Mass Spectral Fragmentation Patterns of Heterocycles
Part 1. 1,4-Benzodioxans (1)

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The mass spectral fragmentation pattern of a series of substituted 1,4-benzodioxans is reported. The 2,3-disubstituted compounds show a characteristic fragment peak at mass 121. The 2-monosubstituted compounds do not show this as fragment peak. The mass peak at 121 has been assigned the empirical formula of $C_7H_5O_2$.

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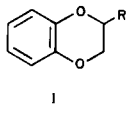
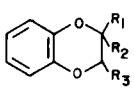
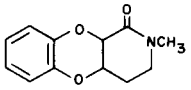
2-Substituted-1,4-benzodioxans (I) represent a series of compounds of considerable medicinal interest. For example: The α-sympatholytic and antihypertensive properties of numerous substituted 2-aminoethyl-1,4-benzodioxans have been described (3,4); the antihypertensive properties of 2-quanidinomethyl-1, 4-benzodioxans, norepinephrine-releasing and depleting angents, have been reported (5,6); and 2-(1,4-benzodioxanyl) analogs of isopropteranol (Isuprel)® have been synthesized and evaluated as potent β-sympatholytic agents (7). As part of a program directed toward investigation of relationships between conconformational and pharmacological properties of this class of compounds, additional substituted-1,4-benzodioxans (II-VII) have been synthesized (8). This report describes the mass spectral fragmentation patterns of the 2- and 2,3-substituted-1,4-benzodioxans prepared.

Although the mass spectra of hetercycles of type (I) have been reported, no attempt has previously been made to systematically examine the fragmentation patterns in these compounds. Our investigation revealed an interesting relationship between the substitution pattern and the fragmentation pathways for 1,4-benzodioxans.



I

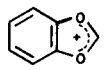




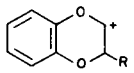
II $R_1 = CO_2C_2H_5$, $R_2 = H$, $R_3 = CH_3$
III $R_1 = CO_2C_2H_5$, $R_2 = H$, $R_3 = H$
IV $R_1 = CH_2CO_2C_2H_5$, $R_2 = H$, $R_3 = H$
V $R_1 = CN$, $R_2 = H$, $R_3 = H$
VI $R_1 = CH_2CO_2C_2H_5$, $R_2 = CH_3$, $R_3 = H$

VII a. *cis*
b. *trans*

In the spectra of the 2,3-disubstituted 1,4-benzodioxans the characteristic fragment, (VIII), is observed. It is the existence of this unique species that makes the identification of the 2,3- and 2,2-disubstituted-1,4-benzodioxans a relatively easy matter (9,10). The relative abundance of fragment (VIII) varies from 40% of the base peak to being the base peak in some spectra. The fragmentation patterns of the 2-substituted-1,4-benzodioxans show a great deal more variability. In these compounds fragments of the



VIII (m/e = 121)



IX

type (IX) play a more significant role.

Ethyl-3-methyl-1,4-benzodioxan-2-carboxylate (II) exhibits two major fragmentation pathways (Scheme I). In the first of these the molecular ion (X), the base peak in this case, initially fragments by the cleavage of the ester function giving the carbonium ion (XI). This fragment has a relative abundance of 90.5%. After this initial fragmentation, a ring contraction occurs with a loss of ethylene yielding (VIII). The driving force for this process is undoubtedly the production of the stable fragment (VIII). Fragment (VIII) has been reported for a number of aryl ethers (10,11), and its stability is well documented.

Compound (II) has a second fragmentation pathway of some importance. This is also shown in Scheme 1.

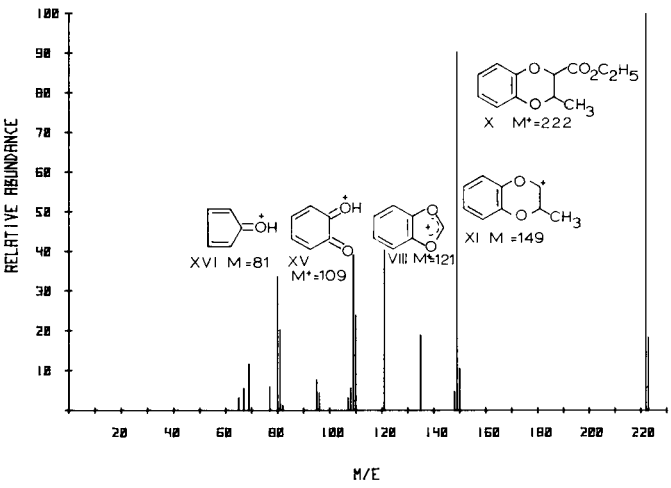


Figure 1: Mass Spectra of Ethyl-3-methyl-1,4-benzodioxan-2-carboxylate.

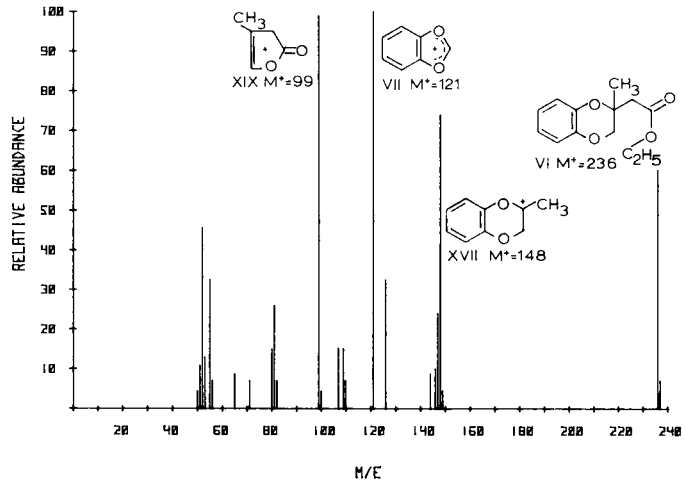


Figure 2: Mass Spectra of Ethyl-2-methyl-1,4-benzodioxanyl-2-acetate.

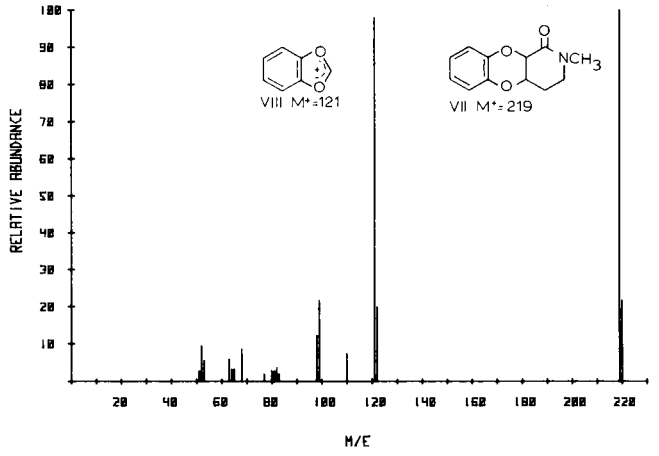


Figure 3: Mass Spectra of 1-methyl-1,2,3,4,5,6-hexahydrobenzo-[*b*]-*p*-dioxino[3,4-*e*]pyrid-2*H*-one. *Cis*- and *trans*-isomers.

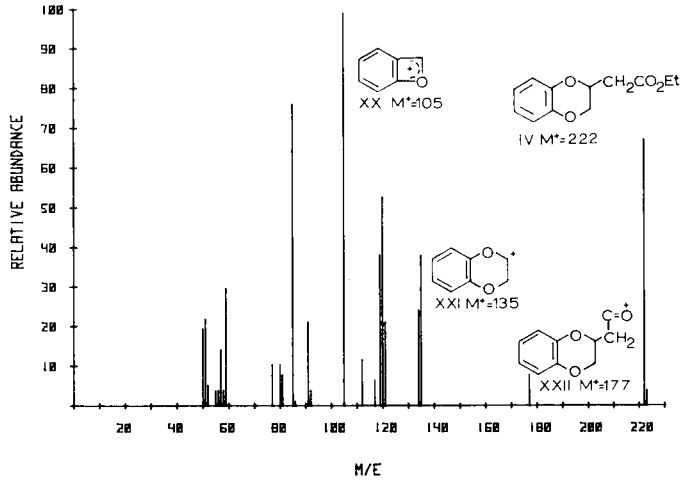
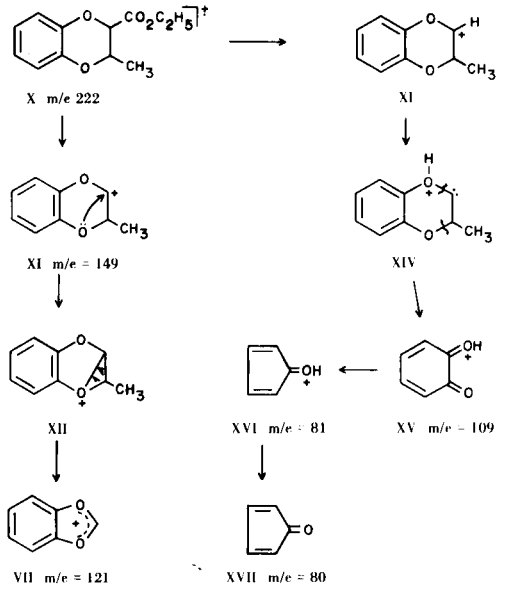


Figure 4: Mass Spectrum of Ethyl-1,4-benzodioxanyl-2-acetate.

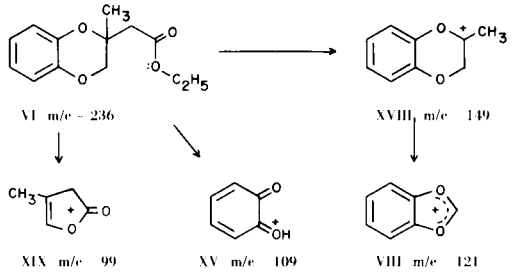
In this pathway the molecular ion (X) cleaves to give fragment (XI) which appears to undergo a proton transfer, followed by the loss of C_3H_4 resulting in (XV). Ion (XV) then goes on to lose carbon monoxide giving (XVI), which in turn readily losses a hydrogen atom giving (XVII).

Ethyl-2-methyl-1,4-benzodioxanyl-2-acetate (VI) is a rather interesting disubstituted case. In addition to showing the characteristic fragment (VIII), which is the base peak in the spectrum, there is a very intense peak at m/e of 99 corresponding to XIX (see Scheme 2). The driving force for the production of this five membered-ring lactone, (XIX) is probably due to the existence of the tertiary center at the 2-position of the benzodioxan ring. This, with the production of the relatively stable quinone-like fragment, (XV), would accound for the relatively high abundance of (XIX).

Scheme 1



Scheme 2



Compound (VII), 1-methyl-1,2,3,4,5,6-hexahydrobenzo[*b*]-*p*-dioxino[3,4-*e*]pyrid-2*H*-one, represents a disubstituted 1,4-benzodioxan wherein the lactam ring affords both the 2, and 3 substitutents. In this case the mass

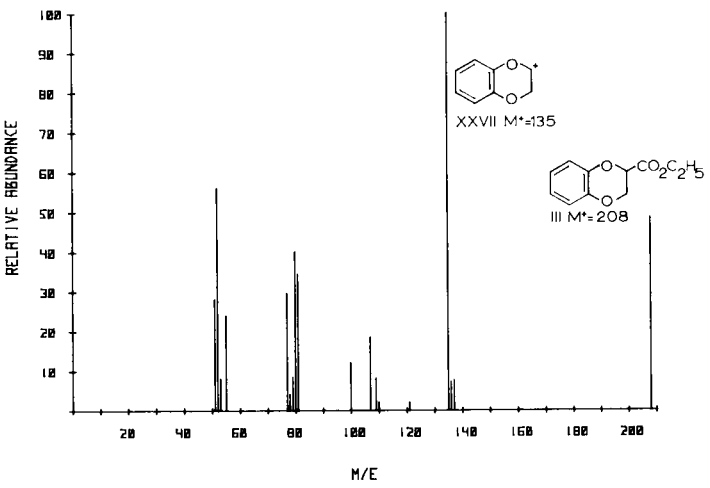


Figure 5: Mass Spectrum of Ethyl-1,4-benzodioxan-2-carboxylate.

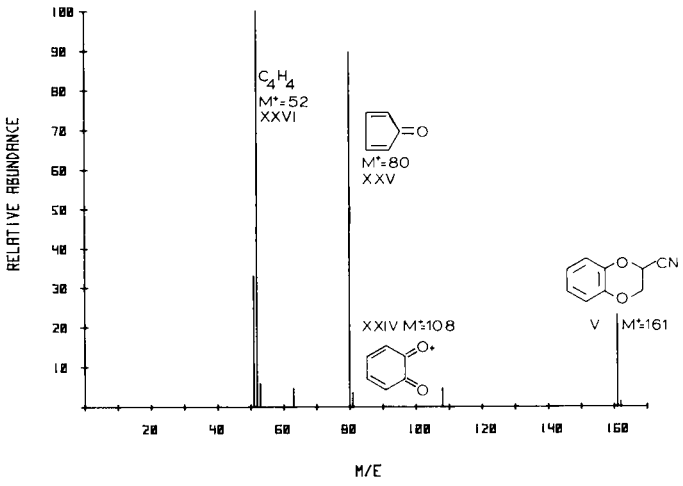
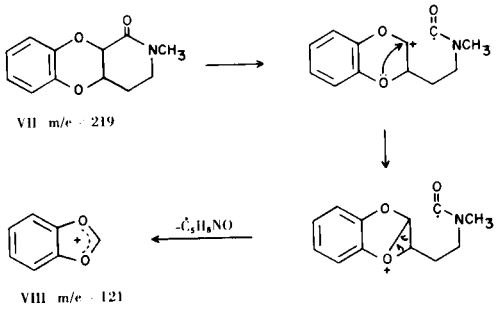


Figure 6: Mass Spectrum of 2-cyano-1,4-benzodioxan.

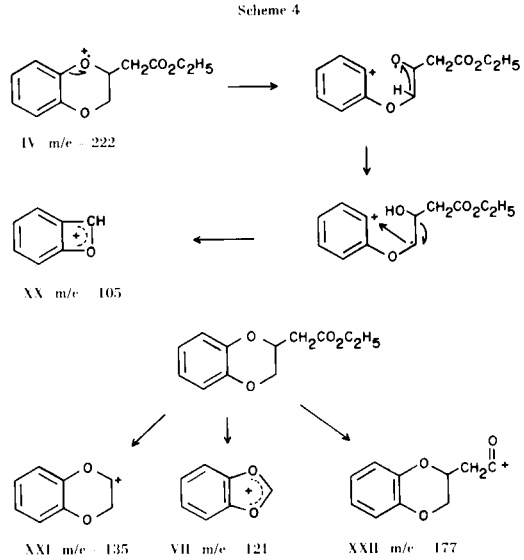
spectrum was very simple, and it indeed showed the characteristic fragment (VIII) (see Scheme 3). The molecular ion, (VII), was 75% of the base peak (VIII). The *cis*- and *trans*-isomers gave identical spectra. The formation of (VIII) is undoubtedly favored by its stability and by the concurrent production of the stable radical (C_5H_8NO).

Scheme 3



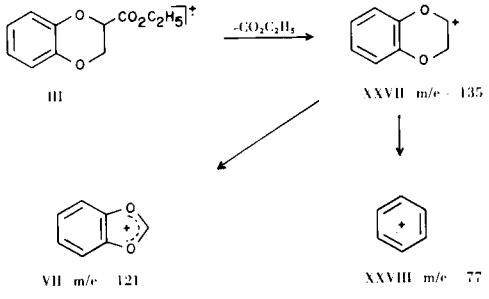
Ethyl-1,4-benzodioxanyl-2-acetate (IV) is a 2-substituted benzodioxan. It does, however, have a somewhat unusual mass spectrum. The base peak has a mass of 105. This corresponds to an empirical formula of C_7H_4O, (XX). The proposed fragmentation pathway is shown in Scheme 4. The fragment ion, (XX), is relatively uncommon, but similar fragments have been reported (11). In addition to ion (XX), two prominent side chain cleavage products are observed, (XXI) and (XXII). In addition to the fragments already mentioned, the fragment (VII), is also present in the spectrum.

Scheme 4



Ethyl-1,4-benzodioxan-2-carboxylate (III) gives a rather straight forward mass spectrum. The base peak in the spectrum corresponds to simple side chain cleavage, resulting in fragment (XXVII). This is the only high mass fragment that appears on the spectrum. Fragment (VII)

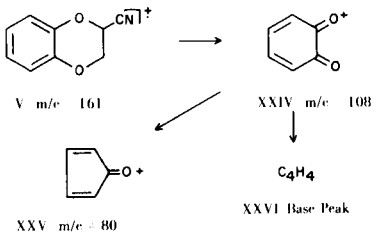
Scheme 5



also appears in this spectrum, however, it is of very low intensity (see Scheme 5).

2-Cyano-1,4-benzodioxan (V) also gives a relatively simple mass spectrum. There are only two major high mass fragments. These are shown in Scheme 6. The molecular ion, (V), readily eliminates C_3H_3N to give an orthoquinone cation (XXIV). This then further fragments

Scheme 6



by the loss of carbon monoxide to give a cyclopentadenone species (XXV). The base peak in the spectrum corresponds to C_4H_4, and probably arises from both (XXIV) and (XXV).

EXPERIMENTAL

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 use of a direct probe with an ion energy of 70 ev.

REFERENCES AND NOTES

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