Synthesis of Hexaoxadiamantanes[1]

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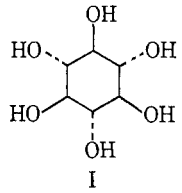
The reaction of scyllitol with triethyl orthoformate in DMSO and other solvents has investigated. The reaction yields a polymeric intermediate which can be pyrolyzed to give hexaoxadiamantane (HOD). No apically substituted HOD homologs were obtained from scyllitol and ortho esters of higher acids. Scyllitol underwent reaction with trimethyl phosphite to give 1,6-diphosphahexaoxadiamantane.

Completely strain-free cage systems have fascinated organic chemists since adamantane was found in crude oil about 30 years ago.[2] One can conceive of an adamantologous series, similar to a homologous series, which begins with adamantane and ends with diamond, the structural framework of each member being composed of cyclohexane rings locked in rigid chair conformation. The preparation of the second and third members of the series, diamantane and triamantane,[3] has only recently been published by Schleyer and coworkers,[5,6] as has our preliminary account of the synthesis of heteroatom analogs of diamantane.[4]

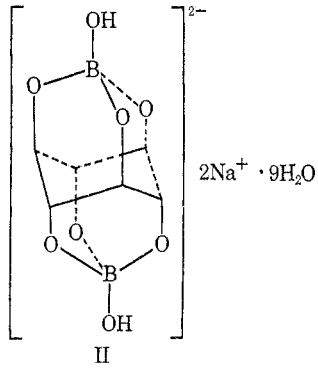
Our approach to the direct chemical synthesis of compounds with a diamantane-type structure made use of the reaction of the hexahydroxycyclohexane isomer scyllitol with appropriate reagents such as orthoformates and phosphites. These reactions proved an interesting challenge since formation of the cage structure required that all six hydroxyls (or their derivatives) be in the energetically unfavorable axial positions.

Results and Discussion

Scyllitol.—The all-*trans* hexahydroxycyclohexane, scyllitol (I), occurs widely distributed in the plant and



I



II

animal world. A laboratory synthesis has been made possible largely through the works of Posternak and Reymond.[7,8] Biological oxidation of *myo*-inositol with *Acetobacter suboxidans* (American Type Culture Collection 621) yields *myo*-inosose-2 which is then reduced with sodium borohydride to give roughly a 50/50 mixture of borate complexes of scyllitol and *myo*-inositol. The scyllitol–borate complex is the much less soluble of the two, and separation of the complexes is easily possible.

The dried complex is converted into scyllitol by treatment with sulfuric acid and methanol.

On the basis of the elemental analysis Weissbach[9] has postulated the structure II for the scyllitol–borate complex. The same product is claimed to result from heating scyllitol with aqueous sodium borate at 100°.[10,11]

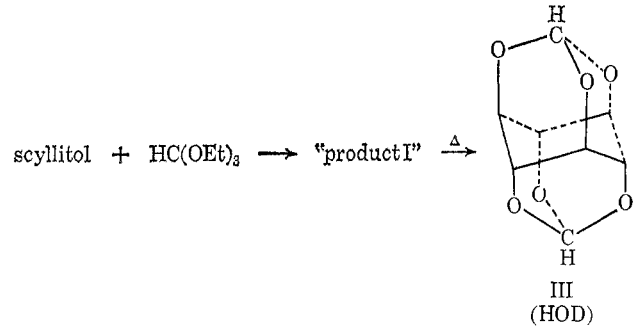
Attempts to isomerize *myo*-inositol directly to the configurationally more stable and more insoluble scyllitol were unsuccessful.

The greatest handicap in carrying out reactions with scyllitol is its low solubility. Most of the reactions studied in this work were carried out in dimethyl sulfoxide or hexamethylphosphoramide.

The high melting point and low solubility of scyllitol point to the high crystal forces present in the crystal lattice. X-ray studies have indicated that the hydroxyl groups all exist in the equatorial position and that the crystal structure is considerably stabilized by intermolecular hydrogen bonding.[12]

Hexaoxadiamantane (HOD).—Stetter and Steinacker[13] have described the preparation of trioxaadamantanes in good yields from *cis*-phloroglucitol and ortho esters.

Dimethyl sulfoxide (DMSO) was the preferred solvent for the scyllitol–triethyl orthoformate reaction, although the reaction was also carried out in hexamethylphosphoramide, succinonitrile, tetramethylene sulfone, and acetic anhydride. In these solvents triethyl orthoformate reacted with scyllitol at 150–200° to give an amorphous product (see below) from which HOD was formed by cracking at 250–350° under re-



III
(HOD)

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duced pressure. The yields of HOD averaged about 15%. The purified product melted at 305° (sealed tube); ir, nmr, and mass spectral data were compatible with the diamantane structure.

Triethyl orthoacetate and other higher ortho esters did not yield the expected apically substituted hexaoxadiamantanes. While reaction with scyllitol occurred, pyrolysis gave no identifiable products.

In DMSO at 150° scyllitol reacted with 3 mol of triethyl orthoformate even when a large excess of ortho ester was used. This product transformed into a glassy polymer on concentration, a rubbery polymer when treated with BF_3, or a tough amorphous polymer when heated in an inert solvent to 200°. A series of intermediates which culminates in three-dimensional polymers is expected from the reaction of a polyhydric alcohol with an ortho ester. All of these products (themselves ortho esters) hydrolyzed back quantitatively to scyllitol when treated with ethanol. Above 250° in an inert solvent these products underwent degradation with carbonization. For the preparation of HOD, the polymeric products were thermally cracked at 220–250°.

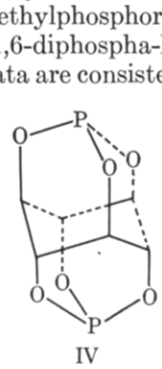
Because of the high temperature involved, numerous side reactions can take place, *e.g.*, (1) dehydration of the scyllitol, (2) disproportionation of the ortho esters,

$$HC(OR)_3 \longrightarrow H\overset{\overset{O}{\|}}{C}OR + ROR$$

and (3) formation of *trans*-dioxolane rings. Since any etherification or esterification of hydroxyl groups on the scyllitol ring will effectively prevent HOD formation, the poor yields are not surprising.

A model of HOD is portrayed in Figure 1. Like diamantane, the HOD is rigid and strain free. The hydrogen atoms on the medial cyclohexane ring are all equatorial and the apical C–H bonds are collinear. HOD can be regarded as a cyclodecane internally bridged and bound by two 2-atom chains.

The reaction of scyllitol with trimethyl phosphite in DMSO or hexamethylphosphoramide led to a material designated as 1,6-diphospha-HOD (IV). Ir, nmr, and mass spectral data are consistent with structure IV.



IV

Experimental Section

Preparation of Scyllitol.—The microbiological oxidation of *myo*-inositol to *myo*-inosose-2 was carried out as described in ref 7. Treatment of the inosose in aqueous solution with sodium borohydride yielded about 50% of theory of insoluble scyllitol–borate complex which was removed by filtration. Evaporation of the aqueous filtrate to dryness left a white residue which yielded *myo*-inositol hexaacetate (40%) on treatment with acetic anhydride. Refluxing the air-dried scyllitol–borate complex with methanol and sulfuric acid as described in ref 8 gave scyllitol in 75–80% yield.

Composition of Scyllitol–Borate Complex.—The air-dried scyllitol–borate complex varies in water content but usually has between 35 and 45%, although apparently dry samples with a water content as high as 65% have been obtained. Vacuum drying for 24 hr (over P_2O_5) removes various amounts of water depending on the temperature used. One sample of air-dried material lost 19.7% of water at 75°, but continued drying for 24 hr at 140° removed an additional 13.9% of water. Two other samples of the borate complex lost 35.8 and 41.7% of water at 125°.

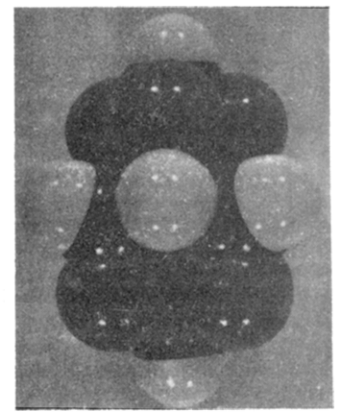


Figure 1.—Model of hexaoxadiamantane.

The wide variation in the water of crystallization made a reexamination of the elemental analysis of the scyllitol–borate complex desirable.[9] Analyses were carried out on two different products: one obtained by reduction of *myo*-inosose with $NaBH_4$, the other by reaction of pure scyllitol with $NaBH_4$. The two products so prepared were apparently identical. They were dried for 20 hr at 153° over phosphorus pentoxide and analyzed. *Anal.* Calcd for $(C_6H_8O_8B_2Na_2)_n$: C, 26.13; H, 2.93; B, 7.85; Na, 16.67. Found: C, 26.11, 26.00; H, 2.95, 3.22; B, 8.14, 8.01; Na, 16.39. Karl Fischer titration gave 13.23 and 13.43% water; 2 mol of water per unit was calculated for 13.07% water, although no water of crystallization shows in the elemental composition.

The borate complex of scyllitol is crystalline, according to a Debye–Scherrer powder diagram. At a heating rate of 15°/min thermal analysis of air-dried material revealed three endotherm peaks at 90, 100, and 117° (loss of water) and a strong peak between 525 and 530° dec. The nmr spectrum of the complex in D_2O was measured at 110° on 60 MHz and 100 MHz instruments. It had a broad peak at −4.10 ppm, representing the protons on the cyclohexane ring. Scyllitol gave a sharp peak at −3.34 ppm under the same conditions.

Preparation of HOD.—A mixture of scyllitol (0.50 g) and dimethyl sulfoxide (20 ml) was heated under a column to 200° in an oil bath. Triethyl orthoformate (2.0 ml) was then added, and the temperature held at 200° for 10 min while the ethanol formed in the reaction distilled out. The mixture was then allowed to cool overnight.

The tan-colored solution was concentrated at 0.1-mm pressure and at a bath temperature of 80°. After all the dimethyl sulfoxide had distilled, the amorphous residue was heated to 200° (0.1 mm). A colorless, crystalline compound started to sublime, and further heating at 250° for 1 hr completed the pyrolysis. The sublimate was washed with pentane to remove an oily portion. The crystalline residue (0.15 g) was twice resublimed, first at 200° (0.1 mm), then at 80° (0.1 mm). *Anal.* Calcd for $C_8H_8O_6$: C, 48.01; H, 4.03; O, 47.96. Found: C, 48.34; H, 4.22; direct O, 47.11.

At atmospheric pressure the product began to sublime at 175° and had completely disappeared at 260° when heated rapidly in a Fisher melting point apparatus. In a sealed tube it melted at 302–304° after recrystallization from dioxane. Heating in a sealed tube at 400° for 10 min did not produce any decomposition.

The ir spectrum of HOD in $CDCl_3$ showed no absorption in the hydroxyl or carbonyl region; it had bands at 2860 (w), 1392 (m), 1344 (m), 1348 (m), 1196 (w shoulder), 1172 (s), 1157 (w shoulder), 1090 (m), 1048 (s), 967 cm^{-1} (s). The nmr spectrum revealed two kinds of protons in a 1:3 ratio: the orthoformate hydrogen atoms at δ 5.67 and the equatorial hydrogen atoms on the central cyclohexane ring at 4.71. The mass spectrum of HOD (Figure 2) showed the main peak at m/e 200, the molecular weight of the compound. The fragmentation masses

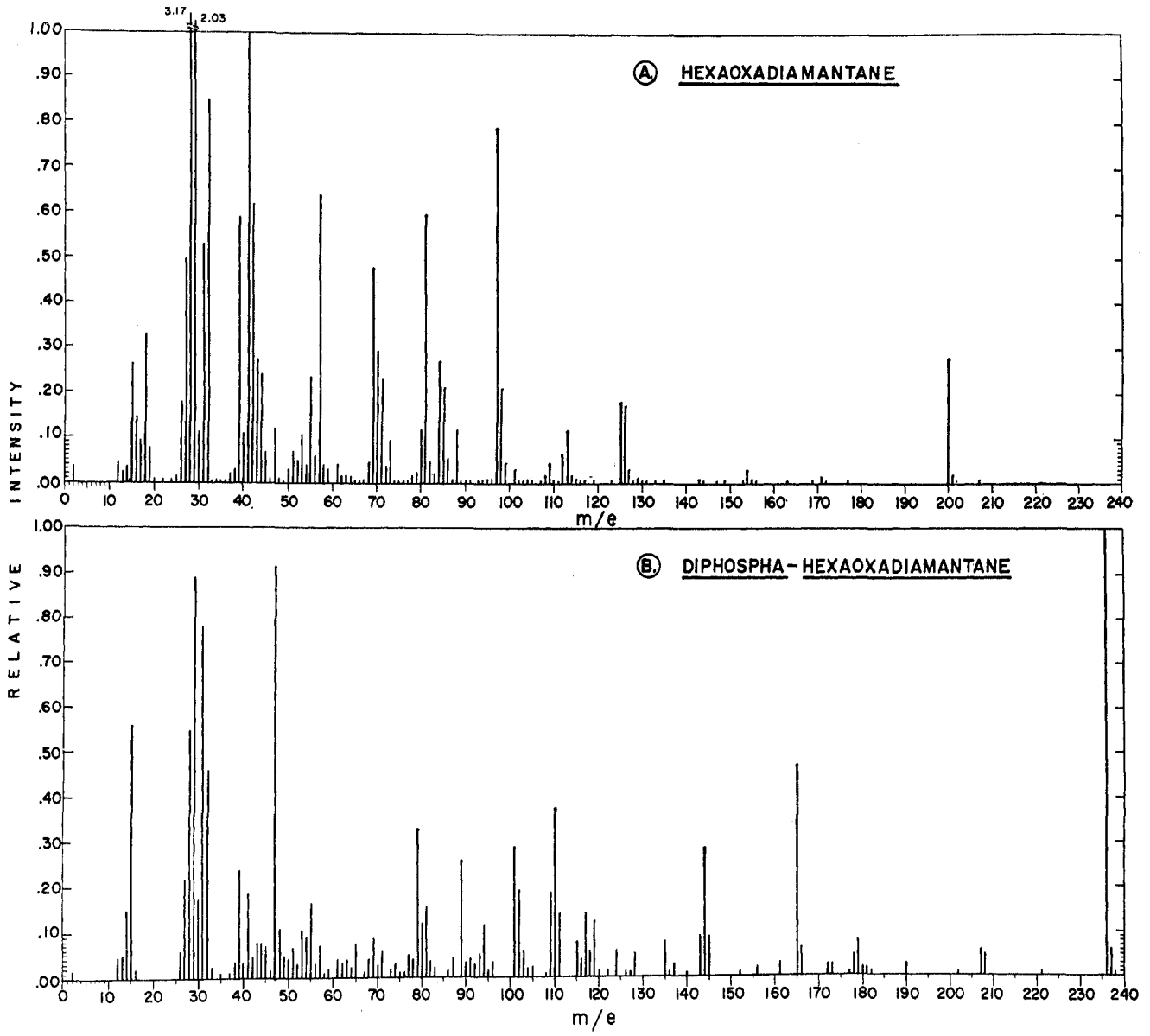


Figure 2.—Mass spectra of HOD and diphospha-HOD.

were all of relatively low molecular weight: 28 (CO), 29 (CHO), and 41 (CHOC).

The influence of the scyllitol–triethyl orthoformate ester ratio on the nature of the reaction product formed in DMSO showed that a 1:6 ratio was necessary to give products completely soluble in cold dioxane.

The initial reaction product formed by the reaction of TEOF with scyllitol in DMSO solution was prepared by a standard technique: Scyllitol (2.7 g) and TEOF (15 ml) were heated at 150° in 50 ml of dimethyl sulfoxide for 30 min. The solution was concentrated at 0.1 mm to about 8 ml; 40 ml of dioxane was added; and stirring was continued until the residue dissolved. Solutions prepared in this manner (except where noted) were used in the following experiments. (a) The solution was treated with 1.6 ml of BF_3–etherate. After 12 hr a polymer was precipitated with anhydrous ether (EtO 1.36, 1.05%). (b) Refluxing the solution for 2 hr gave scyllitol. (c) Decahydronaphthalene (50 ml) was added to the solution, and the dioxane and residual DMSO were removed under reduced pressure. Heating under nitrogen at 195° for 2 hr gave a transparent, brownish yellow film. *Anal.* Calcd for $(C_{16}H_{28}O_{12})_n$: C, 46.60; H, 6.84. Found: C, 46.29; H, 6.32; EtO, 5.77, 5.91. (d) The portionwise addition of anhydrous ether to the solution in dioxane caused the precipitation of "oily" materials. The first fraction (1.0 g) of oil was initially quite viscous, but it changed to a rubbery mass on standing for 1 hr. *Anal.* Calcd for $(C_{12}H_{24}O_{10})_n$: C, 43.90; H, 7.36. Calcd for $(C_{15}H_{30}O_{12})_n$: C, 44.77; H, 7.52. Found: C, 44.61; H, 7.18; EtO, 5.26, 5.42. A second fraction of oil obtained by addition of more ether was more mobile. *Anal.* Calcd for $(C_{15}H_{28}O_{13})_n$: C, 43.27; H, 6.78. Found: C, 43.27, 43.55; H, 6.62, 6.65; EtO, 13.45, 12.83. (e) Solutions of the initial product in dioxane were pyrolyzed in hot tubes at 245, 285, and 340°. Substantial charring was observed at 340° (0.22-g yield of HOD) Only 0.075 g of HOD was obtained at 245°. (f) A 25-ml portion of the dioxane solution was treated with 25 ml of dry ethanol. The initially clear solution precipitated colorless crystals after standing overnight; it was nearly pure scyllitol (97%).

Hydrolysis of HOD.—HOD (80 mg) was sealed in a tube with 1 ml of 6 *N* HCl and was heated in a steam bath for 24 hr. After several days at room temperature, long needles of scyllitol (16.5 mg) crystallized from the solution. It was characterized by its infrared spectrum and mixture melting point with an authentic sample.

Synthesis of 1,6-Diphospha-HOD.—A mixture of 0.88 g of scyllitol, 1.5 g of trimethyl phosphite, and 2 ml of dimethyl sulfoxide was heated under nitrogen on a steam bath for 22 hr. The mixture was filtered to remove the unreacted scyllitol (0.47 g). The filtrate was taken to dryness, and the residue was sublimed at 0.1 mm. Crystals formed at a pot temperature of 140°, and a small amount of the desired compound, mp 276–280° (sealed capillary), was obtained. *Anal.* Calcd for $C_6H_6O_6P_2$: C, 30.52; H, 2.56. Found: C, 30.94; H, 2.47.

The ir spectra of 1,6-diphospha-HOD has only four bands at

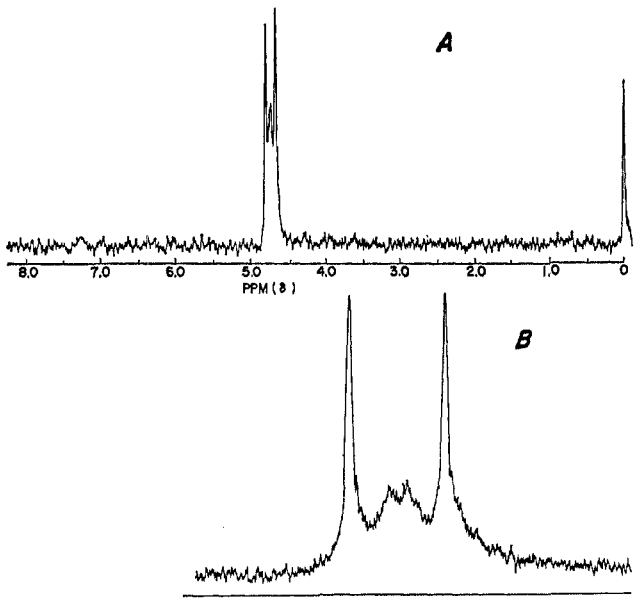


Figure 3—Sweep width (a) 500 cps; (b) 50 cps.

1030, 1010, 770, and 730 cm^{-1} (excluding C–H absorption concealed by the Nujol medium). The nmr spectrum in $CDCl_3$ appeared at first to be a single resonance line, but with higher resolution it was found to be a multiplet (Figure 3). The spectrum appears to be a $X_3AA'X'_3$ type with XX′ interaction, where A and A′ are phosphorus, and X_3 and X'_3 are protons. 1,6-Diphospha-HOD was very stable under the ionizing conditions in the mass spectrometer and *m/e* 236 (the molecular weight) was the most abundant ion in the spectrum; *m/e* 28 (CO), 29 (CHO), and 47 (PO) were also present. From the isotopic abundance ratio, the calculated value for *m/e* 237 is 6.7%. The experimental value obtained was 6.9%.

Attempts to improve the yield of 1,6-diphospha-HOD by changes in reaction times and temperatures or methods of isolation of the product were unsuccessful.

1,6-Diphospha-HOD was oxidized with hydrogen peroxide to give a product, presumably the phosphate, which sublimed about 100° higher. This material darkened at 350°, but did not melt up to 420°. The ir spectrum of this material showed bands at 1090, 1070, and 1010 cm^{-1} (Nujol mull). The region between 800 and 700 cm^{-1} showed no absorption.

Registry No.—II, 15955-20-1; III, 4922-14-9; IV, 4922-15-0.

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Reactions of Phosphorus Compounds. XIX. Reactions of 3-(*o*-Formylphenoxy)propyltriphenylphosphonium Bromide and 3-(*p*-Formylphenoxy)propyltriphenylphosphonium Bromide

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The preparation of 2,3-dihydrobenzoxepin (**7**) was accomplished in high yield from 3-(*o*-formylphenoxy)propyltriphenylphosphonium bromide (**6**). By changing the solvent, 2-methyl-2H-1-benzopyran (**8**) was prepared in high yield. Treatment of **6** with sodium methoxide in CH_3OD gave 2-methyl-2H-1-benzopyran-α,3-d_2 (**18**). Treatment of 3-(*p*-formylphenoxy)propyltriphenylphosphonium bromide (**20**) with sodium ethoxide in ethanol gave a polymer (**21**). A number of possible mechanisms for the formation of **8**, an unusual rearrangement product, are discussed and discarded on the strength of chemical evidence.

There are a number of reactions in the literature illustrating the usefulness of phosphoranes an intermediates in the preparation of cyclic systems. Carbocyclic systems have been prepared from (a) ketophosphoranes,[1] (b) ester phosphoranes,[2] (c) halophosphoranes,[3] (d) diphosphoranes and oxygen,[4] (e) vinyltriphenylphosphonium bromide and keto malonates,[5] and (f) diphosphoranes with dicarbonyl reagents.[6] Heterocyclic systems have been prepared from reagents paralleling d,[3b] e,[7] f,[8] and ketophosphoranes with azides.[9] One of the happy circumstances characterizing these reactions is that there are no apparent skeletal rearrangements occurring in the carbon chains. Maercker has noted this to be a common characteristic of the Wittig reaction.[10]

We wish to report[11] the preparation of 2,3-dihydro-1-benzoxepin, **7**, and 2-methyl-2H-1-benzopyran, **8** (Scheme I). Both heterocycles are formed by the Wittig reaction from 3-(*o*-formylphenoxy)propyltriphenylphosphonium bromide, **6**. The formation of benzopyran **8** is a rare example of a skeletal rearrangement in the Wittig reaction. Four mechanistic pathways for the formation of **8** from **6** are considered and are discarded because of evidence cited.

Large scale preparation of pure 2,3-dihydrobenzoxepin, **7**, was accomplished (70% yield)[12] by adding sodium methoxide (0.95 equiv) in dimethylformamide (DMF) to **6** in DMF under dilute conditions.

Preparation of 2-methyl-2H-1-benzopyran, **8**, was accomplished (88% yield) by adding excess sodium

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