Florisil. Elution with chloroform gave 1.0 g of syrup which soon crystallized. After one recrystallization from acetone–ether, the product melted at 142–143°: ir ($CHCl_3$) 1700 cm^{-1} (indole N—C=O); nmr ($CDCl_3$) τ 2.5–2.9 (3, aromatic), 1.53 (1, indole C_{11}–H deshielded by C=O).

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.19; N, 9.99. Found: C, 76.76; H, 7.27; N, 10.17.

1,2,3,4,6,7,7a,12,12a,12b-Decahydro-7a,12-dihydroxy-1,12(γ-oxo)trimethyleneindolo[2,3-*a*]quinolizine (9).—Further development of the Florisil column described above using acetone as eluent gave 0.8 g of material which was purified by recrystallization from acetone: mp 244–245°; ir (KCl) 1650 (amide C=O); uv (MeOH) 212 mμ (ε 9800), 257 (10,900); nmr (pyridine-d_5), τ 3.40 (s, 1, C_{12}–OH), 3.92 (m, 1, C_{7a}–OH); shaking the pyridine solution with D_2O caused almost complete removal of these signals.

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.76; H, 7.05; N, 8.91. Found: C, 68.61; H, 7.23; N, 9.01.

1,2,3,4,6,7,12,12b-Octahydro-1-propylindolo[2,3-*a*]quinolizine (7).—A mixture of 2.82 g (0.010 mol) of **6a**, 50 ml of ethylene glycol, 20 ml of hydrazine hydrate and 2 g of KOH was heated under a nitrogen atmosphere at 130–132° for 2 hr. The temperature was then raised to 180° and maintained for 1 hr. The thick solution was shaken with 500 ml of ether and the extract washed with 1 l. of cold water. The aqueous extracts were counter-extracted with ether and the combined extract then concentrated *in vacuo* to give 2.9 g of thick syrup. The material was chromatographed on 100 g of neutral alumina using chloroform as eluent. The product (1.69 g) was a yellow syrup which failed to crystallize; ir ($CHCl_3$) 3480 cm^{-1} (indole N–H); uv_{max} (MeOH) 227 mμ (ε 28,000), 283 (6400). Treatment of the free base with 0.6 g of oxalic acid in ether gave an ivory-colored salt (1.95 g) which after two recrystallizations from ether–methanol melted at 177–178° (bubbling); the salt resolidified and melted again at 244–245°.

Anal. Calcd for $C_{18}H_{24}N_2 \cdot (CO_2H)_2$; N, 7.82. Found: N, 7.69.

1,2,3,6,11,12,13,14,15,15a-Decahydro-13-oxo-5H-benz[*i*]indolo[2,3-*a*]quinolizine (13).—To a stirred solution of 11.2 g (0.050 mol) of **2** in 100 ml of dry THF was added a solution of 3.50 g (0.050 mol) of methyl vinyl ketone in 50 ml of benzene over a 30-min period. The solution was stirred for 5 hr, then the solvent was removed *in vacuo*. The crude product (10.7 g) was dissolved in a little $CHCl_3$ and chromatographed on 200 g of Florisil. Elution with USP ether and concentration of the fractions gave 3.9 g of material, which on stirring with anhydrous ether gave 1.4 g of crystalline product, mp 172–177°. Recrystallization from benzene–ether–hexane gave analytically pure **13**: mp 175–176°; ir ($CHCl_3$) 3470 cm^{-1} (indole N–H), 1715 (ketone C=O), no bands in the 2700–2800-cm^{-1} region; uv (MeOH, neutral) 226 mμ (ε 32,000), 283 (7900).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.55; H, 7.55; N, 9.52. Found: C, 77.46; H, 7.53; N, 9.43.

Acknowledgment.—The authors wish to thank Dr. Dale A. Stauffer and associates for the analytical services.

Registry No.—**2**, 5912-12-9; **4a**, 18039-47-9; **4b**, 18039-48-0; **4c**, 18067-03-3; **4d**, 18039-49-1; **6a**, 18031-30-6; **6b**, 18031-31-7; **6b**·HCl, 18031-32-8; **6c**, 18031-33-9; **6c**·HCl, 18031-34-0; **7**, 18039-51-5; **7** oxalate, 18031-35-1; **8**, 18031-36-2; **9**, 18031-37-3; **10** oxalate, 18031-38-4; **11** oxalate, 18031-39-5; **12**, 18039-50-4.

Steric Inhibition of Intramolecular Cyclizations by *ortho* Substituents. The Synthesis of 1H,3H-Thieno[3,4-*c*]thiophene, Its 2,2-Dioxide, and 5-Ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole[1]

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Received July 22, 1968

During our study of the synthesis of anellated five-membered rings on thiophene, we discovered that some intramolecular cyclizations are adversely affected by *ortho* substituents in the aromatic ring. Reaction of 2,5-dibromo-3,4-bis(bromomethyl)thiophene with sodium sulfide furnished 4,6-dibromo-1H,3H-thieno[3,4-*c*]thiophene and ring closure of 2,5-dichloro-3,4-bis(chloromethyl)thiophene with sodium sulfide gave the 4,6-dichloro derivative. On the other hand, reaction of 2,5-dichloro-3,4-bis(chloromethyl)thiophene with ethylamine in acetonitrile does not form a thienopyrrole derivative, while cyclization to 5-ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole was successful when the chlorine atoms on the thiophene nucleus of the tetrachloride were removed prior to the reaction with ethylamine. Our explanation of the steric inhibition of intramolecular cyclization by *ortho* substituents is given.

In an earlier publication[2] we have described the synthesis of 1H,3H-thieno[3,4-*c*]thiophene (**4**) by ring closure of dimethyl 3,4-bis(bromomethyl)thiophene-2,5-dicarboxylate with sodium sulfide, followed by removal of the carbomethoxy groups. In view of the current interest in thienothiophenes,[3,4] we wish to describe here an improved preparation of thienothiophene **4**. Cyclization of 2,5-dibromo-3,4-bis(bromomethyl)thiophene (**1**)[5] with sodium sulfide gave 4,6-dibromo-1H,3H-thieno[3,4-*c*]thiophene (**2**) in 60% yield; the latter could be reduced to 1H,3H-thieno[3,4-*c*]thiophene (**4**) in 75% yield (Scheme I). The cyclization reaction also yielded the dimeric compound 1,3,7,9-tetrabromo-4H,6H,10H,12H,dithieno[3,4-*c*:3′,4′-*h*][1,6]dithiecin (**3**) in 18% yield. Oxidation of sulfide **2**, followed by zinc in acetic acid reduction, furnished 1H,3H-thieno[3,4-*c*]thiophene 2,2-dioxide (**6**) in 60% over-all yield.

As we have described, reaction of methyl 2,3-bis-

(1) Abstracted in part from the Doctoral Thesis of D. J. Z., Groningen, 1967.

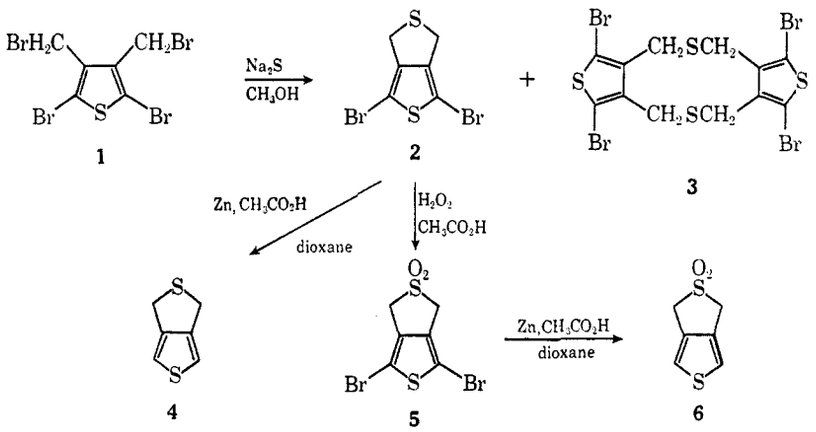
(2) H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.*, **29**, 1919 (1964).

(3) H. Wynberg and D. J. Zwanenburg, *Tetrahedron Lett.*, 761 (1967).

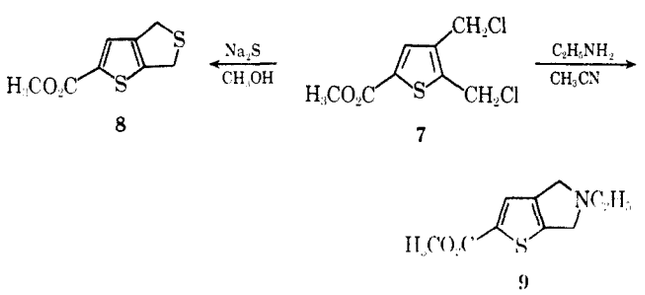
(4) M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.*, **89**, 3639 (1967).

(5) D. J. Zwanenburg and H. Wynberg, *Rec. Trav. Chim. Pays-Bas*, in press.

SCHEME I

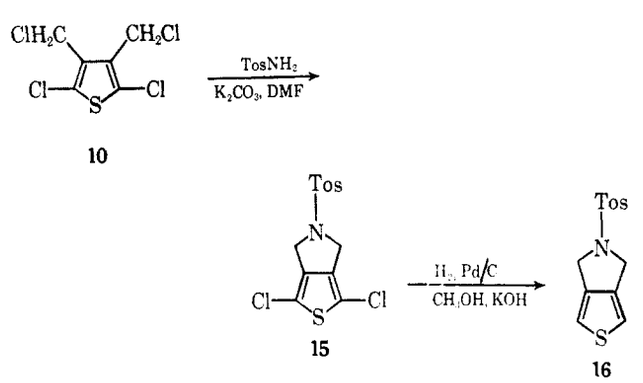


(chloromethyl)thiophene-5-carboxylate (**7**) with sodium sulfide in methanol or with ethylamine in acetonitrile gives the thienothiophene **8**[6] and the thienopyrrole **9**,[7] respectively.



In view of the results of the ring-closure reactions with sodium sulfide, and of the formation of a thienopyrrole derivative in the reaction of **7** with ethylamine, we tried to synthesize 1,3-dichloro-5-ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole by ring closure of 2,5-dichloro-3,4-bis(chloromethyl)thiophene (**10**)[8,9] with ethylamine in acetonitrile, using about the same conditions as were used in the synthesis of the thienopyrrole **9**. The attempts to prepare a thienopyrrole derivative by cyclization of tetrachloride **10** with ethylamine were unsuccessful, however. Two products were isolated, namely, 1,3,7,9-tetrachloro-5,11-diethyl-5,6,11,12-tetrahydro-4H,10H-dithieno[3,4-*c*:3′,4′-*h*][1,6]diazecine (**11**) and the open compound 2,5-dichloro-N,N′-diethyl-3,4-bis(aminomethyl)thiophene (**12**) (Scheme II). Similar results were found for the reaction of 2,5-dichloro-3,4-bis(iodomethyl)thiophene (**13**) and ethylamine in acetonitrile. The bis(iodomethyl) compound **13** was prepared from the reaction of the tetrachloride **10** with sodium iodide in acetone. The open compound **12** was further characterized by the formation of the ditosylate after reaction with *p*-tolylsulfonylchloride.

Whereas reaction of the tetrachloride **10** with ethylamine did not furnish a thienopyrrole derivative, ring closure of the tetrachloride **10** with *p*-toluenesulfonamide in dimethylformamide and potassium carbonate[10,11] as base did furnish 1,3-dichloro-5-tosyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (**15**). Subsequent catalytic dechlorination furnished 5-tosyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (**16**).



Discussion

The striking differences in the behavior of tetrachloride **10** and dichloride **7** toward ethylamine can be rationalized by a working hypothesis in which a SN2 transition state[12,13] leads to the thienopyrrole ring

(6) D. J. Zwanenburg, H. de Haan, and H. Wynberg, *J. Org. Chem.*, **31**, 3363 (1966).

(7) D. J. Zwanenburg, J. Feyen, and H. Wynberg, *Rec. Trav. Chim.*, **86**, 589 (1967).

(8) 2,5-Dichloro-3,4-bis(chloromethyl)thiophene (**10**) was synthesized in 75% yield from 2,5-dichlorothiophene using chloromethyl methyl ether and stannic chloride (see Experimental Section).

(9) Cyclization of tetrachloride **10** with sodium sulfide in methanol furnished in 48% yield the 4,6-dichloro analog of **2**.

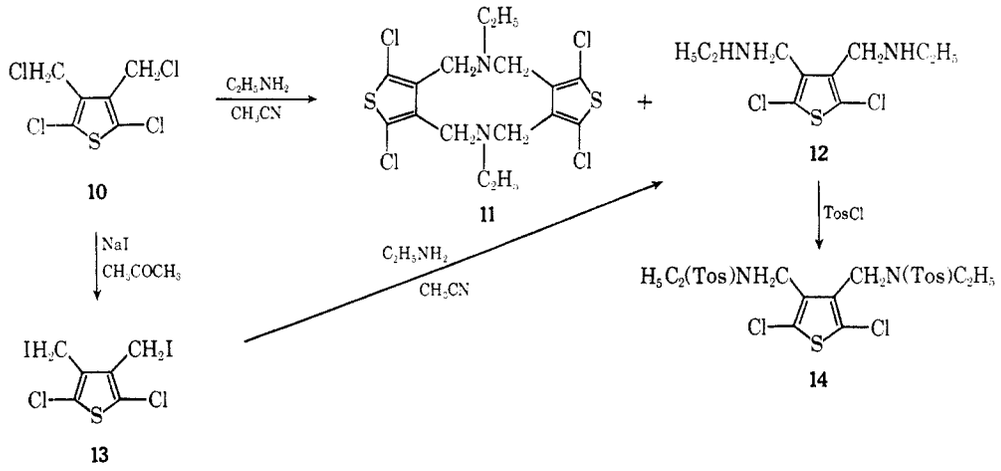
(10) This reaction was first carried out in ethanol with sodium hydroxide as base, in analogy with the reaction of *o*-xylylene dibromide and *p*-toluenesulfonamide giving 2-tosyl-1,3-dihydroisoindole[11] in 48% yield. Under these conditions thienopyrrole **15** was obtained in only 6% yield. From the nmr spectrum of the reaction mixture it appeared that a reaction had taken place between tetrachloride **10** and the solvent.

(11) J. Bornstein, S. C. Lashua, and A. P. Boiselle, *J. Org. Chem.*, **22**, 1255 (1957).

(12) Östman[13] has provided strong experimental evidence for the SN2 character of the reaction of 2- and 3-thenyl chloride with lithium chloride in dimethylformamide. Naturally our working hypothesis—namely, whether all of these cyclization reactions are truly SN2, or whether an SN1-type mechanism also plays a role—needs further investigation. Preliminary experiments indicate that the polarity of the solvent plays a role in some of these reactions, suggesting the need for detailed kinetic work.

(13) B. Östman, *J. Amer. Chem. Soc.*, **87**, 3163 (1965).

SCHEME II



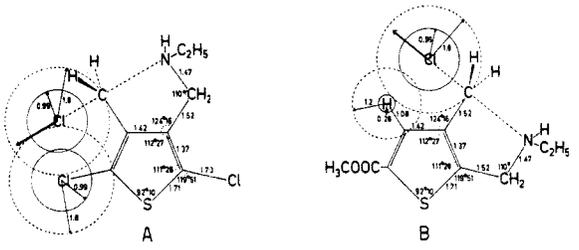
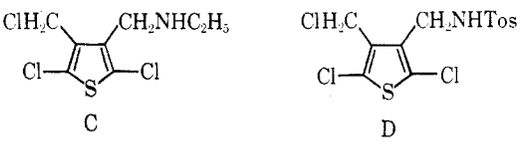


Figure 1.—An approximation of the transition states for the reactions of ethylamine with 2,5-dichloro-3,4-bis(chloromethyl)-thiophene (**10**) and methyl 2,3-bis(chloromethyl)thiophene-5-carboxylate (**7**), respectively, to the corresponding thienopyrrole derivatives. The angles and distances of the thiophene nucleus are of Bak and coworkers.[15] For the distances C_{Ar}–Cl, C_{Ar}–C, C–Cl, C–N and the angles CCN, CCCl are taken the values[16] of chlorobenzene, toluene, 1,2-dichloroethane, diethylamine diethylamine and 1,2-dichloroethane, respectively. The solid circles are the covalent radii of Cl and H respectively, and the dotted circles are the van der Waals radii of these atoms.

system. In Figure 1, an approximation of the transition states is given.[14] The figure clearly suggests that in the ring closure of tetrachloride **10** with ethylamine the leaving chloride anion suffers considerable steric hindrance from the chlorine atom attached to the thiophene nucleus. Crucial to our argument is the reasonable assumption that the entire ring-closure sequence must occur in the plane of the aromatic ring. Steric factors of this nature are not involved in the case of dichloride **7**; the hydrogen atom in this case is so small that there is no steric hindrance for the leaving chloride anion. The energy of activation in case A will be much greater, due to the steric hindrance, than in case B. On the other hand, in the transition state of the reaction of the $-CH_2NHC_2H_5$ group in the intermediate C with a $-CH_2Cl$ group of a second molecule, there will be less steric hindrance, because in this case the nitrogen has the opportunity also to attack the $-CH_2Cl$ group from above and below. The energy of activation in the dimerization reaction consequently will be smaller than those in the cyclization reaction



to a five-membered ring. Likewise, the energy of activation for the reaction of intermediate C with a molecule of ethylamine will be smaller than those for the cyclization reaction to a five-membered ring. Also, the intramolecular cyclization of the intermediate C to a five-membered ring does not occur by reason of the high energy of activation.

The fact that a reaction between tetrachloride **10** and *p*-toluenesulfonamide furnished a thienopyrrole derivative is not in contradiction with the given explanation, for the nucleophilicity of the anion of the $-NHSO_2C_6H_4CH_3$ group in intermediate D is considerably greater than the nucleophilicity of the $-NHC_2H_5$ group in the intermediate C.[15] For the same reason the reaction of tetrachloride **10** with sodium sulfide does furnish a five-membered ring, for the $-CH_2S^-$ group is also a strong nucleophile.

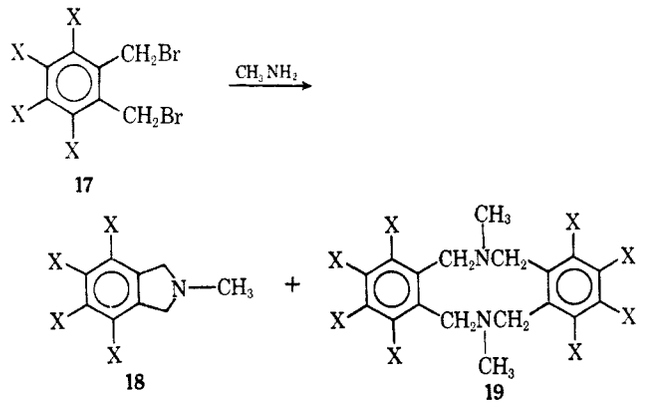
Evidence from the Literature.—In the literature several ring-closure reactions, which support our explanation of steric inhibition of intramolecular cyclizations, are described. Rosen and coworkers[16] obtained only a 5% yield of the isoindoline derivative **18** (X = Cl) in the reaction of 1,2-bis(bromomethyl)-3,4,5,6-tetrachlorobenzene (**17**, X = Cl) with methylamine. The main product (52%) in this reaction was the diazecine derivative **19** (X = Cl). A reaction of 1,2-bis(bromomethyl)benzene (**17**, X = H) with methylamine, however, gives isoindole **18** (X = H) in 56% yield.[17]

(14) The assumption of the transition state B, in which the chloromethyl group in the 2 position has reacted with ethylamine prior to that in which the chloromethyl group in the 3 position has reacted, is based on the work of Östman.[13] B. Bak, D. Christensen, L. Hansen-Nygaard, and J. Rastrup-Anderson, *J. Mol. Spectrosc.*, **7**, 58 (1961). "Tables of Interatomic Distances and Configuration in Molecules and Ions," L. E. Sutton, Ed., The Chemical Society, Burlington House, W.1., London, 1958.

(15) For a discussion on nucleophilicity and activation parameters see J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, pp 62, 243.

(16) W. E. Rosen, V. P. Toohey, and A. C. Shabica, *J. Amer. Chem. Soc.*, **80**, 935 (1958).

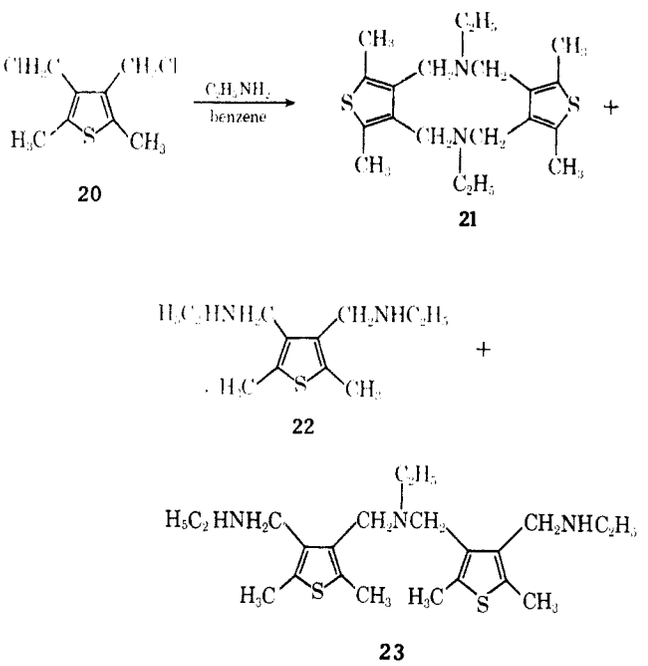
(17) G. Wittig, H. Tenhaeff, W. Schock, and G. Koenig, *Ann.*, **572**, 1 (1951).



17 18 19

Gol'dfarb and Kondakova[18] obtained no formation of a thienopyrrole derivative in the reaction of several primary amines with 3,4-bis(chloromethyl)-2,5-dimethylthiophene (**20**). In the reaction of **20** with ethylamine in benzene, a mixture of products, as indicated in Scheme III, was obtained. On treatment

SCHEME III



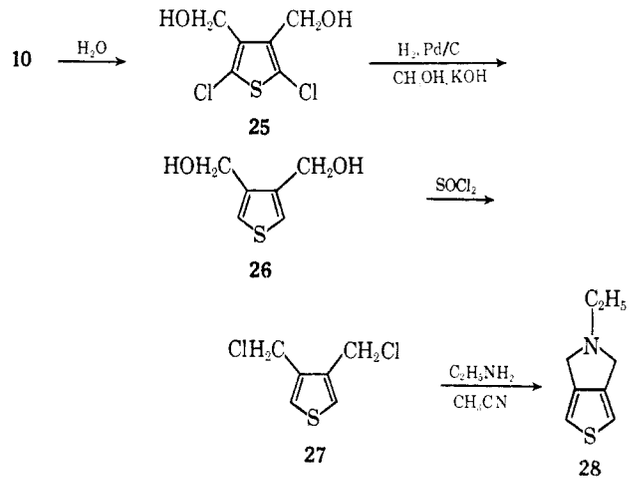
20 21 22 23

of 2,5-di-*t*-butyl-3,4-bis(chloromethyl)thiophene (**24**) with ethylamine in benzene, Gol'dfarb and Litvinov[19] obtained N,N'-diethyl-3,4-bis(aminomethyl)-2,5-di-*t*-butylthiophene in 99% yield. No thienopyrrole derivative could be detected.

The low yield of **18** (X = Cl) in the reaction of **17** (X = Cl) with methylamine and the fact that no thienopyrrole derivatives were found in the reactions of **20** and **24** with primary amines are in accordance with our results obtained in the reaction of tetrachloride **10** with ethylamine. These results are a support of our explanation "steric inhibition of intramolecular cyclizations by *ortho* substituents."

Further Experimental Evidence.—Convincing experimental support for our proposal that appropriate *ortho* substituents can inhibit SN2 cyclization in aromatic systems was found in the observation that cyclization was successful when the chlorine atoms on the thiophene nucleus in **10** were removed *prior* to the reaction with ethylamine. Thus reaction of 3,4-bis(chloromethyl)thiophene (**27**) with ethylamine furnished 5-ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (**28**) in 49% yield (Scheme IV). The formation of thieno-

SCHEME IV



25 26 27 28

pyrrole **28** from the reaction of **27** with ethylamine proves that the chlorine atoms on the thiophene nucleus in tetrachloride **10** are responsible for the fact that no thienopyrrole is formed in the reaction of **10** with ethylamine. It cannot be an electron-withdrawing inductive effect of the chlorine atoms, for then the reaction of 3,4-bis(chloromethyl)-2,5-dimethylthiophene (**20**) with ethylamine should furnish a thienopyrrole derivative. Therefore, steric effects of the chlorine atoms at the thiophene nucleus are responsible for the fact that no thienopyrrole derivative is formed in the reaction of **10** with ethylamine.

Reaction of Methyl 2,3-Bis(chloromethyl)-4-methylthiophene-5-carboxylate (30) with Ethylamine.—The reaction of methyl 2,3-bis(chloromethyl)-4-methylthiophene-5-carboxylate (**30**) with ethylamine in acetonitrile was investigated in order to study a reaction of ethylamine with a 2,3-bis(chloromethyl)thiophene derivative having a substituent in the *ortho* position to a CH_2Cl group. In **30**, there is a considerable steric hindrance to the leaving chloride anion from the methyl group at the 4 position, when ethylamine first attacks the $-CH_2Cl$ group in the 2 position. On the other hand, little or no steric hindrance will occur by prior attack of ethylamine at the $-CH_2Cl$ group in the 3 position.

Compound **30** was synthesized by chloromethylation of methyl 3-methylthiophene-2-carboxylate (**29**)[20,21] using chloromethyl methyl ether and zinc chloride as catalyst (Scheme V). Reaction of **30** with ethylamine in acetonitrile gave methyl 5-ethyl-3-methyl-5,6-dihydro-4H-thieno[2,3-*c*]pyrrole-2-carboxylate (**31**, 37%), dimethyl 5,11-diethyl-3,7-dimethyl-4,5,6,10,11,12-hexahydrodithieno[2,3-*c*:3',2'-*h*][1,6]diazecine-2,8-dicar-

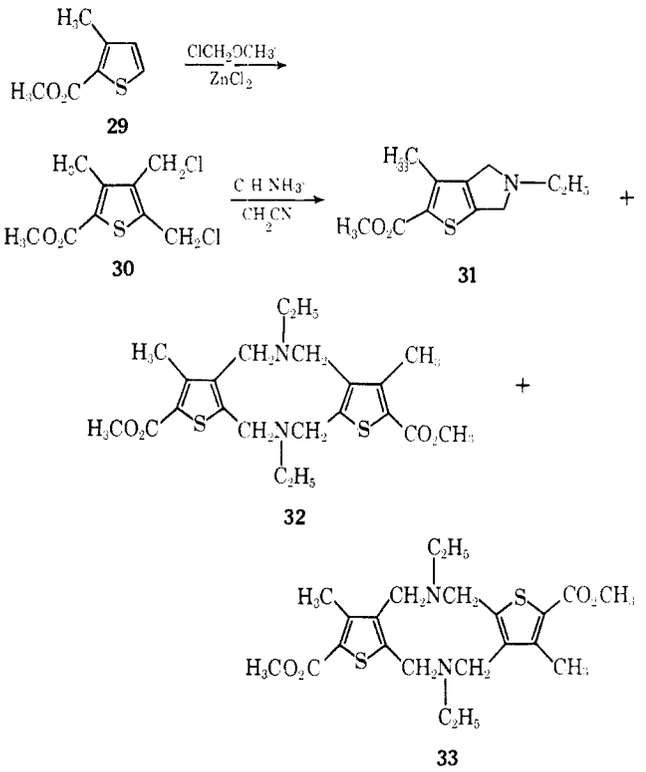
(18) Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*,. 501 (1961).

(19) Ya. L. Gol'dfarb and V. P. Litvinov, *ibid.*, 343 (1963); *Chem. Abstr.*, **59**, 582 (1963).

(20) H. Wynberg and J. de Wit (unpublished results in this laboratory) synthesized **29** *via* a Grignard reaction of 2-bromo-3-methylthiophene.[21]

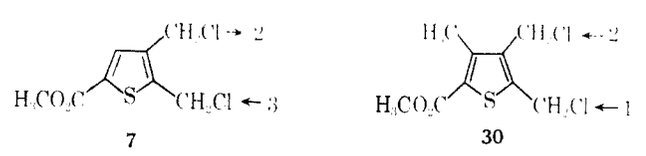
(21) R. M. Kellogg, A. P. Schaap, E. T. Harper, and H. Wynberg, *J. Org. Chem.*, **33**, 2902 (1968).

SCHEME V



boxylate (**32**, 4%)[22] and dimethyl 5,11-diethyl-3,9-dimethyl-4,5,6,10,11,12-hexahydrodithieno[2,3-*c*:2′,3′-*h*][1,6]diazecine-2,8-dicarboxylate (**33**, 3%).[23]

The 37% yield of thienopyrrole **31** was a surprise to us, for we assumed prior attack of ethylamine at the $-CH_2Cl$ group in the 2 position of **30**. Steric hindrance in the intramolecular ring closure reaction should then inhibit the formation of thienopyrrole **31**. The relatively high yield of thienopyrrole **31** suggests prior attack of ethylamine at the $-CH_2Cl$ group in the 3 position of **30** and cyclization of this intermediate to the thienopyrrole can occur because there is no steric hindrance involved in this case. We then decided to determine the relative reactivity of the $-CH_2Cl$ groups in methyl 2,3-bis(chloromethyl)-4-methylthiophene-5-carboxylate (**30**) as well as in methyl 2,3-bis(chloromethyl)thiophene-5-carboxylate (**7**). A reaction of **30** and **7**, respectively, was carried out with sodium iodide in acetone as solvent and the reaction was followed with nmr spectroscopy (see Experimental Section for details). The relative reactivities of the $-CH_2Cl$ groups are indicated in the formulas. The data show that in **7** the $-CH_2Cl$ group in the 2 position is the more reactive group, whereas in **30** it is the $-CH_2Cl$ group in the 3 position which is most reactive. With these data, the results obtained in the reaction of **30** with ethylamine become clear; because of the greater relative reactivity of the $-CH_2Cl$ group in the 3 position, most of the ethylamine reacts with this group first and formation of the thienopyrrole **31** will occur.



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, and ir spectra on a Unicam S.P. 200 spectrofotometer. Microanalyses were carried out in the analytical section of our department under the direction of Mr. W. M. Hazenberg.

4,6-Dibromo-1H,3H-thieno[3,4-*c*]thiophene (**2**).—A warm solution of 8.6 g (0.020 mol) of 2,5-dibromo-3,4-bis(bromomethyl)-thiophene (**1**) in 600 ml of methanol and a solution of 2.0 g (0.025 mol) of sodium sulfide[6] in 100 ml of methanol were added to 250 ml of boiling methanol, during 3 hr. The precipitate in the reaction mixture was collected (see below), the filtrate was concentrated to about 200 ml and 400 ml of water was added. The precipitate was collected and crystallized from methanol giving 3.6 g (60%) of thienothiophene **2**: mp 67–68°; uv max 252.5 mμ (ϵ 9300); nmr (30% in CCl_4) τ 6.20 (s, $ArCH_2S$–).

Anal. Calcd for $C_6H_4Br_2S_2$ (300.06): C, 24.02; H, 1.34; Br, 53.27; S, 21.37. Found: C, 24.2, 24.1; H, 1.4, 1.4; Br, 53.4, 53.3; S, 20.9, 20.9.

The precipitate (1.7 g) from above was crystallized from pyridine–water (10:1) giving 1.1 g (18%) of 1,3,7,9-tetrabromo-4H,6H,10H,12H-dithieno[3,4-*c*:3′,4′-*h*][1,6]dithiecin (**3**), mp 275° dec.

Anal. Calcd for $C_{12}H_8Br_4S_4$: C, 24.02; H, 1.34; Br, 53.27; S, 21.37; mol wt, 600.12. Found: C, 24.3, 24.2; H, 1.2, 1.2; Br, 53.4, 53.5; S, 21.2, 21.3; mol wt (mass spectroscopy[24]), 596 (based upon ^{32}S and ^{79}Br).

The solubility of this compound was too low for determination of the nmr and uv spectra.

1H,3H-Thieno[3,4-*c*]thiophene (**4**).—To a solution of 4.5 g (0.015 mol) of thienothiophene **2** in 45 ml of dioxane was added 5.9 g (0.09 g-atom) of zinc powder and 7.2 g (0.12 mol) of acetic acid. The reaction mixture was stirred and refluxed for 24 hr and the solids were removed by filtration of the warm solvent. The filtrate was concentrated and extracted with ether. The ether solution was extracted with Na_2CO_3 solution, dried ($CaCl_2$), concentrated, and sublimed [55° (0.2 mm)] giving 1.6 g (75%) of thienothiophene **4**: mp 60–62° [from petroleum ether (bp 40–70°)]. This compound was identical (ir spectrum and mixture melting point) with one earlier reported.[2]

4,6-Dibromo-1H,3H-thieno[3,4-*c*]thiophene 2,2-Dioxide (**5**).—A solution of 4.0 g (0.013 mol) of 4,6-dibromo-1H,3H-thieno-[3,4-*c*]thiophene (**2**) in 200 ml of acetic acid was heated at 90° with 4.6 g (0.04 mol) of a 30% H_2O_2 solution for 0.5 hr. The reaction mixture was cooled to 50° and 200 ml of water was added. After cooling to 0°, the precipitate was collected and crystallized from carbon tetrachloride giving 3.95 g (89.5%) of sulfone **5**: mp 182–182.5°; uv max 250 mμ (ϵ 9200), 263 sh (8200); ir (KBr) 1320 and 1128 cm^{-1} (SO_2); nmr (10% in $CDCl_3$) τ 5.78 (s, $ArCH_2SO_2$–).

Anal. Calcd for $C_6H_4Br_2O_2S_2$ (332.06): C, 21.70; H, 1.21; Br, 48.13; S, 19.32. Found: C, 21.8, 21.7; H, 1.2, 1.2; Br, 48.4, 48.6; S, 19.4, 19.0.

1H,3H-Thieno[3,4-*c*]thiophene 2,2-Dioxide (**6**).—To a solution of 3.32 g (0.010 mol) of **5** in 30 ml of dioxane was added 3.90 g (0.060 g-atom) of zinc powder and 4.8 g (0.080 mol) of acetic acid. The mixture was stirred and refluxed for 24 hr, and after filtration the filtrate was concentrated. Water was added to the residue, the precipitate was collected and crystallized from carbon tetrachloride giving 1.2 g (69%) of sulfone **6**: mp 164–165°;

(22) This structure was assigned to compound **32**, and not the alternative structure (dimethyl 5,11-diethyl-3,9-dimethyl-4,5,6,10,11,12-hexahydrodithieno[2,3-*c*:2′,3′-*h*][1,6]diazecine-2,8-dicarboxylate), on the basis of its nmr spectrum (see Experimental Section), which shows for the N-ethyl groups two quartets and two triplets for CH_2 and CH_3, respectively.

(23) This structure was assigned on the basis of the nmr spectrum (see Experimental Section). The CH_2 and CH_3 of the N-ethyl groups show one quartet and one triplet, respectively.

(24) We are indebted to Dr. C. Bokhoven, States Mines, The Netherlands, for the mass spectrometric molecular weight determination.

uv max 244 mμ (ε 6400); ir (KBr) 1320 and 1130 cm^{-1} (SO_2); nmr (5% in $CDCl_3$) τ 2.72 (s, 2, thiophene aromatic), 5.73 (s, 4, Ar**CH$_2$**SO$_2$–).

Anal. Calcd for $C_6H_6O_2S_2$ (174.24): C, 41.35; H, 3.48; S, 36.80. Found: C, 41.0, 41.2; H, 3.4, 3.4; S, 36.2, 36.4.

2,5-Dichloro-3,4-bis(chloromethyl)thiophene (10).—The title compound was prepared recently by Winn and Bordwell[25] by chloromethylation of 2,5-dichlorothiophene using chloromethyl methyl ether in carbon disulfide and tin tetrachloride in 73.8% yield. We obtained tetrachloride **10** in 75% yield by the following procedure.

A solution of 76.5 g (0.5 mol) of 2,5-dichlorothiophene in 500 ml of chloromethyl methyl ether (Fluka, T 52107, n^{20}D 1.397) was cooled in an ice–salt mixture to −5°. Tin tetrachloride (130 g, 0.5 mol) was added in 1.5 hr, keeping the temperature at 0 to −5°. After the addition of $SnCl_4$, the reaction mixture was stirred for 1 hr at 0°, for 2.5 hr at room temperature and boiled for 1 hr. The dark solution was cooled to room temperature and poured with stirring onto 1500 g of crushed ice. The ethereal extract was washed with water, dried (Na_2SO_4), concentrated and distilled giving 93.8 g (75%) of **10**: bp 85° (0.2 mm); mp 40–41° (from petroleum ether, bp 40–60°) [lit.[25] bp 137–145° (2.0 mm), mp 41–42°]; uv max 214 mμ (ε 19,600), 257 (5300); nmr (20% in CCl_4) τ 5.38 (s, Ar**CH$_2$**Cl).

Reaction of 2,5-Dichloro-3,4-bis(chloromethyl)thiophene (10) with Ethylamine.—A solution of 25.0 g (0.1 mol) of tetrachloride **10** in 500 ml of acetonitrile (dried with $CaCl_2$ and distilled, bp 81–82°, n^{20}D 1.3445) and a solution of 13.5 g (0.3 mol) of ethylamine (waterfree, Fluka 50241) in 500 ml of acetonitrile were added to 500 ml of acetonitrile during 30 hr. Stirring was continued for another 90 hr. A precipitate was formed in the reaction mixture. The acetonitrile was removed *in vacuo*, after which the residue was taken up in 300 ml of 2 *N* NaOH solution and 400 ml of ether. The ether solution was extracted with 4 *N* HCl solution. The HCl solution was cooled to about 0° and neutralized with 4 *N* NaOH solution. The separated oil solidified upon standing. The precipitate (23.8 g) was collected[26] and treated with 150 ml of cold methanol in a mortar. The remaining solid was filtered off (for the filtrate, see below). The light brown solid (5.9 g), mp 101–103.5°, was crystallized from methanol giving 5.5 g (27%) of dithienodiazecine **11**: mp 102.5–103.5°; uv max 245 mμ (ε 15,100); ir (KBr) no NH absorption at about 3300 cm^{-1}; nmr (10% in CCl_4) τ 6.27 (s, 8, Ar**CH$_2$**N–), 7.45 (q, 4, *J* = 7 Hz, N**CH$_2$**CH$_3$), 8.95 (t, 6, *J* = 7 Hz, NCH$_2$**CH$_3$**).

Anal. Calcd for $C_{16}H_{18}Cl_4N_2S_2$: C, 43.25; H, 4.09; Cl, 31.92; N, 6.31; mol wt, 444.28. Found: C, 43.6, 43.4; H, 4.2, 4.1; Cl, 31.5, 31.6; N, 6.6, 6.3; mol wt (in benzene), 447, 451.

The filtrate (see above) was concentrated *in vacuo* and distilled giving 4.8 g (20%) of secondary amine **12**: bp 106–116° (0.5 mm); mp 80–81° (from petroleum ether, bp 40–60°, cooling to −60°); uv max 246.5 mμ (ε 6500); ir (KBr) 3300 cm^{-1} (NH); nmr (20% in CCl_4) τ 6.35 (s, 4, Ar**CH$_2$**NH–), 7.40 (q, 4, *J* = 7 Hz, RNH-**CH$_2$**CH$_3$), 8.38 (s, 2, –**NH**–), 8.93 (t, 6, *J* = 7 Hz, RNHCH$_2$-**CH$_3$**).

Anal. Calcd for $C_{10}H_{16}Cl_2N_2S$ (267.22): C, 44.94; H, 6.04; Cl, 26.54; N, 10.48. Found: C, 44.7, 44.9; H, 6.1, 6.0; Cl, 26.5, 26.6; N, 10.8, 10.6.

2,5-Dichloro-N,N′-diethyl-N,N′-ditosyl-3,4-bis(aminomethyl)-thiophene (14) was obtained in 85% yield from **12**, using *p*-toluenesulfochloride in the usual manner: mp 128.5–130°; uv max 233 mμ (ε 27,200); ir (KBr) 1345, 1310, 1115 cm^{-1} (SO_2); nmr (10% in CCl_4) τ 2.39 (d, 4, *J* = 8 Hz, tosyl aromatic), 2.77 (d, 4, *J* = 8 Hz, tosyl aromatic), 5.66 (s, 4, Ar**CH$_2$**N–), 6.86 (q, 4, *J* = 7 Hz, –N**CH$_2$**CH$_3$), 7.60 (s, 6, –C$_6$H$_4$**CH$_3$**), 9.07 (t, 6, *J* = 7 Hz, –NCH$_2$**CH$_3$**).

Anal. Calcd for $C_{24}H_{28}Cl_2N_2O_4S_3$ (575.59): C, 50.08; H, 4.90; N, 4.87. Found: C, 50.1, 50.1; H, 4.9, 5.0; N, 5.1, 5.3.

The reaction of tetrachloride **10** and ethylamine has been carried out several times. The rate of addition was varied from 0 to 30 hr. Dithienodiazecine **11** and the secondary amine **12** always were obtained in about 27 and 20% yield, respectively. No 1,3-dichloro-5-ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole could be detected.

2,5-Dichloro-3,4-bis(iodomethyl)thiophene (13).—A solution of 30.0 g (0.12 mol) of tetrachloride **10** and 39.6 g (0.264 mol) of sodium iodide in 300 ml of acetone was stirred for 3 hr at room temperature. The reaction mixture was concentrated and the residue was crystallized from petroleum ether (bp 40–60°) giving 36.7 g (70%) of iodide **13**: mp 93.5–94.5°; uv max 242 mμ (ε 21,400); nmr (10% in CCl_4) τ 5.62 (s, Ar**CH$_2$**I). The compound is unstable.

Anal. Calcd for $C_6H_4Cl_2I_2S$ (432.87): C, 16.64; H, 0.93; I, 58.63. Found: C, 16.8, 16.6; H, 0.9, 0.9; I, 58.7, 58.6.

Reaction of 2,5-Dichloro-3,4-bis(iodomethyl)thiophene (13) with Ethylamine.—A solution of 10.8 g (0.025 mol) of iodide **13** in 250 ml of acetonitrile and a solution of 3.4 g (0.075 mol) of ethylamine (Fluka 50241) were added to 250 ml of acetonitrile during 4 hr. After stirring overnight the reaction mixture was worked up as described for the reaction of the tetrachloride **10** with ethylamine. Two products were isolated, namely, the secondary amine **12** in 57% yield and the dithienodiazecine **11** in 6% yield. No thienopyrrole derivative could be detected.

1,3-Dichloro-5-tosyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (15).—A solution of 10.0 g (0.04 mol) of tetrachloride **10** and 6.85 g (0.04 mol) of *p*-toluenesulfonamide in 500 ml of dimethylformamide [distilled from $CaCl_2$, bp 47.0–47.5° (15 mm), n^{20}D 1.4305; lit.[27] bp 153° (760 mm), n^{25}D 1.4269] was dropped in 6 hr into a stirred suspension of 150 g (1.08 mol) of K_2CO_3 in 750 ml of dimethylformamide. The temperature during the addition was about 100–110°. After the addition was complete, the reaction mixture was kept at 100–110° for 0.5 hr. The brown reaction mixture was filtered and the solid on the filter was washed with dimethylformamide and with ether. The ether–DMF solution was concentrated *in vacuo*. The residue was treated with water and the remaining solid was crystallized from ethanol (decolorizing charcoal), giving 6.7 g (48%) of 1,3-dichloro-5-tosyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (**15**): mp 176–177.5°; uv max 233 mμ (ε 18,500); ir (KBr) 1340, 1150 cm^{-1} (SO_2); nmr (10% in $CDCl_3$) τ 2.25 (d, 2, *J* = 8 Hz, tosyl aromatic), 2.67 (d, 2, *J* = 8 Hz, tosyl aromatic), 5.72 (s, 4, Ar**CH$_2$**N–), 7.58 (s, 3, –C$_6$H$_4$**CH$_3$**).

Anal. Calcd for $C_{13}H_{11}Cl_2NO_2S_2$: C, 44.81; H, 3.19; N, 4.03; mol wt, 348.27. Found: C, 45.1, 44.9; H, 3.3, 3.2; N, 4.1, 4.0; mol wt (in ethyl acetate), 344, 346.

5-Tosyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (16).—To a solution of 10.0 g (0.029 mol) of **15** in 2.2 l. of warm methanol, a suspension of 8.0 g of 10% palladium on charcoal in 250 ml of methanol, in which was dissolved 6.2 g (0.20 mol) of KOH, was added. The reaction mixture was stirred and heated under reflux. A slow stream of hydrogen was bubbled through the reaction mixture. After a reaction time of 74 hr[28] the hot reaction mixture was filtered and the filtrate was concentrated *in vacuo* to a volume of 10 ml. Water and ether were added to the residue. The ethereal extract was dried (Na_2SO_4) and concentrated after which the residue was crystallized from 95% ethanol, giving 3.2 g (40%) of **16** as white crystals: mp 124.5–125.5°; uv max 232 mμ (ε 18,500); ir (KBr) 1150, 1330 cm^{-1} (–SO_2); nmr (10% in $CDCl_3$) τ 2.26 (d, 2, *J* = 8 Hz, tosyl aromatic), 2.71 (d, 2, *J* = 8 Hz, tosyl aromatic), 3.15 (s, 2, thiophene aromatic), 5.63 (s, 4, Ar**CH$_2$**N–), 7.61 (s, 3, –C$_6$H$_4$**CH$_3$**).

Anal. Calcd for $C_{13}H_{13}NO_2S_2$ (279.38): C, 55.89; H, 4.70; N, 5.02. Found: C, 56.3, 56.1; H, 4.7, 4.7; N, 5.0, 4.9.

2,5-Dichloro-3,4-bis(hydroxymethyl)thiophene (25).—A mixture of 5.0 g (0.02 mol) of tetrachloride **10** and 100 ml of water was refluxed for 6 hr. The warm reaction mixture was filtered and cooled, giving 3.0 g (70%) of the dihydroxy derivative **25**: mp 105–106°; uv max 248 mμ (ε 6700); ir (KBr) 3350 cm^{-1} (OH); nmr (4% in $CDCl_3$) τ 5.42 (broad s, 4, Ar**CH$_2$**OH), τ 6.33 (broad s, 2, CH$_2$**OH**); nmr (10% in CD_3COCD_3) τ 5.44 (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.

3,4-Bis(hydroxymethyl)thiophene (26).—To a suspension of 4.0 g of 10% palladium on charcoal in 100 ml of methanol, in which was dissolved 4.0 g (0.07 mol) of KOH, 4.0 g (0.019 mol) of **25** was added. The reaction mixture was stirred and refluxed, while a slow stream of hydrogen was bubbled through the mixture. After a reaction time of 40 hr,[29] the mixture was filtered, the filtrate concentrated and the residue was extracted with acetone. The acetone was removed by distillation and the residue was taken up in dry ether. The ether solution was cooled until −60° giving 1.2 g (44%) of 3,4-bis(hydroxymethyl)thiophene (**26**): mp 65–66°; uv max 236 mμ (ε 5300), 239 (5300); ir

(25) M. Winn and F. G. Bordwell, *J. Org. Chem.*, **32**, 1610 (1967).

(26) The filtrate, extracted with ether, did not give organic material.

(27) Houben-Weyl, "Methoden der organischen Chemie," Band 1/2, 4th ed, Georg Thieme Verlag, Stuttgart, 1959, p 831.

(28) The reaction was followed with tlc (silica gel, solvent benzene).

(29) The reaction was followed with tlc (silica gel, solvent ethyl acetate).

(KBr) 3300 cm^{-1} (OH); nmr (10% in CD_3COCD_3) τ 2.71 (s, 2, thiophene aromatic), 5.37 (s, 4, ArCH_2OH), 5.67 (broad s, 2, ArCH_2OH).

Anal. Calcd for $C_6H_8O_2S$ (144.18): C, 49.97; H, 5.59; S, 22.24. Found: C, 50.2, 50.3; H, 5.6, 5.6; S, 22.3, 21.9.

3,4-Bis(chloromethyl)thiophene (27).—To a solution of 2.5 g (0.017 mol) of 3,4-bis(hydroxymethyl)thiophene (**26**) in 50 ml of chloroform, 2.5 ml of pyridine was added. In a nitrogen atmosphere, a solution of 6.0 g (0.05 mol) of thionyl chloride in 10 ml of chloroform was added at such a rate that the reaction mixture boiled. After the addition the mixture was refluxed for 0.5 hr. After cooling, the reaction mixture was poured into 400 g of ice–water and stirred for 20 min. The chloroform layer was separated and washed with 50 ml of 1 *N* HCl solution, 50 ml of 10% Na_2CO_3 solution and 50 ml of water. The chloroform solution was dried ($CaCl_2$), concentrated, and distilled giving 2.0 g (65%) of 3,4-bis(chloromethyl)thiophene (**27**): bp 98° (2.2 mm); mp 51–53° [from petroleum ether (bp 40–60°)]; uv max 230 mμ sh (ϵ 5200); ir (KBr) no OH absorption; nmr (10% in CCl_4) τ 2.72 (s, 2, thiophene aromatic), 5.34 (s, 4, ArCH_2Cl).

Anal. Calcd for $C_6H_6Cl_2S$ (181.09): C, 39.80; H, 3.33; Cl, 39.19. Found: C, 39.5, 39.9; H, 3.4, 3.3; Cl, 38.9.

5-Ethyl-5,6-dihydro-4H-thieno[3,4-*c*]pyrrole (28).—A solution of 1.27 g (0.007 mol) of 3,4-bis(chloromethyl)thiophene (**28**) and 0.94 g (0.021 mol) of waterfree ethylamine in 300 ml of acetonitrile was stirred for 100 hr at room temperature. The acetonitrile was removed by distillation *in vacuo*. A mixture of 30 ml of 2 *N* NaOH solution and 40 ml of ether was added to the residue. The ethereal extract was extracted with 2 *N* HCl solution. The acidic extract was neutralized with 4 *N* NaOH solution (temperature about 0°). The basic solution was extracted with ether. The ethereal extract was dried (Na_2SO_4), concentrated, and distilled giving 0.5 g (49%) of thienopyrrole **28**: bp 81° (2.0 mm); $n^{20}D$ 1.5510; uv max 242.5 mμ (ϵ 6200), 232.5 sh (5900); ir (neat) no NH absorption at about 3300 cm^{-1}; nmr (10% in CCl_4) τ 3.28 (s, 2, thiophene aromatic), 6.37 (s, 4, ArCH_2N), 7.29 (q, 2, J = 7 Hz, -N$CH_2$$CH_3$), 8.87 (t, 3, J = 7 Hz, N$CH_2$$CH_3$).

Anal. Calcd for $C_8H_{11}NS$: C, 62.70; H, 7.23; S, 20.93; mol wt, 153.24. Found: C, 62.5, 62.5; H, 7.2, 7.4; S, 20.6, 20.7; mol wt (in benzene), 157, 159.

Methyl 2,3-Bis(chloromethyl)-4-methylthiophene-5-carboxylate (30).—A solution of 14.7 g (0.094 mol) of methyl 3-methylthiophene-2-carboxylate (**29**) in 100 ml of chloromethyl methyl ether was added in 35 min to a boiling solution of 13.6 g (0.1 mol) of $ZnCl_2$ in 350 ml of chloromethyl methyl ether. After the addition the reaction mixture was refluxed for 4.5 hr. After cooling, the reaction mixture was poured into 1.5 l. of ice–water and stirred for 45 min. The precipitate was collected and washed with water, 0.1 *N* NaOH solution and again with water. The solid was taken up in ether. The ethereal extract was dried (Na_2SO_4) and concentrated. The residue was crystallized from petroleum ether (bp 40–60°) giving 19.5 g (82%) of dichloride **30**: mp 98.5–99.5°; uv max 218 mμ (ϵ 14,200), 270 (ϵ 13,400); nmr (10% in CCl_4) τ 5.27 (s, 2, CH_2Cl 2 position), 5.47 (s, 2, CH_2Cl 3 position), 6.17 (s, 3, COOCH_3), 7.44 (s, 3, ArCH_3).

Anal. Calcd for $C_9H_{10}Cl_2O_2S$ (253.15): C, 42.70; H, 3.98; Cl, 28.01. Found: C, 42.8, 42,6; H, 4.2, 3.9; Cl, 28.0, 27.8.

Reaction of Methyl 2,3-Bis(chloromethyl)-4-methylthiophene-5-carboxylate (30) with Ethylamine.—A solution of 7.6 g (0.03 mol) of dichloride **30** and 4.05 g (0.09 mol) of ethylamine in 800 ml of acetonitrile was stirred for 8 days. A precipitate was formed in the reaction mixture. The acetonitrile was removed *in vacuo*, after which the residue was taken up in 125 ml of 2 *N* NaOH solution and 170 ml of ether. The ether solution was extracted with 4 *N* HCl solution. The HCl solution was cooled to about 0°, neutralized with 4 *N* NaOH solution and extracted with ether. The ethereal extract was dried (Na_2SO_4), concentrated and treated with cold methanol giving 0.2 g (3%) of diazecine **33** (for the filtrate, see below): mp 218–219° (from CCl_4); uv max 269 mμ (ϵ 22,300); ir (KBr) no NH absorption at about 3300 cm^{-1}; nmr (15% in $CDCl_3$) τ 6.15 (s, 6, COOCH_3), 6.13 (s, 4, ArCH_2N), 6.64 (s, 4, ArCH_2N), 7.08 (q, 4, J = 7 Hz, N$CH_2$$CH_3$), 7.42 (s, 6, Ar$CH_3$), 8.72 (t, 6, J = 7 Hz, N$CH_2$$CH_3$).

Anal. Calcd for $C_{22}H_{30}O_4N_2S_2$: C, 58.64; H, 6.71; N, 6.22; mol wt, 450.64. Found: C, 58.5, 58.5; H, 6.6, 6.7; N, 6.1, 6.1; mol wt (mass spectroscopy), 450.

The filtrate (see above) was concentrated and distilled giving 2.5 g (37%) of thienopyrrole **31**: bp 128° (0.2 mm); uv max 258 mμ (ϵ 11,000), 286 (8900); ir (neat) no HN absorption at about 3300 cm^{-1}; nmr (10% in CCl_4) τ 6.19 (m, 4, -ArCH_2N-(Et)CH_2–), 6.21 (s, 3, COOCH_3), 7.24 (q, 2, J = 7 Hz, NCH_2-CH_3), 7.61 (s, 3, ArCH_3), 8.87 (t, 3, J = 7 Hz, N$CH_2$$CH_3$).

Anal. Calcd for $C_{11}H_{15}O_2NS$: C, 58.64; H, 6.71; N, 6.22; mol wt, 225.32. Found: C, 58.5, 58.5; H, 6.7, 6.8; N, 6.1, 6.2; mol wt (mass spectroscopy), 225.

The residue in the distillation flask was treated with methanol (decolorizing charcoal) and cooled until −30°, giving 0.25 g (4%) of the dithienodiazecine **32**: mp 142–143° (from CH_3OH); uv max 261 mμ (ϵ 22,300), 270 sh (21,400); ir (KBr) no NH absorption at about 3300 cm^{-1}; nmr (15% in $CDCl_3$) τ 6.07 (s, 4, ArCH_2N), 6.21 (s, 6, COOCH_3), 6.29 (s, 4, ArCH_2N), 6.90–7.45 (two partially overlapping quadruplets 4, N$CH_2$$CH_3$), 7.54 (s, 6, Ar$CH_3$), 8.60–8.90 (two triplets partially falling over each other, 6, N$CH_2$$CH_3$).

Anal. Calcd for $C_{22}H_{30}O_4N_2S_2$: C, 58.64; H, 6.71; N, 6.22; mol wt, 450.64. Found: C, 58.5, 58.6; H, 6.8, 6.7; N, 6.2, 6.2; mol wt (mass spectroscopy), 450.

Determination of the Relative Reactivities of the -CH_2Cl Groups in Dichlorides 7 and 30, Respectively. A. Methyl 2,3-Bis(chloromethyl)thiophene-5-carboxylate (7).—The following reaction mixtures were prepared: I, 1.2 g (5.0 mmol) of **7** in 12 ml of acetone; II, solution I plus 0.375 g (2.5 mmol) of NaI; III, solution II plus 0.375 g (2.5 mmol) of NaI; IV, solution III plus excess NaI. Nmr spectra (sweep width 50 cps) were run of the solutions I, II, III and IV, after filtration (NaCl is insoluble in acetone). In solutions II and III there are four compounds, namely, methyl 2,3-bis(chloromethyl)thiophene-5-carboxylate (**7**, J in Table I), methyl 3-chloromethyl-2-iodomethylthiophene-5- carboxylate (K), methyl 2-chloromethyl-3-iodomethylthiophene-5-carboxylate (L) and methyl 2,3-bis-(iodomethyl)thiophene-5-carboxylate (M). The chemical shifts[30] in cycles per second relative to TMS (0 cps) of the CH_2Cl and CH_2I groups are determined and tabulated in Table I. J_2 means CH_2(Cl) group of J in the 2 position, K_2 means CH_2(I) group of K in the 2 position, etc. The differences in chemical shifts of $J_2 - J_3$, $K_2 - K_3$, etc., in all spectra are about the same, but the chemical shifts relative to TMS of, for instance, the CH_2Cl groups in J in the different spectra are not the same, due to differences in the solvent medium. The data between brackets, behind the chemical shifts, are the relative area of the peaks for each spectrum. From these relative areas, we can determine the relative reactivity of the CH_2Cl groups in the 2 and 3 position, respectively, as (6 + 18):(6 + 10) = 3:2 (for solution II) and as (17 + 18):(17 + 7) = 3:2 (for solution III).

TABLE I

DATA FROM THE NMR SPECTRA OF SOLUTIONS I, II, III, AND IV

	Chemical shifts of solutions, cps (area)			
CH_2X	I	II	III	IV
J_2	295.2 (1)	298.2 (31)	298.1 (7)	
J_3	280.7 (1)	283.9 (31)	283.5 (7)	
$J_2 - J_3$	14.5	14.3	14.6	
K_2		292.7 (18)	292.6 (18)	
K_3		280.1 (18)	279.9 (18)	
$K_2 - K_3$		12.6	12.7	
L_2		295.0 (10)	294.7 (7)	
L_3		274.3 (10)	273.7 (7)	
$L_2 - L_3$		20.7	21.0	
M_2		290.4 (6)	290.1 (17)	292.3 (1)
M_3		271.3 (6)	270.6 (17)	273.1 (1)
$M_2 - M_3$		19.1	19.5	19.2

B. Methyl 2,3-Bis(chloromethyl)-4-methylthiophene-5-carboxylate (30).—The following solutions (reaction mixtures) were prepared: V, 1.26 g (5.0 mmol) of **30** in 13 ml of acetone; VI, solution V plus 0.375 g (2.5 mmol) of NaI; VII, solution VI plus 0.375 g (2.5 mmol) of NaI; VIII, solution VII plus excess NaI. Nmr spectra (sweep width 50 cps) were run of solutions V, VI, VII and VIII, after filtration. In solutions VI and VII, there are four compounds, namely, methyl 2,3-bis(chloromethyl)-4-methylthiophene-5-carboxylate (**30**, indicated as N in Table II), methyl 3-chloromethyl-2-iodomethyl-4-methylthiophene-5-car-

(30) All signals are doublets with J = 0.5 Hz.

TABLE II

DATA FROM THE NMR SPECTRA OF SOLUTIONS V, VI, VII AND VIII

	Chemical shifts of solutions, cps (area)			
CH_2X	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).

(31) All signals are singlets.

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.

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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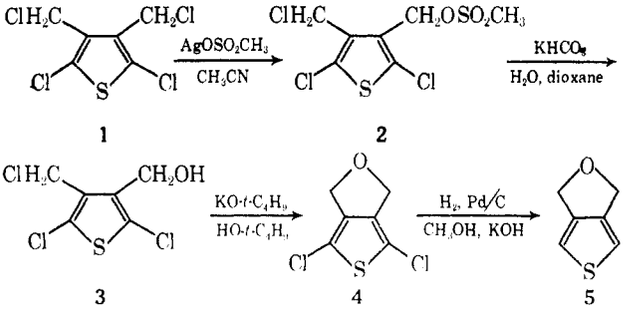
Received July 22, 1968

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

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

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