Improved Synthesis of Indenothiophenes. Part III (1). Synthesis of Indenothiophene-2-carboxylic Acids.

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The synthesis of indenothiophenes and substituted compounds is described starting from indane *via* indanaldehyde. A separation of the isomeric indanaldehydes is developed.

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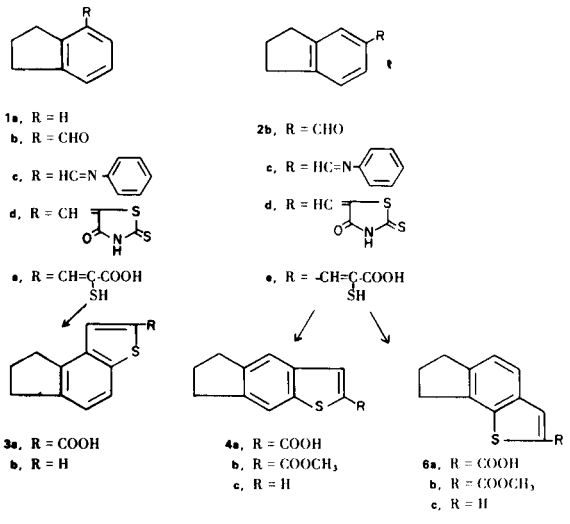
In an earlier paper (3) we reported the synthesis of 5,6-dihydro-4*H*-indeno[5,4-*b*]thiophene (**3b**). For the synthesis of this compound, 4-indanamine served as the starting material. It was transformed into the 4-indanaldehyde **1b** and the condensation product of **1b** with rhodanine was hydrolyzed to give the β-(4-indanyl)-α-mercaptoacrylic acid (**1e**). Compound **1e** was cyclized to the corresponding indenothiophene-2-carboxylic acid (**3a**) and decarboxylated to **3b** (Scheme 1). As the very low yields in the conversion of the indanamine into the aldehyde were unsatisfactory and larger amounts of **3b** were needed, we tried to improve the synthesis.

Mathison, *et al.*, (4) reported the preparation of an isomeric mixture of 4- and 5-indanaldehyde when indane (**1a**) was allowed to react with α,α-dichloromethyl methyl ether. The authors separated the isomeric reaction products *via* the anilides. In our experiments we did not succeed in isolating the 4-indanaldehyde as described; we were able only to separate the 5-indanaldehyde. No further separation of the mother liquor (4-indanaldehyde: 5-indanaldehyde 80:20) was achieved by the method mentioned above. A convenient method for separating the aldehydes was developed. This method consists of column chromatography using petroleum ether saturated with acetonitrile as eluents.

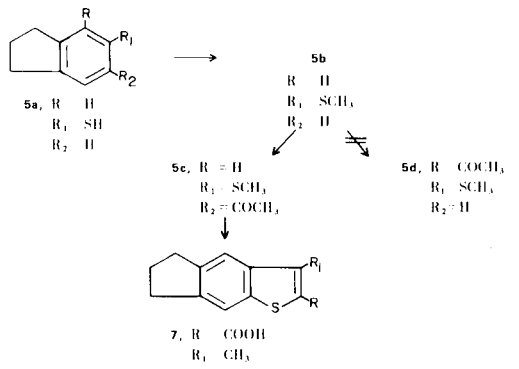
Scheme I



As the indanaldehydes **1b** and **2b** were now readily available we achieved **3b** much quicker and with better yields, **1d, 1e, 3a, 3b.** Thus, 7,8-dihydro-6*H*-indeno-[4,5-*b*]thiophene (**6c**) and 6,7-dihydro-5*H*-indeno[5,6-*b*]-thiophene (**4c**), formerly obtained by another transformation (5), were synthesized by the method mentioned above.

Compound **2c,** when treated with aqueous hydrochloric acid, was converted into 5-indanaldehyde (**2b**). When **2b** and rhodanine were refluxed in a solution of benzene, ammonium acetate and glacial acetic acid, 5-(5-indanylidene)rhodanine (**2d**) was obtained in good yield. The hydrolysis of **2d** with 10% sodium hydroxide solution produced β-(5-indanyl)-α-mercaptoacrylic acid (**2e**) as an amorphous product. Several recrystallizations could not improve the broad melting range of **2e** (3,6), but structure of **2e** was assigned on the basis of mass spectral evidence, analysis and subsequent cyclization, yielding a mixture of indenothiophene-2-carboxylic acids (**4a,6a**). Cyclization was effected by chlorine in carbon tetrachloride following the procedure of Chapman, *et al.*, (7). Treatment of the cyclization mixture with diazomethane and GC-MS-control of the methylated product showed the presence of two methyl esters. This result indicated that both 6,7-dihydro-5*H*-indeno[5,6-*b*]thiophene-2-carboxylic acid (**4a**) and 7,8-dihydro-6*H*-indeno[4,5-*b*]thiophene-2-carboxylic acid (**6a**) were formed during cyclization. Recrystallization from benzene gave the pure **4a.** Chromatographic investi-

Scheme II



gation of the mother liquor, as mentioned above, still confirmed the presence of both **4a** and **6a**. Decarboxylation with copper-bronze in quinoline of **4a** and the mixture **4a** + **6a** yielded 6,7-dihydro-5*H*-indeno[5,6-*b*]thiophene (**4c**) and the mixture **4c** + 7,8-dihydro-6*H*-indeno[4,5-*b*]-thiophene (**6c**).

Subsequently, we tried to separate **4c** and **6c**. Up to a certain percentage, **4c** could be separated by repeated recrystallization from isopropyl alcohol or methanol. No further separation of **4c** from the mixture was possible when a ratio of the isomeres (**4c**:**6c** = 1:1) was reached. Column chromatography with pure and coated materials (successfully used on similar separation problems (8)), failed. Another attempt to separate the picrates of **4c** and **6c** also failed. Finally, using preparative GC methods, we succeeded.

Another reaction sequence to obtain 6,7-dihydro-5*H*-indeno[5,6-*b*]thiophenes is shown in Scheme II. 5-Indanethiol (**5d**) (5) was methylated and the resulting sulfide **5b** was allowed to react in a Friedl-Crafts experiment with acetyl chloride to give **5c**. Substitution occurred exclusively in 6-position of the indane. 4-Acetyl-5-methylthioindane (**5d**) could not be detected. Cyclization of **5c** by reaction with chloroacetic acid (9) yielded 3-methyl-6,7-dihydro-5*H*-indeno[5,6-*b*]thiophene-2-carboxylic acid (**7**). 5,6-Dihydro-4*H*-indeno[5,4-*b*]thiophenes could not be synthesized by this method.

EXPERIMENTAL

Melting points are uncorrected. Nmr spectra were determined with a Varian T-60 using tetramethylsilane (TMS, $\delta = 0$) as the internal standard. The mass spectra were recorded on a Varian MAT 111 (GNOM). Glc was conducted on a Varian Aerograph 1525 B.

The indanaldehydes were prepared by the method described by Mathison, *et al.*, (4). Thus, 100 g. (0.846 mole) of indane reacted with 128.7 g. (1.12 moles) of α,α-dichloromethyl methyl ether to give 72 g. (58%) of a mixture of 4- and 5-indanaldehyde (isomer ratio ~ 23:77). After removal of the 5-aldehyde *via* its anilide up to the mentioned extent we chromatographed the remaining mixture. The chromatographic separation of 4- and 5-indanaldehyde was carried out using a cascade column (length 165 cm., 5 steps, diameters from 6 cm-1.5 cm) filled with silica gel (Merck 0.05-0.2 mm ASTM.) 10 g. of the mixture were applied and eluted with petroleum ether saturated with acetonitrile. The separation yielded 7.4 g. (74%) of 4-indanaldehyde, b.p.$_{24}$ 136°, 2.1 g. (21%) of 5-indanaldehyde, b.p. 255-257°; 0.45 g. (4.5%) of the applied mixture remained unseparated.

Preparation of the Rhodanine Derivatives (**1d**, **2d**).

To a boiling solution of 200 ml. of benzene, 20 ml. of glacial acetic acid, 0.8 g. of ammonium acetate and 12.8 g. (0.096 mole) of rhodanine, 14 g. (0.095 mole) of indanaldehyde were added. A Dean-Stark trap was used to collect the water liberated during the reaction. Benzene (50 ml.) was then distilled from the reaction mixture and the resulting solution was boiled for another 6 hours and then cooled. The product crystallized as a mass of yellow needles and was recrystallized from benzene or ethanol.

5-(4-Indanylidene)rhodanine (**1d**).

The characteristics were reported in a previous paper (3). This compound was obtained in a yield of 81% (20.25 g.), m.p. 224-225°.

5-(5-Indanylidene)rhodanine (**2d**).

This compound was obtained in a yield of 96% (24 g.), m.p. 215-216°; nmr (DMSO-d_6): δ 2.0 (m, 2H, J = 7 Hz), 2.9 (t broadened, 4*H*, J = 7 Hz), 7.3 (s broadened, 3H), 7.45 (s, 1H); mass spectrum, m/e (relative intensity): 261 (71), 174 (100), 173 (17), 141 (3), 129 (14), 117 (23), 115 (12), 87 (14).

Anal. Calcd. for $C_{13}H_{11}NOS_2$: C, 59.73; H, 4.24; S, 24.53; N, 5.35. Found: C, 59.73; H, 4.23; S, 24.76; N, 5.25.

General Procedure for the Preparation of β-(Indanyl-α-mercapto-acrylic Acids (**1e**, **2e**).

Compound **1d** or **2d** was suspended in an excess of a 10% sodium hydroxide solution and heated on a vigorously boiling water-bath until all the material was dissolved. After the solution was cooled rapidly in a freezing mixture it was acidified with 10% hydrochloric acid. The acid precipitated and was collected, washed with water and was recrystallized from benzene. In various runs we obtained different melting points.

β-(4-Indanyl)-α-mercaptoacrylic Acid (**1e**).

From 3 g. (0.011 mole) of **1d** and 10 ml. of a 10% sodium hydroxide solution, 1.9 g. (75%) of **1e**, m.p. 147-149°, was obtained. In other runs the m.p. varied: 170°, 176°, 145-150°. Additional characteristics were reported in a previous paper (3).

β-(5-Indanyl)-α-mercaptoacrylic Acid (**2e**).

From 6 g. (0.022 mole) of **2d** and 20 ml. of a 10% sodium hydroxide solution, 4.2 g. (83%) of **2e** was obtained. The melting points of different runs varied: 200°, 183-186°, 180°, 154-158°; nmr (DMSO-d_6): δ 2.05 (m, 2H, J = 7 Hz), 2.95 (t broadened, 4*H*, J = 7 Hz), 7.3-7.65 (m, 3H), 7.75 (s, 1H); mass spectrum, m/e (relative intensity): 220 (28), 202 (5), 173 (100), 141 (13), 117 (23), 115 (18).

Anal. Calcd. for $C_{12}H_{12}O_2S$: C, 65.45; H, 5.45; S, 14.56. Found: C, 65.68; H, 5.58; S, 14.54.

General Procedure for the Preparation of Indenothiophene-2-carboxylic Acids (**3a**, **4a**, **6a**).

A solution of chlorine in dry carbon tetrachloride was added with swirling to a cooled (10°) solution of **1e** or **2e** in carbon

tetrachloride. After a few minutes a yellow solid precipitated while hydrogen chloride gas was evolved. The reaction mixture was stirred for an additional hour. The solid was filtered off, the solution was concentrated under reduced pressure to half its original volume and the solid produced was collected. The total product was recrystallized from isopropyl alcohol or benzene.

5,6-Dihydro-4*H*-indeno[5,4-*b*]thiophene-2-carboxylic Acid (**3a**).

From 1.6 g. (0.0073 mole) of **1e** in 75 ml. of dry carbon tetrachloride and 0.55 g. (0.0079 mole) of chlorine in 13 ml. of carbon tetrachloride, 1.3 g. (81%) of **3a** were obtained, m.p. 220-220.5°. The characteristics were reported in a previous paper (3).

6,7-Dihydro-5*H*-indeno[5,6-*b*]thiophene-2-carboxylic Acid (**4a**).

From 2.5 g. (0.0114 mole) of **2e** in 118 ml. of dry carbon tetrachloride and 0.8 g. (0.0114 mole) of chlorine in 19.5 ml. of carbon tetrachloride, 1.75 g. (71%) of **4a** + **6a** were obtained.

Methylation of this cyclization product with diazomethane and GC-MS-control confirmed the presence of 2-carbomethoxy-6,7-dihydro-5*H*-indeno[5,6-*b*]thiophene (**4b**); mass spectrum, m/e (relative intensity): 232 (85), 201 (57), 173 (100), 129 (28) and 2-carbomethoxy-7,8-dihydro-6*H*-indeno[4,5-*b*]thiophene (**6b**); mass spectrum, m/e (relative intensity): 232 (68), 201 (56), 173 (100), 129 (25). No attempt was made to separate the esters.

As mentioned above the pure **4a** was obtained by recrystallization from benzene; nmr (DMSO-d_6): δ 2.15 (m, 2H, J = 7 Hz), 3.05 (t broadened, 4H, J = 7 Hz), 7.9 (s broadened, 2H), 8.1 (s, 1H); mass spectrum, m/e (relative intensity): 218 (100), 173 (97), 129 (23).

Anal. Calcd. for $C_{12}H_{10}O_2S$: C, 66.05; H, 4.58; S, 14.69. Found: C, 65.95; H, 4.70; S, 14.40.

General Procedure for the Preparation of Indenothiophenes (**3b, 4c, 6c**).

A stirred mixture of the acid (1 g., 0.0046 mole) was heated with copper-bronze (0.35 g.) in quinoline (7 ml.) at 190-200° for 2 hours under nitrogen. After cooling and filtration from copper-bronze the filtrate was acidified with hydrochloric acid and extracted with ether. After washing the ethereal solutions with sodium hydrogen carbonate and water, drying with sodium sulfate and removing the solvent, we purified the product by chromatography on silica gel (Merck 0.05-0.2 mm ASTM, petroleum/benzene 3:1 as eluent).

6,7-Dihydro-5*H*-indeno[5,6-*b*]thiophene (**4c**).

This compound was obtained by decarboxylation of **4a** in a yield of 95% (0.76 g.), m.p. 95-96° (ethanol). The characteristics were reported in a previous paper (5).

5,6-Dihydro-4*H*-indeno[5,4-*b*]thiophene (**3b**).

This compound was obtained by decarboxylation of **3a** in a yield of 82% (0.66 g.), m.p. 34-34.5° (isopropyl alcohol). The characteristics were reported in a previous paper (3).

7,8-Dihydro-6*H*-indeno[4,5-*b*]thiophene (**6c**).

Decarboxylation of 1 g. of the isomeric mixture of **4a** + **6a** gave a mixture of the compounds **4c** + **6c** in a yield of 89% (0.72 g.). We succeeded in separating **4c** and **6c** by preparative gas chromatography using a 6 m, 3/8″ column packed with 15% CW 1540 coated on ANAPREP. The characteristics of this compound were reported in a previous paper (5).

5-Acetyl-6-methylthioindane (**5c**).

Compound **5b** (2.85 g., 0.017 mole) reacted with 1.4 g. (0.008 mole) of acetyl chloride and 2.7 g. (0.02 mole) of aluminium chloride in 6.8 g. of carbon disulfide to give 2.18 g. (61%) of **5c**, m.p. 89.5-90° (isopropyl alcohol); nmr (carbon tetrachloride): δ 2.0 (m, 2H, J = 7 Hz), 2.8 (t braodened, 4H, J = 7 Hz), 2.2 (s, 3H), 2.35 (s, 3H), 6.9 (s, 1H), 7.35 (s, 1H); mass spectrum, m/e (relative intensity): 206 (32), 191 (100), 163 (8), 147 (6), 117 (10), 116 (22), 115 (20).

Anal. Calcd. for $C_{12}H_{14}OS$: C, 69.86; H, 6.84; S, 15.54. Found: C, 69.76; H, 6.82; S, 15.48.

3-Methyl-6,7-dihydro-5*H*-indeno[5,6-*b*]thiophene-2-carboxylic Acid (**7a**).

Compound **5c** (1.76 g., 0.085 mole) and monochloroacetic acid (9 g., 0.095 mole) were heated on a steam-bath for 5 hours. The mixture was allowed to cool and then diluted with ethanol and acetone (1:1). The precipitate was filtered off and recrystallized from ethanol to give 1.36 g. (68%), m.p. 273-274°; nmr (DMSO-d_6): δ 2.05 (m, 2H, J = 7 Hz), 2.95 (t broadened, 4H, J = 7 Hz), 2.65 (s, 3H), 7.65 (s, 2H); mass spectrum, m/e (relative intensity): 232 (100), 188 (29), 187 (91), 173 (21), 172 (21), 171 (19), 153 (11), 92 (14), 59 (19).

Anal. Calcd. for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21; S, 13.80. Found: C, 67.16; H, 5.29; S, 13.74.

REFERENCES AND NOTES

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