Mass Spectral Fragmentation Pattern of Heterocycles Part I. 1,4-Benzoxthians (10)

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The mass spectral fragmentation pattern of a series of substituted 1,4-benzoxathians is reported. The di-substituted compounds show a characteristic fragment peak at mass 137. This same fragmentation peak is also present in some of the monosubstituted compounds. In the former case the 137 mass peak is quite intense and is the base peak for some of the di-substituted-1, 4-benzoxathians. The mass peak at 137 has been assigned the empirical formula of C_7H_5OS.

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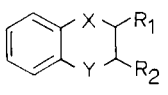
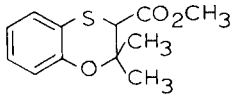
Substituted-1,4-benzodioxans and their congeners represent a series of compounds of considerable medicinal interest (3-8). In an extension of our eariler studies on the benzodioxans (9,10) we have also prepared a series of substituted-1,4-benzoxathians (10). This report describes the mass spectral fragmentation patterns of the latter compounds. The fragmentation patterns of the 1,4-benzoxathians are not as diagnostic of substitution as were those of the 1,4-benzodioxans.





VII

I S = Y = S or O

II S = S, Y = O

$R_1 = CO_2C_2H_5$, $R_2 = CH_3$

III X = O, Y = S

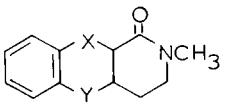
$R_1 = CO_2C_2H_5$, $R_2 = H$

IV X = O, Y = S

$R_1 = CH_2CO_2C_2H_5$, $R_2 = H = H$

V X = O, Y = S

$R_1 = CN$, $R_2 = H$

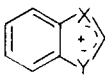


VIII X = S, Y = O

IX X = O, Y = S

Even though mass spectra of heterocycles of type I have been reported, there is little work relating the fragmentation pattern to substitution pattern. This report will attempt to systematically compare the observed fragments with the substitution of these compounds.

Examination of the mass spectra of compounds II-IX revealed an interesting relationship between substitution pattern and fragmentation pattern. In the spectra of the disubstituted benzoxathians, fragments of the type X

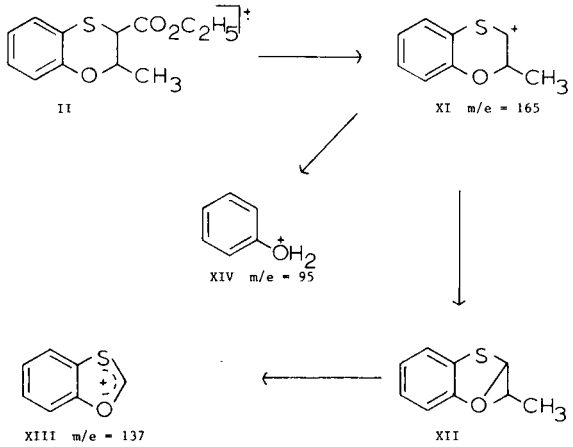


X

play a significiant role (11-13). This fragment, along with the side-chain cleavage fragments, dominate the spectra of the 1,4-benzoxathians.

Ethyl 3-methyl-1,4-benzoxathian-2-carboxylate (II) exhibits two major fragmentation pathways (See Scheme 1).

Scheme 1



The intensity of the molecular ion (II) is 86.7% of the base peak intensity. The base peak corresponds to fragment XI, which appears to be the starting species for both fragmentation pathways. The initial fragmentation process is the cleavage of the carboethoxy group, resulting in fragment XI. Fragment XI is presumed to form the intermediate XII, which then spontaneously loses ethylene, to produce XIII. Fragment XIII has a relative intensity of 24%. This fragment is quite characteristic of fragmentation of the disubstituted compounds. The second fragmentation pathway for XI produces fragment XIV. This fragment is 64% of the base peak, which suggests that it is derived from XI. The analogous 1,4-benzodioxan did not show a fragment similar to XIV (1). The reason for this is not clear.

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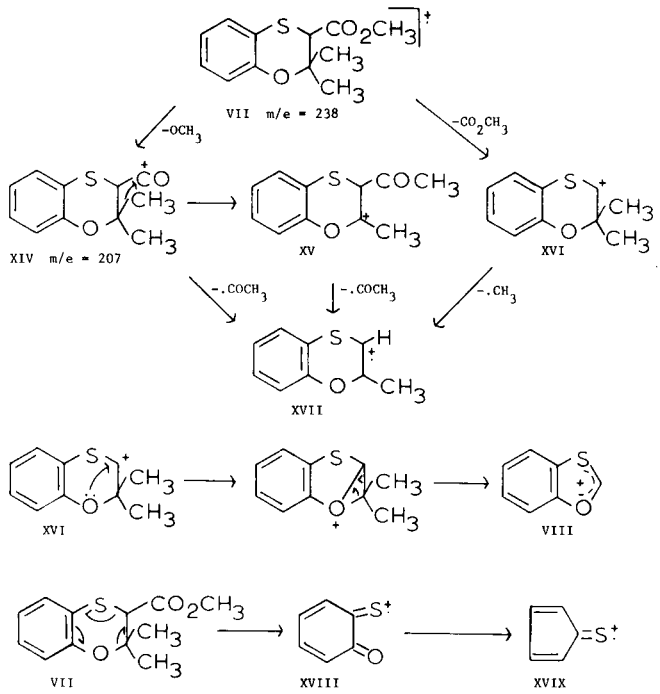
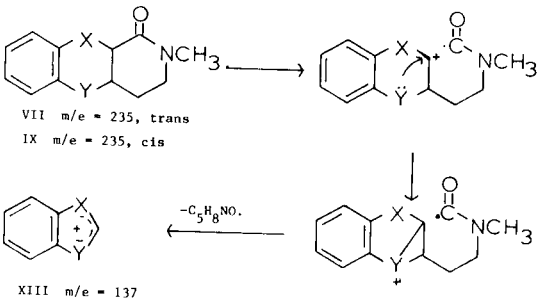
Scheme 2



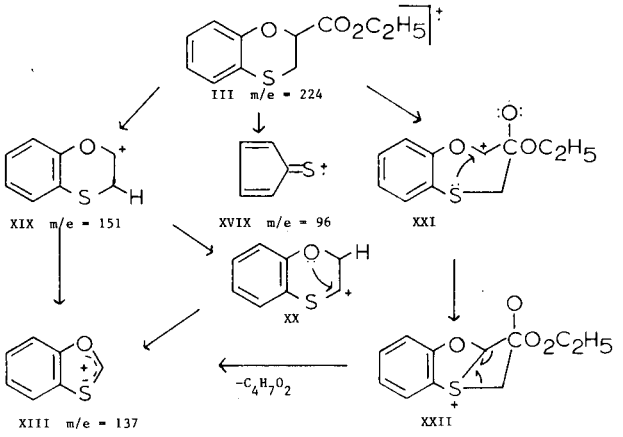
Scheme 3



Methyl 2,2-dimethyl-1,4-benzoxathian-3-carboxylate (VII) gives a rather complex mass spectrum. The first fragmentation pathway is the result of successive side-chain cleavages as shown in Scheme 2. Fragment XVIII, which results from the molecular ion by loss of a methoxy group, and XVIX which comes about by a loss of the entire ester side chain from VII, occur with approximately equal relative intensity. Fragment XVII may arise from XIV and XVI. The former by a methyl transfer followed by the loss of the acetylium radical, and the latter by the loss of a methyl group. Fragment XVI goes on to give XIII, the characteristic fragment for the disubstituted compounds. There is a second pathway which leads to the production of the base peak XVIX. The formation of XVIX (10), is presumably favored in this instance because of the loss of two stable neutral species in succession. If one considers the molecular ion VII, with the charge localized on the sulfur atom, it is easily seen that the loss of β,β-dimethylacrylate in the first step, and the formation of XVIII should be extremely facile. In the second step, XVIII can then spontaneously lose carbon monoxide to give the base peak (XVIX).

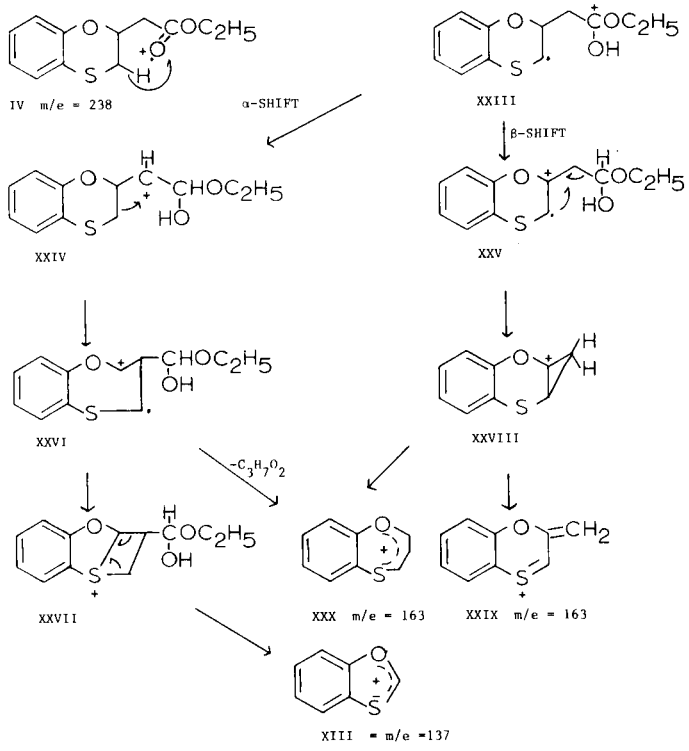
Trans-1-methyl-1,2,3,4,5,6-hexahydrobenzo[*b*]-*p*-1,4-oxathiano[4,5-*e*]pyrid-6(*H*)one (VIII), and *cis*-2-methyl-3,4,4a,10a,-tetrahydropyrido[3,4-*b*][1,4]benzoxathian-1(*H*)one (X), each gave nearly identical spectra. The fragmentation pathways are shown in the composite Scheme 3. Even though both of these compounds are tricyclic, a more important feature is that they each can be considered as disubstituted-1,4-benzoxathians. The base peak in the spectra of both VIII and IX is due to the familiar fragment XIII. This fragment along with the intense molecular ion best characterized these two compounds. The formation of XIII is undoubtedly favored by its stability as well as the stability of the C_5H_8NO radical that is expelled.

Scheme 4

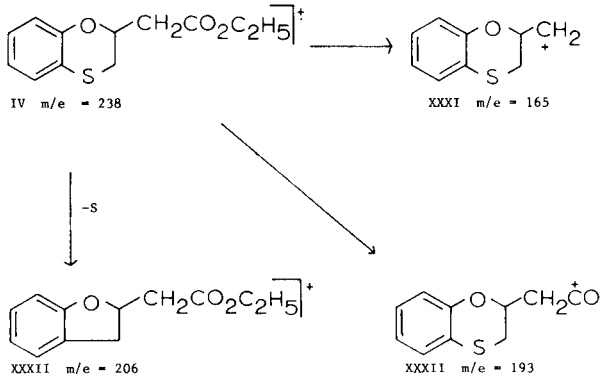


Ethyl 1,4-benzoxathian-2-carboxylate (III) gives a fragmentation pattern which is rather different from its 1,4-benzodioxan analog (1). Compound III fragments more like a disubstituted-1,4-benzodioxan or benzoxathian (See Scheme 4). The base peak in the spectrum corresponds to fragment XIII. A number of possible routes appear to be available for the production of XIII. The first of these pathways starts from the molecular ion, which then undergoes ester celavage to give XIX. Elimination of a carbene from XIX through the three membered ring transition state gives XIII. This process appears to be more favorable when sulfur is involved in the transition state relative to oxygen. In addition, a second pathway appears to be feasabile, wherein a ring expansion occurs from III to XXI, followed by the formation of a four-membered ring transition state (XXII), which then goes on to give the base peak (XIII). Finally, fragment XVIX is quite prominent in the spectrum. It

Scheme 5



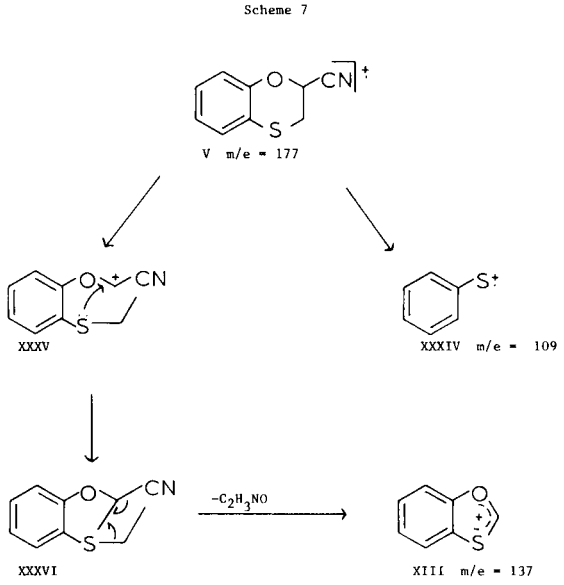
Scheme 6



probably arises from the molecular ion in an analogous fashion to the formation shown in Scheme 2.

Ethyl 1,4-benzoxathianyl-2-acetate (IV), exhibits a complex fragmentation pattern. There are two major fragmentation pathways for IV (See Scheme 5). The first of these is dominated by what appears to be a number of rearrangements of the molecular ion (IV), which eventually cleaves to give XIII, XXX, and XXIX. There is no way of distinguishing between structures XXX and XXIX with the present data. Fragment XIII is rather prominent in the spectrum in contrast to the pattern observed in the oxygen analog reported earlier (1). This difference apparently results from the increased size

Scheme 7



of the sulfur atom and possibly due to d-orbital interactions, all of which may allow for the facile formation of XIII.

The second fragmentation pathway for IV is given in Scheme 6. This pathway is dominated by side-chain cleavages resulting in fragments XXXI and XXXII. In addition, there is a M-32 peak with relative intensity of 20%. This fragment is probably XXXIII or an isomer of some type.

2-Cyano-1-benzoxathian (V) gives a straight forward mass spectrum (See Scheme 7). There are two fragments of major importance, XIII and XXXIV. The base peak is again XIII. It probably arises *via* a ring expansion to give XXXV, followed by the formation of XXXVI which can then spontaneously lose C_2H_3N (the nitrogen analog of ketene). The driving force for this process must be again the relative stability of XIII. A second fragment, XXXIV, is also present and has a relative abundance of 55%.

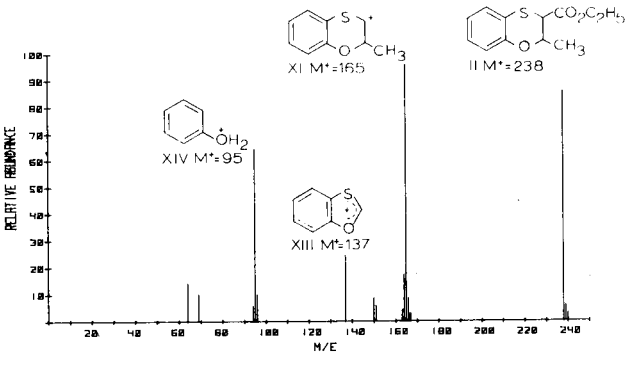


Figure 1 Mass Spectrum of Ethyl 3-Methyl-1,4-benzoxathian-2-carboxylate (II)

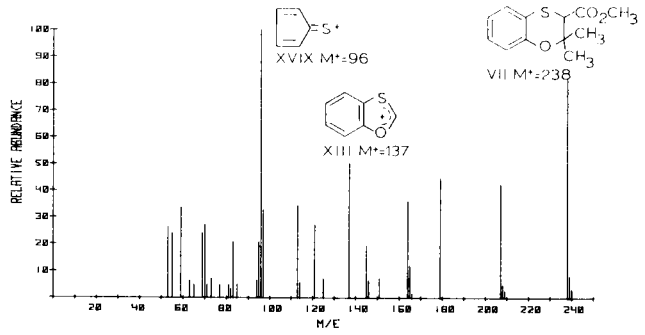


Figure 2 Mass Spectrum of Methyl 2,2-Dimethyl-1,4-benzoxathian-3-carboxylate (VII)

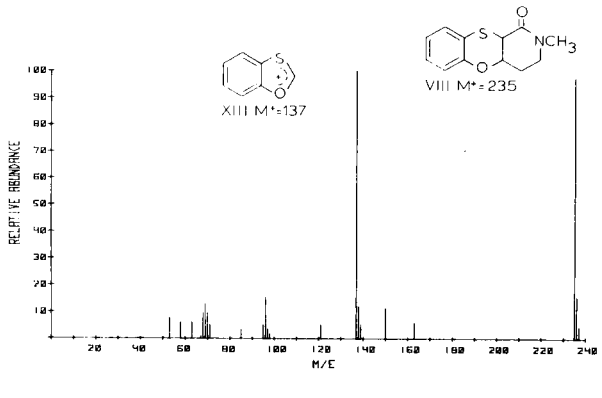


Figure 3 Mass Spectrum of *trans*-1-Methyl-1,2,3,4,5,6-hexahydrobenzo[*b*]-*p*-1,4-oxathiano[4,5-*e*]pyrid-6(*H*)one (VIII)

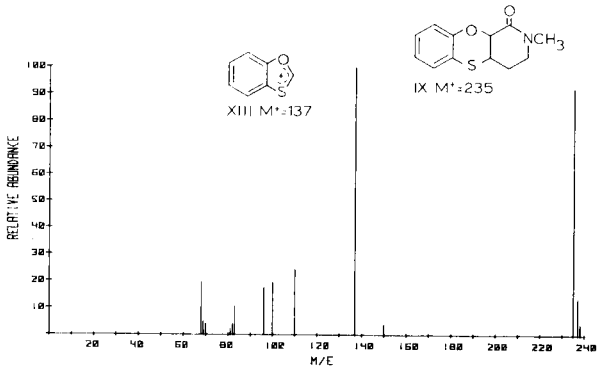


Figure 4 Mass Spectrum of *cis*-2-Methyl-3,4,4a,10a-tetrahydropyrido[3,4-*b*][1,4]benzoxathian-1(*H*)one (X).

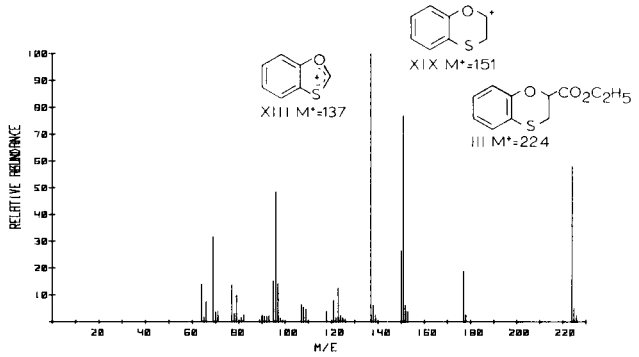


Figure 5 Mass Spectrum of Ethyl 1,4-Benzoxathian-2-carboxylate (III)

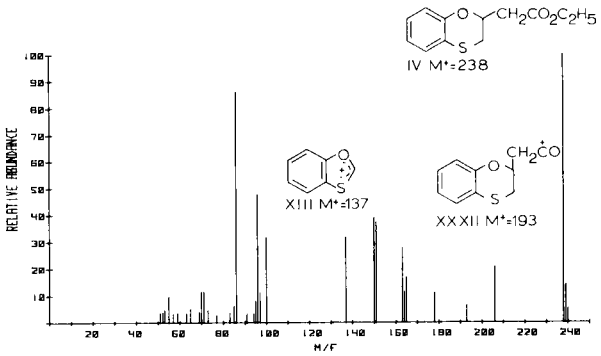


Figure 6 Mass spectrum of Ethyl 1,4-Benzoxathian-2-acetate (IV)

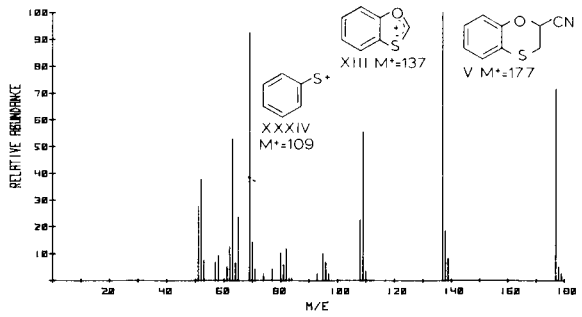


Figure 7 Mass Spectrum of 2-Cyano-1-benzoxathian (V)

Summary.

In our previous report on the mass spectral characteristics of substituted-1,4-benzodioxans (I) there was a clear distinction between the monosubstituted compounds and the disubstituted compounds on the basis of their fragmentation patterns. In the 1,4-benzoxathians reported here, no clear distinction can be made solely on the basis of substitution pattern. Sulfur, due to both its increased size and the availability of its d-orbitals for interaction, plays a critical role in determining the fragmentation pathways followed in these compounds. While it is true that the disubstituted 1,4-benzoxathians give the characteristic fragment ion (XIII) in relatively high abundance, mono and trisubstituted 1,4-benzoxathians also form this fragment.

EXPERIMENTAL

Nmr spectra were determined on a Varian HA-100 spectro-

meter in deuteriochloroform solution using tetramenthylsilane as an internal standard. Chemical shift values are accurate to 0.01 MHz. The melting point was determined on a Thomas-Hoover melting point apparatus and are corrected. The mass spectra were determined on both the varian M66 mass spectrometer and the Finnigan 3200 GC-mass spectrometer. The samples in all cases were analysed by the use of a direct probe with an ion energy of 70 Ev.

Ethyl 1,4-Benzoxathianyl-2-acetate (IV).

A mixture of 19.2 g. (0.1 mole) ethyl 4-bromopropenoate, 12.6 g. (0.1 mole) *o*-mercaptophenol (Polysciences) and 41.4 g. (0.3 mole) of anhydrous potassium carbonate in 200 ml. of dry acetone were stirred under a blanket of nitrogen for 12 hours. After the acetone was removed the residue was taken up in methylene chloride, extracted (in turn) with water, 5% sodium hydroxide, 5% hydrochloric acid and saturated sodium chloride solutions and fired over anhydrous sodium sulfate. Evaporation of the solvent and distillation of the residue *in vacuo* gave 16 g. (67.2%) of a colorless oil, b.p. 126 (0.06 nm); nmr (deuteriochloroform): 6.67-7.1 (m, 4, ArH), 4.67 (m, 1, OCH), 4.15 (q, 2, J=6.9 Hz, ester CH_2), 3.01 (m, 2, SCH_2), 2.82 (m, 2 CH_2CO), 1.2 (t, 3, J= 6.9 Hz, CH_3).

Anal. Calcd. for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.46. Found: C, 60.31; H, 5.83; S, 13.61.

REFERENCES AND NOTES

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