

PSEUDOESTERS AND DERIVATIVES. XVIII<sup>1</sup>. THE REACTION OF  
5-METHOXYFURAN-2(5H)-ONE AND ITS 3-HALO DERIVATIVES  
WITH NITROGEN AND SULPHUR NUCLEOPHILES

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**Abstract** - The 5-methoxyfuran-2(5H)-ones 1 - 3 react with amines and thiols under basic catalysis at room temperature in tetrahydrofuran or carbon tetrachloride yielding the corresponding products of conjugate addition. The nucleophile enters preferentially from the side opposite to the OMe group.

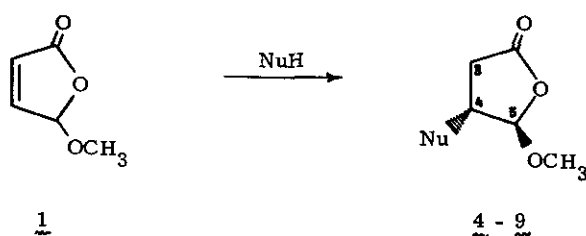
In an earlier paper<sup>2</sup> the behaviour of 5-methoxyfuran-2(5H)-one (1) and its 3- and 4-bromo derivatives in the presence of methoxide ion has been reported. According to these results, the initial attack of the nucleophile occurs either at C-4, yielding the conjugate addition product, or at the carbonyl group with opening of the lactone ring. Recent work<sup>1</sup> showed also that 4-halo-5-methoxyfuran-2(5H)-ones react easily with amines and thiolates giving the products of a nucleophilic vinylic substitution of the 4-halogen atom in very good yields. Furthermore, conjugate addition of amines and thiols to  $\alpha,\beta$ -unsaturated carbonyl compounds and to their  $\alpha$ -halogenated derivatives has ample precedence in the literature<sup>3</sup>. The reactions proceed readily, although the adducts of the halogenated substrates are prone to eliminate hydrogen halide so that their isolation, or in some cases their detection, is not possible.

The subject of the present paper deals with the reaction of 5-methoxyfuran-2(5H)-one (1) and its 3-halo derivatives (2 and 3) with amines and thiols. The substrates 1, 2 and 3 may also be considered as pseudoesters derivated from the cyclic tautomeric form of 4-oxobut-2-enoic acid and, in accord with previous observations, could undergo different types of reactions with nucleophiles.

Reaction of 5-methoxyfuran-2(5H)-one

The furanone 1 reacts with some simple secondary and primary amines (pyrrolidine, piperidine, diethylamine and benzylamine), at room temperature in anhydrous tetrahydrofuran or

carbon tetrachloride, to afford the corresponding products of conjugate addition 4 - 7. Under similar experimental conditions, thiols (phenylmethanethiol and 2-propanethiol), in the presence of a 20% of the corresponding thiolate, were found to add in a Michael fashion to the furanone 1 yielding the adducts 8 - 9. However, formation of by-products originated from ring-opening processes has not been observed. The reaction with thiols under basic catalysis proceeds faster than that of amines as expected from the greater nucleophilicity of the formers <sup>4</sup>.



The above reactions lead in each case to only one diastereomer (the trans isomers 4 - 9 <sup>5</sup>; Table 1) thus indicating that the attack of the nucleophile occurs preferentially from the side opposite to the OMe group, sterically less hindered. Stereochemical assignment of these adducts was based on the <sup>1</sup>H-NMR spectra. The trans arrangement of the substituents was deduced from the small coupling constant ( $J_{4,5} = 1.2 - 2.4$  Hz) between H-4 and H-5. These values are in agreement with those calculated for a trans stereochemistry from the Karplus equation corrected for the effects of electronegativity of the substituents (Altona equation) <sup>6</sup>.

Table 1. Spectral data of compounds 4 - 9

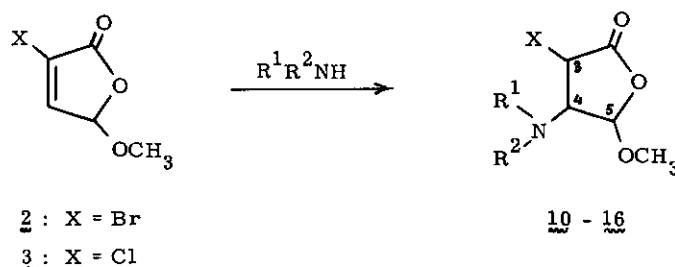
Compound No	Nu	IR <sup>a</sup> C=O	MS (m/e)M <sup>+</sup>	<sup>1</sup> H-NMR <sup>b</sup>							
				H-3a	H-3b	H-4	H-5	$J_{3a,3b}$	$J_{3a,4}$	$J_{3b,4}$	$J_{4,5}$
<u>4</u>	-N(CH <sub>2</sub> ) <sub>4</sub>	1785	185	2.60	2.38	2.96	5.15	-17.4	7.7	4.5	2.2
<u>5</u>	-N(CH <sub>2</sub> ) <sub>5</sub>	1785	199	2.54	2.36	3.05	5.16	-17.9	8.5	4.1	1.9
<u>6</u>	-N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1790	187	2.59	2.33	3.37	5.11	-18.1	8.8	4.2	2.0
<u>7</u>	-NHCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	1780	221	2.66	2.14	3.28	5.01	-17.6	7.1	2.5	1.2
<u>8</u>	-SCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	1780	238	2.79	2.20	3.13	5.03	-18.1	8.7	4.3	2.0
<u>9</u>	-SCH(CH <sub>3</sub> ) <sub>2</sub>	1790	190	2.94	2.28	3.32	5.16	-17.9	8.8	4.7	2.4

<sup>a</sup> Neat. <sup>b</sup> In CCl<sub>4</sub> solution.

#### Reaction of 3-bromo- and 3-chloro-5-methoxyfuran-2(5H)-one

The 3-halo-5-methoxyfuran-2(5H)-ones 2 and 3 react with an equimolar amount of the

above mentioned amines, under similar experimental conditions, yielding a mixture of diastereomers 10 - 16 (Table 2), originated by addition to the conjugated system of the furanones. As the adducts are not stable enough for an analytical sample to be obtained, the reactions were carried out in  $\text{CCl}_4$  as solvent, in order to facilitate the recording of their  $^1\text{H-NMR}$  spectra.



The adducts 10 - 12 and 14 - 16 obtained by reaction with secondary amines were shown by  $^1\text{H-NMR}$  to be a mixture of two main diastereomers which appear in an approximate ratio 4:1. The trans stereochemistry of the substituents at C-4 and C-5 of the major isomers in each case

Table 2. Spectral data of compounds 10 - 16 and relative ratio of diastereomers

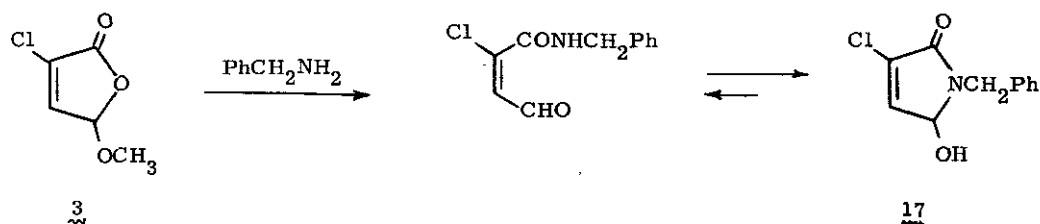
Compound <sup>a</sup>				IR <sup>b</sup> C=O	$^1\text{H-NMR}$ <sup>b</sup>					Ratio <sup>c</sup> %
Nº	X	R <sup>1</sup>	R <sup>2</sup>		H-3	H-4	H-5	J <sub>3,4</sub>	J <sub>4,5</sub>	
<u>10</u>	Br	$-(\text{CH}_2)_4-$		1800	4.32	3.23	5.20	5.7	3.3	70
					4.33	d	5.24	5.9	5.1	20
					4.66	d	d	9.9	-	10
<u>11</u>	Br	$-(\text{CH}_2)_5-$		1800	4.38	3.34	5.21	5.3	3.0	75
					4.48	2.81	5.26	6.4	4.1	25
<u>12</u>	Br	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	1800	4.32	3.62	5.16	5.3	3.0	85
					4.50	3.27	5.23	6.8	4.1	15
<u>13</u>	Br	H	$\text{CH}_2\text{C}_6\text{H}_5$	1800	4.54	3.20	5.03	6.0	4.2	25
					4.18	3.42	5.08	3.6	1.5	30
					4.28	3.28	5.12	1.5	0.8	35
					4.35	3.68	5.20	6.6	4.8	10
<u>14</u>	Cl	$-(\text{CH}_2)_4-$		1805	4.32	3.03	5.15	7.3	4.4	80
					4.42	3.11	5.28	6.2	4.3	20
<u>15</u>	Cl	$-(\text{CH}_2)_5-$		1805	4.40	3.12	5.16	6.9	4.0	80
					4.52	3.12	5.27	6.9	2.7	20
<u>16</u>	Cl	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	1800	4.36	3.53	5.13	7.2	4.2	85
					4.56	3.53	5.26	7.2	2.2	15

<sup>a</sup> Mixture of diastereomers. <sup>b</sup> In  $\text{CCl}_4$  solution. <sup>c</sup> Approximate ratio determined by  $^1\text{H-NMR}$  integration. <sup>d</sup> Signals are hidden within those for other protons.

follows from the  $J_{4,5}$  coupling constants (3.0 - 3.3 Hz and 4.0 - 4.4 Hz for the bromo and chloro derivatives, respectively), on the basis of the afore-mentioned Altona equation. In contrast, from the coupling constants  $J_{3,4}$  (5.3 - 5.7 Hz for the bromo derivatives 10 - 12 and 6.9 - 7.3 Hz for the chloro derivatives 14 - 16) is not possible to assign the stereochemistry of the substituents at C-3 and C-4, since the observed values of the coupling constants are compatible with both the cis and the trans arrangement (dihedral angles  $\phi$  of ca. 35° and 135°, respectively).

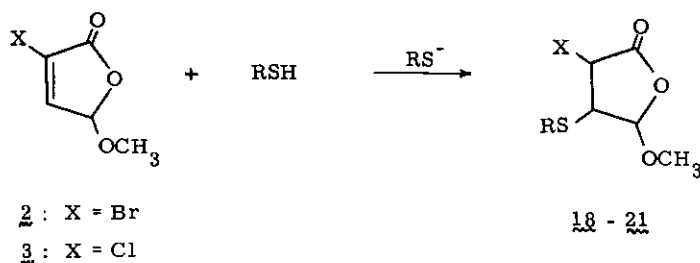
The behaviour of the primary amine (benzylamine) was different towards the two halogenated methoxyfuranones. The reaction with bromofuranone 2 afforded only the four diastereomers originated by conjugate addition. In contrast, the main component from the reaction of the chlorofuranone 3 is 1-benzyl-3-chloro-5-hydroxypyrrolin-2(5H)-one (17), although formation of products from the conjugate addition can also be detected by  $^1\text{H-NMR}$ . Formation of 17 may be rationalized by attack of the amine on the carbonyl group of the methoxyfuranone, which results in opening of the lactone ring, yielding the corresponding aldehyde-amide that cyclizes spontaneously<sup>7</sup> to its ring-tautomer, the hydroxypyrrolinone 17. This result has a precedent in the fact previously reported<sup>8</sup>, that several  $\alpha,\beta$ -unsaturated  $\gamma$ -lactones are cleaved by primary amines, benzylamine among them, yielding finally the corresponding lactams.

The hydroxylactam structure 17 was evidenced by the spectral data. Thus, IR spectrum of the product contained an OH band at  $3270\text{ cm}^{-1}$  and absorptions at  $1680$  and  $1615\text{ cm}^{-1}$  which support the unsaturated lactam structure. The  $^1\text{H-NMR}$  spectrum was also in accord with that expected for 17 and showed a doublet at  $\delta$  6.86 ( $J=0.2\text{ Hz}$ ) assigned to the olefinic proton, a broad signal at  $\delta$  5.26 for the C-5 proton (collapses to a doublet in the presence of  $\text{D}_2\text{O}$ ) and the diastereotopic methylene protons as an AB quartet at  $\delta$  4.97 and 4.33 ( $J=-15\text{ Hz}$ ). The mass spectral data were also in agreement with the structure 17.



Methoxyfuranones 2 and 3 reacted also with phenylmethanethiol and 2-propanethiol as nucleophiles, in the presence of the corresponding thiolate as catalyst. The reaction proceeded in excellent yield by conjugate addition to the  $\alpha,\beta$ -unsaturated lactone system, and led to a mixture of diastereomers. Other side reactions, as lactone ring-opening or dehydrohalogenation, were not observed in this case. The products, purified by column chromatography, are rather unstable and decompose readily after the isolation.

The  $^1\text{H-NMR}$  signals of compounds 18 to 21 completely support their saturated lactone structures (Table 3). The number of diastereomers which are present in the mixtures and their approximate ratios can be deduced from a detailed examination of the  $^1\text{H-NMR}$  spectra. However, the separation of these mixtures was not attempted.



The reactions of both phenylmethanethiol and 2-propanethiol with the bromomethoxyfuranone 2 led to mixtures of four diastereomers, two of which were present in a higher ratio. The major component in each adduct 18 and 19 was the diastereomer in which the substituents in C-4 and C-5 possess a trans arrangement ( $\phi = 115 - 120^\circ$ ;  $J_{4,5} = 2.9$  and  $3.4$  Hz, respectively). In contrast, the diastereomers which showed  $J_{4,5}$  values of  $5.9$  and  $6.3$  Hz respectively presumably possess a cis arrangement of these substituents ( $\phi = 25 - 30^\circ$ ).

Table 3. Spectral data of compounds 18-21 and relative ratio of diastereomers

Compound <sup>a</sup> No	X	R	IR <sup>b</sup> C=O	MS (m/e)M <sup>+</sup>	<sup>1</sup> H-NMR <sup>c</sup>					Ratio <sup>d</sup> %
					H-3	H-4	H-5	$J_{3,4}$	$J_{4,5}$	
<u>18</u>	Br	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	1795	316-318	4.16	3.30	5.17	4.5	2.9	49
					4.42	3.10	5.40	6.8	5.9	23
					e	2.00	5.25	-	7.2	19
					e	e	5.01	-	2.4	9
<u>19</u>	Br	(CH <sub>3</sub> ) <sub>2</sub> CH	1790	268-270	3.93	3.40	4.78	5.8	3.4	45
					4.09	2.68	5.04	6.4	6.3	25
					3.32	3.22	4.94	5.7	2.8	20
					3.67	2.9-2.3	5.23	7.5	5.7	10
<u>20</u>	Cl	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	1795	272-274	4.11	3.21	5.05	6.5	4.0	70
					4.40	3.27	5.28	6.7	4.5	30
<u>21</u>	Cl	(CH <sub>3</sub> ) <sub>2</sub> CH	1795	224-226	3.85	3.23	4.69	7.9	4.9	75
					4.18	3.04	5.05	6.4	5.3	25

<sup>a</sup> Mixture of diastereomers. <sup>b</sup> Neat. <sup>c</sup> 18 was recorded in CDCl<sub>3</sub> solution; 19 and 21 in C<sub>6</sub>D<sub>6</sub> and 20 in CCl<sub>4</sub>. <sup>d</sup> Approximate ratio determined by <sup>1</sup>H-NMR integration. <sup>e</sup> Signals are hidden within those for other protons.

Nevertheless, for the chloro derivatives 20 and 21 it is not possible to assign the stereochemistry of the substituents at C-4 and C-5. In fact, the coupling constants show values between  $4.0$  and  $5.3$  Hz and there are no significant differences in the two observed diastereomers. Furthermore, the coupling constants  $J_{3,4}$  of the different diastereomers of the adducts 18, 19,

20 and 21, as was the case in the above-mentioned amine adducts, are compatible with both the cis and the trans arrangement and do not allow to decide on the stereochemistry of the substituents at C-3 and C-4.

## EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer model 257 grating spectrophotometer,  $\nu$  values in  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  spectra were obtained on a Varian EM-390 spectrometer or on a model XL-100; signals are reported in  $\delta$  units with TMS = 0 ppm as internal standard. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6MG spectrometer.

Silica gel Merck 60 (70 - 230 mesh),  $\text{F}_{254}$  (layers 2 mm) and DC-Alufolien 60  $\text{F}_{254}$  (layers 0.2 mm) were normally used for column, preparative and analytical t.l.c. Analytical g.l.c. was performed on a Perkin-Elmer F-11 model instrument (Reoplex, 4% on Chromosorb G).

Addition of amines to 5-methoxyfuran-2(5H)-one. General Procedure. - To a solution of 5-methoxyfuran-2(5H)-one (1) (460 mg, 4 mmol) in tetrahydrofuran or carbon tetrachloride (20 ml) was added the amine (4.2 mmol). The mixture was kept at room temperature until the starting furanone disappeared (5 days for 4 and 5) or a practically constant concentration was attained (ca. 70 % conversion in 15 days for 6 and 7). The solvent was removed under reduced pressure and the crude product analyzed by IR and NMR (Table 1).

Addition of thiols to 5-methoxyfuran-2(5H)-one. General Procedure. - To a solution of methoxyfuranone 1 (460 mg, 4 mmol) in tetrahydrofuran or carbon tetrachloride (20 ml) was added the thiol (4 mmol) and the respective sodium thiolate (0.8 mmol). The mixture was kept at room temperature until complete consumption of the furanone 1 (15 min; disappearance of 1 was monitored by g.l.c.). The solution was filtered on Florisil and the solvent removed under reduced pressure to afford the addition product in nearly quantitative yield (Table 1).

Addition of amines to 3-halo-5-methoxyfuran-2(5H)-ones. General Procedure. - To a solution of 3-bromo- or 3-chloro-5-methoxyfuran-2(5H)-ones (2 or 3) (2 mmol) in carbon tetrachloride (3 ml) was added the amine (2 mmol) in the same solvent. The mixture was kept at room temperature for short reaction times (ca. 10 min for adducts 10 - 12 and 14 - 15; 1 - 2 h for 13 and 16), and analyzed by IR and  $^1\text{H-NMR}$  (Table 2). In the formation of 13 and 16 a 30 - 40 % of the starting halofuranone remains unreacted, but we have noted that extended reaction periods are not advisable and result in decomposition of the addition products.

1-Benzyl-3-chloro-5-hydroxypyrrolin-2(5H)-one (17). - To a solution of 3-chloro-5-methoxyfuran-2(5H)-one (3) in carbon tetrachloride was added an equimolar amount of benzylamine according to the general procedure. The mixture was kept 7 days at room temperature and then

evaporated to dryness under reduced pressure. The residue was extracted with chloroform, the solvent was removed and the crude product was chromatographed on silica gel (benzene-ethyl acetate 10:1) and/or crystallized from cyclohexane or benzene, m.p. 98-99°C. (Found: C, 58.79; H, 4.51; N, 6.13; Cl, 15.50. Calcd. for  $C_{11}H_{10}ClNO_2$ : C, 59.06; H, 4.47; N, 6.25; Cl, 15.88). IR (nujol): 3270(OH); 1680 (C=O); 1615 (C=C).  $^1H$ -NMR ( $CDCl_3$ ): 7.35 (m, 5H, Ph); 6.86 (d, 1H, C-4,  $J_{4,5} = 0.2$ ); 5.26 (broad signal; d after shaking with  $D_2O$ , 1H, C-5); 4.97, 4.33 (AB q, 2H,  $CH_2Ph$ ,  $J = -15.0$ ); 3.10 (broad signal, OH). MS:  $m/e$  223-225 ( $M^+$ ), 118, 106 (100%), 91.

Addition of thiols to 3-halo-5-methoxyfuran-2(5H)-ones. General Procedure. - To a solution of halofuranones 2 or 3 (4 mmol) was added the thiol (4.2 mmol) and the respective sodium thiolate (0.8 mmol). The mixture was kept for several hours with stirring at room temperature (3 h for 18 and 20; 5 h for 19 and 21). The solution was filtered on Florisil and the solvent was removed in vacuo to afford nearly quantitative yield. The residue was analyzed by  $^1H$ -NMR (Table 3). The purification was carried out by column chromatography on silica gel using benzene-ethyl acetate as eluent.

#### ACKNOWLEDGEMENTS

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