Chemistry of Thienopyridines. XXXIX. Synthesis of [1]Benzothieno[2,3-*h*]isoquinoline and Related Studies [1]

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Benzo[*b*]thiophene-2-carboxaldehyde undergoes condensation with 4-methylpyridine and with 2-methylquinoline to produce *trans*-diarylethenes (52% and 76%, respectively). The former alkene photocyclizes in cyclohexane to yield [1]benzo[2,3-*h*]isoquinoline (35%), while the latter alkene does not give successful, analogous cyclization.

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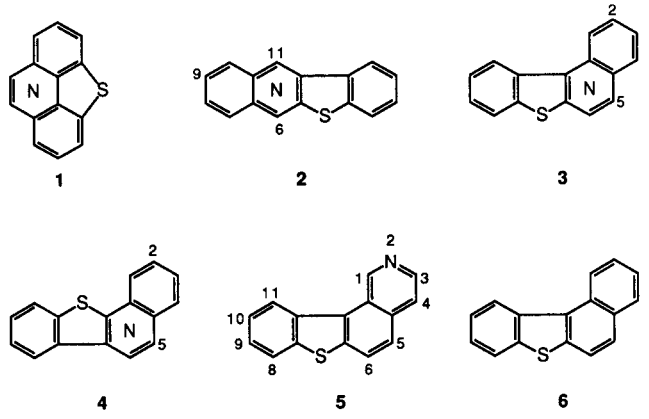
Various workers have established the presence of aromatic thienopyridines with 2-4 condensed rings in petroleum [3,6], liquefied coal [7,8], and in particulate matter from an industrial plant [9]. For tetracyclic components, isomers of both azaphenanthro[4,5-*bcd*]thiophene, $C_{13}H_7NS$, (**1**) and azanaphthobenzothiophene, $C_{15}H_9NS$, (**2-4**) have been implicated. There are four possible isomers for structure **1** and thirty possible isomers for structures **2-4** (10 isomers for each), where N may replace any CH unit. Pertinent to the identification of which isomers are present in complex natural mixtures is the availability of authentic reference compounds. However, syntheses of only six (6-, 9-, and 11-aza-**2**, 5-aza-**3**, and 2- and 5-aza-**4**) of these 34 parent compounds have been reported [10-12]. The present paper reports the synthesis and characterization of a seventh parent molecule, *i.e.* [1]benzothieno[2,3-*h*]isoquinoline (**5** or 2-aza-**3**).



Scheme 1

Scheme 1 shows the synthetic route to **5** and the first step in a proposed analogous route to a pentacyclic thienopyridine. Thus, benzo[*b*]thiophene-2-carboxaldehyde (**7**) condensed with 4-methylpyridine and with 2-methylquinoline in refluxing acetic anhydride, *i.e.* by the procedure of Acheson and Harrison for reaction of **7** with 2-methylpyridine [13]. Each of the diarylethenes **8** (52% yield) and **9** (76%) formed was assigned a *trans* geometry on the basis of its infrared spectrum (absorption at 953 ± 8 cm^{-1}) and its ^1H nmr coupling constant $J_{\alpha,\beta}$ (15.8 ± 0.2 Hz). Consistent with the more extended conjugated system in **9** is its longest wavelength absorption at 386 nm, as compared to that for **8** at 355.5 nm. Correspondingly **8** forms white crystals while **9** forms greenish yellow ones. Both compounds produce molecular ions and (M-H) ions on electron impact, but for **8** the molecular ion is the more abundant--1.3 times that of the (M-H) ion--while for **9** the latter ion is dominant--6.6 times the molecular ion.

Attempts were made to effect photocyclization of **8** and of **9** in cyclohexane as solvent, in the presence of air, and by means of a medium pressure lamp. These conditions are essentially the same as were used by Loader and Timmons to effect cyclizations of some (but not all) styrylquinolines and styrylisoquinolines [14]. Changes in ultraviolet absorption spectra were monitored in order to follow the reaction. For **8** cyclization was successful (35% yield of **5**) while both short wavelenth (210-250 nm) and long wavelength (280-380 nm) absorptions decreased and a new maximum arose at 264 nm. For **9**, however, the short wavelength absorption did not change appreciably while the

Table I

Comparative Ultraviolet Absorption Spectra for Compounds 5, 5•HCl, and 6

Compound	5		5•HCl [a]		6 [15]	
Solvent	abs. ethanol		ethanol		cyclohexane	
	λ max (nm)	log ε	λ max (nm)	log ε	λ max (nm)	log ε
					223	4.34
	233	4.31	235	4.45	234.5	4.46
					250 (sh)	4.49
			253	4.35		
					257	4.66
	264	4.36			264.5	4.73
			274	4.20		
	280 (sh)	4.08			283	3.88
	290	3.96	298	3.99	294.5	4.02
					308.5	4.15
	317 (sh)	4.00			318 (sh)	4.20
	325	4.05			321	4.21
					335	3.67
	345 (sh)	3.64			345	3.35
					351	3.72
	362	3.58	362	3.87		

[a] Solution was obtained from that of 5 by the addition of one drop of concentrated aqueous hydrochloric acid.

long wavelength (340-390 nm) absorption largely disappeared. The reaction mixture from **9** contained a number of components (including insoluble precipitate), but no pure product was isolated. Other conditions tried (benzene as solvent, with or without added iodine) gave largely recovered **9** and/or precipitate (polymer?).

The structure of **5** is established by means of its spectra. Thus, the ^{1}H nmr spectrum consists of a downfield singlet

for H-1 at 10.58 ppm, a multiplet for H-11, a doublet for H-3, and a multiplet for 6 other aromatic protons. Additionally, the infrared spectrum shows C-H out-of-plane deformation bands for a combination of 2 vicinal, 4 vicinal, and one lone aromatic hydrogen atoms. Comparative ultraviolet absorption spectral maxima for **5**, **5** hydrochloride (**5**·HCl), and benzo[*b*]naphtho[1,2-*d*]thiophene (**6**), isosteric with **5**, are presented in Table I [15]. It is apparent from this table that **5** and **6** have very similar ultraviolet absorption spectra, albeit with considerably more fine structure exhibited by **6**, probably due to the difference in solvents used. In particular, it seems pertinent that **5** and **6** show their most intense maxima at the same wavelength, 264 nm. The spectrum of **5** moreover is markedly different from that of benzo[*b*]naphtho[2,1-*b*]thiophene (highest maximum at 253.5 nm) or that of benzo[*b*]naphtho[2,3-*d*]-thiophene (highest maximum at 275 nm) [15], the possible benzonaphthothiophene isomers of **6**. The addition of a small amount of hydrochloric acid to the solution of **5** decreased fine structure in the spectrum even more and gave the highest maximum at 235 nm. The close similarities of the spectra of **5** and **6** are consistent with the presence of essentially the same π-electronic systems in them.

It might be noted that compound **5** was also characterized as a crystalline methiodide. Although **5** itself was not reported before, its 1,2,3,4-tetrahydro derivative and its *N*-substituted compounds have been synthesized and found to be dopamine antagonists by *in vitro* assay [16].

EXPERIMENTAL [17]

trans-1-(2-Benzo[*b*]thienyl)-2-(4-pyridyl)ethene (**8**).

A mixture of 1.5 g (9.3 mmoles) of benzo[*b*]thiophene-2-carboxaldehyde (**7**) [18], 0.95 ml (9.8 mmoles) of 4-methylpyridine, and 1.7 ml (18 mmoles) of acetic anhydride was refluxed for 45 hours. The brown semisolid which formed on cooling the mixture was extracted with boiling cyclohexane. The residue from evaporation of the filtered extract was evaporatively distilled at 185-190° (0.5 mm) to yield 1.14 g (52%) of light yellow product, mp 187-192°. Recrystallization from benzene-cyclohexane produced a cream-colored powder, mp 196.5-200.5° (used in photocyclizations).

Further crystallization from acetonitrile plus sublimation gave white prisms, mp 203-203.5°; ir: 960 (*trans*-CH=CH), 840, and 765 cm^{-1}; ^1H nmr (deuteriochloroform) [19]: δ 8.63 (broadened d, J = 5 Hz, 2 H, H-2 and H-6), 7.53 (d, J = 16 Hz, 1 H, H_α) which is superimposed on 7.15-8.0 (m, 7 H, other aromatic protons), 6.87 (d, 1 H, H_β); uv (cyclohexane): λ max 221.5 nm (log ϵ 4.37), 234 (4.26) shoulder, 264 (3.93), 273 (3.91), 323 (4.47), 337 (4.52), 355.5 (4.36); ms: m/e 238 (21), 237 (M^+, 100), 236 (77), 210 (M^+ -HCN, 13), 208 (18), 186 (metastable ion, 237 → 210), 118.5 (M^{++}, 5).

Anal. Calcd. for $C_{15}H_{11}NS$: C, 75.92; H, 4.67; N, 5.90; S, 13.51. Found: C, 75.84; H, 4.66; N, 6.02; S, 13.42.

[1]Benzothieno[2,3-*h*]isoquinoline (**5**).

A warm, saturated solution of 130 mg of alkene **8** in 820 ml of purified [20] cyclohexane was stirred vigorously while it was irradiated for 3.5 hours by means of a Hanau Q-700 medium pressure lamp, equipped with a pyrex water-cooled jacket and immersed in a cylindrical reaction vessel (open to air). During this time absorption at 264 nm reached a maximum value, while absorption in the ranges of 210-250 and 280-380 nm decreased. The solution was filtered and evaporated to dryness. Combined residues from four runs were dissolved in benzene (by trituration) and chromatographed on a column of 60 ml of Merck neutral alumina (activity III) with benzene as eluent. The first (yellow-orange) and second (fluorescent in uv light) eluted zones were discarded, while the third zone (colorless and non-fluorescent) yielded 181 mg (35%) of cream-colored product, mp 130-137°. A dry, intimate mixture of this product and 4 ml of alumina was placed atop a column of 76 ml of alumina and rechromatographed with pentane-benzene (4:1). The blue fluorescent zone (in uv light) yielded white needles of **5**, recrystallized from acetone, mp 141.5-143°; ir: 900 (medium, lone H at C-1), 845 (strong, two vicinal aromatic H), and 765 and 735 cm^{-1} (strong, four vicinal aromatic H) [21]; ^1H nmr (carbon tetrachloride) [22]: δ 10.58 (broad s, 1 H, H-1), 8.93-9.13 (m, 1 H, H-11), 8.83 (broad d, $J_{3,4}$ = 5.8 Hz, 1 H, H-3), 7.4-8.3 (m, 6 H, other aromatic protons); ms: m/e 236 (19), 235 (M^+, 100), 234 (14), 208 (M^+ -HCN, 11), 184 (metastable ion, 235 → 208), 163 (15), 128 (metastable ion, 208 → 163).

Anal. Calcd. for $C_{15}H_9NS$: C, 76.56; H, 3.86; N, 5.95; S, 13.63. Found: C, 76.62; H, 3.94; N, 5.98; S, 13.58.

The methiodide of **5** was obtained as fine, canary yellow needles from 95% ethanol, sinters at 295°, mp 307° dec.

Anal. Calcd. for $C_{16}H_{12}INS$: C, 50.94; H, 3.21; N, 3.71. Found: C, 50.67; H, 3.17; N, 3.71.

trans-1-(2-Benzo[*b*]thienyl)-2-(2-quinolyl)ethene (**9**).

A mixture of 6 g (37 mmoles) of aldehyde **7**, 5.3 ml (39 mmoles) of 2-methylquinoline (Aldrich), and 6.8 ml (72 mmoles) of acetic anhydride was reacted as in the preparation of **8**. From the cyclohexane extract (including evaporative distillation of mother liquors) was obtained 8.1 g (76%) of **9** as greenish yellow needles, mp 171.5-173°, raised to 172-173° on further evaporative distillation at 180-190° (0.5 mm) plus recrystallizations from benzene-cyclohexane and acetonitrile; ir: 945 (*trans*-CH=CH), 830, 745, and 725 cm^{-1}; ^1H nmr (deuteriochloroform) [23]: δ 8.121 and 8.113 (2 overlapping d, J_{ortho} = 8.4 Hz, 2 H, H-4 and H-8), 7.957 (d, J = 15.7 Hz, 1 H, H_α), 7.7-7.9 (m, 4 aromatic protons), 7.605 (d, J_{ortho} = 8.4 Hz, 1 H, H-3), 7.518 (t, J = 7.8 Hz, 1 aromatic proton), 7.424 (s, 1 H, H-3'), 7.32-7.4 (m, 2 aromatic protons), 7.275 (d, 1 H, H_β); uv (cyclohexane): λ max 218 nm (log ϵ 4.21), 244 (4.08) shoulder, 288 (3.76) shoulder, 298 (3.82), 338 (3.95) shoulder, 352 (4.11), 368 (4.19), 386 (3.93); ms: m/e 288 (15), 287 (M^+, 15), 286 (M^+ -H, 100).

Anal. Calcd. for $C_{19}H_{13}NS$: C, 79.41; H, 4.56; N, 4.88; S, 11.16. Found: C, 79.38; H, 4.71; N, 4.73; S, 11.16.

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