aliquot was removed to determine conversion to PhMe (6.3%). The residual material was treated with 0.5 mL of C_2Cl_4 to serve as a chaser, and ~0.5 mL was distilled off under vacuum and collected in a cold trap. A sample of pure PhMe product was then collected from this distillate by preparative GLC. ^1H NMR spectra in a minimal amount of CCl_4 solvent were taken at 60 and 200 MHz and gave an $[H/(H + D)]_\alpha$ value of 0.13 integrated against the aromatic resonance. The ^2H NMR spectrum was then taken at 30.71 MHz in added $ClCH_2CH_2Cl$ solvent (14 mL), the natural-abundance ^2H in which served as an internal standard. Integration of the (nonobserved) aromatic region against the benzylic resonance after 34 700 accumulations set an upper limit of <0.025 D/mol of PhMe.

Acknowledgment. The synthesis of 1-d_4 was developed by Lawrence A. Zeff, College of Wooster, as a student participant in the Oak Ridge Science Semester of the Great Lakes College Association/Associated Colleges of the Midwest. Some analytical aspects of its thermolysis were performed by Emily C. Douglas. We acknowledge very helpful discussions with and preprints from Professor L. M. Stock. We also acknowledge Professor Gajewski and Dr. Gilbert for a preprint of the companion paper.[55]

Registry No. 1, 1081-75-0; 2, 1083-56-3; 1,2-diphenylethane, 103-29-7.

(55) Gilbert, K. E.; Gajewski, J. J. *J. Org. Chem.*, accompanying paper in this issue.

Photochemistry of 2-Phenylbenzothiazole with Ethoxyacetylene and Ethoxypropyne. Synthesis of 1,5-Benzothiazepines

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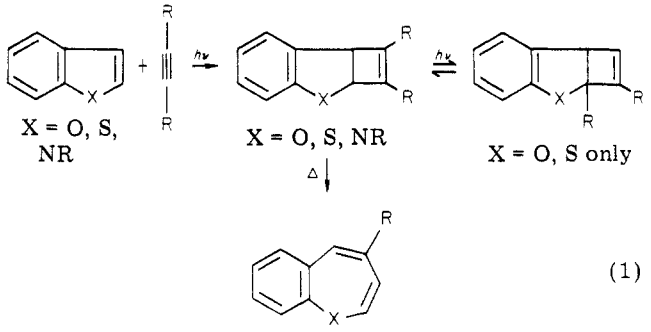
Photocycloaddition reactions of 2-phenylbenzothiazole with electron-rich alkynes, ethoxyacetylene, and ethoxypropyne gave substituted 1,5-benzothiazepines in a one-step processes.

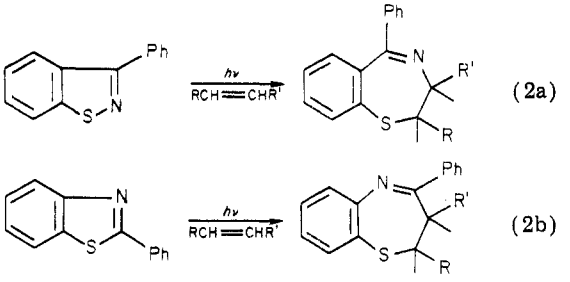
Previous results from our laboratories have shown that $[_\pi 2_s + _\pi 2_s]$ cycloaddition reactions of acetylenes and benzo[*b*]thiophenes, benzo[*b*]furans, or indoles, followed by thermal ring-opening rearrangement, generate, in one synthetic step, benzo[*b*]thiepines, benzo[*b*]oxepines, and benzo[*b*]azepines (eq 1).[1]



(1)

Recent studies[2-5] have extended this chemistry to condensed heteroaromatic systems containing sulfur and nitrogen in view of the potential of this as a synthetic route to potentially pharmacologically active benzothiazepine derivatives. Thus, 3-phenyl-1,2-benzisothiazole and 2-phenyl-1,3-benzothiazole (eq 2), when irradiated in the presence of alkenes such as ethyl vinyl ether or *cis*- and *trans*-2-butene, gave 2,3-dihydro-1,4- and 2,3-dihydro-1,5-benzothiazepines[4] in a regio- and stereospecific way in the first synthesis of these compounds.

Although saturated 1,4- and 1,5-benzothiazepines have been widely studied,[6] there are only a few known unsaturated 1,5-benzothiazepines.[7-11]



We report herein the first general one-step photochemical synthesis of substituted 1,5-benzothiazepines and comment on various aspects of their properties, including their NMR characteristics, UV spectral data, thermal stability, and relative aromaticity.

Results

2-Phenylbenzothiazole (**1**), when irradiated in the presence of ethoxyacetylene (**2a**), gave *two* products, **3a** and **6a** (eq 3), in 25% and 13% yield, respectively. In a similar manner, however, **1**, in the presence of 1-ethoxy-1-propyne (**2b**) gave a complex reaction mixture. Five products could be isolated (**3b–7b**) in 51%, 29%, 5%, 12%, and 1% yields, respectively, and their structures were determined by spectroscopic and chemical means. The major products in both cases were the previously unknown

(1) See: Davis, P. D.; Neckers, D. C.; Blount, J. R. *J. Org. Chem.* **1980**, *45*, 462 and references cited therein.
(2) Sindler-Kulyk, M.; Neckers, D. C. *Tetrahedron Lett.* **1981**, 525.
(3) Sindler-Kulyk, M.; Neckers, D. C. *Tetrahedron Lett.* **1981**, 529.
(4) Sindler-Kulyk, M.; Neckers, D. C. *Tetrahedron Lett.* **1981**, 2081.
(5) Sindler-Kulyk, M.; Neckers, D. C.; Blount, J. R. *Tetrahedron.* **1981**, 3377.
(6) See for example: Sternbach, L. H.; Lehr, H.; Reeder, E.; Hayes, T.; Steiger, N. *J. Org. Chem.* **1965**, *30*, 2812. Wuensch, K. H.; Ehlers, A. *Z. Chem.* **1970**, *10*, 361.
(7) Stephens, W. D.; Field, L. *J. Org. Chem.* **1959**, *24*, 1576.
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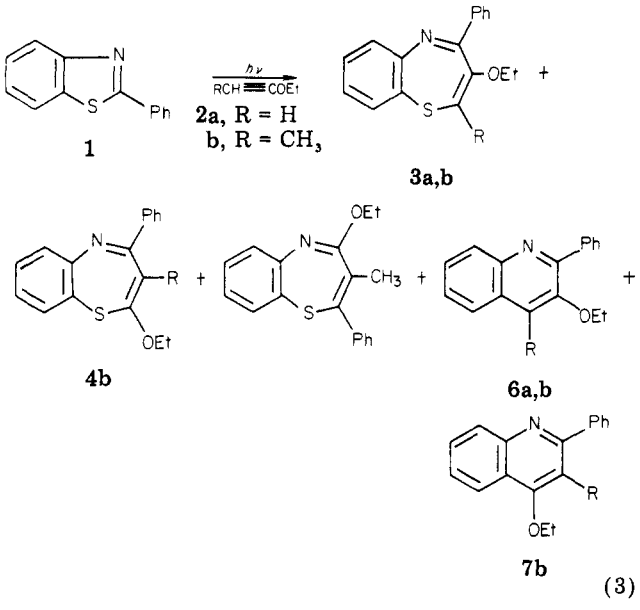
(9) Buggle, K.; Delahunty, J. J.; *Philbin*, E. M. *Proc. R. Ir. Acad., Sect. B* **1971**, *71B*, 257; *Chem. Abstr.* **1972**, *76*, 45872.
(10) Ried, W.; Koenig, E. *Justus Liebigs Ann. Chem.* **1972**, *755*, 24.
(11) Ried, W.; Ochs, W. *Chem. Ber.* **1974**, *107*, 1334.

0022-3263/82/1947-4914$01.25/0



(3)

substituted 1,5-benzothiazepines **3a,b**.

The ^1H NMR spectrum of photoproduct **3a**, 3-ethoxy-4-phenyl-1,5-benzothiazepine, shows a one-proton singlet at δ 5.70 as well as the expected aromatic protons. We ascribe this singlet to the proton on C-2. **3a** also shows a well-resolved quartet and triplet for the ethoxy group on C-3 at δ 3.78 and 1.18. When the hydrogen on C-2 is replaced by a methyl group in photoproduct **3b**, a three-proton singlet appears at δ 2.13, and the quartet and triplet of the ethoxy group on C-3 are shifted upfield to δ 3.40 and 0.86. In **4b**, the methyl group on C-3 is at δ 1.26. When the phenyl group is on C-2 and the ethoxy group on C-4 (product **5b**), the three-proton singlet of the methyl group appears at δ 1.85 and the ethoxy group as a two-proton quartet at δ 4.42 and a three-proton triplet at δ 1.43. The methylene portion of the ethoxy group in 3-ethoxy-2-methyl- as well as in 2-ethoxy-3-methyl-4-phenyl-1,5-benzothiazepine, products **3b** and **4b**, does not appear as a "normal" quartet. The OCH_2 group in **3b** has a quintet-like signal which, when the probe temperature is decreased, changes to the AB part of an ABX_3 spectrum,[12] indicating that conformational isomers exist which interconvert slowly on the NMR time scale[13] Figure 1.

The benzothiazepine **3a** with a less bulky substituent in position 2 has a "normal" quartet for the methylene hydrogens of the ethoxy group in position 3. On the other hand, the double quartet (a quartet with an additional small coupling of 1.5 Hz) in benzothiazepine **4b** does not change on cooling to −30 °C.

Possible cyclic adducts with the 2,5-thiazabicyclo-[3.2.0]heptadiene structure, formed by [2 + 2] cycloaddition to C=N, are ruled out by the absence of a quaternary carbon in ^{13}C NMR. All the 1,5-benzothiazepines (**3a,b**, **4b**, and **5b**) we have isolated show a ^{13}C NMR signal between 163 and 160 ppm which we ascribe to the sp^2-hybridized carbon C-4.[14] We suggest that the nonequivalence of OCH_2 protons results from conformational isomers of the nonplanar seven-membered ring rather than from mesomeric structures involving partial double bonds

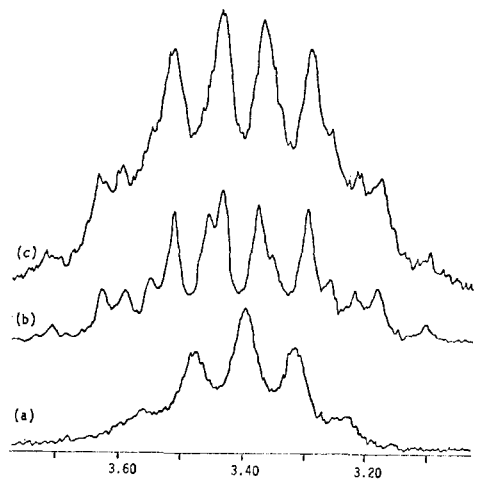


Figure 1. NMR spectra of 2-methyl-3-ethoxy-4-phenyl-1,5-benzothiazepine (**3b**) in acetone-d_6 at (a) room temperature, (b) −55 °C, and (c) −80 °C.

from C-2 to the oxygen atom of the ethoxy function.

The nonequivalence of the methylene protons might also be the result of the presence of a chiral center in the molecule. If chirality were responsible for methylene nonequivalence, however, it would also require an alternative structural assignment for the photoproducts **3b** and **4b**. If cycloaddition, for example, were to occur on the carbon–nitrogen double bond and the formed bicyclic adducts **8** and **9** photochemically rearrange, as we have observed previously in monoheteroatom systems,[1] the isolated compounds might have the structures **10** and **11** (Scheme I). These compounds could ring open and, further, desulfurize to produce the identical quinolines previously described as deriving from the compounds **3b** and **4b**.

The UV spectra of 1,5-benzothiazepines **3a** and **3b** are very similar, and their maxima at approximately 260 and 320 nm resemble the maxima of a general model compound, benzylideneaniline. The absorption of **4b** does not deviate too much from this. The spectrum of **5b**, however, is rather different, indicating the absence of a benzylideneaniline chromophore. The color of the 1,5-benzothiazepines varies from intense yellow (**3a**) to white (**5b**).

Not surprisingly,[15] the main characteristic of all the 1,5-benzothiazepines is thermal instability, i.e., sulfur extrusion. At elevated temperatures, or even upon prolonged standing at room temperature, the photoproducts **3a,b**, **4b**, and **5b** are converted to the corresponding quinolines (Scheme II and eq 4). The structures of the quinolines were confirmed by comparing their properties with independently synthesized authentic materials (see Experimental Section).

We observed that 4-ethoxy-3-methyl-2-phenyl-1,5-benzothiazepine (**5b**) was the most stable benzothiazepine. Thus after 16 h in C_6D_6 at 40 °C, on the basis of NMR data, **3a** gave 22% of **6a**, **3b** gave 42% of **6b**, and **4b** gave 16% of **7b**, while **5b** remained unchanged. Loss of sulfur from **5b** occurs only at higher temperature (150–200 °C). Desulfurization of **3a,b** and **4b** is acid catalyzed even at room temperature. **5b** does not change under similar conditions.

We have also prepared 1,5-benzothiazepine **3a** by dehydrogenation of **15**[4] and converted it to the quinoline **6a** (eq 4).

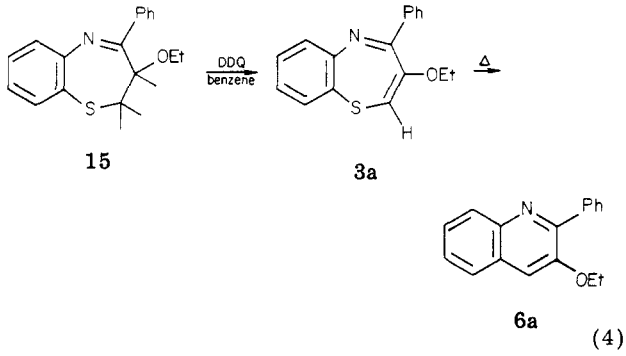
The mass spectra of 1,5-benzothiazepines have parent ions at m/e 281 (**3a**) and 295 (**3b** and **4b**) and base peaks

(12) Similar results were reported for benzazepines: Manschreck, A.; Rissmann, G.; Voegtle, F.; Wild, D. *Chem. Ber.* **1967**, *100*, 335.

(13) Guenther, H. "NMR Spectroscopy"; Wiley: Chichester–New York–Brisbane–Toronto, **1980**; pp 190.

(14) For example, see benzodiazepines: Kovar, K. A.; Linden, D. *Arch. Pharm. (Weinheim Ger.)* **1981**, *314*, 186. Haran, R.; Tuchagues, J. P. *J. Heterocycl. Chem.* **1980**, *17*, 1483. Singh, S. P.; Parmar, S. S.; Farnum, S. A.; Stenberg, V. I. *Ibid.* **1978**, *15*, 1083.

(15) Garrett, P. J. "Aromaticity", McGraw-Hill: New York, 1971.

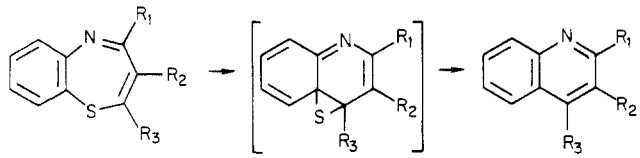


(4)

at m/e 200 (**3a**) and 234 (**3b** and **4b**), respectively. These peaks result from the loss of a sulfur atom and an ethyl fragment. The most stable photoproduct, **5b**, gave a base peak at m/e 266, indicating a preferred loss of an ethyl fragment. If the sample is introduced into the inlet port (not directly into an ionization chamber), the highest masses were m/e 249 (**3a**) and 263 (**3b–5b**) instead of m/e 281 and 295, while the fragmentation was the same as in corresponding quinolines.

Discussion

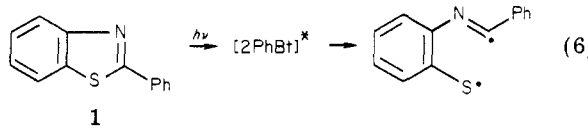
Photoaddition of ethoxyacetylene and 1-ethoxy-1-propyne to 2-phenylbenzothiazole results uniquely in the formation of substituted 1,5-benzothiazepines, a cyclic system with eight π electrons. We assume that the compounds rearrange via an episulfide, a valence tautomer, to the more stable 6-π-electron-ring quinoline (eq 5). This



(5)

explains the presence of quinolines in the irradiated mixture. Though the thermal stability of the 1,5-benzothiazepines depends on the position of ring substituents, 1,5-benzothiazepines (**3–5**) are photochemically stable.

There are several mechanisms which could explain the formation of 1,5-benzothiazepines. In accord with our previous experiments on the one-step photoaddition of alkenes to 2-phenylbenzothiazole,[4] we first considered the process in which the trapping of the intermediate diradical obtained after homolytic cleavage of the sulfur–carbon bond is required (eq 6), but this only explains the forma-



(6)

1

tion of the major photoproducts. An alternate pathway, taking into consideration all the benzothiazepines formed by photoreactions and assuming their formation via the same intermediate, is likely to be that outlined in Scheme III. Photoreaction occurs from the excited state of 2-phenylbenzothiazole, producing biradicals **16** and **17**.

Diradical **16** rearranges to **18** which, upon the ring closure gives the major product **3b**. Intermediate **17** similarly rearranges to **19** which closes to the second major product **4b**. A small amount of the photoproduct **5b** derives from ring opening of the cycloadduct **9** formed by ring closure of the diradical **17**. **12** is not isolated, but the NMR spectra of some TLC fractions indicate that it could be present in very small quantities.

It is interesting to note that the photoreaction with ethoxyacetylene is regiospecific, giving only one isomer, **3a**. This resembles the previous result[5] with ethyl vinyl ether.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded on Varian EM-360 and CFT-20 spectrometers with deuteriochloroform as the solvent and tetramethylsilane as the internal reference. UV spectra were determined in ethanol by using a Varian/Cary 219 spectrophotometer. IR spectra were obtained on a Perkin-Elmer 337 spectrophotometer and mass spectra on a Varian MAT CH7 spectrometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Photolyses were carried out by using a 450-W Hanovia medium-pressure mercury lamp. Samples were contained in degassed, sealed Pyrex tubes and irradiated while immersed in a thermostates water bath. The products were separated by preparative thick-layer chromatography (20 × 20 cm × 2 mm) with 10% ether in hexane as eluent. By adding a small amount of ethanol to the extracted oily material and cooling the solution in the freezer, the products separated in a crystaline form. Ethoxyacetylene (**2a**) and 1-ethoxy-1-propyne (**2b**) were purchased from Farchan Chemical Co.

Irradiation of 2-Phenylbenzothiazole (1) in the Presence of Ethoxyacetylene (2a). A 0.1 M solution of 2-phenylbenzothiazole[16] (**1**) in ethoxyacetylene (**2a**) was irradiated for 240 h at 15 °C. The reaction mixture gradually became darker and darker, and when the irradiation was interrupted, the solution was almost dark brown. Excess ethoxyacetylene was evaporated and the dark residue chromatographed. Preparative thick-layer chromatography gave primarily two bands after elution three times. The faster moving band, intensively yellow, contained **3a** and some starting material. The second, a very intense blue fluorescence band with a smaller R_f value, contained **6a**.

3-Ethoxy-4-phenyl-1,5-benzothiazepine (3a): 25% yield; yellow crystals (from EtOH); mp 83–84 °C; IR (mineral oil) 1620, 1600, 1580 cm^{-1}; ^1H NMR δ 7.80–8.00 (m, 2 H aromatic), 6.98–7.60 (m, 7 H aromatic), 5.70 (s, 1 H), 3.78 (q, 2 H, J = 7.0 Hz), 1.18 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 163.90, 153.26, 149.94, 137.62, 131.54, 130.93, 130.66, 128.81, 128.16, 127.62, 125.67, 125.56, 103.10, 64.35, 14.21; mass spectrum, m/e (relative intensity) 281 (M^+, 27), 280 (M − 1, 27), 249 (M − 32, 93), 234 (M − 47, 80), 220 (M − 61, 100), 211 (M − 70, 33); UV λ_{max} 262 nm (ϵ 5770), 315 (6300), 370 (2710). Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98; S, 11.40. Found: C, 72.48; H, 5.29; N, 4.96; S, 11.33.

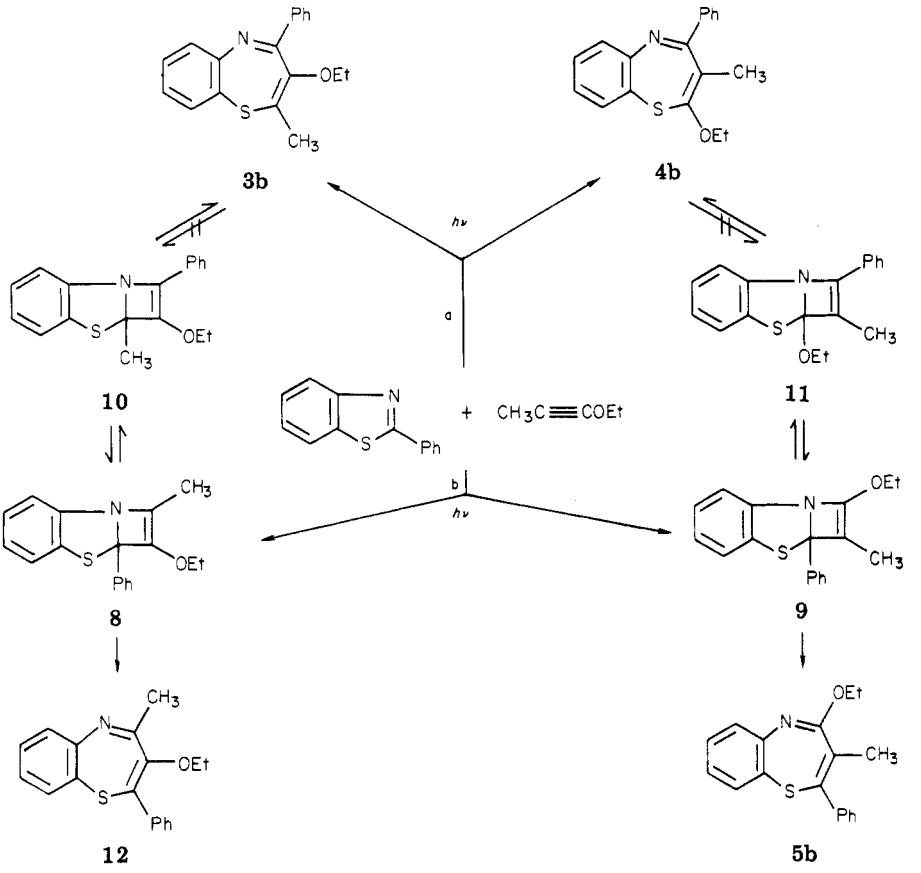
3-Ethoxy-2-phenylquinoline (6a): 13% yield; colorless crystals (from EtOH); mp 63–64.5 °C; IR (mineral oil) 1600 cm^{-1}; ^1H NMR δ 7.35–8.15 (m, 10 H aromatic), 4.17 (q, 2 H, J = 7.0 Hz), 1.46 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 151.06, 143.19, 138.04, 130.89, 129.92, 129.46, 128.66, 127.88, 127.62, 126.71, 126.12, 123.28, 113.72, 64.10, 14.52; mass spectrum, m/e (relative intensity) 249 (M^+, 100), 234 (M − 15, 83), 220 (M − 29, 93); UV λ_{max} 210 nm (ϵ 34 285), 218 (34 480), 251 (32 560), 289 (6943), 336 (9481). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.07; N, 5.62. Found: C, 81.72; H, 5.99; N, 5.55.

Irradiation of 2-Phenylbenzothiazole (1) in the Presence of 1-Ethoxy-1-propyne (2b). A solution of 317 mg (1.5 mmol) of **1** in 25 mL of 1-ethoxy-1-propyne (**2b**) was irradiated at 10–15 °C for 240 h, after which time the starting material was completely reacted. The solvent was carefully recovered by distillation on a high-vacuum line at room temperature. To prevent desulfurization of the benzothiazepines to the corresponding quinolines, one should not use a higher bath temperature than 40 °C. The yellow residue was chromatographed by preparative TLC, and the following products were isolated in order of decreasing R_f values.

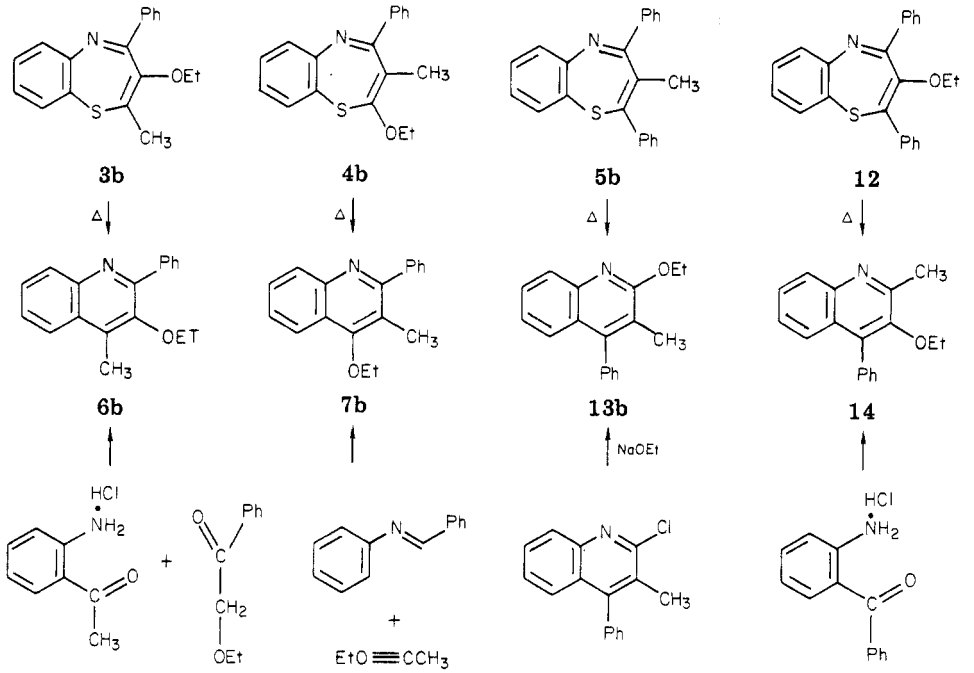
4-Ethoxy-3-methyl-2-phenyl-1,5-benzothiazepine (5b): 5% yield; colorless crystals (from EtOH); mp 127–128 °C; IR (mineral oil) 1630 cm^{-1}; ^1H NMR δ 6.96–7.6 (m, 9 H aromatic), 4.42 (q, 2 H, J = 7.1 Hz), 1.85 (s, 3 H), 1.43 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 163.96, 147.36, 142.67, 140.04, 131.94, 131.45, 129.19, 129.10, 128.76, 128.17, 128.09, 125.34, 124.50, 61.77, 18.25, 14.27; mass

(16) Hofmann, A. W. *Chem. Ber.* **1879**, *12*, 2359.

Scheme I



Scheme II

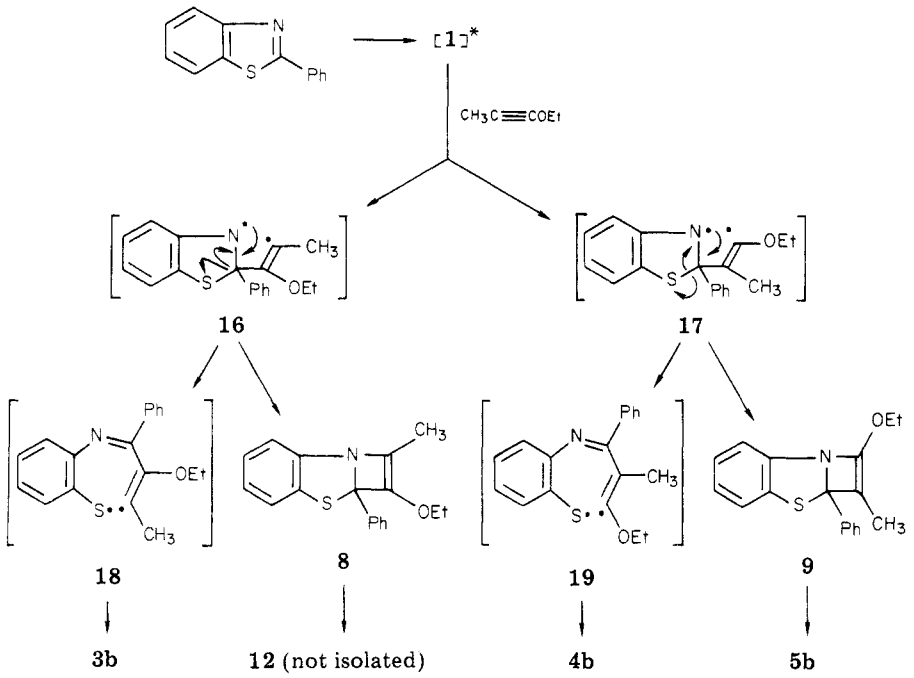


spectrum, m/e (relative intensity) 295 (M^+, 63), 280 (M − 15, 53), 266 (M −29, 100), 250 (M − 45, 30), 248 (M − 47, 17), 234 (M − 61, 23), 179 (M − 116, 20); UV (λ_{max} 230 nm (ϵ 18520), 267 (9340), 324 (1310). Anal. Calcd for $C_{18}H_{17}NOS$: C, 73.18; H, 5.80; N, 4.74; S, 10.86. Found: C, 73.10; H, 5.77; N, 4.77; S, 10.76.

3-Ethoxy-2-methyl-4-phenyl-1,5-benzothiazepine (3b): 51% yield; yellow crystals (from EtOH); mp 75–77 °C; IR (mineral oil) 1640, 1590, 1570 cm^{-1}: ^1H NMR δ 7.05–7.50 (m, 2 H aromatic), 7.85–8.07 (m, 7 H aromatic), 3.40 (dq, 2 H, J = 7.0 Hz), 2.13 (s, 3 H), 0.86 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 165.31, 149.64, 146.12, 137.49, 131.87, 130.69, 130.51, 128.86, 128.64, 128.21, 125.48, 124.76, 66.61, 19.38, 14.93; mass spectrum, m/e (relative intensity) 295 (M^+, 30), 263, (M − 32, 85), 248 (M − 47, 25), 234 (M − 61, 100), 211 (M − 84, 20); UV λ_{max} 263 nm (ϵ 23600), 320 (5384), 370 (2655). Anal. Calcd for $C_{18}H_{17}NOS$: C, 73.18; H, 5.80; N, 4.74; S, 10.86. Found: C, 73.23; H, 5.80; N, 4.74; S, 10.87.

2-Ethoxy-3-methyl-4-phenyl-1,5-benzothiazepine (4b): 96% yield; yellow oil; IR (neat) 1620, 1590, 1570 cm^{-1}; ^1H NMR β 7.7–7.80 (m, 2 H, aromatic), 6.9–7.54 (m, 7 H aromatic), 4.24 (dq, 2 H, J = 7.0 Hz), 1.70 (s, 3 H), 1.26 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 169.27, 151.88, 149.59, 139.25, 132.10, 130.57, 129.37, 128.91, 128.31, 127.55, 125.59, 125.18, 116.34, 65.55, 15.86, 14.98; mass

Scheme III



spectrum, m/e (relative intensity) 295 (M^+, 47), 263 (M − 32, 63), 248 (M − 47, 26), 234 (M − 61, 100), 218 (M − 77, 34); UV λ_{max} 247 nm (ε 23670), 300 (7470), 323 (4790), 350 (2397). Anal. Calcd for $C_{18}H_{17}NOS$: C, 73.18; H, 5.80; N, 4.74; S, 10.86. Found: 73.21; H, 5.74; N, 4.80; S, 10.99.

3-Ethoxy-4-methyl-2-phenylquinoline (6b): 12% yield; viscous oil; IR (mineral oil) 1580 cm^{-1}; ^1H NMR δ 7.8–8.2 (m, 4 H, aromatic), 7.3–8.2 (m, 5 H, aromatic), 3.60 (q, 2 H, J = 7.0 Hz), 2.67 (s, 3 H), 1.18 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 154.69, 148.96, 144.82, 138.76, 134.97, 130.04, 129.31, 128.63, 128.10, 127.78, 126.21, 123.57, 69.31, 15.39, 11.22; mass spectrum, m/e (relative intensity) 263 (M^+, 99), 248 (M − 15, 23), 234 (M − 29, 100), 219 (M − 44, 25); UV (λ_{max} 209 nm (ε 29456), 224 (30 3508), 252 (29 982), 286 (6575), 322 (6378), 329 (6312). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.05; H, 6.55; N, 5.27.

4-Ethoxy-3-methyl-2-phenylquinoline (7b): 1% yield; mp 63–64 °C (from EtOH): IR (mineral oil) 1580 cm^{-1}; ^1H NMR δ 8.0–8.15 (m, 2 H, aromatic), 7.4–7.7 (m, 7 H, aromatic), 4.20 (q, 2 H, J = 7.0 Hz), 2.36 (s, 3 H), 1.55 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 154.32, 148.14, 141.19, 129.71, 128.98, 128.29, 128.21, 126.04, 123.17, 121.79, 120.79, 70.08, 15.87, 13.99; mass spectrum, m/e (relative intensity) 263 (M^+, 64), 248 (M − 15, 34), 234 (M − 29, 100), 218 (M − 45, 36), 204 (M − 59, 40); UV λ_{max} 242 nm (ε 34907), 280 (7890), 290 (7591), 303 (6157), 317 (5021). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.93; H, 6.44; N, 5.28.

Photolysis of Photoproducts. Small quantities of the photoproducts **3a,b**, **4b**, and **5b** were irradiated in the NMR tubes in C_6D_6 at 10 °C for 18 h. No reaction was observed.

Thermal Decomposition. 3a → 6a. A small quantity of **3a** was warmed at 50–60 °C for 5 h. The NMR spectrum of the reaction mixture showed the presence of 40% **6a**.

3b → 6b, 4b → 7b, and 5b → 13. The samples were warmed at 90–100 °C. After 1 h both **3b** and **4b** were completely converted to the corresponding quinolines **6b** and **7b**. **5b** was stable at the same temperature but was converted to the corresponding quinoline **13** by warming at 150–200 °C for 1 h. Small quantities of **3a,b**, **4b**, and **5b** were dissolved in C_6D_6 and kept at 40 °C for 16 h. As shown by NMR analysis, besides unreacted starting material, 22% of **6a**, 42% of **6b**, and 16% of **7b** were formed, and **5b** remained unchanged.

Reaction of the Photoproducts with HCl. 3-Ethoxy-2-methyl-4-phenyl-1,5-benzothiazepine (**3b**) was treated with 3 N HCl at room temperature for 2 h. The reaction mixture was neutralized with Na_2CO_3 and extracted with ether. After the evaporation of solvent, NMR analysis of the residue showed, besides unreacted **3b**, the presence of 60% of **6b**. **5b** (10 mg) was heated in 5 mL of 3 N HCl for 1 h at 50° C and kept at room temperature for an additional 2 days. The reaction mixture was neutralized with Na_2CO_3 and extracted with ether. After evaporation of solvent, the NMR spectrum of the residue showed only starting material **5b**.

Thermal Reaction of 2-Phenylbenzothiazole (1) with 1-Ethoxy-1-propyne (2b). A mixture of 32 mg (0.15 mmol) of **1** and 126 mg (1.5 mmol) of **2b** in 2.5 mL of benzene was heated in a sealed tube at 60 °C for 11 days. After evaporation of the solvent, no benzothiazepine was detected by NMR.

Preparation of 3-Ethoxy-4-phenyl-1,5-benzothiazepine (3a). A benzene solution (20 mL) of 110 mg of 3-ethoxy-4-phenyl-2,3-dihydro-1,5-benzothiazepine (**15**)[5] and 100 mg of DDQ was kept at room temperature for 4 h. The now-dark benzene solution was washed with Na_2CO_3 solution and then with water and dried over $MgSO_4$. After evaporation of the benzene the residue was chromatographed on a TLC plate. From an intensively yellow band was isolated 50 mg of **3a**. It was, in all respects, identical with the product **3a** obtained by irradiation of **1** in the presence of **2a**.

Synthesis of 3-Ethoxy-4-methyl-2-phenylquinoline (6b). This compound was synthesized according to the improved Friedlander condensation[17] from the hydrochloride salt of 2-aminoacetophenone and α-ethoxyacetophenone.[18] Aminoacetophenone hydrochloride (96 mg, 0.59 mmol) was added little by little to the α-ethoxyacetophenone (100 mg, 0.59 mmol) at 120–150 °C. After the addition was completed, stirring at 150 °C was continued for 1 h. The reaction mixture was treated with Na_2CO_3 solution and extracted with ether. After the mixture was dried ($MgSO_4$), the solvent was removed, and the residual oil was chromatographed on TLC (silica gel plate with ether–hexane (1:4) as the eluent), yielding 53 mg (34%) of **6b**. It was, in all respects, identical with the compound **6b** obtained in the photochemical reaction.

Synthesis of 4-Ethoxy-3-methyl-2-phenylquinoline (7b). The compound was synthesized by analogy with the described procedure for the synthesis of 4-ethoxy-2-phenylquinoline.[19] To a solution of 3.62 g (0.02 mmol) of benzylideneaniline in 10 mL of dry ethyl acetate were added a catalytic amount of boron trifluoride etherate (0.1 mL) and then 1.7 g of 1-ethoxy-1-propyne.

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The temperature of the reaction mixture was raised to 30 °C. Stirring at room temperature was continued for 1 h. The reaction mixture was washed with 10% NaOH, dried over $MgSO_4$, and after evaporation of the solvent distilled at 175–90 °C (10 torr) to remove the unreacted benzylideneaniline. The dark residue was chromatographed and the isolated product (5%) shown to be identical with **7b**.

Synthesis of 2-Ethoxy-3-methyl-4-phenylquinoline (13b). Compound **13b** was synthesized by heating under reflux for 15 min 1 g of 2-chloro-3-methyl-4-phenylquinoline[20] and 0.01 mol of NaOEt in 10 mL of absolute ethanol. The solvent was evaporated, the residue was washed with water and extracted with ether, and the ether solution was dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a preparative silica gel plate, and 18% of 2-ethoxy-3-methyl-4-phenylquinoline (**13b**) was obtained: mp 71–72 °C (from EtOH): IR (mineral oil) 1590 cm^{-1}; ^1H NMR δ 7.1–7.9 (m, 9 H, aromatic), 4.60 (q, 2 H, J = 7.0 Hz), 2.08 (s, 3 H), 1.48 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 160.95, 147.96, 145.19, 137.57, 130.35, 129.41, 128.42, 128.10, 127.61, 127.13, 125.94, 123.49, 120.08, 61.71, 14.68, 13.81; mass spectrum, m/e 263 (m^+, 42), 248 (M – 15, 75), 234 (M –29, 100), 218 (M – 45, 46); UV λ_{max} 226 nm (ϵ 31 000), 263 (5780), 272 (5870), 282 (4880), 296 (3000), 309 (4740), 322 (5680). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.17; H, 6.43; N, 5.35.

Synthesis of 3-Ethoxy-2-methyl-4-phenylquinoline (14b). A mixture of 110 mg (1.08 mmol) of ethoxyacetone[21] and 126 mg (0.54 mmol) of 2-aminobenzophenone hydrochloride was heated in a sealed tube at 190 °C for 1 h. The dark reaction mixture was treated with water and ether and neutralized with Na_2CO_3 solution. The ether extracts were dried over $MgSO_4$. After the solvent was evaporated, the residue was purified by preparative TLC, and 21% of **14b** was isolated: mp 68–70 °C; IR (mineral oil) 1590 cm^{-1}; ^1H NMR δ 8.09–7.97 (1 H), 7.2–7.7 (m, 8 H, 3.59 (q, 2 H, J = 7.0 Hz), 2.75 (s, 3 H), 1.06 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 156.18, 153.37, 148.31, 144.87, 134.38, 130.34, 128.77, 128.58, 128.34, 128.09, 127.78, 125.84, 125.41, 69.14, 21.04, 15.53; mass spectrum, m/e 263 (M^3, 82), 248 (M – 15, 4), 235 (M – 28, 100), 234 (M – 29, 50), 206 (M – 57, 50), 204 (M – 59, 20). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.98; H, 6.45; N, 5.28.

Synthesis of 2-Ethoxy-4-phenylquinoline (13a). Compound **13a** was synthesized by heating under reflux 1 g (0.004 mol) of 2-chloro-4-phenylquinoline[22] and 0.01 mol of sodium ethoxide in 10 mL of absolute ethanol for 0.5 h. After evaporation of the ethanol the residue was treated with ether, washed with water, and dried over $MgSO_4$. After evaporation of the ether, the mixture was purified by preparative silica gel TLC. The product (**13a**) was crystallized from ethanol: mp 54–55 °C; yield 15%; IR (neat) 1620, 1600, 1575 cm^{-1}; ^1H NMR δ 7.1–8.0 (m, 9 H), 6.84 (s, 1 H), 4.58 (q, 2 H, J = 7.0 Hz), 1.45 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 161.79, 151.03, 147.46, 138.18, 129.33, 128.42, 128.25, 127.79, 125.73, 124.04, 123.80, 113.07, 61.56, 14.64; mass spectrum, m/e 249 (M^+, 27), 234 (M – 15, 100), 220 (M – 29, 65), 205 (M – 44, 32), 204 (M – 45, 31); UV λ_{max} (ϵ 54 100), 275 (8370), 313 (5150), 326 (5700). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.07; N, 5.62. Found: C, 81.91; H, 6.01; N, 5.55.

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Registry No. 1, 883-93-2; **2a**, 927-80-0; **2b**, 14273-06-4; **3a**, 83463-79-0; **3b**, 83463-81-4; **4b**, 83463-82-5; **5b**, 83463-83-6; **6a**, 83463-80-3; **6b**, 83463-84-7; **7b**, 83463-85-8; **13a**, 83463-88-1; **13b**, 83463-86-9; **14b**, 83463-87-0; **15**, 79091-78-4; 2-aminoacetophenone hydrochloride, 25384-14-9; α-ethoxyacetophenone, 14869-39-7; benzylideneaniline, 538-51-2; 2-chloro-3-methyl-4-phenylquinoline, 37118-76-6; ethoxyacetone, 14869-34-2; 2-aminobenzophenone hydrochloride, 40318-20-5; 2-chloro-4-phenylquinoline, 5855-56-1.

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Synthesis of (5*E*)- and (5*Z*)-11-Deoxy-6,11α-epoxy-Δ^5-prostaglandin $F_{1\alpha}$ Sodium Salts: 6,11α-Enol Ether Isomers of Prostacyclin

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The key intermediates, (5*S*,6*R*)- and (5*R*,6*R*)-11-deoxy-6,11α-epoxy-5-hydroxy cyclic ethers, **22a,b**, were prepared from the reaction of a C-9 silyl $PGF_{2\alpha}$ derivative **12** with mercuric acetate (oxymercuration), followed by conversion of the mercurioacetate substituent to a hydroxy group. Attempts to construct the 6,11α oxygen bridge by reaction of **12** and other C-9 protected $PGF_{2\alpha}$ derivatives [9-tetrahydropyranyl (**11**), 9-acetyl (**13**)] with iodine, *N*-bromosuccinimide, and phenylselenenyl chloride were unsuccessful. Reaction of **11** and **12** with iodine resulted in removal of the C-9 blocking group and the isolation of 6,9-iodo cyclic ether products. Treatment of **13** with phenylselenenyl chloride gave the β-chlorophenylselenenyl addition adduct **18**. Conversion of alcohols **22a,b** to their mesylate derivatives, **25a,b**, and subsequent reaction with potassium methoxide in dimethyl sulfoxide afforded the labile Δ^5 enol ethers, **29a,b**. The success of this elimination reaction was critically dependent on the base, the reaction solvent, and the workup conditions. The structural assignments of **29a,b** were based on their spectral properties and hydrolysis to 6-keto-$PGF_{1\alpha}$ methyl ester. The stereoconfiguration at C-6 was assigned by conversion of the oxymercuration product obtained from **12** to the 5,6-dihydro-6,11α-cyclic ether **20**. The C-5 stereoconfiguration of alcohols **22a,b** was established by the mode of formation of enol ethers **29a,b**. In contrast to PGI_2 methyl ester, **29a,b** in aqueous acid showed a greater tendency to form the internal ketal **34** during hydrolysis to 6-keto-$PGF_{1\alpha}$ methyl ester.

Introduction

Prostacyclin (PGI_2, **1**) is derived biosynthetically from arachidonic acid by way of intermediate prostaglandin endoperoxides, PGG_2 and PGH_2 (**2** and **3**).[1] The formation of PGI_2 from endoperoxide PGH_2 can be envisioned to occur in the following manner:[2] (1) attack by an electrophilic site on the prostacyclin synthetase at the oxygen attached to C-11 causes breaking of the peroxide bond, (2) capture of the electron-deficient C-9 oxygen by the C_5–C_6 double bond, and (3) subsequent loss of the C_6 hydrogen

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