760, 740, 729, 709, 698, and 692 cm^{-1}; nmr δ 2.26 (6 H, s) and 6.9–7.8 (*ca.* 22 H, m); m/e 532 (parent).

Attempted Condensation of 6. 1,2-Dibenzoyl-3,6-dimethylbenzene.—A solution of 0.067 g (0.22 mmol) of **6** in 10 ml of benzene containing 5 mg of *p*-toluenesulfonic acid was heated under reflux for 24 hr. Shorter reflux periods resulted in isolation of substantial quantities of unreacted **6**. The mixture was washed with a saturated solution of sodium bicarbonate and dried over sodium sulfate. Removal of the solvent *in vacuo* left a nearly colorless residue which was recrystallized from ethanol to give 0.042 g (65%) of 1,2-dibenzoyl-3,6-dimethylbenzene: mp 138–142°; ir (Nujol) 1660, 1305, 1265, 1150, 1000, 976, 959, 930, 870, 849, 828, 805, 770, 760, 729, 700, and 689 cm^{-1}; nmr δ 2.3 (6 H, s) and *ca.* 7.4 (12 H, m); m/e 314 (parent).

1,3-Diphenyl-5-methylisobenzothiophene (24).—A mixture of 0.24 g (0.56 mmol) of **3** and 0.05 g of elemental sulfur was heated at 220° for 20 min using an air-cooled condenser. The dark brown mixture was triturated with acetone and the solids were filtered off. The filtrate was concentrated *in vacuo* and the residue was chromatographed on 20 × 20 cm preparative layer plates coated with silica gel PF-254. Elution with 3% methanol in benzene and removal of the yellow band gave a viscous oil upon extraction of the silica with acetone. This material crystallized from hexane–acetone and was recrystallized from ethanol to give **24**, m/e 300 (parent).

1,3-Diphenyl-5,6-dimethylisobenzothiophene (25).—To a stirred mixture of 0.50 g (2 mmol) of phosphorus pentasulfide and 0.5 g of sand in 40 ml of tetralin at 150° was added a solution of 1.01 g (3.2 mmol) of **4** in 20 ml of tetralin during 5 min. The mixture was maintained at 150° for a further 15 min and filtered while hot. The dark red filtrate was washed with 5% sodium hydroxide solution and water and dried over magnesium sulfate. The tetralin solution was diluted with an equal volume of petroleum ether and passed through a short column of alumina (activity II). The eluate, exhibiting green fluorescence, was concentrated to a small volume *in vacuo* and, upon cooling in ice, a yellow, crystalline solid was deposited. This material was recrystallized from acetone to yield **25**: ir (Nujol) 1600, 1240, 1190, 1165, 1120, 1080, 1025, 966, 907, 855, 837, 755, 731, and 694 cm^{-1}; nmr δ 2.14 (6 H, s) and 7.6 (12 H, m); m/e 314 (parent).

Registry No.—**2**, 27720-52-1; **3**, 27720-53-2; **4**, 27720-54-3; **5**, 27720-55-4; **6**, 27720-56-5; **7**, 27720-57-6; **8**, 4276-24-8; **9**, 22948-71-6; **10**, 22948-72-7; **11**, 22948-70-5; **12**, 27720-38-3; **13**, 27720-39-4; **14**, 22948-74-9; **15**, 22948-75-0; **16**, 22948-73-8; **17**, 22942-68-3; **18**, 20944-65-4; **19**, 10287-38-4; **20**, 20944-69-8; **21**, 27720-46-3; **22**, 27720-47-4; **23**, 27720-48-5; **24**, 27720-49-6; **25**, 27720-50-9; 1,2-dibenzoyl-3,6-dimethylbenzene, 6807-35-8.

Acknowledgments.—Financial support was provided by the National Institutes of Health (GM 13932-01) and the Clark fund of the Harvard Graduate Society.

The Chemistry of Indenothiophenes. III. The Metalation of 3-Benzylthiophene and an Alternative Synthesis of 4*H*-Indeno[1,2-*b*]thiophene-4-carboxylic Acid[1]

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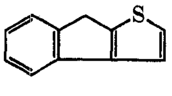
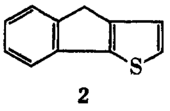
Received September 17, 1970

The metalation of 3-benzylthiophene (**6**) has been shown to yield 88% 4-benzylthiophene-2-carboxylic acid (**8**) and 12% 3-benzylthiophene-2-carboxylic acid (**9**). No 3-thienylphenylacetic acid (**10**) was formed. Both **9** and **10** were synthesized independently. These results are discussed in terms of single-bond bridging between the benzene and thiophene rings which is present in indenothiophenes **1**, **2**, and **3** but absent in **6**. This alters the sites of metalation of **6** when compared to **1**, **2**, and **3**. The cyclization of 3-thienylmandelic acid (**13**) gives 4*H*-indeno[1,2-*b*]thiophene-4-carboxylic acid (**5**).

Previous studies in our laboratories[3] have determined the metalative properties of the three parent indenothiophenes **1**, **2**, and **3**. Compounds **1** and **2** underwent metalation–carbonation at their respective methylene bridges to yield 8*H*-indeno[2,1-*b*]thiophene-8-carboxylic acid (**4**) and 4*H*-indeno[1,2-*b*]thiophene-4-carboxylic acid (**5**). However, metalation of 8*H*-indeno[1,2-*c*]thiophene (**3**) gave a mixture of three products: 8*H*-indeno[1,2-*c*]thiophene-3-carboxylic acid (48%), 8*H*-indeno[1,2-*c*]thiophene-8-carboxylic acid (38%), and 8*H*-indeno[1,2-*c*]thiophene-1-carboxylic acid (14%).


1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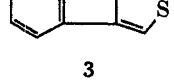
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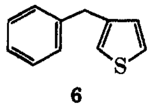
6

In order to determine if direct bridging between the benzene and thiophene rings influences the position of metalation of **2** and **3**, a study of the metalative properties of 3-benzylthiophene (**6**), the open-chain analog of **2** and **3**, was undertaken.

Metalation of **6** could reasonably be expected to take place at the two α positions on the thiophene ring and on the methylene bridge.

Synthesis.—The synthesis of **6** was accomplished as shown below in Scheme I. Hydrolysis of the mixture obtained in the reaction of benzonitrile with 3-thienyllithium at −70° produced 3-benzoylthiophene (**7**) in 69% yield.[4] Reduction to **6** was achieved in 90% yield following the procedure of Nystrom and Burger.[5] Wolff–Kishner reduction gave **6** in 70% yield.

Metalation Experiments. Metalation of **6**, which produced acidic material in 80% yield, was accomplished by reaction with 1 equiv of ethereal *n*-butyllithium followed by carbonation and work-up (Scheme

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[1] Part of this work was presented at the 2nd Central Regional Meeting of the American Chemical Society, Columbus, Ohio, June 1970.

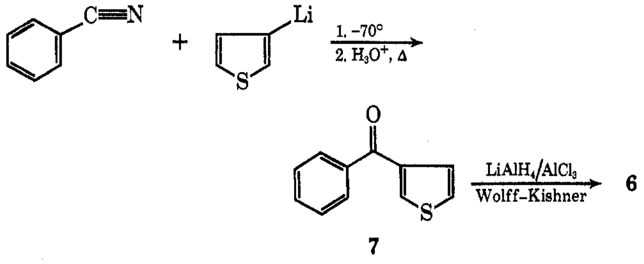
[2] NDEA Fellow, 1967–1970.

[3] D. W. H. MacDowell and T. B. Patrick, *J. Org. Chem.*, **32**, 2441 (1967); D. W. H. MacDowell and A. T. Jeffries, *ibid.*, **35**, 871 (1970).

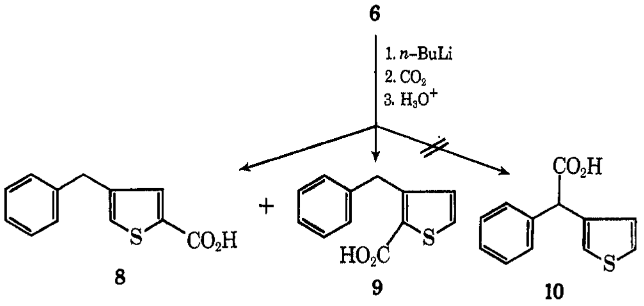
[4] S. Gronowitz, *Ark. Kemi*, **12**, 533 (1958).

[5] R. F. Nystrom and C. R. A. Burger, *J. Amer. Chem. Soc.*, **80**, 2896 (1958).

Scheme I



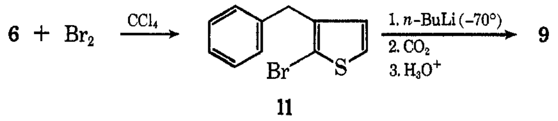
Scheme II



II). The nmr spectrum of the solid contained, besides aromatic absorptions, singlets at τ 5.6 and 6.0 indicating a mixture of products. Fractional recrystallization yielded the major product, 4-benzylthiophene-2-carboxylic acid (**8**). The appearance of a one-proton doublet at τ 2.45 ($J = 1.5$ Hz) for the 3 hydrogen established the 2,4 disubstitution pattern of the thiophene ring.[6] The 5 hydrogen appears as a multiplet at τ 2.60. Normally, the absorption would have been identical with that of the 3 hydrogen; however, additional splitting of the 5 hydrogen is caused by coupling with the benzylic hydrogens.[6]

The minor product, 3-benzylthiophene-2-carboxylic acid (**9**), was not separated from the reaction mixture but was synthesized independently as shown in Scheme III.

Scheme III

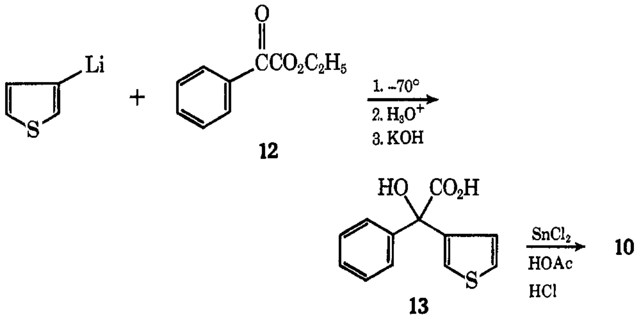


Bromination of **6** following the method of Wynberg, *et al.*,[7] gave 3-benzyl-2-bromothiophene (**10**) in 54% yield. Halogen–metal exchange at −70° followed by carbonation produced **9** in 56% yield.

That **9** was the minor product in the metalation of **6** was demonstrated as follows. An nmr spectrum of the carbonation mixture was recorded and to this mixture was added authentic **9**. The enhancement of the absorption at τ 5.6 relative to the signal at 6.0 and the absence of any other extraneous signals demonstrates that **9** is the minor product in the reaction.

To exclude the possibility that 3-thienylphenylacetic acid (**10**) had been formed in the reaction, it too was synthesized as outlined in Scheme IV.

Scheme IV



The precursor, 3-thienylmandelic acid (**13**), was obtained by the reaction of 3-thienyllithium with ethyl phenylglyoxalate (**12**) at −70°, followed by hydrolysis. Reduction to the desired acid was effected using the method of Sjoberg[8] and gave **10** in 81% yield. The singlet absorption of the methine proton at τ 4.83 clearly demonstrated that **10** was not present in the mixture.

Discussion

The two products, **8** and **9**, occurred in 88 and 12% yield, respectively. Their relative proportions were measured by determining the areas under their respective peaks in the nmr spectrum and are the average of two experiments. These results, along with those reported earlier,[3] distinctly indicate that single-bond bridging between the benzene and thiophene rings is responsible for the methylene protons of **1** and **2** being more acidic than the thiophene protons. The removal of the single bond bridge in **6** causes the thiophene protons to be more acidic than those on the methylene bridge in **2**. Delocalization of the negative charge formed at the methylene bridges of **1** and **2** is responsible for the enhanced acidity of their methylene protons. In the case of **3**, electron delocalization is decreased because of *c* fusion of the thiophene nucleus, but it nevertheless is present. Thus, removal of the single-bond bridge in **2** and **3** removes any possibility of delocalization for an anion formed at the methylene bridge and thus alters the site of metalation in **6**.

These data, combined with the known pK_a value of fluorene as 20–25,[9] the known metalation reactions of **1** and **2**, and the calculation of the pK_a values of **1** and **2** as 24 and 25, respectively,[3] allow the estimation of the pK_a of a thiophene α proton to be somewhat greater than 25 pK_a units.

The decreased acidity of the 2 proton of **6** as compared to the 5 proton and the predominant bromination of **6** in the 2 position indicate that the benzyl function acts as an electron-donating group in both electrophilic and nucleophilic substitution.

The metalation results are also in accord with those reported by Levine and Ramanathan[10] who isolated 61% of 4-methyl-2-thiophenecarboxylic acid and 19% of 3-methylthiophene-2-carboxylic acid from the metalation of 3-methylthiophene.

Reaction of 3-Thienylmandelic Acid with Aluminum Chloride.—As previously reported,[3] indenothiophene **2** gave only **5** upon metalation followed by carbonation. A potential independent synthesis of **5** would lie in the cyclization of **13**. This is analogous to the known

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[6] R. A. Hoffman and S. Gronowitz, *Ark. Kemi*, **16**, 563 (1961).

[7] A. Kraak, A. K. Wiersema, P. Jordans, and H. Wynberg, *Tetrahedron*, **24**, 3381 (1968).

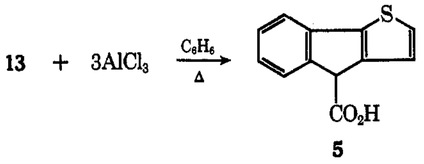
[8] B. Sjoberg, *Ark. Kemi*, **12**, 565 (1958).

[9] D. J. Cram in "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter 1.

[10] V. Ramanthan and R. Levine, *J. Org. Chem.*, **27**, 1667 (1962).

aluminum chloride catalyzed cyclization of mandelic acid to fluorene-9-carboxylic acid.[11] Acid **5** was formed as the product of cyclization of **13** under conditions described for mandelic acid and was identical in all respects with authentic acid formed from the metalation of **2** (Scheme V).

SCHEME V



5

Experimental Section[12]

3-Benzylthiophene (6).—Lithium aluminum hydride (2.025 g, 0.0532 mol) was suspended in 45 ml of anhydrous ether contained in a three-necked 500-ml flask which has been flame dried under nitrogen and protected with a calcium chloride drying tube. This suspension was cooled in an ice bath while aluminum chloride (7.10 g, 0.0532 mol) in 50 ml of anhydrous ether was added slowly. Following removal of the cooling bath, 3-benzoylthiophene[4] (10.0 g, 0.0532 mol, mp 54–59°) dissolved in 100 ml of anhydrous ether was added at such a rate (after a short induction period) as to maintain a gentle reflux. After addition, reflux was maintained for 0.5 hr, followed by cooling in an ice bath, and addition of 10 ml of water and 25 ml of 3 *M* acid, respectively.

The ether layer was decanted, and the aqueous layer was diluted with water (*ca.* 100 ml) and extracted with three portions of ether. The ether layers extracted were combined, washed three times with water and twice with brine, dried ($MgSO_4$), and concentrated to leave 8.56 g (91%) of a yellow oil: bp 109° (2.3 mm); $n^{26}\mathrm{D}$ 1.5890 [lit.[13] bp 120° (20 mm); $n^{25}\mathrm{D}$ 1.5868]; nmr ($CDCl_3$) τ 2.6–3.1 (m, 8), 6.0 (s, 2).

Anal. Calcd for $C_{11}H_{10}S$: C, 75.79; H, 5.78; S, 18.39. Found: C, 76.02; H, 5.93; S, 18.39.

4-Benzylthiophene-2-carboxylic Acid (8).—To a 250-ml three-necked flask fitted with a pressure equalizing addition funnel, reflux condenser, and calcium chloride drying tube, all of which were flame dried and maintained under nitrogen, were added 95 ml of ether and 1.57 g of (9.03 mmol) of 3-benzylthiophene (6) (homogeneous by tlc). To this solution, which was stirred magnetically, was added 6.9 ml of 1.31 *M* ethereal *n*-butyllithium[14] (9.03 mmol) over a 2-min period. The yellow solution was then refluxed for 30 min. The refluxing was stopped and approximately 20 g of freshly chipped Dry Ice was added. Several minutes after the vigorous reaction had subsided, 30 ml of water was added and the layers were separated. The aqueous layer was washed with three portions of ether. The combined ether layers were backwashed with one portion of water. The combined aqueous layers were cooled and acidified with 15 ml of 1 *M* hydrochloric acid and extracted with three portions of ether. The ether solution was washed with three portions of water and two portions of brine, dried ($MgSO_4$), and evaporated to leave 1.58 g (80%) of white solid.

Evaporation of the neutral layer left 0.24 g of dark blue semisolid material.

An analytical sample obtained by fractional recrystallization from benzene–hexane of a sample obtained from a similar experiment had mp 105–105.5°; ir (KBr) 1675 cm^{-1} (acid C═O); nmr (acetone-d_6) τ 2.45 (d, 1, J = 1.5 Hz, 3 position), 2.60 (m, 1, 5 position), 2.80 (s, 5, C_6H_5), 6.03 (s, 2, CH_2); nmr ($CDCl_3$) τ −2.3 (s, 1, CO_2H).

Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 65.96; H, 4.63; S, 14.42.

3-Benzyl-2-bromothiophene (11).—To a rapidly stirred mixture of 140 ml of water and bromine (1.46 ml, 0.0287 mol) contained in a 250-ml three-necked flask at 15° was added as quickly as possible from a 250-ml separatory funnel 3-benzylthiophene (6, 5.0 g, 0.029 mol) contained in 25 ml of carbon tetrachloride (exothermic). After addition, the mixture decolorized rapidly to a pale yellow color. After stirring at 12–15° for 15 min, 100 ml of ether was poured into the mixture. The layers were separated and the aqueous layer was extracted with two portions of ether. The combined organic layers were washed with two portions of saturated sodium bicarbonate solution, three portions of water, two portions of brine, and dried ($MgSO_4$). Evaporation left 6.87 g (94%) of an oil which was rapidly distilled. The fraction boiling at 88–93° (0.03 mm) was collected, 4.01 g (54%), $n^{23}\mathrm{D}$ 1.6116. An analytical sample was obtained by repeated short-path distillation: bp 80–90° (0.03 mm); $n^{23}\mathrm{D}$ 1.6142; nmr (acetone-d_6) τ 2.68 (d, 1, J = 5 Hz, 5 position), 2.85 (s, 5, C_6H_5), 3.26 (d, 1, J = 5 Hz, 4 position).

Anal. Calcd for $C_{11}H_9BrS$: C, 52.20; H, 3.58; Br, 31.58; S, 12.57. Found: C, 51.98; H, 3.72; Br, 31.47; S, 12.46.

3-Benzylthiophene-2-carboxylic Acid (9).—The following apparatus was flame dried and maintained under dry nitrogen for this experiment. A 250-ml two-necked flask was surrounded by a Dry Ice–acetone bath and fitted with a pressure-equalizing addition funnel, mechanical stirring motor, and calcium chloride drying tube. The bottom of this flask was connected by means of a stopcock and standard taper 24/40 joint to a 500-ml three-necked flask. Pressure equalization between the two flasks was maintained by a T-tube and Tygon tubing attached to one neck of the lower flask and the calcium chloride drying tube of the upper flask.

To a solution of 1.60 *M* ethereal *n*-butyllithium (10.8 ml, 0.0173 mol) at −70° was added 3-benzyl-2-bromothiophene (11, 4.00 g, 0.0158 mol, from the previous experiment) in 40 ml of ether. After being stirred for 30 min, the ethereal solution was added slowly into the lower flask which contained approximately 50 g of freshly chipped Dry Ice. After the vigorous reaction had subsided, 50 ml of water was added. The layers were separated and the aqueous layer was washed with three portions of ether. The ethereal layer was washed with one portion of water. The combined aqueous layers were collected and acidified with 20 ml of 1 *M* hydrochloric acid. The white solid was extracted with three portions of ether. The ether solution was washed with three portions of water and two portions of brine and dried ($MgSO_4$). Evaporation left the acid 9, mp 153–155°, 2.0 g (56%). An analytical sample was prepared by recrystallization from benzene–hexane: mp 155–155.5°; ir (KBr) 1650–1670 cm^{-1} (acid C═O); nmr (DMSO-d_6) τ 2.35 (d, 1, J = 4 Hz, 5 position), 2.80 (s, 5, C_6H_5), 3.06 (d, 1, J = 4 Hz, 4 position), 5.65 (s, 2, CH_2).

Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 66.26; H, 4.57; S, 14.52.

3-Thienylmandelic Acid (13).—This experiment was performed in an apparatus identical with that used in the preparation of 3-benzylthiophene-2-carboxylic acid (9).

3-Bromothiophene (12.0 g, 0.0736 mol) dissolved in 120 ml of ether was added to a ethereal 1.32 *M* *n*-butyllithium solution (60 ml, 0.079 mol) at −70°. After being stirred for 5 min at −70°, the lithio salt was added to a solution of ethyl phenylglyoxalate[15] (12, 12.36 g, 0.0695 mol) dissolved in 60 ml of ether at −70° over a 27-min period. After addition, the cooling bath was removed and the flask was allowed to warm to room temperature. The contents were poured onto a slurry of ice and ammonium chloride. The layers were separated and the aqueous layer was extracted with two portions of ether. The ether layers were washed with three portions of water and two portions of brine and dried ($MgSO_4$). Evaporation left 16.5 g (90%) of an oil. This oil was combined with 2.73 g of material obtained from an identical experiment and saponified by refluxing for 5 hr in 70 ml of 10% ethanolic potassium hydroxide solution. The ethanol was evaporated and the residue was dissolved in 300 ml of water. The aqueous solution was extracted with four portions of ether, cooled, and acidified with 130 ml of 1 *M* HCl. The aqueous mixture was extracted with three portions of ether. The ethereal solutions were washed with three portions of water and two portions of brine and dried ($MgSO_4$). Evaporation left 12.5 g of crystalline solid (67% overall), mp 118–122°. An analytical

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[11] H. J. Richter, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 482.

[12] All temperature readings are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nuclear magnetic resonance spectra were recorded on a Varian HA-60 spectrometer using tetramethylsilane as an internal standard (τ 10) and solvents as specified. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer.

[13] J. G. S. Cadogan, D. H. Hey, and W. A. Sanderson, *J. Chem. Soc.*, 3203 (1960).

[14] Analyzed by the double titration method: H. Gilman and R. Jones, *Org. React.*, **6**, 339 (1951).

[15] B. B. Corson, R. A. Dodge, S. A. Harris, and R. K. Hazen, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 241; E. J. Corey and J. P. Schaefer, *J. Amer. Chem. Soc.*, **82**, 918 (1960).

sample was obtained by recrystallization from approximately 1:1 benzene–hexane: mp 129–130° (lit.[16] 133°); ir (KBr) 3400 (OH), 1710 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 2.6–3.2 (m, 8, aromatic), 4.4 (s, 2, OH, CO_2H).

Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.29; S, 13.69. Found: C, 61.36; H, 4.26; S, 13.54.

3-Thienylphenylacetic Acid (10).—Into a 50-ml three-necked flask maintained at 20° and fitted with a thermometer and stirrer were added α-(3-thienyl)mandelic acid (**13**, 2.0 g, 8.85 mmol), stannous chloride (3.30 g, 0.0175 mol), water (0.68 ml, 0.0378 mol), and 28 ml of acetic acid. The flask was maintained at 15–22° for 15 min while hydrogen chloride was bubbled through the mixture. During this time essentially all the stannous chloride disappeared, and the mixture darkened considerably. The mixture was concentrated under reduced pressure and the residue was partitioned between water and ether. The aqueous layer was extracted with two portions of ether. The combined ether layers were washed with ten portions of water and two portions of brine and dried ($MgSO_4$). Evaporation left 1.44 g (78%) of solid, mp 85–87°. An analytical sample was obtained by recrystallization from benzene–hexane followed by sublimation at 80–83° (0.01 mm), mp 88.5–90°: ir (KBr) 1690 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 2.4–3.0 (m, 8, aromatic), 4.83 (s, 1, methine); nmr ($CDCl_3$) τ −1.8 (s, 1, CO_2H).

Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 66.05; H, 4.68; S, 14.43.

***4H*-Indeno[1,2-*b*]thiophene-4-carboxylic Acid (5).**—Into a 100-ml three-necked flask fitted with a reflux condenser and calcium chloride drying tube were added 15 ml of dry benzene and 100 g (4.27 mmol) of 3-thienylmandelic acid (**13**). The mixture was cooled below 0° and the 1.71 g (1.28 × 10^{-2} mol) of aluminum chloride was added in one portion *via* a Gooch tube. The resulting red mixture was refluxed for 3 hr; a continuous evolution of hydrogen chloride was observed. The mixture was cooled in an ice bath and decomposed with a mixture of ice, 10 ml of water, and 5.6 ml of 12 *M* hydrochloric acid. Trituration produced a white crystalline solid which was dissolved in ether. The aqueous phase was washed twice with ether. The combined ether solutions were extracted three times with 10% sodium carbonate. The basic solution was treated with Norite at 60–70°, filtered, cooled, and acidified with 12 *M* hydrochloric acid. The aqueous suspension was extracted three times with ether. The ether solution was washed three times with water and twice with brine and dried ($MgSO_4$). Evaporation left 0.84 g (91%) of solid, mp 167–178°. Recrystallization from benzene–hexane left 0.35 g (38%) of white crystalline solid, mp 209–210° (lit.[3] 212–213° dec). The nmr and ir spectra of this material were identical with those of an authentic specimen of **5** prepared as described in the literature.[3]

Registry No.—**5**, 23062-44-4; **6**, 27921-48-8; **8**, 27921-49-9; **9**, 27921-50-2; **10**, 16199-72-7; **11**, 27921-52-4; **13**, 3193-25-7.

Acknowledgment.—The authors wish to thank Messrs. Robert Smith, James Wisowaty, and Bruce Heitke for recording the nmr spectra.

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[16] M. Robba and R. Moreau, *Ann. Pharm. Fr.*, **23**, 103 (1965).

Studies in the Chemistry of Di-2-pyridylglyoxal

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Addition, disproportionation, and alkylation reactions of di-2-pyridylglyoxal are discussed. Two addition products, 1,2-diethoxy-1,2-dihydroxy-1,2-di(2-pyridyl)ethane dihydrochloride and 1,2-di(2-pyridyl)-1,1,2,2-tetrahydroxyethane dihydrochloride, were prepared and characterized. The tetrahydroxy derivative was found to be stable in the solid state for at least 3 months. However, it completely decomposed after being allowed to reflux 10 min in water under nitrogen. Picolinic acid, 2-pyridinemethanol, and considerable tar were isolated from the reaction mixture. Di-2-pyridylglyoxal is stable in ethanol but rapidly decomposes to give 1,2-di-2-pyridyl-1,2-ethenediol and ethyl picolinate when catalytic amounts of acid are added. Attempts to alkylate di-2-pyridylglyoxal with methyl iodide in either alcohol or nitrobenzene were unsuccessful. When alkylation was attempted in ethanol, disproportionation of the di-2-pyridylglyoxal occurred apparently under the catalytic influence of hydrogen iodide formed by the alcoholysis of the methyl iodide. A general mechanism for the acid-catalyzed disproportionation of di-2-pyridylglyoxal in either alcohol or water under acidic or basic conditions is discussed.

There are many recent reviews of the general chemistry of carbonyl compounds.[2,3] There are also specific treatments of the chemistry of heterocyclic carbonyl compounds.[4] It is interesting to note that the chemistry of pyridine aldehydes and ketones is sometimes quite different from that found with benzene analogs.

Pyridine carbonyl compounds, especially 2- (or 4-) substituted ones such as picolinaldehyde, isonicotinaldehyde, or their quaternary salts, undergo addition easily because of the electron-withdrawing power of the heterocyclic ring. Thus pyridoxal in the crystalline state is mainly in the form of the hemiacetal;[5] 2- (and 4-) formyl-1-methylpyridinium salts form stable hemiacetals and *gem*-glycols.[6] The 2-substituted hemiacetal readily cleaves on refluxing with aqueous sodium hydroxide.[7] 2-Formyl-1-methylpyridinium iodide forms an isolable hydroxylamine adduct which dehydrates on heating.[8]

It was reported that di-2-pyridylglyoxal (**1**) does not undergo the benzilic acid rearrangement in aqueous alkali but decomposes into picolinic acid (**2**) and a small amount of 2-pyridinemethanol (**3**) accompanied by liberation of ammonia.[9] Poziomek, Kronenberg, and Havinga[10] found that di-2-pyridylglyoxal decomposed in refluxing aqueous solution to give 1,2-di(2-pyridyl)-1,2-ethenediol (**4**), **2**, and traces of **3** and pico-

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