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Products from the Nitration of 2,5-Dimethylthiophene and Its 3,4-Dibromo Derivative. Two Modes of the Formation of Dithienylmethanes[1)]

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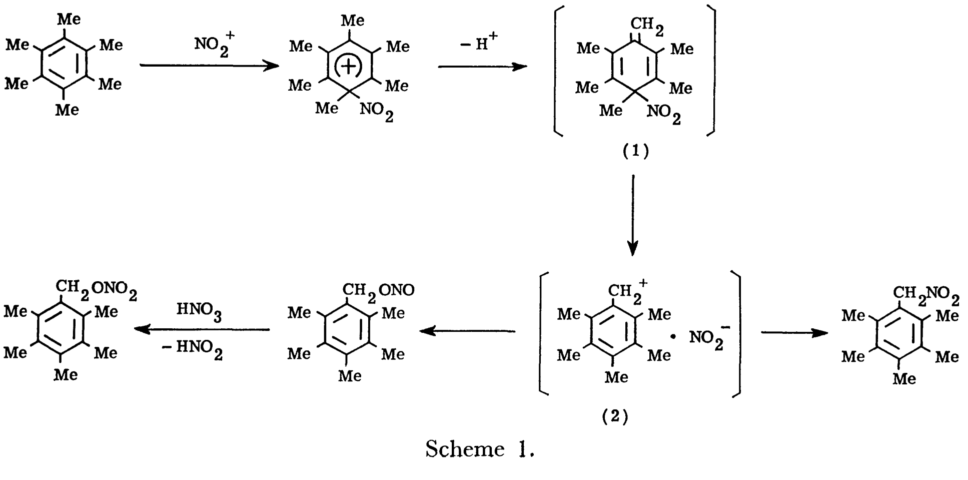
The reaction of 2,5-dimethylthiophene with copper(II) nitrate in acetic anhydride gave 3-nitro-2,5-dimethylthiophene and 2,5-dimethyl-3-(5-methyl-2-thenyl)thiophene as major isolable products. The treatment of 3,4-dibromo-2,5-dimethylthiophene with nitric acid (d=1.5) in dichloromethane in the presence of a catalytic amount of sulfuric acid afforded 3,4-dibromo-5-methyl-2-(nitrooxymethyl)thiophene, which, on thin-layer chromatography over silica gel using hexane as the eluant, underwent a partial novel coupling reaction through the loss of one methylene carbon atom, thus giving 3,3′,4,4′-tetrabromo-5,5′-dimethyldi-2-thienylmethane along with the expected 3,4-dibromo-2-hydroxymethyl-5-methylthiophene and bis(3,4-dibromo-5-methyl-2-thenyl) ether.

When treated with nitric acid in dichloromethane at a low temperature, polymethylbenzenes and their derivatives often undergo the nitrooxylation of the alkyl group to give benzyl nitrates.[2)] Under similar conditions, polymethylnaphthalenes and polymethylanthracenes yield naphthylnitromethanes and anthrylnitromethanes respectively.[3)] For these side-chain reactions of arenes, we have previously proposed an ionic S_N1' mechanism involving a methylenecyclohexadiene intermediate (**1**); the heterolytic fission of the C–N bond in **1** to form a benzyl cation/nitrite anion pair (**2**) and the subsequent recombination of these ions at the benzylic carbon atom, either *via* a C–N bond or *via* a C–O bond, the ratio of the C–N/C–O bond formation being mainly determined by the electronic requirements of the *exo*-cyclic sp^2 carbon atom (Scheme 1).[3,4)] Thus, the marked change in the modes of reaction toward nitrating agents observed on going from the benzenes to naphthalenes and anthracenes has been related to the change in the development of the carbonium ion character on the methylene carbon atom of the intermediate ion pair, **2**. In order to test the validity of our proposal further, we have now investigated the effect of the fused benzene ring on the side-chain reactions of heteroaromatic systems.

There has, to our knowledge, been only one report in the literature pertaining to the side-chain nitration of heteroaromatics; Bordwell and Cutshall treated 2,3-dimethylbenzo[*b*]thiophene (**3**) with nitric acid in acetic anhydride and obtained 3-methyl-2-(nitromethyl)benzo[*b*]thiophene (**4**) and 3-methylbenzo[*b*]thiophene-2-carboaldehyde (**6**) (Scheme 2). The carbonyl compound presumably arose from the initially formed nitrate (**5**). Preferential substitution occurred at an alkyl group attached to the heterocycle.[5)] If the S_N1' mechanism shown in Scheme 1 works in that case, we may reasonably expect that the removal of a fused benzene ring from the benzo[*b*]thiophene system would lead to a change in the mode of the side-chain reaction of the thiophene nucleus from nitration to nitrooxylation. Thus, we have prepared several polymethylthiophenes and their derivatives and treated them with nitrating agents under a variety of conditions.

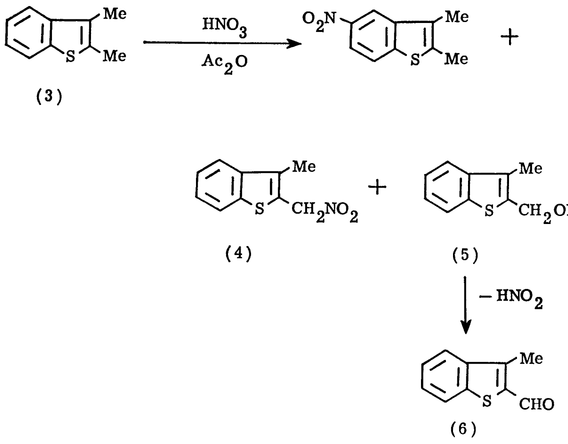
Trimethylthiophenes and tetramethylthiophene were extremely reactive toward a nitrating agent and failed to give any isolable products. A significant part of the substrate suffered the destruction of the thiophene nucleus. Even with such a mild nitrating agent as copper(II) nitrate in acetic anhydride, these reactive thiophenes were converted into a complicated mixture of products which were difficult to separate. We therefore turned our interest to the nitration of 2,5-dimethylthiophene (**7**) and its dibromo derivative (**8**).



Scheme 1.

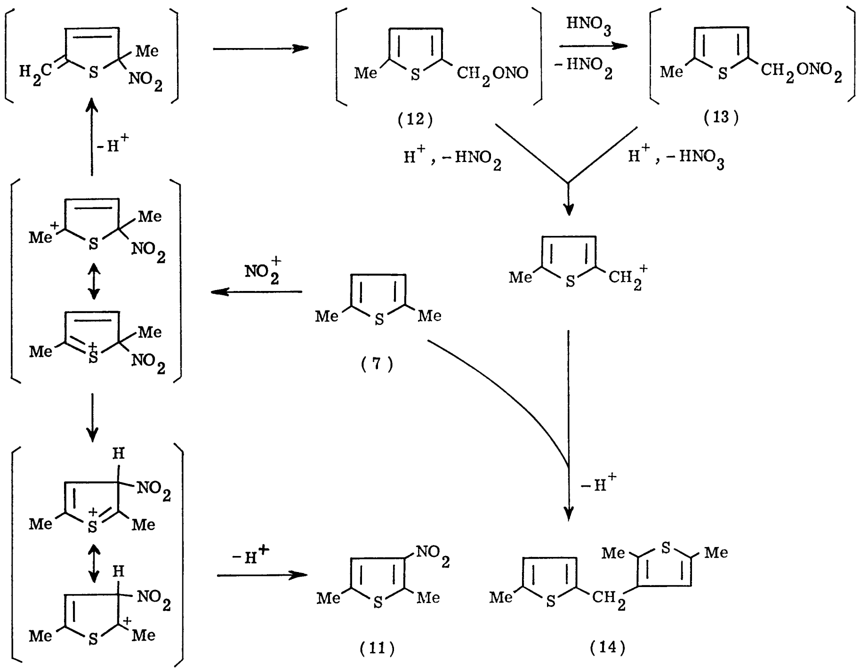
The reaction of **7** with copper(II) nitrate proceeded smoothly in acetic anhydride at a low temperature; the two major products thus obtained were identified as 3-nitro-2,5-dimethylthiophene (**11**) and 2,5-dimethyl-3-(5-methyl-2-thenyl)thiophene (**14**) respectively on the basis of IR, ^{1}H NMR and mass spectroscopy as well as elemental analysis. Although the crude product mixture was shown by its IR and NMR spectra to contain small amounts of a nitrate supposed to be **13**, it could not be isolated as such. However, the significant formation of dithienylmethane, **14**, strongly suggests the initial formation of a nitrite, **12**, or a nitrate, **13**, and the subsequent acid-catalyzed condensation of these with **7** to yield **14** (Scheme 3).

In order to avoid complications arising from a further reaction of the reactive nitrate, **13**, we then filled the unoccupied positions in **7** with bromine atoms and treated the dibromo derivative, **8**, thus obtained with nitric acid. Compound **8** was quite slow to react with nitric acid alone in dichloromethane at a low temperature. However, in the presence of a catalytic amount of sulfuric acid, it underwent a facile side-chain substitution to afford a pasty substance, from which 3,4-dibromo-5-methyl-2-(nitrooxymethyl)thiophene (**15**) was isolated as a major product. Thus, the removal of a benzene ring from the benzo[*b*]thiophene system led to a change in the mode of the side-chain reaction of the thiophene nucleus from nitration to nitrooxylation. This remarkable effect of the fused benzene ring parallels that observed in the reactions of benzenes and higher polybenzenoid hydrocarbons and may be taken to indicate that the side-chain reaction of the thiophenes also proceeds through a heterolytic mechanism similar to that depicted in Scheme 1.

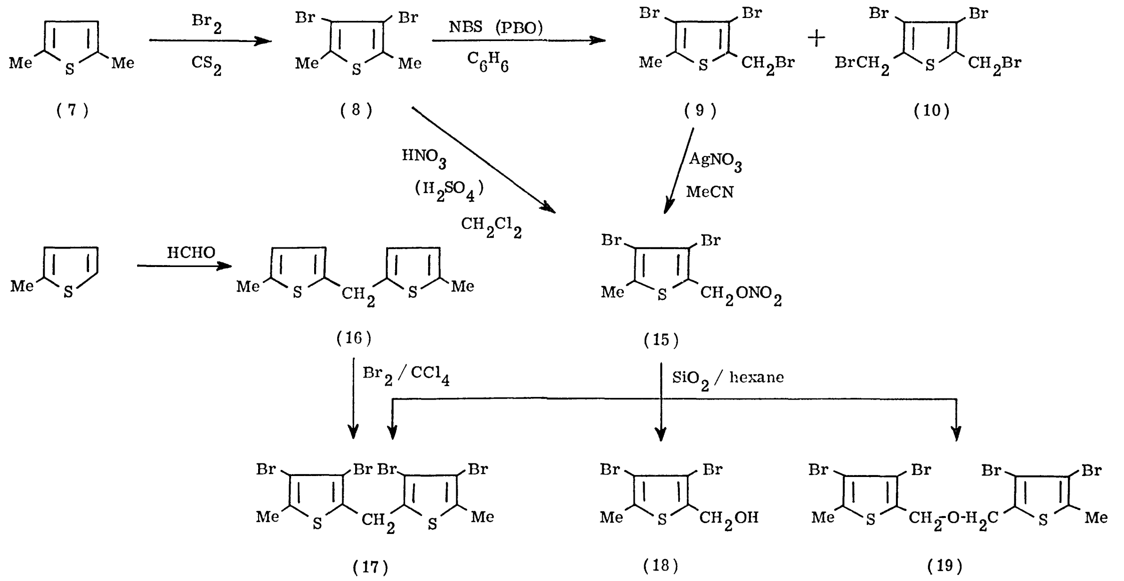


Scheme 2.

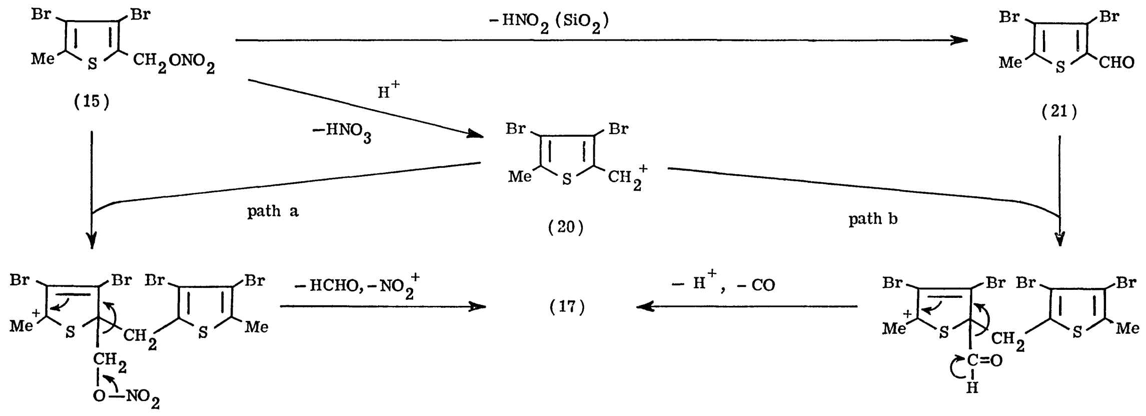
When an attempt was made to purify crude **15** by thin-layer chromatography over silica gel (Merck Kieselguhr 60 GF_{254}), using hexane as the eluant, we obtained a small amount of a crystalline compound, **17** (mp 149—150 °C), in addition to the expected 3,4-dibromo-2-hydroxymethyl-5-methylthiophene (**18**) and bis(3,4-dibromo-5-methyl-2-thenyl) ether (**19**) (Scheme 4). The elemental analysis and molecular weight of **17** were consistent with a formula of $C_{11}H_8Br_4S_2$. Its infrared spectrum (CDCl$_3$) showed prominent bands at ν_{max} 1540, 1420, 1300, 1120, and 835 cm^{-1}, and its ^{1}H NMR spectrum (CDCl$_3$) contained peaks at δ 2.40 and 4.22 ppm, with a relative intensity ratio of 3 : 1. Its mass spectrum exhibited peaks at *m*/*e* 524 (M$^+$), 445 (M$^+$—Br), 364 (M$^+$—2 Br), and 269 (M$^+$—$C_5H_3Br_2S$). These data are consistent with the structure of 3,3′,4,4′-tetrabromo-5,5′-dimethyldi-2-thienylmethane (**17**). This structural assignment was confirmed by an unequivocal synthesis of an authentic sample of **17**; 2-methylthiophene was condensed with formaldehyde in the presence of an acid catalyst to give 5,5′-dimethyldi-2-thienylmethane (**16**), which was



Scheme 3.



Scheme 4.



Scheme 5.

then brominated in the dark to give **17** (mp 150—151 °C), identical in all respects with a sample obtained from **15**. That compound **17** had been formed during chromatography over silica gel was confirmed by an experiment in which **15** and silica gel were stirred together in hexane overnight at room temperature to yield an appreciable amount of **17**, along with other products. The previous literature contains no references to the formation of diarylmethanes during the chromatography of arylalkyl nitrates. The unexpected formation of **17** from **15** lacks a convincing explanation at present; so, too, does the fate of the missing carbon atom. However, we suggest two possible reaction pathways, as outlined in Scheme 5. According to this scheme, nitrate **15** undergoes the acid-induced C–O bond cleavage on the silica gel surface to form a carbonium-ion intermediate, **20**, which may subsequently replace the nitrooxymethyl group in **15** (Path a) or expel the formyl group from aldehyde **21** (Path b). Activated primary nitrates are known to undergo acid-catalyzed decomposition to give aldehydes.[6]

It is interesting to compare this coupling reaction with that reported by King and Brown, where diethyl 4,4′-dimethyl-5,5′-methylenedi-2-pyrrolecarboxylate is obtained in the nitration of ethyl 4,5-dimethyl-2-pyrrolecarboxylate.[7] Although they suggested the implication of a nitromethyl function in the unexpected pyrromethane formation, the present result seems to favor the role of a nitrooxymethyl function. The scope and possible utility of this novel coupling reaction is currently being investigated.

Experimental

The melting points were determined on a hot-stage apparatus and are uncorrected. The infrared spectra were run as Nujol mulls on a Hitachi 215 spectrophotometer. The ^{1}H NMR spectra were determined in deuteriochloroform on a Varian T-60 spectrometer, using TMS as the internal standard, unless otherwise stated. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with an ionizing current of 70 eV, and bromine-containing peaks have been reported for ^{79}Br. Thin-layer chromatographic separations were carried out on Merck Kieselguhr 60 GF$_{254}$ plates. 2,5-Dimethylthiophene (**7**) was prepared from 2,4-pentanedione as has previously been reported.[8] 2,3,5-

Trimethylthiophene and tetramethylthiophene were obtained by treating an appropriate polymethylthiophene with *N*-methylformanilide and phosphoryl chloride and by then reducing the resulting aldehyde by the Wolff-Kishner method.[9,10]

*3,4-Dibromo-2-(bromomethyl)-5-methylthiophene (**9**).* A solution of 3,4-dibromo-2,5-dimethylthiophene (**8**; mp 45—46 °C; 0.9 g; 3.3 mmol) and benzoyl peroxide (BPO; 10 mg; 0.04 mmol) in dry benzene (5 ml) was brought to reflux; a mixture of *N*-bromosuccinimide (0.6 g; 3.4 mmol) and BPO (10 mg; 0.04 mmol) was then added, portion by portion over a period of 10 min. The mixture was kept under reflux for another 10 min and then allowed to cool. A white precipitate was removed by filtration, and the filtrate evaporated under reduced pressure. The solid residue (1.20 g) crystallized out from hexane in two different forms, which were separated by hand-picking.

Large cubes were recrystallized from hexane and identified as **9**. Mp 68—69 °C. Yield, 0.54 g (46%). ^{1}H NMR (CCl$_4$): δ 2.40 (s, 3H) and 4.60 ppm (s, 2H); IR $\nu_{\max}$ 1425, 1300, 1205, 1190, 1160, 1100, and 900 cm^{-1}. Found: C, 20.79; H, 1.46%. Calcd for $C_6H_5Br_3S$: C, 20.65; H, 1.44%.

Needles were recrystallized from hexane and identified as *3,4-dibromo-2,5-bis(bromomethyl)thiophene (**10**)*. Mp 117—118 °C. Yield, 0.20 g (14%). ^{1}H NMR (CCl$_4$): δ 4.61 ppm (s, 4H); IR $\nu_{\max}$ 1420, 1305, 1220, 1200, 1115, and 905 cm^{-1}. Found: C, 17.11; H, 0.97%. Calcd for $C_6H_4Br_4S$: C, 16.84; H, 0.94%.

*3,4-Dibromo-5-methyl-2-(nitrooxymethyl)thiophene (**15**).* Silver nitrate (0.09 g; 0.53 mmol) was added to a solution of **9** (0.175 g; 0.50 mmol) in acetonitrile (5 ml), after which the mixture was stirred at room temperature for 1 h. The silver bromide was removed by filtration, and the filtrate was evaporated to give a solid residue, which was subsequently recrystallized from pentane; white needles; mp 50—51 °C. Yield, 0.09 g (54%). ^{1}H NMR (CCl$_4$): δ 2.47 (s, 3H) and 5.53 ppm (s, 2H); IR: $\nu_{\max}$ 1620, 1295, 950, and 880 cm^{-1}. Found: C, 22.06; H, 1.57%; N, 3.97%. Calcd for $C_6H_5NO_2Br_2S$: C, 21.77; H, 1.52; N, 4.23%.

*5,5′-Dimethyldi-2-thienylmethane (**16**).* A mixture of 2-methylthiophene (3.63 g; 37 mmol), zinc chloride (3.40 g; 25 mmol), and concentrated hydrochloric acid (2.55 ml; 43 mmol) was stirred at -7—0 °C, after which an aqueous solution of formaldehyde (2.35 g; 29 mmol) was added, drop by drop, over a period of 1.5 h. After the addition was complete, stirring was continued for 1 h, and then the mixture was diluted with water. A white precipitate was collected by filtration, the aqueous phase was extracted with ether, and the solvent was evaporated. The solid products were combined and recrystallized from methanol to give **16** as white needles (0.956 g; 25%); mp 32—34 °C. ^{1}H NMR: δ 2.42 (s, 6H), 4.10 (s, 2H), and 6.53 ppm (s, 4H). Found: C, 63.29; H, 5.86%. Calcd for $C_{11}H_{12}S_2$: C, 63.41; H, 5.81%.

*3,3′,4,4′-Tetrabromo-5,5′-dimethyldi-2-thienylmethane (**17**).* Into a solution of the above dithienylmethane, **16** (0.1 g; 48 mmol), in carbon disulfide (5 ml) cooled to -10 °C, bromine (0.308 g; 198 mmol) in the same solvent (5 ml) was stirred, drop by drop, over a period of 4 h. The mixture was kept for 5 h at this temperature and then worked up as usual, giving a crude bromo derivative (0.22 g). This was chromatographed on a thick-layer silica gel plate, using hexane as the eluant, to afford **17** as fine needles (0.089 g; 35%); mp 148—149 °C. ^{1}H NMR: δ 2.43 (s, 6H) and 4.23 ppm (s, 2H); IR: $\nu_{\max}$ 1290 and 940 cm^{-1}.

Reaction of 2,5-Dimethylthiophene with Copper(II) Nitrate in Acetic Anhydride. To a solution of copper(II) nitrate trihydrate (1.2 g; 5 mmol) in acetic anhydride (15 ml), cooled to -10—-15 °C, **7** (1.1 g; 9.8 mmol) in the same solvent (15 ml) was added, drop by drop, over a period of 30 min; the mixture was then stirred at this temperature for an additional 30 min. A change in color from blue to deep green was observed. Water (20 ml) and then ether (20 ml) were added, and the acetic anhydride was allowed to hydrolyze at room temperature. The organic phase was separated, and the aqueous phase was extracted with hexane. The combined organic solutions were washed with water until neutral, and then evaporated. An oily residue (0.937 g) was chromatographed over silica gel, using hexane as the eluant, to give *2,5-dimethyl-3-(5-methyl-2-thenyl)thiophene* (**14**; 0.253 g; 23%) and *3-nitro-2,5-dimethylthiophene* (**11**; 0.263 g; 17%) as major products.

11: yellow needles; mp 29—30 °C; ^{1}H NMR (CCl$_4$): δ 2.42 (s, 3H), 2.70 (s, 3H), and 7.12 ppm (s, H); IR (neat): $\nu_{\max}$ 1530, 1485, 1360, 1315, 1260, 1195, 790, and 750 cm^{-1}. MS: *m/e* 157 (M$^+$), 140, 127, 112, 110, 85, 72, 67, and 59. Found: C, 46.06; H, 4.76; N, 9.16%. Calcd for $C_6H_7O_2NS$: C, 45.85; H, 4.49; N, 8.91%.

14: liquid; ^{1}H NMR (CCl$_4$): δ 2.28 (s, 3H), 2.33 (s, 3H), 2.38 (s, 3H), 3.77 (s, 2H), 6.30 (s, H), 6.33 (s, H), and 6.38 ppm (s, H); IR (neat): $\nu_{\max}$ 1035, 1145, and 1215 cm^{-1}; MS: *m/e* 222 (M$^+$), 207, 124, and 111. Found: C, 64.52; H, 6.55%. Calcd for $C_{12}H_{14}S_2$: C, 64.81; H, 6.35%.

Reaction of 3,4-Dibromo-2,5-dimethylthiophene with Nitric Acid. To a stirred solution of **8** (1.0 g; 3.7 mmol) in dichloromethane (20 ml), nitric acid (1.17 g; d=1.5) in the same solvent (10 ml) was added, drop by drop. The reaction mixture gradually changed from pale violet to red purple. Then a drop of concentrated sulfuric acid was added, and the mixture was heated gently for 1 h. During this period, nitrogen dioxide was slowly evolved. The reaction mixture was then diluted with water, and the organic phase was separated, washed thoroughly with water, and evaporated *in vacuo* to give an oily residue (1.15 g), which solidified to a crystalline mass on standing in a refrigerator. This solid product was extracted with pentane to give **15** as white crystals; mp 47—48 °C. Yield, 0.614 g (50%). Mixed melting point determination with an authentic sample showed no depression (47—49 °C).

When the crude nitrate was subjected to thin-layer chromatography over silica gel, using hexane as an eluant, **17** was obtained along with **18** and **19**. Product **17** was recrystallized from hexane to give fine needles (0.020 g; 4.2%) (mp 150—151 °C), identical in all respects with an authentic sample prepared by the other route.

Found: C, 25.26; H, 1.54%. Calcd for $C_{11}H_8Br_4S_2$: C, 25.04; H, 1.66%.

Coupling of 3,4-Dibromo-5-methyl-2-(nitrooxymethyl)thiophene in the Presence of Silica Gel. Silica gel (1 g) was added to a solution of **15** (70 mg) in hexane (6 ml), after which the mixture was stirred overnight at room temperature. The supernatant liquid was then decanted and evaporated to give a solid residue (53 mg), which was chromatographed on a thin-layer silica gel plate, using hexane as the eluant. From the main band, **17** (7.6 mg; 14%) was obtained and identified by means of its melting point and spectral characteristics.

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