Heterocyclic Compound Studies. II. Synthesis of 1,4-Benzodioxin, 1,4-Benzoxathiin, 1,4-Benzoxazine and 1,4-Benzothiazine Derivatives

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Benzocondensed six-membered heterocyclic rings containing two heteroatoms have been synthesized by a generally applicable method starting from disubstituted benzene compounds and methyl 4-chlorobutynoate (**1**) or methyl 4-bromobutenoate (**2**). The reactions with **1** yield a mixture of *endo* and *exo* (*E* or *Z*) isomers. The ^{13}C nmr spectroscopy was used to assign the structure of the synthesized compounds.

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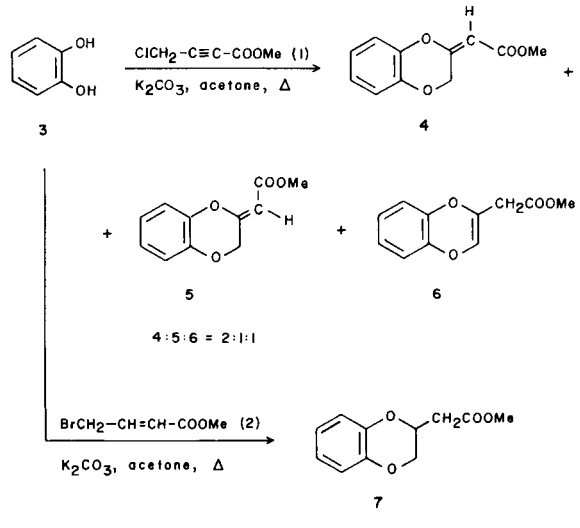
Several years ago a study on the synthesis and reactivity of potentially biologically active compounds, namely the benzocondensed five-, six- or seven-membered heterocyclic compounds containing two heteroatoms, was undertaken [1-6]. Literature results show that upon reaction of bifunctional benzene compounds and acetylene derivatives five- or six-membered heterocyclic rings are obtained depending on the type of functional group present on the aromatic ring: thus, 1,2-benzenediols and 2-hydroxybenzenethiols yield exclusively five-membered heterocycles [2,3], while compounds with amino groups yield six-membered heterocycles [7-10]. The same substrates react also with halogenated aliphatic esters or ketones yielding again either five- or six-membered heterocyclic compounds [1,3,4,11,12].

In order to devise a general synthetic method for the preparation of benzocondensed six-membered heterocyclic compounds which may or may not contain the amino group, we have determined the reaction products obtained upon reaction of several bifunctional benzene compounds with methyl 4-chlorobutynoate (**1**) or methyl 4-bromobutenoate (**2**). The latter compounds belong to classes of compounds rarely used so far in the synthesis of this type of heterocyclic rings [13-16]; on the other hand their structure, an activated unsaturated centre (with probable attack on the 3-carbon) next to a carbon atom having a good halogen leaving group, suggested their likely ability to the formation of six-membered rings.

Scheme I



Equimolar amounts of 1,2-benzenediol (**3**) and **1** in boiling anhydrous acetone in the presence of anhydrous potassium carbonate or in cold (−10°) *N*,*N*-dimethylformamide in the presence of sodium hydride yield three 1,4-benzodioxinic products (Scheme 1): the *E* and *Z* **4**, **5** isomers and the *endo* isomer **6**.

They are easily isolated in pure form from the reaction mixture by column chromatography in the 2:1:1 ratio.

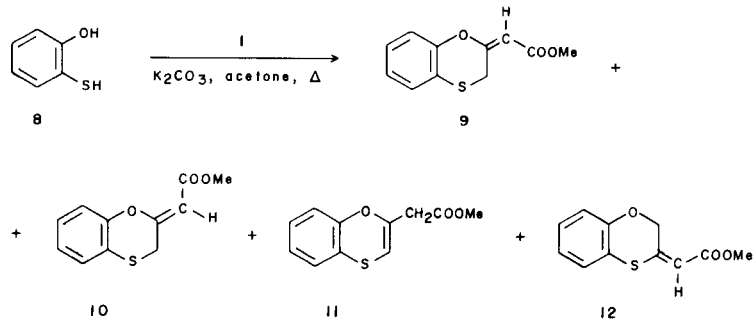
Under the same experimental conditions (acetone, potassium carbonate, reflux) **3** and **2** yield only the expected ester **7**.

The reaction of 2-hydroxybenzenethiol (**8**) with **1** yield four 1,4-benzoxathiinic isomeric products **9**, **10**, **11**, **12** in the 5:1:1:4 ratio (Scheme 2). Compounds **9** and **10** have been easily isolated and purified by column chromatography, while **11** and **12** could not be separated by this method and have been identified by ^{13}C nmr spectroscopy. Their molar ratio was determined by ^{13}C nmr spectroscopy and gas-chromatography.

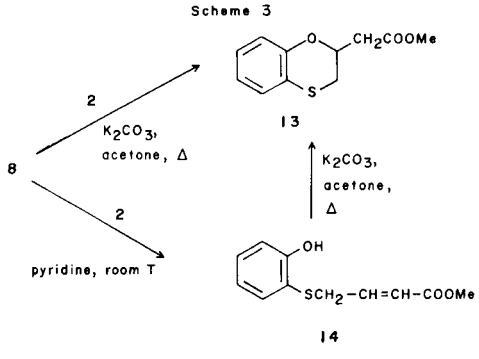
The reaction of **8** with **2** yield only compound **13** (Scheme 3).

2-Methylaminophenol (**15**) reacts with **1** yielding exclusively compound **16** (the *E* isomer), and with **2** yielding compound **17** (Scheme 4).

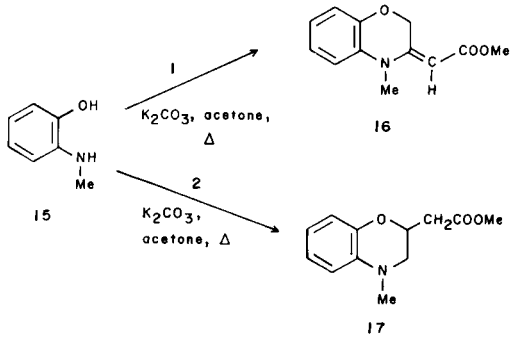
Scheme 2



Scheme 3



Scheme 4

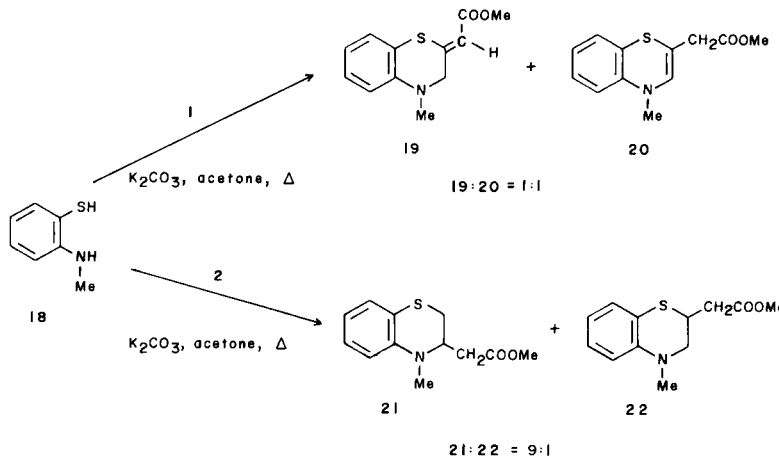


The reaction of 2-methylaminobenzenethiol (**18**) displayed lower selectivity. In fact, it reacts with **1** yielding both *Z* isomer **19** and the *endo* isomer **20** in the 1:1 ratio (Scheme 5). It is worth noticing that this is the only case where the *E* isomer cannot be observed. Compound **18** and **2** yield a mixture of **21** and **22** in a 9:1 ratio.

From the results the following considerations can be drawn:

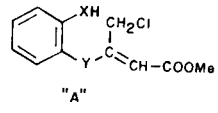
i) The nucleophile **3**, **8**, **15** or **18** reacts with the halogenated ester **2** *via* a nucleophilic substitution at the halogenated carbon followed by a Michael addition at the 3-carbon atom. This is justified by the isolation of the intermediate **14** in the reaction between **2** and **8** in pyridine and its following easy transformation in the final heterocyclic product **13** upon reflux in acetone in the presence of potassium carbonate. ii) The reactions of **2** are fairly selective. It looks like the first substitution is determined by the relative nucleophilicity of the nucleophilic groups of the bifunctional benzenes. iii) The results for the reactions of bifunctional benzenes on **1** agree with data from the literature which indicate that simple thiols, amines and phenols attack exclusively at 3-carbon atom of **1** with relative reactivity S > N ≃ O [15,16]. In the case of bifunctional ben-

Scheme 5



zenes the preliminary attack is followed by a nucleophilic substitution of the halogen at the 4-carbon atom. The variety of isomers and their relative abundance is due to the relative nucleophilicity of the attacking element of the nucleophilic group.

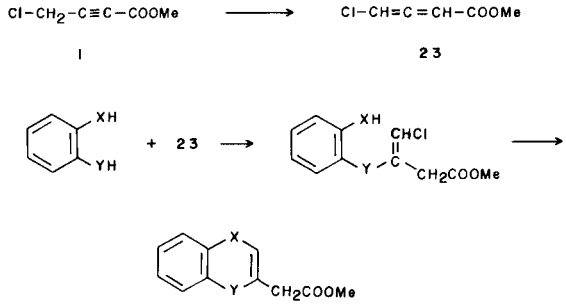
We should mention that the experimental conditions used in this work did not allow us to isolate intermediate "**A**" which would support the proposed mechanism.



"A"

iv) The formation of the *exo* (*E* and *Z*) isomers was expected among the product **1** and is in accord with the formation of intermediate "**A**". On the other hand the formation of the *endo* isomer cannot be accounted for by a simple necleophilic substitution reactions of **1**. It is possible that in the reaction medium **1** undergoes partial isomerization into the corresponding allene **23** [17], followed by nucleophilic attack at the *sp* carbon atom and subsequent ring closure (Scheme 6).

Scheme 6



The formation of the *E* isomer is almost always preferred. This kinetic preference is paralleled by a greater thermodynamic stability. In fact, the *Z* and *endo* isomers tend to isomerize to yield the *E* isomer. In fact, the *endo* isomer **6** tends to isomerize into the corresponding *exo* isomer **4** upon treatment with triethylamine. Compounds **10** and **11** slowly isomerize into **9**; addition of triethylamine accelerates the reaction. An exception is the reaction of **18** where only the *Z* and *endo* isomers have been isolated. Further work is in progress with the aim to collect further evidence in this contest.

In order to determine the structure of the discussed compounds we resorted to ^{13}C nmr spectroscopy. Chemical shifts [18] and multiplicity of the proton coupled spectra, together with a crossed comparison of the data (see Table 1), permitted an easy assignment of all resonance frequences in the aliphatic region for the compounds obtained in the reaction of **2**. We did not attempt to assign every single peak in the aromatic region of the spectra. It is worth while noticing that $^1Js_{CH}$ show a trend which is characteristic for each type of carbon. Particularly, all methylene carbons bound to ethereal groups have $^1J_{CH}$ values around 130 ± 2 Hz, while other methylenes have a wider range (142.5 ± 5 Hz) with single values depending on the heteroatom bound to the 1-carbon and the two ranges do not overlap with each other. We notice also that when the carbon atom is adjacent to nitrogen, $^1J_{CH}$ values are minimal for both methylene and methyne carbons. This holds also when methylenes are bound to a sulfur atom, in good agreement with the literature [19]. Analysis of $^nJ_{CH}$ was unnecessary and, as proton spectra are second order, we did not attempt it. We are aware that $^1J_{CH}$ values have a confidence of ± 5 Hz.

Table 1

^{13}C NMR Spectral Data [a] of Compounds Obtained from **2**

Compound No.	Signals
7	35.6 (*C*H_2-CO, ^1J = 128.7 Hz), 51.5 (O-*C*H_3, ^1J = 147.6 Hz), 66.7 (O-*C*H_2, ^1J = 147.5 Hz), 69.3 (O-*C*H, ^1J = 151.3 Hz), 116-142.3 (aromatics), 177.0 (*C*OO)
13	25.0 (S-*C*H_2, ^1J = 141.3 Hz), 39.0 (*C*H_2-CO, ^1J = 130.0 Hz), 51.1 (O-*C*H_3, ^1J = 146.3 Hz), 70.2 (O-*C*H, ^1J = 152.3 Hz), 116.2-150.0 (aromatics), 168.9 (*C*OO)
17	37.6 (*C*H_2-CO, ^1J = 129.3 Hz), 38.2 (N-*C*H_3, ^1J = 135.0 Hz), 51.2 (O-*C*H_3, ^1J = 147.6 Hz), 52.6 (N-*C*H_2, ^1J = 137.7 Hz), 68.8 (O-*C*H, ^1J = 151.0 Hz), 111.5-142.5 (aromatics), 169.3 (*C*OO)
21 [b]	27.3 (S-*C*H_2, ^1J = 145.0 Hz), 34.3 (*C*H_2-CO, ^1J = 132.0 Hz), 37.4 N-*C*H_3, ^1J = 135.9 Hz), 49.7 (O-*C*H_3, ^1J = 147.0 Hz), 53.2 (N-*C*H, ^1J = 140.0 Hz), 108.1-141.2 (aromatics), 170.3 (*C*OO)

[a] All the spectra were obtained in deuteriochloroform. Chemical shifts are in ppm (δ) downfield from hexamethyldisiloxane. "J have not been analyzed (see discussion). [b] A small amount (10%) of isomer **22** is mixed together so that accuracy is smaller.

A more difficult task was the structure attribution for the group of reactions with **1**. In this case we had to face the formation of a variety of isomers, as discussed in the general part. The large difference in chemical shift for *endo*- or *exo*-cyclic vinylic carbons [18] made it possible to discriminate between these two groups (see Table 2). Chemical shift criteria based on the methylene carbons allowed to distinguish between the different possible positional isomers. They were also a further mean to distinguish between the *exo* and *endo* double bond compounds.

Eventually we have to assign the *E* or *Z* configuration to the *exo* double bond compounds. While, as already noted, the *exo* position of the double bond was assigned on a chemical shift basis, in order to chose between the *E* and *Z* isomers it was convenient to study $^3J_{CH}$ values of the vinylic proton and the methylenic carbon. In this case it

was an easy task, for the proton spectra are virtually first order. It is firmly established in the literature [20] that this coupling constant is larger in the *E* than in the *Z* form (*E* and *Z* refer in this discussion to the two coupled atoms). When both isomers were obtained, the attribution was clear cut. In one case (compound **4**) configuration was confirmed by X-ray analysis [21].

When we had only one isomer, we assumed that $^3J_{CH}$ values of more than 7 or less than 5 Hz were sufficient proof of *E* or *Z* isomers respectively. This was inferred from the literature [20] as well as from our own data. In fact, in one case (compound **16**) the configuration was determined by X-ray analysis [21].

We can note that $^3J_{CH}$ between methylenic protons and vinylic carbons are too small to be measured accurately for the *exo* double bond compounds. On the other hand they are well resolved for the *endo* compounds. This is a further proof for the structure of compound **20** which could not be identified with certainty by other criteria. For this compound, in fact, large values have been observed for both $^1J_{CH}$ for =C-H (199.9 Hz) and the $^3J_{CH}$ (6.2 Hz) for the methylenic carbon and the vinylic proton.

Compounds **11** and **6** have also a quite large $^1J_{CH}$ values for =C-H (180.0 + 2 Hz) compared to the mean value of the *exo* compounds ($^1J_{CH}$ = 161 ± 5 Hz). This is due to the fact that the protonated vinylic carbon for the *endo* double bond compounds is flanked by a heteroatom instead of a carbon. This is a further proof for the assigned structures to compounds **11** and **6**. For compound **19** the structure assignment is only a tentative one as, during the accumulation time necessary to obtain the ^1H coupled ^{13}C spectrum, the substance partly decomposed. For this reason in the table are reported only the few signals whose chemical shifts and J values are compatible with and support the assigned structure.

Table 2

^{13}C NMR Spectral Data [a] of Compounds Obtained from **1**

Compound No.	Signals
4	49.3 (COO*C*H$_3$, ^1J = 143.0 Hz), 59.1 (O-*C*H$_2$, ^1J = 153 Hz, ^3J = 7 Hz) 95.6 (C=*C*H, ^1J = 158 Hz, ^3J unresolved), 114.1-142.2 (aromatics) 159.1 (*C*=CH, ^2J unresolved), 165.1 (*C*OO)
5	51.0 (COO*C*H$_3$, ^1J = 148 Hz), 64.9 (O-*C*H$_2$, ^1J = 151 Hz, ^3J = 4 Hz), 96.1 (C=*C*H, ^1J = 164 Hz, ^3J unresolved), 117.0-142.7 (aromatics), 155.4 (*C*=CH, ^2J unresolved), 164.5 (*C*OO)
6	33.1 (=C-*C*H$_2$, ^1J = 126 Hz, ^3J = 2 Hz), 50.4 (COO*C*H$_3$, ^1J = 145 Hz), 114.1-140.2 (aromatics), 122.2 (C=*C*H, ^1J = 180 Hz, ^3J = 5 Hz), 123.6 (*C*=CH, ^2J unresolved), 167.6 (*C*OO)
9	23.8 (S*C*H$_2$, ^1J = 149 Hz, ^3J = 7.5 Hz), 50.4 (COO*C*H$_3$, ^1J = 142 Hz), 96.2 (C=*C*H, ^1J = 158 Hz, ^3J unresolved), 117.9-150.7 (aromatics), 163.4 (*C*=CH, ^2J unresolved), 168.6 (*C*OO)
10	27.1 (S*C*H$_2$, ^1J = 144.4 Hz, ^3J = 4.1 Hz), 48.4 (COO*C*H$_3$, ^1J = 146 Hz), 92.6 (C=*C*H, ^1J = 163 Hz, ^3J unresolved), 114.9-140.0 (aromatics), 146.6 (*C*=CH, ^2J unresolved), 153.3 (*C*OO)
11 [b]	36.6 (=C-*C*H$_2$, ^1J = 130 Hz, ^3J = 3.4 Hz), 49.5 (COO*C*H$_3$, ^1J = 147.6 Hz), 92.2 (C=*C*H, ^1J = 179 Hz, ^3J = 4.5 Hz)
12	49.6 (COO*C*H$_3$, ^1J = 142 Hz), 67.9 (O-*C*H$_2$, ^1J = 148 Hz, ^3J = 7.3 Hz), 108.3 (C=*C*H, ^1J = 166 Hz, ^3J unresolved), 116.5-147.8 (aromatics and *C*=CH), 162.6 (*C*OO)
16	33.1 (N-*C*H$_3$, ^1J = 139.2 Hz), 50.5 (COO*C*H$_3$, ^1J = 145.8 Hz), 64.1 (O-*C*H$_2$, ^1J = 152.3 Hz, ^3J = 7.8 Hz), 86.2 (C=*C*H, ^1J = 159.3 Hz, ^3J unresolved), 113.9-146.6 (aromatics), 152.5 (*C*=CH, ^2J unresolved), 167.3 (*C*OO)
19 [c]	37.6 (N-*C*H$_3$, ^1J = 139.8 Hz), 49.4 (COO*C*H$_3$, ^1J = 148.9 Hz), 55.6 (N-*C*H$_2$, ^1J = 135 Hz, ^3J unresolved), 106.6 (C=*C*H)
20	28.7 (N-*C*H$_3$, ^1J = 136.2 Hz), 34.4 (=C-*C*H$_2$, ^1J = 131.2 Hz, ^3J = 6.2 Hz), 45.7 (COO*C*H$_3$, ^1J = 147.3 Hz), 113.0 (C=*C*H, ^1J = 199.9 Hz, ^3J = 5.5 Hz), 100.6-147.9 (aromatics), 127.9 (*C*=CH, ^2J unresolved), 167.8 (*C*OO)

[a] All the spectra were obtained in deuteriochloroform. Chemical shifts are in ppm (δ) downfield from hexamethyldisiloxane. [b] The attribution of other signals is not possible as compound **11** is the minor (20%) component of the mixture. [c] See text.

EXPERIMENTAL

The ^1H and ^{13}C nmr spectra were recorded on a Varian FT 80A spectrometer and the chemical shifts were determined using hexamethyldisiloxane as the internal standard; the ^{13}C nmr spectra were obtained operating at 20 MHz at room temperature in the Fourier transform mode both under conditions of complete proton-noise decoupling as well as in the fully proton coupled mode. The ir spectra were obtained on a Perkin-Elmer Model 1310 spectrophotometer. The glc analyses were performed on a Carlo Erba 4200 instrument equipped with SE-30 column (2 m x 0.2 cm, 10% on carbowax 20 M). Melting points were determined by the capillary method on an electrically heated melting point apparatus (Electrothermal) and are uncorrected. Elemental analyses for CHNS were carried out on a Carlo Erba Model 1106 Elemental Analyzer.

Acetone and *N,N*-dimethylformamide (DMF) were distilled from calcium chloride and from calcium hydride, respectively, prior to use. 1,2-Benzenediol (**3**) was obtained from Carlo Erba and was used directly. Methyl 4-chlorobutynoate (**1**) [22], methyl 4-bromobutenoate (**2**) [23], 2-hydroxybenzenethiol (**8**) [24], 2-methylaminophenol (**15**) [25] and 2-methylaminobenzenethiol (**18**) [26] were prepared by literature procedures.

Reaction of **1** with **3**. Procedure A.

A mixture of **3** (50 mmoles), **1** (50 mmoles), anhydrous potassium carbonate (150 mmoles) and dry acetone (50 ml) was stirred under reflux for about 10 hours. After the acetone was removed under reduced pressure, the residue was poured into water and extracted with ether. The extract was washed (in turn) with 10% aqueous sodium hydroxide, water and dried over anhydrous sodium sulfate. The glc analysis of this ethereal solution showed three peaks in the percentage ratio of 2:1:1. The solvent evaporation *in vacuo* gave a paste (yield 66%), which was chromatographed on a silica gel column using petroleum ether-ether (8:1) as eluent. Elution of the first fraction afforded methyl *E*-2,3-dihydro-1,4-benzodioxin-2-ylidene acetate (**4**) as colourless crystals, yield 33%, mp 35-36°; ir (nujol): 1720 (C=O), 1665 cm^{-1} (C=C).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 64.07; H, 4.88. Found: C, 64.17; H, 4.81.

Elution of a second fraction afforded 1,4-benzodioxin-2-acetic acid

methyl ester (**6**) as a pale yellow oil, yield 16%, bp 115° (6 mm Hg), n_D^{14} = 1.5450; ir (neat): 1745 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 64.07; H, 4.88. Found: C, 63.88; H, 4.79.

This compound gave in almost quantitative yield the *E* isomer **3** after treatment with triethylamine at room temperature.

Elution of the third fraction afforded methyl *Z*-2,3-dihydro-1,4-benzodioxin-2-ylidene acetate (**5**) as colourless crystals, yield 16%, mp 84-86°; ir (nujol): 1720 (C=O), 1660 cm^{-1} (C=C).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 64.07; H, 4.88. Found: C, 64.26; H, 4.75.

Procedure B

A suspension of **3** (22 mmoles) and sodium hydride (60% in mineral oil, 44 mmoles) in dry DMF (50 ml) was stirred at −10° for 10 minutes. The compound **1** was added dropwise to the suspension and the mixture was stirred for 24 hours at −10°. Workup as described for Procedure A gave **4**, **5**, **6** in the percentage ratio of 2:1:1, total yield 61%.

Reaction of **1** with **8**.

The same procedure as for **3** (Procedure A) was employed starting from **8** and **1**. The glc analysis of the ethereal solution showed four peaks in the percentage ratio of almost 5:4:1:1. The solvent evaporation *in vacuo* gave a paste (yield 71%); which was chromatographed on a silica gel column using petroleum ether-ether (6:1) as eluent. Elution of the first fraction gave methyl *E*-2,3-dihydro-1,4-benzoxathiin-2-ylidene acetate (**9**) as pale yellow crystals, yield 32%, mp 68-70°; ir (nujol): 1715 (C=O), 1640 cm^{-1} (C=C).

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 59.44; H, 4.54; S, 14.42. Found: C, 59.35; H, 4.38; S, 14.28.

Elution of a second fraction gave a mixture of two compounds, as a pale yellow oil, in the percentage ratio of 4:1 (glc). The ^{13}C nmr spectra show that the major product is methyl *E*-2,3-dihydro-1,4-benzoxathiin-3-ylidene acetate (**12**) and the minor 1,4-benzoxathiin-2-acetic acid methyl ester (**11**), yield 32%; ir (neat): 1750 (C=O of **11**), 1700 (C=O of **12**), 1660 cm^{-1} (C=C of **12**).

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 59.44; H, 4.54; S, 14.42. Found: C, 59.40; H, 4.60; S, 14.35.

Elution of the third fraction gave methyl *Z*-2,3-dihydro-1,4-benzoxathiin-2-ylidene acetate (**10**) as pale yellow crystals, yield 7%, mp 79-81°; ir (nujol): 1720 (C=O), 1635 cm^{-1} (C=C).

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 59.44; H, 4.54; S, 14.42. Found: C, 59.31; H, 4.42; S, 14.25.

The isomers **10** and **11** gave in almost quantitative yield the *E* isomer **9** within a month, if allowed to stand at room temperature, or within a few hours after treatment with triethylamine.

Reaction of **15** with **1**.

The same procedure as for **3** (Procedure A) was employed starting from **15** and **1**. The glc analysis of the ethereal solution showed one peak. The solvent evaporation *in vacuo* gave a paste, which was chromatographed on a silica gel column using petroleum ether-ether (1:1) as eluent. The elution afforded methyl *E*-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazin-3-ylidene acetate (**16**) as light brown crystals, yield 72%, mp 128°; ir (nujol): 1700 (C=O), 1620 cm^{-1} (C=C).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.97; N, 6.39. Found: C, 65.51; H, 5.96; N, 6.48.

Reaction of **18** with **1**.

The same procedure as for **3** (Procedure A) was employed starting from **18** and **1**. The glc analysis of the ethereal solution showed two peaks in the percentage ratio of 1:1. The solvent evaporation *in vacuo* gave a paste (yield 59%) which was chromatographed on a silica gel column using petroleum ether-ether (7:1) as eluent. Elution of the faster fraction afforded 4-methyl-4*H*-1,4-benzothiazin-2-acetic acid methyl ester (**20**) as brown crystals, yield 25%, mp 55-58°; ir (nujol): 1745 cm^{-1} (C=O).

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.56; N, 5.95; S, 13.62. Found: C, 61.09; H, 5,41; N, 5.80; S, 13.49.

Elution of the slower fraction gave methyl *Z*-3,4-dihydro-4-methyl-2*H*-1,4-benzothiazin-2-ylidene acetate (**19**) as brown crystals, yield 25%, mp 84-85°; ir (carbon tetrachloride): 1740, 1700 (C=O), 1660 cm^{-1} (C=C).

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.56; N, 5.95; S, 13.62. Found: C, 61.14; H, 5.48; N, 5.88; S, 13.43.

Reaction of **2** with **3**.

A mixture of **2** (40 mmoles), **3** (40 mmoles), anhydrous potassium carbonate (120 mmoles) and dry acetone (40 ml) was worked up in the same manner above described (Procedure A). The glc analysis of the ethereal solution showed one peak. The solvent evaporation *in vacuo* gave a product, which was purified by column chromatography through silica gel. On elution with petroleum ether-ether (3:1), 2,3-dihydro-1,4-benzodioxin-2-acetic acid methyl ether (**7**) was obtained as a pale yellow oil, yield 67%, bp 132-133° (1 mm Hg), n_D^{16} = 1.5448; ir (neat): 1740 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.25; H, 5.73.

Reaction of **2** with **8**.

The same procedure as for **7** above described was employed starting from **2** and **8**. The glc analysis of the ethereal solution showed one peak. The solvent evaporation *in vacuo* gave a product, which was chromatographed on a silica gel column using petroleum ether-ether (3:1) as eluent. The elution afforded 2,3-dihydro-1,4-benzoxathiin-2-acetic acid methyl ester (**13**), yield 64%, bp 150° (0.7 mm Hg), n_D^{16}1.5860; ir (neat): 1730 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{12}O_3S$: C, 58.90; H, 5.39; S, 14.29. Found: C, 58.63; H, 5.25; S, 14.14.

Methyl 4-[(2-Hydroxyphenyl)thio]-2-butenoate (**14**).

To a stirred mixture of **8** (40 mmoles), pyridine (40 mmoles) and water (12 ml) **2** (40 mmoles) was added dropwise at room temperature. After stirring for almost 8 hours, the mixture was poured into water and extracted with chloroform. The chloroform extracts were washed (in turn) with 10% hydrochloric acid, water and dried over anhydrous sodium sulfate. The glc analysis of this solution showed one peak. The solvent evaporation *in vacuo* gave a pale yellow oil, which was purified by column chromatography through silica gel. On elution with petroleum ether-ether (2:1), the product was obtained in 85% yield, bp 151-152° (0.6 mm Hg), n_D^{16} = 1.5998; ir (neat): 3400 (OH), 1714 (C=O), 990 cm^{-1} (*trans* CH=CH); ^1H nmr (deuteriochloroform): δ 7.05 (m, 4H, Ar-*H*), 5.85 (m, 1H, CH=C*H*-COO), 5.40 (m, 1H, CH_2-C*H*=CH), 3.59 (s, 3H, OCH_3), 3.30 (m, 2H, SCH_2).

Anal. Calcd. for $C_{11}H_{12}O_3S$: C, 58.90; H, 5.39; S, 14.29. Found: C, 58.74; H, 5.40; S, 14.10.

Conversion of **14** to **13**.

A mixture of **14** (20 mmoles), anhydrous potassium carbonate (40 mmoles) and dry acetone (30 ml) was stirred under reflux for almost 8 hours and worked up in the same manner above described to furnish **13** in 88% yield. The ir and nmr spectra were identical with those of the above product.

Reaction of **2** with **15**.

The same procedure above described was employed starting from **2** and **15**. The glc analysis of the ethereal solution showed one peak. The solvent evaporation *in vacuo* gave a product which was purified by column chromatography through silica gel. On elution with petroleum ether-ether (1:1), 3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine-2-acetic acid methyl ester (**17**) was obtained as green bottle crystals, yield 67%, mp 42-44°; ir (nujol): 1745 cm^{-1} (C=O).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.03; H, 6.76; N, 6.18.

Reaction of **2** with **18**.

The same procedure above described was employed. The glc analysis of the ethereal solution showed two peaks in the percentage ratio of 9:1. After removal of the solvent afforded the two products. For the characterization and purification, the crude mixture was chromatographed on silica gel. Elution with petroleum ether-ether (6:1) followed by distillation

gave a yellow oil. The ^{13}C nmr spectra show that the major product is 3,4-dihydro-4-methyl-2*H*-1,4-benzothiazine-3-acetic acid methyl ester (**21**), the minor 3,4-dihydro-4-methyl-2*H*-1,4-benzothiazine-2-acetic acid methyl ester (**22**), yield 84%, bp 170° (5 mm Hg); ir (neat): 1730 cm^{-1} (C=O).

Anal. Calcd. for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 60.54; H, 6.18; N, 5.81; S, 13.33.

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