

## Heterocyclic Amines. IV. Urethan and Urea Derivatives of 3-Aminothiophene (1)

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Following the method used previously for the methyl and ethyl esters in the 2-thienyl (3,4) and 3-thienyl (4) series, 3-thienoyl azide (I) was rearranged in boiling *t*-butyl alcohol to give *t*-butyl *N*-(3-thienyl)carbamate. The azide (I) was also rearranged in boiling toluene to 3-thienyl isocyanate (II), which, without isolation, was reacted directly with various alcohols and amines to produce the corresponding urethans and ureas. Neopentyl *N*-(3-thienyl)carbamate (III) was alkylated to the tertiary amide (IV) with methyl iodide and sodium hydride.

Neopentyl *N*-methyl-*N*-(3-thienyl)carbamate (IV), as well as two other urethans in this series and several other 3-substituted thiophenes previously recorded (4,5,6), exhibit

an unexpectedly simple n.m.r. pattern for the ring protons, apparently because the protons in the 4- and 5-positions exhibit almost identical chemical shifts. Abraham and Bernstein (7) have discussed such "deceptively simple spectra" and have shown that the typical 12-line ABX pattern becomes a 5-line spectrum when the difference in chemical shift between protons A & B is small compared to  $J_{AB}$  and  $J_{BX}$  is small compared to  $J_{AX}$ . Under such conditions, only the average value of  $J_{AX}$  and  $J_{BX}$  can be derived from analysis of the spectrum. In confirmation of this interpretation, after selective deuteration of neopentyl *N*-methyl-*N*-(3-thienyl)carbamate in the 2-position, the 4- and 5-protons appear as a singlet in the n.m.r. spectrum.

## EXPERIMENTAL

*t*-Butyl *N*-(3-Thienyl)carbamate.

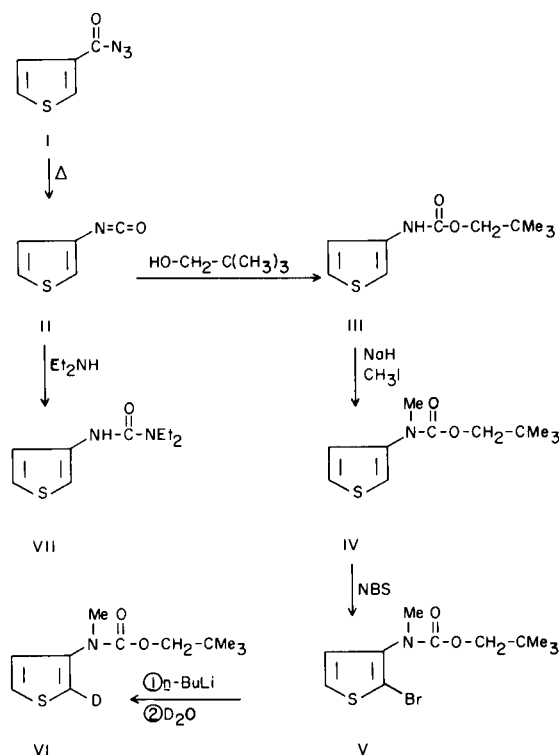
A solution of 11.5 g. (0.075 mole) of 3-thienoyl azide (I) (4) in 100 ml. of anhydrous *t*-butyl alcohol was heated under reflux for 12 hours. The excess alcohol was removed under reduced pressure; the residue was recrystallized from dilute acetone to give a 14.9 g. (92%) yield, m.p. 139.5-140.5°, n.m.r. spectrum in deuteriochloroform:  $\tau = 8.48$  (s, CH<sub>3</sub>, 9H), 3.09 (t, 2-H of ring with superimposed broad band of NH, 2H), 2.83 (d, 4 and 5-H of ring, 2H). The peaks centered at 3.09 and 2.83 show a separation or averaged coupling constant ( $\gamma$ ) of 3.5 c.p.s.

*Anal.* Calcd. for C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub>S: C, 54.25; H, 6.58; N, 7.03; O, 16.06; S, 16.09. Found: C, 54.44; H, 6.62; N, 7.30; O, 16.23; S, 16.03.

Neopentyl *N*-(3-Thienyl)carbamate (III).

A solution of 9.3 g. (0.06 mole) of I and 15.9 g. (0.18 mole) of neopentyl alcohol in 50 ml. of anhydrous toluene was heated under reflux for 12 hours. The solvent and excess alcohol were removed under reduced pressure; the residue was recrystallized from dilute alcohol to give a yield of 11.7 g. (91%), m.p. 141-142°, n.m.r. spectrum in deuterioacetone:  $\tau$  9.05 (s, CH<sub>3</sub>, 9H), 6.16 (s, CH<sub>2</sub>, 2H), 2.88 (t, 2-H of ring, 1H), 2.70 (d, 4 and 5-H of ring, 2H), 1.20 (broad peak, NH, 1H). The peaks centered at 2.88 and 2.70 show a separation or averaged coupling constant ( $\gamma$ ) of 3.4 c.p.s.

*Anal.* Calcd. for C<sub>10</sub>H<sub>15</sub>NO<sub>2</sub>S: C, 56.31; H, 7.08; N, 6.57; O, 15.00; S, 15.03. Found: C, 56.25; H, 6.98; N, 6.56; O, 15.26; S, 15.11.



Neopentyl *N*-Methyl-*N*-(3-thienyl)carbamate (IV).

Following the method reported earlier for a related compound (8), there was obtained from 21.3 g. (0.1 mole) of III in xylene with excess methyl iodide and sodium hydride, after decolorization with charcoal and recrystallization from petroleum ether, 15.14 g. (71%) of light tan crystals, m.p. 45-46°, n.m.r. spectrum in carbon tetrachloride:  $\tau = 9.09$  (s, CH<sub>3</sub>, 9H), 6.72 (s, N-CH<sub>3</sub>, 3H), 6.23 (s, CH<sub>2</sub>, 2H), 3.11 (t, 2-H of ring, 1H), 2.89 (d, 4 and 5-H of ring, 2H). The peaks centered at 3.11 and 2.89 show a separation or averaged coupling constant ( $\tau$ ) of 2.2 c.p.s.

*Anal.* Calcd. for C<sub>11</sub>H<sub>17</sub>NO<sub>2</sub>S: C, 58.12; H, 7.54; N, 6.16; O, 14.08; S, 14.11. Found: C, 58.43; H, 7.67; N, 5.99; O, 14.02; S, 14.30.

Neopentyl *N*-Methyl-*N*-(2-deuterio-3-thienyl)carbamate (VI).

A solution of 3.4 g. (0.015 mole) of IV in 25 ml. of carbon tetrachloride was heated under reflux and 2.6 g. (0.015 mole) of *N*-bromosuccinimide was added in small portions. After refluxing for 10 hours and subsequent removal of the succinimide, evaporation of the organic layer left a dark oily residue which resisted all attempts at crystallization. Upon vacuum distillation of neopentyl *N*-methyl-*N*-(2-bromo-3-thienyl)carbamate (V), the major fraction came over at 99-101° (0.25 mm.), 2.9 g. (63%), n.m.r. spectrum in carbon tetrachloride:  $\tau = 9.20$  (s, CH<sub>3</sub>, 9H), 6.82 (s, N-CH<sub>3</sub>, 3H), 6.24 (s, CH<sub>2</sub>, 2H), 3.17 (d, 4-H of ring, 1H), 2.76 (d, 5-H of ring, 1H);  $J_{45} = 5.7$  c.p.s.

A solution of 1.005 g. (0.003 mole) of V in 15 ml. of anhydrous ether under nitrogen was cooled to dry ice-acetone temperature and 3 ml. of a 15% solution of *n*-butyl lithium in hexane was added. The mixture was stirred with continual cooling for ½ hour and then 1 ml. of deuterium oxide (99.85 mole %) was injected into the reaction mixture. With constant stirring, the reaction mixture was allowed to warm to room temperature. Anhydrous sodium sulfate was added and stirring was continued for 1 hour. The mixture was filtered through decolorizing carbon and the organic solvents were removed under vacuum at low temperature. The residue was crystallized from petroleum ether; n.m.r. spectrum in carbon tetrachloride:  $\tau = 9.07$  (s, CH<sub>3</sub>, 9H), 6.70 (s, N-CH<sub>3</sub>, 3H), 6.21 (s, CH<sub>2</sub>, 2H), 2.86 (s, 4 and 5-H of ring, 2H).

 $\beta$ -Dimethylaminoethyl *N*-(3-Thienyl)carbamate.

A solution of 3-thienyl isocyanate (II) was prepared by thermal rearrangement of 3 g. of I in 20 ml. of toluene by heating under reflux until evolution of nitrogen was complete (about 1 hour). A solution of 6 g. of freshly distilled  $\beta$ -dimethylaminoethanol in 10 ml. of toluene was added and this mixture was heated under reflux. The excess amino alcohol and toluene were removed under reduced pressure to leave a residue of viscous oil which resisted all attempts at crystallization.

Hydrogen chloride gas was passed through a portion of the oily product dissolved in ether and the precipitated *hydrochloride salt*, after decolorizing with charcoal and recrystallizing from a mixture of alcohol and ether gave a melting point of 155-156°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>2</sub>S: C, 43.11; H, 6.03; Cl, 14.13; N, 11.17; O, 12.76; S, 12.79. Found: C, 43.20; H, 6.10; Cl, 14.02; N, 11.03; O, 12.93; S, 12.82.

A sample of the *free base* isolated from the purified hydrochloride salt showed an n.m.r. spectrum in carbon tetrachloride of:  $\tau = 7.80$  (s, N-CH<sub>3</sub>, 6H), 7.49 (t, N-CH<sub>2</sub>, 2H), 5.85 (t, O-CH<sub>2</sub>, 2H), 3.08 (m, ring Hs, 3H), 1.84 (broad peak, NH, 1H);  $J_{CH_2CH_2} = 5.7$  c.p.s.

*N*-(3-Thienyl)urea.

A solution of II was prepared as above by thermal rearrangement of 3.0 g. of I in toluene. Ammonia gas bubbled through the cold reaction mixture gave an immediate precipitate. The solvent was evaporated under reduced pressure and the residue was recrystallized from a mixture of acetone and toluene to give a yield of 2.4 g. (63%), m.p. 149-150°, n.m.r. spectrum in deuterioacetone:  $\tau = 4.41$  (broad peak, NH<sub>2</sub>, 2H), 3.04 (t, 2-H of ring, 1H), 2.78 (d, 4 and 5-H of ring, 2H), 1.6 (broad peak, NH, 1H). The peaks centered at 3.04 and 2.78 show a separation or averaged coupling constant ( $\tau$ ) of 3.2 c.p.s.

*Anal.* Calcd. for C<sub>5</sub>H<sub>6</sub>N<sub>2</sub>OS: C, 42.24; H, 4.25; N, 19.70; O, 11.25; S, 22.55. Found: C, 42.27; H, 4.28; N, 19.66; O, 11.23; S, 22.55.

*N,N*-Diethyl-*N'*-(3-thienyl)urea (VII).

To a solution of II in toluene, prepared as above by thermal rearrangement of 3 g. of I was added 10 ml. of diethylamine. The excess base and solvent were removed in a rotary evaporator, the residue was decolorized with charcoal and recrystallized from dilute alcohol to give 1.11 g. (29%) of white crystals, m.p. 113-114°, n.m.r. spectrum in carbon tetrachloride:  $\tau = 8.93$  (t, CH<sub>3</sub>, 6H), 6.67 (q, CH<sub>2</sub>, 4H), 2.93 (m, ring Hs, 3H), 2.05 (broad peak, NH, 1H);  $J_{CH_3CH_2} = 7.0$  c.p.s.

*Anal.* Calcd. for C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>OS: C, 54.51; H, 7.12; N, 14.13; O, 8.07; S, 16.17. Found: C, 54.74; H, 7.04; N, 14.19; O, 8.08; S, 16.07.

*N*- $\beta$ -Dimethylaminoethyl-*N'*-(3-thienyl)urea.

A solution of II was prepared as above from 6.6 g. of I in 30 ml. of toluene, 13.5 g. of  $\beta$ -dimethylaminoethylamine was added, and the mixture was heated under reflux. Upon cooling, crystallization occurred, and the product was recrystallized from hot toluene to give 6.6 g. (72%) of white crystals, m.p. 145-147°, n.m.r. spectrum in deuteriochloroform:  $\tau = 7.78$  (s, N-CH<sub>3</sub>, 6H), 7.58 (t, CH<sub>2</sub>-NMe<sub>2</sub>, 2H), 6.70 (q, CO-N-CH<sub>2</sub>, 2H), 3.93 (broad peak, NH-CH<sub>2</sub>, 1H), 3.15 (t, 2-H of ring, 1H), 2.86 (d, 4 and 5-H of ring, 2H), 1.18 (broad peak, thienyl-NH, 1H);  $J_{CH_2CH_3} = 5.6$  c.p.s. The peaks centered at 3.15 and 2.86 show a separation or averaged coupling constant ( $\tau$ ) of 3.2 c.p.s.

*Anal.* Calcd. for C<sub>9</sub>H<sub>15</sub>N<sub>3</sub>OS: C, 50.68; H, 7.09; N, 19.70; O, 7.50; S, 15.03. Found: C, 50.91; H, 7.01; N, 19.68; O, 7.60; S, 14.94.

## REFERENCES

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