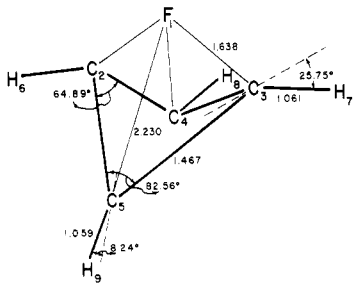

Figure 4. Optimized geometry (3-21G) of $F^-C_4H_4^{2+}$ with a C_{2v} symmetry constraint. The C_2–H_6 and C_3–H_7 bonds form an angle of 25.75° with the bisectors of $\angle C_4C_3C_5$ and $\angle C_4C_2C_5$ and are on the opposite side of the planes formed by these angles from the fluorine. The C_4–H_8 and C_5–H_9 bonds form an angle of 8.24° with the bisectors of $\angle C_2C_4C_3$ and $\angle C_2C_5C_3$ and are on the same side of the planes formed by these angles as the fluorine.

au. This suggests that the highest filled orbital of the C_s structure for the dianion is also likely to be bound when a cation is introduced.

We have also studied the influence of a counterion on the structure of the dication of cyclobutadiene by optimizing the structure of $F^-C_4H_4^{2+}$ (Figure 4) with the C_{2v} symmetry constraint (3-21G basis). Although the basic puckered character of the ring remains, the two dihedral angles of the ring (102.9, 91.1°) are considerably smaller than those found in the dication in the absence of the fluoride ion (164.4°).

The structure of $C_4H_4^{2+}$ in the presence of two fluoride ions has been studied by Kos and Schleyer.[16] However, they imposed a planar C_{4v} structure on the $C_4H_4^{2+}$ group. As can be seen from the above results, this is a fairly poor approximation to the structure of this species, either with or without counterions.

In summary, it has been found that the addition of or removal of two electrons from cyclobutadiene leads to two very different structures both of which minimize overlap of their potential π systems, in agreement with our earlier prediction[1] of nonaromatic character for these two diions.

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Registry No. 2, 36685-24-2.

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Methyl Group Functionalization in 6-Methylazulene

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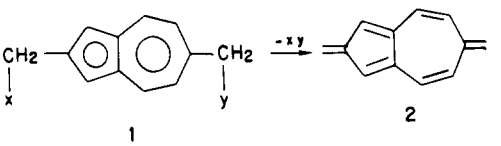
Our interest in the features of the electronic structures of unstable polyenes[1] that are revealed by photoelectron spectra led us to consider the azulylene family of which **2** is the 2,6-isomer. Gram quantitites of an appropriate precursor (**1**) are required to provide such spectra, and methods of functionalizing methyl groups on azulenes are



1 2

not altogether trivial.[2] We therefore have developed a useful method that accomplishes this purpose for 6-methylazulene (Scheme I).[3]

The key metalation reaction was suggested by the previous results of Hafner.[4] Treatment of 6-methylazulene with sodium*N*-methylanilide in tetrahydrofuran generated sodium 6-methyleneazulenate. The solution of this sodium salt may then be converted to either the chloride (**3**) using trifluoromethanesulfonyl chloride[5] or alternatively the oxime (**4**) by treating the sodium salt with isoamyl nitrite. The chloride (**3**), as expected, is an excellent substrate for nucleophilic substitution.

Table I shows the results for a number of new compounds that are easily obtained by the reaction of 6-(chloromethyl)azulene with several nucleophiles. Competitive initial rate experiments for the reaction of **3**, compared with 1-(chloromethyl)naphthalene, were also investigated with the nucleophiles shown in Table I. The tabulated results indicate that 6-(chloromethyl)azulene reacts slightly faster than 1-(chloromethyl)naphthalene with anionic nucleophiles but at approximately the same rate with the uncharged nucleophile diethylamine. This could be rationalized by the polarity of the charge distribution of the nonalternant azulene system.[6]

The rates of solvolysis of certain arylmethyl chlorides have been measured and interpreted in terms of a molecular orbital treatment.[7] This model predicts a linear correlation between the logarithm of the solvolysis rate and the coefficient of the nonbonding molecular orbital at the methylene carbon atom of the corresponding carbocation. The respective HMO coefficients for the 1-methylnaphthalene and the 6-methylazulene systems are both 0.67. The equivalence of these coefficients suggests identical rates of solvolysis and S_N2 displacement[7] for the respective chlorides in satisfactory agreements with the experimental results. This model, using the HMO coefficients for the nonalternant azulene system, does not account for the high reactivity of 1-methylazulene derivatives[8] or the relatively low reactivity of 4-methylazulene derivatives,[4b] and the agreement between the model and experiments in the present case might be fortuitous.

The main point of the present work is that 6-(chloromethyl)azulene is now readily available via chlorination of 6-methylazulene and has been shown to be a reactive substrate in displacement reactions. Derivatives of this

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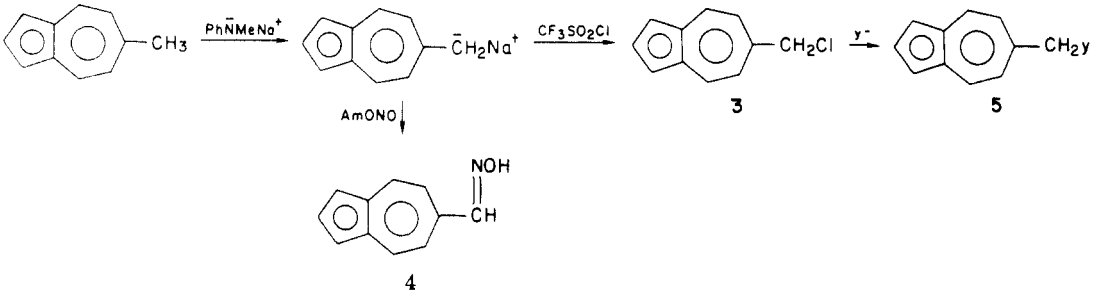
Scheme I[a]



[a] y = NEt_2, PhS, NCS, $Mn(CO)_5$.

Table I. Reactivity of 6-(Chloromethyl)azulene

nucleophile	yield, %	rel rate[a] at 27 °C
$HNEt_2$	79	1[b]
$^-SC_6H_5Na^+$	91	2[b]
$^-SCNK^+$	79	10[c]
$^-Mn(CO)_5Na^+$	74	

[a] Relative initial rate of substitution of **3** compared with 1-(chloromethyl)naphthalene as indicated by ^1H NMR. [b] In DMF-d_7. [c] In acetone-d_6.

chloride, possessing a C_2 symmetry axis, are now accessible. The unique fluorescent properties make these azulene derivatives of considerable interest, for example as fluorescent biophysical probes.[13]

Experimental Section

Spectra were recorded on the following instruments: NMR, Varian XL-100; IR, Seargent Welch 3-200 IR spectrometer; UV, Beckman DU-7 spectrophotometer. Melting points were determined on a Meltemp apparatus, and all reported values are uncorrected. Microanalysis were performed by Organic Microanalysis, Tucson, AZ. Mass spectra were obtained on a CEC-110B mass spectrometer. 1-(Chloromethyl)naphthalene and trifluoromethanesulfonyl chloride were obtained from Aldrich Chemical Co. The 1-(chloromethyl)naphthalene was recrystallized from petroleum ether (40–60 °C) until a melting point of 33 °C was obtained. 6-Methylazulene was prepared (28% yield) by a modification of the method of Hafner.[9] 1-(Thiophenoxymethyl)naphthalene was synthesized by using a slightly modified procedure of Paquette et al.[10] The compound had a melting point of 73–73.5 °C (lit.[10] mp 72–73.5 °C), and NMR, IR, and MS data consistent with the assigned structure. 1-(Thiocyanatomethyl)naphthalene, which was prepared by treating 1-(chloromethyl)naphthalene with potassium thiocyanate, in acetone as solvent displayed a melting point of 89–89.5 °C (lit.[11] mp 88–90 °C). 1-[(*N*,*N*-diethylamino)methyl]naphthalene was the product of the reaction between diethylamine and 1-(chloromethyl)-naphthalene in chloroform. The tertiary amine was treated with hydrogen chloride, and the resulting crystals had a melting point of 216–217.5 °C (lit.[12] mp 217–218 °C).

6-(Chloromethyl)azulene (3). A solution of sodium amide was prepared from 0.68 g (29.6 mmol) of sodium and 70 mL of anhydrous liquid ammonia in 20 mL of tetrahydrofuran (THF) in a nitrogen atmosphere. The ammonia was allowed to evaporate, and THF was added. *N*-Methylaniline (2.8 mL, 25.6 mmol) was added dropwise, and the mixture was stirred 1 h. The solution was transferred by nitrogen pressure to a second three-necked flask containing a solution of 2.81 g (19.8 mmol) of 6-methylazulene in 15 mL of dry THF, precooled in a bath of dry ice/carbon tetrachloride, and preflushed with nitrogen. The cooling bath was replaced by an ice–salt bath, and the mixture was stirred for 20 min. The red-brown solution was transferred to a third dry round-bottomed flask containing 5.0 g (29.7 mmol) of trifluoromethanesulfonyl chloride which had been precooled in an ice–salt bath and preflushed with nitrogen. The new mixture was stirred at 0 °C for 2 h and then was poured into cold water. The aqueous mixture was extracted with ether. Combined ether extracts were washed twice with 1% aqueous hydrochloride acid solution, twice with water, twice with 1% aqueous sodium bicarbonate solution, and finally with water until the pH of the washing was 7. The organic layer was dried (anhydrous sodium sulfate) and the solvent evaporated under reduced pressure. Sublimation at 22 °C (0.005 torr) gave 1.84 g of a mixture of 6-methylazulene (19 mol %) and 6-(chloromethyl)azulene **3** (81 mol % by ^1H NMR). Since the unreacted 6-methylazulene is an innocuous impurity, most of the subsequent experiments used the mixture obtained at this point as the source of **3**. A pure sample of **3** was obtained with substantial loss of compound after column chromatography on silica gel using carbon tetrachloride as the elution solvent. Sublimation provided blue crystals: mp 71.5–73 °C; ^1H NMR ($CDCl_3$) δ 4.52 (s, 2 H, CH_2Cl), 7.04 (d, 2 H, J = 10 Hz, $H_{5,7}$), 7.32 (d, 2 H, J = 4 Hz, $H_{1,3}$), 7.85 (t, 1 H, J = 4 Hz, H_2), 8.17 (d, 2 H, J = 10 Hz, $H_{4,8}$); UV–vis (CH_2Cl_2) [λ, nm (log ε)] 706 sh (2.09), 638 sh (2.55), 592 (2.64), 346 (3.82), 331 (3.67), 285 (4.91), 280 (4.92), 240 (4.26); mass spectrum, calcd for $C_{11}H_9{}^{35}Cl$ 176.039, found 176.039. Anal. Calcd for $C_{11}H_9Cl$: C, 74.79; H, 5.12. Found: C, 74.38; H, 5.12.

6-[(*N*,*N*-Diethylamino)methyl]azulene. A mixture of 12.4 mg of 6-methylazulene and 49.6 mg (0.28 mmol) of 6-(chloromethyl)azulene was dissolved in 2.5 mL of chloroform, and 150 mg (2.24 mmol) diethylamine was added to the resulting blue solution. The mixture was stirred for 20 h at room temperature, excess diethylamine and the solvent were evaporated under reduced pressure, and the resulting oil was dissolved in ether. Aqueous 10% hydrochloric acid solution was used to extract the desired product into the aqueous layer; this layer was washed twice with ether and then made slightly alkaline through addition of 10% aqueous sodium hydroxide solution. The alkaline solution was extracted with ether; the ether layer was washed twice with water and dried with anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, 47.5 mg (79.4%) of a dark blue oil was obtained which was pure (by NMR and TLC), 6-[(*N*,*N*-diethylamino)methyl]azulene: ^1H NMR (100 MHz, $CDCl_3$) δ 8.31 (d, J = 10 Hz, 2 H, $H_{4,8}$), 7.84 (t, J = 4 Hz, 1 H, H_2), 7.35 (d, J = 4 Hz, 2 H, $H_{1,3}$), 7.31 (d, J = 10 Hz, 2 H, $H_{5,7}$), 3.72 (s, 2 H, CH_2 Az), 2.59 (q, J = 7.5 Hz, 4 H, CH_2CH_3), 1.07 (t, J = 7.5 Hz, 6 H, CH_2CH_3); UV–vis (hexanes) [λ nm (log ε)] 681 (1.99), 652 (2.23), 641 (2.12), 620 (244), 592 (2.42), 571 (2.47), 343 (3.70), 337 (3.51), 329 (3.55), 282 (4.83), 277 (4.80), 223 (4.75), 210 (4.62); mass spectrum, calcd for $C_{15}H_{19}N$ 213.152, found 213.152. Anal. Calcd: C, 84.46; H, 8.98. Found: C, 84.58; H, 8.61.

6-(Thiophenoxymethyl)azulene. 6-(Chloromethyl)azulene (104 mg, 0.59 mmol, along with 23 mg of 6-methylazulene) was dissolved in 2 mL of dimethylformamide. A dimethylformamide solution (4 mL) containing 120 mg (0.91 mmol) of sodium thiophenoxide was added to the mixture, and the total was allowed to stand at room temperature for 5 min. The reaction mixture was then poured onto ice, extracted with chloroform, washed four times with water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the 6-methylazulene was removed from the residue by sublimation at 22 °C (0.01 torr). Recrystallization of the residue from petroleum ether (35–60 °C) gave 138 mg (91%) of the desired product as blue crystals: mp 133–134 °C; ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 10 Hz, 2 H, $H_{4,8}$), 7.84 (t, J = 4 Hz, 1 H, H_2), 7.11 (m, 9 H), 4.22 (s, 2 H, CH_2); IR (CaF_2, $CHCl_3$; in cm^{-1}) 3090 (m), 3012 (m), 1578

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(s), 1486 (m), 1455 (m), 1445 (m), 1401 (s), 1309 (w); UV–vis (CH_2Cl_2) [λ, nm (log ε)] 226 (4.25), 238 (4.28), 283 (4.61), 332 (3.79), 348 (3.82), 362 (3.26), 581 (2.56), 621 (2.48), 689 (2.03); mass sectrum, calcd for $C_{17}H_{14}S$ 250.082, found 250.083. Anal. Calcd: C, 81.11; H, 5.49. Found: C, 81.55; H, 5.63.

6-(Thiocyanatomethyl)azulene. An acetone solution containing 277 mg (1.57 mmol) of **3** (along with some 6-methylazulene) and 263 mg (2.71 mmol) of potassium thiocyanate was refluxed for 9 h. The solvent was evaporated and the residue chromatographed on silica gel with carbon tetrachloride as the elution solvent. The 6-(thiocyanatomethyl)azulene was obtained from the third of the four bands eluted; 245 mg (79%). Final purification by sublimation at 42–55 °C (0.005 torr) provided a blue solid: mp 118–119 °C dec.; ^{1}H NMR ($CDCl_3$) δ 4.27 (s, 2 H, CH_2), 7.13 (d, 2 H, J = 10 Hz, $H_{5,7}$), 7.42 (d, 2 H, J = 4 Hz, $H_{1,3}$), 7.93 (t, 1 H, H_2), 8.30 (d, 2 H, $H_{4,8}$); IR (CaF_2, $CHCl_3$; in cm^{-1}) 2930, 2850 (vs), 2160 (w) [SCN], 1730 (w), 1575 (m), 1450 (s). Anal. Calcd for $C_{12}H_9NS$: C, 72.33; H, 4.55; N, 7.03. Found: C, 71.83; H, 4.30; N, 6.74.

Pentacarbonyl[(6-azulenyl)methyl]manganese. A mixture containing 150 mg (0.850 mmol) of 6-(chloromethyl)azulene (and 26 mg of 6-methylazulene) was placed in a 50-mL Schlenk flask and dissolved in 4 mL of anhydrous ether. The flask was sealed with a septum cap and degassed with two freeze–thaw cycles. An ether solution (20 mL) containing 0.85 mmol of sodium manganese pentacarbonyl was added to the stirred mixture maintained at room temperature. The color of the blue solution changed to blue-green, and a white precipitate was formed. After 2 h of stirring, 5 mL of water was added to the solution and the two layers separated in a separatory funnel. The ether layer was dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to afford a blue-green solid. 6-Methylazulene was removed by sublimation at 22 °C (0.03 torr) to leave 212 mg (74%) of the desired product, a dark green solid. This compound was further purified by sublimation at 60–70 °C (0.01 torr): mp 108–110 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 2 H, CH_2), 7.02 (d, J = 10.5 Hz, 2 H, 2 H, $H_{5,7}$), 7.19 (d, J = 3.5 Hz, 2 H, $H_{1,3}$), 7.60 (t, J = 3.5 Hz, 1 H, H_2), 8.10 (d, J = 10.5 Hz, 2 H, $H_{4,8}$); mass spectrum, calcd for $C_{16}H_9MnO_5$ 335.983, found 335.984. Anal. Calcd: C, 57.14; H, 2.68. Found: C, 57.02; H, 2.50.

6-(Oximinomethyl)azulene. Freshly distilled isoamyl nitrite (1.47 g, 12.5 mmol) was placed in a 50-mL, round-bottomed flask, flushed with nitrogen, sealed with a septum cap, and cooled with a −40 °C cold bath. A 0.4 M solution of the sodium azulenate in THF was prepared from 1.19 g (8.4 mmol) of 6-methylazulene, chilled to −20 °C, and subsequently added, via syringe, over a period of 10 min to the flask containing the nitrite. A green color developed immediately. The solution was stirred at ice bath temperature (ca. 0 °C) for 1$^1/_2$ h and poured into 300 mL of cold water, and the aqueous layer was extracted with ether. The ether layer was washed three times with 5% aqueous hydrochloric acid solution and twice with water, and then dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the residue subjected to reduced pressure (0.05 torr) for 1 h. The residue was extracted with 200 mL of 5% aqueous potassium hydroxide solution and washed four times with petroleum ether. The alkaline layer was acidified, in the presence of dichloromethane, with cold 10% aqueous acetic acid. The oxime was extracted into the dichloromethane layer. The combined organic layers were washed with water and dried over anhyrous sodium sulfate. Evaporation of the solvent yielded 1.10 g (77%) of essentially pure oxime as a blue-green solid. Further purification of this oxime for elemental analysis was effected by recrystallization from petroleum ether/dichloromethane and subsequent sublimation at 60 °C (0.01 torr): mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 10 Hz, 2 H, $H_{4,8}$), 8.28 (s, 1 H, N=CH), 7.92 (t, J = 4 Hz, 1 H, H_2), 7.48 (d, J = 10 Hz, 2 H, $H_{5,7}$), 7.40 (d, J = 4 Hz, 2 H, $H_{1,3}$); mass spectrum, calcd for C_9H_9NO 171.068, found 171.068. Anal. Calcd: C, 77.17; H, 5.30. Found: C, 77.23; H, 5.15.

Competition Experiments. A 1:1 (molar) mixture of 1-(chloromethyl)naphthalene and 6-(chloromethyl)azulene was dissolved in a measured amount (typically in the order of 0.3 mL, concentration typically 0.06 M for each of the chlorides) of deuterated acetone or DMF. A small measured amount of nucleophile was added and the progress of the reaction monitored by NMR spectroscopy, via multiple integration of the methylene proton absorption of the chlorides and their corresponding substitution products. The assignment of the proton signals was ascertained by comparison with authentic derivatives of both the 1-methylnaphthalene and the 6-methylazulene. The reactions with SCN^- and $HNEt_2$ were carried to 7 and 10% completion, respectively. In the case of PhS, the displacement was too fast to be monitored by NMR; 0.55 equiv (with respect to the total amount of chloride) of the nucleophile was added and the product distribution of the completed reaction (less than 5 min after addition) determined by multiple integration of the CH_2 singlets in the ^{1}H NMR spectrum.

Registry No. **3**, 99458-96-5; **4**, 99459-00-4; **5** (Y = H), 1654-52-0; **5** (Y = NEt_2), 99458-97-6; **5** (Y = SPh), 99458-98-7; **5** (Y = SCN), 99458-99-8; **5** (Y = $Mn(CO)_5$), 99459-01-5; sodium thiophenoxide, 930-69-8; potassium thiocyanate, 333-20-0; sodium pentacarbonyl manganate, 13859-41-1; 1-(chloromethyl)naphthalene, 86-52-2.

Efficient Synthesis of 5,6-Diacetoxyindole: A Stable Eumelanin Precursor

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Received June 25, 1985

5,6-Diacetoxyindole (**7**) is a stable, protected form of 5,6-dihydroxyindole (DHI), a key intermediate in melanogenesis.[1] Diacetate **7** is of interest because it can be hydrolyzed in situ for studies of eumelanin formation and structure, thus eliminating handling of the unstable diol.

Classical procedures[2,3] for conversion of piperonal (**1**) to **7** involve steps that are inefficient or tedious. For example, the iron salts generated during Fe–CH_3CO_2H cyclization of 4,5-diacetoxy-2,β-dinitrostyrene (**6**) are difficult to separate from **7**, and they cause polymerization of the DHI generated during cyclization. In addition, standard catalytic methods[4,5] for reductive cyclization of 2,β-dinitrostyrenes have not been used for **6**, due to the variety of side reactions that occur under the cyclization conditions (50 psi H_2, 10% Pd/C, ethyl acetate–acetic acid–ethanol).

Results and Discussion

Nitration of piperonal (**1**) normally results in a 4.5:1 molar ratio of 6-nitropiperonal to 4-nitro(methylenedioxy)benzene (by displacement of the aldehyde).[5] However, in cold (−15 °C) dichloroethane, 6.4 equiv of fuming HNO_3 cleanly converted 25 g of **1** to **2** in 99% yield. The reaction was less successful at higher temperatures (−10 to 0 °C) or with a larger excess of HNO_3. ^{1}H NMR showed that, under these conditions, displacement of the aldehyde group of **2** resulted in 10–15% of 4,5-dinitro(methylenedioxy)benzene.

Demethylenation of **2**, rather than condensation with nitromethane, was the second step, since 4,5-(methylenedioxy)-2,β-dinitrostyrene is deprotected in low yield. Similarly, the best deprotection reagent (BBr_3) for 5,6-

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