SYNTHESIS OF 3-UNSUBSTITUTED 1-AMINOPYRROLES

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Abstract - 3-Unsubstituted 1-aminopyrroles have been obtained by mild reaction of some α–halohydrazones with β-dicarbonyl compounds in basic medium. The reaction takes place by formation of conjugated azoalkene intermediate and, in turn, of Michael-type adduct, which cyclizes into title compounds by subsequent treatment in methanol under reflux, or in tetrahydrofuran with sulfuric acid at room temperature.

The reaction of conjugated azoalkenes with the compounds containing active methylenic or methinic groups has been shown to be a powerful entry to fully substituted pyrrole heterocycles.[1-4] However, this general reaction strategy frequently is not applicable with success to the synthesis of partially substituted pyrrole rings, mainly due to two reasons: *i*) the poor stability of starting conjugated azoalkenes not bearing appropriate stabilizing substituents on the azo-ene system;[4,5] *ii*) the fact that, in some 1,4-adduct intermediates which possess good leaving groups, the olefination process is competitive with the heterocyclization process thus leading to stable α,β-unsaturated hydrazone derivatives.[6a] As a matter of fact, in our previous paper we reported the reaction between conjugated azoalkenes and α-oxotriphenylphosphoranes to give both 3-unsubstituted 1-aminopyrroles and α,β-unsaturated hydrazones.[6b] Obviously, these concomitant behaviours reduce the yields of 3-unsubstituted 1-aminopyrroles ranging from 6% to 35%.[6b]

Indeed, 3-unsubstituted 1-aminopyrroles represent both interesting products and useful intermediates in organic chemistry as they permit a regioselective introduction of functional groups in a position otherwise not easily accessible. In fact, with few exceptions, many electrophilic substitutions of pyrrole rings occur preferentially at the position 2, and frequently afford various mixtures of disubstituted products from which the selective removal of a specific substituent is not always practicable.[1-2,7-10] Furthermore, such products often exhibt biological activities, especially those related to pyrrolnitrin derivatives.[3,7-11]

Therefore, we decided to investigate in detail the treatment of α–halohydrazones (**1a-i**) with 1-benzoylacetone (**2a**) and 2,4-pentanedione (**2b**) in order to set up a more convenient and simpler access to 3-unsubstituted 1-aminopyrroles (**4aa-ib**).

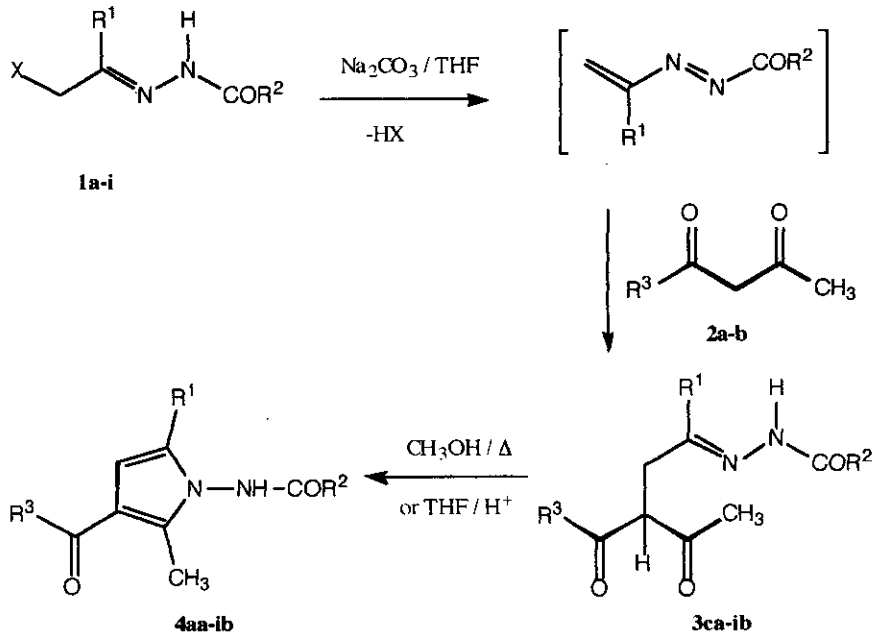
When anhydrous sodium carbonate was added to α–halohydrazones (**1a-i**), dissolved in tetrahydrofuran, a prompt reaction was observed, in some cases with the formation of the isolable 1,4-adduct intermediates (**3ca-ib**), or more often giving rise to a mixture of both 1,4-adduct intermediates and 1-aminopyrrole derivatives. The 1,4-adduct intermediates (**3ca-ib**), as well as some pyrrole-adduct mixtures, exhibit smooth conversion into 3-unsubstituted 1-aminopyrroles (**4aa-fb**) and (**4gb-ib**) by heating in methanol under reflux. An exception is represented by the production of **4ga** that requires a drop of sulfuric acid to the crude addition reaction mixture dissolved in tetrahydrofuran at room temperature (see Scheme 1). Yields are listed in Table 1.

The reaction clearly proceeds by means of the relevant conjugated azoalkene intermediates, as visibly shown by the yellow or orange colour appeared in consequence of anhydrous sodium carbonate addition to the colourless solution of α-halohydrazones. In the case of α-chlorohydrazone **1c**, the formation of the pertinent conjugated azoalkene was confirmed by immediately recorded ^{1}H-nmr (DMSO-d_6) spectrum of an organic extract derived from the rapid treatment of **1c** with base [δ: 1.79 (3H, s, CH_3), 6.24 and 6.29 (2H, 2s, CH_2), 7.61 and 7.65 (2H exchangeable, br s, NH_2)].

EXPERIMENTAL

α–Halohydrazones were prepared according to known methods.[12] 1-Benzoylacetone and 2,4-pentanedione were commercial materials and were used without further purification. Melting points were determined in open capillary tubes with a Gallenkamp apparatus and are uncorrected. Ir spectra were obtained as liquid film in a Nujol mull or neat with a Perkin-Elmer 298 spectrophotometer. FT-ir spectra were performed with a Nicolet Impact 400 spectrophotometer. Ms spectra were made with a Hewlett

Packard 5995 C spectrometer. ^{1}H Nmr spectra at 60 MHz were recorded on Varian EM 360 L and at 200 MHz on Bruker AC 200 spectrometers and performed in DMSO-d_6. Chemical shifts (δ) are reported in ppm downfield from internal TMS and coupling constants (J) in Hz. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Macherey-Nagel precoated silica gel SIL G-25UV$_{254}$ plates (0.25 mm) were employed for analytical thin layer chromatography (tlc) and silica gel Amicon LC 60 Å (35-70 mμ) for column chromatography.



1a-i **2a-b** **4aa-ib** **3ca-ib**

1	**R^1**	**R^2**	**X**	**2**	**R^3**
a	CH_3	$OC(CH_3)_3$	Cl	**a**	C_6H_5
b	CH_3	OCH_3	Cl	**b**	CH_3
c	CH_3	NH_2	Cl		
d	CH_3	NHC_6H_5	Cl		
e	$CH_2COOC_2H_5$	$OC(CH_3)_3$	Cl		
f	$CH_2COOC_2H_5$	NH_2	Cl		
g	$CH_2COOC_2H_5$	NHC_6H_5	Cl		
h	C_6H_5	$OC(CH_3)_3$	Br		
i	C_6H_5	NH_2	Br		

Scheme 1

Table 1

Reagents		Products		Yields of **4**
1	**2**	**3**	**4**	(%)
1a	**2a**		**4aa**	95.0
	2b		**4ab**	86.3
1b	**2a**		**4ba**	77.1
	2b		**4bb**	83.5
1c	**2a**	**3ca**	**4ca**	77.7
	2b		**4cb**	78.4
1d	**2a**	**3da**	**4da**	81.6
	2b	**3db**	**4db**	81.2
1e	**2a**		**4ea**	71.7
	2b		**4eb**	63.5
1f	**2a**		**4fa**	70.7
	2b		**4fb**	67.6
1g	**2a**		**4ga**	65.4
	2b		**4gb**	75.0
1h	**2a**		**4ha**	65.4
	2b		**4hb**	70.4
1i	**2a**	**3ia**	**4ia**	65.0
	2b	**3ib**	**4ib**	57.0

Synthesis of 3-unsubstituted 1-aminopyrroles (4aa-4ib): typical procedure. Anhydrous sodium carbonate (0.159 g, 1.5 mmol) was added to a stirred solution of α–halohydrazones (**1a-i**) (1 mmol) dissolved in tetrahydrofuran (10 ml) at room temperature. When the colourless solution turned into yellow or orange, β-dicarbonyl compounds (**2a-b**) (1 mmol) were added. The colour of the reaction mixture slowly turned from yellow or orange to colourless and the reaction was allowed to stand at room temperature until the complete disappearance of the reagents (monitored by tlc) (3-6 h). After the evaporation of the tetrahydrofuran under reduced pressure, the mixture was extracted with ethyl acetate and the organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated. In the case of the intermediates (**3ca**, **3da**, **3db**, **3ia** and **3ib**) the obtained crude directly afforded pure and

isolable 1,4-adduct intermediates by crystallization from ether-petroleum ether. Crystals were collected by suction for the characterization. The formation of the corresponding 3-unsubstituted 1-aminopyrrole derivatives (**4ca**, **4da**, **4db**, **4ia** and **4ib**) required an additional time (3-6 h) under reflux until the intermediate (**3**) was completely converted into the pertinent product (**4**), using methanol as solvent. In all other cases a tlc check of the organic layer revealed, as major components, two spots corresponding to the intermediate (**3**) and its related product (**4**) in different ratios. Therefore, after the evaporation of the extraction solvent under reduced pressure, the complete conversion into 3-unsubstituted 1-aminopyrrole derivatives was carried out heating, under reflux, the crude dissolved in methanol for an additional time (0.5-10 h). In order to obtain a better yield of the compound (**4ga**), the crude addition reaction mixture, after the evaporation of the extraction solvent under reduced pressure, was dissolved in tetrahydrofuran and a drop of 96% sulfuric acid was added to reach the conversion into **4ga** at room temperature in 24 h. Further purification was effected by column chromatography on silica gel (elution: cyclohexane-ethyl acetate mixtures) and by crystallization from appropriate solvents.

3ca: white crystals; mp 124-125 °C (ether); ir (KBr) 3480, 3330, 1710, 1660, 1595 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.79 (3H, s, CH_3), 2.17 (3H, s, CH_3), 2.77-2.82 (2H, m, CH_2), 5.40 (1H, t, J=7 Hz, CH), 5.90 (2H exchangeable, br s, NH_2), 7.52-7.72 (3H, m, Ar), 8.08 (2H, d, J=7 Hz, Ar), 8.96 (1H exchangeable, s, NH) ppm; ms found M^+ 275.05, $C_{14}H_{17}N_3O_3$ requires M, 275.30. Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.06; H, 6.18; N, 15.29.

3da: white crystals; mp 133-134 °C (ether/petroleum ether); ir (KBr) 3370, 3320, 3180, 1670, 1650, 1590 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.90 (3H, s, CH_3), 2.24 (3H, s, CH_3), 2.90-2.96 (2H, m, CH_2), 5.51 (1H, t, J=7 Hz, CH), 6.95 (1H, t, J=7 Hz, Ar), 7.17-7.30 (4H, m, Ar), 7.50-7.65 (3H, m, Ar), 8.09-8.13 (3H, m, 1H exchangeable, NH and 2H Ar), 9.55 (1H exchangeable, s, NH) ppm; ms found M^+ 351.10, $C_{20}H_{21}N_3O_3$ requires M, 351.40. Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.34; H, 6.06; N, 11.98.

3db: white crystals; mp 158-162 °C (ether/petroleum ether); ir (KBr) 3350, 3200, 3190, 1690, 1670, 1600, 1590 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.87 (3H, s, CH_3), 2.20 (6H, s, 2 CH_3), 2.78-2.82 (2H, m, CH_2), 4.38 (1H, t, J=7 Hz, CH), 6.99 (1H, t, J=7 Hz, Ar), 7.30 (2H, t, J=7 Hz, Ar), 7.63 (2H, d, J=7 Hz, Ar),

8.28 (1H exchangeable, s, NH), 9.59 (1H exchangeable, s, NH) ppm; ms found M^+ 289.05, $C_{15}H_{19}N_3O_3$ requires M, 289.33. Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.25; H, 6.66; N, 14.49.

3ia: white crystals; mp 130-131 °C (ether/petroleum ether); ir (KBr) 3480, 3330, 3250, 3180, 1670, 1650, 1620, 1595, 1570 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.49 and 1.67 (3H, 2s, CH_3), 2.85-2.95 (2H, m, CH_2), 4.40-4.43 (1H, m, CH), 7.08 (3H exchangeable, br s, NH_2 and NH), 7.41-8.15 (10H, m, 2 Ar) ppm; ms found M^+ 337.15, $C_{19}H_{19}N_3O_3$ requires M, 337.38. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.66; H, 5.71; N, 12.47.

3ib: white crystals; mp 79-81 °C (ether/petroleum ether); ir (KBr) 3380, 3340, 3260, 3200, 1710, 1670, 1620, 1575 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.35 and 1.54 (3H, 2s, CH_3), 2.20 and 2.32 (3H, 2s, CH_3), 2.75-2.82 (2H, m, CH_2), 3.26-3.34 (1H, m, CH), 7.01 (2H exchangeable, br s, NH_2), 7.34-7.40 (3H, m, Ar), 7.81 (1H exchangeable, s, NH), 7.86-7.91 (2H, m, Ar) ppm; ms found M^+ 275.05, $C_{14}H_{17}N_3O_3$ requires M, 275.30. Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.10; H, 6.24; N, 15.23.

4aa: white crystals; mp 144-146 °C (ether/petroleum ether); ir (KBr) 3210, 1735, 1610, 1535 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.47 (9H, s, $OC(CH_3)_3$), 2.04 (3H, s, CH_3), 2.29 (3H, s, CH_3), 5.97 (1H, s, CH), 7.49-7.67 (5H, m, Ar), 10.31 (1H exchangeable, s, NH) ppm; ms found M^+ 314.15, $C_{18}H_{22}N_2O_3$ requires M, 314.38. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.75; H, 7.08; N, 8.93.

4ab: brown oil; ir (KBr) 3170, 1740, 1630, 1580 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.46 (9H, s, $OC(CH_3)_3$), 2.02 (3H, s, CH_3), 2.26 (6H, s, 2 CH_3), 6.21 (1H, s, CH), 10.23 (1H exchangeable, s, NH) ppm; ms found M^+ 252.90, $C_{13}H_{20}N_2O_3$ requires M, 252.31. Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.70; H, 7.96; N, 11.13.

4ba: orange oil; ir (KBr) 3230, 1740, 1620, 1595 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 2.04 (3H, s, CH_3), 2.30 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 6.01 (1H, s, CH), 7.44-7.68 (5H, m, Ar), 10.64 (1H exchangeable, s, NH) ppm; ms found M^+ 272.00, $C_{15}H_{16}N_2O_3$ requires M, 272.30. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C,

66.16; H, 5.92; N, 10.29. Found: C, 66.18; H, 5.90; N, 10.27.

4bb: pale yellow crystals; mp 128-130 °C (ether/hexane); ir (KBr) 3160, 1750, 1660, 1580 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 2.03 (3H, s, CH_3), 2.27 (6H, s, 2 CH_3), 3.71 (3H, s, OCH_3), 6.24 (1H, s, CH), 10.55 (1H exchangeable, s, NH) ppm; ms found M^+ 210.05, $C_{10}H_{14}N_2O_3$ requires M, 210.23. Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.11; H, 6.74; N, 13.30.

4ca: white crystals; mp 214-224 °C (ether/petroleum ether); ir (KBr) 3400, 3260, 1670, 1620 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 2.04 (3H, s, CH_3), 2.30 (3H, s, CH_3), 5.98 (1H, s, CH), 6.29 (2H exchangeable, s, NH_2), 7.43-7.68 (5H, m, Ar), 9.20 (1H exchangeable, s, NH) ppm; ms found M^+ 257.10, $C_{14}H_{15}N_3O_2$ requires M, 257.29. Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33; Found: C, 65.35; H, 5.85; N, 16.31.

4cb: white crystals; mp 248-250 °C (ether/petroleum ether); ir (KBr) 3380, 3240, 3190, 1670, 1640, 1580 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 2.02 (3H, s, CH_3), 2.28 (6H, s, 2 CH_3), 6.19 (1H, s, CH), 6.22 (2H exchangeable, s, NH_2), 9.12 (1H exchangeable, s, NH) ppm; ms found M^+ 195.10, $C_9H_{13}N_3O_2$ requires M, 195.22. Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.39; H, 6.69; N, 21.55.

4da: white crystals; mp 220-221 °C (ether/petroleum ether); ir (KBr) 3300, 3250, 3180, 1640, 1630, 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 2.09 (3H, s, CH_3), 2.35 (3H, s, CH_3), 6.02 (1H, s, CH), 6.99 (1H, t, *J*=8 Hz, Ar), 7.28 (2H, t, *J*=8 Hz, Ar), 7.46-7.70 (7H, m, Ar), 9.35 (1H exchangeable, s, NH), 9.46 (1H exchangeable, s, NH) ppm; ms found M^+ 333.15, $C_{20}H_{19}N_3O_2$ requires M, 333.39. Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.07; H, 5.71; N, 12.62.

4db: white crystals; mp 197-202°C (ether/petroleum ether); ir (KBr) 3280, 3190, 1660, 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 2.06 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.32 (3H, s, CH_3), 6.24 (1H, s, CH), 6.98 (1H, t, *J*=8 Hz, Ar), 7.27 (2H, t, *J*=8 Hz, Ar), 7.45 (2H, d, *J*=8 Hz, Ar), 9.29 (1H exchangeable, s, NH), 9.38 (1H exchangeable, s, NH) ppm; ms found M^+ 271.10, $C_{15}H_{17}N_3O_2$ requires M, 271.32. Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.38; H, 6.35; N, 15.51.

4ea: pale yellow crystals; mp 127-130 °C (ether/petroleum ether); ir (KBr) 3210, 1740, 1720, 1615, 1595 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.17 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 1.46 (9H, s, $OC(CH_3)_3$), 2.30 (3H, s, CH_3), 3.53 (2H, q, *J*=10 Hz, CH_2), 4.06 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.16 (1H, s, CH), 7.50-7.68 (5H, m, Ar), 10.36 (1H exchangeable, s, NH) ppm; ms found M^+ 386.15, $C_{21}H_{26}N_2O_5$ requires M, 386.45. Anal. Calcd for $C_{21}H_{26}N_2O_5$ C, 65.27; H, 6.78; N, 7.25. Found: C, 65.25; H, 6.80; N, 7.27.

4eb: white crystals; mp 114-116 °C (ethyl acetate/n-hexane); ir (KBr) 3150, 1730, 1630, 1580 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.20 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 1.44 (9H, s, $OC(CH_3)_3$), 2.29 (6H, s, 2 CH_3), 3.49 (2H, q, *J*=10 Hz, CH_2), 4.06 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.38 (1H, s, CH), 10.29 (1H exchangeable, s, NH) ppm; ms found M^+ 324.00, $C_{16}H_{24}N_2O_5$ requires M, 324.37. Anal. Calcd for $C_{16}H_{24}N_2O_5$ C, 59.24; H, 7.46; N, 8.64. Found: C, 59.26; H, 7.43; N, 8.62.

4fa: white crystals; mp 137-140 °C (dichloromethane/petroleum ether); ir (KBr) 3400, 3320, 3160, 1740, 1700, 1670, 1620 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.21 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.33 (3H, s, CH_3), 3.55 (2H, q, *J*=10 Hz, CH_2), 4.10 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.16 (1H, s, CH), 6.33 (2H exchangeable, s, NH_2), 7.49-7.70 (5H, m , Ar), 9.23 (1H exchangeable, s, NH) ppm; ms found M^+ 329.00, $C_{17}H_{19}N_3O_4$ requires M, 329.35. Anal. Calcd for $C_{17}H_{19}N_3O_4$ C, 62.00; H, 5.81; N, 12.76.Found: C, 62.02; H, 5.80; N, 12.74.

4fb: white crystals; mp 170-175 °C (dichloromethane/petroleum ether); ir (KBr) 3370, 3240, 3180, 1730, 1680, 1640 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.19 (3H, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.27 (6H, s, 2 CH_3), 3.49 (2H, q, *J*=10 Hz, CH_2), 4.07 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.23 (2H exchangeable, s, NH_2), 6.35 (1H, s, CH), 9.12 (1H exchangeable, s, NH) ppm; ms found M^+ 267.10, $C_{12}H_{17}N_3O_4$ requires M, 267.28. Anal. Calcd for $C_{12}H_{17}N_3O_4$ C, 53.92; H, 6.41; N, 15.72. Found: C, 53.94; H, 6.39; N, 15.73.

4ga: white crystals; mp 164-167°C (dichloromethane/petroleum ether); ir (KBr) 3330, 3280, 1730, 1690, 1630, 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.13 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.36 (3H, s, CH_3), 3.59 (2H, q, *J*=10 Hz, CH_2), 4.05 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.20 (1H, s, CH), 6.99 (1H, t, *J*=8 Hz, Ar), 7.28 (2H, t, *J*=8 Hz, Ar), 7.45-7.70 (7H, m, Ar), 9.26 (1H exchangeable, s, NH), 9.41 (1H exchangeable, s, NH) ppm; ms found M^+ 405.15, $C_{23}H_{23}N_3O_4$ requires M, 405.45. Anal. Calcd for $C_{23}H_{23}N_3O_4$ C, 68.13; H, 5.72;

N, 10.36. Found: C, 68.15; H, 5.70, N, 10.38.

4gb: pale yellow crystals; mp 170-176 °C (dichloromethane/petroleum ether); ir (KBr) 3310, 3200, 3140, 1720,1680, 1650, 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.15 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.30 (3H, s, CH_3), 2.33 (3H, s, CH_3), 3.55 (2H, q, *J*=10 Hz, CH_2), 4.05 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.41 (1H, s, CH), 6.99 (1H, t, *J*=8 hz, Ar), 7.27 (2H, t, *J*=8 Hz, Ar), 7.44 (2H, d, *J*=8 hz, Ar), 9.17 (1H exchangeable, s, NH), 9.33 (1H exchangeable, s, NH) ppm; ms found M^+ 343.00, $C_{18}H_{21}N_3O_4$ requires M, 343.38. Anal. Calcd for $C_{18}H_{21}N_3O_4$ C, 62.96; H, 6.16; N, 12.24 . Found: C, 62.98; H, 6.14; N, 12.27.

4ha: pale yellow crystals; mp 160-165 °C (ether/petroleum ether); ir (KBr) 3200, 1740, 1680, 1620 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.41 (9H, s, $OC(CH_3)_3$), 2.38 (3H, s, CH_3), 6.43 (1H, s,CH), 7.31-7.38 (10H, m, 2 Ar), 10.55 (1H exchangeable, s, NH) ppm; ms found M^+ 376.30, $C_{23}H_{24}N_2O_3$ requires M, 376.45. Anal. Calcd for $C_{23}H_{24}N_2O_3$ C, 73.38; H, 6.43; N, 7.44. Found: C, 73.40; H, 6.46; N, 7.42.

4hb: pale yellow crystals; mp 143-147 °C (ether/petroleum ether); ir (KBr) 3150, 1740, 1630, 1605 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 1.48 (9H, s, $OC(CH_3)_3$), 2.46 (6H, s, 2 CH_3), 6.81 (1H, s, CH), 7.49-7.56 (5H, m, Ar), 10.55 (1H exchangeable, s, NH) ppm; ms found M^+ 314.00, $C_{18}H_{22}N_2O_3$ requires M, 314.38. Anal. Calcd for $C_{18}H_{22}N_2O_3$ C, 68.77; H, 7.05; N, 8.91. Found: C, 68.79; H, 7.07; N, 8.89.

4ia: white crystals; mp 236-238 °C (ethyl acetate/petroleum ether); ir (KBr) 3420, 3300, 3180, 1670, 1620, 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 2.38 (3H, s, CH_3), 6.33 (2H exchangeable, s, NH_2), 6.41 (1H, s, CH), 7.29-7.78 (10H, m, 2 Ar), 9.43 (1H exchangeable, s, NH) ppm; ms found M^+ 319.00, $C_{19}H_{17}N_3O_2$ requires M, 319.36. Anal. Calcd for $C_{19}H_{17}N_3O_2$ C, 71.46; H, 5.37; N, 13.16.Found: C, 71.44; H, 5.40; N, 13.18.

4ib: white crystals; mp 223-228 °C (ethyl acetate/petroleum ether); ir (KBr) 3410, 3300,3200, 1675, 1655, 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 2.36 (6H, s, 2 CH_3), 6.25 (2H exchangeable, s, NH_2), 6.71 (1H, s, CH), 7.29-7.52 (5H, m, Ar), 9.36 (1H exchangeable, s, NH) ppm; ms found M^+ 257.10, $C_{14}H_{15}N_3O_2$ requires M, 257.29. Anal. Calcd for $C_{14}H_{15}N_3O_2$ C, 65.36; H, 5.88; N, 16.33. Found: C, 65.38; H, 5.85; N, 16.30.

ACKNOWLEDGEMENTES

This work was supported by financial assistance from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (M.U.R.S.T.-Roma) and Consiglio Nazionale delle Ricerche (C.N.R.-Roma).

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Received, 4th March, 1996