in 0.42 M ethanolic (95%) silver perchlorate. In view of the well-known low reactivity of *gem*-dihalides toward silver ions[25] this difference would otherwise by surprisingly small.

An approximate value of 970 for k_{Br}/k_{Cl} at 92.8 °C for removal of bromide and chloride from the dimethylcyclopropyl compounds was obtained using an activation enthalpy of 20.6 kcal/mol for the more reactive bromochloro isomer. For bromo- and chlorocyclopropane the ratio was 400 ± 25, and for acetolyses of the monohalo compounds at 100 °C the ratio has been reported to be 32.[16c] According to Hammond's postulate,[26] the larger ratio for the silver ion promoted ethanolyses would seem to indicate greater progress along the reaction coordinate than has been postulated for the effect of alkyl substituents in the acetolysis reactions.

Experimental Section

Infrared spectra were determined on neat liquids using Beckman IR-5A and Perkin-Elmer 521 spectrophotometers. ^{1}H NMR spectra were recorded with JEOL Minimar and Varian A-60 and HA-100 spectrometers using 15–20% carbon tetrachloride solutions. ^{13}C NMR spectra were obtained on 20% hexadeuterioacetone solutions using a JEOL FX-60 spectrometer. Analytical GLC was performed with a Hewlett-Packard 5700-A gas chromatograph using a 76 m × 0.2 mm open tubular column coated with OV-17. An Autoprep 700 with a glass 2.7 m × 8 mm column packed with SE-30 on Chromosorb was used for preparative separations. Hewlett-Packard 5930 and Perkin-Elmer 270 GS–mass spectrometers were used. Microanalyses were performed by Galbraith Laboratory, Knoxville, Tenn.

Halocyclopropanes. Dihalocyclopropanes were prepared by carbene addition to the appropriate olefins except for 1,1-dichlorocyclopropane, which was prepared with chlorocyclopropane by vapor phase photochlorination of cyclopropane.[27] The dihalocarbenes were generated from the appropriate haloform and potassium *tert*-butoxide alcoholate.[8] The physical properties of the adducts agreed with published values[3,5,8,20,28] for each compound. Cyclopropyl bromide was obtained from Aldrich Chemical Co. and was found to contain less than 2% impurities.

1-Bromo-1-chloro-*cis*-2,3-dimethylcyclopropanes. Chlorodibromomethane (0.34 mol) was added over 1 h to a stirred mixture of 0.50 mol of potassium *tert*-butoxide alcoholate, 1 mol of *cis*-2-butene, and 250 ml of petroleum ether (bp 38–57 °C) held at −10 °C. Stirring was continued for 3 h while the temperature rose to room level. The mixture was washed with water (3 × 50 ml) and dried before being distilled first through a 0.5-m Vigreux column and then through a Teflon annular still under reduced pressure. The yield was 50 g (0.27 mol, 80%): bp 72–73 °C (38 mm); n^{25}D 1.4856; d^{25} 1.453; IR (film) 3020, 2936, 1127, 945, 717 cm^{-1} (s).

Anal. Calcd for C_5H_8ClBr: C, 32.73; H, 4.40. Found: C, - 32.58; H, 4.39.

Reaction of *endo*-1-Bromo-*exo*-1-chloro-*cis*-2,3-dimethylcyclopropane in Methanolic Silver Perchlorate. The less reactive isomer (1.22 mmol) in 4 ml of methanol containing 3.61 mmol of silver perchlorate was heated in a sealed vial at 64 °C for 27 h. The precipitate was collected in a Gooch crucible, washed, and dried at 120 °C to a constant weight of 183.4 mg (1.28 mmol silver chloride equivalent). The remaining silver salt in the combined filtrate and washings was precipitated with excess 0.3754 M aqueous sodium chloride. The resulting mixture was extracted (2 × 2 ml) with petroleum ether. Aliquots of the aqueous layer (17 ml) were neutralized with 0.0107 M methanolic sodium methoxide and required 6.85 ± 0.01 ml per ml of aqueous solution indicating the formation of 1.25 mmol of acid during the reaction. The neutralized aliquots were titrated by Mohr's method to determine by difference that 1.22 mmol of silver ions had been consumed in the reaction. GC–MS of the petroleum ether extracts showed one major component with molecular ion masses of 178 and 180 in a ratio of about one, consistent with an assignment of this major product as 3-bromo-4-methoxy-2-pentene. The chromatograms also showed a minor component that had molecular ion masses of 134 and 136 in a ratio of 3:1 as expected for 3-chloro-4-methoxy-2-pentene. The ratio of bromopentene to chloropentene in the petroleum ether extracts was 9:1.

Kinetic Studies. Temperatures were constant within 0.1 °C. Runs at 25 °C were quenched by pipetting aliquots into excess aqueous sodium chloride. The quenched mixtures were then titrated first with methanolic sodium methoxide to the thymol blue end point and then with silver perchlorate by Volhard's or Mohr's method. For runs at elevated temperatures aliquots of the reaction solutions were first cooled to 0 °C and sealed in glass ampules before being immersed in the constant temperature bath. Thermal expansion was approximately corrected for with the formula $k = (1 + 10^{-3}t)k_{app}$ where t is the bath Celsius temperature and k_{app} is the uncorrected, observed rate constant.

Registry No.—Bromochlorocarbene, 13590-47-1; *cis*-2-butene, 590-18-1; cyclohexene, 110-83-8; cyclopentene, 142-29-0; dibromocarbene, 4371-77-1.

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Syntheses of the Syn and Anti Isomers of [2.2](1,4)Naphthalenophane-1,13-diene

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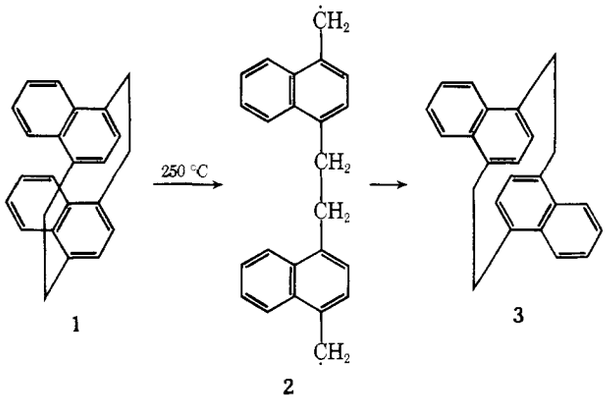
A synthesis of *anti*-[2.2](1,4)naphthalenophane (**3**) was first reported by Cram in 1963,[1] and later, via an improved method, by Brown and Sondheimer.[2] In 1969, Wasserman and Keehn reported a synthesis of *syn*-[2.2](1,4)naphthalenophane (**1**) and its thermal conversion on melting to *anti*-[2.2](1,4)naphthalenophane (**3**).[3] It was suggested that the

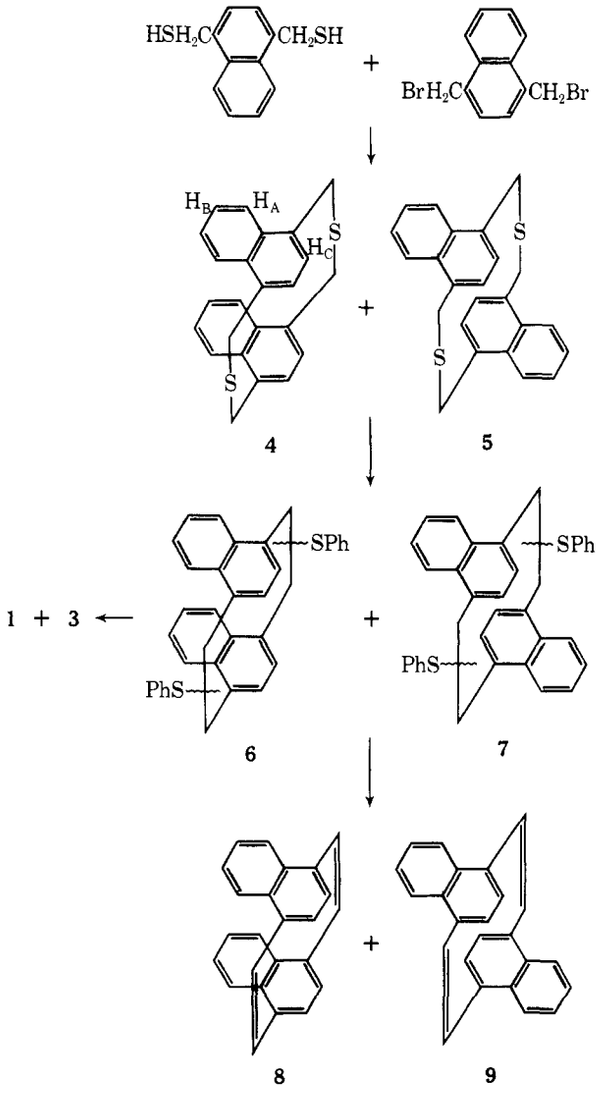


1 2 3

thermal conversion of the syn to anti isomer probably proceeded via an intermediate diradical **2.**

Since it would be desirable to have thermally stable syn and anti isomers of the naphthalenophanes for a comparative study of their physical and chemical properties, we undertook the syntheses of the syn and anti isomers of [2.2](1,4)-naphthalenophane-1,13-diene (**8** and **9**), which no longer have the possibility of thermal ring opening to a diradical such as **2.** The synthetic approach followed the general procedure we have described recently for preparing cyclophanedienes,[4] and is outlined in Scheme I.

Scheme I



4 5 6 7 8 9

A coupling reaction between 1,4-bis(bromomethyl)naphthalene and 1,4-bis(mercaptomethyl)naphthalene,[5] carried out as described earlier for similar couplings,[6] gave a mixture of the syn and anti isomers of 2,15-dithia[3.3](1,4)naphthalenophane (**4** and **5**). These were separated and purified by chromatography over silica gel, giving the syn isomer **4** in 11% yield and the anti isomer **5** in 53% yield.

Treatment of either pure **4** or pure **5** with benzyne, generated in situ by the reaction of anthranilic acid with isoamyl nitrite in 1,2-dichloroethane, led to essentially the same mixture, as analyzed by NMR, of the syn and anti stereoisomers represented by **6** and **7.** In proof of these structural assignments, the yellow oil, containing the mixture of **6** and **7** derived from the pure syn isomer **4,** was heated with Raney nickel in ethanol. As expected, this gave a mixture of the known syn and anti isomers of [2.2](1,4)naphthalenophane (**1** and **3**) in a ratio of 1:2.7. When the benzyne–Stevens rearrangement product from the pure anti isomer **5** was likewise treated with Raney nickel, the syn and anti isomers, **1** and **3,** were again formed and in essentially the same ratio. This suggests that the benzyne–Stevens rearrangements of **4** and **5** involve the same intermediate.

When the mixture of **6** and **7** was oxidized with *m*-chloroperbenzoic acid in chloroform, a mixture of the corresponding bis sulfoxides was formed in quantitative yield as a yellow oil. Pyrolysis of this yellow oil at 300 °C in a gradient sublimator gave a crystalline solid which was chromatographed over silica gel. From the first eluate fraction pure anti isomer **9** was isolated as white crystals, mp 252 °C dec, in 4% yield. From the second eluate fraction the pure syn isomer **8** was obtained as white crystals, mp 200 °C dec, in 0.6% yield.

The two isomers are readily distinguishable from their ^{1}H NMR spectra. In the anti isomer **9** the H_c protons feel the ring current of the opposite naphthalene ring and appear at high field (τ 4.26), whereas in the syn isomer **8,** this effect is much smaller and the H_c protons appear at τ 3.28.

The deshielding effect of the benzene ring current on bridging vinyl hydrogens has already been noted for the examples of [2.2]paracyclophane-1,9-diene, where the signal for the vinyl protons is at τ 2.80,[4] and of [2.2.2](1,3,5)cyclophane-1,9,17-triene, where the vinyl protons are at τ 2.63.[7] As would be expected, the deshielding effect of the naphthalene ring current is even greater so that the signal for the vinyl protons of the anti isomer **9** appears at τ 2.55 and that of the syn isomer **8** at τ 2.36, a truly remarkable chemical shift for an unconjugated vinyl proton.

Experimental Section[8]

Syn and Anti Isomers of 2,15-Dithia[3.3](1,4)naphthalenophane, 4 and 5. A solution of 628 mg of 1,4-bis(bromomethyl)naphthalene and 440 mg of 1,4-bis(mercaptomethyl)naphthalene[5] in 200 ml of benzene was added dropwise under a nitrogen atmosphere to a boiling solution of 355 mg of potassium hydroxide in 1.0 l. of ethanol. When the addition was complete (48 h), the reaction mixture was concentrated and the residue was extracted with chloroform. Concentration of the extract followed by chromatography over silica gel, using chloroform for elution, gave 560 mg (75%) of a colorless solid whose NMR spectrum indicated it to be a mixture of **4** and **5.** The anti isomer, **5,** proved to be sparingly soluble in benzene and the syn isomer could be removed by benzene extraction. Chromatography of the crude syn isomer **4,** so obtained, over silica gel using a 1:1 benzene–hexane mixture for elution gave 83 mg (11%) of the pure syn isomer **4** as colorless prisms: mp 230–235 °C dec; NMR ($CDCl_3$) doublet of doublets at τ 2.14 (4 H, J = 6.5, J' = 3.5 Hz, H_A), a doublet of doublets at 2.94 (4 H, J = 6.5, J' = 3.5 Hz, H_B), a singlet at 3.07 (4 H, H_C), and an AB quartet at 5.67 (8 H, J = 15 Hz, CH_2S–); mass spectrum *m/e* 372.098 (calcd for $C_{24}H_{20}S_2$, 372.100).

Anal. Calcd for $C_{24}H_{20}S_2$: C, 77.40; H, 5.41. Found: C, 77.25; H, 5.45.

The samples of anti isomer **5** from the extraction and chromatography were combined and sublimed at 200 °C at 0.03 mm to give 395 mg (53%) of pure anti isomer **5** as white crystals: mp 280 °C dec; NMR ($CDCl_3$) a doublet of doublets at τ 1.90 (4 H, J = 6.0, J' = 3.0 Hz, H_A), doublet of doublets at 2.40 (4 H, J = 6.0, J' = 3.0 Hz, H_B), a singlet

at 3.73 (4 H, H_C), an AB quartet at 5.46 (4 H, J = 15 Hz, $-CH_2S-$) and at 6.05 (4 H, J = 15 Hz, $-CH_2S-$); mass spectrum m/e 372.100 (calcd for $C_{24}H_{20}S_2$, 372.101).

Anal. Calcd for $C_{24}H_{20}S_2$: C, 77.40; H, 5.41. Found: C, 77.31; H, 5.27.

Benzyne–Stevens Rearrangement of 4 and 5. To a boiling solution of 74 mg of **5** and 210 mg of isoamyl nitrite in 30 ml of 1,2-dichloroethane under a nitrogen atmosphere there was added dropwise a solution of 68 mg of anthranilic acid in 10 ml of 1,2-dichloroethane. The addition required 1.5 h and the resulting reaction mixture was boiled under reflux for an additional 15 min. After concentration of the reaction mixture under reduced pressure, the residue was taken up in carbon tetrachloride and transferred to a silica gel column. Elution with benzene gave 60 mg (58%) of a pale yellow oil: mass spectrum m/e 524 (calcd for $C_{36}H_{28}S_2$, 524); NMR spectrum ($CDCl_3$) showing complex multiplets at τ 1.0, 2.0–3.6, 4.0–4.6, and 5.0–7.0, suggesting the presence of a mixture of **6** and **7**.

Similarly, when 19 mg of pure **4** was treated in an analogous way, there was isolated 17 mg (64%) of a pale yellow oil showing a parent molecular ion at m/e 524 and an essentially identical NMR spectrum as above.

Raney Nickel Desulfurization of the Benzyne–Stevens Rearrangement Products. A solution of 60 mg of the yellow oil (mixture of **6** and **7**) from the benzyne–Stevens rearrangement of pure **5** and 1 g of Raney nickel catalyst in 30 ml of absolute ethanol containing enough benzene for solubility of the organic constituents was boiled under reflux for 20 h. After removal of the catalyst and solvent, the residue was chromatographed over silica gel using a 1:2 mixture of carbon tetrachloride–hexane for elution. The first fraction of eluate gave 15 mg (41%) of the pure anti isomer **3**: mp 298–301 °C;[2] NMR ($CDCl_3$) a doublet of doublets at τ 2.26 (4 H, J = 6.0, J' = 3.0 Hz, H_A), a doublet of doublets at 2.59 (4 H, J = 6.0, J' = 3.0 Hz, H_B), a singlet at 4.23 (4 H, H_C), and an A_2B_2 multiplet at 6.1–7.2 (8 H, $-CH_2-$).

From the second fraction of eluate there was isolated 6 mg (16%) of white crystals of the pure syn isomer **1**: mp 242–245 °C;[3] NMR ($CDCl_3$) a doublet of doublets at τ 2.51 (4 H, J = 6.0, J' = 3.0 Hz, H_A), a doublet of doublets at 3.15 (4 H, J = 6.0, J' = 3.0 Hz, H_B), a singlet at 3.28 (4 H, H_C), and an A_2B_2 multiplet at 6.0–6.8 (8 H, $-CH_2-$).

Similarly, when 17 mg of the benzyne–Stevens rearrangement product from the pure syn isomer **4** was subjected to Raney nickel desulfurization, the products were the anti isomer **3** in 40% yield and the syn isomer **1** in 15% yield.

Syn and Anti Isomers of [2.2](1,4)Naphthalenophane-1,13-diene, 8 and 9. A solution of 59.5 mg of the benzyne–Stevens rearrangement product from **5** and 40 mg of *m*-chloroperbenzoic acid (85%) in 10 ml of chloroform was allowed to stand at room temperature overnight under a nitrogen atmosphere. The chloroform solution was washed successively with aqueous sodium bicarbonate and water, dried, and concentrated to give the corresponding bis sulfoxide as 63 mg (100%) of a pale yellow oil. This oil was pyrolyzed directly using a gradient sublimator at 300 °C and under 0.02 mm pressure. The mixture, which collected on the cold finger, was chromatographed over silica gel using a 1:2 mixture of carbon tetrachloride–hexane for elution. The first fraction of eluate gave 1.3 mg (4%) of the pure anti isomer **9** as white crystals: mp 252 °C dec; NMR ($CDCl_3$) a doublet of doublets at τ 2.37 (4 H, J = 6.0, J' = 3.0 Hz, H_A), a singlet at 2.55 (4 H, $-CH{=}CH-$), a doublet of doublets at 2.63 (4 H, J = 6.0, J' = 3.0 Hz, H_B), and a singlet at 4.26 (4 H, H_C).

Anal. Calcd for $C_{24}H_{16}$: mol wt, 304.125. Found (high-resolution mass spectrum): mol wt, 304.124.

The second fraction of eluate gave 0.2 mg (0.6%) of white crystals: mp 200 °C dec; NMR ($CDCl_3$) a singlet at τ 2.36 (4 H, $-CH{=}CH-$), a doublet of doublets at 2.72 (4 H, J = 6.0, J' = 3.0 Hz, H_A), a doublet of doublets at 3.23 (4 H, J = 6.0, J' = 3.0 Hz, H_B), and a singlet at 3.28 (4 H, H_C).

Anal. Calcd for $C_{24}H_{16}$: mol wt, 304.125. Found (high-resolution mass spectrum): mol wt, 304.125.

Acknowledgment. We thank the National Science Foundation for their support of this investigation.

Registry No.—**1**, 23284-44-3; **3**, 14724-91-5; **4**, 61158-76-7; **5**, 61216-66-8; **6**, 61158-81-4; **6** sulfoxide, 61247-61-8; **7**, 61216-68-0; **7** sulfoxide, 61158-82-5; **8**, 61158-77-8; **9**, 61216-67-9; 1,4-bis(bromomethyl)naphthalene, 58791-49-4; 1,4-bis(mercaptomethyl)-naphthalene, 59045-58-8; anthranilic acid, 118-92-3.

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Highly Stereoselective Synthesis of 9-*epi*-Prostaglandin $F_{2\alpha}$ and 11-*epi*-prostaglandin $F_{2\alpha}$ by the Aluminum Hydride Reduction of Prostaglandin E_2 and 11-*epi*-Prostaglandin E_2 Derivatives[1]

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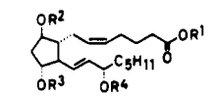
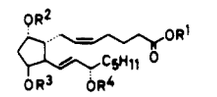
In connection with another study in progress in these laboratories, we required substantial quantities of 9-*epi*-prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$) (**1a**) and 11-*epi*-prostaglandin $F_{2\alpha}$ (**2a**). $PGF_{2\beta}$) or derivatives thereof) has been obtained as one component of the mixtures formed on the sodium borohydride reduction[2-5] of PGE_2 (**3a**) (or analogues), or the aluminum amalgam[5,6] reduction of the mixed 10,11-α- and -β-epoxides of PGA_2 (or derivatives). Analogous procedures[5,6] have been utilized to prepare 11-*epi*-$PGF_{2\alpha}$, but the efficiency of these processes is very low (see Table I, for example). Weinshenker et al.[7] have described a synthesis of this compound (**2a**) the



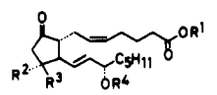
1

a) R^1, R^2, R^3, R^4 = H
b) R^1 = CH_3; R^2, R^3 = H; R^4 = CH_3CO
c) R^1 = CH_3; R^2, R^3, R^4 = H
d) R^1 = CH_3; R^2 = H; R^3, R^4 = THP



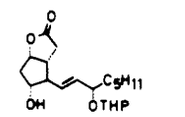
2

a) R^1, R^2, R^3, R^4 = H
b) R^1 = CH_3; R^2, R^3 = H; R^4 = CH_3CO
c) R^1 = CH_3; R^2, R^3, R^4 = H



3

a) R^1, R^3, R^4 = H; R^2 = OH
b) R^1, R^2, R^4 = H; R^3 = OH
c) R^1 = CH_3; R^2 = OH; R^3 = H; R^4 = CH_3CO
d) R^1 = CH_3; R^2 = H; R^3 = OH; R^4 = CH_3CO
e) R^1 = CH_3; R^2 = OTHP; R^3 = H; R^4 = THP
f) R^1, R^3, R^4 = H; R^2 = $OSi(CH_3)_3$
g) R^1 = CH_3; R^2 = H; R^3 = $OSi(CH_3)_3$; R^4 = CH_3CO



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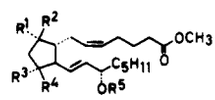

5

a) R^1, R^3 = OH; R^2, R^4 = H; R^5 = CH_3CO
b) R^1, R^3 = H; R^2, R^4 = OH; R^5 = H or CH_3CO
c) R^1 = OH; R^2, R^4 = H; R^3 = OTHP; R^5 = THP

crucial aspect of which involved the nucleophilic inversion (tetraethylammonium formate on the tosylate) of the prostaglandin intermediate[8] **4**. Very recently, Corey and coworkers[9] have shown that both **1a** and **2a** were readily available by the stereospecific inversion of suitably protected 9- and 11-tosylates of $PGF_{2\alpha}$ with superoxide ion. This process, though useful, requires large amounts of the costly reagent 18-crown-6 to solubilize the potassium superoxide.