Evidence for the formation of *exo* and *endo* aziridines in the reaction of *cis–endo* and *cis–exo*-bicyclo[2·2·1]-5-heptene-2,3-dicarboxylic anhydride and benzenesulfonyl azide[1,2]

A. C. Oehlschlager[3] and L. H. Zalkow

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332, and Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74075

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Benzenesulfonyl azide has been found to react with *cis–endo* and *cis–exo* bicyclo[2·2·1]-5-heptene-2,3-dicarboxylic anhydride to give in both cases, predominantly the more hindered *endo* aziridine in addition to the *exo* aziridine in apparent violation of the "*exo*-addition rule" (3). The stereochemistry of the aziridine rings were determined by nuclear magnetic resonance analysis and by conversion of the *endo*-aziridine-*exo*-anhydride to 2-*endo*-benzenesulfonamidobicyclo[2·2·1]heptane. The *endo*-aziridine-*endo*-anhydride has been previously (4) converted into a lactone-*N*-benzenesulfonyl-lactam.

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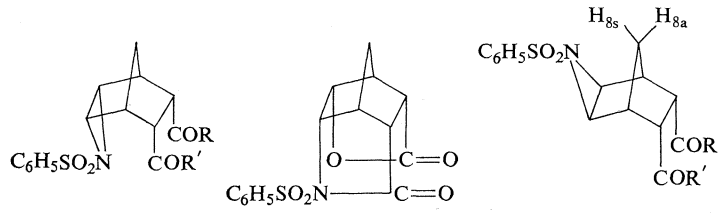


1 R = R′ = O
3 R = R′ = OCH_3

2

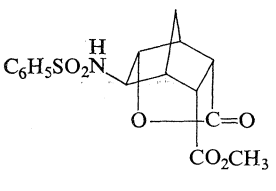
4 R = R′ = OCH_3

We have previously reported (4) that benzenesulfonyl azide reacts with bicyclo[2·2·1]-5-heptene-*endo*-cis-2,3-dicarboxylic anhydride in refluxing carbon tetrachloride to give the *endo* aziridine **1**, which was converted in two steps into **2**. After removal of crystalline **1**, the mother liquors were esterified with diazomethane in methanol–ether and then chromatographed on alumina. In addition to **3**, the dimethyl ester derived from **1**, there was thus obtained the previously unreported *exo* aziridine **4** in about 20% yield.

The infrared spectrum of **4** showed the presence of ester (1740 cm^{-1}) and benzenesulfonamido (1325, 1200, 1160 cm^{-1}) groups but the absence of N—H and C=N absorptions. The nuclear magnetic resonance (n.m.r.) spectrum of **4** showed two protons, by integration, at low field (δ 3.13) which could be assigned to carbons bearing nitrogen. Since this signal was much sharper (width at half-height, $w_{1/2h}$ = 2 c.p.s.), then the corresponding signal (δ 2.63, $w_{1/2h}$ = 6.5 c.p.s.) in **3** the *exo* aziridine structure was suggested. Additional support for the assignment of an *exo* aziridine structure to **4** was found in the positions of the C-8 protons in the n.m.r. Thus one proton (C-8*a*) appeared as a doublet: $J_{8a,8s}$ = 10.5 c.p.s.) at δ 0.90 whereas the other (C-8s) appeared at δ 1.70. By contrast, in **3** the C-8 protons gave similar doublets but centered at δ 1.54 and δ 1.98. Tori *et al.* (5) have shown that an *exo* aziridine ring produces an anisotropic shielding effect on the 8-*anti* proton. Additional support for structure **4** has been provided (6) by the conversion of **4** to the lactone **5**, which differs from the previously reported (6) **6** in not being readily converted into **2**. Finally, the carbomethoxy groups and the bridgehead protons in **4** are each magnetically equivalent, indicating that no epimerization of the carbomethoxy groups occurred in the reaction.

The reaction of benzenesulfonyl azide with bicyclo[2·2·1]-5-heptene-*exo–cis*-dicarboxylic anhydride in refluxing carbon tetrachloride also led to the formation of two isomeric products

[1]For a preliminary account of this work see ref. 1.
[2]Bridged ring compounds. XIV. For Part XIII, see ref. 2.
[3]Present address: Department of Chemistry, Simon Fraser University, Burnaby 2, British Columbia.



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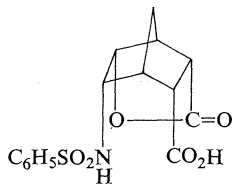

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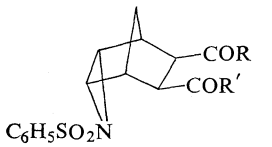
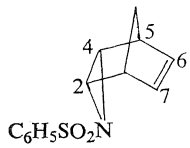


7*a* R=R′=O
7*b* R=R′=OCH_3

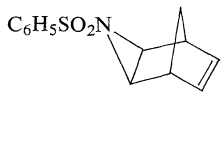
which could be separated in a manner similar to that described above. The predominant product (≃74%), which crystallized from the reaction mixture in benzene, was originally assigned (4) the *exo* aziridine structure. This product is now known to be the *endo* aziridine **7***a*. Thus the n.m.r. spectrum of **7***b*, the dimethyl ester derived from **7***a*, showed a broad signal ($w_{1/2h}$ = 6.5 c.p.s.) for the C-6, C-7 protons centered at δ 3.50. However, a more definitive proof of the stereochemistry of the aziridine ring in **7** was sought and provided as follows.

Anhydride **7***a* was converted into the corresponding *exo–cis* dicarboxylic acid in boiling water. That no epimerization occurred under these conditions was shown by conversion of a small amount of the diacid into **7***b* with methanolic diazomethane. On treatment with lead tetraacetate in pyridine the diacid gave **8**. The unsaturated aziridine **8** was found to differ from the previously reported (7) **9**, the latter being very unstable and readily rearranging to **10**. Hydrogenation of **8** gave **11** which again differed from the previously reported (8) *exo* aziridine **12**. In particular, the C-2 and C-4 protons in **11** appeared as a broad signal ($w_{1/2h}$ = 6 c.p.s.) whereas in **12** they appear as a sharper singlet ($w_{1/2h}$ ~2 c.p.s.). Finally, treatment of **11** with potassium thiophenoxide gave **13** which on reductive removal of the thiophenoxy group gave the known (9) 2-*endo*-benzenesulfonamidobicyclo[2·2·1]heptane, **14**. The preparation of **14** from **7** shows that



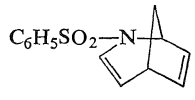
8

11 6,7-dihydro



9

12 6,7-dihydro



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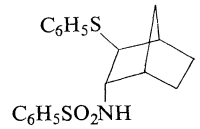

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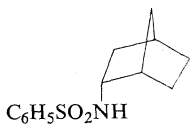

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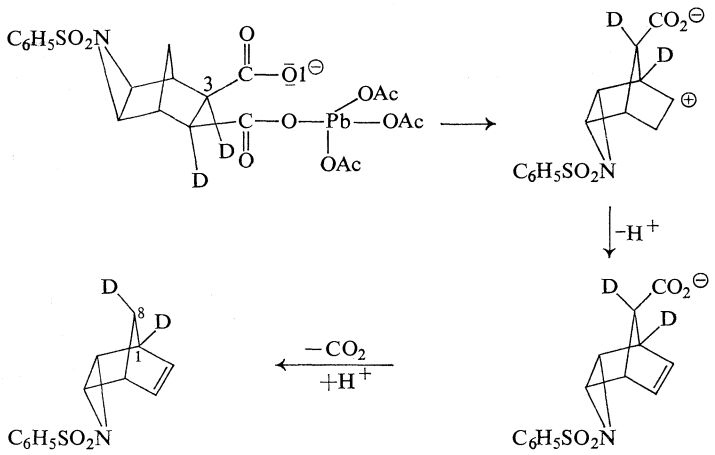
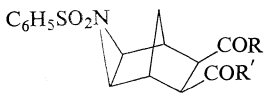
the aziridine ring in **7** is *endo* if no skeletal rearrangement has occurred. However, it is not unreasonable that during decarboxylation skeleton rearrangement did occur and that **7** therefore possesses an *exo* aziridine ring as illustrated in Scheme I. It is well known (10) that cationic intermediates are generated during oxidative decarboxylations using lead tetraacetate and the bicyclo[2·2·1]heptane ring system is particularly prone to rearrangment in reactions in which a nuclear cationic charge is generated (11). In such a rearrangement (illustrated in Scheme I), the original carbon atoms C-6 and C-7 end up at positions C-1 and C-8. To determine if rearrangement occurred carbon atoms C-6 and C-7 were labeled with deuterium as follows. Maleic anhydride-d_2 and cyclopentadiene were condensed in a Diels–Alder reaction to give 2,3-*exo*-dideuterio-2,3-*endo*-dicarboxybicyclo[2·2·1]-5-heptene anhydride, which was partially converted into 2,3-*endo*-dideuterio-2,3-*exo*-dicarboxybicyclo-[2·2·1]-5-heptene anhydride on heating at 200°. The latter, on treatment with benzenesulfonyl azide in refluxing carbon tetrachloride, gave 2,3-dideuterio-**7** which contained 71±2% deuterium at C-6 and C-7. Hydrolysis in D_2O gave the corresponding acid, which on oxidative decarboxylation with lead tetraacetate gave **8** which contained 72±2% deuterium at C-6 and C-7. Thus no skeletal rearrangement occurred during the decarboxylation.

The n.m.r. spectrum of the dimethyl ester of the minor product (~22%) from the reaction of benzenesulfonyl azide and bicyclo[2·2·1]-5-heptene-*exo–cis*-2,3-dicarboxylic anhydride has

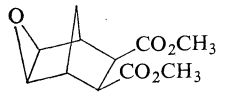


SCHEME I

been assigned structure **16** on the basis of the following evidence. The protons at C-6 and C-7 appeared as a sharp singlet ($w_{1/2h}$ = 2.5 c.p.s.) at δ 3.03, characteristic of *endo* protons and therefore an *exo* aziridine ring. Because of the presence of *exo*-carbomethoxy groups in **16**, the deshielding of the 8-*anti* proton by the *exo* aziridine ring is not so apparent in this case. The n.m.r. spectrum of **16** was very similar to that of



15 R = R′ = O
16 R = R′ = OCH_3



17

17. Thus in **16** the protons at C-1, C-2, C-4, and C-5 appeared as a narrow signal at δ 2.82, while in **17** these protons gave a similar signal at δ 2.80. In **16** the C-8 protons showed an AB quartet (J = 11 c.p.s.) with the two doublets centered at δ 1.47 and 1.75 while in **17** the two doublets (J = 10.5 c.p.s.) appeared at δ 1.33 and 1.64.

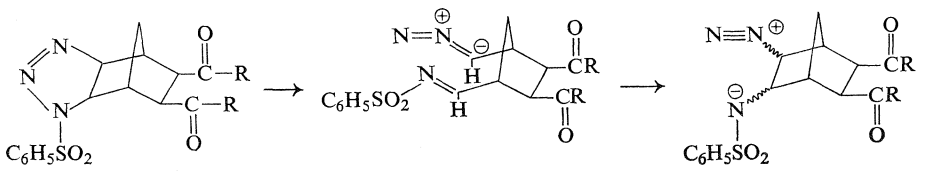
Detailed studies of the reactions of aryl and aryl-sulfonyl azides with bicyclo[2·2·1]heptene derivatives have provided an insight into the mechanism by which bicyclo[2·2·1]-5-heptene *endo* and *exo–cis*-2,3-dicarboxylic anhydrides react with benzene sulfonyl azide to give both *exo* and *endo* aziridine products (6). These investigations indicate the reaction involves the conversion of an initially formed, unstable *exo*-1,2,3-Δ^2 triazoline adduct **18** to a diazoimine intermediate **19** which rearranges with loss of nitrogen (via **20**) to the observed *exo* and *endo* aziridine products.

Experimental

Melting points were taken on a Fisher–Johns apparatus and are uncorrected. Infrared (i.r.) spectra were recorded with a Beckman IR-5 spectrophotometer, n.m.r. spectra were obtained with the Varian A-60 spectrometer, using tetramethylsilane (TMS) as an internal standard (δ = 0) and using deuteriochloroform, carbon tetrachloride, or carbon disulfide as a solvent. Carbon and hydrogen analyses were performed by Midwest Microlabs, Inc., Indianapolis, Indiana.

Reaction of Benzenesulfonyl Azide with Bicyclo[2·2·1]-5-heptene-endo–cis-2,3-dicarboxylic Anhydride

A solution of bicyclo[2·2·1]-5-heptene-2,3-*endo–cis*-dicarboxylic anhydride (4.4 g, 26.8 mmole) and benzenesulfonyl azide (6.0 g, 32.8 mmole) in 65 cm^3 carbon tetrachloride was refluxed for 48 h. The solvent was removed *in vacuo* and **1** (4.13 g, 13.0 mmole) crystallized from benzene–acetone to give m.p. 206–210°. The crystalline product had m.p. 215–216° (lit. (4), m.p. 215–216.5°)



18 **19** **20**

after recrystallization from acetone. The mother liquors were combined and concentrated. The concentrate was treated with excess diazomethane in ether–methanol. The esterified mixture was concentrated and chromatographed directly on 250 g of Merck acid-washed alumina. Elution with 0.5 l of benzene gave 0.71 g of benzenesulfonyl azide. Elution with 1 l of benzene–chloroform (9:1) gave dimethyl bicyclo[2·2·1]-5-heptene-2,3-*endo–cis*-dicarboxylate (0.252 g, 1.2 mmole). Elution with 1 l (8:2), 0.5 l (7:3), and 0.7 l benzene–chloroform (6:4) gave **4** (1.76 g, 4.8 mmole). The analytical sample, prepared by crystallization from methanol, had m.p. 113–114°; ν_{max}(KBr) 1740, 1325, 1200, 1160, and 880 cm^{-1}; n.m.r. (in $CDCl_3$) δ 0.90 (*anti* C-8 proton, doublet, J = 10.5 c.p.s.), 1.70 (*syn* C-8 proton, doublet, J = 10.5 c.p.s.), 2.83 (protons at C-1 and C-5), 3.13 (protons at C-2 and C-4), 3.53 (protons at C-6 and C-7), 3.67 (6 protons of dimethyl ester), and 7.5–8.1 (5 aromatic protons).

Anal. Calcd. for $C_{17}H_{19}O_6NS$: C, 55.88; H, 5.24. Found: C, 56.22; H, 5.45.

Continued elution with 0.4 l of benzene–chloroform (6:4) gave **3** (0.86 g, 2.4 mmole) which had m.p. 129–130° after recrystallization from ether (lit. (4), m.p. 130–131°). Elution with 2 l of chloroform gave 0.77 g of an unidentified oil containing N—H absorption in the i.r. and whose n.m.r. spectrum showed several methoxyl signals. Thin-layer chromatographic analysis showed this material to be a mixture of several very polar components.

Reaction of Benzenesulfonyl Azide with Bicyclo-[2·2·1]-5-heptene-exo–cis 2,3-dicarboxylic Anhydride

A solution of bicyclo[2·2·1]-5-heptene-*exo–cis*-2,3-dicarboxylic anhydride (4.77 g, 29 mmole) and benzenesulfonyl azide (5.95 g) in 62 cm^3 of carbon tetrachloride was refluxed for 48 h during which time a gummy solid precipitated. The solvent was stripped *in vacuo* and the precipitate partially crystallized from benzene to give **7** (4.18 g, 13.1 mmole), m.p. 167–168°, (lit. (4), 168–168.5°). The mother liquors were concentrated and treated with excess diazomethane in ether–methanol. The esterified mixture was chromatographed on 500 g of Merck acid-washed alumina. Elution with 0.5 l benzene gave 0.69 g of benzenesulfonyl azide. Continued elution with 1.5 l of benzene gave 0.65 g (3.1 mmole) of dimethylbicyclo-[2·2·1]-5-heptene-*exo–cis*-dicarboxylate. Elution with 1 l (9:1), 1 l (8:2), and 1 l (7:3) benzene–chloroform gave 0.245 g of a mixture which was shown by n.m.r. analysis to contain 1.5 1 mmole of dimethylbicyclo[2·2·1]-5-heptene-*exo–cis*-dicarboxylate and 0.6 mmole of **8**. Elution with 1 l (6:4) benzene–chloroform gave 2.94 g of a mixture of 4.3 mmole of **8** and 3.7 mmole of **16**. Elution with 1 l (1:1) benzene–chloroform gave 1.12 g of a mixture of 1.05 mmole **8** and 2.05 mmole **16**. Crystallization of the last mentioned eluate from ether gave 0.35 g of **16**, m.p. 149–149°; ν_{max}(KBr) 1740, 1365, 1322, 1220, and 1160 cm^{-1}; n.m.r. (in $CDCl_3$) δ 1.47 (*anti* C-8 proton, doublet, J = 11 c.p.s.), 1.75 (*syn* C-8 proton, doublet, J = 11 c.p.s.), 2.82 (protons at C-1, C-2, C-4, and C-5), 3.03 (protons at C-6 and C-7), 3.68 (6 protons of dimethyl ester), and 7.5–8.0 (5 aromatic protons).

Anal. Calcd. for $C_{17}H_{19}O_6NS$: C, 55.88; H, 5.24. Found: C, 56.11; H, 5.07.

Elution with 1 l (1:9) benzene–chloroform gave 0.35 g of an unidentified oil which showed N—H absorption in the i.r. and several methoxyl signals in the n.m.r. spectrum. Thin-layer chromatographic analysis showed this to be a mixture of several polar components.

*Decarboxylation of 7: Preparation of N-Benzenesulfonyl-3-azatricyclo[3·2·1·$0^{2,4\ endo}$]-5-octene (**8**)*

Aziridine **7** (2.37 g) was dissolved in 100 cm^3 of hot water over a period of 20 min. Upon cooling 2.08 g of aziridine diacid precipitated and had m.p. 180–182°. The dimethyl ester was prepared using diazomethane and after recrystallization from petroleum ether had m.p. 102–103° (lit. (4), m.p. 102–103)°.

The aziridine diacid (1.49 g) was dissolved in 50 cm^3 dry pyridine at 50° under nitrogen. Lead tetraacetate (4.33 g) was added and the temperature was raised to 80° over a period of 20 min. The reaction mixture was cooled and the pyridine evaporated under vacuum. The residue remaining was taken up in 50 cm^3 of chloroform which was washed with 30 cm^3 of dilute hydrochloric acid and filtered. The chloroform portion was decanted, dried over anhydrous magnesium sulfate, and evaporated to give ca. 0.9 g of a dark oil. Thin-layer chromatography on Silica Gel-G (15 cm) in chloroform gave three small spots below R_f 0.25 and one large spot at R_f 0.60. Chromatography of this residue on 29 g of Merck acid-washed alumina gave 0.67 g (58%) of **8** m.p. 90–92°, eluted in benzene. The analytical sample of **8** was prepared by recrystallization from ethanol and had m.p. 92–93.5°; ν_{max}(KBr) 1305, 1155, 715 cm^{-1}; n.m.r. (in $CDCl_3$) δ 1.76 (2 protons at C-8), 2.87 (protons at C-1 and C-5), 3.55 (protons at C-2 and C-4, triplet, J = 1.8 c.p.s.), 5.86 (protons at C-6 and C-7, triplet, J = 1.5 c.p.s.), and 7.3–8.1 (5 aromatic protons).

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 63.04; H, 5.29.

*Preparation of N-Benzenesulfonyl-3-azatricyclo-[3·2·1·$0^{2,4\ endo}$]-octane (**11**)*

The unsaturated aziridine **8** (0.24 g) was hydrogenated in the presence of 0.2 g of 10% palladium-on-charcoal catalyst in 50 cm^3 of methanol under hydrogen at atmospheric pressure. The theoretical volume of hydrogen was absorbed in 15 min. Removal of the catalyst by filtration followed by evaporation of the methanol gave 0.21 g of **9**, b.p. (0.03 mm) 150±5°; ν_{max}(film) 1310, 1160, and 910 cm^{-1}; n.m.r. (in CS_2) δ 1.2–1.5 (5 protons), 1.83 (1 proton, doublet, J = 9.5 c.p.s.), 2.31 (protons at C-1 and C-5), 3.29 (protons at C-2 and C-4, triplet, J = 2 c.p.s.), and 7.4–8.0 (5 aromatic protons).

*Preparation of 2-exo-Thiphenoxy-3-endo-benzenesulfonamidobicyclo[2·2·1]heptane (**8**)*

A solution of 0.83 g of **11** and thiophenol (0.70 g) in 7 cm^3 of 0.1 *N* potassium *tert*-butoxide in *t*-butyl alcohol was refluxed overnight. The reaction mixture was poured onto water and neutralized with 5% hydrochloric acid. The aqueous solution was extracted with ether which was then dried over anhydrous magnesium sulfate. Evaporation of the ether extract gave 1.15 g of **13** which, after washing with petroleum ether, had m.p. 114–115°; n.m.r. (in nitrobenzene containing CF_3COOH); δ 1.1–1.9 (6 protons), 2.08 (proton at C-1, broad multiplet), 2.25 (proton at C-4, broad multiplet), 2.98 (proton at C-2, quartet, $J_{2,3}$ = 4 c.p.s., $J_{2,7\text{-}anti}$ = 2 c.p.s.), and 3.54 (proton at C-3, triplet, $J_{2,3} = J_{3,4}$ = 4 c.p.s.).

Anal. Calcd. for $C_{19}H_{21}NO_2S_2$: C, 63.48; H, 5.89. Found: C, 63.37; H, 6.05.

Conversion of ***13*** *to 2-endo-Benzenesulfonamidobicyclo-[2·2·1]heptane (****14****)*

The thiophenol addition product **13** (0.71 g) was refluxed for 15 h with a slurry of 6 g of Raney nickel (W-2) in 15 cm³ of isopropyl alcohol. The solution was filtered and the catalyst was washed several times with ethanol. Evaporation of the alcohol filtrate gave 0.18 g of **14**, m.p. 104–105°. The mixture melting point with authentic **14** which had m.p. 104–105°, prepared as described previously (9), was undepressed. Mixture melting point with 7-benzenesulfonamidobicyclo[2·2·1] heptane, m.p. 103–104°, prepared as described earlier (9), gave m.p. 90–93°. Authentic 2-*exo*-benzenesulfonamidobicyclo[2·2·1]heptane gave m.p. 89–91°, well below that of **14**.

Preparation of N-Benzenesulfonyl-3-azatricycolo [3·2·1·$0^{2,4\ endo}$]-octane-6,7-endo-dideuterio-6,7-exo-dicarboxylic Anhydride

A mixture (3.9 g) of 2,3-*exo*-dideuterio-2,3-*endo*-dicarboxybicyclo[2·2·1]-5-heptene anhydride and the protio species were prepared by the reaction of maleic anhydride-d_2 and cyclopentadiene according to the procedure of Van Sickle and Rodin (12). Analysis of the mixture by n.m.r. showed 70 ± 5% deuterium in the 2,3 positions.

Heating 3.3 g of the *endo* anhydride in an open flask at 200° for 2 h gave a mixture of *endo* and *exo* anhydrides from which 0.72 g of the *exo* anhydride crystallized in benzene (13). Gas–liquid chromatography using a 0.25 in. × 10 ft column of 5% SE-30 on acid-washed Chromosorb at 180° with helium flow rate of 80 cm³ per min showed the *exo* anhydride to be uncontaminated with the *endo* anhydride. Analysis by n.m.r. showed the *exo* anhydride to contain 71 ± 2% deuterium in the 2,3-positions.

A solution of 0.65 g deuterated *exo* anhydride and 0.59 g benzenesulfonyl azide in 10 cm³ of carbon tetrachloride was refluxed for 36 h. The carbon tetrachloride was decanted and the residue was crystallized thrice from benzene to give 0.4 g of **7**-6,7-$d_{1,4}$, m.p. 167–168°. Analysis by n.m.r. showed 71 ± 2% deuterium at C-6 and C-7.

Preparation of N-Benzenesulfonyl-3-azatricyclo-[3·2·1·$0^{2,4\ endo}$]-6,7-dideuterio-5-octene

Aziridine **7**-6,7-$d_{1,4}$ (0.4 g) was dissolved in 15 cm³ of hot 80% D_2O over a period of 30 min. Evaporation of the aqueous portion *in vacuo* gave 0.41 g of the corresponding diacid which after drying over phosphorus pentoxide for 12 h had m.p. 181–183°; ν_{max}(KBr) 1750 cm^{-1}.

The aziridine diacid (0.41 g) was dissolved in 13 cm³ dry pyridine under nitrogen at 50° and 1.19 g of lead tetraacetate was added. The reaction mixture was stirred at 75° for 20 min and then worked up by the usual procedure. Chromatography of the reaction mixture directly on Merck acid-washed alumina gave 35 mg of **8**-6,7-$d_{1,4}$, m.p. 90–91°, eluted in benzene. Analysis of **8**-6,7-$d_{1,4}$ by n.m.r. showed 72 ± 2% deuterium at C-6 and C-7.

1. A. C. Oehlschlager and L. H. Zalkow. Chem. Commun. 5, 1 (1966).
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