# The Synthesis, Structure Proof, and Spectral Properties of the Six Pyridylthiophenes[1]

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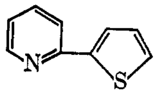
The synthesis and spectra of the six isomeric pyridylthiophenes are described. The 3-thienyl isomers (IV, V, and VI) could be prepared uniquely by reaction of the appropriate lithiopyridines with 3-ketotetrahydrothiophene and subsequent aromatization of the carbinols in over-all yields ranging from 2 to 10%. A specific synthesis for III (yield 2%) was accomplished starting from the 2-thienyl Grignard reagent and 1-benzoyl-4-chloro-1,4-dihydropyridine. II was obtained pure in 40% yield after chromatographic separation of the reaction mixture resulting from the interaction of the 3-pyridyl radical with thiophene, while I could be isolated in 1% yield from a mixture of two isomers obtained from the reaction of 2-thienylmagnesium iodide with pyridine. Their structures are proved by desulfurization to butylpyridines and by comparison of their proton magnetic resonance spectra with those of the phenylpyridines.

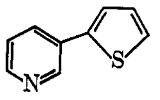
Since a reasonably large number of phenyl-, thienyl-, and alkyl-substituted thiophenes have been shown to undergo photochemical rearrangements,[2] we decided to prepare and study the pyridylthiophenes. The photochemical behavior of nitrogen-containing aromatic systems is of obvious intrinsic interest, and competition between photochemical reactions of the thiophene ring and those of the pyridine ring could be examined. To this end the six isomeric pyridylthiophenes were prepared and subjected to a variety of photochemical reaction conditions. Preliminary investigations with I, II, and III indicate that the normal[2] photochemical rearrangement in the thiophene ring does not obtain.

The present paper describes the synthesis of the isomers I–VI. Future communications will deal with some photochemical reactions.



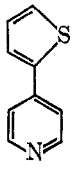
I

2-(2′-pyridyl)thiophene



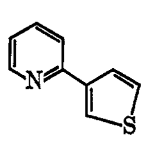
II

2-(3′-pyridyl)thiophene



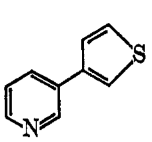
III

2-(4′-pyridyl)thiophene



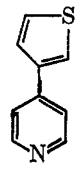
IV

3-(2′-pyridyl)thiophene



V

3-(3′-pyridyl)thiophene

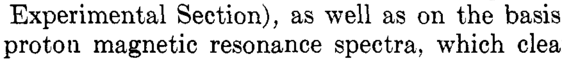


VI

3-(4′-pyridyl)thiophene

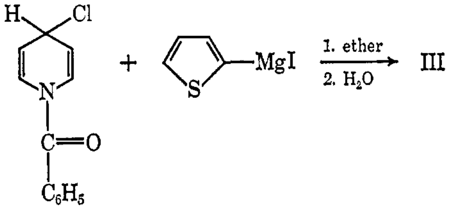
Although in principle a number of synthetic schemes are feasible we limited ourselves to a route involving coupling reactions between appropriately substituted intact thiophenes and pyridines.

**A. 2-(2′-Pyridyl)thiophene (I)[3] and 2-(4′-Pyridyl)thiophene (III).**—In 1964 Kahmann, Sigel, and Erlenmeyer[4] described the synthesis of a pyridylthiophene by addition of 2-thienylmagnesium bromide to pyridine and subsequent aromatization of the dihydro product at 160°. Repetition of their work with the Grignard reagent of 2-thienyl iodide and some other minor modifications (see Experimental Section) led to the isolation of a mixture of two pyridylthiophenes with melting points of 60.5–62 and 92–92.5° in a combined yield of 4%, separated by column chromatography.



Kahmann, Sigel, and Erlenmeyer ascribed to their pyridylthiophene, mp 90–91°, structure I. We have assigned structure I, 2-(2′-pyridyl)thiophene, to the low melting isomer and structure III, 2-(4′-pyridyl)thiophene, to the high melting isomer. This assignment appears unambiguous on the basis of desulfurization experiments to 2- and 4-*n*-butylpyridine, respectively (see Experimental Section), as well as on the basis of the proton magnetic resonance spectra, which clearly differentiate between a 2-substituted (I) and 4-substituted (III) pyridyl isomer (see Structure Proofs and Spectra).[5]

An independent synthesis of 2-(4′-pyridyl)thiophene (III) using 2-thienylmagnesium iodide and 1-benzoyl-4-



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[1] According to the usual nomenclature rules these ring systems should be called thienylpyridines. However, in order to stress the similarities and/or differences in the reaction of the thiophene ring, we prefer the nomenclature used in this paper.

[2] R. M. Kellogg and H. Wynberg, *Tetrahedron Lett.*, 5895 (1968).

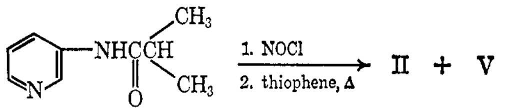
[3] Attempts to prepare I from pyridine and 2-thienyllithium, a route similar to the one used for the synthesis of 2-phenylpyridine and 2-*n*-butylpyridine [see K. Ziegler and H. Zieser, *Liebigs Ann. Chem.*, **485**, 174 (1931)], were all unsuccesfull.

[4] K. Kahmann, H. Sigel, and H. Erlenmeyer, *Helv. Chim. Acta*, **47**, 1754 (1964).

[5] Kahmann, *et al.*, assumed preferential 1,2 addition of the Grignard reagent to pyridine.[4] However, 1,4 addition, *e.g.*, of benzylmagnesium chloride and *n*-butylmagnesium bromide to pyridine, concomitant with 1,2 addition has been reported: R. A. Benkeser and D. S. Holton, *J. Amer. Chem. Soc.*, **73**, 5861 (1951); W. von E. Doering and V. Z. Pasternak, *ibid.*, **72**, 145 (1950). The formation of I and III in a similar reaction is consistent with such a 1,2 and 1,4 addition.

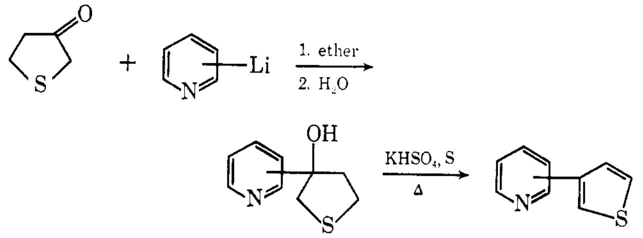
chloro-1,4-dihydropyridine was also carried out.[6] Although yields were low (2%), the product (III), mp 92.5–93.5°, was identical in all respects with that obtained *via* the 1,4 addition of the Grignard reagent.[7]

**B. 2-(3′-Pyridyl)thiophene (II).**—This substance was prepared using a modified Gomberg reaction generating the 3-pyridyl radical in thiophene.[8] Two



components in a ratio of 6:1 were obtained in a combined yield of 47%. Separation by preparative thin layer chromatography (tlc) yielded two pyridylthiophenes: an oil, bp 121–122° (0.4 mm), as the main product, and a solid of mp 72–74°. We assigned structure II, 2-(3′-pyridyl)thiophene, to the oil and structure V, 3-(3′-pyridyl)thiophene, to the solid on the basis of their spectral data and the desulfurization of II to 3-*n*-butylpyridine.

**C. 3-(2′-Pyridyl)thiophene (IV), 3-(3′-Pyridyl)thiophene (V), and 3-(4′-Pyridyl)thiophene (VI).**—A rational method for the preparation of the three substituted thiophene isomers in this series[9a,b] was found to be the reaction between 3-ketotetrahydrothiophene and the lithiopyridines.[9c,d] The crude inter-



mediate carbinols obtained in yields of 50–70% were dehydrated and aromatized in one step by heating with potassium hydrogen sulfate and sulfur.[9a]

The pyridylthiophene, mp 27–28°, obtained from 2-lithiopyridine[9c] in an over-all yield of 10% showed spectral properties consistent with an α-substituted pyridine ring. On the basis of spectral data (see Structure Proofs and Spectra) we assigned structure IV, 3-(2′-pyridyl)thiophene, to it.

Another isomer, mp 75–76.5°, was isolated in the same over-all yield starting from 3-lithiopyridine.[9c] This material was identical in all respects with the minor product obtained from synthesis B and gave spectra agreeing with V, 3-(3′-pyridyl)thiophene. Desulfurization produced 3-*sec*-butylpyridine.

When 4-lithiopyridine[9d] was used as a starting material a pyridylthiophene, mp 138.5–139°, was obtained in an over-all yield of 2%. Its spectral properties were characteristic for a 4-substituted pyridine ring and were consistent with those expected for 3-(4′-pyridyl)thiophene (VI).

**Structure Proofs and Spectra.**—The assignment of the structures to the six isomers (I–VI) is based on three pieces of evidence: (a) the method of synthesis, (b) the identification of the desulfurization products, and (c) the spectra—especially pmr spectra—of the pyridylthiophenes themselves.

**Identification of the Desulfurization Products.**—The desulfurization products of I, II, and III (2-, 3-, and 4-*n*-butylpyridine, respectively) showed aliphatic pmr absorptions identical with those of separately prepared 2-*n*-butylpyridine[3] and aromatic absorption patterns identical with those reported for 2-, 3-, and 4-methylpyridine,[10a] respectively. Upon desulfurization V furnished 3-*sec*-butylpyridine. Its pmr spectrum was compared with that of 3-methylpyridine (aromatic region identical) and *sec*-butyl alcohol and *sec*-butylamine (aliphatic region identical).

The ultraviolet (uv) spectra of these four desulfurization products were virtually indistinguishable from one another.

**Pmr Spectra (Table I).**—The chemical shift and splitting patterns of the α-pyridyl hydrogen atoms of a monosubstituted pyridine ring are characteristic for the place of the substituent.[10] Therefore we compared these absorptions of the pyridylthiophenes with those of the phenylpyridines[3,6,8] prepared in our laboratory (see Table I). A close similarity between the spectra of I and IV, II and V, and III and VI with 2-, 3-, and 4-phenylpyridine, respectively, is evident.

TABLE I

PROTON MAGNETIC RESONANCE SPECTRA[a]

| Compd | α-Pyridyl hydrogen atoms | Other hydrogen atoms |
|---|---|---|
| I | 1.4[b] (t[c]–t) (1)[d] | 2.3–3.1 (m) (6) |
| II | 1.1 (d) (1) | 2.2–2.4 (t–t) (1) |
| | 1.5 (d–d) (1) | 2.7–3.1 (m) (4) |
| III | 1.5 (d–d) (2) | 2.5–2.7 (m) (4) |
| | | 2.8–3.1 (d–d) (1) |
| IV | 1.5 (t–t) (1) | 2.1–3.1 (m) (6) |
| V | 1.3 (d) (1) | 2.1–2.4 (t–t) (1) |
| | 1.6 (d–d) (1) | 2.5–3.0 (m) (4) |
| VI | 1.6 (d–d) (2) | 2.4–2.8 (m) (5) |
| 2-Phenylpyridine[e] | 1.4 (t–t) (1) | 2.1–2.3 (m) (8) |
| 3-Phenylpyridine[f] | 1.4 (d) (1) | 2.1–2.3 (t–t) (1) |
| | 1.6 (d–d) (1) | 2.4–2.9 (m) (6) |
| 4-Phenylpyridine[g] | 1.5 (d–d) (2) | 2.3–2.7 (m) (7) |

[a] Measured in carbon tetrachloride against tetramethylsilane as an internal standard. [b] τ values. [c] t, triplet; m, multiplet; d, doublet; s, singlet. [d] Number of hydrogen atoms. [e] Reference 3. [f] Reference 8. [g] Reference 6.

**Uv Spectra (Table II).**—Interesting changes are apparent when the uv spectra of the pyridylthiophenes and their pyridinium ions are compared. In accordance with expectations and the spectral changes in the

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(6) This is a method for the preparation of 4-phenylpyridine: J. E. Lowman, Doctoral dissertation, Columbia University, 1948, cited in E. Klingsberg, "Heterocyclic Compounds, Pyridine," Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1961, p 220.

(7) These structure proofs make it clear that the conclusions of Kahmann, *et. al.*, concerning the ability of aromatic bonded sulfur to participate in chelate formation[4] need revision.

(8) 3-Phenylpyridine was obtained in 39% yield from an identical procedure carried out in benzene: H. Rapoport, M. Look, and G. J. Kelly, *J. Amer. Chem. Soc.*, **74**, 6293 (1952).

(9) (a) H. Wynberg, A. Logothetis, and D. Verploeg, *ibid.*, **79**, 1972 (1957); (b) J. Szmuszkovicz and E. J. Modest, *ibid.*, **72**, 571 (1950); (c) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951); (d) J. P. Wibaut and L. G. Heeringa, *Rec. Trav. Chim. Pays Bas*, **74**, 1003 (1955).

(10) (a) H. J. Bernstein and W. G. Schneider, *J. Chem. Phys.*, **24**, 469 (1956). (b) A 2-pyridyl ring shows one α-pyridyl hydrogen atom; a 3-pyridyl ring has two low-field protons with different chemical shifts and splitting patterns; two α-pyridyl hydrogen atoms with a clear doublet-doublet pattern are characteristic for a 4-substituted pyridine ring. (c) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book, Co., New York, N. Y., 1959, p 266.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA

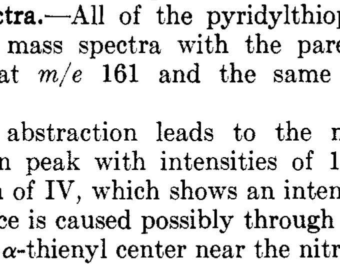
| Compd | In 96% ethanol, $\lambda_{max}$, mμ (ε) | In 2 *N* hydrochloric acid, $\lambda_{max}$, mμ (ε) |
|---|---|---|
| I | 303 (13,200) | 334 (15,300) |
| | 262 (7,800) | 268 (6,700) |
| II | 287 (13,100) | 295 (10,700) |
| | 262 (sh)[a] (8,600) | 242 (8,400) |
| III | 295 (15,900) | 335 (20,300) |
| | 266 (8,400) | 275 (5,400) |
| | 226 (5,200) | 239 (5,200) |
| IV | 285 (8,500) | 312 (11,800) |
| | 255 (10,100) | 253 (7,200) |
| | 228 (11,200) | |
| V | 259 (13,700) | 305 (sh) (4,600) |
| | 227 (12,900) | 265 (13,200) |
| | | 228 (sh) (12,800) |
| | | 221 (14,800) |
| VI | 268 (16,400) | 307 (17,100) |
| | 228 (11,300) | 270 (sh) (8,000) |
| | | 245 (3,800) |
| 2-Phenylpyridine[b] | 277 (8,900) | 295 (13,800) |
| | 244 (11,100) | 242 (8,700) |
| 3-Phenylpyridine[c] | 275 (sh) (6,100) | 285 (sh) (5,900) |
| | 246 (13,700) | 255 (11,100) |
| | | 232 (13,400) |
| 4-Phenylpyridine[d] | 256 (16,000) | 288 (16,900) |

[a] sh, shoulder. [b] Reference 3. [c] Reference 8. [d] Reference 6.

phenylpyridines,[11] a considerable greater bathochromic shift is observed for the 2 and 4 isomers than for the 3 isomer upon going from the pyridyl compounds to the pyridinium ions. Conjugation interaction between the nitrogen atom and the second aryl ring is not possible for 3-substituted pyridines. This effect becomes more important in the protonated species owing to a more electron-attracting nitrogen center. In addition this effect is more pronounced in the pyridylthiophenes than in the phenylpyridines because of a greater electron-donating effect of the thiophene ring.

**Mass Spectra.**—All of the pyridylthiophenes show very similar mass spectra with the parent peak (is base peak) at $m/e$ 161 and the same degradation fragments.

Hydrogen abstraction leads to the most intense fragmentation peak with intensities of 12–20% with the exception of IV, which shows an intensity of 51%. This difference is caused possibly through the presence of a reactive α-thienyl center near the nitrogen atom.[12]



Other fragments in less than 15% of the highest intensity are found at $m/e$ 135 ($M - C_2H_2$), 134 ($M - HCN$), 128 ($M - HS$), 117 ($M - CS$), 108 ($M - C_3H_3N$), and 116 ($M - HCS$ or $160 - CS$). Correct metastable peaks are present for the formation of the first five fragments out of the parent ion.

## Experimental Section

Melting points were determined with a Reichert melting point microscope and are uncorrected. Ultraviolet spectra were recorded on a Zeiss PMQ II spectrophotometer. Pmr spectra were taken on a Varian A-60 spectrometer in carbon tetrachloride with tetramethylsilane as an internal standard and are reported in τ values. An A.E.I. MS 902 mass spectrometer equipped with an all-glass heated inlet system at 150° was used. The ionization potential and current were 70 eV and 100 μA. Microanalysis were performed by the analytical department of our laboratory under the supervision of Mr. W. M. Hazenberg.

A. **2-(2'-Pyridyl)- and 2-(4'-Pyridyl)thiophene (I and III).**—A Grignard solution free from magnesium turnings was prepared in the usual manner using 42 g (0.22 mol) of 2-iodothiophene[13] in 130 ml of dry ether. To this well-stirred solution under nitrogen atmosphere kept at room temperature was added dropwise a solution of 20.5 g (0.25 mol) of dry pyridine in 100 ml of dry ether. A white precipitate formed immediately. Stirring was continued for 20 min and the ether was evaporated while keeping the volume constant by adding 250 ml of dry xylene. Refluxing the mixture for 20 hr yielded two separate layers. Hydrolysis with a concentrated ammonium chloride solution, extraction of the organic layer with dilute hydrochloric acid, and subsequent steam distillation removed all volatile nonbasic components. The residue was made alkaline and a second steam distillation yielded 1.4 g (4%) of colorless crystals. Glpc and tlc showed that even after recrystallization from petroleum ether (bp 40–60°) a mixture of to components was present in a ratio of 1:3. Chromatography over a silica gel column yielded 2-(2'pyridyl)-thiophene (I), mp 60.5–62° [recrystallized from petroleum ether (bp 40–60°)], with benzene as eluent and 2-(4'-pyridyl)thiophene (III), mp 92–92.5° [recrystallized from petroleum ether (bp 40–60°)] as the major product with ether as eluent.

*Anal.* Calcd for $C_9H_7NS$: C, 67.12; H, 4.38; N, 8.68; S, 19.92. Found for I: C, 66.61; H, 4.31; N, 8.46; S, 19.84. Found for III: C, 66.71; H, 4.27; N, 8.59; S, 19.92.

**2-(4'-Pyridyl)thiophene (III).**—A Grignard solution free from magnesium turnings was prepared using 72 g (0.34 mol) of 2-iodothiophene[13] and 9.7 g (0.34 g-atom) of magnesium, both in 100 ml of dry ether. This solution was kept under a dry nitrogen atmosphere and added dropwise to ice-cooled, well-stirred crude 1-benzoyl-4-chloro-1,4-dihydropyridine obtained by heating 27 g (0.34 mol) of dry pyridine, 49 g (0.34 mol) of freshly distilled benzoylchloride, and 0.7 g of copper powder.[14] A thick green precipitate was formed which prevented further stirring. The mixture was refluxed for 14 hr, hydrolyzed, and extracted with dilute hydrochloric acid solution. The acid layers were steam distilled to remove all nonbasic volatile organic components and the residue was made alkaline. Another steam distillation yielded 1 g (2%) of 2-(4'-pyridyl)thiophene (III), mp 92.5–93.5° [recrystallized from petroleum ether (bp 40–60°)]. The mixture melting point with the material obtained above was 92.5–93.5°.

B. **2-(3'-Pyridyl)thiophene (II).**—The reaction was carried out as described by Rapoport, *et al.*, for 3-phenylpyridine[8] replacing benzene by thiophene. The thiophene was removed by distillation and the residue was extracted with dilute hydrochloric acid solution. The acid extracts were steam distilled to remove all volatile nonbasic compounds. The residue was made alkaline with sodium hydroxide and submitted to a second steam distillation. The distillate was extracted with ether and the extracts were dried ($CaCl_2$). After evaporation of the solvent the residue upon distillation furnished 13.9 g (0.08 mol, 47%) of an oil [bp 102–111° (1.9 mm)] consisting of two components (ratio of 1:6, glpc). With preparative tlc on silica gel (Merck, PF-254) and a petroleum ether (bp 40–60°)-acetone mixture (4:1) as eluent, pure 2-(3'-pyridyl)thiophene (II), bp 121–122° (4.0 mm), $n^{20}{}_D$ 1.6502, could be obtained as the major product. A second fraction consisting of a 1:1 mixture of both components yielded 3-(3'-pyridyl)thiophene (V), mp 72–74°, upon two recrystallizations from an excess of petroleum ether (bp 40–60°). This material still contained 2.5% II (estimated from glpc).

*Anal.* Calcd for $C_9H_7NS$: C, 67.12; H, 4.38; N, 8.68; S, 19.92. Found for II: C, 67.11; H, 4.42; N, 8.53; S, 20.09. Found for V: C, 67.01; H, 4.46; N, 8.48; S, 19.60.

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[11] P. Krumholz, *J. Amer. Chem. Soc.*, **73**, 3487 (1951); G. Favini, *Gazz. Chim. Ital.*, **93**, 635 (1963).

[12] In comparison with 2-alkylpyridines: H. Budzikiewicz, C. Djerassi, and D. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 566.

[13] W. Minnis, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1950, p 35 ff.

[14] E. Koenigs and E. Ruppolt, *Liebigs Ann. Chem.*, **509**, 142 (1934).

**C. 3-(2′-Pyridyl)-, 3-(3′-Pyridyl)-, and 3-(4′-Pyridyl)thiophene (IV, V, and VI).**—Over a period of 15 min a solution of 10 g (0.063 mol) of bromopyridine in 25 ml of dry ether was added to a well-stirred solution of 0.063 mol of *n*-butyllithium in 32 ml of hexane diluted with 100 ml of dry ether under a nitrogen atmosphere. During the addition the temperature was maintained between −75 and −60°. After a second 15-min period of stirring, a solution of 6.4 g (0.063 mol) of 3-ketotetrahydrothiophene[15] in 25 ml of dry ether was added in 15 min. The stirring of the gray suspension was continued for another 15-min period raising the temperature to −40°. The reaction mixture was poured into 100 ml of water and the aqueous layer was extracted with ether (in the case of the 4-pyridyl compound chloroform must be used). The combined organic layers were dried (CaCl$_2$) and the solvent was evaporated. Removal of unused ketone through distillation at the water pump [up to 85° (20 mm)] left 6.0–8.0 g (0.033–0.044 mol, 52–70%) of a viscous oil (for the 4-pyridyl compound a solid), mainly the tertiary carbinol.

This oil was heated with 2.5 g of sulfur and 2.0 g of KHSO$_4$. At 160° water began to distil from the reaction mixture and hydrogen sulfide was evolved. The heating was continued for 30 min and the temperature was slowly raised to 225°. Steam distillation of the reaction mixture yielded crystalline plates of 3-(3′-pyridyl)- and 3-(4′-pyridyl)thiophene (V and VI). With the 2-pyridyl compound an oil was obtained, which was further purified through preparative tlc on silica gel (Merck PF-254) with chloroform as eluent to remove some unchanged carbinol. Distillation furnished an analytical sample of 3-(2′-pyridyl)-thiophene (IV), bp 93–95° (0.45 mm). See Table III for analytical data.

**Bromopyridines.**—The 2- and 3-bromopyridines were commercially available. The unstable[16] 4-brompyridine was obtained from the commercially available hydrogen chloride salt through addition of an equimolar amount of concentrated sodium hydroxide solution at 0°. Extraction with ether, drying of the organic layers (Na$_2$SO$_4$), and evaporation of the solvent below 30° yielded almost pure 4-bromopyridine. Because of its instability, it was used immediately for further reactions.

**Desulfurizations.**—The desulfurizations were accomplished by refluxing the individual highly purified pyridylthiophenes (I, II, III, and V) with 10 times their weight of Raney nickel W-5[17] in absolute ethanol for 30 min. The Raney nickel was removed by filtration through a glass filter and was washed carefully with absolute ethanol. The concentrated filtrates were dissolved in ether and dried (CaCl$_2$). Evaporation of the solvent yielded a crude oil giving pmr spectra (Table IV) consistent with butylpyridines (25–70%).

Table III

| Compd | Mp, °C | Overall yield, % | Analysis, % Found C | H | N | S |
|---|---|---|---|---|---|---|
| IV | 27–28 | 10 | 67.16 | 4.50 | 8.59 | 19.71 |
| V | 75–76.5 | 10 | 66.70 | 4.39 | 8.59 | 19.94 |
| VI | 138.5–139 | 2 | 66.99 | 4.41 | 8.62 | 19.75 |
| | | | Calcd for C$_9$H$_7$NS | | | |
| | | | 67.12 | 4.38 | 8.68 | 19.92 |

Table IV

| Desulfurization product of | Pmr spectra Aromatic | Alkyl |
|---|---|---|
| I | 1.7 (t–t) (1), 2.2–3.2 (m) (3) | 7.2 (t) (2), 8.0–8.9 (m) (4), 9.0 (t) (3) |
| II | 1.7 (s) (2), 2.5–3.2 (m) (2) | 7.5 (t) (2), 8.2–8.9 (m) (4), 9.1 (t) (3) |
| III | 1.7 (d) (2), 3.1 (d) (2) | 7.6 (t) (2), 8.1–8.8 (m) (4), 9.1 (t) (3) |
| V | 1.7 (s) (2), 2.4–3.1 (m) (2) | 7.2 (m) (1), 8.0–8.8 (m) (5), 9.0 (t) (3) |

**Registry No.**—I, 3319-99-1; II, 21298-53-3; III, 21298-54-4; IV, 21298-55-5; V, 21308-81-6; VI, 21308-82-7; 2-phenylpyridine, 1008-89-5; 3-phenylpyridine, 1008-88-4; 4-phenylpyridine, 939-23-1.

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# An Unusually Facile Anilide Ethanolysis

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Refluxing ethanol promptly converts the 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilides (Ia–e) into ethyl 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxylate (II) in good yields. The facility with which this ethanolysis occurs appears to be related to the higher energy state of I relative to II. Lack of enol character of I, presumably due to steric hindrance, and the hydrogen-bonded stabilization of its enolate anion (V) impart substantial acidic character to this molecule, and this property provides the proton which is believed to catalyze the ethanolysis.

Treatment of carboxylic acid esters with amines is generally a convenient method for the preparation of amides.[1] Alcohols, which often facilitate this reaction,[2,3] are generally considered to be sufficiently poor nucleophiles as to allow the intermediate tetrahedral complex formed by nucleophilic attack of an amine on carbonyl carbon to lead, irreversibly, to amide formation.[4] Furthermore, the inertness of alcohols toward amides and anilides frequently suggests their use as recrystallization solvents.[5]

Quite unexpectedly, therefore, in the course of purifying 2′-chloro-2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (Ib) it was discovered that refluxing ethanol converted this substance into ethyl 2-methyl-1,3-(2H,4H)-dioxoisoquinoline-4-carboxylate (II) in a yield of better than 90% and this unusual alcoholysis was subsequently found to be characteristic for related anilides (Table I). To gain insight into the mechanism of this uncommon and extraordinarily facile reaction, the physical properties of these anilides and related substances were investigated.

The 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-car-

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