Mass Spectrometry in Structural and Stereochemical Problems. CI.[1] A Study of the Fragmentation of Some Azabicyclo Lactams[2]

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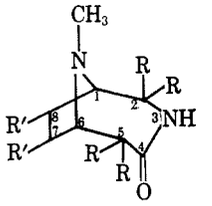
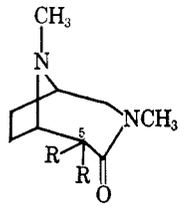
The mass spectra of five azabicyclo lactams (I–V) have been measured in order to examine the effect upon the fragmentation pattern of two different functional groups in close proximity to each other. From the utilization of deuterated analogs, supplemented by high-resolution mass spectrometry, rationalizations are presented for the principal fragments observed in the spectra of these compounds. Increasing the ring size from eight to ten membered did not affect greatly the principal fragmentation modes.

The detailed interpretation of the mass spectrometric fragmentation of tropane alkaloids[4] permitted scrutiny of the effects of differing heteroatoms upon the electron impact induced fission of these compounds. Recently the ability of amide groupings substituted with aliphatic[5a] and aromatic[5b] moieties or incorporated in alicyclic[5c] or aromatic heterocyclic systems[5d] to control the mass spectrometric fragmentation of organic molecules has been investigated. It was considered of some interest in view of these results and the known ability of the amino group to direct the electron-induced fragmentation of amines[4a,6] to determine the effect on the observed fragmentation of compounds containing both the lactam and the amino groups within the same molecule. Azabicyclo lactams[7] constitute a group of compounds admirably suited for this purpose especially as deuterated analogs were available for the confirmation of the sites of hydrogen transfer in the rearrangement ions formed subsequent to electron impact. In addition, this class of compounds promised the possibility of determining the effect, if any, of ring size on the mass spectral fragmentation patterns generated within this group.

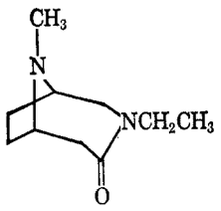
The mass spectra of the unlabeled azabicyclo lactams I–V are reproduced in Figures 1–5. All display molecular ions of appreciable intensity while the loss of a methyl group, although noticeable in each instance, generates ions of almost negligible intensity. In all probability the expulsion of a methyl group is attained by the ejection of a carbon atom from the alicyclic framework rather than of an N-methyl group, similar to what had been observed with N-methylated cyclic amines.[6b]



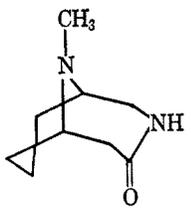
Ia, R = R′ = H
b, R = D; R′ = H
c, R = H; R′ = D



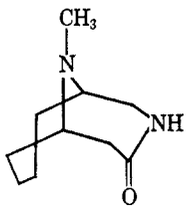
IIa, R = H
b, R = D



III



IV



V

The principal ions of diagnostic interest in the spectrum (Figure 2) of the lactam IIa occur at mass 82, 87, 96, and 97. These ions are either present, or displaced by increments of 14 mass units, in the spectra (Figures 1, 3, 4, and 5) of the remaining compounds investigated, so that at least qualitatively the mass spectral shift technique[8] can be applied. High-resolution mass spectrometry[9] furnished the empirical compositions indicated in Figure 2 for the peaks at *m/e* 82, 87, 96, and 97 in the spectrum of the azabicyclo lactam IIa.

The base peak in the spectrum (Figure 2) of compound IIa occurs at *m/e* 82 (M − 86) and was shown by high-resolution mass spectrometery to be due exclusively to $C_5H_8N^+$. Furthermore, this peak was undisturbed in the spectra (Figures 1 and 3) of the N-demethyl (Ia) and N-ethyl (III) analogs, respectively. The spectrum of the 5,5-d_2 analog IIb exhibited a displacement of 25% of the peak at *m/e* 82 to 83, the remainder being unaffected. This result indicates that although the ion of mass 82 is homogeneous in terms of empirical formula, it need not necessarily be

(1) For paper C, see C. Djerassi, M. Fischer, and J. B. Thomson, *Chem. Commun.* (London), 12 (1966).

(2) We are indebted to the U. S. Public Health Service (Grants No. GM-11309 and AM-04257 to Stanford University) and to the National Science Foundation (Grant No. GP-2939 to The Ohio State University) for financial assistance.

(3) Alfred P. Sloan Foundation Fellow.

(4) (a) E. C. Blossey, H. Budzikiewicz, M. Ohashi, G. Fodor, and C. Djerassi, *Tetrahedron*, **20**, 585 (1964); H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, p 92. (b) J. Parello, P. Longevialle, W. Vetter, and J. A. McCloskey, *Bull. Soc. Chim. France*, 2787 (1963); L. W. Daasch, paper presented at the American Society for Testing Materials Committee E-14, Mass Spectrometry Conference, St. Louis, Mo., May 1965; Abstracts, pp 409–414.

(5) (a) J. A. Gilpin, *Anal. Chem.*, **31**, 935 (1959); C. P. Lewis, *ibid.*, **36**, 1582 (1964); Z. Pelah, M. A. Kielczewski, J. M. Wilson, M. Ohashi, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2470 (1963). (b) K. G. Das, P. T. Funke, and A. K. Bose, *ibid.*, **86**, 3729 (1964). (c) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *ibid.*, **86**, 5536 (1964); **87**, 2913 (1965); A. M. Duffield and C. Djerassi, *ibid.*, **87**, 4554 (1965). (d) A. M. Duffield, C. Djerassi, G. Schroll, and S.-O. Lawesson, submitted for publication.

(6) (a) R. S. Gohlke and F. W. McLafferty, *Anal. Chem.*, **34**, 1281 (1962). (b) For leading references to recent studies, see A. M. Duffield, H. Budzikiewicz, D. H. Williams, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 810 (1965); Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *ibid.*, **87**, 574 (1965).

(7) (a) L. A. Paquette and L. D. Wise, *J. Org. Chem.*, **30**, 228 (1965); (b) *J. Am. Chem. Soc.*, **87**, 1561 (1965).

(8) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., N. Y., 1962, pp 305–312. See also H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day, Inc., San Francisco, Calif., 1964, pp 46–49.

(9) Determined by Dr. D. J. Goldsmith at Stanford University using an A.E.I. MS-9 double-focussing mass spectrometer with an apparent resolution of 12,000.

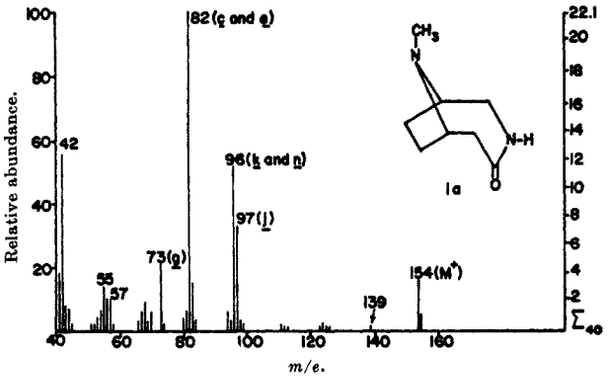


Figure 1.—Mass spectrum of azabicyclo lactam Ia.

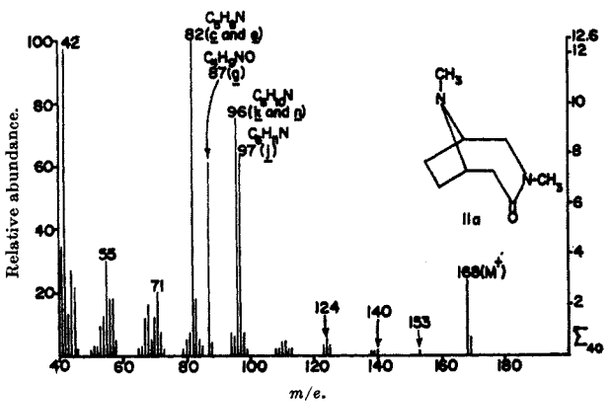


Figure 2.—Mass spectrum of azabicyclo lactam IIa.

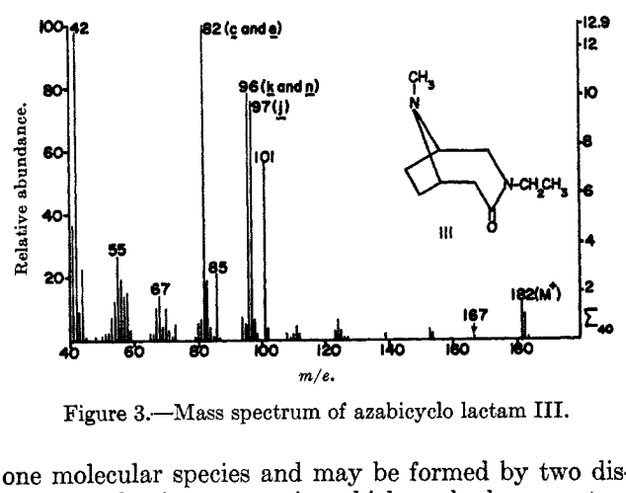


Figure 3.—Mass spectrum of azabicyclo lactam III.

one molecular species and may be formed by two distinct mechanisms—one in which a hydrogen atom adjacent to the lactam carbonyl group is retained (25%) and the other in which both of these hydrogen atoms are lacking. Two plausible general rationalizations for the formation of the ion of mass 82 (illustrated for compound IIa in Scheme I) are represented by IIa → b → c (*m/e* 82), and IIa → d → e (*m/e* 82).

Preparation of the 7,8-d_2 analog Ic afforded evidence [95% of the ion yield at *m/e* 82 being dispersed between *m/e* 83 (~50%) and 84 (~45%)] supporting both the above rationalizations. Further results, compatible with these two rationalizations, were encountered in the spectrum of the 2,2,5,5-d_4 analog Ib in which the peak at *m/e* 82 was transposed in 20% yield to *m/e* 83, the rest being unaffected.

The peak present at *m/e* 87 (M − 81) in the spectrum (Figure 2) of the azabicyclo lactam IIa was absent in that (Figure 1) of compound Ia which, however, did display a peak 14 mass units removed at *m/e* 73. In contrast, the spectrum (Figure 3) of the N-ethyl lactam III possessed a corresponding ion of mass 101 and it was thus evident that in the fragmentation of the lactams Ia, IIa, and III to yield ions of mass 73, 87, and 101, respectively, the nitrogen atom and its attached carbon atoms were retained in the charged species. The spectra (see Table I) of the

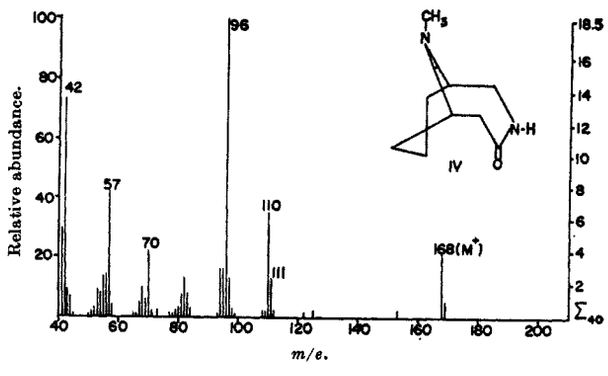


Figure 4.—Mass spectrum of azabicyclo lactam IV.

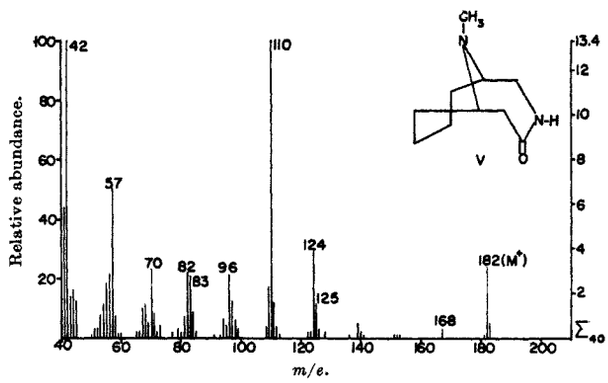


Figure 5.—Mass spectrum of azabicyclo lactam V.

TABLE I

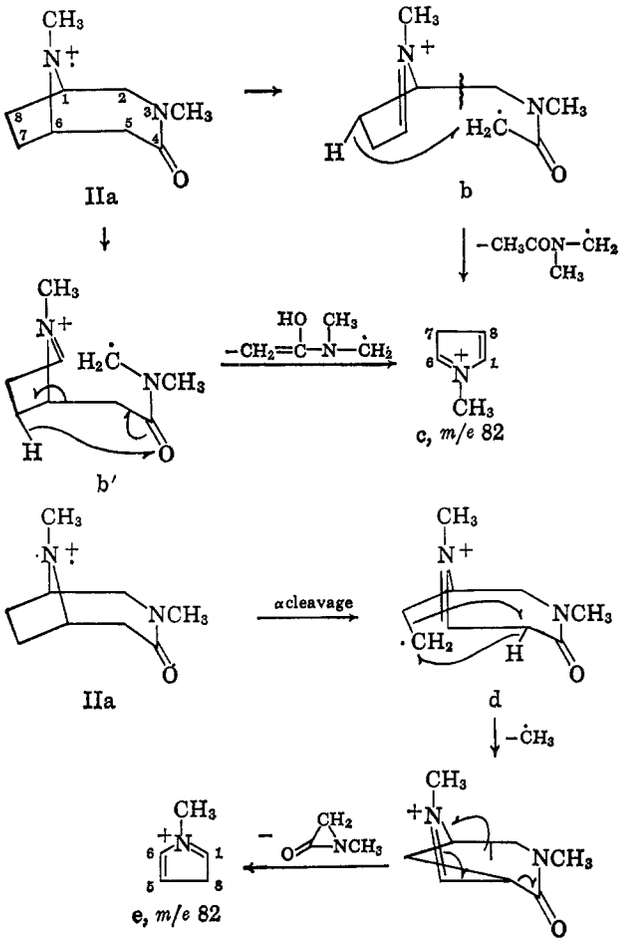
PRINCIPAL MASS SPECTRAL PEAKS OF THE AZABICYCLO LACTAMS I AND II AND DEUTERATED ANALOGS[a]

Compd	Isotopic purity	*m/e* (%)			
Ia	...	73	82	96	97
Ib	85% d_4	77 (>90)	82 (80)	98 (70)	99 (>90)
	15% d_3		83 (20)	97 (25)	
Ic	67% d_2	73 (50)		98 (>90)	99 (>90)
	24% d_1	74 (27)	83 (~50)	98 (>90)	99 (>90)
	9% d_0	75 (23)	84 (~45)		
IIa	...	87	82	96	97
IIb	62% d_2	89 (>90)	82 (75)	98 (70)	99 (>90)
	28% d_1		83 (25)	97 (25)	
	10% d_0				

[a] The per cent transfers quoted under the heading *m/e* in this table have been corrected for species incompletely deuterated and the values quoted are considered reliable to within ±7%.

deuterated analogs Ib and IIb required that the carbon atoms tagged with deuterium be incorporated into the charged species. Furthermore, the source of the double hydrogen transfer in the production of these ions was neatly revealed by the spectrum of the 7,8-d_2 compound Ic in which the peak at *m/e* 73 was now dispersed between *m/e* 73, 74, and 75 to the extent of 50, 27, and 23%, respectively. The homogeneity and composition of the ion of mass 87 in the spectrum

SCHEME I

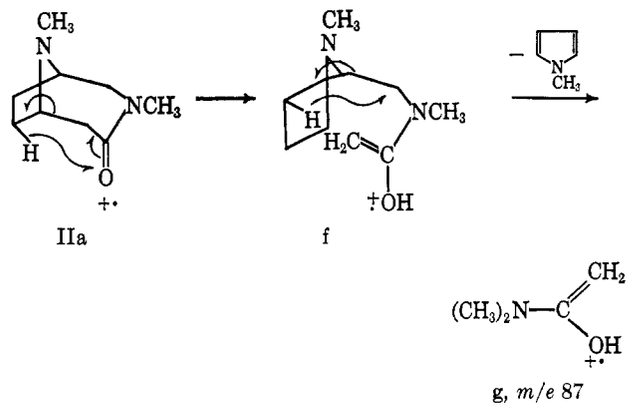


(Figure 2) of lactam IIa was established as $C_4H_9NO^+$. Recognition of a metastable ion at mass 45.0 ($87^2/168 = 45.0$) implied that at least a portion of the ion of mass 87 in the spectrum (Figure 2) of compound IIa arose from a single-step decomposition of the molecular ion. A rationalization, consistent with the evidence cited above, is depicted by IIa → f → g (*m/e* 87) (Scheme II). It envisages the transfer of hydrogen through a McLafferty rearrangement[10] to yield the species f which transfers an allylically activated hydrogen and expels the stable neutral species N-methylpyrrole. The order of events given and the localization of the charge on the oxygen rather than nitrogen atom of the amide linkage is purely arbitrary.

Ions of prominence at mass 96 and 97 occur in the spectra (Figures 1 and 2) of the azabicyclo lactams Ia and IIa and high-resolution mass spectrometry[9] established their composition to be $C_6H_{10}N^+$ and $C_6H_{11}N^+$, respectively. The location of metastable ions at mass 55.0 ($96^2/168 = 54.9$) and 95.0 ($96^2/97 = 95.0$) in the spectrum (Figure 2) of lactam II is indicative of the ion at mass 96 owing its genesis to at least two processes; one by decomposition of the molecular ion and the other by ejection of a hydrogen atom from the species of mass 97. Substitution of the lactam nitrogen atom by an ethyl group (see Figure 3) resulted in no peak shift while enlargement of the lactam ring by one methylene (IV, Figure 4) and two methylene

(10) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959). For latest studies of the McLafferty rearrangement, see H. Budzikiewicz, C. Fenselau, and C. Djerassi, *Tetrahedron*, in press.

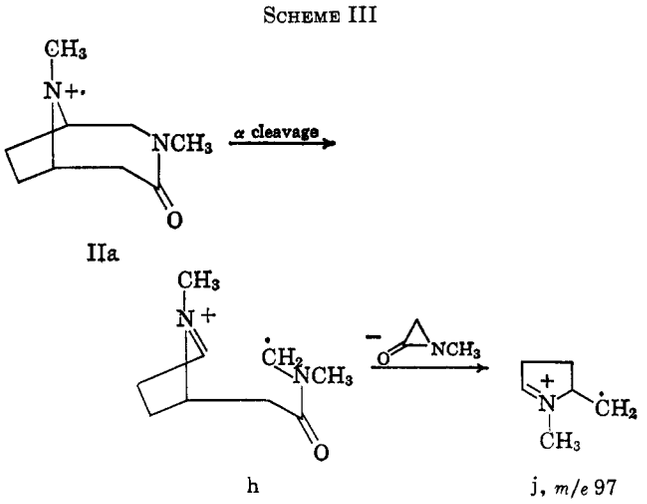
SCHEME II



groups (V, Figure 5) afforded peak shifts by 14 and 28 mass units, respectively. This evidence mitigated against inclusion of the lactam nitrogen atom into the charged species, but required that the carbon atoms of the bridged amino ring be incorporated.

Deuterium labeling (Table I) substantiated these conclusions as was evidenced by transfers (>90%) of two mass units of the peaks at *m/e* 96 and 97 to *m/e* 98 and 99 in the spectrum of the 7,8-d_2 analog Ic. In addition, the peak present at *m/e* 97 in the spectrum (Figure 1) of the unlabeled lactam Ia was displaced to *m/e* 99 (>90%) in the 2,2,5,5-d_4 analog Ib, and a similar result was noted (Table I) in the spectrum of the 5,5-d_2 analog IIb. This evidence is consistent with the rationalization IIa → h → j (*m/e* 97) (illustrated for the lactam IIa by Scheme III) for the formation of the ion of mass 97 in the spectra (Figures 1, 2, and 3) of compounds Ia, IIa, and III and at mass 111 and 125 in the spectra (Figures 4 and 5) of the azabicyclo lactams IV and V.

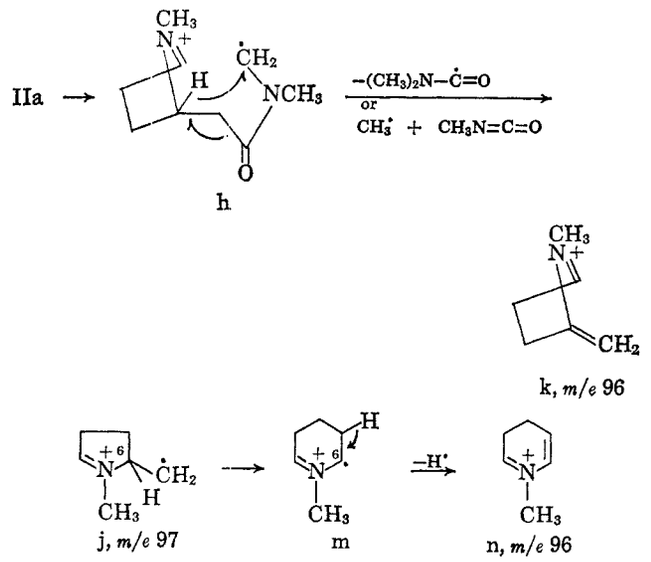
SCHEME III



Deuterium labeling (Table I) supported the evidence obtained from the recognition of metastable ions (see above) in demonstrating the existence of two modes of formation of the ion of mass 96 in the spectra (Figures 1 and 2) of the azabicyclo lactams Ia and IIa. The origin of the transferred hydrogen is clear in the two geneses of this ion, and the deuterium labeling results are summarized in Table I. Migration from C-6 (see h → k (*m/e* 96)) occurs to the extent of 70%,

while most of the remainder arises from C-5. This latter alternative is most conveniently visualized (Scheme IV) as ring expansion of j to m followed by loss of one of the C-5 hydrogen atoms and production of n (*m/e* 96).

SCHEME IV



In conclusion, the present study clearly demonstrates that the amino group (see, for instance, the formation of the ions c, e, j, and k) is much more capable of controlling and directing the fragmentation processes induced by electron impact than the lactam grouping (generation of the ion g) when these two entities exist within the same molecule. The present compounds offer still another example of the great advantage in considering charge localization at specific centers as the trigger responsible for subsequent fragmentations of the molecular ions.

Experimental Section[11]

9-Methyl-3,9-diazabicyclo[4.2.1]nonan-4-one (Ia) was prepared from tropinone according to the procedure of Michaels and Zaugg:[12] mp 86–88°.

2,2,5,5-Tetradeuterio-9-methyl-3,9-diazabicyclo[4.2.1]nonan-4-one (Ib) was prepared from 2,2,4,4-tetradeuteriotropinone by the method of Paquette and Wise:[7a] mp 84–85°.

7,8-Dideuterio-9-methyl-3,9-diazabicyclo[4.2.1]nonan-4-one (Ic).—A solution of 26.0 g (0.20 mole) of 2,5-dimethoxy-2,5-dihydrofuran in 100 ml of dioxane was deuterated at atmospheric pressure over platinum oxide for 48 hr. The catalyst was separated by filtration and the filtrate was evaporated under reduced pressure. Careful fractionation of the residual liquid afforded 13.7 g of a center cut, bp 65° (65 mm).

A solution of 13.7 g (0.10 mole) of 3,4-dideuterio-2,5-dimethoxy-2,5-dihydrofuran and 80 ml of 0.2 *N* sulfuric acid was stirred for 15 min under nitrogen and allowed to stand for 5 hr in this atmosphere. The resulting solution was neutralized by the addition of approximately 4 g of barium carbonate, and the precipitated barium sulfate was collected and washed with water. The filtrate was added to a solution of 17.6 g (0.120 mole) of acetonedicarboxylic acid, 8.1 g (0.120 mole) of methylamine hydrochloride, 14.5 g of disodium hydrogen phosphate, and 8.5 g of potassium dihydrogen phosphate in 1 l. of water. The solution was stirred for 48 hr while carbon dioxide was evolved. The mixture was basified to pH 10–12, filtered to remove some polymeric material, and extracted several times with methylene chloride. Evaporation of the solvent and distillation of the residue afforded a yellow oil which was carefully redistilled to yield 3.45 g of pale yellow semisolid, bp 132–135° (40 mm).

To a solution of 3.45 g (24.5 mmoles) of 6,7-dideuteriotropinone in 30 ml of chloroform cooled to −5° was slowly added 7 ml of concentrated sulfuric acid, keeping the temperature below 15°. Sodium azide (3.2 g, 49 mmoles) was added portionwise over a 1-hr period below 35°. After the usual work-up,[7,12] there was obtained 3.1 g of hydroscopic white crystals of Ic, mp 83–84°, which was shown by mass spectrometry to consist of 67% d_2, 24% d_1, and 9% d_0 species.

3,9-Dimethyl-3,9-diazabicyclo[4.2.1]nonan-4-one (IIa) was prepared from Ia by the procedure of Paquette and Wise:[7b] bp 152–157° (13 mm).

5,5-Dideuterio-3,9-dimethyl-3,9-diazabicyclo[4.2.1]nonan-4-one (IIb).—A solution of 1.7 g (0.01 mole) of IIa and 100 mg of powdered potassium *t*-butoxide in 10 ml of *t*-butyl alcohol-*d* was refluxed overnight with protection from atmospheric moisture. On cooling, 2 ml of deuterium oxide was added. The solution was treated with 25 ml of chloroform and the organic solution was washed with water to remove the base. The chloroform layer was dried, filtered, and evaporated, and the residue was distilled through a Holtzmann column. The colorless liquid which distilled at 89–93° (1 mm), 1.25 g, was collected. This material consisted of 62% d_2, 28% d_1, and 10% d_0 species (mass spectrometry).

3-Ethyl-9-methyl-3,9-diazabicyclo[4.2.1]nonan-4-one (III).—A mixture of 4.6 g (0.03 mole) of Ia and 1.7 g (0.035 mole) of 50% sodium hydride–mineral oil dispersion in 50 ml of dimethylformamide was heated at 60° with stirring for 1 hr. With ice cooling, 6.25 g (0.04 mole) of ethyl iodide was slowly added. The usual work-up[7b] was followed to give 3.1 g (57.5%) of colorless liquid, bp 107–110° (0.75 mm), $n^{26.5}$D 1.4982.

10-Methyl-3,10-diazabicyclo[4.3.1]decan-4-one (IV) was prepared from pseudopelletierine according to the procedure of Paquette and Wise:[7b] mp 164–166°.

11-Methyl-3,11-diazatricyclo[4.4.1]undecan-4-one (V) was also prepared from homopseudopelletierine according to the procedure of Paquette and Wise:[7b] mp 111.5–112°.

(11) Mass spectra, other than high-resolution spectra,[9] were obtained with a Consolidated Electrodynamics Corp. mass spectrometer, Model No. 21-103C, using an all-glass inlet system maintained at 200°. An ionizing energy of 70 ev was used with an ionizing current of 50 μa.

(12) R. J. Michaels and H. E. Zaugg, *J. Org. Chem.*, **25**, 637 (1960).