Heterocyclic Amines. I. 3-Thienyl Tertiary Amines[1]

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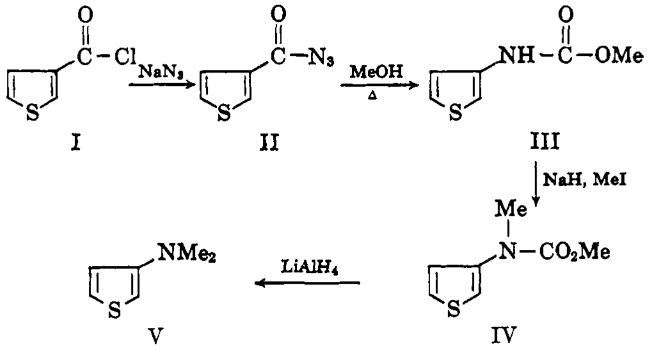
Acyl derivatives of aminothiophenes can be readily isolated, as can substituted aminothiophenes containing a stabilizing group, such as acyl, carboxyl, or sulfonyl, attached to the ring. Simple aminothiophenes, however, as the free base, have long been noted for their instability.[3] Although 2-aminothiophene[4] could be isolated by vacuum distillation, the free base polymerized rapidly to gum. 3-Aminothiophene has never been isolated although its presence could be demonstrated by the preparation of acyl derivatives[5,6] and by observation of its n.m.r. spectrum.[7]

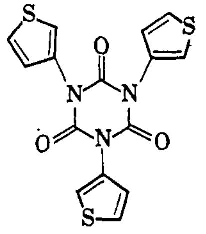
The instability of amino, hydroxy, and mercapto derivatives of thiophene and furan has frequently been ascribed to the existence of tautomeric forms.[8a-d] If this be part of the reason for the instability of these compounds, the tertiary amines should be more stable than the primary or secondary amines, much as alkoxy and acyloxy derivatives of furan and thiophene are more stable than the parent hydroxy compounds. Because of the potential importance, if sufficiently stable, of thienyl tertiary amine derivatives as medicinal agents and as dyestuffs, a suitable preparative route has been sought. Since this article was submitted for publication the synthesis of several closely related 3-thienyl tertiary amines by a different method has been reported.[8e]

3-Thenoyl chloride (I) was converted through the azide II, by rearrangement in methanol, to methyl N-(3-thienyl)carbamate (III). This urethan was alkylated in xylene with sodium hydride dispersion and methyl iodide to give methyl N-methyl-N-(3-thienyl)carbamate (IV). The latter compound was reduced with lithium aluminum hydride in tetrahydrofuran to 3-dimethylaminothiophene (V), which was isolated by preparative gas chromatography on a QF-1 (fluorocarbon silicone) column. This tertiary amine is stable when stored under vacuum or under nitrogen atmosphere for several weeks, or for several months when similarly stored in the freezing compartment of the refrigerator, but the compound darkens rapidly and polymerizes to a tar within hours in contact with air. Attempts to isolate salts of this amine derived from proton acids have not been successful, but the quaternary salts derived from reactions with alkyl halides are white crystalline compounds, hygroscopic, but stable in the presence of air and moisture.



Methyl N-(3-thienyl)carbamate was also alkylated with benzyl chloride and sodium hydride, and the resulting urethan was reduced with lithium aluminum hydride to prepare another tertiary amine, N-methyl-N-benzyl-3-aminothiophene, which was isolated as the methiodide.

Attempted ethylation of methyl N-(3-thienyl)carbamate by the usual method gave, instead of the expected derivative, a compound presumed to be a self-condensation product of the urethan, tris(3-thienyl)isocyanurate (VI). Modification of the alkylation procedure by addition of the ethyl iodide at the start of the reaction then gave the desired ethylation product.



VI

Many 3-substituted thiophenes[9] show a characteristic infrared absorption band in the range 760–780 cm.$^{-1}$. The 3-thienyl urethans reported herein show absorption within this range, but 3-dimethylaminothiophene and the 3-thienylammonium salts show the corresponding absorption peaks outside this range.[10] Methyl N-(3-thienyl)carbamate shows absorption peaks at 760 and 770 cm.$^{-1}$. Methyl N-methyl-N-(3-thienyl)carbamate, methyl N-ethyl-N-(3-thienyl)carbamate, and ethyl N-ethyl-N-(3-thienyl)carbamate all show an absorption peak at 770 cm.$^{-1}$. 3-Thienyltrimethylammonium iodide and 3-thienyldimethylethylammonium iodide both show an absorption peak at 788 cm.$^{-1}$ and a shoulder at 794 cm.$^{-1}$, while 3-thienyldimethylbenzylammonium iodide shows peaks at 791 and 797 cm.$^{-1}$. 3-Dimethylaminothiophene shows an absorption peak at 748 cm.$^{-1}$.

2-Thenoyl chloride was also converted to methyl N-(2-thienyl)carbamate, which was alkylated to methyl N-methyl-N-(2-thienyl)carbamate and methyl N-benzyl-N-(2-thienyl)carbamate. Reduction of the latter two compounds failed to yield any pure amine.

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[3] H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, pp. 228–235.

[4] W. Steinkopf, *Ann.*, **403**, 17 (1914).

[5] W. Steinkopf and T. Höpner, *ibid.*, **501**, 174 (1933).

[6] E. Campaigne and P. A. Monroe, *J. Am. Chem. Soc.*, **76**, 2447 (1954).

[7] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, **16**, 515 (1961).

[8] (a) Ref. 3, pp. 229, 287, 428; (b) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 170; (c) S. Gronowitz, "Advances in Heterocyclic Chemistry," Vol. 1, Academic Press Inc., New York, N. Y., 1963, pp. 82–87; (d) A. R. Katritzky and J. M. Lagowski, *ibid*, Vol. 2 1963, pp. 1–22; (e) F. A. Buiter, J. H. Sperna Weiland, and H. Wynberg, *Rec. trav. chim.*, **83**, 1160 (1964).

[9] S. Gronowitz, ref. 8c, p. 13.

[10] Several of these infrared spectra are reproduced in the Ph.D. Thesis of J. B. Sullivan, University of Washington, 1963.

Experimental

3-Thenyl Bromide.—The preparation of this intermediate in the synthesis of 3-thenoyl chloride was modified by replacement of the benzoyl peroxide catalyst[11] with an equal weight of azobisisobutyronitrile. There was no change in yield, but a cleaner reaction mixture was produced.

Methyl N-(3-Thienyl)carbamate (III).—A solution of 25 g. (0.38 mole) of sodium azide in 94 ml. of water was added at 0° to 13 g. (0.089 mole) of 3-thenoyl chloride[11] in 100 ml. of acetone. The mixture was shaken for 30 min. at 0°. The solvent was removed in a rotary evaporator and the oily residue was extracted with ether. After drying over anhydrous magnesium sulfate and removal of the solvent, the crude, oily 3-thenoyl azide was dissolved in 100 ml. of methanol. The mixture was refluxed for 8 hr., the excess methanol was removed in a rotary evaporator, and the oily product was crystallized from ligroin and recrystallized from water, m.p. 77–78°, yield, 12 g. (86%).

The n.m.r. spectrum[12] in deuterated chloroform was $\delta = 3.74$ (s, CH_3, 3H), 6.94 (m, ring H, 1H), and 7.20 (m, 2 ring-H and NH, 3H) p.p.m.

Ethyl N-(3-Thienyl)carbamate.—This was prepared similarly to the above, except that the azide was rearranged in anhydrous ethanol. The product was recrystallized from water, m.p. 71–72°. Identity of this product was confirmed by its n.m.r. spectrum in CCl_4: $\delta = 1.25$ (t, CH_3, 3H), 4.14 (q, CH_2, 2H), 7.05 (m, ring H, 3H), and 7.85 (broad band, NH, 1H) p.p.m.

Methyl N-Methyl-N-(3-thienyl)carbamate (IV).—A solution of 3.2 g. (0.02 mole) of III in 100 ml. of anhydrous xylene was added to a stirred suspension of 6.0 g. (0.125 mole) of 50% sodium hydride dispersion in 150 ml. of anhydrous xylene, refluxed for 8 hr. under nitrogen, and cooled; 90 g. (0.6 mole) of methyl iodide was added. After refluxing an additional 8 hr., the mixture was filtered, the residue was washed with benzene, and the combined filtrate and washings were evaporated. The oily residue was vacuum distilled, and 3.0 g. (85%) of crude product was collected from 126 to 134° at 10 mm. Although contaminated by a small amount of mineral oil from the sodium hydride dispersion, it was suitable for subsequent reduction. The analytical sample was extracted with cold hexane, and again vacuum distilled, b.p. 136–137° (12 mm.).

The n.m.r. spectrum in CCl_4 was $\delta = 3.25$ (s, N–CH_3, 3H), 3.67 (s, O–CH_3, 3H), 6.89 (t, probably 2-H of ring, 1H) ($J =$ 2.3 c.p.s.), and 7.12 (d, probably 4,5-H of ring, 2H) ($J = 2.3$ c.p.s.) p.p.m.[13]

Anal. Calcd. for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18; O, 18.69; S, 18.73. Found[14]: C, 49.83; H, 5.47; N, 8.22; O, 18.56; S, 18.33.

3-Dimethylaminothiophene (V).—A solution of 3.0 g. (0.0175 mole) of IV in 25 ml. of anhydrous tetrahydrofuran was added dropwise, with stirring, under nitrogen to 2.0 g. (0.0525 mole) of lithium aluminum hydride in 50 ml. of anhydrous tetrahydrofuran. After refluxing for 24 hr., the reduction complex was decomposed with water. This mixture was filtered under nitrogen, the residue was washed with ether, and the solvent was partly removed in a rotary evaporator. The amine was purified by gas chromatography in a Beckman GC-2 instrument at 100° through a 10-ft. QF-1 (fluorocarbon silicone) column with helium as the carrier gas.

The n.m.r. spectrum in CCl_4 was $\delta = 2.79$ (s, $2CH_3$, 6H), 5.86 (q, 2-H of ring, 1H), 6.70 (q, 4-H of ring, 1H), and 7.14 (q, 5-H of ring, 1H) p.p.m., $J_{24} = 1.7$, $J_{25} = 3.4$, and $J_{45} = 5.4$ c.p.s. (all ± 0.2 c.p.s.).

Anal. Calcd. for C_6H_9NS: C, 56.65; H, 7.13; N, 11.01 S, 25.21. Found: C, 56.79, 56.88; H, 7.26, 7.17; N, 10.90, 11.18; S, 25.14, 24.98.

The amine was further characterized by conversion to its methiodide, m.p. 211–212° after recrystallization from ethanol.

Anal. Calcd. for $C_7H_{12}INS$: C, 31.23; H, 4.46; I, 47.21; N, 5.20; S, 11.90. Found: C, 31.82, 31.70; H, 4.62, 4.71; I, 47.02, 46.92; N, 4.92, 5.05; S, 11.70, 11.58.

N-Methyl-N-benzyl-3-aminothiophene Methiodide.—A solution of 5 g. (0.038 mole) of III in 150 ml. of anhydrous xylene was added to a suspension of 4 g. (0.083 mole) of 50% sodium hydride dispersion in 50 ml. of anhydrous xylene, refluxed for 12 hr., cooled, and 22 g. (0.17 mole) of benzyl chloride was added. After refluxing an additional 8 hr., the mixture was filtered, the residue was washed with benzene, and the combined filtrate and washings were evaporated. The product was isolated by vacuum distillation, with 3.32 g. (45%) collected at 140–160° at 0.3 mm. A solution of 2.5 g. (0.011 mole) of this benzylated urethan in 50 ml. of anhydrous tetrahydrofuran was added dropwise, with stirring, under nitrogen, to 2 g. (0.053 mole) of lithium aluminum hydride in 50 ml. of anhydrous tetrahydrofuran. After refluxing 24 hr. and hydrolyzing the reduction complex with water, the mixture was filtered and the residue was washed with ether. The combined filtrate and washings were dried with anhydrous magnesium sulfate and evaporated, an equal volume of benzene was added to the oily residue, and methyl iodide was then added. The solid product was recrystallized from methanol, m.p. 152.5–153.5°.

Anal. Calcd. for $C_{13}H_{16}INS$: C, 45.23; H, 4.67; I, 36.76; N, 4.06; S, 9.29. Found: C, 45.27; H, 4.90; I, 36.81; N, 3.96; S, 9.26.

Tris(3-thienyl)isocyanurate (VI).—A solution of 10 g. (0.064 mole) of III in 150 ml. of anhydrous xylene was added to a suspension of 6 g. (0.125 mole) of 50% sodium hydride dispersion in 50 ml. of anhydrous xylene, refluxed for 12 hr., cooled, and 29.2 g. (0.27 mole) of ethyl bromide was added. After refluxing an additional 8 hr., the mixture was filtered and the residue was washed with benzene. The combined filtrate and washings gave a crystalline product which, after recrystallization from ethanol, melted at 225.5–226.5°.

Anal. Calcd. for $C_{15}H_9N_3O_3S_3$: C, 48.01; H, 2.42; N, 11.20; O, 12.79; S, 25.59; mol. wt., 375.5. Found: C, 48.10; H, 2.61; N, 11.12; O, 12.65; S, 25.73; mol. wt. (Rast), 391.

Ethyl N-Ethyl-N-(3-thienyl)carbamate.—A mixture of 4 g. (0.08 mole) of 50% sodium hydride dispersion, 150 ml. of anhydrous xylene, 10 g. (0.06 mole) of ethyl N-(3-thienyl)carbamate, and 40 g. (0.25 mole) of ethyl iodide was refluxed for 10 hr. After filtration, alcoholysis of excess sodium hydride, and evaporation of the solvent, the product was vacuum distilled to give 4 g. (36%) and was collected at 134–144° (11 mm.). Part of this product was purified by preparative gas chromatography in a Beckmann GC-2 instrument at 185° through a 5-ft. Carbowax column. The structure was confirmed by the n.m.r. spectrum in CCl_4: $\delta = 1.17$ and 1.25 (2 overlapping t, $2CH_3$, 6H), 3.69 (q, NCH_2, 2H), 4.14 (q, OCH_2, 2H) and 7.07 (m, ring, 3H) p.p.m.

Methyl N-(2-Thienyl)carbamate.—This was prepared in 83% yield by rearrangement of 2-thenoyl azide in anhydrous methanol analogous to the method used for the ethyl ester by Curtius and Thyssen,[15] m.p. 101–102° after recrystallization from ligroin.

Anal. Calcd. for $C_6H_7NO_2S$: C, 45.86; H, 4.46; N, 8.92; S, 20.38. Found: C, 46.27; H, 4.53; N, 9.09; S, 20.35.

Methyl N-Methyl-N-(2-thienyl)carbamate.—This was prepared in like manner to the 3-substituted compound in 59% yield from 8 g. of methyl N-(2-thienyl)carbamate, with the product collected at 132–140° (7 mm.). The analytical sample was purified by gas chromatography in a Beckman GC-2 instrument at 200° through a 5-ft. Carbowax column.

Anal. Calcd. for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18; O, 18.69; S, 18.73. Found: C, 49.30; H, 5.39; N, 7.97; O, 19.00; S, 18.50.

Methyl N-Benzyl-N-(2-thienyl)carbamate.—This was prepared by a method analogous to that used above from 8.3 g. (0.05 mole) of methyl N-(2-thienyl)carbamate, 4 g. (0.08 mole) of 50% sodium hydride dispersion, and 20 g. (0.16 mole) of benzyl chloride. The product, 8 g. (62%), was collected at 142–143° (0.3 mm.).

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66; O, 12.94; S, 12.97. Found: C, 63.94; H, 5.28; N, 5.39; O, 12.86; S, 12.56.

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(11) E. E. Campaigne and W. M. LeSuer, *J. Am. Chem. Soc.*, **70**, 1555 (1948).

(12) We wish to acknowledge our indebtedness to Mr. B. J. Nist of the Department of Chemistry, University of Washington, for the determination of all n.m.r. spectra reported herein. These spectra were measured at 60 Mc., and the chemical shifts are reported as δ-values (p.p.m.) from tetramethylsilane (internal standard). The multiplicity is shown by s = singlet, d = doublet, t = triplet, q = quadruplet, and m = incompletely resolved multiplet. Assignments are shown in parentheses. Coupling constants are reported in c.p.s.

(13) This is an unexpectedly simple spectrum for the ring protons of a monosubstituted thiophene. It appears that the protons at positions 4 and 5 must experience a similar magnetic environment, and that the coupling constants, J_{24} and J_{25}, must be almost identical. Hoffman and Gronowitz, ref. 7, report a similar n.m.r. spectrum for 3-iodothiophene in cyclohexane.

(14) Elemental analyses were by A. Bernhardt, Mülheim (Ruhr), Germany.

(15) T. Curtius and H. Thyssen, *J. prakt. Chem.*, **65**, 5 (1902).