

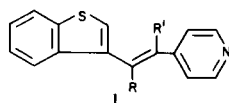
Photochemical Synthesis of [1|Benzothieno[3,2-*h*]|isoquinoline

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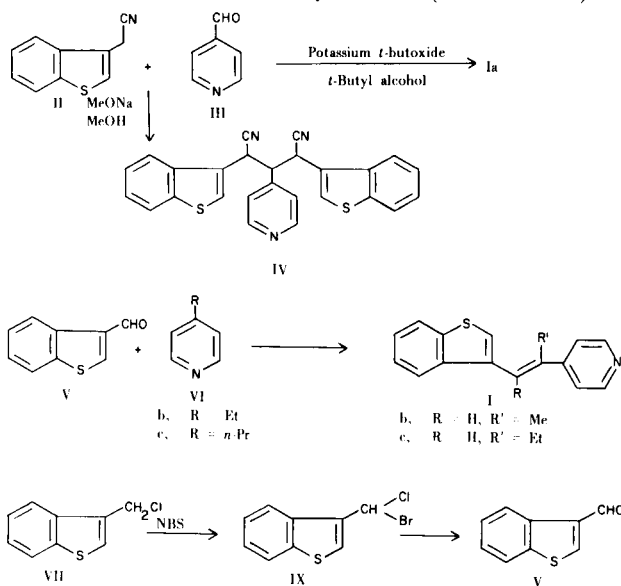
Received September 11, 1975

The photochemical behaviour of a series of benzo-*b*]thiophene derivatives Ia-c was investigated as a part of a program directed toward the synthesis of various thia-analogues of indole alkaloids (e.g., subicanine (1)).



- a, R = CN      R' = H  
 b, R = H      R' = CH<sub>3</sub>  
 c, R = H      R' = C<sub>2</sub>H<sub>5</sub>

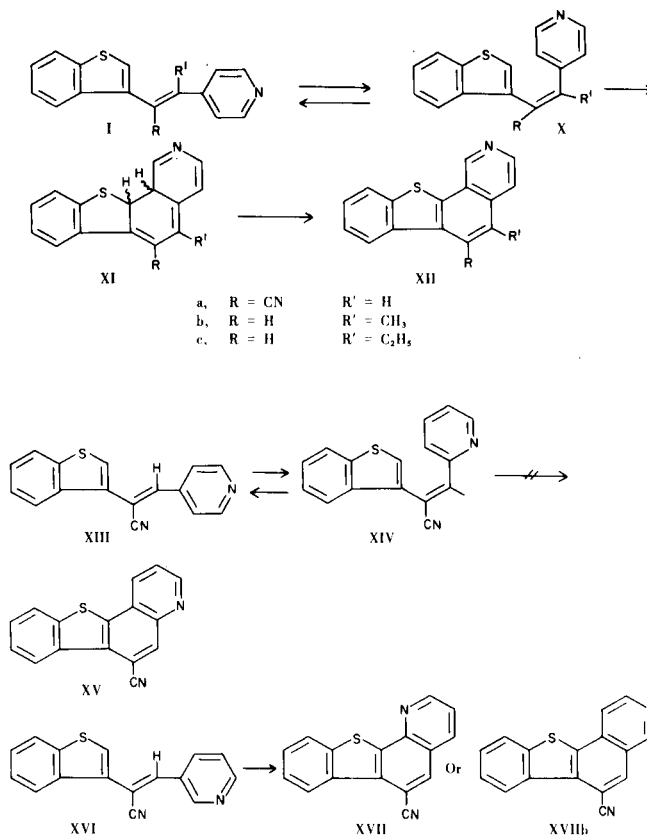
In pursuit of this goal, the synthesis of compounds Ia-c were attempted. Condensation of 3-benzo-*b*]thienyl-acetonitril (II) with 4-pyridinecarboxaldehyde (III) in the presence of sodium methoxide would be expected to give the desired compound Ia. Although a similar reaction was previously reported to be quite successful (2); in this case the compound IV was obtained in 60% yield and only a very small amount of the desired compound Ia was isolated by tlc. A similar result was obtained with potassium *t*-butoxide in absolute ethanol. Using sodium hydride as a base in THF did not give any product, and only starting materials were isolated. Finally, the desired compound Ia was obtained in relatively good yield using potassium *t*-butoxide in *t*-butyl alcohol (See Scheme I).



Scheme I

Compound Ib and Ic could be prepared from condensation of benzo-*b*]thiophene-3-carboxaldehyde (V) and 4-alkylpyridine (VI) in the presence of acetic anhydride. The uv spectra of Ia-c were similar to *trans*-stilbene and *trans*-stilbazole (3,4).

Of the several methods reported for the preparation of V (5-11), the Sommelet reaction employed by Campaigne (11) and direct bromination of 3-methylbenzo-*b*]thiophene (12) are reported to give good yields of V. We could obtain this aldehyde in high yield, starting from readily available 3-chloromethylbenzo-*b*]thiophene (VII) (13). Bromination of VII with one equivalent of *N*-bromosuccinimide afforded compound IX which was not purified, but characterized by nmr. Hydrolysis of IX afforded the desired compound V (See Scheme I).



Scheme II

Irradiation of compound Ia-c would be expected to cause rapid *trans-cis* isomerization ( $I \rightleftharpoons X$ ) and subsequent cyclization to dihydro compound XI which should be readily oxidized to [1]benzothieno[3,2-*h*]isoquinoline (XII) (See Scheme II).

The mechanism of photocyclization of stilbene derivatives has received considerable attention. It is generally believed that dihydrophenanthrene analogues of XI are formed which subsequently oxidize to the final compounds (14,15); Dihydrophenanthrenes have been isolated and well documented (16).

Like the stilbene derivatives, photolysis of compounds Ia-c in the presence of oxygen gave the desired compounds XIIa-c in good to moderate yield. In the above cases we were not able to isolate the *cis* isomers under different experimental conditions. However, if the photolysis of one of the isomers of Ia, namely XIII, was terminated after brief exposure to light, the *cis* compound XIV could be isolated in 55% yield. Prolonged irradiation of compound XIII or XIV resulted in a complex mixture of products from which the expected product XV could not be isolated (See Scheme II). In addition, we have also studied the photochemical behavior of 1-(3-benzo[*b*]thienyl)-2-(3-pyridyl)acrylonitrile XVI. This compound also cyclizes very rapidly to only one compound, XVIIa or XVIIb (See Scheme II). This compound was very insoluble in most organic solvents and nmr could not be used to differentiate between structures XVIIa and XVIIb. Also, the latter compound resisted acidic or basic hydrolysis.

#### EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Leitz Model III spectrograph. Nmr spectra were determined using a Varian T-60 spectrometer and chemical shifts ( $\delta$ ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian MAT CH-5 spectrometer at 70 eV.

Benzo[*b*]thiophene-3-carboxaldehyde (V).

A mixture of 3-chloromethylbenzo[*b*]thiophene (VII, 3.65 g., 0.02 mole) (13) and *N*-bromosuccinimide (3.92 g., 0.022 mole) in 100 ml. of carbon tetrachloride was irradiated with a 500 W. lamp, while heating at reflux temperature for 2 hours. The reaction mixture was cooled and filtered. The solvent was distilled under reduced pressure to give 5.12 g. (98%) of IX (as an oil); nmr (carbon tetrachloride): 8.33-7.30 (m, 5H, aromatic), 7.01 (s, 1H, CHClBr).

A mixture of IX (5.23 g., 0.02 mole) and 40.8 ml. of 10% sodium carbonate was stirred and refluxed for 2 hours. This mixture was cooled and extracted with benzene. The solvent was washed with water, dried and evaporated. The residue was crystallized from petroleum-ether to give 2.72 g. (85%) of V, m.p. 57-58° [lit (11) m.p. 57.5-58.5°]; nmr (carbon tetrachloride): 10.10 (s, 1H, CHO), 8.83-8.66 (m, 1H, H<sub>4</sub>), 8.20 (s, 1H, H<sub>2</sub>), 7.94-7.36 (m, 3H, aromatic); mass spectrum:  $m/e$  162 ( $M^+$ ).

*Anal.* Calcd. for C<sub>9</sub>H<sub>6</sub>OS: C, 66.67; H, 3.70; S, 19.75. Found: C, 66.85; H, 3.62; S, 19.94.

1-(3-Benzo[*b*]thienyl)-2-(4-pyridyl)acrylonitrile (Ia).

Method A.

A solution of 3-benzo[*b*]thienylacetonitrile (II, 1.73 g., 0.01 mole) (15) and 4-pyridinecarboxaldehyde (III, 1.07 g., 0.01 mole) in 15 ml. of absolute methanol was warmed to 50°. A solution of sodium methoxide (0.55 g.) in 3 ml. absolute methanol was added and the reaction mixture was maintained at 50-60° for 1 hour. The white precipitate was filtered. Recrystallization from ethanol gave 2.22 g. (51%) of IV, m.p. 230-232°; ir (potassium bromide): 2240 cm<sup>-1</sup> (C≡N); nmr (deuteriochloroform): 8.60 (m, 2H, pyridine  $\alpha$ -H), 8.00-6.94 (m, 12H, pyridine  $\beta$ -H, Ar-H), 4.60 (d, 2H, HCC≡N), 4.03 (unresolved t, 1H, CH); mass spectrum:  $m/e$  435, 263, 172, 171.

*Anal.* Calcd. for C<sub>26</sub>H<sub>17</sub>N<sub>3</sub>S<sub>2</sub>: C, 71.71; H, 3.90; N, 14.71. Found: C, 71.65; H, 4.12; N, 14.83.

The filtrate was evaporated, and the residue was chromatographed [tlc, silica gel, chloroform:methanol (98:2)]. The desired compound was crystallized from methanol to give 15 mg. of compound Ia; m.p. 139-140°; uv ( $\lambda$  max (methanol), log  $\epsilon$ ): 330 (4.14), 292 (3.67), 260 (4.15); uv ( $\lambda$  max (methanol), one drop 0.1 *N* hydrochloric acid): 355, 264; nmr (deuteriochloroform): 8.83-8.56 (m, 2H, pyridine  $\alpha$ -H), 8.06-7.20 (m, 8H, HC=C, pyridine  $\beta$ -H, Ar-H); ir (potassium bromide): 2262 cm<sup>-1</sup> (C≡N); mass spectrum:  $m/e$  262, 261, 107, 106, 78, 51.

*Anal.* Calcd. for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>S: C, 73.28; H, 3.82; N, 10.69. Found: C, 73.41; H, 3.95; N, 10.75.

Method B.

To a stirring solution of compound II (460 mg., 4.97 mmole) and 4-pyridinecarboxaldehyde (2 ml., 19 mmoles) in 8 g. *t*-butyl alcohol at 40° was added a solution of potassium *t*-butoxide (560 mg., 5 mmoles) in 8 ml. of *t*-butyl alcohol during 20 minutes. The stirring was continued for 1 hour. To the mixture water was added and the organic compound was extracted with chloroform. The chloroform was washed with water, dried and evaporated. The residue was crystallized from methanol to give 650 mg. (50%) of compound Ia; m.p. 139-140°.

1-(3-Benzo[*b*]thienyl)-2-(4-pyridyl)prop-1-ene (Ib).

A mixture of benzo[*b*]thiophene-3-carboxaldehyde (V, 670 mg., 4.13 mmoles) and 3-ethylpyridine (2 ml., 18.5 mmoles) in 20 ml. of acetic anhydride was refluxed for 15 hours. Approximately two-thirds of the solvent was evaporated off and to the residue ice-water was added. The mixture was made alkaline with sodium carbonate and extracted with chloroform. The chloroform was washed with water, dried and evaporated. The excess 4-ethylpyridine was distilled under reduced pressure (1 mm-Hg.) and the residue was chromatographed [tlc, silica gel, chloroform:methanol (98:2)], and the desired compound was crystallized from methanol to give 200 mg. (30%) of compound Ib; m.p. 183-184°; uv ( $\lambda$  max (methanol), log  $\epsilon$ ): 310 (4.13), 280 (3.51); uv ( $\lambda$  max (methanol), one drop 0.1 *N* hydrochloric acid): 368, 270; nmr (carbon tetrachloride): 8.74-8.16 (m, 2H, pyridine  $\alpha$ -H), 7.94-6.94 (m, 8H, pyridine  $\beta$ -H, C=CH, Ar-H), 2.21 (d, 3H, CH<sub>3</sub>, J<sub>CH<sub>3</sub></sub>, C=CH = 1.8 Hz); mass spectrum:  $m/e$  251, 236, 208, 171, 147, 115, 89, 69, 51, 46.

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>NS: C, 76.49; H, 5.18; N, 5.58. Found: C, 76.51; H, 5.23; N, 5.43.

1-(3-Benzo[*b*]thienyl)-2-(4-pyridyl)but-1-ene (Ic).

This compound was prepared similar to Ib with a 54% yield, m.p. 113-115°; uv ( $\lambda$  max (methanol), log  $\epsilon$ ): 310 (4.16), 270 (4.13); uv ( $\lambda$  max (methanol), one drop 0.1 *N* hydrochloric acid): 362, 276, 270; nmr (deuteriochloroform): 8.85-8.41 (m, 2H,

pyridine  $\alpha$ -H), 8.10-6.90 (m, 8H, pyridine  $\beta$ -H, C=CH, Ar-H), 2.80 (q, 2H, CH<sub>2</sub>), 1.10 (t, 3H, CH<sub>3</sub>); mass spectrum: *m/e* 265, 250, 236, 221, 208, 206, 187, 171, 147, 139, 134, 115, 89, 51, 45.

*Anal.* Calcd. for C<sub>17</sub>H<sub>15</sub>NS: C, 76.98; H, 5.66; N, 5.28. Found: C, 76.82; H, 5.45; N, 5.03.

#### 1-(3-Benzo[*b*]thienyl)-2-(2-pyridyl)acrylonitrile (XIII).

This compound was prepared similar to Ia (Method B) in 77% yield; m.p. 97-98° (methanol); uv ( $\lambda$  max (methanol), log  $\epsilon$ ): 338 (4.16), 295 (shoulder, 4.14), 260 (4.17); uv ( $\lambda$  max (methanol), one drop 0.1 *N* hydrochloric acid): 343, 280 (shoulder), 262; ir (potassium bromide): 2188 cm<sup>-1</sup> (C≡N); nmr (deuteriochloroform): 8.90 (m, 1H, pyridine  $\alpha$ -H), 7.83 (s, 1H, HC=C or S-C=), 7.67 (s, 1H, S-C= or HC=C), 8.33-7.17 (m, 7H, pyridine  $\beta$  and  $\gamma$ -H, Ar-H); mass spectrum: *m/e* 262, 235, 172, 170, 129.

*Anal.* Calcd. for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>S: C, 73.28; H, 3.82; N, 10.69. Found: C, 73.35; H, 3.69; N, 10.78.

#### 1-(3-Benzo[*b*]thienyl)-2-(3-pyridyl)acrylonitrile (XVI).

This compound was prepared similar to Ia (Method B) with 41% yield; m.p. 124-125° (methanol); uv ( $\lambda$  max (methanol), log  $\epsilon$ ): 340 (3.92), 300 (3.37), 260 (4.15); uv ( $\lambda$  max (methanol) one drop 0.1 *N* hydrochloric acid): 382, 280, 268, 226; nmr (deuteriochloroform): 9.00-8.67 (m, 2H, pyridine  $\alpha$ -H), 8.65-7.37 (m, 8H, pyridine  $\beta$  and  $\gamma$ -H, HC=C, Ar-H); mass spectrum: *m/e* 262, 235, 121.

*Anal.* Calcd. for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>S: C, 73.28; H, 3.82; N, 10.69. Found: C, 73.41; H, 3.71; N, 10.82.

#### Photolysis of 1-(3-Benzo[*b*]thienyl)-2-(4-pyridyl)acrylonitrile (Ia).

A solution of Ia (454 mg., 1.73 mmoles) in 150 ml. ethanol was irradiated for 3 hours. The precipitate was filtered to give 350 mg. (78%) of 6-cyano-[1]-benzothieno[3,2-*h*]isoquinoline (XIa). Recrystallization from ethanol gave pure compound, m.p. 279-280°; uv ( $\lambda$  max (methanol), log  $\epsilon$ ): 378 (3.22), 310 (shoulder, 3.33), 290 (4.13), 248 (4.15), 240 (4.15); uv ( $\lambda$  max (methanol), one drop 0.1 *N* hydrochloric acid): 418, 390, 300, 289, 248, 231; mass spectrum: *m/e* 260 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>16</sub>H<sub>8</sub>N<sub>2</sub>S: C, 73.85; H, 3.08; N, 10.77. Found: C, 73.98; H, 3.19; N, 10.63.

#### Photolysis of 1-(3-Benzo[*b*]thienyl)-2-(4-pyridyl)prop-1-ene (Ib).

A solution of Ib (100 mg., 0.4 mmole) in 150 ml. of ethanol was irradiated for 1 hour. The solvent was evaporated, and the residue was chromatographed [tlc, silica gel, chloroform:methanol (98:2)]. The desired compound was crystallized from methanol to give 50 mg. (50%) of 5-methyl-[1]-benzothieno[3,2-*h*]isoquinoline (XIb); m.p. 163-164°; uv ( $\lambda$  max (methanol), log  $\epsilon$ ): 323 (4.16), 280 (4.44), 255 (4.40); uv ( $\lambda$  max (methanol), one drop 0.1 *N* hydrochloric acid): 398, 390, 303, 265, 248; nmr (deuteriochloroform): 9.53 (broad s, 1H, pyridine  $\alpha$ -H), 8.70 (broad d, 1H, pyridine  $\alpha$ -H), 8.30-7.13 (m, 6H, HC=C and Ar-H), 2.80 (d, 3H, CH<sub>3</sub>, J<sub>CH<sub>3</sub></sub>, HC=C = 1 Hz); mass spectrum: *m/e* 249.

*Anal.* Calcd. for C<sub>16</sub>H<sub>11</sub>NS: C, 77.11; H, 4.42; N, 5.62. Found: C, 77.05; H, 4.61; N, 5.81.

#### Photolysis of 1-(3-Benzo[*b*]thienyl)-2-(4-pyridyl)but-1-ene (Ic).

A solution of Ic (439 mg., 1.65 mmoles) in 150 ml. of ethanol was irradiated for 1.5 hours and worked up as above to give 200 mg. (46%) of 5-ethyl-[1]-benzothieno[3,2-*h*]isoquinoline (XIc); m.p. 154-155° (petroleum-ether); uv ( $\lambda$  max (methanol), log  $\epsilon$ ): 330 (3.90), 280 (4.24), 255 (4.26), 239 (4.29); uv ( $\lambda$  max

(methanol), one drop 0.1 *N* hydrochloric acid): 389, 300, 260, 228; nmr (deuteriochloroform): 9.51 (s, 1H, pyridine  $\alpha$ -H), 8.70 (d, 1H, pyridine  $\alpha$ -proton), 8.32-7.37 (m, 6H, HC=C and Ar-H), 3.07 (q, 2H, CH<sub>2</sub>), 1.40 (t, 3H, CH<sub>3</sub>); mass spectrum: *m/e* 263 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>17</sub>H<sub>13</sub>NS: C, 77.57; H, 4.94; N, 5.32. Found: C, 77.69; H, 5.12; N, 5.45.

#### Photolysis of 1-(3-Benzo[*b*]thienyl)-2-(2-pyridyl)acrylonitrile (XIII).

A solution of XIII (262 mg., 1 mmole) in 386 ml. of *t*-butyl alcohol and 14 ml. of benzene was irradiated for 15 minutes. The solvent was evaporated and the residue was chromatographed [tlc, silica gel, chloroform:methanol (98:2)] to give 144 mg. (55%) of XIV; m.p. 99-100° (benzene-hexane); uv ( $\lambda$  max (methanol), log  $\epsilon$ ): 330 (3.24), 284 (3.67), 258 (3.99), 231 (4.13); uv ( $\lambda$  max (methanol), one drop 0.1 *N* hydrochloric acid): 343, 280, 262, 228; ir (potassium bromide): 2205 cm<sup>-1</sup> (C≡N); nmr (deuteriochloroform): 8.70-8.37 (m, 1H, pyridine  $\alpha$ -H), 7.67 (s, 1H, HC=C or S-C=), 7.60 (s, 1H, HC=C or S-C=), 8.00-6.71 (m, 7H, pyridine  $\beta$  and  $\gamma$ -H, Ar-H); mass spectrum: *m/e* 261 (M-1).

*Anal.* Calcd. for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>S: C, 73.28; H, 3.82; N, 10.69. Found: C, 73.41; H, 3.63; N, 10.72.

#### Photolysis of 1-(3-Benzo[*b*]thienyl)-2-(3-pyridyl)acrylonitrile (XVI).

A solution of XVI (262 mg., 1 mmole) in 150 ml. of ethanol was irradiated for 3 hours. The precipitate was filtered and crystallized from dimethyl sulfoxide to give 160 mg. (62%) of compound XVIIa or XVIIb; m.p. 303-305°; uv ( $\lambda$  max (methanol), one drop 0.1 *N* hydrochloric acid): 382, 318, 310, 280; ir (potassium bromide): 2218 cm<sup>-1</sup> (C≡N); mass spectrum: *m/e* 260 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>16</sub>H<sub>8</sub>N<sub>2</sub>S: C, 73.85; H, 3.08; N, 10.77. Found: C, 73.98; H, 3.22; N, 10.63.

#### Acknowledgement.

We are grateful to the Iranian Ministry of Science and Higher Education Research Development Department for supporting this work.

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