Table II

Data from the Nmr Spectra of Solutions V, VI, VII and VIII

CH₂X	Chemical shifts of solutions, cps (area)			
	V	VI	VII	VIII
N_2	303.6 (1)	299.3 (30)	301.1 (9)	
N_3	288.6 (1)	284.3 (30)	286.4 (9)	
$N_2 - N_3$	15.0	15.0	14.7	
O_2		293.7 (7)	295.6 (5)	
O_3		282.2 (7)	284.3 (5)	
$O_2 - O_3$		11.5	11.3	
P_2		296.3 (19)	298.0 (24)	
P_3		272.4 (19)	274.7 (24)	
$P_2 - P_3$		23.9	23.3	
Q_2		291.4 (3)	293.4 (15)	297.2 (1)
Q_3		270.1 (3)	272.5 (15)	276.1 (1)
$Q_2 - Q_3$		21.3	20.9	21.1

boxylate (O), methyl 2-chloromethyl-3-iodomethyl-4-methylthiophene-5-carboxylate (P) and methyl 2,3-bis(iodomethyl)-4-methylthiophene-5-carboxylate (Q). The chemical shifts[31] in cycles per second, relative to TMS (0 cps) of the CH_2Cl and CH_2I groups are determined and tabulated in Table II. The meaning of the letters N_2, N_3, etc., is analogous to those in A.

From the relative area (in brackets, behind the chemical shifts) the relative reactivity of the CH_2Cl groups in the 2 and 3 position, respectively, of **30** can be determined as $(3 + 7):(3 + 19) = 1:2$ (for solution VI) and as $(15 + 5):(15 + 24) = 1:2$ (for solution VII).

Registry No.—**2**, 18354-60-4; **3**, 18354-61-5; **4**, 250-35-1; **5**, 18354-63-7; **6**, 18354-64-8; **10**, 10095-90-6; **11**, 18354-66-0; **12**, 18354-67-1; **13**, 18354-68-2; **14**, 18354-69-3; **15**, 18354-70-6; **16**, 18354-71-7; **25**, 18354-72-8; **26**, 18354-73-9; **27**, 18448-62-9; **28**, 18354-74-0; **30**, 18354-75-1; **31**, 18354-76-2; **32**, 18354-77-3; **33**, 18354-78-4.

Acknowledgment.—We thank Mr. K. Hovius for help in the syntheses of several compounds described in this article.

[31] All signals are singlets.

The Synthesis of 1H,3H-Thieno[3,4-*c*]furan. Another Example of Steric Inhibition of Intramolecular Cyclization by *ortho* Substituents[1]

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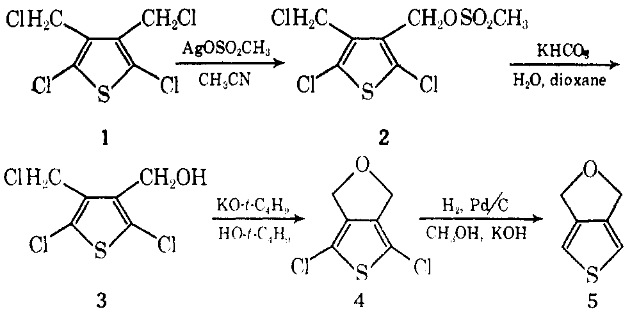
For the synthesis of 1H,3H-thieno[3,4-c]furan (**5**), it was found necessary to prepare 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (**3**). Cyclization, with potassium *t*-butoxide as base, and catalytic dechlorination furnished the title compound **5**. Attempts to synthesize 4,6-dichloro-1H,3H-thieno[3,4-*c*]furan (**4**) by treatment of the hydroxy chloride **3** with sodium hydroxide in water–dioxane were unsuccessful and bis(2,5-dichloro-3-hydroxymethyl-4-thenyl) ether (**9**) was obtained. This is another example of steric inhibition of intramolecular cyclization by *ortho* substituents.

In continuation of our studies of the synthesis and properties of anellated five-membered rings on thiophene,[2–7] we wish to describe the synthesis of 1H,3H-thieno[3,4-*c*]furan (**5**).

Reaction of 2,5-dichloro-3,4-bis(chloromethyl)thiophene (**1**)[6] with 0.5 equiv of silver methanesulfonate[8] in acetonitrile gave the mesylate of 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (**2**) in 55% yield. Treatment of a solution of mesylate **2** in water–dioxane with potassium hydrogen carbonate furnished 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (**3**) in 82% yield (Scheme I). Ring closure of hydroxy chloride **3** to 4,6-dichloro-1H,3H-thieno[3,4-*c*] furan (**4**) was effected in 25% yield, using potassium *t*-butoxide in *t*-butyl alcohol. Catalytic dechlorination of **4** furnished 1H,3H-thieno[3,4-*c*]furan (**5**), mp 53–54°, in 45% yield.

Scheme I



In the reaction of tetrachloride **1** with 0.5 equiv of silver methanesulfonate, dimesylate **6** was isolated as a by-product in 9% yield (Scheme II). Dimesylate **6** was obtained in 71% yield on treatment of tetrachloride **1** with more than 2 equiv of silver methanesulfonate. Reaction of dimesylate **6** with potassium carbonate in water–dioxane gave 2,5-dichloro-3,4-bis(hydroxymethyl)thiophene (**7**) in 87% yield. The same product was obtained in 65% yield on boiling dimesylate **6** with water. Dihydroxy compound **7** was obtained in 70% yield on treatment of tetrachloride **1** with boiling water.[6] The last-mentioned reactions normally give the dihydroxy analogs, in contrast to the reaction

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[1] Abstracted in part from the doctoral dissertation of D. J. Z., Sept 8, 1967, Groningen.

[2] H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.*, **29**, 1919 (1964).

[3] D. J. Zwanenburg, H. de Haan, and H. Wynberg, *ibid.*, **31**, 3363 (1966).

[4] H. Wynberg and D. J. Zwanenburg, *Tetrahedron Lett.*, 761 (1967).

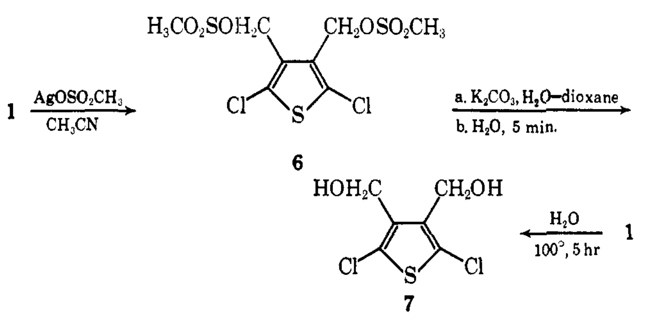
[5] D. J. Zwanenburg, J. Feyen, and H. Wynberg, *Rec. Trav. Chim. Pays-Bas*, **86**, 589 (1967).

[6] D. J. Zwanenburg and H. Wynberg, *J. Org. Chem.*, **34**, 335 (1969).

[7] Doctoral dissertation of D. J. Z.

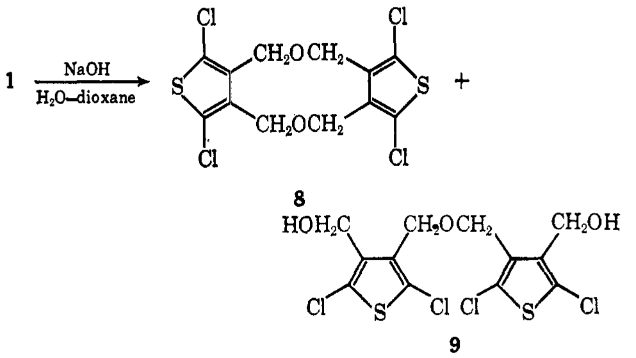
[8] W. D. Emmons and A. F. Ferris, *J. Amer. Chem. Soc.*, **75**, 2257 (1953).

SCHEME II



of 3,4-bis(chloromethyl)-2,5-dimethylthiophene with water at 70–80°. Gol'dfarb and Kondakova[9] obtained 1,3,7,9-tetramethyl-4H,6H,10H-dithieno[3,4-c]:[3',4'-f]oxocin in 51% yield in the last reaction.

Reaction of tetrachloride **1** with sodium hydroxide in water–dioxane gave two products, namely, 1,3,7,9-tetrachloro-4H,6H,10H,12H-dithieno[3,4-c:3',4'-h][1,6]dioxecin (**8**) and bis(2,5-dichloro-3-hydroxymethyl-4-thenyl) ether (**9**).



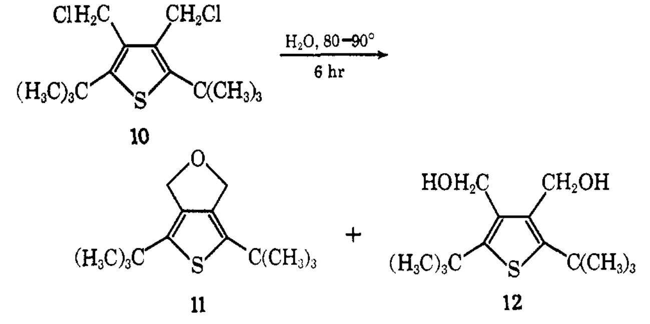
Attempts to cyclize hydroxy chloride **3** to thienofuran **4** using sodium hydroxide in water–dioxane were unsuccessful. Instead, ether **9** was obtained in 49% yield.

$$3 \xrightarrow[\text{H}_2\text{O–dioxane}]{\text{NaOH}} 9$$

Discussion

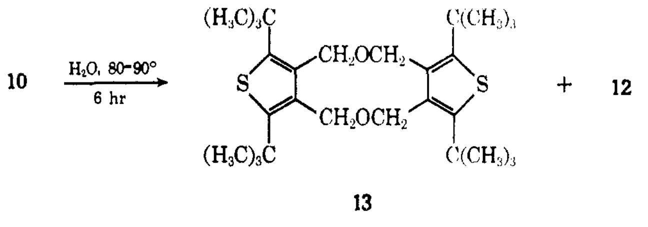
Reaction of 2,5-dichloro-3chloromethyl-4-hydroxymethylthiophene (**3**) with potassium *t*-butoxide in *t*-butyl alcohol furnished thienofuran **4**, whereas reaction of **3** with sodium hydroxide in water–dioxane did not. In the last case, sodium hydroxide is not basic[10,11] enough to abstract a proton from the OH group in **3**. The formation of intermolecular products (**8** and **9**) or intramolecular product **4** as a function of reaction conditions indicates that the two reaction paths are sensitive to a number of factors which are not readily unraveled. The intramolecular alcoholysis of **3** to a thienofuran is sterically inhibited by the chlorine atoms at the nucleus of thiophene and other reactions take place. This is another example of steric inhibition of intramolecular cyclization by *ortho* substituents.[6] In the reaction of **3** with potassium *t*-butoxide, the base[10] abstracts a proton from the OH group in **3** to form anion $-CH_2O^-$. The steric hindrance of the chlorine atoms at the thiophene nucleus can be overcome with this highly nucleophilic anion.

The Reaction of 2,5-Di-*t*-butyl-3,4-bis(chloromethyl)thiophene (10) with Water.—Gol'dfarb and Kondakova obtained a product with mp 220–221° and 2,5-di-*t*-butyl-3,4-bis(hydroxymethyl)thiophene (**12**) in the reaction of 2,5-di-*t*-butyl-3,4-bis(chloromethyl)thiophene (**10**) with water.[9] Gol'dfarb and Kondakova



assigned structure **11** to the compound with mp 220–221° on the basis of the elemental analysis and the reaction with thionyl chloride, giving dichloride **10**.

The formation of thienofuran **11** in the reaction of dichloride **10** with the weakly nucleophilic water seemed unlikely to us. We repeated the reaction of dichloride **10** with water using the method described by Gol'dfarb and Kondakova.[9] Our results were in accordance with those of the Russian authors. The compound with mp 220–221° was found to have a molecular weight of 478 and 476. Therefore, structure **11**, claimed by Gol'dfarb and Kondakova, cannot be correct. The spectral properties (nmr and ir spectra, see Experimental Section), the elemental analysis and the molecular weight are in accordance with the structure 1,3,7,9-tetra-*t*-butyl-4H,6H,10H,12H-dithieno[3,4-c:3',4'-h][1,6]dioxecin (**13**). The "structure proof" of Gol'dfarb and Kondakova holds of course for the dimeric structure **13** as well; with thionyl chloride, the latter will give dichloride **10**, as would compound **11**.



Experimental Section

All melting points are corrected. The boiling points are uncorrected. Nmr spectra were determined on a Varian A-60, using tetramethylsilane (TMS, τ 10) as internal standard, uv spectra in 95% alcohol using a Zeiss P.M.Q. II, ir spectra on a Unicam S.P. 200, and mass spectra on MS-9 mass spectrometer. Microanalyses were carried out in the analytical section of our department under the direction of Mr. W. M. Hazenberg.

Mesylate of 2,5-Dichloro-3-chloromethyl-4-hydroxymethylthiophene (2).—A solution of 20.3 g (0.10 mol) of silver methanesulfonate[8] in 250 ml of anhydrous acetonitrile was added to a boiling solution of 50.0 g (0.20 mol) of 2,5-dichloro-3,4-bis(chloromethyl)thiophene (**1**)[6] in 500 ml of anhydrous acetonitrile, during 2 hr. After the addition the reaction mixture was re-

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[9] Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1208 (1956).

[10] The pK_a values[11] of benzyl alcohol, *t*-butyl alcohol and water are 18, 19 and 15.7, respectively.

[11] D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 4.

fluxed for 2 hr. After cooling, the reaction mixture was filtered, concentrated *in vacuo* and extracted with benzene. The benzene solution was concentrated and the residue was extracted with hot petroleum ether (bp 60–80°). The petroleum ether solution was treated with charcoal and concentrated to a volume of 500 ml. After cooling to −20°, 15.4 g of monomesylate **2** was obtained: mp 58–59°; uv max 257 mμ (ε 5700); ir (KBr) 1360 and 1175 cm^{-1} ($ROSO_2R$); nmr (10% in CCl_4) τ 4.84 (s, 2, Ar**CH$_2$**OSO$_2$CH$_3$), 5.43 (s, 2, Ar**CH$_2$**Cl), 7.03 (s, 3, -OSO$_2$**CH$_3$**).

Anal. Calcd for $C_7H_7Cl_3O_3S_2$ (309.62): C, 27.16; H, 2.26; S, 20.72. Found: C, 27.1, 27.3; H, 2.2, 2.5; S, 20.9, 20.9.

The petroleum ether filtrate was concentrated to 250 ml and cooled to −80° giving 27.5 g of the starting material **1**.

The residue which remained behind after the petroleum ether extraction was crystallized from carbon tetrachloride giving 3.1 g, mp 83–85°, of the dimesylate of 2,5-dichloro-3,4-bis(hydroxymethyl)thiophene (**6**, see below). The yield of **2** and **6**, based on recovered **1**, was 55 and 9%, respectively.

2,5-Dichloro-3-chloromethyl-4-hydroxymethylthiophene (3).—A solution of 13.9 g (0.045 mol) of mesylate **2** in 225 ml of dioxane and 150 ml of water was warmed up to the boiling point. Potassium hydrogen carbonate was added until the CO_2 liberation stopped. The reaction mixture was refluxed for 15 min. After cooling the solution was saturated with NaCl and extracted with ether. The ethereal extract was dried ($CaCl_2$) and concentrated. The residue was purified by column chromatography (silica gel, tube 40 cm long and 2.4 cm diameter, eluent benzene). After 0.1 g of mesylate **2**, 8.5 g (82%) of 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (**3**) was obtained: mp 79–80° (from petroleum ether, bp 60–80°); uv max 251 mμ (ε 5900); ir (KBr) 3300 cm^{-1} (OH); nmr (10% in $CDCl_3$) τ 5.37 (s, 2, **CH$_2$**OH), 5.39 (s, 2, **CH$_2$**Cl), 7.56 (broad s, 1, **OH**).

Anal. Calcd for $C_6H_5Cl_3OS$ (231.52): C, 31.11; H, 2.18; Cl, 45.95. Found: C, 31.1, 31.4; H, 2.3, 2.3; Cl, 45.6, 45.6.

4,6-Dichloro-1H,3H-thieno[3,4-*c*]furan (4).—A solution of 9.3 g (0.04 mol) of hydroxy chloride **3** in 200 ml of anhydrous *t*-butyl alcohol and a solution of 2.3 g (0.06 g-atom) of potassium in 200 ml of anhydrous *t*-butyl alcohol were added to 400 ml of boiling *t*-butyl alcohol during 3 hr, in a nitrogen atmosphere. After the addition, the reaction mixture was stirred and boiled for 2 hr, and concentrated *in vacuo*. The residue was taken up in ether and water. The ethereal extract was dried ($CaCl_2$) and concentrated. The residue was purified by column chromatography (silica gel, tube 40 cm long and 2.4 cm diameter, eluents CCl_4 and benzene) giving 1.95 g (25%) of thienofuran **4**: mp 48–49°, after sublimation [30° (0.1 mm)]; uv max 247 mμ (ε 10,000); ir (KBr) 1130 cm^{-1} (-CH_2OCH_2-); nmr (10% in CCl_4) τ 5.36 (s, Ar**CH$_2$**O-).

Anal. Calcd for $C_6H_4Cl_2OS$: C, 36.94; H, 2.07; S, 16.43; mol wt, 195.06. Found: C, 36.9, 36.8; H, 2.1, 2.1; S, 16.4, 16.3; mol wt (in ethyl acetate), 202, 203.

1H,3H-Thieno[3,4-*c*]furan (5).—To a suspension of 1.8 g of 10% Pd/C in 50 ml of methanol was added a solution of 1.1 g (5.7 mmol) of **4** and 1.8 g (32 mmol) of KOH in 50 ml of methanol. The reaction mixture was refluxed and a slow stream of hydrogen was bubbled through the mixture. After a reaction time of 22 hr a suspension of 0.5 g of 10% Pd-C in 50 ml of methanol was added to the reaction mixture and hydrogen was bubbled through the mixture for another 18 hr. The reaction mixture was filtered and concentrated *in vacuo*. The residue was taken up in water and ether. The ethereal solution was dried ($CaCl_2$) and concentrated. The residue was crystallized from petroleum ether (bp 40–60°) at low temperature (−70°) giving 320 mg (45%) of 1H,3H-thieno[3,4-*c*]furan (**5**): mp 53–54°; uv max 244 mμ (ε 6600); nmr (10% in CCl_4) τ 3.26 (s, 2, thiophene aromatic), 5.26 (s, 4, Ar**CH$_2$**O-).

Anal. Calcd for C_6H_6OS (126.17): C, 57.11; H, 4.78; S, 25.42. Found: C, 57.1; H, 4.9; S, 24.6.

Dimesylate of 2,5-Dichloro-3,4-bis(hydroxymethyl)thiophene (6).—To a solution of 20.4 g (0.1 mol) of silver methanesulfonate[8] in 100 ml of anhydrous acetonitrile was added 10.0 g (0.04 mol) of 2,5-dichloro-3,4-bis(chloromethyl)thiophene (**1**). The solution was stirred for 3 hr at room temperature and refluxed for 1 hr. After cooling, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was extracted with benzene. The benzene solution was concentrated and the residue was crystallized from carbon tetrachloride giving 10.5 g (71%) of the unstable dimesylate **6**: mp 85–86°; uv max 256 mμ (ε 5800); ir (KBr) 1350 and 1190 cm^{-1} ($ROSO_2R$); nmr (20% in $CDCl_3$) τ 4.75 (s, 2, Ar**CH$_2$**O-), 6.92 (s, 3, OSO$_2$**CH$_3$**).

Anal. Calcd for $C_8H_{10}Cl_2O_6S_3$ (369.26): C, 26.02; H, 2.72; S, 26.05. Found: C, 25.9, 25.9; H, 2.8, 2.8; S, 25.5, 25.5.

2,5-Dichloro-3,4-bis(hydroxymethyl)thiophene (7).—A solution of 3.7 g (0.01 mol) of dimesylate **6** in 75 ml of water and 75 ml of dioxane was refluxed for 5 min and 2.1 g (0.02 mol) of Na_2CO_3 was added in 5 min. The reaction mixture was boiled for 5 min and after cooling saturated with NaCl. The reaction mixture was extracted with ether. The ethereal extract was dried ($CaCl_2$) and concentrated. The residue was crystallized from carbon tetrachloride giving 1.85 g (87%) of the dihydroxy compound **7**: mp 107–107.5°; uv max 248 mμ (ε 6700); ir (KBr) 3350 cm^{-1} (OH); nmr (4% in $CDCl_3$) τ 5.42 (broad s, 4, **CH$_2$**OH), 6.33 (broad s, 2, CH$_2$**OH**); nmr (10% in CD_3COCD_3) τ 5.36–5.52 (m).

Anal. Calcd for $C_6H_6Cl_2O_2S$ (213.08): C, 33.82; H, 2.84; S, 15.04. Found: C, 34.0, 33.7; H, 2.9, 2.9; S, 15.2, 14.8.

The dihydroxy compound **7** was obtained in 65% yield on boiling 2.0 g (5.4 mmol) of dimesylate **6** with 75 ml of water for 5 min. The hot reaction mixture was filtered and after cooling 0.75 g (65%) of **7**, mp 106–107°, was obtained.

Reaction of 2,5-Dichloro-3,4-bis(chloromethyl)thiophene (1) with Sodium Hydroxide in Water–Dioxane.—A solution of 3.2 g (0.08 mol) of NaOH in 100 ml of water and 100 ml of dioxane was added to a stirred, boiling solution of 10.0 g (0.04 mol) of tetrachloride **1** during 8 hr. After the addition the reaction mixture was refluxed and stirred for 15 hr. After cooling the precipitate was collected (for the filtrate, see below) and crystallized from chloroform giving 3.0 g (38%) of the dithienodioxecin **8**: mp 270–271°; uv max (CH_2Cl_2)[12] 246 mμ (ε 14,400); ir (KBr) 1090 cm^{-1} (CH_2OCH_2), nmr (5% in pyridine) τ 5.49 (s, Ar**CH$_2$**O-).

Anal. Calcd for $C_{12}H_8Cl_4O_2S_2$: C, 36.94; H, 2.07; S, 16.43; mol wt, 390.12. Found: C, 36.9, 36.7; H, 2.1, 2.1; S, 16.3, 16.3; mol wt (mass spectroscopy), 388 (on basis of ^{32}S and ^{35}Cl).

The filtrate was poured into water. The precipitate (3.0 g) was collected and crystallized from $CHCl_3$ giving 0.85 g (10%) of ether **9**: mp 179.5–180.5°; uv max 247.5 mμ (ε 12,400); ir (KBr) 3350 (OH) and 1070 cm^{-1} (-CH_2OCH_2-); nmr (10% in pyridine) τ 5.17 (s, 4, **CH$_2$**OH), 5.23 (s, 4, -**CH$_2$**O**CH$_2$**-).

Anal. Calcd for $C_{12}H_{10}Cl_4O_3S_2$: C, 35.30; H, 2.49; Cl, 34.75; S, 15.71; mol wt, 408.16. Found: C, 35.0, 35.2; H, 2.4, 2.5; Cl, 35.0, 35.2; S, 15.7, 15.6; mol wt (in ethyl acetate), 397, 408.

In the $CHCl_3$ mother liquors, **9** and **4** could not be detected (tlc, silica gel, eluent benzene).

Reaction of 2,5-Dichloro-3-chloromethyl-4-hydroxymethylthiophene (3) with Sodium Hydroxide in Water–Dioxane.—A solution of 1.15 g (0.005 mol) of hydroxy chloride **3** in 25 ml of water and 25 ml of dioxane was added in 2.5 hr to a boiling solution of 0.40 g (0.01 mol) of NaOH in 25 ml of water and 25 ml of dioxane. After the addition the reaction mixture was boiled for 1 hr. After cooling in ice the precipitate was collected and crystallized from carbon tetrachloride giving 0.5 g (49%) of ether **9**: mp 179–180°. In the mother liquor no thienofuran **4** could be detected.

Reaction of 2,5-Di-*t*-butyl-3,4-bis(chloromethyl)thiophene (10) with Water According to Gol'dfarb and Kondakova.[9]—A stirred mixture of 5.0 g (0.017 mol) of 2,5-di-*t*-butyl-3,4-bis(chloromethyl)thiophene (**10**)[13] and 70 ml of water was heated at 80–90° for 6 hr. After the work-up as described by Gol'dfarb and Kondakova[9] 0.8 g of dihydroxy compound **12**, mp 167–169° (lit.[9] mp 167–169°), and 0.5 g of a colorless solid, mp 220–221°, were obtained. The spectral data and the elemental analysis are in accordance with dithienodioxecin **13**: ir (KBr) 1090 cm^{-1} (CH_2OCH_2); nmr (10% in CCl_4) τ 5.40 (s, 4, Ar**CH$_2$**O-), 8.58 (s, 18, C(**CH$_3$**)$_3$).

Anal. Calcd for $C_{28}H_{44}O_2S_2$: C, 70.53; H, 9.31; S, 13.45; mol wt, 476.78. Found: C, 70.9, 70.8; H, 9.3, 9.2; S, 13.2, 13.3; mol wt (in ethyl acetate), 478, 476.

Registry No.—**2,** 18366-66-0; **3,** 18366-67-1; **4,** 18366-68-2; **5,** 250-34-0; **6,** 18366-70-6; **7,** 18354-72-8; **8,** 18366-72-8; **9,** 18366-73-9; **13,** 18366-74-0.

Acknowledgment.—We thank Mr. K. Hovius for help in the syntheses of several compounds described in this article.

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[12] Uv spectrum of thienofuran **4** in CH_2Cl_2, 248 mμ (ε 10,200).

[13] Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 495 (1956).