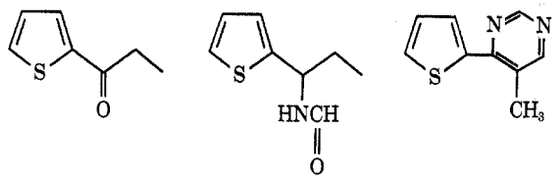
4-(2-Thienyl)-5-methylpyrimidine. An Anomalous Leuckart Product

DAVID T. HILL AND BERNARD LOEV*

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101

Received February 7, 1973

The Leuckart reaction is a well-known procedure for the direct conversion of aldehydes and ketones to primary amines upon heating with formic acid or certain of its derivatives.[1] When this reaction is carried out using 2-propionylthiophene (**1**) and formamide, one obtains in addition to the expected 1-(2-thienyl)-1-aminopropane,[2,3] a minor product I, mp 74–76°, previously[2] assigned the *N*-formyl structure **2**. The correct structure of I has now been determined to be the thienyl-substituted pyrimidine **3**.



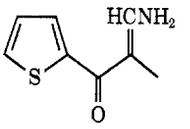
1 **2** **3**

N-Formyl derivatives are frequently obtained as by-products in the Leuckart reaction,[4] but the formation of pyrimidines in this reaction has not previously been reported. Authentic **2**, bp 121–122° (0.6 mm), has now also been prepared.

Doubts concerning the assigned structure of I were raised by the absence of a carbonyl absorption in the ir spectrum. The mass spectrum of I indicated a molecular ion of 176 rather than the expected peak of 169 and a parent M − 1 peak of 175 with little further significant fragmentation. These data, coupled with the elemental analysis, gave a molecular formula of $C_9H_8N_2S$. The nmr spectrum showed two low-field singlets at δ 9.03 and 8.58, a complex aromatic resonance centered at 7.38 due to the thienyl protons, and an aromatic methyl singlet at 2.53 in a ratio of 1:1:3:3. The low-field singlets are characteristic of pyrimidine resonances and the chemical shifts (see Experimental Section) are virtually identical with those found for 5-methylpyrimidine.[5a] Further, the aromatic portion of the nmr spectrum is qualitatively similar to the published spectrum of 4-(2-thienyl)-5-bromopyrimidine.[6] These data are consistent only with structure **3**.

4-(2-Thienyl)-5-methylpyrimidine (**3**) has not previously been reported; however, certain analogs have been synthesized by the acid-catalyzed condensation of formamide with 2-thienyl ethynyl ketone[7] or by the addition of 2-thienyllithium across the azomethine bond of the appropriate pyrimidine followed by oxidation.[6,8] Other pyrimidines have been prepared by the reaction of formamide with aromatic ketones possessing an active methylene group, but only in the presence of strong acids.[5a,9]

The formation of pyrimidine **3** during the Leuckart reaction may proceed *via* intermediate **4**, formed as a result of condensation catalyzed by small amounts of formic acid that may be liberated during the reaction, followed by further condensation of **4** with formamide.[10]



4

This suggests that pyrimidines may also have been formed as by-products in other Leuckart reactions but, being very much higher boiling, have been discarded with the distillation residues and hence have not been previously observed.

Experimental Section[12]

1-(2-Thienyl)-1-aminopropane and 4-(2-Thienyl)-5-methylpyrimidine (3).—A mixture of 56 g (0.4 mol) of 2-propionylthiophene (Columbia Organic Chemical Co.) and 72 g (1.6 mol) of formamide was heated at 180–190° under N_2 for 24 hr. Ammonium carbonate (13.2 g) sublimed into the condenser and was periodically removed. The reaction mixture was cooled to room temperature, 200 ml of 30% sodium hydroxide solution was added, and the mixture was again heated at reflux. After 10 hr the mixture was cooled and extracted with ether and the combined ether extracts were washed with water and then 50% hydrochloric acid. The acidic solution was rendered alkaline with aqueous sodium hydroxide and extracted with ether and the combined ether extracts were dried ($MgSO_4$). After removal of the solvent, the residual oil (48.3 g) was fractionated to give 35.4 g (63%) of 1-(2-thienyl)-1-aminopropane: bp 45–48° (1.2 mm); $n^{25}D$ 1.5330 [lit.[2] bp 89–91° (13 mm)]; nmr ($CDCl_3$) δ (TMS) 7.08 (m, 3, ArH), 4.10 (t, 1, methine), 1.75 (m, 2, J = 7.5, 6.8 Hz, $-CH_2-$), and 0.91 (t, 3, J = 7.5 Hz, $-CH_3$).

Further fractionation gave 7.4 g (11%) of 4-(2-thienyl)-5-methylpyrimidine (**3**): bp 104–105° (1.2 mm); mp 74–76° (needles from ethanol) [lit.[2] (erroneously assigned structure **2**) bp 174–178° (12 mm), mp 75–76°]; nmr ($CDCl_3$) δ (TMS) 9.03 (s, 1, pyrimidine H_2), 8.58 (s, 1, pyrimidine H_4), 7.83–7.08 (m, 3, thiophene H), and 2.53 ppm (s, 3, $-CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 178 (5), 177 (15), 176 (98), 175 (100), 148 (8), 131 (8), 121 (9).

Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.89. Found: C, 61.34; H, 4.61; N, 15.78.

Compound **3** readily forms salts: hydrochloride, mp 237–239° (from ethanol) (lit.[2] mp 234–235°); picrate, mp 195–197° (from ethanol).

***N*-[1-(2-Thienyl)]propylformamide (2).**—A mixture of 2.00 g (14.1 mmol) of 1-(2-thienyl)-1-aminopropane and 1.82 g (16

(1) R. Leuckart, *Chem. Ber.*, **18**, 2341 (1885); for other references see M. L. Moore, *Org. React.*, **5**, 301 (1949).

(2) F. F. Blicke and J. H. Burckhalter, *J. Amer. Chem. Soc.*, **64**, 477 (1942).

(3) M. Bellenghi, *et al.*, *Gazz. Chim. Ital.*, **82**, 773 (1952).

(4) H. E. Smith and V. Rajevsky, *J. Heterocycl. Chem.*, **5**, 715 (1968).

(5) (a) T. J. Batterham in "The Pyrimidines," Vol. 16, Suppl. 1, O. Weissberger and E. C. Taylor, Ed., Wiley-Interscience, New York, N. Y., 1970, p 368; (b) *ibid.*, p 60.

(6) S. Gronowitz and J. Roe, *Acta Chem. Scand.*, **19**, 1749 (1965).

(7) H. Bredereck, R. Gompper, and H. Herlinger, *Chem. Ber.*, **91**, 2832 (1958).

(8) S. Gronowitz and J. Boler, *Ark. Kemi*, **28**, 587 (1967); T. Kauffmann, P. Bandi, W. Brinkwerth, and P. Greving, *Angew. Chem., Int. Ed. Engl.*, **11**, 848 (1972).

(9) H. Bredereck, R. Gompper, H. Schuh, and G. Theilig, "Newer Methods of Preparative Organic Chemistry," Vol. 3, W. Foerst, Ed., Academic Press, New York, N. Y., 1964, p 241.

(10) A number of mechanistic pathways are possible; however, on the basis of current ideas concerning the mechanism of the Leuckart reaction[11] this route seems to be the most likely.

(11) A. Lukasiewicz, *Tetrahedron*, **19**, 1789 (1963).

(12) Melting and boiling points are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Jeolco C60H model spectrometer and mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. We wish to thank Miss M. Carroll, Dr. E. White, and Mr. R. Warren and coworkers of the Analytical and Physical Chemistry Section, Smith Kline & French Laboratories, for the elemental analyses, mass spectra, and nmr spectra.

mmol) of ethyl formate was refluxed for 12 hr. All volatiles were removed at reduced pressure, the residual oil was dissolved in methylene chloride, washed with dilute hydrochloric acid, then water, and the organic phase was dried ($MgSO_4$). The solvent was removed and the residual oil was distilled, giving 1.39 g (58%) of formamide **2**: bp 121–122° (0.6 mm); $n^{25}D$ 1.5433; ir (neat) 1675 (amide C=O) and 3290 cm^{-1} (amide NH); nmr ($CDCl_3$) δ (TMS) 8.15 (s, 1, HCON), 7.13 (m, 3, ArH), 6.75 (m, 1, NH), 5.23 (m, 1, J = 16.5, 7.5 Hz, CH), 1.87 (m, 2, J = 7.5 Hz, $-CH_2-$), and 0.93 ppm (t, 3, J = 7.5 Hz, $-CH_3$); mass spectrum (70 eV) m/e (rel intensity) 169 (30), 140 (100), 113 (36), 97 (7), 85 (25).

Anal. Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.60; H, 6.43; N, 8.44.

Addition of deuterium oxide and a trace of trifluoroacetic acid to the nmr solution ($CDCl_3$) resulted in the complete loss of the peak at δ 6.75 due to the amide proton and the collapse of the methine AB quartet at δ 5.23 to a triplet, J = 7.5 Hz.

Registry No.—**1**, 13679-75-9; **2**, 39207-57-4; **3**, 39204-58-5; **3** picrate, 39204-59-6; 1-(2-thienyl)-1-aminopropane, 6315-55-5; formamide, 75-12-7; ethyl formate, 109-94-4.

Preparation and Purification of Tetrasodium *meso*-Tetra(*p*-sulfophenyl)porphine. An Easy Procedure[1]

TAPESHWARI S. SRIVASTAVA AND MINORU TSUTSUI*[2]

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received October 27, 1972

Tetraphenylporphine sulfonate was first reported by Winkelman, who studied localization of this compound in tumors. He found that it could be localized with a higher concentration ratio in animal tumors than in other tissues.[3,4] It was later found that Winkelman's sample is, in fact, a mixture of various isomers.[5] The sodium salt of *meso*-tetra(*o*-sulfophenyl)porphine was recently prepared in low yield by condensing pyrrole and benzaldehyde sulfonic acid (sodium salt) in *n*- or *tert*-butyl alcohol in the presence of sodium acetate.[6] *meso*-Tetra(*p*-sulfophenyl)porphine was prepared by heating *meso*-tetraphenylporphine and concentrated sulfuric acid on a steam bath for 4 hr. The diacid was precipitated by adding the requisite amount of water. The tetraammonium salt was precipitated by dissolving the diacid in methanolic ammonia and then adding acetone. Further purification of the tetraammonium salt was carried out by a cumbersome procedure involving six successive reprecipitations from a methanolic solution with acetone. The tetraammonium salt of *meso*-tetra(*p*-sulfophenyl)-porphine was further converted to the tetrasodium salt by treating the former with sodium methoxide.[4] We wish to report an easy preparation and purification procedure for the tetrasodium *meso*-tetra(*p*-sulfophenyl)porphine (60% yield).

(1) Unusual Metalloporphyrins. XVI.
(2) To whom correspondence should be addressed.
(3) J. Winkelman, *Cancer Res.*, **22**, 589 (1962).
(4) J. Winkelman, *Experientia*, **23**, 949 (1967).
(5) E. B. Fleischer, J. M. Palmer, T. S. Srivastava, and A. Chatterjee, *J. Amer. Chem. Soc.*, **93**, 3162 (1971).
(6) A. Triebs and N. Haverle, *Justus Liebigs. Ann. Chem.*, **718**, 183 (1968).

Experimental Section

Finely powdered *meso*-tetraphenylporphine (2 g)[7] was mixed with 50 ml of concentrated sulfuric acid. The mixture was heated on a steam bath for 4–5 hr. After cooling to room temperature, the solution was filtered through a sintered glass frit and the filtrate was diluted carefully to 1. The dilute solution was heated and a sludge of lime was added slowly with stirring until the solution changed to a permanent purple color. Calcium sulfate was filtered off and washed with a minimum quantity of hot water, which was then combined with the filtrate. Crushed Dry Ice was added to the filtrate and was filtered. The filtrate was concentrated to a small volume (about 100 ml) and the pH of the final warm solution was regulated at 8–10 by adding the required quantity of concentrated sodium carbonate solution. Calcium carbonate was removed by filtration and washed with water, which was then combined with the filtrate. Hot ethanol (90%) in small quantities was periodically added to the filtrate, which was further concentrated on a steam bath. The saturated solution was cooled at room temperature and crystals of tetrasodium *meso*-tetra(*p*-sulfophenyl)porphine (I) were obtained. They were filtered off and washed with a minimum quantity of cold 90% ethanol. Finally the material was dried at 100° for 1 hr. The water content in compound I was determined by heating it under vacuum at 140° for 15 hr. I has an empirical formula of $C_{44}H_{50}N_4O_{24}S_4Na_4$ with 12 water molecules. *Anal.*[8] Calcd for $C_{44}H_{26}N_4O_{12}S_4Na_4 \cdot 12H_2O$: N, 4.50; S, 10.29. Found: N, 4.54; S, 10.55. The compound is very soluble in water. The visible spectrum of I (H_2O) shows five peaks at 413 (soret), 506 (I), 543 (II), 570 (III), and 634 (IV) nm (rel intensity I > II > III > IV). The ir spectrum of I (KBr) shows four strong bands at 1226, 1194, 1134, and 1046 cm^{-1} due to sulfonic acid (salt) absorption[9] in addition to free porphyrin vibrations. The ^1H nmr (T-60 Varian Associates) of I (D_2O) shows pyrrole protons at δ 7.51 and two doublets due to protons of phenyl groups centered at δ 6.85 and 7.85 with a coupling constant of 8 Hz.[4] The ratio of peak areas of pyrrole protons and phenyl protons is 1:2. This excludes the possibility of substitution of the pyrrole protons and supports the substitution of the phenyl protons by four sulfonate groups. Furthermore, the presence of the two doublets at δ 6.85 and 7.85 in the ^1H nmr of I shows clearly that four sulfonate groups are substituted only at para positions of the phenyl groups.

Registry No.—Tetrasodium *meso*-tetra(*p*-sulfophenyl)porphine, 39050-26-5; *meso*-tetraphenylporphine, 917-23-7.

Acknowledgment.—This work was supported by NSF (Grant No. GP-28685). We thank Dr. James Francis for valuable discussions.

(7) A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour, and T. Korsakoff, *J. Org. Chem.*, **32**, 476 (1967).
(8) Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. 11377.
(9) N. B. Colthup, L. H. Daly, and S. E. Wilberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964.

The Rearrangement of α-Ethynyl Alcohols to Unsaturated Carbonyl Compounds (The Rupe Reaction)

RICHARD W. HASBROUCK* AND ANN D. ANDERSON KIESSLING[1]

Department of Chemistry, Central Washington State College, Ellensburg, Washington 98926

Received December 5, 1972

The identity of the products from, and the mechanism of, the Rupe reaction has been debated in the

(1) Abstracted in part from the M.S. thesis of A. D. Anderson, Central Washington State College, Aug 1967. The Research Corporation provided funds that allowed Miss Anderson's work.