# PSEUDOESTERS AND DERIVATIVES. XXVIII[1]. THE REACTION OF 5-METHOXY-3-PYRROLIN-2-ONE AND ITS 3-BROMO DERIVATIVE WITH NITROGEN AND SULPHUR NUCLEOPHILES

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Abstract - 5-Methoxy-3-pyrrolin-2-one (**1**) reacts with dimethylamine yielding the corresponding conjugate addition product **3a**. By using pyrrolidine, piperidine and diethylamine the addition product **3** is accompanied by the 5-dialkylamino-5-pyrrolin-2-one **4**, which in the latter case is the main component. Similar results are obtained with 3-bromo-5-methoxy-3-pyrrolin-2-one (**2**) and the afore-mentioned amines. The reaction of **1** and **2** with thiols under basic catalysis gives only the conjugate addition products **7** and **13** respectively.

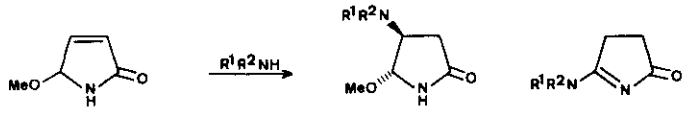
The chemistry of pyrrolinones has received considerable attention[2] as a result of the presence of its lactam ring in some antibiotics, in the bile pigments[3] and in the natural alkaloid jatropham, which shows inhibitory activity towards the P-388 lymphocytic leukemia[4] test system.

However, the behaviour of 3-pyrrolin-2-one derivatives towards nucleophiles appears to have been little studied and only recently we have reported[5] that 4-bromo-5-methoxy-3-pyrrolin-2-one reacts with nitrogen and sulphur nucleophiles to yield the expected products of vinylic nucleophilic substitution and/or the corresponding 4,5-bis(dialkylamino)-5-pyrrolin-2-ones when secondary amines are used as nucleophiles.

In the present paper we study the reaction of the same type of secondary amines and sulphur nucleophiles with the parent 5-methoxy-3-pyrrolin-2-one (**1**) and its 3-bromo derivative **2**, in which the Michael-type addition was the expected reaction.

## Reaction of 5-methoxy-3-pyrrolin-2-one

The reaction of pyrrolinone **1** with an equimolar amount of dimethylamine affords only the expected conjugate addition product **3a**, whereas by using pyrrolidine or piperidine the addition products **3c** and **3d** are accompanied by substantial amounts of the corresponding 5-pyrrolin-2-ones **4c** and **4d**. By contrast, diethylamine leads to 5-diethylamino-5-pyrrolin-2-one (**4b**) as the main product.




1 3a-d 4b-d

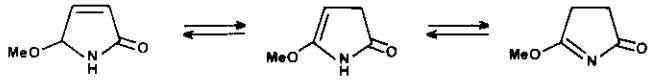
The reactivity of the secondary amines towards the Michael-type addition is found to be in the sequence: dimethylamine > pyrrolidine = piperidine >> diethylamine. The reaction has been performed under different experimental conditions to determine if changing reaction variables (solvent, temperature, ratio substrate-nucleophile) might promote a variation in the product distribution. From the results summarized in Table 1, we conclude that the use of a protic solvent such as methanol, an excess of amine and a higher temperature all accelerate the reaction but have little or no effect on the proportion of the products **3** and **4**.

Table 1. Reaction of pyrrolinone **1** with secondary amines

| | $R^1$ | $R^2$ | Nucleophile | Equiv. | Solvent | Temp. (°C) | Reaction time | Products (ratio)[a] 3 | 4 | 1 |
|---|---|---|---|---|---|---|---|---|---|---|
| a: | Me | Me | Dimethylamine | 1 | THF | 20 | 2 days | 100 | 0 | 0 |
| | | | | 1 | MeOH | 20 | 8 h | 100 | 0 | 0 |
| b: | Et | Et | Diethylamine | 1 | THF | 20 | 30 days | 3 | 52 | 45 |
| | | | | 1 | MeOH | 20 | 8 days | 8 | 92 | 0 |
| | | | | 1 | THF | 67 | 24 h | 0 | 87 | 13 |
| | | | | 3 | THF | 20 | 7 h | 5 | 95 | 0 |
| c: | $-(CH_2)_4-$ | | Pyrrolidine | 1 | THF | 20 | 18 days | 43 | 41 | 16 |
| | | | | 1 | MeOH | 20 | 12 h | 75 | 25 | 0 |
| | | | | 1 | THF | 67 | 24 h | 58 | 42 | 0 |
| d: | $-(CH_2)_5-$ | | Piperidine | 1 | THF | 20 | 30 days | 64 | 28 | 8 |
| | | | | 1 | MeOH | 20 | 21 h | 75 | 25 | 0 |
| | | | | 1 | THF | 67 | 24 h | 60 | 40 | 0 |

[a] Approximate ratio determined by $^1$H-nmr integration.

The formation of compounds of the type **4** may be attributed to the basicity of secondary amines, which facilitate the isomerization to the pyrrolinones **5** or **6**. The competitive reaction may occur through the 4-pyrrolinone **5**, as suggested previously by us[5] in the 4-bromo derivative, or through the 5-pyrrolinone **6**, which it is known[6] that reacts with secondary amines to give the corresponding 5-dialkylamino-5-pyrrolin-2-one.

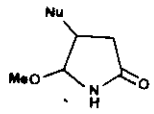



**1** **5** **6**

It is noteworthy the fact that dimethylamine only yields the conjugate addition product **3a**, while diethylamine affords the 5-pyrrolinone **4b** as the main product. Presumably, in the latter case, the formation of the Michael-type addition product is relatively slow[7], thereby allowing the isomerization to **5** or **6** and subsequent reaction with the amine to occur.

In all cases the conjugate addition of amines to **1** involves the attack of the nucleophile from the side opposite to the OMe group to give the *trans* isomers **3** (Tables 2 and 3), as reported in the corresponding furanones[8].

Table 2. Ir and $^1$H-nmr data of compounds **3** and **7**




| Compound | | Ir | | $^1$H-nmr | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nº | Nu | NH | C=O | H-3a | H-3b | H-4 | H-5[d] | $J_{3a,3b}$ | $J_{3a,4}$ | $J_{3b,4}$ | $J_{4,5}$ |
| **3a** | $-N(CH_3)_2$ | 3245[a] | 1720 | 2.56 | 2.28 | 3.10 | 4.76 | -17.7 | 8.4 | 4.1 | 1.7 |
| **3b** | $-N(C_2H_5)_2$ | 3240[b] | 1720 | 2.70 | 2.38 | 3.52 | 4.89 | -17.9 | 8.2 | 4.6 | 2.0 |
| **3c** | $-N\frown(CH_2)_4$ | 3270[c] | 1725 | 2.25 | 2.97 | 3.35 | 4.82 | -17.4 | 7.8 | 4.1 | 1.9 |
| **3d** | $-N\frown(CH_2)_5$ | 3280[c] | 1725 | 2.55 | 2.28 | 3.15 | 4.79 | -17.7 | 8.5 | 4.0 | 1.5 |
| **7e** | $-SCH_2C_6H_5$ | 3215[c] | 1720 | 2.85 | 2.15 | 3.22 | 4.65 | -17.8 | 8.4 | 2.8 | 1.3 |
| **7f** | $-SCH(CH_3)_2$ | 3285[b] | 1730 | 2.97 | 2.20 | 3.38 | 4.76 | -17.7 | 8.4 | 3.0 | 1.4 |
| **7g** | $-SC(CH_3)_3$ | 3215[c] | 1725 | 3.00 | 2.24 | 3.30 | 4.78 | -17.7 | 8.8 | 3.4 | 1.6 |

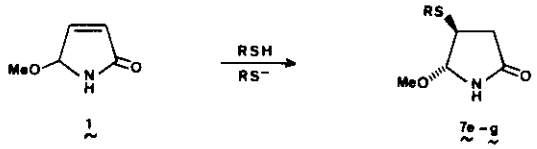
[a]Nujol. [b]Film. [c]KBr. [d]Fine splitting by the NH proton which disappears in the presence of $D_2O$.

Stereochemical assignment of these adducts was based on the $^1$H-nmr spectra (Table 2). The *trans* arrangement of the substituents was deduced from the small coupling constants (1.3-2.0 Hz) between H-4 and H-5. These values are in agreement with those reported for a *trans* stereochemistry in the corresponding furanones[8].

Table 3. $^{13}$C-nmr data of compounds **3** and **7**

| Compound | | C-2 | C-3 | C-4 | C-5 | $CH_3O$ | Cα,C-4 | Cβ,C-4 |
|---|---|---|---|---|---|---|---|---|
| Nº | Nu | | | | | | | |
| **3a** | $-N(CH_3)_2$ | 177.26 | 31.93 | 65.89 | 89.05 | 54.59 | 41.32 | |
| **3b** | $-N(C_2H_5)_2$ | 175.07 | 32.26 | 62.14 | 89.76 | 54.81 | 43.58 | 12.60 |
| **3c** | $-N\frown(CH_2)_4$ | 176.97 | 34.29 | 65.15 | 90.57 | 54.91 | 51.20 | 23.46 |
| **3d** | $-N\frown(CH_2)_5$ | 177.27 | 32.37 | 66.62 | 88.81 | 54.79 | 50.66 | 26.02 |
| **7e** | $-SCH_2C_6H_5$ | 176.35 | 36.89 | 43.54 | 92.57 | 54.65 | 50.26 | |
| **7f** | $-SCH(CH_3)_2$ | 176.67 | 35.33 | 36.94 | 93.69 | 54.78 | 43.12 | 23.55<br>23.44 |
| **7g** | $-SC(CH_3)_3$ | 178.30 | 38.40 | 41.66 | 94.82 | 55.19 | 110.29 | 31.18 |

The reaction of the pyrrolinone **1** with thiols, in the presence of the corresponding sodium thiolate, yields only the expected conjugate addition products **7e-g**, whose *trans* stereochemistry has been deduced from the nmr data (Tables 2 and 3), using arguments similar to those mentioned above.



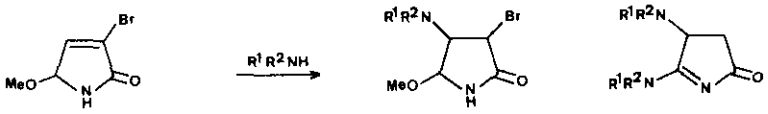

1 → 7e-g

**Reaction of 3-bromo-5-methoxy-3-pyrrolin-2-one**

The reactions of bromopyrrolinone **2** with the afore-mentioned amines, have been effected in a 1:1 ratio substrate/nucleophile using methanol as the solvent. As in the above case, we have observed a substantial variation in the rate of the reaction depending on the amine used.

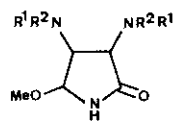
Thus, the reaction of **2** with dimethylamine is complete after 30 min yielding the Michael-type adduct, as a mixture of diastereomers $\mathbf{8a_1}$-$\mathbf{8a_3}$ in different proportions (Table 4). By contrast, the reaction with diethylamine, after 6 days, affords 4,5-bis(diethylamino)-5-pyrrolin-2-one **9b**, as the sole product, in only a 50% conversion.

The reaction of **2** with pyrrolidine and piperidine is complete after 30 min leading respectively, as the main components, to **8c** and **8d** (as mixtures of diastereomers) (Table 4), along with small amounts of **9c**



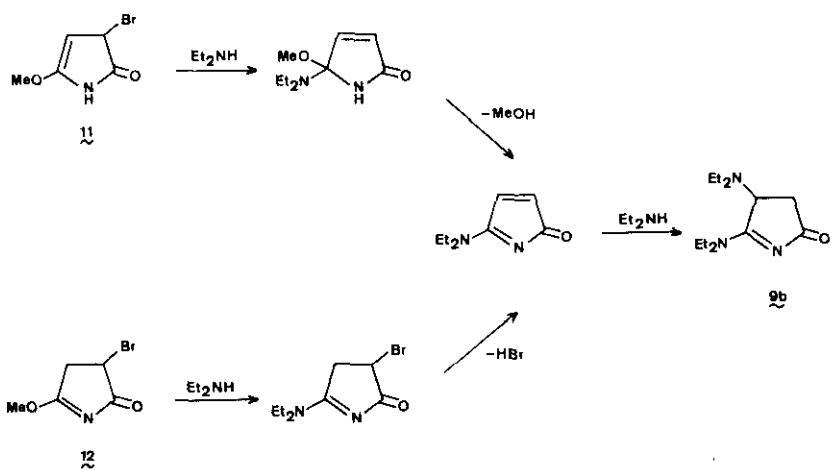

**2** **8a,c,d** **9b,c,d**

and **9d**, respectively, and recovered starting material. When the reaction is effected with an excess of amine, we also obtain the 3,4-bis(dialkylamino)-5-methoxypyrrolidin-2-one **10**.




**10a-d**

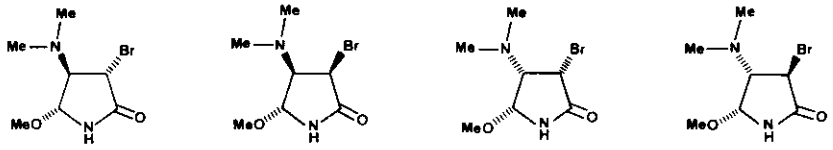
The formation of **9b** in the reaction with diethylamine could be interpreted through isomerization[5] of **2** to the 4-pyrrolin-2-one **11**, addition of amine, which is now favoured by the tendency of the $Br^-$ to leave[9], followed by elimination of methanol and subsequent amine addition. An alternative explanation for the formation of **9b** involves the isomerization of **2** to the 5-pyrrolin-2-one **12**, substitution of the MeO by $Et_2N$ followed by elimination of HBr and subsequent conjugate addition of amine.




**11** **9b** **12**

The adducts **8a-d** obtained from the reaction of **2** with secondary amines were shown by $^1$H-nmr to be mixtures of three diastereomers whose ratios are given in Table 4. The diastereomers can be separated by column chromatography, although they are relatively unstable and decompose on standing at room temperature.

The nmr spectra, in particular the coupling constants[10] $J_{3,4}$ and $J_{4,5}$, and the stereoselectivity observed in the conjugate addition of secondary amines to **1**, helped to establish tentatively the structures of the diastereomers, although a definitive assignment could only be made by a complete X-ray analysis. Thus, it is reasonable to assume that the attack of dimethylamine occurs preferentially *trans* to the OMe group. We therefore assign the *trans,trans* configuration to the major diastereomer **8a$_1$**, which shows small coupling constants ($J_{3,4}$ = 4.4; $J_{4,5}$ = 2.3), and the *cis,trans* configuration to **8a$_2$**, showing a larger coupling constant $J_{3,4}$ = 6.3. The stereochemistry of the minor diastereomer **8a$_3$** was deduced from the magnitude of the $J_{3,4}$ = 9.2, which suggests a *cis* arrangement of the $NMe_2$ and Br groups.




**8a$_1$** (55%) **8a$_2$** (30%) **8a$_3$** (15%) **8a$_4$** (0%)

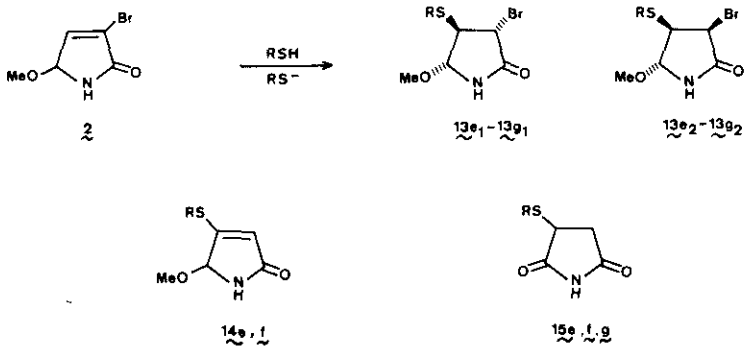
The arguments given above also can be used to assign the diastereomers obtained from pyrrolidine and piperidine.

Table 4. Ir and $^1$H-nmr data of compounds **8** and relative ratio of diastereomers

| Compound[a] | | Ir[b] | | $^1$H-nmr | | | | | Ratio[c] (%) |
|---|---|---|---|---|---|---|---|---|---|
| Nº | -NR$^1$R$^2$ | NH | C=O | H-3 | H-4 | H-5[d] | $J_{3,4}$ | $J_{4,5}$ | |
| **8a$_1$** | $-N(CH_3)_2$ | 3245 3120 | 1720 | 4.30 | 3.45 | 4.83 | 4.4 | 2.3 | 55 |
| **8a$_2$** | | | | 4.47 | 2.78 | 4.84 | 6.3 | 3.8 | 30 |
| **8a$_3$** | | | | 4.62 | 3.29 | 4.77 | 9.2 | 5.2 | 15 |
| **8c$_1$** | -N◯$(CH_2)_4$ | 3210 3120 | 1720 | 4.33 | 3.37 | 4.89 | 4.4 | 2.4 | 60 |
| **8c$_2$** | | | | 4.36 | 2.74 | 4.87 | 6.1 | 4.7 | 15 |
| **8c$_3$** | | | | 4.60 | 3.13 | 4.67 | 8.8 | 5.1 | 25 |
| **8d$_1$** | -N◯$(CH_2)_5$ | 3200 3110 | 1715 | 4.31 | 3.47 | 4.85 | 4.0 | 2.1 | 60 |
| **8d$_2$** | | | | 4.56 | 2.93 | 4.85 | 6.6 | 3.1 | 15 |
| **8d$_3$** | | | | 4.67 | 3.20 | 4.78 | 9.0 | 5.2 | 25 |

[a]Mixture of diastereomers. [b]Nujol. [c]Approximate ratio determined by $^1$H-nmr integration. [d]Fine splitting by the NH proton which disappears in the presence of $D_2O$.

The reaction of pyrrolinone **2** with thiols in methanol, catalyzed by the corresponding thiolate, yields the expected adducts **13** as mixtures of two diastereomers (Table 5). Also in this case the reaction is stereoselective and the sulphur nucleophile attacks in *trans* with respect to the OMe group.



After chromatography or when the reaction mixture of **2** with phenylmethanethiol or 2-propanethiol is allowed to stand after completion of the reaction, compounds **14** and **15** are also isolated. The former is originated by elimination of HBr and **15** is known to be a degradation product from **14**[5]. When the reaction is effected with 2-methyl-2-propanethiol, compound **14** is not isolated.

Table 5. Ir and $^1$H-nmr data of compounds **13** and relative ratio of diastereomers

| Compound[a] N° | -SR | Ir NH | Ir C=O | $^1$H-nmr H-3 | H-4 | H-5[e] | $J_{3,4}$ | $J_{4,5}$ | Ratio[d] (%) |
|---|---|---|---|---|---|---|---|---|---|
| **13e$_1$** | $-SCH_2C_6H_5$ | 3200[b] 3080 | 1720 | 4.10 | 3.43 | 4.69 | 2.4 | 1.3 | 60 |
| **13e$_2$** | | | | 4.50 | 3.29 | 4.85 | 6.8 | 4.1 | 40 |
| **13f$_1$** | $-SCH(CH_3)_2$ | 3200[c] 3100 | 1725 | 4.18 | 3.59 | 4.79 | 2.8 | 1.5 | 65 |
| **13f$_2$** | | | | 4.70 | 3.46 | 4.86 | 6.7 | 4.4 | 35 |
| **13g$_1$** | $-SC(CH_3)_3$ | 3210[c] 3120 | 1725 | 4.19 | 3.52 | 4.86 | 2.6 | 1.3 | 80 |
| **13g$_2$** | | | | 4.57 | 3.39 | 4.73 | 6.6 | 5.1 | 20 |

[a]Mixture of diastereomers. [b]KBr. [c]Nujol. [d]Approximate ratio determined by $^1$H-nmr determination. [e]Fine splitting by the NH proton which disappears in the presence of $D_2O$.

Table 6. $^{13}$C-nmr data of compounds **8** and **13**

| Compound N° | Nu | C-2 | C-3 | C-4 | C-5 | $CH_3O$ | Cα,C-4 | Cβ,C-4 |
|---|---|---|---|---|---|---|---|---|
| **8a$_1$** | $-N(CH_3)_2$ | 172.70 | 40.61 | 76.08 | 88.35 | 55.64 | 42.08 | |
| **8c$_1$** | $-N\frown(CH_2)_4$ | 172.29 | 43.52 | 74.55 | 89.29 | 55.53 | 51.48 | 23.30 |
| **8d$_1$** | $-N\frown(CH_2)_5$ | 173.08 | 40.69 | 76.37 | 88.35 | 55.56 | 51.00 | 25.80 |
| **13e$_1$** | $-SCH_2C_6H_5$ | 173.22 | 55.55 | 43.43 | 91.22 | 51.92 | 36.48 | |
| **13f$_1$** | $-SCH(CH_3)_2$ | 172.99 | 55.78 | 44.59 | 91.97 | 55.02 | 36.16 | 23.38 |
| **13g$_1$** | $-SC(CH_3)_3$ | 173.12 | 50.90 | 45.72 | 93.18 | 55.77 | 45.22 | 31.28 |

## EXPERIMENTAL

Mps are uncorrected. Ir spectra were recorded on a Pye-Unicam SP-1100 grating spectrometer, ν values in $cm^{-1}$. $^1$H-nmr spectra were obtained on a Hitachi Perkin-Elmer R-24-A/60 MHz or a Bruker-200 SY, $^{13}$C-nmr spectra on a Bruker-200 SY spectrometer for $CDCl_3$ solutions (unless otherwise stated) and the chemical shifts are reported in δ (ppm from internal TMS). Mass spectra were determined on a Hewlett-Packard 5985 spectrometer. Uv spectra were recorded on a Perkin-Elmer 402 spectrophotometer for acetonitrile solutions, $\lambda_{max}$nm (ε). Silica gel Merck 60 (70-230 mesh), 60 (230-400 mesh) and DC-Alufolien 60 $F_{254}$ were used for conventional, flash column chromatography and analytical tlc, respectively.

### Reaction of 5-Methoxy-3-pyrrolin-2-one (1) with Amines. General Procedure

To a solution of 5-methoxy-3-pyrrolin-2-one (1) (0.56 g, 5 mmol) in methanol or tetrahydrofuran (10 ml) was added the amine (5.2 mmol). The mixture was kept at room temperature or at reflux (Table 1) until the starting pyrrolinone **1** disappeared or a practically constant concentration was attained. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (chloroform-methanol 4:1).

**Reaction with dimethylamine.**- The reaction in methanol (Table 1), after column chromatography, afforded **4-dimethylamino-5-methoxypyrrolidin-2-one (3a)**. Yield 92%. Colourless solid, mp 42-44°C (from cyclohexane-benzene). (Found: C, 52.85; H, 9.25; N, 17.40. $C_7H_{14}O_2N_2$ requires, C, 53.16; H, 8.86; N, 17.78). Ms, m/z: 158 ($M^+$), 127, 71 (100%).

**Reaction with diethylamine.**- The reaction in methanol (Table 1), after column chromatography, afforded **4-diethylamino-5-methoxypyrrolidin-2-one (3b)** (4%) and **5-diethylamino-5-pyrrolin-2-one (4b)** (62%).

**3b.**- The compound was obtained as an oil and the spectral data were identical with those of a sample obtained by an alternative procedure[13]. (Found: C, 58.18; H, 9.66; N, 14.87. $C_9H_{18}O_2N_2$ requires, C, 58.06; H, 9.68; N, 15.05). Ms, m/z: 186 ($M^+$), 155, 99 (100%).

**4b.**- The compound was obtained from the column as an oil. Ir (nujol): 1770 (C=O); 1595 (C=N). $^1$H-nmr: 3.67 (q, 2H, $CH_2N$, C-5, J = 7.2); 3.41 (q, 2H, $CH_2N$, C-5, J = 7.2); 2.5-2.8 (m, 4H, C-3, C-4); 1.28 (t, 3H, C-5, J = 7.2); 1.23 (t, 3H, C-5, J = 7.2). $^{13}$C-nmr: 192.41 (C=O, C-2); 182.98 (C=N, C-5); 43.20 ($CH_2N$, C-5); 42.74 ($CH_2N$, C-5); 30.91 ($CH_2$, C-3); 27.29 ($CH_2$, C-4); 13.05 ($CH_3$-$CH_2$-N, C-5); 11.86 ($CH_3CH_2$-N, C-5). Uv: 242 (23.000). Ms, m/z: 154 ($M^+$) (100%), 139, 98, 83, 71, 56.

**Reaction with pyrrolidine.**- The reaction in methanol (Table 1), after column chromatography, afforded **4(*N*-pyrrolidinyl)-5-methoxypyrrolidin-2-one (3c)** and **5(*N*-pyrrolidinyl)-5-pyrrolin-2-one (4c).**

**3c.**- Yield 53%. Colourless solid, mp 68-70°C (from hexane-benzene). (Found: C, 58.40; H, 8.47; N, 14.99. $C_9H_{16}N_2O_2$ requires, C, 58.69; H, 8.69; N, 15.21). Ms, m/z: 184 ($M^+$), 153, 97 (100%), 69, 55.

**4c.**- Yield 31%. Colourless solid, mp 127-129°C (from benzene) (lit.[6], mp 127-129°C). Ir (KBr): 1715 (C=O), 1605 (C=N). $^1$H-nmr: 3.61 (t, 2H, $CH_2N$, C-5, J = 6.5); 3.44 (t, 2H, $CH_2$-N, C-5, J = 6.5); 2.60 (m, 4H, C-3, C-4); 1.97 (m, 4H, $CH_2$).

**Reaction with piperidine.**- The reaction in methanol (Table 1), after column chromatography, afforded **4-piperidino-5-methoxypyrrolidin-2-one (3d)** and **5-piperidino-5-pyrrolidin-2-one (4d).**

**3d.**- Yield 48%. Colourless solid, mp 81-83°C (from hexane). (Found: C, 60.47; H, 8.95; N, 14.00. $C_{10}H_{18}O_2N_2$ requires, C, 60.61; H, 9.10; N, 14.14). Ms, m/z: 198 ($M^+$) 167, 111 (100%), 55.

**4d**.- Yield 20%. Colourless solid, mp 101-102°C (from benzene) (lit.[6], mp 101-102°C). Ir (KBr): 1700 (C=O), 1580 (C=N). $^1$H-nmr: 3.86 (t, 2H, $CH_2N$, C-5, J = 5.7); 3.45 (t, 2H, $CH_2$-N, C-5, J = 5.7); 2.70 (m, 4H, C-3, C-4); 1.70 (*m*, 6H, $CH_2$).

**Reaction of 5-Methoxy-3-pyrrolin-2-one (1) with Thiols. General Procedure**

To a solution of the pyrrolinone **1** (0.23 g, 2 mmol) in methanol (6 ml) was added the thiol (2.2 mmol) and the corresponding sodium thiolate (0.02 mmol) in methanol (9 ml). The mixture was kept at room temperature until complete consumption of the pyrrolinone **1** monitored by tlc (ethyl acetate-hexane 8:2).

**Reaction with phenylmethanethiol.**- The mixture was kept at room temperature for 15 min. The solvent was removed under reduced pressure. The crude mixture was washed with hexane to afford **4-benzylthio-5-methoxypyrrolidin-2-one (7e)**.- Yield 90%. Colourless solid, mp 104°C (from benzene). (Found: C, 60.82; H, 6.64; N, 5.85; S, 13.07. $C_{12}H_{15}O_2NS$ requires, C, 60.76; H, 6.33; N, 5.91; S, 13.50. Ms, m/z: 237 ($M^+$), 146, 145 (100%), 91, 78.

**Reaction with 2-propanethiol.**- The mixture was kept at room temperature for 30 min. The solvent was removed in vacuo and the crude mixture was chromatographed on column (ethyl acetate-hexane 8:2) to afford **4-isopropylthio-5-methoxypyrrolidin-2-one (7f)** as an oil. Yield 65%. (Found: C, 51.00; H, 8.10; N, 7.42; S, 16.78. $C_8H_{15}O_2NS$ requires, C, 50.79; H, 7.93; N, 7.41; S, 16.93). Ms, m/z: 189 ($M^+$), 158, 157 (100%), 115, 102.

**Reaction with 2-methyl-2-propanethiol.**- The mixture was kept at room temperature for 3 h. The solvent was removed in vacuo and the crude mixture was chromatographed on column (ethyl acetate-hexane 8:2) to afford 4-*tert*-**butylthio-5-methoxypyrrolidin-2-one (7g)**. Yield 63%. Colourless solid, mp 56-58°C (from hexane). (Found: C, 52.95; H, 8.12; N, 7.20; S, 15.98. $C_9H_{17}O_2NS$ requires, C, 53.20; H, 8.37; N, 6.90; S, 15.76). Ms, m/z: 203 ($M^+$), 146, 116, 114.

**Reaction of 3-Bromo-5-methoxy-3-pyrrolin-2-one (2) with Amines. General Procedure**

To a solution of the pyrrolinone **2** (0.6 g, 3 mmol) in methanol (10 ml) was added the amine (3.3 mmol). The mixture was kept at room temperature until the starting pyrrolinone **2** disappeared or remanined constant. The solvent was removed under reduced pressure. The crude mixture was chromatographed on silica gel (dichloromethane-ethyl acetate-methanol 6:3:1).

**Reaction with dimethylamine.**- The reaction mixture was kept at room temperature 30 min. After column chromatography, the diastereomers **8a$_1$**, **8a$_2$** and **8a$_3$** of **3-bromo-4-dimethylamino-5-methoxypyrrolidin-2-one** were obtained.

**8a$_1$**.- Yield 52%. Colourless solid, mp 86-87°C (from benzene-hexane). (Found: C, 35.40; H, 5.72; N, 11.74; Br, 33.20. $C_7H_{13}N_2O_2Br$ requires, C, 35.59; H, 5.50; N, 11.86; Br, 33.47). Ms, m/z: 236-238 ($M^+$), 205-207, 157, 98 (100%).

**8a$_2$**.- Yield 20%. Colourless solid, mp 102-103°C (from benzene). Ms, m/z: 236-238 ($M^+$), 205-207, 160-162, 157, 98 (100%).

**8a$_3$**.- Yield 8%. Colourless solid, mp 110-112°C (from benzene). Ms, m/z: 236-238 ($M^+$), 205-207, 157, 98 (100%).

When dimethylamine was added in excess (6 mmol of dimethylamine, 3 mmol of pyrrolinone **2**) and the crude mixture was kept at room temperature for 15 min, the mixture analyzed by $^1$H-nmr after removal

of the solvent contained the diastereomers **8a$_1$**, **8a$_2$**, **8a$_3$** and **3,4-bis(dimethylamino)-5-methoxypyrrolidin-2-one (10a)** which was separated by column chromatography (dichloromethane-ethyl acetate-methanol 6:3:1).

**10a.**- Yield 4%. Colourless solid, mp 82-85°C (from benzene). Ir (nujol): 3110,3100 (NH); 1700 (C=O). $^1$H-nmr: 8.33 (br, 1H, NH); 4.65 (d, 1H, C-5, $J_{4,5}$ = 2.3); 3.30 (d, 1H, C-3, $J_{3,4}$ = 5.1); 2.95 (dd, 1H, C-4, $J_{3,4}$ = 5.1, $J_{4,5}$ = 2.3); 2.45 (s, 6H, $CH_3N$); 2.32 (s, 6H, $CH_3N$). $^{13}$C-nmr: 175.6 (C=O, C-2); 85.9 (CH, C-5); 68-65 (CH, C-3); 66.05 (CH, C-4); 55.47 (O-$CH_3$); 45.96 ($CH_3$-N, C-3), 41.81 ($CH_3$-N, C-4), Ms, m/z: 201 ($M^+$), 156, 101 (100%).

**Reaction with diethylamine.**- The reaction mixture was kept at room temperature and, after 6 days, a 30% of the starting halopyrrolinone **2** remained unreacted. The **4,5-bis(diethylamino)-5-pyrrolin-2-one (9b)** was purified by chromatography (dichloromethane-ethyl acetate-methanol 3:1:1). Yield 47%. Identical with a sample obtained from the reaction of 4-bromo-3-pyrrolin-2-one with diethylamine[5].

**Reaction with pyrrolidine.**- The reaction mixture was kept at room temperature for 30 min. After column chromatography the diastereomers of **3-bromo-4(*N*-pyrrolidinyl)-5-methoxypyrrolidin-2-one (8c$_1$, 8c$_2$, 8c$_3$)** and small amounts of **9c**[5], **10c** and recovered starting material were obtained.

**8c$_1$.**- Yield 44%. Colourless solid, mp 102-104°C (benzene-hexane). (Found: C, 41.30; H, 5.71; N, 10.90; Br, 30.22. $C_9H_{15}O_2Br$ requires, C, 41.06; H, 5.70; N, 10.65; Br, 30.42). Ms, m/z: 262-264($M^+$), 233, 124 (100%).

**8c$_2$.**- Yield 7%. Colourless solid, mp 105-106. Ms, m/z: 262-264($M^+$), 233, 124 (100%).

**8c$_3$.**- Yield 16%. Colourless solid, mp 108-110°C. Ms, m/z: 262-264 ($M^+$), 233, 124 (100%).

When pyrrolidine was added in excess (6 mmol of pyrrolidine, 3 mmol of pyrrolinone **2**) and the crude mixture was kept at room temperature for 5 h, the **3,4-bis(*N*-pyrrolidinyl)-5-methoxypyrrolidin-2-one (10c)** and **9c**[5] were separated by chromatography (chloroform-ethyl acetate-methanol 6:3:1).

**10c.**- Yield 18%. Colourless solid, mp 104-105°C (from benzene-hexane). Ir (nujol): 3200, 3100 (NH),1700 (C=O). $^1$H-nmr: 8.0 (br, 1H, NH); 4.80 (d, 1H, C-5, $J_{4,5}$ = 2.4); 3.67 (d, 1H, C-3, $J_{3,4}$ = 5.3); 3.03 (dd, 1H, C-4, $J_{3,4}$ = 5.3, $J_{4,5}$ = 2.4); 3.05-2.90 (m, 2H, C-4, $CH_2$-N); 2.8-2.7 (m, 6H, $CH_2N$); 1.87-1.75 (m, 8H, $CH_2$). $^{13}$C-nmr: 176.15 (C=O, C-2); 87.85 (CH, C-5); 68.13 (CH, C-3); 64.34 (CH, C-4); 55.31 (O-$CH_3$, C-5), 51.10 ($CH_2N$, C-3); 49.86 ($CH_2N$, C-4); 23.87, 23.12 ($CH_2$, C-3, C-4). MS, m/z: 253 ($M^+$), 182, 127 (100%).

**Reaction with piperidine.**- The reaction mixture was kept at room temperature 30 min. After column chromatography, the diastereomers of **3-bromo-4-piperidino-5-methoxypyrrolidin-2-one (8d$_1$, 8d$_2$, 8d$_3$)** and small amounts of **9d**[5], **10d** and recovered starting material were obtained.

**8d$_1$.**- Yield 41%. Colourless solid, mp 110-112°C (from benzene-hexane). (Found: C, 43.60; H, 6.30; N, 9.95; Br, 28.92. $C_{10}H_{17}O_2N_2Br$ requires, C, 43.47; H, 6.15; N, 10.14; Br, 28.62). Ms, m/z: 245-247, 197, 138 (100%).

**8d$_2$.**- Yield 4%. Colourless solid, mp 110-112°C (from benzene-hexane). Ms, m/z: 245-247, 197, 138 (100%).

**8d$_3$.**- Yield 9%. Colourless solid, mp 120-122°C (from benzene-hexane). Ms, m/z: 245-247, 197, 138 (100%).

When piperidine was added in excess (6 mmol of piperidine, 3 mmol of pyrrolinone **2**) and the crude mixture was kept at room temperature for 5 h, the **3,4-bis(*N*-piperidinyl)-5-meothoxypyrrolidin-2-one (10d)** and **9d**[5] were separated by chromatography (chloroform-ethyl acetate-methanol 6:3:1).

**10d.**- Yield 8%. Colourless solid, mp 108°C (decomp) (from benzene-hexane). Ms, m/z: 281 ($M^+$), 141 (100%),

126. Ir (nujol): 3200, 3100 (NH), 1700 (C=O). $^1$H-nmr: 8.20 (br, 1H, NH); 4.58 (d, 1H, C-5, $J_{4,5}$ = 2.0); 3.25 (d, 1H, C-3, $J_{3,4}$ = 4.8); 2.89 (dd, 1H, C-4, $J_{3,4}$ = 4.8, $J_{4,5}$ = 2.0); 2.78-2.70 (m, 2H, $CH_2N$); 2.51-2.40 (m, 6H, $CH_2N$); 1.48-1.43 (m, 12H, $CH_2$). $^{13}$C-nmr: 175.4 (C=O, C-2); 86.42 (CH, C-5); 69.72 (CH, C-3); 66.79 (CH, C-4); 54.96 ($O-CH_3$, C-5); 51.36 ($CH_2N$, C-3); 50.70 ($CH_2N$, C-4); 24.41-24-23 ($CH_2$, C-3, C-4). Ms, m/z: 281 ($M^+$), 141 (100%).

**Reaction of 3-Bromo-5-methoxy-3-pyrrolin-2-one (2) with Thiols. General Procedure**

To a solution of bromopyrrolinone **2** (0.6 g, 3 mmol) in methanol (6 ml) was added the thiol (3.3 mmol) and the corresponding sodium thiolate (0.02 mmol) in methanol (9 ml). The mixture was kept at room temperature (30 min for **13e** and **13g**; 1 h for **13f**). The solvent was removed under reduced pressure.

**Reaction with phenylmethanethiol.**- The crude mixture contains (by $^1$H-nmr) **3-bromo-4-benzylthio-5-methoxypyrrolidin-2-one** as a mixture of the diastereomers **13e$_1$** and **13e$_2$**. The compound **13e$_1$** precipitated as a white solid when hexane-ethyl acetate was added to the mixture. Column chromatography of the mother liquors (ethyl acetate-hexane-dichloromethane 4:2:1) afforded **14e**[5], **15e**[5] and small amounts of **13e$_1$**.

**13e$_1$**.- Yield 36%. Colourless solid, mp 72°C (from ethyl acetate-hexane). (Found: C, 45.43; H, 4.60; N, 4.40; Br, 25.96; S, 9.86. $C_{12}H_{14}O_2NBrS$ requires, C, 45.57; H, 4.43; N, 4.43; Br, 25.32; S, 10.13). Ms, m/z: 315-317 ($M^+$), 236, 177, 91 (100%).

When the crude mixture was kept at room temperature for longer periods of time, the compounds **14e**[5] and **15e**[5] were also identified.

**Reaction with 2-propanethiol.**- The crude mixture contains (by $^1$H-nmr) **3-bromo-4-isopropylthio-5-methoxypyrrolidin-2-ones** as a mixture of diastereomers **13f$_1$** and **13f$_2$**. After column chromatography (dichloromethane-methanol-ethyl acetate 6:2:1) compounds **13f$_1$**, **14f**[5] and **15f**[5] were obtained.

**13f$_1$**.- Yield 60%. Colourless solid, mp 79-80 (from benzene). (Found: C, 36.08; H, 5.38; N, 5.17; Br, 30.23; S, 11.63. $C_8H_{14}O_2NBrS$ requires, C, 35.82; H, 5.22; N, 5.22; Br, 29.85; S, 11.94). Ms, m/z: 267-269 ($M^+$), 188, 129 (100%).

When the crude mixture was kept at room temperature for longer periods of time, the compounds **14f**[5] and **15f**[5] were also identified.

**Reaction with 2-methyl-2-propanethiol.**- The crude mixture contains (by $^1$H-nmr) **3-bromo-4-*tert*-butylthio-5-methoxypyrrolidin-2-one** as a mixture of diastereomers **13g$_1$** and **13g$_2$**. After column chromatography (ethyl acetate-hexane-dichloromethane 4:2:1) compounds **13g$_1$** and **15g**[5] were obtained.

**13g$_1$**.- Yield 68%. Colourless solid, mp 64°C (from benzene-hexane). (Found: C, 38.70; H, 5.83; N, 4.93; Br, 28.07; S, 11.20. $C_9H_{16}O_2NBrS$ requires, C, 38.43; H, 5.69; N, 4.98; Br, 28.11; S, 11.38). Ms, m/z: 281-283 ($M^+$), 202, 143 (100%).

When the crude mixture was kept at room temperature for longer periods of time, the compound **15g**[5] was also identified.

**Dedicatory.** We would like to dedicate this paper to the memory of the late Prof. Dr. Juan Borges del Castillo.

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13. Compound **3b** was also obtained as follows: Ammonolysis[14] of 4-diethylamino-5-methoxytetrahydrofuran-2-one[8] afforded 4-diethylamino-5-hydroxypyrrolidin-2-one as a mixture of two diastereomers. Yield 60%. The *trans* diastereomer was recrystallized from ethyl acetate-hexane as a colourless solid, mp 84-86°C. (Found: C, 55.68; H, 9.10; N, 15.98. $C_8H_{16}O_2N_2$ requires, C, 55.81; H, 9.30; N, 16.28). Ir (nujol): 3185 (OH, NH), 1735 (C=O). $^1$H-nmr: 7.35 (br, 1H, NH); 5.19 (d, 1H, C-5, $J_{4,5}$ = 2.5); 3.41 (ddd, 1H, C-4, $J_{4,5}$ = 2.5, $J_{3a,4}$ = 5.7, $J_{3b,4}$ = 7.1); 2.6 (m, 4H, $CH_2N$); 2.33 (dd, 1H, C-3, $J_{3b,4}$ = 5.7, $J_{3a,3b}$ = 17.7); 1.07 (t, 6H, $CH_3$, J = 7.1). The mixture of the diastereomers obtained, treated with acid-catalyzed methanol yielded two diastereomers one of them identical with **3b**.
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