[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Sulfur Analogs of Isoquinolines

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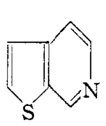
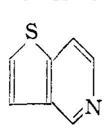
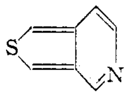
If the benzene ring of isoquinoline is replaced by a thiophene nucleus, three thienopyridines, all isosteres of isoquinoline, are obtained: thieno(2,3-c)-pyridine (I), thieno(3,2-c)pyridine (II) and thieno-(3,4-c)pyridine (III). The only representative of this class of compounds which the literature appears to record is 1,3-dimethyl-7-hydroxythieno-(3,2-c)pyridine,[1] prepared as an intermediate in the route to the corresponding thiopyrindigo. In view of the pronounced physiological effects exhibited by a number of naturally-occurring and synthetic isoquinolines, the synthesis of model compounds containing these ring systems appeared to be of interest. This communication reports the preparation of several 1-substituted derivatives of I and II. Experiments aimed at the synthesis of the parent substances are being undertaken.



I



II



III

The synthesis of compounds of type II was accomplished by use of the Bischler–Napieralski[2] reaction which had previously been found applicable in the thianaphthene series.[3] Barger and Easson[4] reported that they were unable to prepare a tetrahydroisoquinoline analog by condensation of β-2-thienylethylamine with formaldehyde. It has been found now that the acetyl and benzoyl derivatives of this amine may be cyclized in fair yield, using the method recommended by Whaley and Hartung.[5] The resulting 1-substituted 3,4-dihydrothieno(3,2-c)pyridines were converted to the aromatic compounds by dehydrogenation with palladium black.

1-Phenylthieno(2,3-c)pyridine, a representative of type I, was synthesized in essentially the same manner. 3-Bromoethylthiophene, prepared by the bromination of 3-methylthiophene with N-bromosuccinimide,[6] was converted to 3-thienylacetonitrile. Although Campaigne and LeSuer[6a] had isolated 3-thiopheneacetic acid by hydrolysis of the mixture obtained on reaction of 3-bromomethylthiophene with sodium cyanide, the low yields made it desirable to establish even more conclusively the absence of an allylic rearrangement observed previously on treatment of 2-[7] and 3-chloromethylfuran[8] with cyanide. Such a rearrangement in the thiophene series would have resulted in the formation of 3-methyl-2-thenylamine instead of the desired β-3-thienylethylamine on reduction with lithium aluminum hydride. However, the acetyl and benzoyl derivatives of our product were quite different from the corresponding derivatives of 3-methyl-2-thenylamine, the latter product being obtained from a Mannich reaction between 3-methylthiophene, formaldehyde and ammonium chloride.[9] The structure of β-3-thienylethylamine may, therefore, be regarded as established.

N-Acetyl- and N-benzoyl-β-3-thienylethylamine on cyclization formed 1-methyl- and 1-phenyl-3,4-dihydrothieno(2,3-c)pyridine. Due to shortage of material, only the second substance was dehydrogenated to the completely aromatic compound.

Acknowledgment.—We wish to thank the Socony–Vacuum Company, New York, N. Y., for a generous supply of thiophene and 3-methylthiophene.

Experimental[10]

β-2-Thienylethylamine.—Reduction of 125 g. of β-2-thienylacetonitrile, prepared by the method of Blicke and Leonard,[11] with lithium aluminum hydride[12] gave 39 g. of the amine, b.p. 65° at 2 mm.

N-Acetyl-β-2-thienylethylamine.—Eleven and one-half grams of the amine was treated with 140 ml. of 20% sodium hydroxide solution and then portionwise with 40 ml. of acetic anhydride. The oily product solidified on chilling to 0° but liquefied on warming up to room temperature. The mixture was chilled again and the aqueous layer decanted. The solid was taken up in benzene and residual water was removed by azeotropic distillation. A small portion of the benzene solution, approximately one-tenth, was treated with charcoal, filtered, cooled and diluted with cold ligroin. Crystals gradually separated on keeping in the refrigerator, but liquefied at room temperature (30–38°) unless they were freed from adhering solvent by transferral to a vacuum desiccator immediately after filtration. Another such purification followed by vacuum drying yielded material melting at 45.5–46.5° which still appeared to retain solvent.

Anal.[13] Calcd. for $C_8H_{11}NOS$: C, 56.79; H, 6.55; N, 8.28. Found: C, 57.70; H, 7.06; N, 7.83.

N-Benzoyl-β-2-thienylethylamine.—A mixture of 9 g. of β-2-thienylethylamine, 40 ml. of water and 11 ml. of benzoyl chloride was treated with 45 ml. of 20% sodium hydroxide solution. The product solidified on keeping in the cold and was obtained in quantitative yield. A benzene solution was decolorized with charcoal and diluted with sufficient ligroin to barely avoid cloudiness at 4°. Addition of a seed crystal followed by cooling caused separation of nicely formed crystals. Another recrystallization gave material melting at 61°, which, like the acetyl derivative, stubbornly retained solvent.

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 68.36; H, 5.85; N, 5.36.

1-Methyl-3,4-dihydrothieno(3,2-c)pyridine.—Concentration of the benzene solution of N-acetyl-β-2-thienylethylamine yielded approximately 12 g. of residue which was taken up in 120 ml. of anhydrous xylene and treated with 20 g. of phosphorus pentoxide and 20 g. of phosphorus oxychloride. After one hour of refluxing, the solution was

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(1) Koenigs and Kantrowitz, *Ber.*, **60**, 2097 (1927).

(2) Bischler and Napieralski, *ibid.*, **26**, 1903 (1893).

(3) Herz, THIS JOURNAL, **72**, 4999 (1950).

(4) Barger and Easson, *J. Chem. Soc.*, 2100 (1938).

(5) Whaley and Hartung, *J. Org. Chem.*, **14**, 650 (1949).

(6) (a) Campaigne and LeSuer, THIS JOURNAL, **70**, 155 (1948); (b) Dittmer, Martin, Herz and Cristol, *ibid.*, **71**, 1201 (1949).

(7) Runde, Scott and Johnson, *ibid.*, **52**, 1284 (1930); Scott and Johnson, *ibid.*, **54**, 2549 (1932).

(8) Sherman and Amstutz, *ibid.*, **72**, 2195 (1950).

(9) Hartough and Meisel, *ibid.*, **70**, 4018 (1948).

(10) Melting points are uncorrected.

(11) Blicke and Leonard, THIS JOURNAL, **68**, 1934 (1946).

(12) Nord and Crowe, *J. Org. Chem.*, **15**, 81 (1950).

(13) Analyses by Clark Microanalytical Laboratory, Urbana, Illinois.

cooled and decomposed with ice. The aqueous layer was separated, washed with benzene, made basic with concentrated sodium hydroxide and extracted with benzene. Approximately 10 g. of a viscous black sirup was obtained by removal of the benzene at reduced pressure. Distillation at a bath temperature of 140° (0.5 mm.) gave an almost colorless liquid in 40% yield.

Anal. Calcd. for C_9H_9NS: C, 63.55; H, 6.00; N, 9.27. Found: C, 63.27; H, 5.96; N, 9.12.

The orange-yellow picrate, prepared in the usual manner,[14] decomposed at 204°.

Anal. Calcd. for $C_{14}H_{12}N_4O_7S$: C, 44.21; H, 3.18; N, 14.73. Found: C, 44.50; H, 3.13; N, 14.87.

1-Phenyl-3,4-dihydrothieno(3,2-c)pyridine.—Cyclization of 16 g. of N-benzoyl-β-2-thienylethylamine in the manner described above gave a black viscous residue which, when subjected to fractional distillation, yielded 5.1 g. of a red oil, b.p. 149–152° (0.5 mm.), and 2.1 g. boiling in the range 155–170°, consisting largely of the same material.

Anal. Calcd. for $C_{13}H_{11}NS$: C, 73.20; H, 5.20; N, 6.57. Found: C, 72.90; H, 4.94; N, 6.83.

The picrate, yellow needles from ethanol, melted at 160.5° (dec.).

Anal. Calcd. for $C_{19}H_{14}N_4O_7S$: C, 51.38; H, 3.19; N, 12.66. Found: C, 51.93; H, 3.32; N, 12.79.

1-Methylthieno(3,2-c)pyridine.—Three and six-tenths grams of the black oil obtained from the cyclization of N-acetyl-β-2-thienylethylamine was mixed with 3.6 g. of palladium black and heated at 200° for one-half hour. Extraction with acetone and removal of the solvent on the steam-bath gave 2.1 g. of a black oil. The major fraction, 1.0 g., boiled at 86° (1 mm.).

Anal. Calcd. for C_8H_7NS: C, 64.50; H, 4.73; N, 9.39. Found: C, 64.25; H, 4.76; N, 9.59.

The yellow picrate, difficultly soluble in hot ethanol, melted at 245.5–246° (dec.) with previous darkening.

Anal. Calcd. for $C_{14}H_{10}N_4O_7S$: C, 44.45; H, 2.66; N, 14.81. Found: C, 44.73; H, 2.67; N, 14.66.

1-Phenylthieno(3,2-c)pyridine.—Seven-tenths gram of the unpurified oil obtained by cyclization of N-benzoyl-β-2-thienylethylamine was heated at 190–200° with 0.5 g. of palladium-charcoal for one-half hour. Evaporative distillation at a bath temperature of 140–160° (0.5 mm.) yielded 0.35 g. of a colorless liquid with a quinoline odor.

Anal. Calcd. for $C_{13}H_9NS$: N, 6.63. Found: N, 6.91.

The picrate, recrystallized twice from ethanol, melted at 175° (dec.).

Anal. Calcd. for $C_{19}H_{12}N_4O_7S$: C, 51.81; H, 2.75; N, 12.72. Found: C, 52.12; H, 2.87; N, 12.71.

β-3-Thienylethylamine.—A solution of 45 g. of crude 3-bromomethylthiophene (b.p. 51–65° at 1–2 mm.; $n^{28}D$ 1.5990), obtained by the bromination of 50 g. of 3-methylthiophene with 88.6 g. of N-bromosuccinimide in the presence of 0.8 g. of benzoyl peroxide and still containing appreciable quantities of 2-bromo-3-methylthiophene, in 50 ml. of ethanol was added dropwise to a stirred and heated mixture of 15 g. of potassium cyanide, 100 ml. of water and 100 ml. of ethanol. After stirring and keeping at reflux for 3 hours, the alcohol was removed at reduced pressure, the residue diluted with water and extracted with ether. Distillation of the dried ether extract yielded 23.5 g. of nitrile, b.p. 70–75° (1–2 mm.).

Reduction of 26 g. of 3-thienylacetonitrile with 8 g. of lithium aluminum hydride in the usual manner[15] resulted in 5.1 g. of a base, b.p. 60–62° (2-3 mm.). A solid picrate could not be isolated.

Anal. Calcd. for C_6H_9NS: N, 11.01. Found: N, 10.89.

N-Acetyl-β-3-thienylethylamine.—To a mixture of 1.6 g. of the amine, 20 ml. of water and 20 ml. of 20% sodium hydroxide was added 5 ml. of acetic anhydride in small portions. The oil solidified on stirring and keeping in the refrigerator. Recrystallization from benzene–ligroin gave small needles, m.p. 70.5°.

Anal. Calcd. for $C_8H_{11}NOS$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.62; H, 6.55; N, 8.32.

The previously unreported N-acetyl-3-methyl-2-thenylamine, prepared from 3-methyl-2-thenylamine[9] in the same manner, melted at 95°.

Anal. Calcd. for $C_8H_{11}NOS$: N, 8.28. Found: N, 8.23.

N-Benzoyl-β-3-thienylethylamine.—A mixture of 4.4 g. of the amine, 10 ml. of water and 5.5 ml. of benzoyl chloride was treated with 40 ml. of 20% sodium hydroxide solution. The solid product weighed 8 g. and was recrystallized from benzene–petroleum ether, m.p. 108.5–109°.

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.79; H, 5.54; N, 6.01.

N-Benzoyl-3-methyl-2-thenylamine melted at 86°.

Anal. Calcd. for $C_{13}H_{13}NOS$: N, 6.06. Found: N, 6.08.

1-Methyl-3,4-dihydrothieno(2,3-c)pyridine.—Cyclization of 1.4 g. of the N-acetyl derivative in the usual manner gave a brown oil. It was taken up in petroleum ether, transferred to a semimicro distilling flask and distilled, giving 0.26 g. of colorless liquid, b.p. 75° (1–2 mm.). The product decomposed fairly rapidly so that analysis was not attempted.

The picrate, after several recrystallizations from ethanol, melted at 191° (dec.).

Anal. Calcd. for $C_{14}H_{12}N_4O_7S$: C, 44.21; H, 3.18; N, 14.73. Found: C, 44.54; H, 3.05; N, 14.74.

1-Phenyl-3,4-dihydrothieno(2,3-c)pyridine.—Distillation of the dark oil, weight 4.8 g., obtained by the cyclization of 8 g. of N-benzoyl-β-3-thienylethylamine, at a bath temperature of 150° (0.5 mm.) gave a viscous liquid which did not decompose quite as rapidly as the methyl analog.

Anal. Calcd. for $C_{13}H_{11}NS$: C, 73.20; H, 5.20; N, 6.57. Found: C, 73.00; H, 4.99; N, 6.50.

The picrate decomposed at 165°. It was fairly soluble in ethanol.

Anal. Calcd. for $C_{19}H_{14}N_4O_7S$: C, 51.38; H, 3.19; N, 12.66. Found: C, 52.27; H, 3.14; N, 12.93.

1-Phenylthieno(2,3-c)pyridine.—One and two-tenths grams of the viscous liquid was heated at 200–210° with 1.2 g. of palladium black. The cold mixture was extracted with acetone and the acetone removed on the steam-bath. Distillation of the residue at 0.5 mm. (bath temperature 150°) gave a colorless mobile liquid with a pyridine odor.

Anal. Calcd. for $C_{13}H_9NS$: N, 6.63. Found: N, 6.56.

The picrate melted at 156° (dec.).

Anal. Calcd. for $C_{19}H_{12}N_4O_7S$: N, 12.72. Found: N, 12.85.

Summary

The Bischler–Napieralski reaction has been applied successfully to acyl derivatives of β-2- and β-3-thienylethylamine. Dehydrogenation of the products yielded representatives of two new ring systems, thieno(2,3-c)pyridine and thieno(3,2-c)-pyridine. These compounds may be regarded as sulfur analogs of 1-substituted isoquinolines.

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(14) Shriner and Fuson, "The Systematic Identification of Organic Compounds," Third Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 180.

(15) Nystrom and Brown, THIS JOURNAL, **70**, 3738 (1948).