 5.61 ; Cl, 14.08.

6e (R^1, R^2 = -$(CH_2)_4$ -, R = CH_2CH_3, X = Cl) : (52 % yield) ; m.p. 96°C (EtOH) ; IR (Nujol) 3465. 3351, 3167, 1682 cm^{-1} ; ^1H NMR (DMSO) δ_H 1.09 (t, 3H, ^1J=7.01, CH_3), 1.77 (m, 4H) (- $(CH_2)_4$-) and 2.29 (m, 4H), 3.26 (m, 1H, ^1J=7.06, CH_3), 3.57 (m, 1H, ^1J = 7, CH_2), 6.21 (br, 1H, OH), 7.28 (s, 1H) and 7.57 (s, 1H) ($CONH_2$,) ; ^{13}C NMR (DMSO) δ_C 15.17 (q, ^1J = 126.08, CH_3), 22.25 (m) and 22.43 (m) and 36.96 (m) and 37.55 (m) (- $(CH_2)_4$ -), 58.24 (t, ^1J = 141.35, CH_2), 85.03 (s, CCl), 98.51 (s, COH). 170.70 (s,$CONH_2$); Anal. calc for $C_9H_{16}NO_3Cl$: C, 48.74 ; H, 7.27 ; N, 6.32 . Found : C, 48.29 ; H, 7.37 ; N, 6.55.

7a (R^1 = $pClC_6H_4$, R^2 = H, R = $CH(CH_3)_2$, X = Cl) : (52 % yield) ; m.p. 156°C (iPrOH) ; IR (Nujol) 3464, 3350, 1668, cm^{-1} ; ^1H NMR (DMSO) δ_H 1.00 (d, 3H, ^1J=6.15, CH_3), 1.09 (d, 3H, ^1J=6.06, CH_3). 3.80 (m, 1H, CH) ($CH(CH_3)_2$), 5.35 (s, 1H, CHCl), 6.52 (br, 1H, OH), 7.40 (m, 4H, $pClC_6H_4$), 7.43 (s, 1H) and 7.50 (s, 1H) ($CONH_2$) ; ^{13}C NMR (DMSO) δ_C 23.05 (d, ^1J=106.58, CH_3), 24.40 (d, ^1J=102.74, CH_3) 65.40 (d, ^1J=154.10, CHCl), 65.74 (d, ^1J=141.66, $CH(CH_3)_2$), 97.32 (s, COH), 127.70, 131.04, 132.98, 135.97 ($pClC_6H_4$), 170.59 (CO) ; Anal. calc. for $C_{12}H_{15}NO_3Cl$: C, 49.33 ; H, 5.17 ; N, 4.79 ; Cl, 24.27. Found : C, 49.38 ; H, 5.12 ; N, 5.03 ; Cl, 23.88.

7c (R^1 = $pNO_2C_6H_4$, R^2 = H, R = $CH(CH_3)_2$, X = Cl) : (48 % yield) ; m.p. 153°C (iPrOH) : IR (Nujol) 3460, 3348, 1667, cm^{-1} ; ^1H NMR (DMSO) δ_H 1.15 (d, 3H, CH_3), 1.23 (d, 3H, CH_3) and 3.90 (m, 1H, CH), 5.35 (s, 1H, CHCl), 6.78 (br, 1H, OH), 7.65 (m, 4H, $pClC_6H_4$), 7.58 (s, 1H) and 7.65 (s, 1H) ($CONH_2$) ; Anal. calc. for $C_{12}H_{15}N_2O_5Cl$: C, 47.61, H, 4.99 ; N, 9.25 ; Cl, 11.71. Found : C, 46.78 ; H, 4.86 ; N, 9.46 ; Cl, 11.8.

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