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Synthesis of *t*-Butyl-$^2H_9$-thiophenes

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SUMMARY

Interaction of 2-thienylmagnesium bromide with t-*butyl chloride-*$^2H_9$ *yielded 2-(*t-*butyl-*$^2H_9$*) thiophene and 3-(*t-*butyl-*$^2H_9$*) thiophene. Likewise, interaction of 5-*t-*butyl-2-thienylmagnesium bromide with* t-*butyl chloride-*$^2H_9$ *yielded 2,4-di(*t-*butyl-4-*$^2H_9$*)thiophene and 2,5-di(*t-*butyl-5-*$^2H_9$*)thiophene. The labeled mono-*t-*butylthiophenes and the labeled di-*t-*butylthiophenes were separated by preparative gas chromatography. The structures of the four labeled compounds were established from infrared and nuclear magnetic resonance spectra. Nuclear magnetic resonance and mass spectral data indicated that each of the deuterium labeled isomers were of high isotopic purity (99.22 % or better).*

Isotopically labeled alkylthiophenes have proved useful in the delineation of fragmentation and rearrangement processes of alkylthiophenes ionized by electron impact (1,2,3). A study (4) in 1966 of the mass spectra or *t*-butylthiophenes posed many questions concerning the mechanism of fragmentation that could be answered if the mass spectra of several isotopically labeled *t*-butylthiophenes were determined and analyzed. This paper reports the synthesis of 2-(*t*-butyl-$^2H_9$)thiophene, 3-(*t*-butyl-$^2H_9$)thiophene, 2,4-di(*t*-butyl-4-$^2H_9$)thiophene and 2,5-di(*t*-butyl-5-$^2H_9$)thiophene, each of high isotopic purity (99.22 % or better). A study of the mass spectra of these compounds will be published at a later date.

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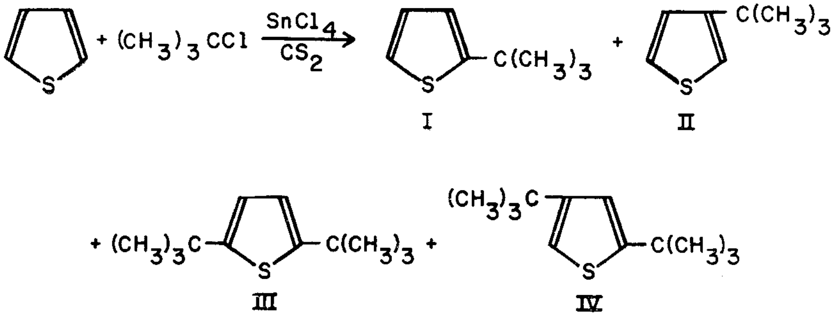
RESULTS.

Reference samples of each isomer were prepared, namely 2-*t*-butylthiophene, 3-*t*-butylthiophene, 2,4-di-*t*-butylthiophene and 2,5-di-*t*-butylthiophene. A mixture of isomeric *t*-butylthiophenes, I-IV, were prepared according to the method of Sy (5). Fractional distillation separated the reaction mixture into one fraction containing the mono-*t*-butylthiophenes and one containing the di-*t*-butylthiophenes. The mono-*t*-butylthiophenes were separated by using a "Teflon" spinning band column. The di-*t*-butylthiophenes were separated by preparative gas chromatography. Gas chromatography under conditions capable of separation of all four isomers showed each isomer to be uncontaminated with any of the other possible isomers. Purities were 99 % or better. Physical properties agreed with those reported in the literature (6,7,8).

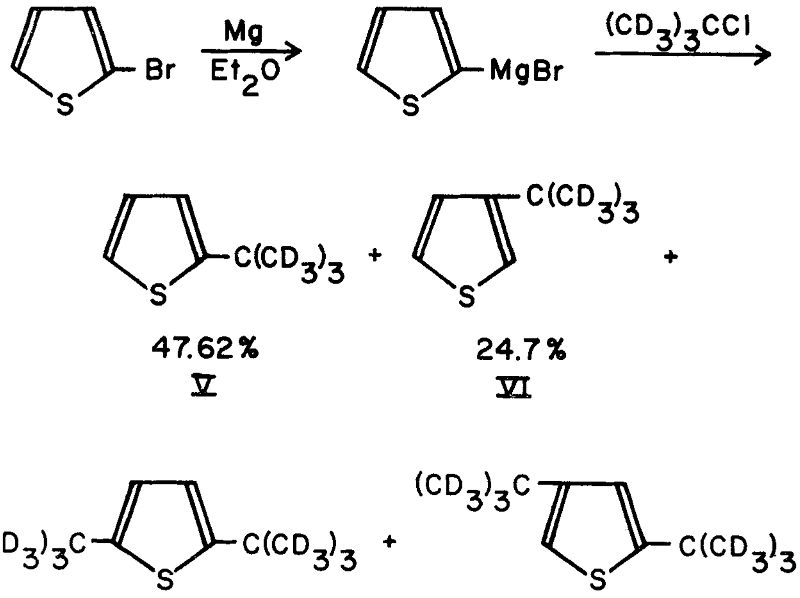


The synthesis of 2-(*t*-butyl-$^{2}H_{9}$)thiophene and 3-(*t*-butyl-$^{2}H_{9}$)-thiophene was carried out by a Grignard reaction in a yield of 27 %. The overall synthesis is shown in Scheme II.

Interaction of 2-bromothiophene (99.5+%) with excess magnesium in anhydrous ethyl ether yielded 2-thienylmagnesium bromide. The Grignard reagent was siphoned off and at 0° C, *t*-butyl chloride-$^{2}H_{9}$ was added and the mixture was stirred at room temperature for 24 hours.

Hydrolysis and analysis of the reaction mixture by vapor phase chromatography indicated four products with retention times corresponding with those of the four *t*-butylthiophene isomers. The product distribution was determined by gas chromatography. Preparative gas chromatography separated the reaction mixture into one group containing the labeled mono-*t*-butylthiophenes and one containing the labeled di-*t*-butylthiophenes. The 2-(*t*-butyl-$^{2}H_{9}$)-thiophene and the 3-(*t*-butyl-$^{2}H_{9}$)thiophene were separated by preparative gas chromatography.

Comparison of the infrared spectra of 2-*t*-butylthiophene and 3-*t*-butylthiophene with those of the 2-(*t*-butyl-$^{2}H_{9}$)thiophene and 3-(*t*-butyl-$^{2}H_{9}$)-



47.62%
V

24.7%
VI

15.48%
VII

12.20%
VIII

thiophene showed the characteristic shift of the absorption bands (C-D) to a lower frequency. The difference in positional substitution, as well as the shift of the absorption bands (C-D), is shown in Table I.

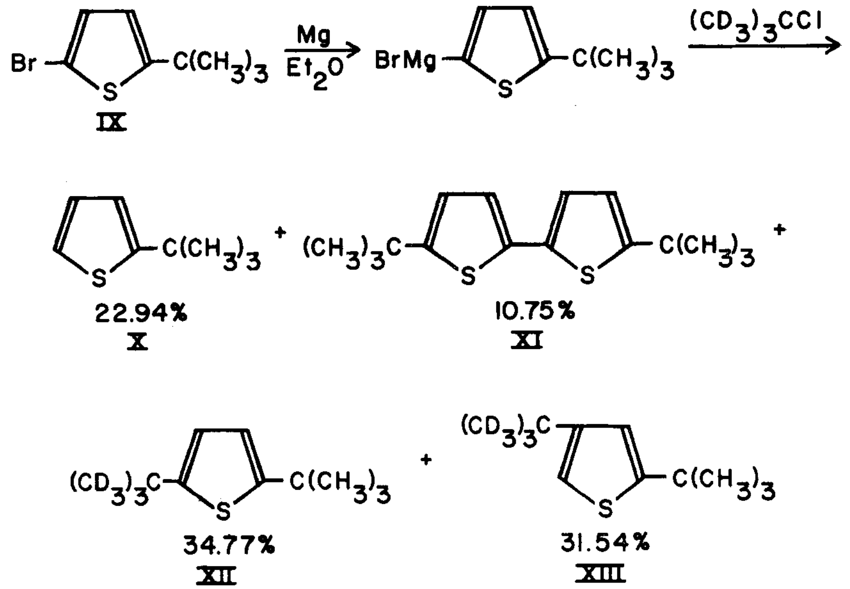
The nuclear magnetic resonance spectra of 2-(*t*-butyl-$^2H_9$)-thiophene and 3-(*t*-butyl-$^2H_9$)-thiophene exhibited resonance signals only for the ring hydrogens. The absence of other resonance signals in the spectrum of each isomer

TABLE I.

2-*t*-Butylthiophene (6, 7) (cm^{-1})	3-*t*-Butylthiophene (6, 7) (cm^{-1})	2-(*t*-Butyl-$^2H_9$)-thiophene (cm^{-1})	3-(*t*-Butyl-$^2H_9$)-thiophene (cm^{-1})
—	—	2,200-2,040	2,200-2,040
	910		885
	775		765
535	538	545	550
598	—	580	—
520	—	508	—

confirmed the complete deuteration of the *t*-butyl group. Low-voltage mass spectrometry confirmed one molecular ion at m/e 149 for the 2-(*t*-butyl-$^{2}H_{9}$)-thiophene and 3-(*t*-butyl-$^{2}H_{9}$)thiophene. The isotopic purity of the 2-(*t*-butyl-$^{2}H_{9}$)thiophene was 96.3 % and for the 3-(*t*-butyl-$^{2}H_{9}$)thiophene was 96.7 % based on the intensity of the M + 1 peak.

The synthesis of 2,4-di(*t*-butyl-4-$^{2}H_{9}$)thiophene and 2,5-di(*t*-butyl-5-$^{2}H_{9}$)-thiophene involved a Grignard reaction. The overall synthesis is shown in Scheme III.



Bromination$^{(9)}$ of 2-*t*-butylthiophene with *N*-bromosuccinimide gave 2-bromo-5-*t*-butylthiophene (IX), and the formation of the Grignard reagent from (IX) followed by addition of *t*-butyl chloride-$^{2}H_{9}$ and hydrolysis gave 2,5-di(*t*-butyl-5-$^{2}H_{9}$)thiophene (XII), 2,4-di(*t*-butyl-4-$^{2}H_{9}$)thiophene (XIII), 2-*t*-butylthiophene (X) and the dimer (XI) in 39 % yield. The product distribution was determined by gas chromatography. The dimer (XI) was removed by column chromatography. The 2-*t*-butylthiophene, 2,4-di(*t*-butyl-4-$^{2}H_{9}$)thiophene and 2,5-di(*t*-butyl-5-$^{2}H_{9}$)thiophene were separated by preparative gas chromatography.

Comparison of the infrared spectra of the 2,4-di-*t*-butylthiophene and 2,5-di-*t*-butylthiophene with the spectra of the 2,4-di(*t*-butyl-4-$^{2}H_{9}$)thiophene and 2,5-di(*t*-butyl-5-$^{2}H_{9}$)thiophene exhibited the characteristic shift of the absorption bands (C-D) to a lower frequency. The difference in positional substitution, as well as the shift of the absorption bands, is shown in Table II.

TABLE II.

2,4-Di-*t*-butylthiophene (10)	2,5-Di-*t*-butylthiophene (10)	2,4-Di(*t*-butyl-4-$^2H_9$)thiophene	2,5-Di(*t*-butyl-5-$^2H_9$)thiophene
—	—	2,210-2,040	2,220-2,080
	1,720		1,730
1,648	1,650	1,670	1,655
	1,585		1,590
1,525	1,540	1,540	1,545

The nuclear magnetic resonance spectrum of the 2,5-di(*t*-butyl-5-$^2H_9$)-thiophene exhibited a singlet for the ring hydrogens (τ 3.5) and a singlet at 8.64 for the *t*-butyl group (area ratio 2 : 9). The 2,4-di(*t*-butyl-4-$^2H_9$)thiophene displayed a quartet for the ring hydrogens (τ 3.5-3.36) and a singlet at τ 8.65 for the *t*-butyl group (area ratio 2 : 9). Low-voltage mass spectrometry confirmed one molecular ion at m/e 205 for the 2,5-di(*t*-butyl-5-$^2H_9$)thiophene and the 2,4-di(*t*-butyl-4-$^2H_9$)thiophene. The isotopic purity of the 2,5-di(*t*-butyl-5-$^2H_9$)thiophene was 98.72 % and the 2,4-di(*t*-butyl-4-$^2H_9$)thiophene was 95.22 % based on the intensity of the M + 1 peak.

DISCUSSION.

The preparation of the four labeled *t*-butylthiophenes *via* a Grignard reaction yielded four products, each of high isotopic purity. The Grignard reaction is unusual in that both pairs of isomers were obtained in each case. Previously, interaction of 2-thienylmagnesium bromide with *t*-butyl bromide was reported (7) to yield pure 2-*t*-butylthiophene. Contrarily to this report, we have always obtained all four *t*-butylthiophene isomers (I-IV). The four products were separated by preparative gas chromatography. The structure of each isomer was confirmed by nuclear magnetic resonance, infrared, and mass spectrometry. The four *t*-butylthiophenes were shown to be identical with compounds I through IV prepared *via* the Friedel-Crafts reaction. In the reactions described in this publication, the spectra of all compounds were carefully examined for evidence of hydrogen exchange reactions. No unaccountable absorptions were observed in any of the spectra obtained.

EXPERIMENTAL.

N.m.r. spectra were determined on a Varian A-60A with tetramethylsilane as an internal reference; i.r. spectra were determined on a Perkin-Elmer 225 grating infrared spectrometer; mass spectra were determined on a Consolidated Electrodynamics Corporation (CEC) single focus mass spectrometer model 21-104. All v.p.c. analyses were determined on a Varian 1520-B gas chromatograph, using a 10 % Apiezon J on Chromosorb P (60-80 mesh) column 10 feet long and 1/4-inch in diameter at 140° C. Preparative gas chromatography was done with a Wilkens Aerograph A-700 Autoprep. *t*-Butyl-chloride-$^2H_9$ (99 atom % D) was purchased from Columbia Organic Chemicals Company.

*2-*t*-Butylthiophene (I).* — To an ice-cooled mixture of 168 g of thiophene (2 moles) and 222 g of *t*-butyl chloride (2.4 moles) dissolved in 2,500 ml of carbon disulfide, 625 g of stannic chloride (2.4 moles) was added over a period of three hours ⁽⁵⁾. Six hours of stirring at room temperature completed the reaction. After hydrolysis of the reaction mixture, 100 g (b.p. 162-170° C) of the mono-*t*-butylthiophenes and 28 g (b.p. 220-225° C) of the di-*t*-butylthiophenes were collected by distillation at atmospheric pressure.

The lower boiling fraction was distilled by use of an annular "Teflon" spinning-band column (Nester-Faust). Fifty-two grams of 99.9+% pure (v.p.c.) 2-*t*-butylthiophene was obtained. The infrared spectrum was identical with that reported for the 2-*t*-butylthiophene by Appleby ⁽⁶⁾ and Cagniant ⁽⁷⁾. The n.m.r. spectrum agreed with that reported by Wynberg and Wiersum ⁽⁸⁾.

*3-*t*-Butylthiophene (II).* — The pot residue from the above distillation contained a 1 : 2.2 mixture of 2- and 3-*t*-butylthiophene. This residue was distilled using the spinning-band column. The best fractions were combined to furnish 8 g of 99.9+% pure (v.p.c.) 3-*t*-butylthiophene. The infrared spectrum was identical with that reported by Appleby ⁽⁶⁾. The n.m.r. spectrum agreed with that reported by Wynberg and Wiersum ⁽⁸⁾.

*2,5-Di-*t*-butylthiophene (III) and 2,4-Di-*t*-butylthiophene (IV).* — The residue from the initial distillation (b.p. 220-225° C) contained a 3.44 to 1 mixture of 2,5-di-*t*-butylthiophene and 2,4-di-*t*-butylthiophene. Using a 30 % QF-1 column, 10 g of 99.9+% pure (v.p.c.) 2,5-di-*t*-butylthiophene, and 3 g of 99.9+% pure (v.p.c.) 2,4-di-*t*-butylthiophene were obtained by preparative gas chromatography at 138° C. The infrared spectra for the 2,5-isomer and the 2,4-isomer corresponded to those reported by Foster ⁽¹⁰⁾. The n.m.r. spectra for the 2,5-isomer and the 2,4 isomer agreed with those reported by Wynberg and Wiersum ⁽⁸⁾.

*2-(*t*-Butyl-$^2H_9$)thiophene (V) and 3-(*t*-Butyl-$^2H_9$)thiophene (VI).* — The synthesis of 2-(*t*-butyl-$^2H_9$)thiophene and 3-(*t*-butyl-$^2H_9$)-thiophene was carried out using a modification of the method reported by the Cagniants ⁽⁷⁾. The Grignard reagent was formed by the reaction of redistilled 2-bromothiophene (16.93 g, 0.11 mole) with magnesium (3.0 g, 0.125 mole) in 100 ml of anhydrous ethyl ether. The mixture was refluxed 4 hr ; the Grignard reagent was then transferred to another reaction flask, cooled to 0° C, and *t*-butyl chloride-$^2H_9$

(10 g, 0.10 mole) was added during a period of 1.5 hr. The reaction mixture was stirred at room temperature for 4 hr, refluxed 10 hr, cooled and hydrolyzed with 10 % hydrochloric acid. The two layers were separated, the aqueous layer was extracted with ether, and the organic layer and ether extracts were combined and dried over $MgSO_4$. Removal of the ether and distillation of the residue gave 3.8 g (68°/22 mm, 27 % yield) of 2-(*t*-butyl-$^2H_9$)thiophene and 3-(*t*-butyl-$^2H_9$)thiophene. The product distribution of 2-(*t*-butyl-$^2H_9$)thiophene to 3-(*t*-butyl-$^2H_9$)thiophene was 1.9 to 1. The 2-(*t*-butyl-$^2H_9$)thiophene and 3-(*t*-butyl-$^2H_9$)thiophene was separated by preparative gas chromatography using a 30 % QF-1 column at 138° C.

The infrared spectrum of 2-(*t*-butyl-$^2H_9$)thiophene showed characteristic absorptions at 2,200-2,040 cm^{-1}, 545 cm^{-1}, 580 cm^{-1}, 508 cm^{-1}; the n.m.r. spectrum showed a multiplet at 3.32-2.96; and low-voltage mass spectrometry exhibited one molecular ion at m/e 149. The infrared spectrum of 3-(*t*-butyl-$^2H_9$)thiophene showed characteristic absorptions at 2,200-2,040 cm^{-1}, 885 cm^{-1}, 765 cm^{-1}, 550 cm^{-1}; the n.m.r. spectrum showed a multiplet at 3.15-2.75; and low-voltage mass spectrometry exhibited one molecular ion at m/e 149.

*2,5-Di(*t*-butyl-5-$^2H_9$)thiophene (XII) and 2,4-Di(*t*-butyl-4-$^2H_9$)thiophene (XIII).* — 2-bromo-5-*t*-butylthiophene was prepared by treatment of 2-*t*-butylthiophene (14 g, 0.1 mole) with *N*-bromosuccinimide (19.84 g, 0.112 mole) in 60 ml of refluxing CCl_4 for 48 hours (9). The reaction mixture was filtered, and the organic layer was washed with 5 % KOH and then dried over $MgSO_4$. Removal of the solvent and distillation of the residue gave 2-bromo-5-*t*-butylthiophene (15.6 g, 71 %), b.p. 96-98° C/15 mm. V.p.c. (Apiezon J, 10 ft) (QF-1, 8 ft) showed the product to be pure. Low voltage mass spectrometry exhibited one molecular ion at m/e 218 or m/e 220.

The Grignard reagent was formed by reaction of 2-bromo-5-*t*-butylthiophene (23.1 g, 0.11 mole) with magnesium (3.0 g, 0.125 mole) in 100 ml of anhydrous ethyl ether. The mixture was refluxed 4 hr ; the Grignard reagent was then transferred to another reaction flask, cooled to 0 °C, and *t*-butylchloride-$^2H_9$ (10 g, 0.10 mole) was added during a period of 1.5 hr. The reaction mixture was stirred at room temperature for 4 hr; refluxed 10 hr, cooled and hydrolyzed with 10 % hydrochloric acid. The two layers were separated, the aqueous layer was extracted with ether, and the organic layer and ether extracts were combined and dried over $MgSO_4$. The ether was removed, and the residue was passed through a short alumina column using chloroform as the eluent to remove the dimer (XI). Removal of the chloroform and distillation of the residue gave 7.7 g (115-117°/22 mm, 39 %) of 2-*t*-butylthiophene, 2,4-di(*t*-butyl-4-$^2H_9$)thiophene and 2,5-di(*t*-butyl-5-$^2H_9$)thiophene. The product distribution of 2,5-di(*t*-butyl-5-$^2H_9$)thiophene and 2,4-di-(*t*-butyl-4-$^2H_9$)thiophene was 1.1 to 1. The 2-*t*-butylthiophene, 2,4-di(*t*-butyl-4-$^2H_9$)thiophene and 2,5-di(*t*-butyl-5-$^2H_9$)thiophene were separated by preparative gas chromatography using a 30 % QF-1 column at 148° C.

The infrared spectrum of 2,4-di(*t*-butyl-4-$^2H_9$)thiophene showed characteristic absorptions at 2,210-2,040 cm^{-1}, 1,670 cm^{-1}, and 1,540 cm^{-1}; the n.m.r. spectrum displayed a quartet at τ 3.5-3.35 and a singlet at τ 8.65 (area ratio 2 : 9); and low-voltage mass spectrometry exhibited one molecular ion at m/e 205. The infrared spectrum of 2,5-di(*t*-butyl-5-$^2H_9$)thiophene showed characteristic absorptions at 2,220 cm^{-1}, 1,730 cm^{-1}, 1,655 cm^{-1}, 1,590 cm^{-1}, and 1,545 cm^{-1}; the n.m.r. spectrum exhibited a singlet at τ 8.64 (area ratio 2 : 9); and low-voltage mass spectrometry exhibited one molecular ion at m/e 205. The dimer (XI) exhibited one molecular ion at m/e 278 when examined by low-voltage mass spectrometry.

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