Catalytic Synthesis of Heterocycles. XI.[1] Dehydrocyclization of *o*-Ethylbenzeneselenol to Selenonaphthene[2]

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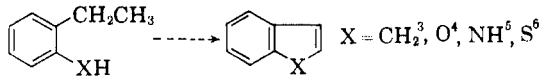
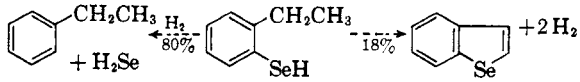
A procedure for the synthesis of *o*-ethylbenzeneselenol has been developed. The vapor phase catalytic dehydrogenation of this benzeneselenol to selenonaphthene in 18% yield is discussed.

In continuing our work on the catalytic synthesis of heterocycles it was decided to attempt to extend ring closures of the type to selenium compounds.



Of the four types of ring closures indicated above, those involving the thiol group go most easily and in best yield. With chromium oxide catalysts the thiophene ring forms *via* dehydrogenation at temperatures of 425–450° while temperatures of 525–625° are necessary for the formation of the furan, pyrrole, and cyclopentadiene rings. With sulfur compounds, a side reaction which may be serious is the hydrogenolysis of the C—S bond to hydrogen sulfide and the hydrocarbon. Thus, from the work with other heterocycles it was expected that *o*-ethylbenzeneneselenol would dehydrocyclize at relatively low temperatures of around 400°, but it was also expected that hydrogenolysis might predominate over dehydrocyclization. This proved to be true. Under the best conditions about 80% hydrogenolysis occurred along with 18% cyclization. Although part of the hydrogen for the hydrogenolysis indicated in Equation B below could be obtained from reaction A, this would not be sufficient.



Some of the hydrogen must come from the conversion of the ethyl group to a vinyl group and no doubt considerable styrene formed along with the ethylbenzene, although no attempt was made to determine the amount. No unreacted *o*-ethylbenzeneselenol was found.

EXPERIMENTAL

o-Bromoethylbenzene. In a 2-l. beaker was placed 121 g. of commercial grade of *o*-ethylaniline and 225 ml. of 48% hydrobromic acid. The mixture was warmed to dissolve the salt and then quickly cooled with stirring to 0°. The resulting slurry was diazotized with a solution of 69 g. of sodium nitrite in 125 ml. of water. Although the temperature was held below 5° during this process, considerable amounts of ethylphenol were observed to form. After the diazotization was completed the diazonium solution was poured onto a solution of cuprous bromide made from 250 g. of $CuSO_4$-$5H_2O$.[7]

The cuprous bromide so made was dissolved in 75 ml. of 48% hydrobromic acid. The cold diazonium salt was added to a cold solution of the cuprous bromide with stirring and the mixture allowed to come slowly to room temperature. It was then warmed and finally steam distilled. The organic layer was separated from the distillate and washed first with sodium hydroxide solution, then concentrated sulfuric acid, and then water. After the solution was dried over calcium chloride, it was distilled. The yield was 104.5 g. (56.5%) b.p. 195–197°/730 mm. A boiling point of 199.5° has been reported for material made by another procedure.[8]

o-Ethylbenzeneselenol. In the synthesis of this compound the general procedure of Foster[9] was used. The Grignard reagent from 55 g. of o-bromoethylbenzene was prepared in 250 ml. of dry ether in a three-neck flask fitted with a dropping funnel, a reflux condenser, and a sealed stirrer. After the reagent was prepared the dropping funnel was removed and an addition tube with 22 g. of selenium attached. During the preparation of the Grignard reagent as well as during the preparation of the beneneselenol, the system was kept under a nitrogen atmosphere. The ether solution of the Grignard reagent was brought to the boiling point and the selenium was added slowly over a period of about 45 min. with good stirring. Stirring and refluxing were continued for an additional 45 min. and then the mixture was poured onto crushed ice. After acidification with hydrochloric acid it was filtered through glass wool into a separatory funnel. The product was extracted with ether and the ether extracts were combined and dried over magnesium sulfate. Evaporation of the ether and distillation gave 26.5 g. (48.2%) of *o*-ethylbenzeneselenol b.p. 61–67°/0.9 mm. A center cut showed n_D^{25} 1.5728.

Anal. Calcd. for $C_8H_{10}Se$: C, 51.90; H, 5.45. Found: C, 51.96; H, 5.88.

Selenonaphthene. The procedure for the dehydrogenation was similar to that previously described.[10] Two different catalysts were investigated. One consisted of 1% platinum on coconut charcoal supplied commercially by the Baker Company and the other was a copper-chromium-charcoal catalyst used in our earlier work.[8] Essentially the same yield was obtained with each catalyst. In a typical experiment 10 g. of *o*-ethylbenzeneneselenol was dissolved in 25 ml. of dry thiophene-free benzene. This solution was then passed over the catalyst at a temperature of 425° during the course of 30 min. The gas evolved in the dehydrogenation was passed through a weighed ascarite tube to remove any hydrogen selenide and then measured in a wet test meter. (After the run the system was swept out with hydrogen to

(1) For the previous paper in this series, see *J. Org. Chem.* **23**, 1924 (1958).

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insure that all the hydrogen selenide was absorbed by the ascarite.) The rate of gas evolution remained almost constant during the 30-min. period with the copper-chromium catalyst, indicating that at least a rapid rate of poisoning did not occur. The platinum catalyst was much more susceptible to poisoning and at the end of 20 min. the rate of hydrogen evolution was less than one third of an initial rate more rapid than that of the copper-chromium catalyst. Running the benzeneselenol over the catalyst at slower rates or higher or low temperatures did not increase the yield. In a typical experiment (using 10 g. of *o*-ethylbenzeneselenol) with the copper-chromium catalyst, the ascarite tube gained 0.355 g. which would indicate that about 80% of the benzeneselenol underwent hydrogenolysis to give hydrogen selenide. After the run the catalyst tube was washed with benzene which was allowed to run down into the condensate. The benzene solution was then washed with dilute sodium hydroxide and then water. After the solution was dried over magnesium sulfate most of the benzene was removed by distillation through an efficient column. The residue which still contained some benzene was flash distilled to give first a forerun of benzene with some selenonaphthene. The material which boiled above 200° was collected and after crystallization from methanol, 1.72 g. of material of m.p. 50–51° was obtained. The picrate of this material melted at 155–157°. When the forerun from the distillation was treated with picric acid, 0.4 g. of picrate of m.p. 151–153° was obtained. The melting point of selenonaphthene has been reported as 50–51° and its picrate as 156–157°.[11]

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III. Synthesis of Dihydrosphingosine-1,3-cyclophosphate[1]

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In a previous communication,[2] it was reported that in the preparation of dihydrosphingosine-1-phosphate from sphingosine which is D-erythro-1,3-dihydroxy-2-amino-4-trans-octadecene,[3] *N*-carbobenzoxydihydrosphingosine reacted with only 1 mole of diphenylphosphoryl chloride to yield *N*-carbobenzoxy-1-diphenylphosphoryl dihydrosphingosine. It was thought that knowledge of this reaction would possibly be utilized in the synthesis of several phosphate diesters in which the primary hydroxyl group of dihydrosphingosine and another nitrogen-containing moiety, such as ethanolamine, choline, or serine, are esterified with phosphoric acid. In a series of reactions under a variety of conditions, *N*-carbobenzoxydihydrosphingosine-1-phenylphosphoryl *N*-carbobenzoxyethanolamine, the desired intermediate in the preparation of dihydrosphingosine-1-phosphoryl-ethanolamine, could not be obtained by the addition of *N*-carbobenzoxyethanolamine to *N*-carbobenzoxydihydrosphingosine and phenylphosphoryl dichloride. Similar results were obtained when choline chloride was substituted for the protected ethanolamine in the above reaction. However, from each reaction mixture a crystalline derivative was isolated in reasonable yield. These derivatives had the same melting point and similar contents of nitrogen and phosphorus. Removal of the protective groups by catalytic hydrogenolysis over platinum yielded a monophosphate ester of dihydrosphingosine. Since this compound consumed no periodic acid under conditions that cleaved dihydrosphingosine-1-phosphate, it was concluded to be dihydrosphingosine-1,3-cyclophosphate and its immediate precursor thus was *N*-carbobenzoxydihydrosphingosine-1,3-phenylcyclophosphate. Further confirmation of this structure was provided by its conversion to the phosphate monoester by opening of the diester ring after acid hydrolysis. This yielded essentially the 1-isomer, the 3-isomer being undetected, which was ascertained by the finding of palmitaldehyde after periodic acid oxidation of the isolated phosphate monoester.

EXPERIMENTAL

N-Carbobenzoxydihydrosphingosine-1,3-phenylcyclophosphate (I). A chilled solution of 6.5 g. of *N*-carbobenzoxydihydrosphingosine[2] in 30 ml. of anhydrous pyridine was added with vigorous stirring for 3–5 min. to 3.2 g. of phenylphosphoryl dichloride[4] in 10 ml. of pyridine surrounded by an ice bath. After standing for 30 min. at 0°, the reaction mixture, upon attaining room temperature, was poured into 500 ml. of crushed ice water. When the precipitate aggregated, it was removed by suction filtration, dried over phosphorus pentoxide *in vacuo*, and crystallized from 200 ml. of n-heptane; yield 3.1 g. (36% of theory); m.p., 81–82°.

Anal. Calcd. for $C_{32}H_{48}O_6NP$ (573.4): C, 66.87; H, 8.44; N, 2.44; P, 5.40. Found: C, 66.86; H, 8.72; N, 2.45; P, 5.47.

Dihydrosphingosine-1,3-cyclophosphate (II). 2.0 g. of I were dissolved in 50 ml. of glacial acetic acid containing 200 mg. of platinum oxide and hydrogenated under slightly above atmospheric pressure and room temperature. When the uptake of hydrogen ceased, the reaction mixture was filtered; the filtrate was diluted with 6 volumes of water and brought to *p*H 4.0–5.0 (*p*H paper) with 5*N* NaOH. After chilling the solution in an ice bath, the precipitate was removed, dried over phosphorus pentoxide, and crystallized from 100 ml. of 85% ethanol. The moist precipitate obtained after crystallization was washed successively on the filter with 20 ml. portions of ethanol (twice), acetone, and ether; yield 0.45 g. (35% of theory). Dihydrosphingosine-1,3-cyclophosphate is insoluble in water and most organic solvents but soluble in glacial acetic acid and acid or alkaline ethanol. It consumed no periodic acid.

Anal. Calcd. for $C_{18}H_{38}O_4NP$ (363.3): C, 59.45, H, 10.54, N, 3.85, P, 8.53. Found: C, 59.72, H, 10.63, N, 3.78, P, 8.56.

Conversion of dihydrosphingosine-1,3-cyclophosphate to dihydrosphingosine-1-phosphate (III). 151. 8 mg. of dihydrosphingosine-1,3 cyclophosphate were heated under reflux for 18 hr. in a solvent mixture consisting of 5 ml. of glacial acetic acid, 15 ml. of 34% hydrobromic acid, and 5 ml. of

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