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PSEUDOESTERS AND DERIVATIVES. XXIII[1]. REACTION OF 3-BROMO-5-METHOXYFURAN-2(5H)-ONE WITH NUCLEOPHILES. FORMATION OF CYCLOPROPANE DERIVATIVES.

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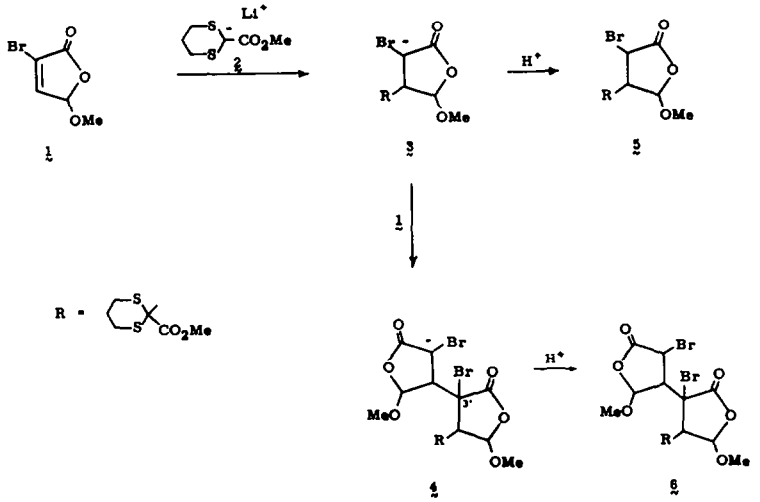
Abstract - The reactions of 3-bromo-5-methoxyfuran-2(5H)-one (1) with nucleophiles in acetonitrile, in the presence of potassium carbonate and tetrabutylammonium bromide as a catalyst, are reported. The bromofuranone 1 reacts with several carbon and oxygen nucleophiles to give the cyclopropane bis-lactones 7, 8, 11 or 12. When 1 is reacted with diethylamine or propane-2-thiol in a 2:1 ratio, similar cyclopropane bis-lactones 16 or 21, respectively, are formed. This behaviour is explained on the basis of a mechanism involving a double Michael addition, followed by ring closure via internal nucleophilic substitution of the halogen.

We have earlier reported[2,3] that 3-bromo-5-methoxyfuran-2(5H)-one (1) behaves as a Michael acceptor towards oxygen, nitrogen and sulphur nucleophiles. Recently, we have also described[4] that 1 reacts readily with carbon nucleophiles, such as lithio derivatives of the type 2, to give the Michael adduct 5 and/or the bis-lactone 6.



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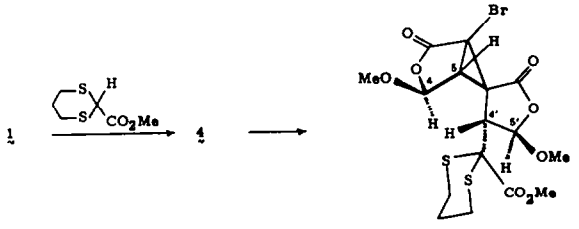
A recent report[5] describes that Michael additions of related carbanions to α,β-unsaturated ketones can be effected in a solid-liquid two-phase system by using potassium carbonate in the presence of a tetraalkylammonium salt as a catalyst. In view of the advantages of this new system[6] we decided to investigate the behaviour of the bromofuranone 1 towards carbanions and other nucleophiles under these conditions.

RESULTS AND DISCUSSION

Carbon nucleophiles

Reaction of bromofuranone 1 with methyl 1,3-dithiane-2-carboxylate in acetonitrile at room temperature, in the presence of potassium carbonate and tetrabutylammonium bromide as a catalyst, afforded a single product which was isolated in 50 % yield. This result was not modified using different ratios substrate / reagent. The product was different from those (5 and 6) previously obtained upon protonation of the carbanions formed when 1 was reacted with the lithio derivative 2 at -76° C in THF as solvent.

According to the mass spectrum and combustion analysis the new compound had a molecular formula $C_{16}H_{19}O_8S_2Br$. The presence of two methoxyfuranone moieties was deduced from the ^{1}H-NMR spectrum, which showed two signals at δ 5.74 and 6.03 assignable to acetal type protons, and two OCH_3 singlets at δ 3.53 and 3.55. Evidence supporting the presence of the methoxycarbonyl dithiane group was obtained from the mass spectrum which displayed the base peak at m/z 177. On the basis of these data, and from the presence of an IR band at 3.070 cm^{-1}, assignable to a C-H stretching in a cyclopropane ring, the structure 7 was proposed for the new compound.



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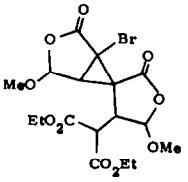
The ^{13}C-NMR spectrum of the compound was also consistent with the proposed structure; in particular it showed a signal at δ 38.39 with a coupling constant $J_{C-H} \simeq 176$ Hz, which is in agreement with the presence of a cyclopropane ring. The product was homogeneous by t.l.c. and the presence of sharp singlets for the OCH_3 and CO_2CH_3 groups was indicative of a single diastereomer. The proposed stereochemistry was based on the ^{1}H-NMR spectrum, in which the absence of coupling constants between the vicinal protons H-4/H-5 and H-4'/H-5' establishes a trans relationship. Moreover, the exo arrangement of both the OCH_3 group at C-4 and the CO of the spirolactone with respect to the oxabicyclo [3.1.0] hexane system was verified with the aid of the nuclear Overhauser enhancement on H-4 which arises from the irradiation of H-4'. This fact confirmed the proximity of both protons, only compatible with the above stereochemistry.

The formation of 7 presumably occurs by ring closure from the enolate anion 4 via internal nucleophilic substitution, displacing the bromide at position 3', to yield the cyclopropane derivative. Since our investigations were completed, a report has appeared in the literature[7] describing the formation of simple cyclopropane derivatives in a similar approach via double Michael addition. The cyclopropanes were obtained from different anions, generated with n-butyllithium at -50° C, and two molar equiv. of alkyl α-bromoacrylates. The authors indicated, however, that β-substituted alkyl α-bromoacrylates do not react because of the easy reversibility

of the conjugate addition.

We have found that temperature is the determining factor in order to achieve the conversion of the anion 4 into the cyclopropane 7. In fact, under the experimental conditions previously reported[4] (-76° C) the anion 4 is stable enough to be protonated to the bis-lactone 6. However, when the reaction mixture is allowed to reach -15° C, in the absence of protons, the enolate anion 4 undergoes the ring closure to give the cyclopropane 7.

Here we extended the investigations to include other reagents capable to give carbanions under the above mentioned conditions. Thus, treatment of the bromofuranone 1 with one molar equiv. of diethyl malonate, afforded the cyclopropane bis-lactone 8 as the major component, together with minor amounts of the cyclopropane lactone 9. The formation of 8 can be interpreted as above and it shows that the double Michael addition and the subsequent intramolecular ring closure are very favoured under these conditions. However, the presence in this case of an acidic methine proton in the first Michael adduct allows the formation of 9 by internal



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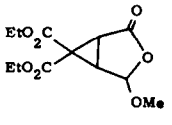

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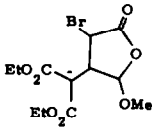

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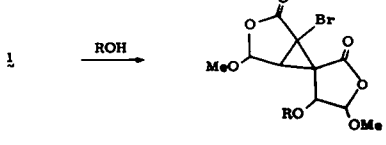
nucleophilic substitution of the halogen in the carbanionic intermediate 10.

We have also investigated the reaction of the bromofuranone 1 with methyl chloro- and bromoacetate, under the above mentioned conditions. In both cases, however, the reaction afforded the same cyclopropane bis-lactone 12, which possesses the $EtO_2C\text{-}CH_2O$- instead of the expected $EtO_2C\text{-}CHX$- group. The structure 12 was supported by elemental analysis and spectroscopic data. These results indicate that the reaction proceeds with previous displacement of the halogen by the hydroxy group, the corresponding alkoxide being the anionic species that initiate the conjugate addition. In view of this result, we have studied the reaction using methanol as a simple oxygen nucleophile.

Oxygen nucleophiles

The reaction of the bromofuranone 1 with methanol, under the conditions indicated above, occurred readily and afforded the cyclopropane bis-lactone 11. The crude product appeared by ^{1}H-NMR analysis to be a 9:1 mixture of two diastereomers, which could be separated by chromatography. The analysis indicated the formula $C_{11}H_{13}O_7Br$ and the ^{1}H- and ^{13}C-NMR spectra were very similar to those of compound 7, in which a methoxy group has replaced the methoxycarbonyldithiane moiety.



11, R = Me
12, R = CH_2CO_2Et

The formation of the diastereomers 11 involves: (i) generation of the methoxide ion, (ii) Michael addition to the bromofuranone 1 to yield a carbanion of the type 3 (R = OCH_3), (iii) conjugate addition to a second furanone molecule to give a new carbanionic intermediate 4 (R = OCH_3) and (iv) internal nucleophilic substitution to yield the cyclopropane bis-lactone 11. The

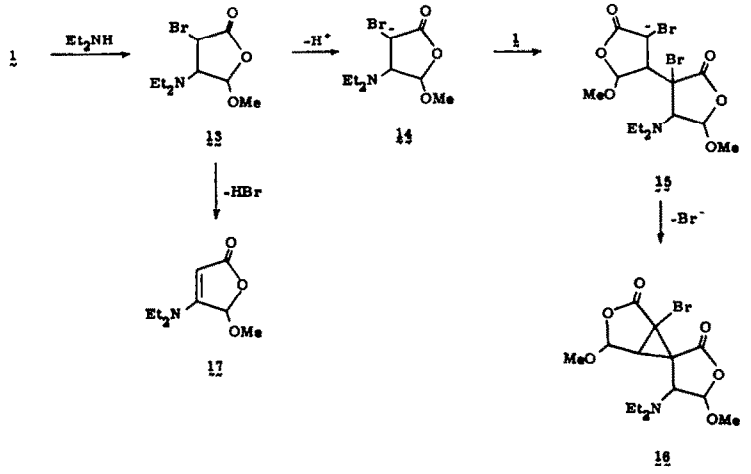
second Michael addition and the ring closure is, as in the case of 7, very favoured and we have found that even by using a 1:2 ratio bromofuranone/methanol, the cyclopropane bis-lactone 11 is obtained as the sole product.

Nitrogen nucleophiles

Reaction of 1 with nitrogen nucleophiles was investigated next. Earlier studies from our laboratory indicated that the reaction of bromofuranone 1 with secondary amines, in tetrahydrofuran or carbon tetrachloride as solvent, provided a diastereomeric mixture of the expected conjugated addition product. Therefore, we have extended the investigation using a catalytic solid-liquid two-phase system to include a nitrogen nucleophile such as diethylamine.

The reaction of the bromofuranone 1 with diethylamine, under the above mentioned conditions, using a ratio substrate/reagent of approximately 1:1, led mainly to the conjugated addition product 13, as a diastereomeric mixture similar to that obtained formerly[3,8].

In an attempt to obtain the corresponding cyclopropane bis-lactone, we have increased the ratio substrate/reagent. Thus, when the bromofuranone 1 and diethylamine were reacted in a 2:1 ratio, in the presence of potassium carbonate and tetrabutylammonium bromide, the main product was the cyclopropane bis-lactone 16.



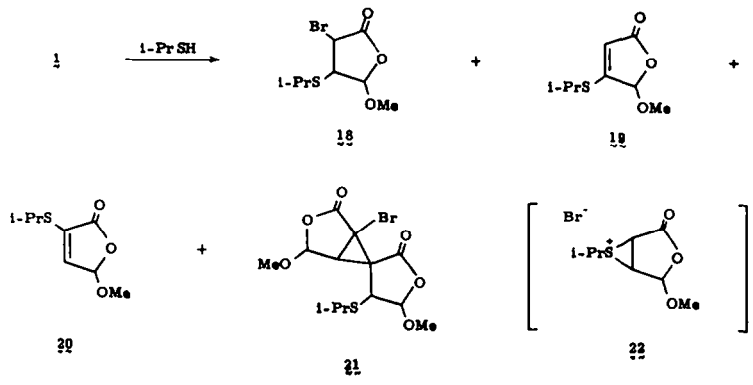
Presumably, the initial reaction in this case is also the conjugated addition to give 13. This adduct is then deprotonated under the basic conditions, and the enolate 14 undergoes a second Michael addition to the bromofuranone 1 to give the bis-lactone enolate 15, which by subsequent ring closure is converted into 16.

In order to confirm the proposed pathway, we have obtained first an approximately equimolar mixture of the adduct 13 and the bromofuranone 1 by reacting diethylamine with 2 molar equiv. of 1 in acetonitrile at room temperature. Subsequent treatment of this mixture with potassium carbonate and tetrabutylammonium bromide also afforded the cyclopropane bis-lactone 16 as the main product.

Sulphur nucleophiles

A previous report from our laboratory[3] indicated that the bromofuranone 1 reacted readily with thiols, in the presence of thiolate as catalyst, to give the expected Michael adduct as a diastereomeric mixture.

In contrast, we have found that the reaction of 1 with propane-2-thiol in a ratio of approximately 1:1, in the above solid-liquid two-phase system, afforded after chromatography



the expected Michael adduct 18 and the 4-isopropylthiofuranone 19 as main components; in addition, minor amounts of the 3-isopropylthiofuranone 20 and the cyclopropane bis-lactone 21 could also be isolated. Compounds 19, 20 and 21 are presumably originated from the initial adduct 18; thus, 4-isopropylthiofuranone 19 might arise by HBr elimination and the formation of the cyclopropane bis-lactone 21 can be explained in terms of initial deprotonation of 18 followed by Michael addition to 1 and ring closure, as postulated for 7, 8, 11, 12 and 16. The formation of the unexpected 3-isopropylthiofuranone 20 can be rationalized from 18 by nucleophilic substitution of the halogen, followed by thiol elimination or, alternatively, via intramolecular substitution of the halogen through an intermediate as 22.

On the other hand, when the above reaction was effected with two molar equiv. of bromofuranone 1 for 1 equiv. of propane-2-thiol, under the same conditions, a mixture was obtained which, after chromatography, afforded the cyclopropane bis-lactone 21 (47%) and compound 19 (25%) as major components.[10]

Formation of the bis-lactone 21 via the Michael aduct 18 was also confirmed in this case. In fact, when an equimolar mixture of the bromofuranone 1 and the Michael adduct 18 (previously obtained by thiolate catalyzed addition of the thiol to 2 molar equiv. of 1) was treated with potassium carbonate and tetrabutylammonium bromide, the cyclopropane bis-lactone 21 was also obtained in 39% yield.

CONCLUSIONS

The bromofuranone 1 behaves as an excellent Michael acceptor towards carbon, oxygen, nitrogen and sulphur nucleophiles. Under the above conditions, the conjugate addition of the nucleophile to the bromofuranone 1 leads, in a first step, to an intermediate of the type 3 but the course of the reaction is dependent upon the nucleophile.

When an anion, such as a carbanion or an alkoxide ion, is used as nucleophile, the carbanionic intermediate of type 3, in the absence of a proton donor, adds to a second molecule of bromofuranone 1 to give a new anionic intermediate 4. This intermediate, at room temperature, suffers an internal nucleophilic substitution of the halogen to yield the cyclopropane derivative 7, 8, 11 or 12. By contrast, when the anionic intermediate 4 generated under basic conditions, is protonated at low temperature (<-40° C) the double addition product 6 is produced.

When 1 reacts with a nitrogen or sulphur nucleophile, in a 1:1 ratio, the initial intermediate of the type 3 is readily protonated to give as main components the Michael adduct 13 or 18 and/or the respective HBr elimination product 17 or 18. However, under the conditions used, an equilibrium is established between the Michael adduct and the carbanionic

intermediate of type 3. Thus, the formation of cyclopropane derivatives by using a 2:1 ratio bromofuranone/nucleophile occurs by addition of this carbanion to a second molecule of 1 followed by ring closure.

EXPERIMENTAL

Melting points have been determined on a Kofler hot stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 257 grating spectrophotometer, $\bar{\nu}$ values in cm^{-1}. ^{1}H-NMR were obtained in $CDCl_3$ solution on a Varian EM-390 spectrometer or on a Brucker WM 200 SY. Signals are reported in δ units with TMS = 0 ppm as internal standard. Mass spectra were recorded on a Hewlett-Packard 5985 GC-MS System. 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 t.l.c., respectively.

Reactions of 3-bromo-5-methoxyfuran-2(5H)-one with nucleophiles. General Procedure.

The furanone 1 (0.58 g, 3 mmol) is added to a stirred mixture of finely powdered anhydrous potassium carbonate (1.66 g, 12 mmol), tetrabutylammonium bromide (48 mg, 0.15 mmol) and the nucleophile in acetonitrile (6 ml). The mixture is kept at room temperature with stirring until a practically constant concentration of the starting furanone 1 is attained (consumption of 1 is monitored by t.l.c. or g.l.c.). After addition of acetonitrile (60 ml), the reaction mixture is filtered and the salts are washed with the same solvent (20 ml). The solvent is removed under reduced pressure to yield the crude mixture.

Reaction of 1 with methyl 1,3-dithiane-2-carboxylate

a) Molar ratio furanone/dithiane 1:1; reaction time 4 days. The crude mixture obtained following the general procedure is chromatographed on silica gel (carbon tetrachloride-ethyl acetate 10:1) to afford pure compound 7 in 50% yield.

Cyclopropane bis-lactone 7.- M.p. 184-186°C (from cyclohexane). (Found: C, 39.95; H, 3.93; S, 13.19; Br, 16.59. Calcd. for $C_{16}H_{19}O_8S_2Br$: C, 39.75; H, 3.93; S, 13.25; Br, 16.56). IR (KBr): 3070 ([C - H); 1800, 1780, 1730 (C=O). ^{1}H-NMR: 6.03 (s, 1H, C-5'); 5.74 (s, 1H, C-4); 3.78 (s, 3H, CO_2CH_3); 3.55, 3.53 (2s, 3H, 3H, OCH_3); 3.22 (s, 1H, C-5); 2.95 (s, 1H, C-4'); 3.35-2.60 (m, 4H, CH_2S); 2.20-1.75 (m, 2H, CH_2). Irradiation into the methine signal at δ 2.95 (H-4') caused a NOE-enhancement (19%) of the H-4 signal at δ 5.74. ^{13}C-NMR: 168.75, 168.57, 167.72 (C=O); 104.76, 101.97 (C-4, C-5'); 56.56 (OCH_3); 53.97 (C$\lesssim^{S}_{S}$); 53.41 (CO_2CH_3); 52.52 (C-4', J_{C-H} = 118); 40.10, 35.81 (C-1, C-6); 38.39 (C-5, J_{C-H} = 176); 27.56 (CH_2S); 23.38 (CH_2). MS, m/z: 482-484 (M^+), 451-453, 423-425, 403, 177 (100).

Using molar ratios furanone/dithiane 2:1 (7 days) and 1:2 (2 days), compound 7 was obtained in 48% and 51% yield, respectively.

b) A solution of furanone 1 (3 mmol) in tetrahydrofuran (5 ml) is added dropwise at -76°C under argon, to a solution of methyl 2-lithio-1,3-dithiane-2-carboxylate[4] (1.5 mmol) in the same solvent (14 ml). After 1 h at -76°C, a portion is quickly quenched by adding saturated ammonium chloride solution and after work-up the main product is shown to be the dibromo bis-lactone 6 (^{1}H-NMR). The remainder solution is allowed to reach -15°C (ca. 3 h). After work-up the crude product consists of a 1:2 mixture of compounds 6 and 7 (^{1}H-NMR).

Reaction of 1 with diethyl malonate

Molar ratio furanone/diethyl malonate 1:1; reaction time 5 h. The crude mixture obtained following the general procedure, which contains compounds 8 and 9 (70:30 by ^{1}H-NMR), is separated by short column chromatography (petroleum ether-ethyl acetate 8:1).

Cyclopropane bis-lactone 8.- Yield 62%, m.p. 136-138°C (from cyclohexane-benzene). (Found: C, 44.11; H, 4.75; Br, 16.90. Calcd. for $C_{17}H_{21}O_{10}Br$: C, 43.89; H, 4.55; Br, 17.18). IR (nujol): 3070 ([C - H); 1805, 1785, 1740 (C=O). ^{1}H-NMR: 5.66, 5.47 (2s, 1H, 1H, C-4 and C-5'); 4.23, 4.21 (2q, 4H, $CO_2CH_2CH_3$, J = 7.2); 3.57, 3.53 (2s, 3H, 3H, OCH_3); 3.32 [d, 1H, CH ($CO_2C_2H_5)_2$, J = 4.2]; 3.10 (s, 1H, C-5); 2.74 (d, 1H, C-4'); 1.28 (t, 6H, $CO_2CH_2CH_3$). ^{13}C-NMR: 168.84, 167.72, 166.41, 166.38 (C=O); 104.76, 100.18 (C-4, C-5'); 63.06, 62.53 ($CO_2CH_2CH_3$); 56.93, 56.89 (OCH_3); 50.44, 44.42 [CH($CO_2C_2H_5)_2$, C-4']; 37.96 (C-5); 37.66, 34.36 (C-1, C-6); 13.93, 13.70 ($CO_2CH_2CH_3$). MS, m/z: 464-466 (M^+), 436-438, 433-435, 279, 143, 85 (100).

Cyclopropane lactone 9.- Yield 24%, m.p. 72-74°C (from cyclohexane). (Found: C, 52.93; H, 6.07. Calcd. for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92). IR (nujol): 3115 ([C - H); 1805, 1740 (C=O). ^{1}H-NMR: 5.34 (s, 1H, C-4); 4.23 (q, 4H, $CO_2CH_2CH_3$, J = 7.2); 3.52 (s, 3H, OCH_3);

2.83 (s, 2H, C-1, C-5); 1.27 (t, 6H, $CO_2CH_2\underline{CH_3}$). ^{13}C-NMR: 169.69, 165.98, 163.53 (C=O); 102.32 (C-4); 63.07, 62.67 ($CO_2\underline{CH_2}CH_3$); 56.85 (OCH_3); 38.16 (C-6); 34.28 (C-1); 29.53 (C-5); 13.96, 13.75 ($CO_2CH_2\underline{CH_3}$). MS, m/z: 271 $(M-1)^+$, 241, 228, 199, 123 (100).

Reaction of 1 with methyl chloroacetate and bromoacetate

Molar ratio furanone/haloester 1:1; reaction time 19 and 12 days, respectively. The crude mixture obtained following the general procedure is chromatographed on a short column (petroleum ether-ethyl acetate 3:1) to afford compound 12. The yields are 30% and 32% from methyl chloroacetate and bromoacetate, respectively.

Cyclopropane bis-lactone 12. - M.p. 175-177°C (from cyclohexane-benzene). (Found: C, 39.65; H, 3.87; Br, 20.01. Calcd. for $C_{13}H_{15}O_9Br$: C, 39.51; H, 3.83; Br, 20.22). IR (nujol): 3070 (>C-H); 1790, 1750 (C=O). ^{1}H-NMR: 5.86, 5.48 (2s, 1H, 1H, C-4 and C-5'); 4.20, 4.07 (AB system, $OCH_2CO_2CH_3$, J = 16.2); 3.77 (s, 3H, CO_2CH_3); 3.72 (s, 1H, C-4'); 3.58, 3.54 (2s, 3H, 3H, OCH_3); 3.12 (s, 1H, C-5). ^{13}C-NMR (DMSO-d_6): 169.54, 168.31, 167.34 (C=O); 103.97, 101.07 (C-4, C-5'); 79.23 (C-4'); 66.01 ($OCH_2CO_2CH_3$); 56.36, 56.14 (OCH_3); 51.57 (CO_2CH_3); 38.54, 33.77 (C-1, C-6); 36.29 (C-5). MS, m/z: 394-396 (M^+), 363-365, 335-337, 305-307 (100), 255,197.

Reaction of 1 with methanol

Molar ratio furanone/methanol 1:1; reaction time 36 h. The crude mixture obtained following the general procedure is chromatographed on silica gel (toluene-acetone 10:1) to yield compound 11 (56%) as a 9:1 mixture of two diastereomers, 11a and 11b eluted successively. By using a molar ratio furanone/methanol 1:2, the same result is obtained in 24 h.

Cyclopropane bis-lactone 11a. - M.p. 213-216°C (from cyclohexane). (Found: C, 39.29; H, 4.09; Br, 23.88. Calcd. for $C_{11}H_{13}O_7Br$: C, 39.17; H, 3.86; Br, 23.74), IR (KBr): 3100, 3040 (>C-H); 1790 (C=O). ^{1}H-NMR: 5.55, 5.43 (2s, 1H, 1H, C-4 and C-5'); 3.58, 3.55 (2s, 3H, 3H, OCH_3); 3.53 (s, 1H, C-4'); 3.43 (s, 3H, OCH_3); 3.11 (s, 1H, C-5). ^{13}C-NMR: 168.45, 167.70 (C=O); 104.02, 101.01 (C-4, C-5'); 82.13 (C-4'); 57.54, 56.74, 56.66 (OCH_3); 37.97 (C-5); 38.49, 33.97 (C-1, C-6). MS, m/z: 305-307 $(M-31)^+$, 273-275, 248-250, 247-249 (100), 197, 169, 125, 109, CIMS (CH_4) m/z: 337-339 $(M+1)^+$.

Cyclopropane bis-lactone 11b. - IR (film): 3090, 3030 (>C-H); 1795 (C=O). ^{1}H-NMR: 5.29, 5.10 (2s, 1H, 1H, C-4 and C-5'); 3.49 (s, 6H, OCH_3); 3.47 (s, 1H, C-4'); 3.39 (s, 3H, OCH_3); 2.82 (s, 1H, C-5). MS, m/z: 248-250 $(M-88)^+$, 247-249 (100), 197, 157, 125, 109. CIMS (CH_4), m/z: 337-339 $(M+1)^+$.

Reaction of 1 with diethylamine

a) Molar ratio furanone/diethylamine 1:1; reaction time 90 min. The crude mixture (650 mg) obtained following the general procedure consists mainly of 3-bromo-4-diethylamino-5-methoxytetrahydrofuran-2-one (13) as a diastereomeric mixture[3] (^{1}H-NMR). After chromatography under pressure (hexane-benzene-acetone 5:2:2) a mixture of bromofuranone 1, adduct 13 and 4-diethylamino-5-methoxyfuran-2 (5H)-one (17)[9] is obtained in a ratio of approximately 64:24:12.

b) Molar ratio furanone/diethylamine 2:1; reaction time 2 days. The mixture obtained according to the general procedure is triturated with chloroform and the solution filtered on Florisil to yield the bis-lactone 16 (60%). An analytical sample is obtained by chromatography on silica gel under pressure (toluene-ethyl acetate 10:0.5).

Cyclopropane bis-lactone 16. - M.p. 141-143°C (from cyclohexane). (Found: C, 44.29; H, 5.03; N, 3.53; Br, 20.99. Calcd. for $C_{14}H_{20}O_6NBr$: C, 44.44; H, 5.29; N, 3.70; Br, 21.16). IR (nujol): 3080 (>C-H); 1790, 1780 (C=O). ^{1}H-NMR: 5.92, 5.43 (2s, 1H, 1H, C-4 and C-5'); 3.55, 3.51 (2s, 3H, 3H, OCH_3); 3.25 (s, 1H, C-4'); 3.07 (s, 1H, C-5); 2.68, 2.50 (2m, 4H, NCH_2CH_3, J = 13.1, J = 7.1); 1.05 (t, 6H, $NCH_2\underline{CH_3}$. J = 7.1). ^{13}C-NMR: 170.02, 167.88 (C=O); 102.75, 100.46 (C-4, C-5'); 64.92 (C-4'); 56.52, 56.46 (OCH_3); 43.34 ($N\underline{CH_2}CH_3$); 37.78 (C-5); 36.37, 34.99 (C-1, C-6); 13.20 ($NCH_2\underline{CH_3}$). MS, m/z: 377-379 (M^+), 376-378, 346-348, 298, 258-260, 225 (100), 197, 166.

c) Diethylamine (1.5 mmol) is added to bromofuranone 1 (3 mmol) in acetonitrile (6 ml). After 15 min, this mixture (which contains adduct 13 and bromofuranone 1 in a ca. 1:1 ratio) is treated with anhydrous potassium carbonate (1.66 g, 12 mmol) and tetrabutylammonium bromide (48 mg, 0.15 mmol). The mixture is kept at room temperature, with stirring, during 2 days. After work-up, the crude bis-lactone 16 is obtained in 69% yield.

Reaction of 1 with propane-2-thiol

a) Molar ratio furanone/thiol 1:1; reaction time 90 min. The crude mixture obtained following the general procedure is chromatographed on silica gel (toluene-ethyl acetate 10:0.5) to yield: 4-isopropylthiofuranone 19 (40%)[9], 3-bromo-4-isopropylthiotetrahydrofuranone 18 (13%)[3], 3-isopropylthiofuranone 20 (9%)[9], cyclopropane bis-lactone 21 (4%) and recovered

bromofuranone 1 (17 mg).

Cyclopropane bis-lactone 21.- M.p. 168-170ºC (from cyclohexane). (Found: C, 40.62; H, 4.64; S, 8.10; Br, 21.29. Calcd. for $C_{13}H_{17}O_6SBr$: C, 40.94; H, 4.46; S, 8.40; Br, 21.00). IR (KBr): 3020 ([C-H); 1790 (C=O). ^{1}H-NMR: 5.89, 5.42 (2s, 1H, 1H, C-4 and C-5'); 3.58, 3.55 (2s, 3H, 3H, OCH_3); 3.09, 3.08 (2s, 1H, 1H, C-4' and C-5); 3.07 [m, 1H, $SCH(CH_3)_2$]; 1.32 (d, 3H, $SCH-CH_3$, J = 7.5); 1.30 (d, 3H, $SCH-CH_3$, J = 6.8). ^{13}C-NMR: 168.22, 167.58, (C=O); 108.25, 100.43 (C-4, C-5'); 56.63 (OCH_3); 47.11, 37.15, 36.42 [C-4', C-5, $SCH(CH_3)_2$]; 38.49, 34.41 (C-1, C-6); 23.30, 23.17 [$SCH(CH_3)_2$]. MS, m/z: 380-382 (M^+), 349-351, 291-293, 277-279, 249-251, 241, 181, 167 (100).

b) Molar ratio furanone/thiol 2:1; reaction time 6 h. The crude mixture is separated by column chromatography on silica gel (toluene-ethyl acetate 10:0.5) to afford cyclopropane bis-lactone 21 (47%), 4-isopropylthiofuranone 19 (25%), 3-isopropylthiofuranone 20 (11%) and 5-methoxyfuran-2 (5H)-one (9%).

c) To a solution of bromofuranone 1 (1.93 g, 10 mmol) in acetonitrile (14 ml) is added propane-2-thiol (0.38 g, 5 mmol) in the same solvent (6 ml) and sodium propane-2-thiolate (98 mg, 1 mmol). After stirring 3 h at room temperature, tetrabutylammonium bromide (161 mg, 0.5 mmol) and anhydrous potassium carbonate (5.52 g, 40 mmol) are added. The mixture is kept with stirring at room temperature until complete consumption of the adduct 18 (monitored by t.l.c.). The solution is filtered on Florisil and the solvent is removed in vacuo. The crude mixture is chromatographed on silica gel under pressure (toluene-ethyl acetate 10:0.5) to afford cyclopropane bis-lactone 21 (38%) and 4-isopropylthiofuranone 19 (37%).

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REFERENCES AND NOTES

1. Part XXII: F. Fariña, M.V. Martín, M.C. Paredes, M.C. Ortega and A. Tito, Heterocycles, 22, 1733 (1984).
2. F. Fariña, M.C. Maestro, M.R. Martín, M.V. Martín and F. Sánchez, J. Chem. Research, (S) 188; (M) 2662 (1980).
3. F. Fariña, M.C. Maestro, M.R. Martín, M.V. Martín and F. Sánchez, Heterocycles, 20, 1761 (1983).
4. F. Fariña, M.C. Maestro, M.R. Martín, M.V. Martín and F. Sánchez, J. Chem. Research, (S) 44; (M) 0534 (1984).
5. J. González, F. Sánchez and T. Torres, Synthesis, 911 (1983).
6. M. Fedorynski, K. Wojciechowski, Z. Matazac and M. Makosza, J. Org. Chem., 43, 4682 (1978).
7. M. Joucla, B. Fouchet, J. Le Brun and J. Hamelin, Tetrahedron Lett., 25, 1221 (1985).
8. The adduct 13 is rather unstable, and during purification by column chromatography in part undergoes HBr elimination and a reverse Michael addition to afford 4-diethylamino-5-methoxyfuran-2(5H)-one[9] (17) and the starting furanone 1, respectively.
9. F. Fariña, M.C. Maestro, M.R. Martín, M.V. Martín and F. Sánchez, Synthesis, 397 (1983).
10. Minor amounts of 3-isopropylthiofuranone 20 (11%) and 5-methoxy-2 (5H)-furanone (9%) were also isolated by chromatography.