Seven-Membered Heterocycles. 9. Synthesis and Properties of Some 5-Alkyl and 5-Aryl Derivatives of 1-Benzothiepin

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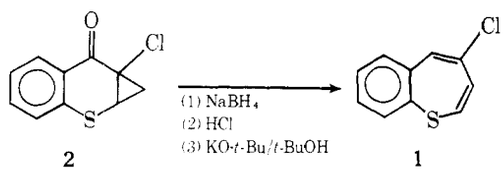
Received February 6, 1978

7a-Chlorocyclopropa[*b*][1]benzothiopyran-7-one (**2**) and 7a-bromocyclopropa[*b*][1]benzothiopyran-7-one (**3**) each reacted with Grignard reagents to give the corresponding cyclopropyl alcohols **4–10** (Table I). The alcohols **5, 7,** and **8** were oxidized to the corresponding sulfones **11, 12,** and **13,** respectively, and 7a-chloro-7-hydroxy-7-phenylcyclopropa[*b*][1][benzothiopyran was oxidized to the corresponding sulfoxide **14.** The reaction of **4** with HCl gave the ring-opened product 2,4-dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (**15**) in high yield, and the reaction of **4** with HBr produced 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (**20**) in excellent yield. The reaction of **15** with potassium *tert*-butoxide produced only low yields of the desired 4-chloro-5-phenyl-1-benzothiepin (**16**), and reactions of **15** and **20** utilizing a variety of reagents and conditions attempting to form **16** were tried. Interestingly, the alcohol **4** rearranged when heated in the presence of a trace of *p*-toluenesulfonic acid to produce 2-chloro-1-phenylnaphthalene (**17**), presumably via extrusion of sulfur from **16.** 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) promoted the dehydrobromination reaction at room temperature, which conveniently provided the corresponding 1-benzothiepins **1, 16, 24, 26, 27,** and **28** (Table III) and the sulfones **22** and **25.** The phenyl- and benzyl-substituted 1-benzothiepins **16, 24,** and **26** were crystalline compounds. The thermal decomposition of the 1-benzothiepins was studied by NMR spectroscopy, and the effect of substituents on the stability of the ring is discussed.

Several methods have become available for the synthesis of 1-benzothiepins. One approach involves the derivatization of enolized ketones,[3–6] while another involves ring opening of annulated benzo[*b*]thiophenes.[7,8] Both of these methods have produced highly substituted and relatively stable 1-benzothiepins. The enolization approach has also been recently utilized to obtain 1-benzothiepin 1-oxides,[9] which are thermally less stable than the corresponding 1-benzothiepins, and 1-benzothiepinium ions,[10] which are thermally more stable than the corresponding 1-benzothiepins. We have reported[11] the use of a halogenation–dehydrohalogenation sequence for the synthesis of the parent 1-benzothiepin and chlorinated derivatives. Another synthesis[12,13] of 1-benzothiepin and other derivatives has been reported utilizing a rhodium complex promoted isomerization. As yet, however, the properties of 1-benzothiepins have not been fully investigated. In particular, the effect of structure on the the thermal stability of these compounds remains unresolved.

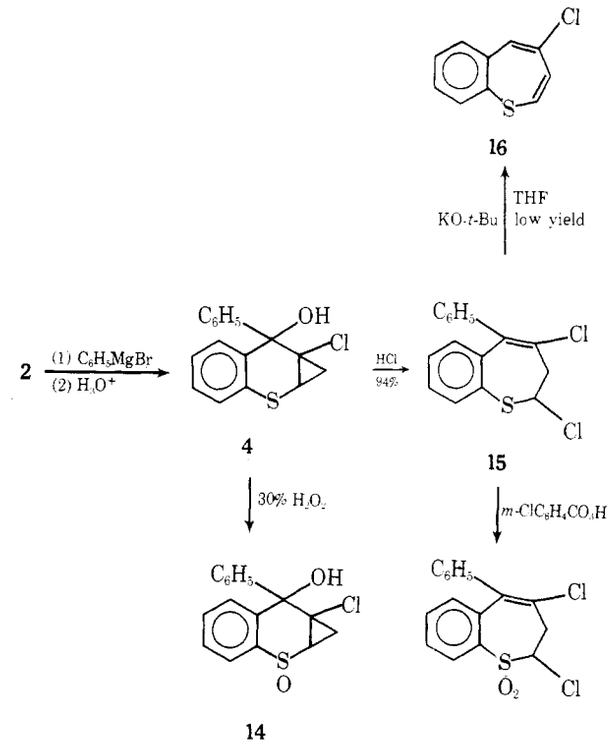
We previously reported[11] the preparation of 4-chloro-1-benzothiepin (**1**), achieved via the key intermediate 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one (**2**). The ketone **2**



2 **1**

underwent reduction with sodium borohydride to give the corresponding alcohol which was ring opened with HCl to provide the precursor to **1.** We also observed that **2** underwent a Grignard reaction which provided the prospect of synthesizing various 5-alkyl or 5-aryl derivatives of 1-benzothiepin, and in this paper we report the successful isolation of such compounds.

Ketone **2** and 7a-bromocyclopropa[*b*][1]benzothiopyran-7-one (**3**)[14] were each reacted with various Grignard reagents and upon hydrolysis gave the corresponding alcohols listed in Table I. The alcohols **4–9** were characterized by IR and NMR spectral data and elemental analyses. Compounds **5, 7,**[15] and **8** were oxidized with *m*-chloroperbenzoic acid to the corresponding sulfones **11, 12,**[15] and **13,** respectively, and **4** was oxidized with 30% hydrogen peroxide to the corresponding sulfoxide **14** (Table I). The stereochemistry of the alcohols was not determined. The reaction of **4** with HCl provided the precursor, 2,4-dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (**15**), in excellent yield, and **15** was characterized by IR, NMR, and mass spectral data, elemental analyses, and further as its sulfone. Treatment of **15** with potassium *tert*-butoxide at room temperature in THF produced the desired 4-chloro-5-phenyl-1-benzothiepin (**16**); however, low yields and difficulties in purification led to further investigations.



The facile ring opening of the cyclopropyl alcohol **8** by HCl prompted an attempt to obtain **16** in one step from **4** by treatment with a trace of *p*-toluenesulfonic acid in refluxing benzene. 2-Chloro-1-phenylnaphthalene (**17**) was isolated from the reaction, which indicates that **16** may have formed but was unable to survive the conditions. The formation of **17** could be rationalized by the loss of a proton from the intermediate homoallylic cation **18** formed after the loss of H_2O from **4.**

2,4-Dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (**15**) did not react with the following reagents at the temperatures given

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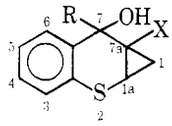
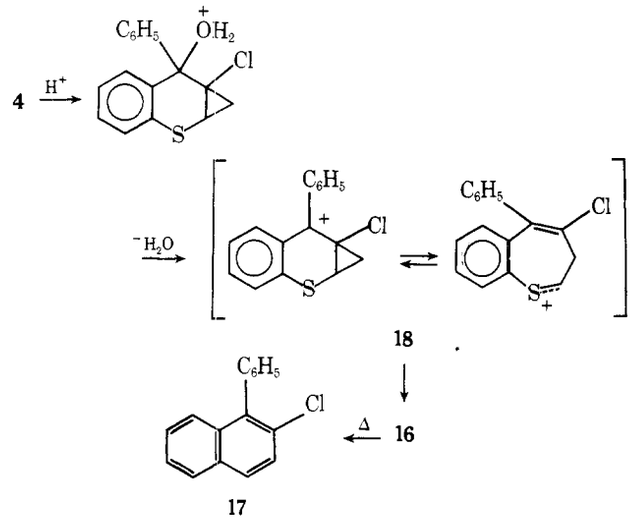
Table I. Properties of the Cyclopropyl Alcohols



Compd	Registry no.	Substituents	Melting point, °C	Isolated yield,[a] %
4	66768-90-9	R = C_6H_5; X = Cl	132.5–134	82
5	66768-91-0	R = C_6H_5; X = Br	129–131	22
6	66768-92-1	R = $CH_2C_6H_5$; X = Cl	87–88	84
7[15]	66768-93-2	R = CH_3; X = Cl	Oil	90
8	66768-94-3	R = CH_2CH_3; X = Cl	Oil	90
9	66768-95-4	R = CH_2CH_2-CH_2CH_3; X = Cl	Oil	100
10	66768-96-5	R = CH_3; X = Br	Oil	95
11	66768-97-6	Sulfone of 5	186–188	16
12[15]	66768-98-7	Sulfone of 7	106–107	50
13	66768-99-8	Sulfone of 8	151–153	20
14	66769-00-4	Sulfoxide of 4	201–204 (dec)	53

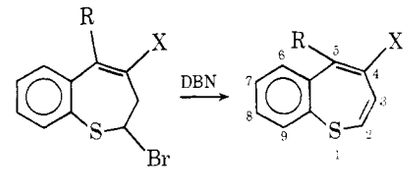
[a] Yields for sulfones and sulfoxide were not optimized.



and for at least 1 h of reaction time: *tert*-butoxide (−78, −20, and 0 °C); 1,8-bis(dimethylamino)naphthalene (30 °C); 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (23 and 66 °C); and lithium chloride in DMF (23, 50, 75, and 100 °C). Interestingly, compound **15** underwent substitution at C-2 in water–acetone solution to give 4-chloro-2-hydroxy-5-phenyl-2,3-dihydro-1-benzothiepin (**19**). The structural assignment of **19** was based on IR, which had strong absorption at 3580 cm^{-1}, NMR, which had a doublet of doublets at δ 5.93 and a singlet at δ 5.67, and elemental analyses. Sodium ethoxide also promoted substitution according to NMR analyses of reaction product mixtures.

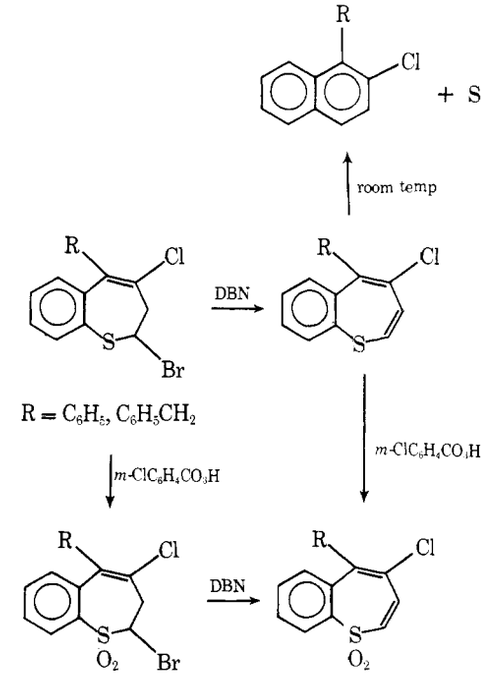
These results led to the introduction of bromine at C-2 in place of chlorine simply by treating the cyclopropyl alcohol **8** with HBr. 2-Bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (**20**) gave results similar to those for **15** when reacted with potassium *tert*-butoxide or potassium 2,6-di-*tert*-butylphenoxide at room temperature. However, reaction of **20** with DBN in THF at room temperature provided, after chromatography on alumina, an 82% yield of 4-chloro-5-phenyl-1-benzothiepin (**16**) as a white crystalline solid, mp 87–88 °C. The structural assignment of **16** was based on IR and NMR spectral data, elemental analyses, an extrusion reaction, and oxidation to the corresponding sulfone **22**. 4-Chloro-5-phenyl-1-benzothiepin 1,1-dioxide (**22**) was also prepared in good yield by DBN treatment of 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin 1,1-dioxide (**23**). The sulfone **22** was characterized by IR and NMR spectral data and elemental analyses.

Table II. Properties of the 1-Benzothiepins and 1-Benzothiepin 1,1-Dioxides



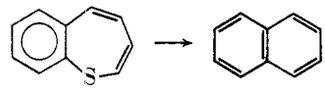
Compd	Registry no.	Substituents	Physical appearance	Melting point, °C	Isolated yield, %
1	44887-88-1	4-Chloro	Yellow oil		35[a]
16	66769-01-5	4-Chloro-5-phenyl	Crystalline	87–88	76
24	66769-02-6	4-Chloro-5-benzyl	Crystalline	80–81	82
26	66769-03-7	4-Bromo-5-phenyl	Crystalline	81–82	24
27	66768-76-1	4-Chloro-5-methyl	Colorless oil		43[a]
28	66768-77-2	4-Bromo-5-methyl	Colorless oil		29[b]
22	66768-78-3	Sulfone of 16	Crystalline	170–172	74 (33)[c]
25	66768-79-4	Sulfone of 24	Crystalline	181–182	82 (66)[c]

[a] Overall yield from ketone **2**. [b] Overall yield from ketone **3**. [c] Yield from oxidation of the corresponding 1-benzothiepin.



Utilizing DBN in the final step thus permitted the synthesis of several 5-aryl- and 5-alkyl-1-benzothiepin derivatives, which are listed in Table II. 4-Chloro-5-benzyl-1-benzo-

Table III. Thermal Decomposition of 1-Benzothiepins



Compd	Substituents	Approximate half-life,[a] h: Room temp	30 °C
29	None	17[11]	
1	4-Chloro	22[11]	12[c]
30	2-Chloro	42[11]	
16	4-Chloro-5-phenyl	27[c]	17[c]
24	4-Chloro-5-phenyl	46[c]	22[c]
26	4-Bromo-5-phenyl	47[b]	
27	4-Chloro-5-methyl		25[c]
28	4-Bromo-5-methyl		29[c]

[a] First order. [b] $CDCl_3$ as solvent (present work). [c] CCl_4 as solvent (present work).

thiepin (**24**) and its corresponding sulfone **25** were prepared similarly to and characterized the same as **16** and **22**, respectively. 4-Bromo-5-phenyl-1-benzothiepin (**26**) was prepared in a manner similar to that for **16** and **24** by ring opening of **5** followed by DBN treatment of **21**. The 1-benzothiepin **26** was characterized by IR and NMR spectral data, elemental analyses, and an extrusion reaction. The preparation of the methyl-substituted 1-benzothiepins and 4-chloro-1-benzothiepin (**1**) was accomplished by reacting the crude product from HBr ring opening of the cyclopropyl alcohols with an excess of DBN. Thus, 4-chloro-5-methyl-1-benzothiepin (**27**) (43% overall yield from ketone **2**), 4-bromo-5-methyl-1-benzothiepin (**28**) (29% overall yield from ketone **3**), and 4-chloro-1-benzothiepin (**1**) (35% overall yield from ketone **2**) were isolated as oils and characterized by IR and NMR spectral properties and a thermal extrusion reaction.

The NMR spectral data for the 1-benzothiepins **16, 24, 26, 27,** and **28** were consistent with the data for other known 1-benzothiepins. The protons at C-2 and C-3 appear in the olefinic reagion (δ 5.9–6.5) as a doublet of doublets, and the coupling constants are 8–10 Hz. In the case of **24**, the benzylic protons appear as a singlet at δ 4.20, and for **27** and **28** the methyl protons appear as a singlet at δ 2.43 and 2.33, respectively. The NMR spectra for all of the corresponding naphthalene compounds do not contain absorption in the olefinic region, and benzyl and methyl protons are shifted downfield by 11–22 Hz.

The extrusion reactions were thus conveniently followed by NMR spectroscopy. We previously reported half-lives at room temperature in CCl_4 for 1-benzothiepin (**29**), 2-chloro-1-benzothiepin (**30**), and 4-chloro-1-benzothiepin (**1**). Reactions of 1-benzothiepins **16, 24,** and **26** were thus monitored by NMR spectroscopy at room temperature in CCl_4 (**26** in $CDCl_3$). In order to eliminate any temperature variation, the 1-benzothiepins **1, 16, 24, 27,** and **28** were monitored by NMR spectroscopy at 30 ° in CCl_4, and the results are given in Table III. From this table it is apparent that a slight increase in the stability of the thiepin ring by phenyl, benzyl, methyl, chloro, and bromo substituents is suggested. Furthermore, greater stabilization is achieved by groups with greater electron-donating ability. This trend supports the recent observations reported by Murata and Tatsuoka.[13] An explanation for these observations awaits further study. Hopefully, more work on the mechanism of sulfur extrusion, which is believed to procede via a thianorcaradiene intermediate,[3,8] would offer a reasonable solution.

After the extrusion reactions of **16, 24, 27,** and **28** were complete, the corresponding naphthalenes were isolated and characterized by IR and NMR spectra. Elemental analyses were consistent with the molecular formulas of the new naphthalene compounds, 2-chloro-1-phenylnaphthalene (**17**) and 1-benzyl-2-chloronaphthalene (**31**). Sulfur was also isolated from the decomposition reactions of **16** and **24.**

Experimental Section

General. All melting points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. IR spectra were determined on a Beckman IR-8 spectrophotometer, NMR spectra were recorded on a Varian Model T-60 or EM-360 spectrometer, and the mass spectra were obtained on a Nuclide Corp. 12-90G high-resolution mass spectrometer. Reagents were used as received unless otherwise stated.

7a-Chloro-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (4). A solution of 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one[14] (2.7 g, 0.013 mol) in anhydrous ether (30 mL) was added dropwise over a period of 25 min to a solution containing phenylmagnesium bromide (prepared from 7.5 g of bromobenzene and 0.95 g of magnesium turnings in 40 mL of ether). The mixture was heated at reflux for 1 h. The yellow solution was allowed to cool to room temperature and was then hydrolyzed by careful addition of first 10% NH_4Cl and then 10% H_2SO_4. The mixture was finally extracted with 50 mL of ether, and the ether portion was washed with water (2 × 50 mL) and then dried ($MgSO_4$). Removal of the solvent gave a yellow solid which was recrystallized from hexane–benzene to give 3.07 g (82%) of pale yellow crystals of **4**: mp 132.5–134 °C; IR ($CHCl_3$) 3580 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.53 (overlapping dd, 2, $J_{C_{1a}-C_{1x}}$ = 9 Hz, $J_{C_{1a}-C_{1y}}$ = 7 Hz, C_1 H's), 3.00 (dd, 1, $J_{C_{1a}-C_{1x}}$ = 9 Hz, $J_{C_{1a}-C_{1y}}$ = 7 Hz, C_{1a} H), 3.20 (s, 1, OH), 7.00–7.50 (m, 7, C_4 H, C_5 H and phenyl H's), 7.64–8.16 (m, 2, C_3 H and C_6 H); mass spectrum (70 eV), *m/e* (relative intensity) 288 (58), 253 (51), 105 (100), 77 (65).

Anal. Calcd for $C_{16}H_{13}ClOS$: C, 66.54; H, 4.53; Cl, 12.28. Found: C, 66.44; H, 4.44; Cl, 12.00.

7a-Bromo-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (5). Using the same procedure described for the preparation of **4**, 7a-bromocyclopropa[*b*][1]benzothiopyran-7-one[14] (0.85 g, 3.9 mmol) provided, after recrystallization from cyclohexane, 280 mg (22%) of **5**: mp 129–131 °C; IR ($CHCl_3$) 3565 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.6 (dd, 2, J = 8 Hz, C_1 H's), 3.1 (m, 2, OH, C_{1a} H's), 7.2–7.9 (m, 9, aromatic H's).

Anal. Calcd for $C_{16}H_{13}OSBr$: C, 57.84; H, 3.64; S, 9.65; Br, 24.05. Found: C, 57.63; H, 3.80; S, 9.58; Br, 23.89.

7a-Chloro-7-hydroxy-7-benzylcyclopropa[*b*][1]benzothiopyran (6). Using the same procedure described for the preparation of **4**, 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one[14] (3.7 g, 18 mmol) in ether (20 mL) was added to a solution containing benzylmagnesium chloride (prepared from 3.70 g of benzyl chloride and 0.69 g of magnesium turnings in 40 mL of ether). After reaction and workup, 2.4 g (84%) of colorless crystals of **6** was isolated: mp 84–86 °C; IR ($CHCl_3$) 3590 (OH) cm^{-1}; NMR ($CDCl_3$) δ 1.0–1.4 (m, 2, C_1 H's), 2.45–2.80 (m, 3, $C_6H_5CH_2$ and C_{1a} H), 3.43 (s, 1, OH), 6.5–7.3 (m, 9, aromatic H's). Recrystallization from hexane–$CHCl_3$ provided an analytical sample, mp 87–88 °C.

Anal. Calcd for $C_{17}H_{15}ClOS$: C, 67.43; H, 4.99; S, 10.59. Found: C, 67.45; H, 5.04; S, 10.45.

7a-Chloro-7-hydroxy-7-methylcyclopropa[*b*][1]benzothiopyran (7). Using the same procedure described for the preparation of **4**, 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one[14] (1.30 g, 6.2 mmol) in ether (25 mL) was added to a solution of methylmagnesium chloride in THF (25 mL, 80 mmol) (Fisher Scientific Co.). After workup, the solvent was removed under vacuum to give 1.25 g (90%) of **7** as a yellow oil: IR ($CHCl_3$) 3450 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.22 (dd, 2, $J_{C_{1x}-C_{1a}}$ = 8 Hz, $J_{C_{1y}-C_{1a}}$ = 7 Hz, C_1 H's), 1.60 (s, 3, CH_3), 2.41–2.70 (dd, 1, $J_{C_{1a}-C_{1x}}$ = 8 Hz, $J_{C_{1a}-C_{1y}}$ = 7 Hz, C_{1a} H), 3.1 (s, 1, OH), 6.95–7.25 (m, 3, aromatic H's), 7.7–7.88 (m, 1, C_9 H); mass spectrum (70 eV), *m/e* (relative intensity) 226 (48), 191 (38), 175 (100), 147 (83). Elemental analyses were performed on the corresponding sulfone **12**.[15]

7a-Chloro-7-hydroxy-7-ethylcyclopropa[*b*][1]benzothiopyran (8). Using the same procedure described for the preparation of **4**, 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one[14] (5.00 g, 24 mmol) in ether (40 mL) was added to a solution containing ethylmagnesium iodide (prepared from 11.1 g of ethyl iodide and 1.74 g of magnesium turnings in 60 mL of ether). After workup, the solvent was removed under vacuum to give 5.15 g (90%) of **8** as a yellow oil: IR (neat) 3490 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.67 (t, 3, J = 8 Hz, CH_3), 1.33 (dd, 2, J = 6 Hz, C_1 H's), 2.20 (s, 1, OH), 2.21 (q, 2, J = 8 Hz, CH_2), 2.65 (dd, 1, J = 6 Hz, C_{1a} H), 7.1–7.9 (m, 4, aromatic H's).

Anal. Calcd for $C_{12}H_{13}ClOS$: C, 59.86; H, 5.44. Found: C, 59.79; H, 5.53.

7a-Chloro-7-hydroxy-7-*n*-butylcyclopropa[*b*][1]benzothiopyran (9). Using the same procedure described for the preparation of **4**, 7a-chlorocyclopropa[*b*][1]benzothiopyran-7-one[14] (1.6 g, 7.6 mmol) in ether (15 mL) was added to a solution containing *n*-butylmagnesium bromide (prepared from 3.18 g of *n*-butyl bromide and 0.56 g of magnesium turnings in 35 mL of ether). Workup gave 2.05 g (100%) of **9** as a yellow oil: IR (neat) 3420 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.7–1.4 (m, 11, *n*-butyl and C_1 H's), 2.59 (dd, 1, J = 8 Hz, C_{1a} H), 4.93 (s, 1, OH), 7.0–7.8 (m, 4, aromatic H's).

Anal. Calcd for $C_{14}H_{17}ClOS$: C, 62.56; H, 6.37. Found: C, 62.78; H, 6.20.

7a-Chloro-7-hydroxy-7-ethylcyclopropa[*b*][1]benzopyran 2,2-Dioxide (13). After a solution of 7a-chloro-7-ethyl-7-hydroxycyclopropa[*b*][1]benzothiopyran (1.10 g, 4.6 mmol) in $CHCl_3$ (20 mL) was added in one portion to a stirred solution of *m*-chloroperbenzoic acid (2.42 g, 14 mmol) in $CHCl_3$ (25 mL) maintained at 0 to −5 °C, the reaction mixture was allowed to warm to room temperature and was kept overnight at ambient temperature. *m*-Chlorobenzoic acid was removed by filtration and washed with $CHCl_3$ (2 × 10 mL). The combined $CHCl_3$ portions were washed with 10% Na_2CO_3 (2 × 20 mL) and water (2 × 20 mL) and dried ($MgSO_4$). The solvent was removed, and two recrystallizations of the colorless oil from 95% ethanol gave 0.25 g (20%) of **13:** mp 151–153 °C; IR ($CHCl_3$) 3460 (OH), 1290 and 1130 (–SO_2–) cm^{-1}.

Anal. Calcd for $C_{12}H_{13}ClO_3S$: C, 52.84; H, 4.80. Found: C, 53.00; H, 4.92.

7a-Chloro-7-hydroxy-7-methylcyclopropa[*b*][1]benzothiopyran 2,2-Dioxide (12). A solution of 7a-chloro-7-hydroxy-7-methylcyclopropa[*b*][1]benzothiopyran (1.07 g, 4.7 mmol) in $CHCl_3$ (30 mL) was added in one portion to a solution of *m*-chloroperbenzoic acid (2.47 g, 14.2 mmol) in $CHCl_3$ (20 mL) at −20 °C, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was processed as described in the preparation of **13** and gave, after recrystallization from $CHCl_3$–hexane, 0.60 g (50%) of **12:** mp 106–107 °C; IR ($CHCl_3$) 3500 (OH), 1320 and 1140 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 1.33–1.70 (m, 2, C_1 H's), 1.85 (s, 3, CH_3), 3.26–3.62 (dd, 1, C_1 H), 4.88 (s, 1, OH), 7.33–8.08 (m, 4, aromatic H's).

Anal. Calcd for $C_{11}H_{11}ClO_3S$: C, 51.07; H, 4.29; Cl, 13.78; S, 12.39. Found: C, 51.29; H, 4.28; Cl, 14.01; S, 12.51.

7a-Bromo-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran 2,2-Dioxide (11). A solution of 7a-bromo-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (0.76 g, 2.3 mmol) in $CHCl_3$ (3 mL) was added dropwise to a solution of *m*-chloroperbenzoic acid (0.77 g, 4.5 mmol) in $CHCl_3$ (12 mL) at −10 to −15 °C, and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was processed as described in the preparation of **13** and gave, after recrystallization from 95% ethanol, 0.13 g (16%) of **11:** mp 186–188 °C; IR (KBr) 3460 (OH), 1295 and 1140 (SO_2) cm^{-1}; NMR (acetone-d_6) δ 1.9 (m, 2, C_1 H's), 1.95 (s, 1, OH), 3.95 (dd, 1, C_{1a} H), 7.2–7.8 (m, 9, aromatic H's).

Anal. Calcd for $C_{16}H_{13}BrO_3S$: C, 52.61; H, 3.58; S, 8.78. Found: C, 52.75; H, 3.50; S, 8.56.

7a-Chloro-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran 2-Oxide (14). A solution of 7a-chloro-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (500 mg, 1.73 mmol) in acetone (10 mL) and 30% hydrogen peroxide (3.5 mL) was refluxed for 3 h, after which time 30% hydrogen peroxide (3.5 mL) was again added and the solution was heated at reflux for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (25 mL). The ether portion was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the solvent was removed, crystallization of the residue from 95% ethanol gave 280 mg (53%) of **14:** mp 201–204 °C dec; IR ($CHCl_3$) 3570 (OH) and 1020 (SO) cm^{-1}.

Anal. Calcd for $C_{16}H_{13}ClO_2S$: C, 63.05; H, 4.30; S, 10.52. Found: C, 63.35, 63.52; H, 4.45, 4.42; S, 10.57, 10.39.

2,4-Dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (15). Hydrogen chloride was bubbled into a solution of 7a-chloro-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (6.60 g, 0.023 mmol) in $CHCl_3$ (30 mL) for 15 min at room temperature. The excess HCl was then removed from the solution under a stream of nitrogen, and the $CHCl_3$ solution was dried ($MgSO_4$). Removal of the solvent gave 6.60 g (94%) of **15,** mp 119–121 °C. Several recrystallizations from hexane–benzene gave an analytical sample: mp 123–124 °C; IR ($CHCl_3$) 3050 (w), 1600 (m), 1490 (m), 1460 (m), 1430 (m), 1160 (m), 1075 (m), 1050 (m), 950 (m), 680 (s) cm^{-1}; NMR ($CDCl_3$) δ 3.05 (m, 2, C_3 H's), 6.02 (dd, 1, $J_{C_2-C_{3a}}$ = 6 Hz, $J_{C_2-C_{3b}}$ = 11 Hz, –SCHClCH$_a$H$_b$–), 6.89–7.86 (m, 9, aromatic H's); mass spectrum (70 eV), *m/e* (relative intensity) 306 (6), 271 (18), 244 (100), 235 (67).

Anal. Calcd for $C_{16}H_{12}Cl_2S$: C, 62.55; H, 3.94; Cl, 23.08. Found: C, 62.58; H, 3.85; Cl, 22.92.

2-Bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (20). HBr gas (generated by the addition of water to PBr_3) was bubbled into a solution of 7a-chloro-7-phenyl-7-hydroxycyclopropa[*b*][1]benzothiopyran (4.30 g, 14.9 mmol) in $CHCl_3$ (50 mL) for 30 min at room temperature. The excess HBr was then removed from the solution under a stream of nitrogen, and the $CHCl_3$ solution was dried ($MgSO_4$). The solvent was removed under vacuum and gave 4.82 g (92%) of **20,** mp 118–122 °C. Several recrystallizations from hexane–benzene gave an analytical sample: mp 121–122 °C; IR ($CHCl_3$) 3070 (w), 3010 (w), 1600 (w), 1495 (m), 1465 (m), 1435 (m), 1150 (m), 1085 (m), 955 (m), 695 (s) cm^{-1}; NMR ($CDCl_3$) δ 3.11 (m, 2, C_3 H's), 6.09 (dd, 1, $J_{C_2-C_{3a}}$ = 6 Hz, $J_{C_2-C_{3b}}$ = 11 Hz, C_2 H), 6.89–7.95 (m, 9, aromatic H's); mass spectrum (70 eV), *m/e* (relative intensity) 350 (8), 315 (23), 271 (76), 244 (100), 235 (88).

Anal. Calcd for $C_{16}H_{12}BrClS$: C, 54.64; H, 3.44; S, 9.12. Found: C, 54.82; H, 3.55; S, 8.95.

2,4-Dibromo-5-phenyl-2,3-dihydro-1-benzothiepin (21). Using the same procedure described for the preparation of **15,** 7a-bromo-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (0.41 g, 1.2 mmol) provided, after recyrstallization from hexane, 0.47 g (95%) of **21:** mp 108–110 °C; IR ($CHCl_3$) 1150 (m), 690 (s), 650 (m), 600 (m) cm^{-1}; NMR ($CDCl_3$) δ 3.30 (m, 2, C_3 H's), 6.15 (dd, 1, $J_{C_2-C_{3x}}$ = 6 Hz, $J_{C_2-C_{3y}}$ = 12 Hz, C_2 H's), 7.25 (m, 9, aromatic H's).

Anal. Calcd for $C_{16}H_{12}Br_2S$: C, 48.49; H, 3.05; S, 8.09; Br, 40.34. Found: C, 48.60; H, 3.02; S, 8.14; Br, 39.90.

2-Bromo-4-chloro-5-benzyl-2,3-dihydro-1-benzothiepin (32). Using the same procedure described for the preparation of **20,** 7-benzyl-7a-chloro-7-hydroxycyclopropa[*b*][1]benzothiopyran (2.85 g, 9.4 mmol) provided, after recrystallization from hexane–$CHCl_3$, 3.03 g (88%) of **32:** mp 102–103 °C; IR ($CHCl_3$) 3070 (m), 2940 (w), 1625 (m), 1600 (m), 1495 (s), 1465 (s), 1430 (s), 1145 (s), 955 (s), 685 (s) cm^{-1}; NMR ($CDCl_3$) δ 3.13 (m, 2, C_3 H's), 3.99 (d, 2, $C_6H_5CH_2$), 6.11 (dd, 1, $J_{C_2-C_{3a}}$ = 6 Hz, $J_{C_2-C_{3b}}$ = 11 Hz, C_2 H), 7.0–8.0 (m, 9, aromatic H's).

Anal. Calcd for $C_{17}H_{14}BrClS$: C, 55.83; H, 3.86; S, 8.77. Found: C, 55.64; H, 3.78; S, 8.59.

4-Chloro-2-hydroxy-5-phenyl-2,3-dihydro-1-benzothiepin (19). A solution of 2,4-dichloro-5-phenyl-2,3-dihydro-1-benzothiepin (0.30 g, 0.98 mmol), acetone (10 mL), and water (4 mL) was allowed to stand overnight at room temperature. An additional 1 mL of water was added, and white solid precipitate formed which was filtered and allowed to dry. The yield of crystalline **19** was 0.24 g (84%): mp 159–161 °C; IR ($CHCl_3$) 3580 cm^{-1} (OH); NMR (acetone-d_6) δ 2.80 (m, 2, C_3 H's), 5.67 (s, 1, OH), 5.93 (dd, 1, $J_{C_2-C_{3x}}$ = 5 Hz, $J_{C_2-C_{3y}}$ = 10 Hz, C_2 H), 6.83–7.72 (m, 9, aromatic H's). Several recrystallizations from hexane–benzene gave an analytical sample, mp 160–161 °C.

Anal. Calcd for $C_{16}H_{13}ClOS$: C, 66.54; H, 4.54; S, 11.10. Found: C, 66.67, 66.52; H, 4.44, 4.48; S, 10.90, 10.83.

Reaction of 7a-Chloro-7-hydroxy-7-phenylcyclopropa[*b*][1]benzothiopyran (4) with Trace Amounts of *p*-Toluenesulfonic Acid in Refluxing Benzene. In a 100-mL round-bottom flask fitted with a Dean-Stark trap and reflux condenser a solution of 7a-chloro-7-phenyl-7-hydroxycyclopropa[*b*][1]benzothiopyran (0.80 g, 2.8 mmol) and *p*-toluenesulfonic acid (20 g, 0.10 mmol) in 50 mL of benzene was stirred magnetically and refluxed for 1 h. The yellow solution was allowed to cool and then was washed with 10% Na_2CO_3 (2 × 45 mL) and water (45 mL) and dried over $MgSO_4$. Removal of the solvent under vacuum left an orange oil which had IR and NMR spectra which were identical with those of 2-chloro-1-phenylnaphthalene. Repeated vacuum sublimation provided white crystals of 2-chloro-1-phenylnaphthalene, mp 49–51 °C.

2-Bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin 1,1-Dioxide (23). After a solution of 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (2.00 g, 5.7 mmol) in $CHCl_3$ (7 mL) was added dropwise over a 15-min period to a stirred solution of *m*-chloroperbenzoic acid (2.45 g, 14 mmol) in $CHCl_3$ (20 mL) maintained at 0 to −5 °C, the reaction mixture was allowed to warm to room temperature and was kept overnight at ambient temperature. *m*-Chlorobenzoic acid was removed by filtration and washed with $CHCl_3$ (2 × 7 mL). The combined $CHCl_3$ portions were washed with 10% Na_2CO_3 (2 × 40 mL) and water (2 × 40 mL) and dried ($MgSO_4$). The solvent was removed, and recrystallization of the solid residue from 95% ethanol and benzene gave 0.85 g (39%) of **23:** mp 208–211 °C dec; IR ($CHCl_3$) 1330, 1140, 1115 cm^{-1} (–SO_2–); NMR ($CDCl_3$) δ 3.27 (m, 2, C_3 H's), 5.47 (dd, 1, C_4 H), 6.98–8.28 (m, 9, aromatic H's). Several recrystallizations from 95% ethanol gave an analytical sample, mp 209–211 °C dec.

Anal. Calcd for $C_{16}H_{12}BrClO_2S$: C, 50.09; H, 3.15; S, 8.36. Found: C, 50.22; H, 3.20; S, 8.19.

2-Bromo-4-chloro-5-benzyl-2,3-dihydro-1-benzothiepin 1,1-Dioxide (33). Following the procedure described for the preparation of **23**, 5-benzyl-2-bromo-4-chloro-2,3-dihydro-1-benzothiepin (1.00 g, 2.7 mmol) gave, after recrystallization from 95% ethanol and benzene, 0.68 g (67%) of **33**: mp 181–183 °C; IR ($CHCl_3$) 1325 and 1115 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 3.21 (m, 2, C_3 H's), 4.11 (s, 2, $C_6H_5CH_2$), 5.49 (dd, 2, $J_{C_2-C_{3x}}$ = 6 Hz, $J_{C_2-C_{3y}}$ = 10 Hz, C_2 H's), 7.2–7.8 (m, 8, aromatic H's except C_9 H), 8.20 (m, 1, C_9 H). Recrystallization from 95% ethanol and benzene gave an analytical sample, mp 182–183 °C.

Anal. Calcd for $C_{17}H_{14}BrClO_2S$: C, 51.34; H, 3.55; S, 8.06. Found: C, 51.25; H, 3.64; S, 7.95.

4-Chloro-5-phenyl-1-benzothiepin (16). A solution of 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin (1.02 g, 2.84 mmol) in THF (3 mL) was added in one portion to a solution of 1,5-diazabicyclo[4.3.0]-5-nonene (DBN) (0.52 g, 4.2 mmol) in THF (3 mL) at room temperature. After the reaction mixture was stirred for 2 h, the red solution containing some precipitate was poured into 10% HCl solution (20 mL) and the aqueous solution was extracted with $CHCl_3$ (2 × 15 mL). The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo (below room temperature). The yellow oil which solidified on cooling was chromatographed on aluminum oxide (Merck 71707, 25 g) with hexane as the eluent, and the first 50-mL fraction gave 0.58 g (76%) of **16** as a white crystalline solid: mp 86–88 °C; IR ($CHCl_3$) 3070 (m), 3020 (m), 1590 (m), 1490 (m), 1470 (s), 1445 (m), 1080 (s), 1045 (s), 845 (s), 695 (s) cm^{-1}; NMR (CCl_4) δ 6.20 (d, 1, $J_{C_3-C_2}$ = 9 Hz, C_2 H), 6.44 (d, 1, $J_{C_2-C_3}$ = 9 Hz, C_3 H), 6.8–7.6 (m, 9, aromatic H's). Recrystallization from pentane–$CHCl_3$ gave an analytical sample, mp 87–88 °C (sent out packed in dry ice).

Anal. Calcd for $C_{16}H_{11}ClS$: C, 70.97; H, 4.09; S, 11.83. Found: C, 70.81; H, 4.21; S, 11.70.

4-Chloro-5-benzyl-1-benzothiepin (24). Using the same procedure described for the preparation of **16**, 5-benzyl-2-bromo-4-chloro-2,3-dihydro-1-benzothiepin (1.00 g, 2.7 mmol) in THF (5 mL) was reacted with DBN (0.51 g, 4.1 mmol) in THF (5 mL) at room temperature. Chromatography provided 0.63 g (82%) of **24** as a light yellow crystalline solid: mp 80–81 °C; IR (CCl_4) 3075 (m), 3040 (m), 2960 (w), 1495 (m), 720 (m), 690 (s) cm^{-1}; NMR (CCl_4) δ 4.20 (s, 2, $C_5H_5CH_2$), 6.20 [d, 2 (total weight of C_3 H and C_2 H), $J_{C_3-C_2}$ = 10 Hz, C_2 H], 6.40 [d, 2 (total weight of C_2 H and C_3 H), $J_{C_2-C_3}$ = 10 Hz, C_3 H], 7.0–7.4 (m, 9, aromatic H's). Recrystallization from hexane provided an analytical sample, mp 80–81 °C.

Anal. Calcd for $C_{17}H_{13}ClS$: C, 71.69; H, 4.60. Found: C, 71.81; H, 4.60.

4-Bromo-5-phenyl-1-benzothiepin (26). Using the same procedure described for the preparation of **16**, 2,4-dibromo-5-phenyl-1-benzothiepin (150 mg, 0.38 mmol) in THF (6 mL) was reacted with DBN (0.99 g, 0.80 mmol) in THF (5 mL) at room temperature. Chromatography followed by recrystallization from pentane provided 30 mg (24%) of **26**: mp 81–82 °C; IR ($CDCl_3$) 3060 (w), 1035 (m), 840 (m) cm^{-1}; NMR ($CDCl_3$) δ 6.50 (dd, 2, C_2 H and C_3 H), 7.4 (m, 9, aromatic H's).

Anal. Calcd for $C_{16}H_{11}BrS$: C, 60.96; H, 3.52; S, 10.17. Found: C, 60.86; H, 3.45; S, 9.92.

4-Chloro-5-methyl-1-benzothiepin (27). 7a-Chlorocyclopropa[*b*][1]benzothiopyran-7-one (3.00 g, 14.2 mmol) was reacted with excess methylmagnesium chloride and provided the alcohol **7** as previously described. Reaction of **7** with HBr, following the procedure described for the preparation of **20**, gave 2.90 g of crude 2-bromo-4-chloro-5-methyl-1-benzothiepin. The olefin (1.00 g, 3.4 mmol) was converted to **27** with a threefold excess of DBN following the procedure described for the preparation of **16**. The crude product was passed through two columns of alumina (15 g each) eluting with hexane to provide 0.44 g (43% overall yield from ketone **2**) of **27** as a colorless oil: IR (neat) 3070 (w), 2970 (w), 1475 (m), 985 (s), 840 (s), 760 (s), 725 (s) cm^{-1}; NMR (CCl_4) δ 2.43 (s, 3, CH_3), 6.07 [d, 2 (total weight of C_3 H and C_2 H), $J_{C_3-C_2}$ = 9 Hz, C_2 H], 6.25 [d, 2 (total weight of C_2 H and C_3 H), $J_{C_2-C_3}$ = 9 Hz, C_3 H], 7.1–7.4 (m, 4, aromatic H's). Further characterization was provided by examination of the products from thermal decomposition.

4-Bromo-5-methyl-1-benzothiepin (28). Using the same procedure described for the synthesis of **27**, 7a-bromocyclopropa[*b*][1]-benzothiopyran-7-one (3.00 g, 11.8 mmol) was converted to **28** (29% overall yield from ketone **3**), isolated as a pale yellow oil: IR (neat) 3070 (w), 2990 (w), 760 (s) cm^{-1}; NMR (CCl_4) δ 2.33 (s, 3, CH_3), 5.90 [d, 2 (total weight of C_3 H and C_2 H), $J_{C_3-C_2}$ = 8.5 Hz, C_2 H], 6.29 [d, 2 (total weight of C_2 H and C_3 H), $J_{C_2-C_3}$ = 8.5 Hz, C_3 H], 7.0–7.6 (m, 4, aromatic H's). Further characterization was provided by examination of the products from thermal decomposition.

4-Chloro-5-phenyl-1-benzothiepin 1,1-Dioxide (22). Method A. To a stirred solution of 1,5-diazabicyclo[4.3.0]-5-nonene (0.23 g, 1.85 mmol) in THF (5 mL) was added at room temperature, in one portion, 2-bromo-4-chloro-5-phenyl-2,3-dihydro-1-benzothiepin 1,1-dioxide (0.48 g, 1.25 mmol) in THF (11 mL). After the reaction mixture was stirred for 2 h at room temperature, the yellow mixture was poured into 10% HCl solution (25 mL). The aqueous solution was extracted with $CHCl_3$ (2 × 15 mL), washed with H_2O, and dried ($MgSO_4$). The $CHCl_3$ was removed under pressure and left 0.31 g (82%) of **22**: mp 178–180 °C; IR (KBr) 1300 and 1160 cm^{-1} (–SO_2–); NMR ($CDCl_3$) δ 6.77 [d, 2 (total weight of C_3 H and C_2 H), $J_{C_2-C_3}$ = 14 Hz, C_2 H], 6.94 [d, 2 (total weight of C_2 H and C_3 H), $J_{C_3-C_2}$ = 14 Hz, C_3 H], 7.1–7.8 (m, 8, aromatic H's except for C_9 H), 8.10 (m, 1, C_9 H). Two recrystallizations from hexane–$CHCl_3$ provided an analytical sample, mp 181–182 °C.

Anal. Calcd for $C_{16}H_{11}ClO_2S$: C, 63.47; H, 3.66; S, 10.59. Found: C, 63.33; H, 3.72; S, 10.59.

Method B. To a solution of *m*-chloroperbenzoic acid (222 mg, 1.3 mmol) in $CHCl_3$ (3 mL) maintained at −15 to −20 °C was added dropwise over a 10-min period 4-chloro-5-phenyl-1-benzothiepin (174 mg, 0.64 mmol) in $CHCl_3$ (3 mL). The reaction mixture was stirred overnight at 0 °C. After the reaction mixture was filtered, the precipitate was washed with $CHCl_3$ (2 × 3 mL) and the washings were combined with the filtrate and washed with 10% Na_2CO_3 solution and water and dried ($MgSO_4$). Removal of the solvent left 127 mg (66%) of a colorless oil which solidified upon cooling and addition of hexane. Recrystallization from $CHCl_3$–hexane gave **22**, mp 180–181 °C. A mixture melting point with an authentic sample was not depressed, and the IR spectrum was identical with that of an authentic sample.

4-Chloro-5-benzyl-1-benzothiepin 1,1-Dioxide (25). Method A. Following the same procedure described for the preparation of **22**, 5-benzyl-2-bromo-4-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (0.51 g, 1.3 mmol) gave, after recrystallization from hexane–benzene, 0.30 g (74%) of **25**: mp 160–162 °C; IR ($CHCl_3$) 1325 and 1145 cm^{-1} (SO_2). Two more recrystallizations from hexane–benzene provided an analytical sample, mp 170–172 °C.

Anal. Calcd for $C_{17}H_{13}ClO_2S$: C, 64.45; H, 4.14. Found: C, 64.51; H, 4.20.

Method B. Following the same procedure described for the preparation of **22** (except the reaction was left at room temperature overnight), 5-benzyl-4-chloro-1-benzothiepin (232 mg, 0.8 mmol) gave, after chromatography on aluminum oxide (Merck 71707, 20 g) eluting with a 1:1 mixture of hexane–$CHCl_3$, 1-benzyl-2-chloronaphthalene (100 mg, 49%) and **25** (84 mg, 33%), each identified by comparison of its IR spectrum with that of an authentic sample.

Thermal Decomposition of 1-Benzothiepins. Approximately 1 M solutions of **1**, **12**, **19**, **22**, and **23** in CCl_4 and **21** in $CDCl_3$ were prepared, and the decomposition to sulfur and the corresponding naphthalenes was monitored by NMR spectroscopy (see Table III).

After the decomposition of 4-chloro-5-phenyl-1-benzothiepin (**16**) (46 mg, 0.17 mmol) was complete, the solvent was evaporated and the resulting solid was washed with pentane (20 mL). The solid (1 mg, 19%) was identified as sulfur by a mixed melting point with an authentic sample, mp 120–121 °C. Removal of the solvent under vacuum left 30 mg (75%) of 2-chloro-1-phenylnaphthalene (**17**) as a colorless oil: IR (CCl_4) 3070 (m), 1130 (s), 855 (m, two adjacent H's) cm^{-1}; NMR (CCl_4) δ 7.2–7.9 (m, aromatic H's). Recrystallization from methanol provided an analytical sample, mp 50–51 °C.

Anal. Calcd for $C_{16}H_{11}Cl$: C, 80.50; H, 5.64. Found: C, 80.37; H, 4.66.

A similar workup for the decomposition of 5-benzyl-4-chloro-1-benzothiepin (224 mg, 0.8 mmol) gave 4 mg (16%) of sulfur and 140 mg (69%) of 1-benzyl-2-chloronaphthalene (**31**): mp 59–61 °C; IR ($CHCl_3$) 3070 (m), 3010 (m), 1130 (s), 945 (s), 825 (m, two adjacent H's), 800 (s), 700 (m), 690 (m) cm^{-1}; NMR (CCl_4) δ 4.56 (s, 2, $C_6H_5CH_2$), 7.1–8.1 (m, 11, aromatic H's).

Anal. Calcd for $C_{17}H_{13}Cl$: C, 80.79; H, 5.18. Found: C, 80.61; H, 5.37.

A similar workup for the decomposition of 4-chloro-5-methyl-1-benzothiepin gave 2-chloro-1-methylnaphthalene:[16] IR (neat) 830 (m, two adjacent H's), 800 (s), 760 (m), 735 (m) cm^{-1}; NMR (CCl_4) δ 2.65 (s, 3, CH_3), 7.2–7.9 (m, 6, aromatic H's).

A similar workup for the decomposition of 4-bromo-5-methyl-1-benzothiepin gave 2-bromo-1-methylnaphthalene:[17] IR (neat) 815 (m, two adjacent H's), 800 (s), 760 (m), 735 (m) cm^{-1}; NMR (CCl_4) δ 2.61 (s, 3, CH_3), 7.2–8.0 (m, 6, aromatic H's).

Registry No.—**2**, 40322-30-3; **3**, 40322-58-5; **15**, 66768-80-7; **17**,

66768-81-8; **19**, 66768-82-9; **20**, 66768-83-0; **21**, 66768-84-1; **23**, 66768-85-2; **31**, 66768-86-3; **32**, 66768-87-4; **33**, 66768-88-5; 2-bromo-4-chloro-5-methyl-1-benzothiepin, 66768-89-6; 2-chloro-1-methylnaphthalene, 20601-21-2; 2-bromo-1-methylnaphthalene, 20601-22-3.

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Direction of Cyclization in the Fischer Indole Synthesis. Mechanistic Considerations

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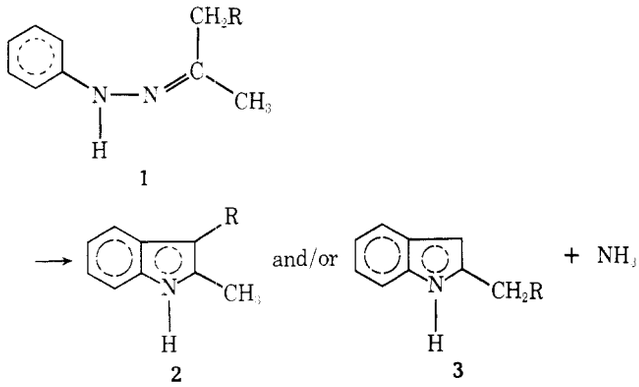
Received January 18, 1978

The effects of acid catalysts and temperature in the uncatalyzed reaction on the direction of cyclization of unsymmetrical ketone phenylhydrazones in the Fischer indole synthesis have been examined. Higher acidity, as previously reported, and higher temperature in the thermal process cause cyclization toward the less substituted position. The observations are considered in terms of a refined version of the first two stages of the mechanism of the reaction.

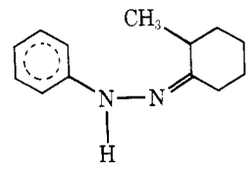
A perplexing aspect of the Fischer indole synthesis[2] has been the cyclization of phenylhydrazones of unsymmetrical ketones to form two possible indoles. The early generalizations of Plancher,[3] suggesting that the course of the reaction depends only on the structure of the ketone moiety of the

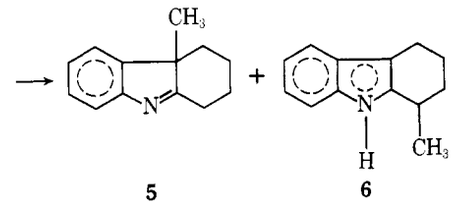


phenylhydrazone, have not been sustained by more recent investigations[4-7] in which the ratio of the products has been found to vary with the nature of the acid used as the catalyst, its concentration, or its absence in a thermal cyclization.

While Lyle and Skarlos[5] suggested that the direction of cyclization was an effect of the size of the acid, Illy and Funderburk[6] and Palmer and McIntyre[7] independently provided convincing evidence that the course of the reaction was governed by the acidity of the reaction medium. The trend evident in the results of these more recent studies[5-7] is that weaker acids or lower acid concentrations promote cyclization toward the more branched carbon atom (**1** → **2**) and stronger acids or higher acid concentrations enhance the extent of cyclization at the less branched position (**1** → **3**).

Most of these observations have been made on a variety of phenylhydrazone structures with several acid catalysts under nonuniform conditions. Since the direction of enolization is necessarily central to the mechanism[2] of the Fischer indole synthesis, a systematic examination of this phenomenon should provide further information regarding the character of the mechanistic steps. For this purpose, 2-alkylcyclohexanone phenylhydrazones were selected for cyclization under varying conditions of acidity and temperature. This substrate provides two reaction pathways of similar energy requirements since both products are known to form in good yield under moderate reaction conditions.[4c,c,8]





In Table I are listed the product ratios observed in the cyclization of 2-methylcyclohexanone phenylhydrazone (**4**) with various acids at 80 °C. The trend is similar to that found previously.[4a,8a] The results also parallel those of Illy and Funderburk[6] for the phenylhydrazone of methyl isopropyl ketone.

The product ratios observed with various concentrations of sulfuric acid in ethanol as the catalyst at 80 °C are given in Table II. As with the results reported by Illy and Funderburk[6] and Palmer and McIntyre[7] for acyclic ketone phenylhydraz-