A Mass Spectrometric Study of 1,4-Dioxa-8-azaspiro[4.5]decane

William E. Solomons

Chemistry Department, The University of Tennessee at Martin,
Martin, Tennessee 38237

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The mass spectrum of 1,4-dioxa-8-azaspiro[4.5]decane (4-ethylenedioxypiperidine) showed a prominent peak at m/e 87. Ethylenedioxy ketals commonly give a fragment of m/e 86 and other fragments of higher mass than 87. A mechanism for formation of a m/e 87 fragment was formulated and evidence for this mechanism and the structure of the fragment was obtained by deuterium labelling. Structures and mechanisms of formation of other major fragments were also studied.

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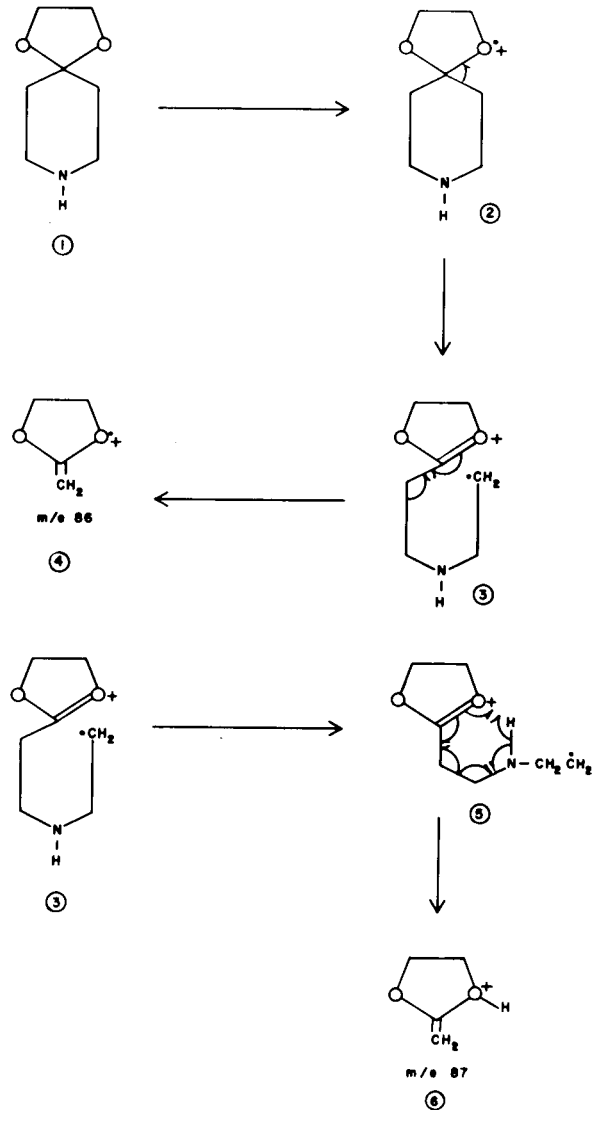
As part of a synthetic scheme to produce potential new antipsychotic agents 1,4-dioxa-8-azaspiro[4.5]decane, **1**, was utilized as an intermediate. A routine examination of the mass spectrum of **1** revealed a fragment at m/e 87. The structure of this fragment was eventually formulated. An examination of the literature indicated the ketal of cyclohexanone and ethylene glycol gave major fragments at m/e 86 and m/e 99 (1). The acetal from acetaldehyde and ethylene glycol gave m/e peaks of 88, 87, 74 and 73 (2,3). The structure of the acetal and fragmentations like those of ethylenedioxycyclohexane account for these m/e fragments. However, similar fragmentation mechanisms for 1,4-dioxa-8-azaspiro[4.5]decane did not account for the masses of the fragments obtained from this compound nor did they explain the changes observed for the m/e values when the compound is labelled with deuterium. Scheme I contains fragmentation routes of 1,4-dioxa-8-azaspiro[4.5]-decane for m/e 86 and m/e 87. Figure 1 is a drawing of the mass spectrum of 1,4-dioxa-8-azaspiro[4.5]-decane, **1**. The relative intensities of the peaks are not meant to be precise. For clusters of peaks assume that each peak differs from its neighbor by one mass unit.

SCHEME I



Structures **1-4** show a mechanism whereby a fragment of m/e 86 can reasonably be obtained but is not obtained in significant amounts. A mechanism, structures **3, 5,** and **6,** was proposed as a route to the 87 fragment. Treatment of 1,4-dioxa-8-azaspiro[4.5]decane with deuterium oxide would produce 8-deutero-1,4-dioxa-8-azaspiro[4.5]decane and according to the mechanism proposed this compound should yield a fragment of significant intensity at m/e 88. Furthermore, one would expect the m/e 87 peak to decrease in intensity relative to m/e 88 and to decrease in intensity relative to other peaks in the spectrum whose intensity would not be expected to be changed by deuterium labelling at the 8-postion. This was found to be the case.

From the mass spectra of the nondeuterated and the deuterated compounds, Fig. 1 and Fig. 2, respectively, it was observed that the m/e 87 peak of **1** was greatly diminished relative to the m/e 88 peak of the deuterated compound.

The m/e 42 peak was not found to change in intensity with 8-position deuterium labelling. The m/e 87 fragment decreased in intensity significantly relative to the m/e 42 which indicates that there was not merely an increase in

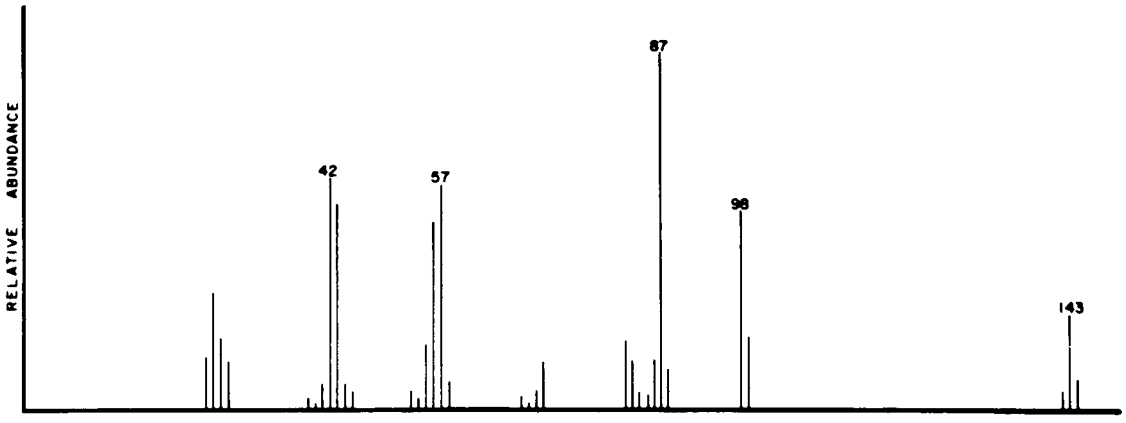


FIG 1 MASS SPECTRUM OF 1,4-DIOXA-8-AZASPIRO [4.5] DECANE, I.

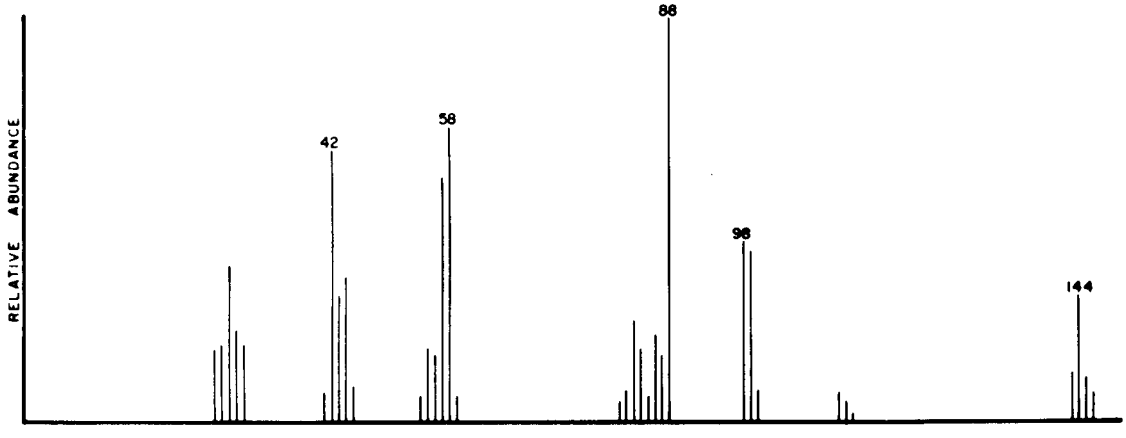


FIG 2 MASS SPECTRUM OF 8-DEUTERO-1,4-DIOXA-8-AZASPIRO [4.5] DECANE (THE SAMPLE CONTAINS A SMALL QUANTITY OF THE NONDEUTERATED COMPOUND)

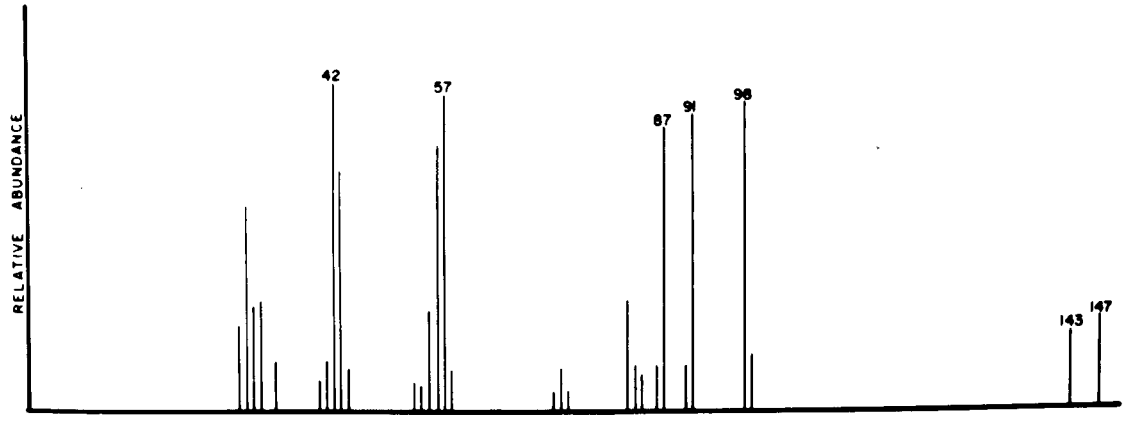
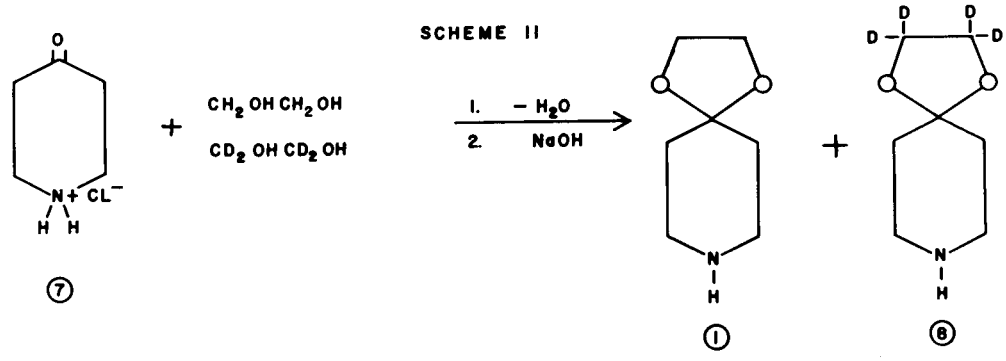


FIG 3 MASS SPECTRUM OF 2,2,3,3-TETRADEUTERO-1,4-DIOXA-8-AZASPIRO [4.5] DECANE AND OF THE NONDEUTERATED COMPOUND IN A 1:1 RATIO, I AND 8

the intensity of m/e 88 but that there was also a simultaneous decrease in the intenstiy of m/e 87.

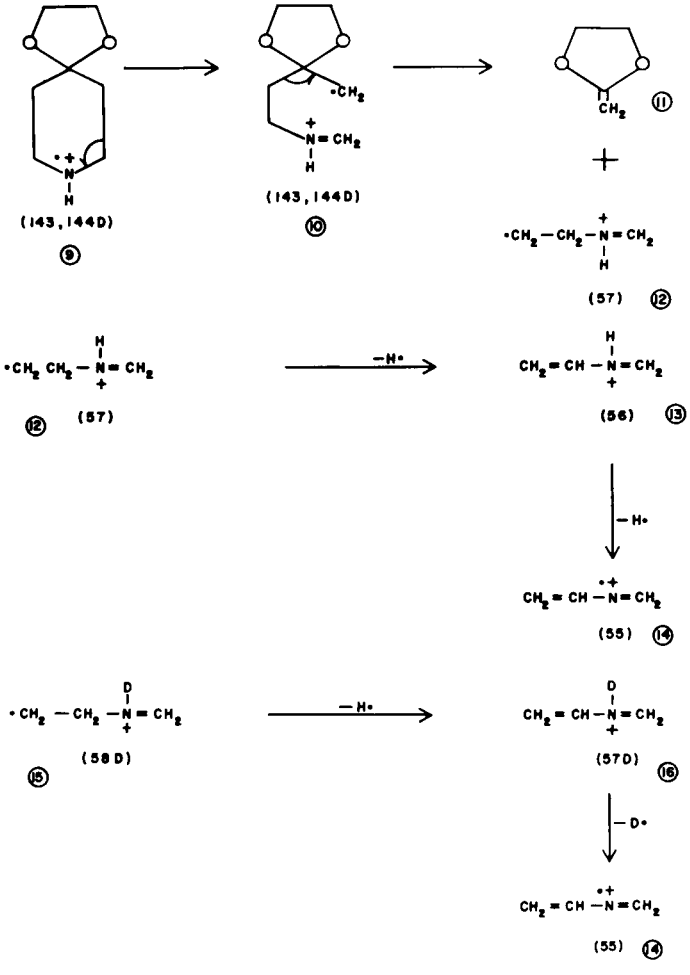
This evidence strongly favored the proposed mechanism but there existed the possibility that a fragment of m/e 87 (88 deuterium) could arise from the *N*-heterocyclic portion of the molecule by an unknown pathway and especially



since the deuterium label was located in this ring. Therefore the ketal was synthesized from 1,1,2,2-tetradeuteroethylene glycol (a solution of 50% ethylene glycol and 50% 1,1,2,2-tetradeuteroethylene glycol) and 4-piperidone hydrochloride by the usual method of removing water with a Dean-Stark trap and a refluxing benzene solution. The mass spectrum of these compounds is found in Fig. 3.

SCHEME III

m/e 42, 43, 44D, 55, 56, 57, 57D, 58D, 98, 99D.



The most outstanding features of this spectrum are the m/e 87 peak followed by a peak of almost equal intensity 4 mass units later at m/e 91 and the two molecular ions, m/e 143 and m/e 147. There appears to be no other major changes in the spectrum. These undoubtedly link the m/e 87 peak to the -O-CH_2-CH_2-O- portion of the molecule and further supports the proposed structure of the m/e 87 fragment.

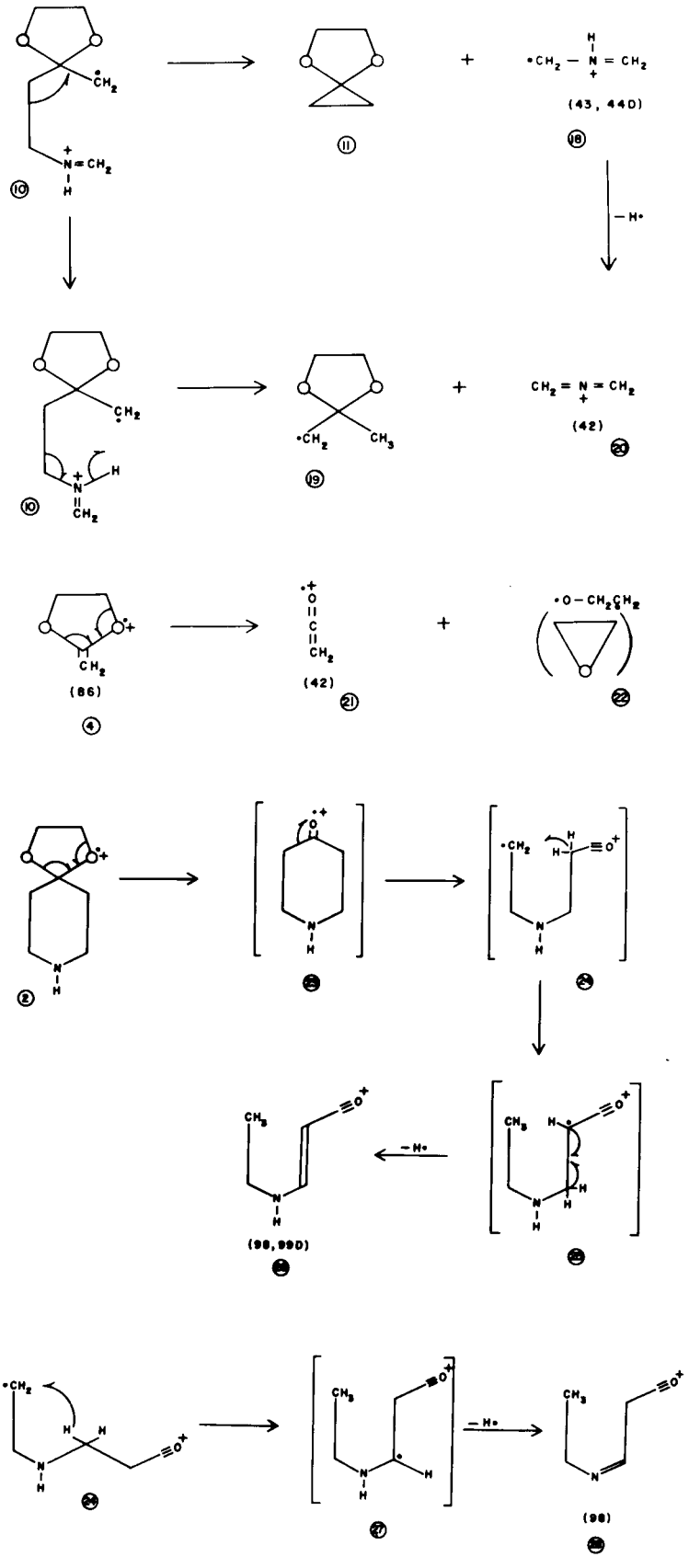
Other fragments of significant intensity in the spectrum which were studied are: m/e 42, 43, 44(D), 55, 56, 57(D), 59(D), 98 and 99(D). The m/e values given above and followed by (D) are those which increased in intensity due to 8-position deuterium labelling.

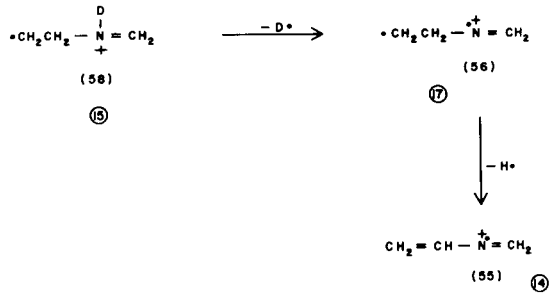
Mechanisms and proposed structures for these fragments are given in Scheme III and Scheme IV.

Structures **9**, **10**, **11** and **12** show a likely process by which fragments of m/e 57 and 58D are obtained. The spectra confirmed this fragment, **12**, in two ways. First the m/e 58 peak from **1** (no deuterium) is very small compared to the 57 peak and the spectrum of deuterated **1** (Fig. 2) showed m/e 58 increase greatly in intensity. Secondly, however, the expected decrease in the m/e 57 peak for the 8-deutero compound did not occur as much as one might expect. This strengthens the existence of **12** and of the pathway **12**, **13**, **14** and therefore the analogous pathway **15**, **16**, **14**. Pathway **12**, **13**, **14** accounts for fragments m/e 56 and 55 and the same pathway involving 8-deuterium (**15**→**16**→**14**) accounts for the large 57 peak in Fig. 2. Since the deuterated fragment **15** expelled a H• atom, an m/e 57 fragment is produced by this pathway for the **8**-deuterated compound and therefore the m/e 57 is not as small as might first be expected. However, as would be expected the m/e 56 (Fig. 2) is much smaller than the m/e 56 (Fig. 1) because the m/e 56 fragment is not formed significantly by this pathway from the 8-deutero compound.

The following path seemed possible at one point but is largely ruled out by the above reasoning.

SCHEME IV





It would seem reasonable that the H• atom would be more easily expelled with concomitant double bond formation especially when conjugation with the double bond formed is possible as in **16**.

Pathway **10, 11, 18** accounts for the m/e 43, 44D peaks (Scheme IV). The m/e 44 increases dramatically for the **8**-deuterated compound with a simultaneous decrease in the intensity of m/e 43. However, the m/e 43 does not decrease as much as one would expect (compare the 87, 88 peaks in Fig. 1 and Fig. 2) It appears that some fragmentation pathway other than those described is preducing a fragment of m/e 43 from the **8**-deuterated molecule.

By both pathways **10, 11, 18, 20** and **10, 19, 20** a m/e 42 fragment may be formed. Both pathways show loss of deuterium in formation of m/e 42. One would expect, by these mechanisms, a 42 peak whose intensity would remain constant with or without deuterium labelling; this is observed. A third pathway **4, 21, 22** can also yield a m/e 42 independent of deuterium labelling. This pathway is attractive since it can explain the very small m/e 86 peak observed in the spectra. If the structure 4, m/e 86, rapidly fragments to give **21**, m/e 42, then m/e 86 would be small and again a deuterium intensity independent m/e 42 is formed.

For fragments m/e 98 and 99 it is necessary to construct reasonable mechanisms which allow the formation of predominantly a 98 fragment for the 8-position nondeuterated molecule and which also account for only a small decrease in the m/e 98 fragment with a large increase in the m/e 99 fragment for the 8-deutero molecule. Mechanisms are proposed for this in Scheme IV.

The above mechanisms fulfill the requirements. Both occur with significant frequency. The major difference between the two is whether the H• atom of structure 24 is transferred through a five-membered ring intermediate or a six-membered ring intermediate. Mechanism **2, 23, 24, 25, 26** allows a significant 98 or 99 peak depending on whether the compound is deuterated in the 8-position or not whereas mechanism **24, 27, 28** allows only the formation of a m/e 98 peak whether or not the compound is deuterated in the 8-position.

Summary.

The intense m/e 87 peak (base peak) in the mass spectrum of 1,4-dioxa-8-azaspiro[4.5]decane arises through a novel rearrangement and fragmentation of the parent ion. This rearrangement and fragmentation of the parent ion was well documented through deuterium labelling of the 8-position (N-atom) and by deuterium labelling of the C-atoms of the -O-CH_2-CH_2-O- bridge. The other major fragments of the spectrum were identified through more conventional rearrangement and fragmentation patterns. However, deuterium labelling particularly of the N-atom (8-position) allowed additional evidence to be obtained for the structure of these fragments.

Interestingly, the dioxolane ring appears to be involved as a portion of only one major pathway (with the possible exceptions of an m/e 86 rapidly yielding an m/e 42 and in participation in the formation of the 98 and 99 fragments), the formation of the m/e 87 fragment. Deuterium labelling of the -O-CH_2CH_2-O- bridge gave peaks of increased mass only at 91 and 147 with the possible exception of fragments in the region of m/e 1-35. Assignment of the structure of the remaining fragments was based both on similar rearrangements (4,5) of heterocyclic compounds found in the literature and on deuterium labelling of the 8-position.

EXPERIMENTAL

All mass spectra were obtained from instruments operated at 70 electron volts. The original data was obtained from a Varian EM-600 mass spectrograph and later confirmed on a Hewlett-Packard 5985 gas chromatograph-mass spectrometer system.

8-Deutero-1,4-dioxa-8-azaspiro[4.5]decane.

This compound is very water soluble. To 2.0 g of the nondeuterated compound, 1.0 g of deuterium oxide was added and the mixture (protected from the atmosphere) was allowed to sit overnight. After adding 0.5 g of dried sodium chloride and shaking, the heterocyclic compound was extracted with dichloromethane. The dichloromethane was removed by evaporation. This process was repeated twice more and the final extract was distilled, bp 117-119°/38 mm. The literature boiling point for the nondeuterated compound is 108-110°/26 mm (6).

2,2,3,3-Tetradeutero-1,4-dioxa-8-azaspiro[4.5]decane (**8**).

To a 200 ml round-bottom flask fitted with a Dean-Stark trap, condenser, and calcium chloride drying tube, 10.0 g (0.16 mole) of ethylene glycol (1,1,2,2-tetradeuteroethylene glycol: ethylene glycol in a 1:1 ratio), 7.68 g (0.05 mole) of 4-piperidone monohydrate hydrochloride and 100 ml of benzene was added. Over a 48 hour period the mixture was refluxed, stirred, and occasionally water was removed from the Dean-Stark trap. After allowing the reaction mixture to cool to room temperature, 8-12 mesh, 3 Å molecular sieve was added and stirring was continued for 1 hour. The reaction mixture was shaken vigorously with 30 ml of 30% sodium hydroxide solution. The aqueous layer was extracted with five 20 ml portions of chloroform, the organic solutions were combined, dried over anhydrous magnesium sulfate, filtered, and the solvents were removed on a rotary-evaporator. The remaining liquid was distilled under reduced pressure (7 mm Hg) yielding 6.35 g (88%) of the desired compound, bp 112-115°/30 mm.

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