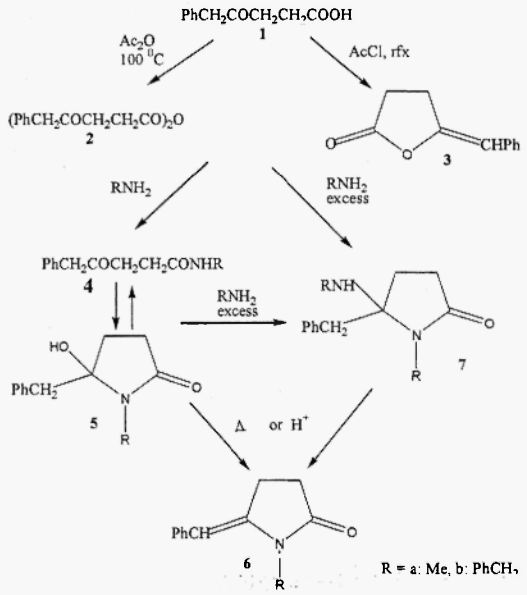
SOME OBSERVATIONS CONCERNING THE TAUTOMERIZATION OF γ-KETO AMIDES SCHIFF BASES TO 2-AMINOPYRROLIDIN-5-ONES

Georgia Tsolomiti, Kyriaki Tsolomiti and Athanase Tsolomitis*
The Laboratory of Organic Chemistry, The School of Chemical Engineering, The National Technical University of Athens, Athens 157 80, Greece.

Abstract : The reactions of excess of primary amines, with the anhydride or the lactone, (γ-benzylidene-γ-butyrolactone), of 4-oxo-5-phenylpentanoic acid or with its amides, and with α-angelicalactone and 4-oxopentanoic acid amides, resulted to the corresponding 2-aminopyrrolidin-5-ones, the cyclic tautomers of the Schiff bases of γ-keto amides.
Keywords: 2-Aminopyrrolidin-5-ones, 4-Oxo-5-phenylpentanamides, 4-oxo-pentanamides, Tautomerism of γ-keto amides Schiff bases.

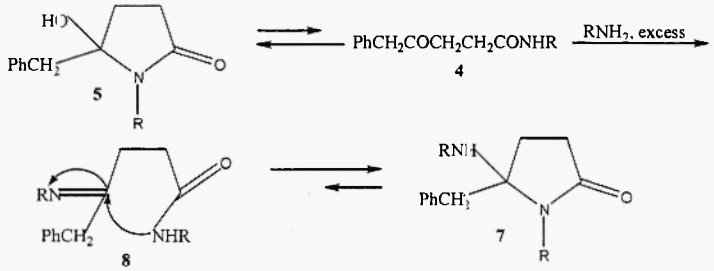
Recently we have reported[1] the synthesis of amides of 4-oxo-5-phenylpentanoic acid **1** from the reaction of its activated derivatives, the anhydride **2** and the lactone **3** with primary amines, (Scheme-1), depending on the nature of the amine substituent the γ-keto amides **4** or their cyclic tautomers, the 2-hydroxypyrrolidin-5-ones **5** or mixture of them, were separated. This work also refered to the conversion of these derivatives to the corresponding 2-benzylidenepyrrolidin-5-ones **6**.



Scheme-1

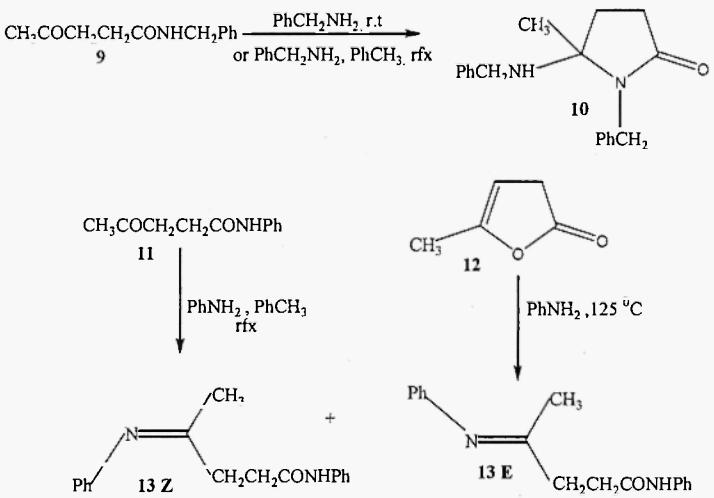
Now we report an unexpected evolution of the reaction of those acid derivatives **2** and **3** with a large excess of two amines, methylamine and benzylamine, resulting in entirely different products, which are formulated as 2-aminopyrrolidin-5-ones **7**. The same 2-aminopyrrolidin-5-ones **7** were also prepared from the reaction of the corresponding 2-benzyl-2-hydroxypyrrolidin-5-ones **5** with a large excess of the referred amines. The structure of these new compounds is derived from analytical and spectroscopic data. Specifically the UV spectra showed a simple benzenoid absorption between 240-270 nm, the IR spectra showed an intense carbonyl band corresponding to the pyrrolidinone at ~1660 cm^{-1} and a sharp band at ~3300 cm^{-1} attributed to the –NH-. ^1H NMR spectra showed a exchangeable singlet characteristic of the –NH- proton of an aliphatic amine, a complex non-symmetrical multiplet for the two methylene protons $-CH_2CH_2-$ of the pyrrolidinone ring, and the benzylic protons (CCH_2Ph and/or $>NCH_2Ph$, $-NHCH_2Ph$) corresponding to an AB system of non-equivalent protons, explained by the steric hindrance of these bulky groups on the pyrrolidinone ring. In agreement with this structure the 2-aminopyrrolidin-5-ones **7a** and **7b** are easily converted to the corresponding 2-

benzylidenepyrrolidin-5-ones **6a** and **6b**, by loss of the amine moiety, e.g. by heating over their melting points or by acid treatment. The formation of 2-aminopyrrolidin-5-ones **7a** and **7b**, from the reaction of the anhydride **2** or the lactone **3** with a large excess of amines, as well as from the reaction of 2-hydroxypyrrolidin-5-ones **5a** and **5b,** (which were prepared from the same reactants as the above referred reactions with a less excess of the amines or/and shorter reaction time), with the same amines under mild reaction conditions, can be explained as proceeding through the corresponding γ-keto amides **4**, the open chain tautomers of the 2-hydroxypyrrolidin-5-ones **5**, which react with the excess of the amines to form the Schiff bases **8**, that are the open chain tautomers of 2-aminopyrrolidin-5-ones **7** (Scheme-2).



Scheme-2

A probable explanation for the formation of 2-aminopyrrolidin-5-ones **7**, from 2-hydroxypyrrolidin-5-ones **5,** which are the more stable tautomers,[1] can be the formation of a small amount of γ-keto amide **4**, (the less stable tautomer), in equilibrium to the corresponding 2-hydroxypyrrolidin-5-one **5** which by the Schiff base **8** formation can shift the equilibrium to the γ-keto amide side, through, the stable 2-aminopyrrolidin-5-one **7** formation. In agreement to this supposition we prepared a known γ-keto amide, derivative of levulinic acid, the 4-oxo-pentan-N-benzylamide[2] **9** and reacted it with excess of benzylamine, at room temperature conditions, and under reflux in toluene at azeotropic distillation conditions of the produced water. The resulting product from the two above reactions was the 2-benzylaminopyrrolidin-5-one **10** (Scheme-3).



Scheme-3

On the other hand, the reaction of another amide of levulinic acid, the 4-oxopentan-N-phenylamide[2], (**11**), on reaction with aniline, or the reaction of α-angelicalactone **12** with excess of aniline gave a mixture from which two different configurational isomers were separated, as attributed by elemental and spectroscopic analysis data. These two products were assigned as the configurational isomers of the Schiff bases **13Z** and **13E** (otherwise *syn* and *anti* isomers, respectively). On the basis of ^{13}C NMR spectra of these two products we found a substantial chemical shift difference between the *syn*

and *anti* carbons alfa to the imine moiety, (the methyl carbon and the α-methylene to the imine moiety). The major factor responsible for affecting chemical shift differences between *syn* and *anti* carbons is a steric compression effect,[3,4,5] which results in upfield shifts for *syn* α-carbons, in accordance to several literature reports on the ^{13}C NMR spectra of hydrazones[6] and oximes.[7,8] We found (see experimental) that the upfield shift of α-carbons *syn* to the imine moiety is about 6 ppm in comparison to the corresponding *anti*.

The difference on the reaction products from the two γ-keto amides **9** and **11** can be explained on the basis of the lower nucleophilicity of the –NHPh group in the Schiff base **13** in comparison to the corresponding $-NHCH_2Ph$ and $-NHCH_3$, in the Schiff base **8**, from the one hand and to stereochemical factors from the other.

The possibility of formation of 2-aminopyrrolidin-5-ones from the reaction of γ-keto acids activated derivatives (anhydrides or lactones) or γ-keto amides tautomers with amines, must be controlled by factors such as the existence of an open-chain tautomer (γ-keto amide) as pure or in equilibrium to the cyclic tautomer, the reactivity of the ketone carbonyl goup, the amine nucleophilicity and the tendency of the Schiff base to exist as the cyclic tautomer, (aminopyrrolidinone).

Experimental

General. NMR spectra were recorded at ambient temperature using a Varian Gemini 2000 300 MHz spectrometer. The data are reported as follows: chemical shift are quoted in ppm on δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants are given in (Hz). Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer (as nujol mulls).

2-Benzyl-1-methyl-2-methylaminopyrrolidin-5-one, (7a).[9] A solution of the anhydride **2** 0.5 g (1.4 mmol) in 2 ml (22.60 mmol) of aqueous methylamine 35 %, was left overnight at room temperature, 5 ml of water were added to the solution and extracted with diethyl ether. The combined extracts were washed with water some times, dried and concentrated under vacuum, (without heating), to give 0.3 g of a solid assigned as pure (^{1}NMR) aminopyrrolidinone **7a**, after recrystallization from diethyl ether an analytical product 0.24 g (80 %), mp 104-106 ^{0}C was received. Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.54; H, 8.18; N, 12.87. UV (EtOH), λ_{max}nm ($\log\varepsilon_{max}$): 242 (1.87), 247.5 (2.01), 252 (2.15), 258 (2.25), 264 (2.14), 267 (1.89). IR (Nujol mull, cm^{-1}): 3322 and 1664. ^{1}NMR ($CDCl_3$): δ 1.50-2.31 (m, 4H, $-CH_2CH_2-$), 1.84 (s, 1H, -NH-, exchangeable), 2.21 (s, 3H, $-NHCH_3$), 2.28 (s, 3H, $>NCH_3$), 2.86 (d AB, J=1.5 Hz, 2H, $-CH_2Ph$), 7.00-7.50 (m, 5H, arom.).

2-Benzylamino-1,2-dibenzylpyrrolidin-5-one, (7b). Method A: In a mixture of the anhydride **2** 0.3 g (0.82 mmol) in 5 ml of dry diethyl ether, 2 ml (18.7 mmol) of benzylamine were added. The resulting solution after seven days at room temperature was washed some times with water, dried and concentrated under vacuum to a solid 0.28 g which appears to be pure (^{1}H NMR) the aminopyrrolidinone **7b**. After recrystallization from diethyl ether 0.22 g (72.6 %) of an analytical product mp 95-97 ^{0}C was received. Anal. Calcd for $C_{25}H_{26}N_2O$: C, 81.04; H, 7.07; N, 7.56. Found: C, 80.91; H, 6.99; N, 7.82. UV (EtOH), λ_{max}nm ($\log\varepsilon_{max}$): 247.5 (2.80), 252 (2.87), 258 (2.89), 264 (2.78), 268 (2.61). IR (Nujol mull, cm^{-1}): 3279, 1661. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 1H, -NH-, exchangeable) 1.88-2.45 (m, 4H, $-CH_2CH_2-$), 2.88 (s, 2H, $-CCH_2Ph$), 3.21 and 3.53 (q, AB, J= 13 Hz, 2H, $-NHCH_2Ph$), 4.60 (s, 2H, $>NCH_2Ph$), 6.94-7.58 (m, 15H, arom.).

Method B: In a mixture of the lactone **3** 1.91 g (5.15 mmol) in 10 ml of dry diethyl ether 4 ml (36.70 mmol) of benzylamine were added dropwise under cooling in an ice bath. The resulting solution was left under stirring at room temperature for 6 days, then was washed some times with water, the organic layer was dried and concentrated to a solid assigned as pure (^{1}NMR) aminopyrrolidinone **7b**, after recrystallization from diethyl ether 3.37 g (83 %) of the product mp 95-97 ^{0}C were received.

Method C: In a mixture of 1,30 g (4.62 mmol) of the hydroxypyrrolidinone **5b** in 10 ml of dry diethyl ether, 3.60 ml (33.03 mmol) of benzylamine were added. The resulting solution after stirring at room temperature for 6 days, was treated as above to give 1.42 g (83 %) of the aminopyrrolidinone **7b**, mp 95-97 ^{0}C.

1-Benzyl-2-benzylamino-2-methylpyrrolidin-5-one,[10] (10). A mixture of the 4-oxopentan-N-benzylamide, **9**, 0.5 g (2.40 mmol) and 0.5 ml (4.60 mmol) of benzylamine in 30 ml of dry xylene, (mixture of o, m, p-xylenes), was refluxed for 4 h, on an apparatus containing a dean-stark trap, the solution was concentrated under vacuum to an oily product. This oily concentrate after dissolution in diethyl ether was washed with water some times and concentrated to a solid residue 0.6 g, assigned as an almost pure (^{1}H NMR) aminopyrrolidinone **10**, after recrystallization from diethyl ether an of analytical grade sample, 0.53 g (74.65 %), mp 84-86 ^{0}C was received. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.51. Found: C, 77.33; H, 7.33; N, 9.64. UV (EtOH), λ_{max}nm ($\log\varepsilon_{max}$): 242 (2.31), 247 (2.38), 252 (2.48), 258 (2.56), 264 (2.44), 267 (2.24). IR (Nujol mull, cm^{-1}): 3257 and 1656. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 3H, -CH_3), 1.71 (s, 1H, -NH-, exchangeable), 2.00-2.70 (m, 4H, -CH_2CH_2-), 3.32 and 3.60 (q AB, J=12 Hz, 2H, -$NHCH_2Ph$), 4.35 and 4.59 (q AB, J=16 Hz, 2H, >NCH_2Ph), 7.00-7.60 (m, 10H, arom.).

(E)-4-Phenyliminopentan-N-phenylamide,[11] (13E). α-angelicalactone 2 g (20 mmol) and 5.5 ml (60 mmol) of freshly distilled aniline was mixted, (exothermally), the resulting solution next was heated on an oil bath at 125 ^{0}C for 1h. This solution was diluted with 15 ml of benzene, after cooling of this new solution the precipitated solid (mp 117-125 ^{0}C), was recrystallized from benzene to an analytical product 1.8 g (33.80 %), mp 113-115 ^{0}C. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.44; H, 6.79; N, 10.33. IR (Nujol mull, cm^{-1}): 3390, 1675, 1595, 1515, 1492. ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 3H, -CH_3)), 2.15-2.91 (m, 4H, -CH_2CH_2-), 4.21 (s br, 1H, -NH-, exchangeable), 6.65-7.70 (m, 10H, arom.). ^{13}C NMR ($CDCl_3$): 16.01, 29.84, 37.51, 121.63, 122.34, 124.47, 127.52, 129.07, 130.11, 138.51, 149.06, 171.71, 173.74.

(Z)-4-Phenyliminopentan-N-phenylamide,[11] (13Z). Repeating the same reaction as above until the point of precipitation, (from benzene), of the product mp 117-125 ^{0}C, this product after recrystallization from acetone gave an analytically pure product 2.6 g (48.80 %), mp 137-140 ^{0}C. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.89; H, 6.86; N, 10.44. IR (Nujol mull, cm^{-1}): 3387, 1678, 1595. ^{1}H NMR ($CDCl_3$): δ 1.50 (s, 3H, -CH_3), 1.83-2.86 (m, 4H, -CH_2CH_2-), 4.18 (s br, 1H, -NH-, exchangeable), 6.66-7.60 (m, 10H, arom.). ^{13}C NMR ($CDCl_3$): 22.06, 29.81, 31.52, 121.61, 122.34, 124.47, 127.35, 129.05, 130.11, 138.52, 149.06, 171.70, 173.70.

References and Notes

1. Tsolomiti, G.; Tsolomitis, A. *Heterocycl. Commun.* In press
2. Chiron, R.; Graff, Y. *Bull. Soc. Chim. Fr.* 575-583 (1970).
3. Bunnel, C. A.; Fuchs, P. L. *J. Org. Chem.* **42**, 2614-2617 (1977).
4. Levy, G. C.; Nelson, G. L. *J. Amer. Chem. Soc.* **94**, 4897-4901 (1972).
5. Wilson, N. K. Stothers, J. B. *Top. Stereochem.* **8**, 1-158 (1974).
6. Naulet, N.; Filleux, M. L.; Martin, G. J.; Pornet, J. *Org. Magn. Reson.* 7, 326-330 (1975).
7. Wolkowski, Z. W.; Vauthler, E.; Gonbeau, B.; Sauvaltre, H.; Musso, J. A. *Tetrahedron Lett.* 565-568 (1972).
8. Gurudata, M. *Can. J. Chem.* **50**, 1956-1958 (1972).
9. This aminopyrrolidinone, **7a**, was also obtained from the reactions of the lactone **3** or 2-benzyl-2-hydroxy-1-methylpyrrolidin-5-one[1] with excess of aqueous methylamine (35%), in yields 85 and 77 %, respectively.
10. This product was also obtained from the reaction of α-angelicalactone with excess of benzylamine under the same conditions as for the 4-oxopentan-N-benzylamide, in 72 % yield.
11. This product was also obtained from the reaction of 4-oxopentan-N-phenylamide, (11), with excess of aniline under the same conditions as for the α-angelicalactone, and in about the same yield.

Received on May 29, 2006