

## A NEW CONDENSED TRIHETEROCYCLIC SYSTEM: 6-AZA-8H-INDENO [2,1-b] THIOPHENE

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**Abstract** — Cyclization of 2,6-dimethyl-4-(3-thienyl)pyridine-3,5-dicarboxylic acid resulted in the formation of 5,7-dimethyl-8-oxo-6-aza-8H-indeno[2,1-b]thiophene derivatives.

As part of our project for the synthesis and evaluation of the biological properties of fused heterocyclic compounds containing a thiophene ring, we have recently described the synthesis of some pyrrolothienopyrazines <sup>1</sup>, pyrimidines <sup>2</sup>, diazepines <sup>3</sup>, thienopyrrolizines <sup>4</sup> and cyclopenta [cb] thiophene <sup>5</sup>. We wish to describe here a convenient route to a new system namely 6-aza-8H-indeno [2,1-b]thiophene.

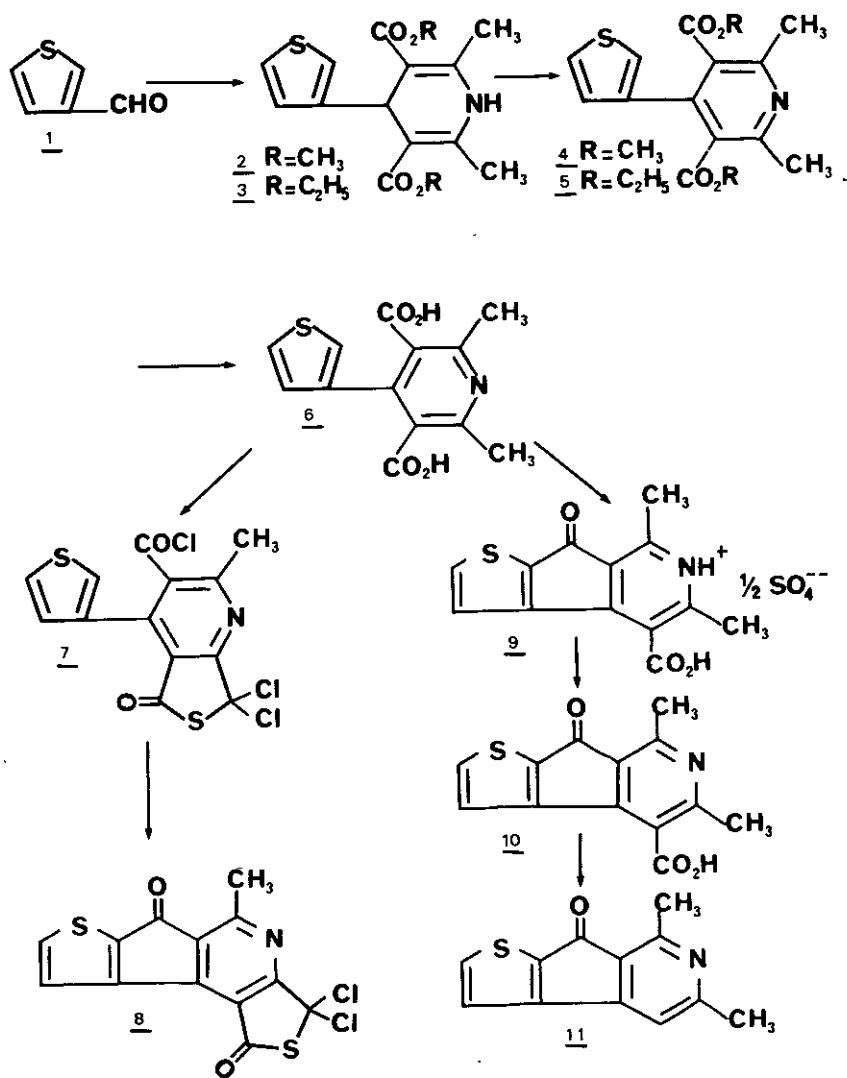
The 5,7-dimethyl-8-oxo-6-aza-8H-indeno[2,1-b]thiophene 11 was obtained in six steps starting from 3-thenaldehyde 1.

Treatment of 1 with methyl 2-aminocrotonate and methyl acetoacetate according to the Hantzsch pyridine synthesis <sup>6</sup> gave the dimethyl 1,4-dihydropyridinecarboxylate 2. Similarly, ethyl 2-aminocrotonate yielded the diethyl carboxylate 3. The treatment of the latter with nitric acid in diluted aqueous sulfuric acid at 70°C gave the corresponding pyridines 4 and 5.

Saponification of diester groupings could be achieved by treatment with sodium hydroxide in alcoholic solution, but better results were obtained by refluxing in hydrazine hydrate. The dicarboxylic acid 6 was then isolated after treatment of the resulting mixture with hydrochloric acid.

Conversion of this diacid into its dichloride with thionyl chloride gave the unexpected compound 7. The structure of this chlorocarbonylthiolactone was supported by analytical data and is in agreement with the results of Oka concerning the reaction of thionyl chloride with nicotinic acid. <sup>7</sup> The tricyclic thiolactone 8 was then obtained in high yield by an intramolecular Friedel-Crafts cyclization with aluminium chloride in carbon disulfide.

On the other hand, the method for cyclization of indenopyridines described by Mills, Palmer and Tomkinson<sup>8</sup> could be adapted in our thiophenic series. Treatment of the diacid 6 with hot concentrated sulfuric acid gave the tricyclic sulfate 9. Displacement of the crude salt was achieved first by heating in sodium hydroxyde solution followed by treatment with acetic acid ; the free acid 10 crystallized from the resulting mixture. Decarboxylation of this acid was realized by heating at 200°C with copper powder to give the tricyclic ketone 11. Further studies concerning these compounds and biological evaluation are in progress.



## EXPERIMENTAL

General notes

Melting points are uncorrected. All new compounds gave satisfactory microanalysis. Ir spectra were recorded on a Perkin Elmer 257 G spectrometer and only noteworthy absorptions ( $\text{cm}^{-1}$ ) are listed. Nmr spectra were recorded in  $\text{DMSO-d}_6$  with TMS as international standard on a Varian EM 390 spectrometer.

3,5-Dicarbomethoxy-2,6-dimethyl-4-(3-thienyl)-1,4-dihydropyridine 2

A solution of 3-thenaldehyde (46g, 0.4 mol), methyl 2-aminocrotonate (46g, 0.4 mol) and methyl acetoacetate (46g, 0.4 mol) in 400 ml of methanol is refluxed for 6 h. The reaction mixture is left at room temperature overnight and the yellow precipitate is washed with petroleum ether, dried and recrystallized from methanol (61.2g, 50%) ; mp  $180^\circ\text{C}$  ; ir (KBr)  $\rightarrow$  max. NH : 3345, CO : 1695 and  $1650\text{ cm}^{-1}$  ; nmr (DMSO)  $\delta$  ppm 6.82(2H,m,H2-H4), 7.23(1H,dd,J=4.5 and 3 Hz,H5), 4.90(1H,s,H4'), 2.21(6H,s,2CH<sub>3</sub>), 3.53(6H,s,2CH<sub>3</sub>), 8.83(1H,s,NH).

Anal. Calc. for  $\text{C}_{15}\text{H}_{17}\text{O}_4\text{NS}$  : C, 58.62 ; H, 5.58 ; N, 4.56 ; S, 10.43. Found : C, 58.51 ; H, 5.58 ; N, 4.48 ; S, 10.48.

3,5-Dicarbomethoxy-2,6-dimethyl-4-(3-thienyl)-1,4-dihydropyridine 3

A solution of 3-thenaldehyde (23g, 0.2 mol), ethyl 2-aminocrotonate (26g, 0.2 mol) and ethyl acetoacetate (31g, 0.2 mol) in 200 ml of ethanol is treated as above to provide 3 (33.5g, 50%) ; mp  $166^\circ\text{C}$  ; ir (KBr)  $\rightarrow$  max NH : 3340, CO : 1690 and  $1645\text{ cm}^{-1}$  ; nmr (DMSO)  $\delta$  ppm 6.80 (2H,m, H2-H4) 7.23(1H,dd,J=4.5 and 3 Hz,H5), 4.95(1H,s,H4'), 4.00(4H,q,J=7.5 Hz,2CH<sub>2</sub>), 2.21(6H,s, 2CH<sub>3</sub>), 1.13(6H,t,J=7.5 Hz,2CH<sub>3</sub>), 8.77(1H,s,NH).

Anal. Calc. for  $\text{C}_{17}\text{H}_{21}\text{O}_4\text{NS}$  : C, 60.87 ; H, 6.31 ; N, 4.17 ; S, 9.55. Found : 60.78 ; H, 6.27 ; N, 4.13 ; S, 9.71.

3,5-Dicarbomethoxy-2,6-dimethyl-4-(3-thienyl) pyridine 4

Sulfuric acid (14 ml) and nitric acid (4 ml) are poured into 40 ml of water. When the temperature of the solution reaches  $70^\circ\text{C}$ , compound 2 (14g, 0.045 mol) is added by small fractions. The reaction mixture is stirred for 2 h, then it is cooled and the reaction product precipitates as a salt. This salt is dissolved in water (100 ml) and displaced by addition of concentrated ammonia (40 ml) to provide 4. Recrystallization from diethyl ether gives yellow crystals (12g, 87%), mp  $130^\circ\text{C}$  ; ir (KBr)  $\rightarrow$  max. CO :  $1730\text{ cm}^{-1}$  ; nmr spectrum (DMSO)  $\delta$  ppm 6.92(1H,dd,J=4.5 and 1.2Hz,H2), 7.37(1H,dd,J=3Hz and 1.2Hz,H4), 7.60(1H,dd,J=4.5 and 3Hz,H5), 3.58(6H,s,2CH<sub>3</sub>), 2.62(6H,s,2CH<sub>3</sub>).

Anal. Calc. for  $\text{C}_{15}\text{H}_{15}\text{O}_4\text{NS}$  : C, 59.00 ; H, 4.95 ; N, 4.59 ; S, 10.50. Found : C,58.98 ; H, 4.94 ; N, 4.65 ; S,10.35.

### 3,5-Dicarbomethoxy-2,6-dimethyl-4-(3-thienyl) pyridine 5

Compound 3 (5g, 0.015 mol) is treated as above to provide 5 (4.5g, 90%) ; mp 78°C (Et<sub>2</sub>O) ; ir (KBr)  $\nu$  max. CO 1715 cm<sup>-1</sup> ; nmr (DMSO)  $\delta$  ppm 7.57(1H,dd,J=4.5 and 3Hz,H5), 7.36(1H,dd, J=3 Hz and 1.2Hz,H4), 6.90(1H,dd,J=4.5Hz and 1.2Hz,H2), 4.03(4H,q,J=7.5Hz,2CH<sub>2</sub>), 2.43(6H,s, 2CH<sub>3</sub>), 0.95(6H,t,J=7.5Hz,2CH<sub>3</sub>).

Anal. Calc. for C<sub>17</sub>H<sub>19</sub>O<sub>4</sub>NS : C, 61.24 ; H, 5.74 ; N, 4.20 ; S, 9.61. Found : C, 61.22 ; H, 5.65 ; N, 4.20 ; S, 9.79.

### 2,6-Dimethyl-4-(3-thienyl)-3,5-pyridinedicarboxylic acid 6

Compound 4 (10g, 0.032 mol) is dissolved in 100 ml of hydrazine hydrate. The reaction mixture is refluxed for 3 h. After evaporation of the excess of hydrazine, the residue is dissolved in water (100 ml) and the solution is acidified with concentrated hydrochloric acid (10 ml). The diacid precipitates, it is dried and washed with water (7.5g, 85%), mp 250°C (crude) ; ir (KBr)  $\nu$  max. CO : 1650 cm<sup>-1</sup> ; nmr (DMSO)  $\delta$  ppm 7.03(1H,dd,J=4.5Hz and 1.2Hz,H2), 7.50(2H,m,H4-H5), 2.47(6H,s,2CH<sub>3</sub>).

Anal. Calc. for C<sub>13</sub>H<sub>11</sub>O<sub>4</sub>NS : C, 56.31 ; H, 4.00 ; N, 5.05 ; S, 11.56. Found : C, 55.98 ; H, 4.15 ; N, 4.87 ; S, 11.36.

### 6-Chloroformyl-3,3-dichloro-5-methyl-1-oxo-7-(3-thienyl)-2,3-dihydro-2-thia-4-azaindene 7

Compound 6 (8g, 0.03 mol) is dissolved in 300 ml of thionylchloride. The reaction mixture is refluxed for 4 h. The excess of reagent is then removed under reduced pressure. The residue is triturated with ether, dried and recrystallized from ether (6.5g, 59%), mp 148°C, ir (KBr)  $\nu$  max. CO : 1780 and 1700 cm<sup>-1</sup> ; nmr (DMSO)  $\delta$  ppm 7.60(2H,m,H2-H5), 7.13(1H,dd,J=4.5 and 1.2 Hz, H4), 2.73(3H,s,CH<sub>3</sub>).

Anal. Calc. for C<sub>13</sub>H<sub>6</sub>O<sub>2</sub>NS<sub>2</sub>Cl<sub>3</sub> : C, 41.23 ; H, 1.60 ; N, 3.70 ; S, 16.93 ; Cl, 28.09. Found : C, 41.48 ; H, 1.70 ; N, 3.74 ; S, 16.65 ; Cl, 27.84.

### 3,3-Dichloro-5-methyl-1,6-dioxo-3,6-dihydro-1H-2,7-dithia-4-aza-dicyclopenta[a,g]indene 8

Compound 7 (5g, 0.013 mol) is dissolved in 100 ml of carbon disulfide and 19g of aluminium chloride are added by small portions. The reaction mixture is refluxed for 2 h. The solvent is then removed and the residue is triturated with cold water (50 ml), dried and recrystallized from acetone (2.5g, 56%), mp 205°C ; ir (KBr)  $\nu$  max. CO : 1700 cm<sup>-1</sup> ; nmr (DMSO)  $\delta$  ppm 8.16(1H,d, J=4.6Hz,H8), 7.23(1H,d,J=4.6Hz,H9), 2.56(3H,s,CH<sub>3</sub>) ; ms(70 ev) m/z = 345 (M<sup>+</sup>+4), 343 (M<sup>+</sup>+2), 341(M<sup>+</sup>).

Anal. Calc. for C<sub>13</sub>H<sub>5</sub>O<sub>2</sub>NS<sub>2</sub>Cl<sub>2</sub> : C, 45.23 ; H, 2.33 ; N, 4.05 ; S, 18.57. Found : C, 45.40 ; H, 2.03 ; N, 4.19 ; S, 18.47.

5,7-Dimethyl-8-oxo-6-aza-8H-indeno[2,1-b]thiophene-4-carboxylic acid 10

Compound 6 (5g, 0.018 mol) is dissolved in sulfuric acid (13 ml). The reaction mixture is heated for 2 h at 90°C and then 2 h at 110°C. Iced water (13 ml) is then added, and the solution is left 24 h at 0°C. The precipitate formed is filtered, dissolved in water and the solution is treated with sodium hydroxide (5g, pellets) and then slowly acidified with acetic acid (35 ml). The yellow precipitate is filtered, washed and dried (1g, 21%), mp >250°C ; ir (KBr)  $\nu$  max. CO : 1700 cm<sup>-1</sup>, nmr (DMSO)  $\delta$  ppm 8.16(1H,d,J=4.6Hz,H2), 7.23(1H,d,J=4.6Hz,H3), 2.53(6H,s,2CH<sub>3</sub>).

Anal. Calc. for C<sub>13</sub>H<sub>9</sub>O<sub>3</sub>NS : C, 60.22 ; H, 3.50 ; N, 5.40 ; S, 12.37. Found : C, 60.05 ; H, 3.43 ; N, 5.30 ; S, 12.25.

5,7-Dimethyl-8-oxo-6-aza-8H-indeno[2,1-b]thiophene 11

A mixture of compound 10 (0.2g, 0.8 mmol) and copper powder (0.2g) is heated at 200°C for 15 minutes. The reaction product is then submitted to sublimation at 200°C under reduced pressure (0.05 mmHg) to provide yellow crystals (0.1g, 58%) ; mp 182°C ; ir (KBr)  $\nu$  max. CO : 1695 cm<sup>-1</sup>; nmr (DMSO)  $\delta$  ppm 8.15(1H,d,J=4.6Hz,H2), 7.38(1H,d,J=4.6Hz,H3), 7.10(1H,s,H4), 2.50(3H,s,CH<sub>3</sub>), 2.40(3H,s,CH<sub>3</sub>).

Anal. Calc. for C<sub>12</sub>H<sub>9</sub>ONS : C, 66.95 ; H, 4.21 ; N, 6.51 ; S, 14.89. Found : C, 67.00 ; H, 4.30 ; N, 6.47 ; S, 14.74.

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