

# Synthesis of Azulene, a Blue Hydrocarbon

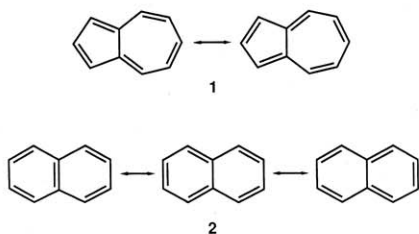
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Azulene is a simple, beautiful, and theoretically interesting compound with many unusual properties. For all of these reasons one might expect it to enjoy a place in the undergraduate laboratory curriculum, but it is a rare undergraduate who has ever seen crystals of the blue hydrocarbon. An explanation is not hard to find. Azulene is exceedingly expensive (Aldrich 1987 price: \$78.10/g), and its synthesis is generally considered to be beyond the scope of the undergraduate organic laboratory.

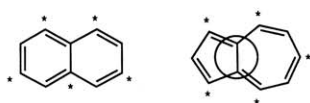
We have adapted for advanced undergraduates (and beginning graduate students) the elegant synthesis of azulene briefly described by Copland, Leaver, and Menzies (1). It is a five-step, convergent synthesis that incorporates several interesting ideas. It can be performed by a single student or conveniently divided between two students who each carry out two reactions, then combine forces for the culminating step. We have found this synthesis to be reliable and not difficult to execute. It offers the students experience in inert atmosphere technique and the use of ultraviolet spectroscopy to monitor a reaction.

## The Nature of Azulene

The title compound ( $C_{10}H_8$ , 1) (2) is an aromatic hydrocarbon isomeric with naphthalene (2). It enjoys much stabilization energy, though only about half that of naphthalene (33 vs 61 kcal/mol) (3). The lesser stabilization of azulene can be understood qualitatively in terms of the resonance method, since only two Kekulé forms can be written for 1 as compared with three for 2.



A fundamental difference between the benzenoid naphthalene and the nonbenzenoid azulene is that the former is an alternant hydrocarbon while the latter is nonalternant (4). The carbon atoms of an alternant hydrocarbon can be divided into two sets, called "starred" and "unstarred", neither of which contains two adjacent atoms. As shown below, this criterion is not met in azulene, nor is it met in other conjugated systems containing odd-membered rings.



Alternant hydrocarbons have the interesting property that their Hückel molecular orbitals come in pairs arranged symmetrically about the nonbonding energy level  $\alpha$ . The absolute magnitudes of all atomic orbital coefficients are identical for a "mirror-related" pair of orbitals; signs are switched, however, for one of the two sets. This is illustrated in Figure

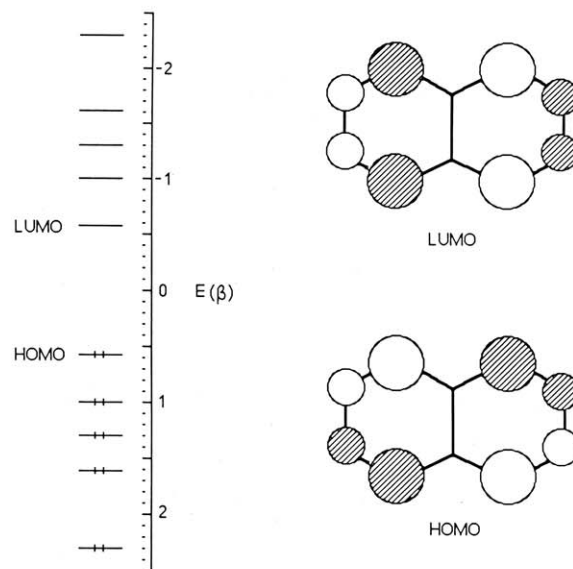
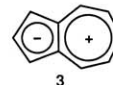


Figure 1. Hückel molecular orbital energies and the frontier orbitals of naphthalene (2).

1 for one of the mirror-related pairs of naphthalene, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). Electronic charge is distributed uniformly over the atoms which comprise the conjugated system of an alternant hydrocarbon.

In contrast, nonalternant hydrocarbons do not have "mirror-related" molecular orbitals, and their charge distribution is nonuniform. In azulene there is a significant buildup of electronic charge in the five-membered ring at the expense of the seven-membered ring, so the molecule has a significant dipole moment (1.0 Debye) (4). This situation can be represented as a contribution from the form 3, a composite of a cyclopentadienide ion and a tropylium ion (each of which in isolation is especially stable because it obeys the Hückel  $4N + 2$  rule).



The most striking characteristic of azulene and its derivatives is their beautiful blue color. Blue organic compounds are quite rare, and blue hydrocarbons other than azulenenes are exceedingly so. The colors of organic compounds are generally understandable qualitatively within the framework of simple, "one-electron" molecular orbital theory, i.e. Hückel theory. The narrower the gap between the HOMO and LUMO of a molecule, the less the energy required for an electronic transition and thus the longer the wavelength of the light that excites the transition. On this basis, however, one would predict that azulene should be colorless like naph-

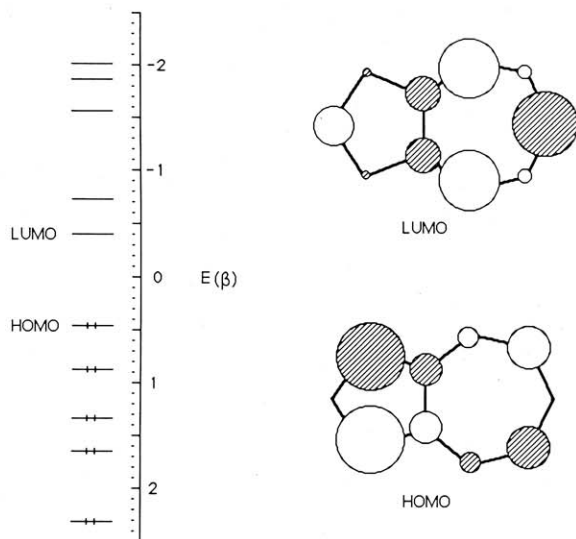
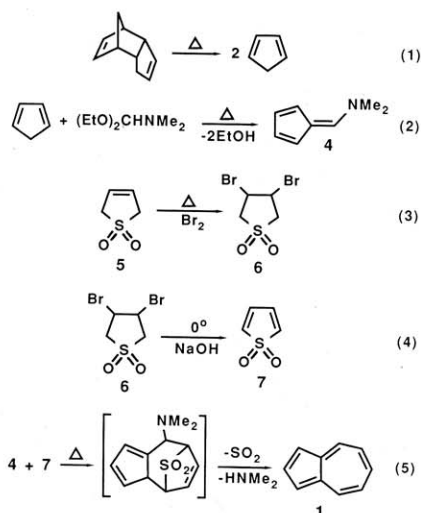


Figure 2. Hückel molecular orbital energies and the frontier orbitals of azulene (1).

thalene.<sup>1</sup> To understand the striking color, one must take into account the mutual repulsion between electrons as well as the form of the HOMO and LUMO (5). Since azulene is nonalternant, the HOMO and LUMO are not mirror-related and in fact the absolute values of the atomic orbital coefficients in these two orbitals differ greatly at many of the skeletal atoms, as indicated in Figure 2. As a result, promotion of one of the pair of electrons in the HOMO to the LUMO increases the average distance between the members of the pair, thereby reducing considerably the mutual repulsion of that pair. The consequence is a lower transition energy than anticipated from the HOMO–LUMO gap. In an alternant hydrocarbon this transition does not change the charge distribution much because of the mirror relationship.<sup>2</sup>

### Synthetic Plan

The structure of azulene was determined and confirmed by synthesis in 1936 (6). Since that time a wide variety of synthetic pathways to azulene and its derivatives have been discovered. The route we will follow to the parent molecule is presented below (1):



Step 1 is a *retro*-Diels–Alder ([4 + 2] cycloelimination) in which the reactive cyclopentadiene is prepared from its stable dimer. There is a more efficient method than Step 2 for

preparing 6-dimethylaminofulvene (4) from cyclopentadiene (7), but the condensation shown is much simpler to run (8). In Step 3 bromine is added across the double bond of 2,5-dihydrothiophene 1,1-dioxide (5) (9), also called butadiene sulfone since it is made by cheletropic addition<sup>3</sup> of sulfur dioxide to butadiene. Twofold dehydrobromination of 5 produces the very reactive thiophene dioxide (6), which cannot be isolated because it undergoes Diels–Alder dimerization if the solvent is removed. Since thiophene dioxide is also susceptible to attack by base, the dehydrobromination is run heterogeneously, using powdered sodium hydroxide (10). The course of the reaction is followed by ultraviolet spectroscopy, and the reaction solution is used directly.

The stage is now set for the remarkable final step in which fulvene 4 and diene 6 are combined. Step 5 begins with a thermally allowed [6 + 4] cycloaddition (11), which plays the key role of assembling the azulene skeleton. This reaction seems to be very facile, as judged by the change in color of the reaction mixture from red to yellow while it is warming to room temperature. It is a reasonable surmise that the next transformation is another [4 + 2] cycloelimination: cheletropic extrusion of sulfur dioxide to introduce the penultimate double bond. The driving force of aromatization then facilitates elimination of dimethylamine, giving the deep blue azulene.

### Experimental Procedure

#### Cyclopentadiene

In a 50-mL round-bottom flask place 10 mL dicyclopentadiene and several boiling chips. Fit the flask with a Vigreux column equipped with distillation adapter and thermometer; connect the sidearm to a condenser with a vacuum adapter attached to its lower end. Cool the receiver, a 10-mL round-bottom flask, in an ice–salt bath. Protect the apparatus from atmospheric moisture with a drying tube connected to the vacuum outlet. Distill very slowly, so that the vapor temperature does not exceed 50 °C (to minimize the amount of dimer that is carried over); the cracking is stopped when about 5 mL of distillate has been collected. This process requires some patience.

The diene should be used immediately if possible, since it dimerizes readily at room temperature. If it is necessary to store the compound, it should be in a tightly stoppered flask in a freezer. Even with these precautions it may be necessary to redistill the product before use.

#### 6-Dimethylaminofulvene (4)

In a 25-mL round-bottom flask place 6.0 g dimethylformamide diethyl acetal (41 mmol) and a few boiling chips. Attach a reflux condenser fitted with a nitrogen inlet and flush the system with nitrogen. Quickly introduce 2.7 g (41 mmol) cyclopentadiene, and reclose the assembly, maintaining the nitrogen atmosphere. Heat the mixture on the steam bath under nitrogen until refluxing becomes very slow (about 3 h). The reaction mixture will become orange–red during this period. Be sure the joints of the apparatus are well greased to prevent intrusion of moisture. Remove volatiles on a rotary evaporator, finally taking the bath temperature up to 70 °C. Cool the residue, and induce crystallization by scratching, adding a little petroleum ether if necessary. Recrystallize the fulvene from petroleum ether; a rather large volume (about 150 mL) will be required. The yield of yellow crystals, m.p. 67 °C, is about 1.5 g (30%). Store the fulvene in the dark, because it is light-sensitive.

#### 3,4-Dibromotetrahydrothiophene (6)

Equip a 50-mL three-necked flask with stir bar, reflux condenser protected with a drying tube, small pressure-equalizing addition

<sup>1</sup> Azulene's HOMO–LUMO gap closely matches that of anthracene, which is colorless.

<sup>2</sup> Since electron density is given by the *square* of an electronic wavefunction, the sign differences between HOMO and LUMO do not affect the relative electron density distribution in the two orbitals in the Hückel (zero overlap) approximation.

<sup>3</sup> A cheletropic reaction is a cycloaddition (or *retro*-cycloaddition) in which two bonds are formed (or broken) at the same atom.

funnel, and a stopper in the third neck. Introduce 5.0 g (0.042 mol) 2,5-dihydrothiophene dioxide and 8 mL chloroform. Heat the mixture to the reflux temperature with stirring, then add a solution of bromine (6.8 g, 0.043 mol) in 6 mL chloroform from the dropping funnel over a half hour. **Caution:** Bromine is extremely corrosive; avoid skin contact and inhalation! After heating and stirring has been continued for another two hours, allow the mixture to cool and stand overnight. Filter the bright red mixture, preferably using a sintered glass funnel, and wash the crystals with chloroform until they are colorless. Use suction to begin drying, and then spread them out in the hood to complete the drying process. The yield is about 9 g (75–80%), m.p. 142.5–143.5 °C. If desired, more dibromide can be recovered from the mother liquor.

#### Thiophene 1,1-dioxide (7)

Place 2.22 g (8.00 mmol) 3,4-dibromotetrahydrothiophene in a 100-mL round-bottom flask with septum-capped side tubulation, stir bar, and gas inlet tube leading to a nitrogen bubbler. Flush the vessel well with nitrogen, and introduce 80 mL tetrahydrofuran that has been freshly distilled (preferably by a teaching assistant) under nitrogen from benzophenone ketyl. Cool the mixture in an ice bath with stirring, then add quickly (to minimize exposure to the air) 4 g (0.1 mol) finely powdered sodium hydroxide, and continue to stir vigorously under nitrogen. Monitor the reaction by observing the growth of an ultraviolet maximum at 290 nm. Prepare samples for analysis by withdrawing a 100- $\mu$ L aliquot with a syringe, transferring it to a 10-mL volumetric flask and diluting to the mark with cyclohexane. The reaction is complete when the optical density reaches 1.0. If it stops significantly short of this value, add more sodium hydroxide and continue, maintaining the bath at 0 °C. Filter the cold mixture by suction through a filter-aid pad, and use the clear, colorless filtrate right away for the final step.

#### Azulene (1)

Fit a 100-mL round-bottom flask with a reflux condenser equipped with nitrogen inlet. Introduce a stir bar and 0.80 g (6.6 mmol) 6-dimethylaminofulvene (4). Flush the system with nitrogen, and then introduce the cold thiophene 1,1-dioxide solution. Stir the mixture to dissolve the fulvene, producing a red solution. As it warms to room temperature, this solution becomes yellow. Heat it to the reflux temperature, noting the color changes as azulene starts to form. Continue heating under reflux for 4 h in a nitrogen atmosphere.

Cool the mixture, and remove the tetrahydrofuran at room temperature with a rotary evaporator. Triturate the dark residue with 2 mL pentane, and place the blue pentane solution on top of a column of alumina (16 g) packed in pentane. Allow the sample to be adsorbed on the column, then repeat the procedure with additional very small portions of pentane until the solvent is no longer strongly colored. Elute with pentane, collecting just the blue band. Evaporate the solvent, weigh the blue crystalline residue (about 250 mg, 30%), and recrystallize it from a small amount of 95% ethanol in a

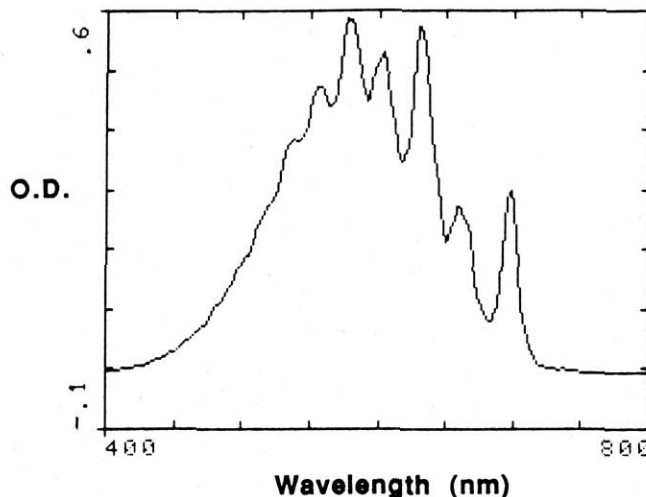


Figure 3. Visible spectrum of azulene in cyclohexane ( $\lambda_{\text{max}}$  580 nm,  $\epsilon$  270) (12).

test tube or 10-mL pear-shaped flask. After cooling the mixture in ice, remove the mother liquor with a pipet, and quickly wash the crystals with a very small amount of ice-cold ethanol. Use suction to dry the crystals at the aspirator, but do not continue this process too long since azulene is moderately volatile. The beautiful deep-blue leaflets of azulene, which have a naphthalenelike odor, melt at 98.5–99.5 °C. Azulene's visible spectrum is conveniently measured with a diode array spectrophotometer (e.g., Hewlett-Packard Model 8451A) using a solution prepared from 2–3 mg in 10 mL cyclohexane, as shown in Figure 3.

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## Making Operating Instructions Transparent

It is a common practice to mount written operating instructions, user rules, or important graphics in close proximity to an instrument. Usually, the protection of these fragile documents is problematic. They are subject to a variety of insults ranging from simple spills to grubby fingers. After a while, the paper yellows with age and crumbles.

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