The Synthesis and Deamination of a Deuterium-Labeled Spiropentylamine

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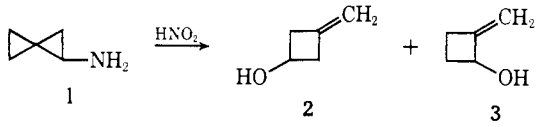
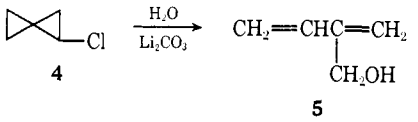
Abstract: Spiropentylamine has been synthesized with a deuterium label in the 4 position. Nitrous acid deamination has yielded 2- and 3-methylenecyclobutanols with deuterium distributed such as to suggest a mechanism involving initial ring enlargement or bicyclobutonium ion formation. Comparison is made with hydrolysis of spiropentyl chloride, which gives 2-hydroxymethyl-1,3-butadiene as the major product.

Previous work in this laboratory[1] has shown that the nitrous acid deamination of spiropentylamine (**1**) gives mainly the methylene cyclobutanols, **2** and **3**.



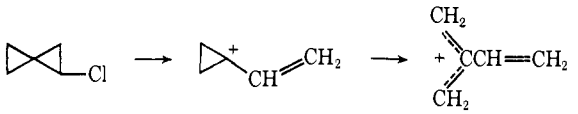
In contrast, the hydrolysis of spiropentyl chloride (**4**) at 95° gives only 2-hydroxymethylbutadiene (**5**).[3] The solvolysis of **4** in 50% aqueous ethanol at 200° is[4] slightly faster than that of cyclopropyl chloride,



suggesting little cyclopropylcarbinyl participation in **4**, though this conclusion is weakened by the knowledge that the solvolysis of cyclopropyl derivatives is itself assisted by delocalization.[5]

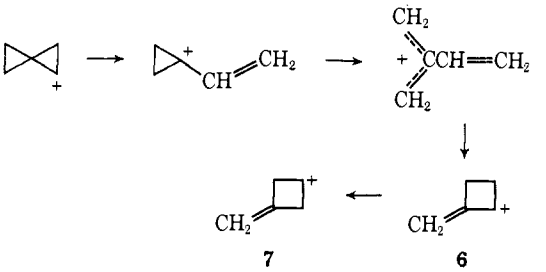
The product **5** and the solvolysis rate of **4** are most readily accounted for by a mechanism involving two successive or simultaneous ring openings of cyclopropyl cations (Scheme I). The mechanistic path for the

Scheme I



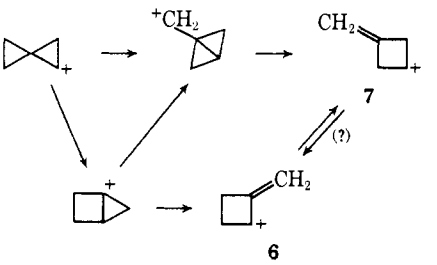
deamination of **1**, however, is less obvious and has been the subject of at least three discussions.[1,2,6] Two fundamentally different classical ways of accounting for the methylenecyclobutanols have been suggested. The first, shown in Scheme II, is an extension of the solvolysis mechanism proposed above, with an added ring closure of the isoprenyl cation to account for 2-methylenecyclobutanol, and a rearrangement of the allylic cation to the homoallylic one to account for 3-methylenecyclobutanol. The second mechanism, shown

Scheme II



in Scheme III, differs from the first in that the initial skeletal change is a reaction typical of cyclopropylcarbinyl (not cyclopropyl) cations, either a ring enlargement or a rearrangement to an isomeric cyclopropylcarbinyl cation. In this mechanism, the 2- and

Scheme III



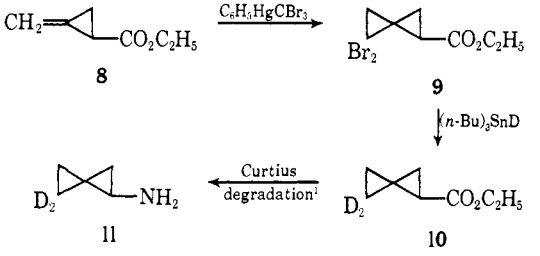
3-methylenecyclobutyl cations (**6** and **7**) may interconvert, but such interconversion is unnecessary to account for the products, since the cations may be formed independently by rational paths. It will be shown below that such interconversion is in fact not important, whatever the overall mechanisms may be.

The bicyclic cations in Scheme III may have some or all[1] of the delocalized character generally associated with cyclopropylcarbinyl and cyclobutyl cations. Classical structures provide an adequate framework for the discussion of the results reported here and are used for simplicity.

To distinguish the mechanisms represented in Schemes II and III, we have synthesized and deaminated a deuterium-labeled spiropentylamine. The synthesis (Chart I) employed familiar reactions and was noteworthy primarily in that the addition of dibromocarbene to **8** apparently gave only one of the two stereoisomers (*syn* or *anti*) of **9**. The product showed the simple 100-MHz nmr spectrum expected for one isomer (especially the unsplit triplet and quartet for the ethyl group) and was unresolvable by glpc on five different

(1) D. E. Applequist and G. F. Fanta, *J. Amer. Chem. Soc.*, **82**, 6393 (1960). The result has been confirmed by Konzelman and Conley.[2]
(2) L. M. Konzelman and R. T. Conley, *J. Org. Chem.*, **33**, 3828 (1968).
(3) (a) D. E. Applequist and W. A. Bernett, *Tetrahedron Lett.*, 3005 (1968); (b) W. A. Bernett, Ph.D. Thesis, University of Illinois, 1966.
(4) J. A. Landgrebe and D. E. Applequist, *J. Amer. Chem. Soc.*, **86**, 1536 (1964).
(5) P. von R. Schleyer and R. D. Nicholas, *ibid.*, **83**, 182 (1961).
(6) E. F. Kiefer and J. D. Roberts, *ibid.*, **84**, 784 (1962).

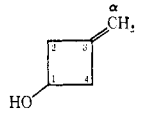
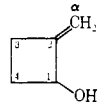
Chart I. Synthesis of Labeled Spiropentylamine



columns. The final deuterated spiropentylamine (**11**) was also presumably a single isomer, since none of the steps leading to it would be expected to epimerize the function-bearing carbon. As will be seen below, the results of the deamination reaction are most readily interpreted if the amine was at least preponderantly one epimer, if not a pure epimer.

The expected distribution of deuterium in the methylenecyclobutanols is easily derived by tracing through the steps in Schemes II and III. These distributions are summarized in Table I, together with the experimental

Table I. Label Distributions in Products of Deamination of 4,4-Dideuteriospiropentylamine (**11**)

Product	Scheme II	Scheme III (no **6** ⇄ **7**)	Obsd
 **2**	50% 2 50% α	50% 2 50% α	75% 2 25% α (26% yield)
 **3**	50% 3 50% α	50% 3 50% 4	100% (3,4) (5.4% yield)

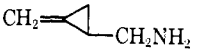
observations here reported. The deuterium distribution was obtained from the deuterium magnetic resonance spectra of the isolated alcohols. The resonances for positions 3 and 4 in alcohol **3** were not resolvable. The expected distributions for Scheme III are derived assuming no interconversion of cations **6** and **7**. If such interconversion were to occur, it would lead to labeling of **3** in the exocyclic methylene and/or an increase in ring label (as opposed to $=CH_2$ label) in **2**. The precise effects cannot be calculated without some assumptions of the relative rate constants in Scheme III, but since no label appears in the exocyclic methylene of **3** and since some *does* appear in the exocyclic methylene of **2**, it is clear that the interconversion **6** ⇄ **7** cannot be significant in the backward direction to yield **3** and in the forward direction cannot be the sole route to **2**.

The observed label distribution in alcohol **3** is clearly consistent with Scheme III and inconsistent with Scheme II. The label distribution in **2**, however, is consistent with neither mechanism in its simple form, since either mechanism requires (neglecting the secondary isotope effect) equal distributions of deuterium between exocyclic and endocyclic positions. The observations can be reconciled with modified forms of Scheme III, however. One possibility, as indicated above, is that some of the product **2** is formed by the pathway **6** → **7** → **2**. Evidence against this interpretation is offered below. A second possibility is that in the deamination of **11** rearrangement occurs simultaneously with loss of nitrogen[7] or at least before symmetrical solvation is achieved. The fully symmetrical spiropentyl cation is never formed. Under these conditions, more cation **12** may be formed than

cation **13**, with the result that **2** would be labeled more in the ring methylene than in the exocyclic methylene. This interpretation requires that **11** be predominantly one epimer, which is consistent with observations made in the synthesis, *vide supra*. If one assumes that the migrating group prefers to be *trans* to the departing nitrogen, then the *anti* configurations of **9**–**11** may be assigned from the labeling observed in product **2**. This assignment would also be consistent with a sterically determined stereoselectivity in the addition of dibromocarbene.

The possibility of involvement of the interconversion **6** ⇄ **7** has been tested by some independent experiments and by some observations in the literature. Roberts and Kiefer[6] found only 3-methylenecyclobutanol (**2**) as a product of nitrous acid deamination of 3-methylenecyclobutylamine in water. We have repeated this experiment to confirm the absence of **3** by the glpc analysis used in this laboratory. Wiberg, *et al.*,[8] have reported that 1-hydroxymethylbicyclobutane (**14**) reacts with triphenyl phosphite and benzyl bromide to give only 3-methylenecyclobutyl bromide (**15a**), or with *p*-toluenesulfonyl chloride in ether to give only 3-methylenecyclobutyl *p*-toluenesulfonate (**15b**). Nishimura, Kato, and Ohta[9] have reported that de-

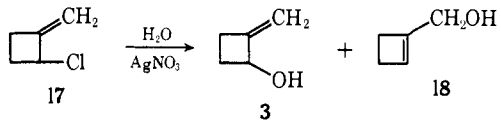
amination of 2-methylenecyclopropylcarbinylamine (**16**) gives product mixtures including 3-methylenecyclobutyl derivatives, but no 2-methylenecyclobutyl derivatives.



16

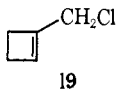
In this laboratory, it has been found that the 2-methylenecyclobutyl cation is likewise not prone to rearrange under at least some conditions. 2-Methylenecyclobutyl chloride (**17**), prepared in 19% yield by reaction of methylenecyclobutane with *t*-butyl hypochlorite, underwent silver ion induced hydrolysis at 55–60° to give only the allylic alcohols **3** and **18**. The

(7) M. Cherest, H. Felkin, J. Sicher, F. Sipos, and M. Tichy, *J. Chem. Soc.*, 2513 (1965).
(8) K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connor, P. Schertler, and J. Lavanish, *Tetrahedron*, 21, 2749 (1965).
(9) A. Nishimura, H. Kato, and M. Ohta, *J. Amer. Chem. Soc.*, **89**, 5083 (1967).



17 3 18

ratio of **3** to **18** varied between 4 and 7 with variation in the concentration of silver nitrate. Compound **18** was characterized by its spectra. The infrared spectrum was closely similar to that reported by Heyns, Molge, and Walter,[10] but the nmr spectrum showed rather different chemical shifts. The four broadened singlets in CCl_4 observed in this laboratory were at δ 1.58 (1 H), 2.47 (4 H), 4.00 (2 H), and 5.83 (1 H). Hydrolysis of 1-cyclobutenylcarbinyl chloride (**19**), also formed in the chlorination of methylenecyclobutane, gave the same alcohols **3** and **18**, but in ratios of 1–2.



19

In summary, the results of the deamination of labeled spiropentylamine support a mechanism in which cyclopropylcarbinyl rearrangement occurs (as in Scheme III) to give, by independent pathways, the methylenecyclobutyl cations **6** and **7**, which do not interconvert. It is further indicated that bridging or rearrangement of the spiropentyl cation occurs prior to complete removal of the nitrogen from the solvent shell, and may occur in part synchronously with breaking of the C–N bond. The contrast between the deamination reaction and the chloride solvolysis is thus not due to a trivial difference in relative rates of product-forming steps, but indicates a fundamentally different behavior of the spiropentyl cation intermediate, or of the transition states leading to it, when the leaving group is changed from chloride to nitrogen. The explanation cannot very well be found in the usual conformational "memory effects,"[11] but might be due either to differences in the solvation shells or to special structural–thermodynamic differences between the two cases. Further discussion at this time would be speculative.

Experimental Section[12]

Ethyl Methylenecyclopropanecarboxylate (8). A dry glass bomb liner fitted with a male joint of a Dry Ice trap was cooled in a Dry Ice–isopropyl alcohol bath (the small hole in the liner sealed from the atmosphere by means of electrical tape). A volume of *ca.* 25 ml of allene (Columbia Chemicals Co.) was distilled into the glass liner and 30.0 g (0.236 mol) of ethyl diazoacetate dissolved in 30 ml of methylene chloride was added, along with a mixture of 1.13 g of freshly ignited copper sulfate and 0.3 g of copper bronze. The electrical tape was removed and the liner placed in a steel bomb. The bomb was rapidly sealed and placed in a rocker assembly where it was heated to 90° and rocked for 6 hr. The bomb was first cooled to room temperature and then to −60° in a Dry Ice–isopropyl alcohol bath. The bomb was rinsed with methylene chloride, the liner was fitted with a gas outlet connected to a Dry Ice–isopropyl alcohol trap (the small hole in the liner again was covered with electrical tape), and the excess allene was removed by allowing the liner to warm to room temperature. The reaction mixture was filtered through Filter-Cel and the combined organic phases were extracted with two 100-ml portions of 3% hydrochloric acid, two 100-ml portions of water, and two 100-ml portions of 5% sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate for 24 hr. The organic phases from three such reactions were combined and the methylene chloride was removed by distillation through a 10-cm Vigreux column. The residue was distilled through a 50-cm glass helix packed column, and the product, 10.4 g (8.2%), was collected at 56–59° (15 mm) (lit.[13] 152–154°, 150–153°). The infrared and pmr spectra were identical with those of a sample prepared by the method of Carbon, *et al.*[13a]

Yields were erratic. Use of a larger portion of ethyl diazoacetate resulted in a damaging explosion. Methylene chloride seemed to moderate the reaction and perhaps improved the yields.

Ethyl 4,4-Dibromospiropentanecarboxylate (9). A dry 100-ml round-bottomed flask fitted with reflux condenser, gas inlet, and magnetic stirrer was charged with 75 ml of benzene which had been freshly distilled from calcium hydride, 28.1 g (0.053 mol) of phenyl(tribromomethyl)mercury, and 6.55 g (0.052 mol) of ethyl methylenecyclopropanecarboxylate under an argon atmosphere. The stirred mixture was immersed in an oil bath preheated to 95°. Most of the solid dissolved before reflux was reached and after 30 min a white precipitate appeared. The mixture was refluxed for an additional 7 hr, after which the reaction mixture was cooled and filtered to yield 18.9 g (99%) of phenylmercuric bromide, mp 281–283° (lit.[14] mp 283–285°). The benzene was then removed by distillation through a 10-cm Vigreux column. Distillation of the residue afforded 11.8 g (79.4%) of material of approximately 99% purity as determined by glpc (10% Apiezon L on Anakrom, 0.25 in. × 12 ft). The pmr spectrum at 100 MHz showed ethoxy signals at δ 4.08 (quartet, 2 H, J = 7.5 Hz) and 1.20 (triplet, 3 H, J = 7.5 Hz), a pair of overlapping quartets centered at 2.19 for the 1-hydrogen and at 2.08 for the 5-hydrogens, and a multiplet at 1.75 for the 2-hydrogens. Additional glpc columns used in attempts to separate stereoisomers included Apiezon L on Chromosorb W, Carbowax 20M on Chromosorb B, Apiezon L on Gaschrom Cl, and Carbowax 20M on Gaschrom Cl.

Anal. Calcd for $C_8H_{10}O_2Br_2$: C, 32.23; H, 3.36; Br, 53.66. Found: C, 32.47; H, 3.46; Br, 53.90.

Tri-*n*-butyltin Deuteride. A dry 500-ml round-bottomed flask fitted with a 100-ml equilibrating addition funnel, reflux condenser, magnetic stirrer, and gas inlet was charged with 1.321 g (0.0316 mol) of lithium aluminum deuteride and 200 ml of dry diethyl ether. The mixture was stirred and heated to reflux under a nitrogen atmosphere and a solution of 41.0 g (0.129 mol) of tri-*n*-butyltin chloride in 50 ml of dry ether was slowly added from the addition funnel. The solution was refluxed for an additional 14 hr, cooled and 0.50 g of hydroquinone was added. The solution was then treated with 50 ml of saturated potassium tartrate solution and filtered. The aqueous phase was separated and extracted with five 50-ml portions of ether. The combined ether phases were dried over sodium sulfate and the ether was removed by distillation through a 10-cm Vigreux column. The active deuterium content of the residue was determined after mixing known amounts of the residue and carbon tetrachloride by analyzing the mixture for deuteriochloroform by glpc (20% Apiezon L on Chromosorb W at 125°). The residue weighed 43.4 g and was 25.6% active reducing agent, corresponding to a 24% yield. The crude product was used without further purification.

Ethyl 4,4-Dideuteriospiropentanecarboxylate (10). A dry 250-ml round-bottomed flask fitted with reflux condenser, equilibrating addition funnel, gas inlet, and magnetic stirrer was charged with 81.6 g (0.0612 mol) of 22.8% tri-*n*-butyltin deuteride. The flask was stirred while 7.403 g (0.0250 mol) of ethyl 4,4-dibromospiropentanecarboxylate was added from the addition funnel, and a spontaneous reaction was noted. The stirred mixture was heated to 100° and after 30 min an aliquot was analyzed by glpc (Apiezon L on Chromosorb W at 175°). The chromatogram showed a peak with retention time of 21.0 min (identical with that of **9**) and two peaks which were not cleanly separated, with retention times of 11.4 and 12.6 min. After 1 hr the chromatogram showed only peaks at 11.4 and 12.6 min, and a peak at 3.2 min (identical with that of authentic ethyl spiropentanecarboxylate). The reaction was continued until after 3 hr the only peak present was that appearing at 3.2 min. The ester was then removed by distillation at reduced pressure (1.5 mm, maximum pot temperature 120°) into a Dry

(10) K. Heyns, K. Molge, and W. Walter, *Chem. Ber.*, **94**, 1015 (1961). Solvents were not identified.

(11) J. A. Berson, *Angew. Chem. Intern. Ed. Engl.*, **7**, 779 (1968).

(12) Temperatures are uncorrected. Pmr and dmr spectra and most of the infrared spectra were obtained by Mr. R. Thrift and his associates. Microanalyses were done by Mr. J. Nemeth and associates.

(13) (a) J. A. Carbon, W. B. Martin, and L. R. Swett, *J. Amer. Chem. Soc.*, **80**, 1002 (1958); (b) E. F. Ullman and W. J. Fanshawe, *ibid.*, **83**, 2379 (1961).

(14) D. Seyferth and J. M. Burlitch, *J. Organometal. Chem.*, 4, 127 (1965).

Ice trap, to yield 6.89 g of material. The distillate was analyzed by glpc and found to be 40% of the ester (overall yield of the reaction was 80.6%), with the only contaminant being ether. A portion of the distillate was purified by glpc (Apiezon L on Gaschrom Cl at 145°), and analytical and spectral data were obtained. The mass spectrum showed a parent peak at *m/e* 142. The infrared spectrum was closely similar to that of authentic ethyl spiropentanecarboxylate, and the pmr spectra differed only as expected in the intensity of the signal at δ 0.84 for the 4 and 5 positions.

Anal. Calcd for $C_8H_{10}D_2O_2$: C, 67.57; H, 8.66; atom % D, 16.67. Found: C, 67.42; H, 8.59; atom % D, 15.30.

β-Naphthyl 4,4-dideuteriospiropentylcarbamate was prepared from **10** by the published procedure[1] as a crystalline solid, mp 116–117° (lit.[1] for undeuterated material, 117–118.5°) in 32% yield. The mass spectrum showed a parent peak at *m/e* 255.

Anal. Calcd for $C_{16}H_{13}D_2NO_2$: C, 75.29; H, 5.92; Atom % D, 13.3. Found: C, 74.90; H, 5.90; Atom % D, 12.35.

Deamination of 4,4-dideuteriospiropentylamine from hydrolysis of the β-naphthyl carbamate was carried out as previously described.[1] Final separation of the products by glpc (20% didecyl phthalate on Chromosorb W at 95°) gave **2** and **3** at retention times of 26.0 and 20.8 min and in 26.2 and 5.4% yields, respectively. There were four minor products in smaller amounts.[2]

The dmr spectrum (15.35 MHz) of **2** showed two equal signals at δ 2.65 and 2.95 ppm, the same chemical shifts observed for the AB system of the ring methylene in the pmr spectrum, and another signal at 4.83 ppm, corresponding to the pmr shift of the exocyclic methylene. The ratio of the first pair to the last signal was 3.0:1.0. (The chemical shifts of deuterons are known to be the same as those of the corresponding protons.[15]) The region between 2.95 and 4.83 ppm, where the 1 proton of **2** occurs in pmr, was blank. The dmr spectrum of **3**, isolated in impure form by glpc, showed a resonance at δ 2.22 ppm, corresponding to the ring methylenes in pmr, but was blank in the regions corresponding[1] to the exocyclic methylene and the methine hydrogen at carbon-1.

2-Methylenecyclobutyl Chloride (17). A solution of 10.0 ml (7.35 g, 0.108 mol) of methylenecyclobutane, 15 ml of fluorotrichloromethane, and 10.0 ml (9.10 g, 0.084 mol) of *t*-butyl hypochlorite was illuminated with a 275-W General Electric sunlamp from a distance of 1 m. The yellow color faded after about 1 hr; irradiation was continued for an additional 30 min. Most of the fluorotrichloromethane was removed by distillation and the residue was separated by preparative vapor phase chromatography at 90° on a 6 ft × 3/8 in. column of 20% diisodecyl phthalate on Gaschrom P (base-washed) 100–120 mesh with 600-μl injections. Collection in Dry Ice cooled receivers gave 1.62 g (19%) of impure 2-methylenecyclobutyl chloride (**17**), $n^{24}D$ 1.4668, and 1.05 g (12%) of impure 1-(chloromethyl)cyclobutene (**19**), $n^{24}D$ 1.4683. Identification was done by pmr. The spectrum of **17** showed doublets at 4.92 and 5.13 ppm (J = 1.8 Hz) for the exocyclic methylene, a multiplet for the 1-hydrogen at 4.72 ppm, and a multiplet for the four ring methylene hydrogens at 2.50 ppm. The spectrum of **19** contained sharp singlets for the vinyl proton at δ 5.98 ppm and the $-CH_2Cl$ at 3.91 ppm, and a narrow multiplet for the ring methylenes at 2.52 ppm.

Anal. Calcd for C_5H_7Cl: C, 58.55; H, 6.88; Cl, 34.57. Found for methylenecyclobutyl chloride: C, 57.03; H, 7.14; Cl, 35.56. Found for 1-(chloromethyl)cyclobutene: C, 54.99; H, 6.71; Cl, 36.83.

Hydrolysis of Chlorides 17 and 19. In a typical run, 0.156 g of **19**, 0.38 g of silver nitrate, 0.10 g of dioxane, and 20 ml of water were mixed and stirred for 36 hr in a stoppered flask at 55–60°. The mixture was extracted continuously with ether for 36 hr. The ether extract was dried over sodium sulfate and concentrated through a Holzman column to a volume 5–10% of that of the initial aqueous solution. The concentrated extract was analyzed by vapor phase chromatography on a 6 ft × 3/8 in. column of 20% diisodecyl phthalate on Gaschrom P (base-washed, fluxed diatomaceous earth) 100–120 mesh at 85–90°. Peaks observed included one for **17** at t_d (time relative to dioxane) = 1.18 (21% of total area, identified by retention time only), recovered **19** at t_d = 1.61 (1.3%), **3** at t_d = 2.32 (52%), and **18** at t_d = 3.59 (26%). In similar runs with **17** and **19**, the range of results cited in the discussion were obtained, and the product alcohols were identified by comparison with authentic samples and literature spectroscopic data, also as discussed above.

Acknowledgments. This work was supported in part by the National Science Foundation and in part by the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the National Science Foundation and to the donors of the Petroleum Research Fund.

(15) L. K. Montgomery, A. O. Clouse, A. M. Crelier, and L. E. Applegate, *J. Amer. Chem. Soc.*, **89**, 3453 (1967).