[Contribution No. 758 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington 98, Del.]

Thiacyanocarbons. IV. The Oxidation of Disodium Dimercaptomaleonitrile in the Presence of Olefins and the Structure of 1,2-Dithietes

By Howard E. Simmons, Dale C. Blomstrom and Robert D. Vest

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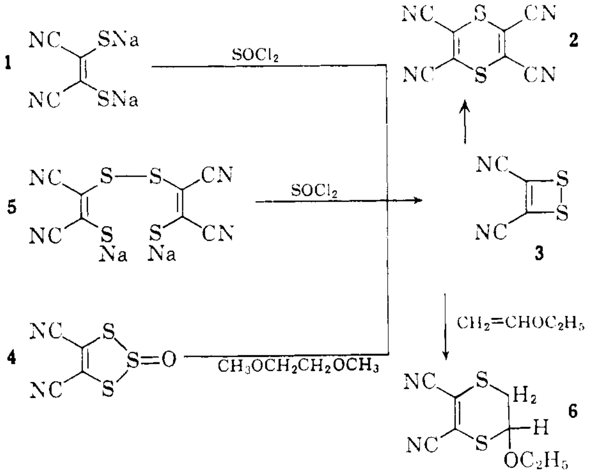
In previous papers in this series evidence was presented that the oxidation of disodium dimercaptomaleonitrile with diverse reagents gives a highly reactive, electrically neutral intermediate, $C_4N_2S_2$, dicyano-1,2-dithiete (**3**). Further observations bearing on the intermediacy of **3** are given in the present paper. The trapping of **3** by electron-rich olefins has provided a synthetic route to 2,3-dicyano-5-substituted-5,6-dihydro-1,4-dithiins. Qualitative theoretical calculations were carried out to investigate the factors that stabilize the bis-(thiocarbonyl) or 1,2-dithiete nuclei of the substituted $[C_2S_2]$ system. It was concluded that electron-withdrawing substituents strongly favor the ring structure.

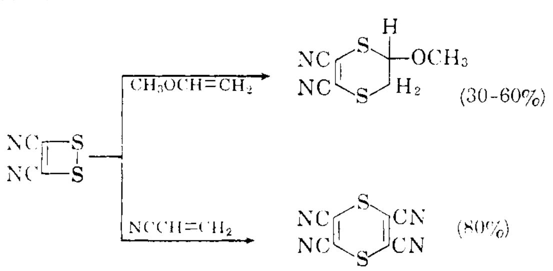
Introduction.—In previous papers[1] evidence was presented that oxidation of disodium dimercaptomaleonitrile (**1**)[2] and disodium *cis-cis*-bis-(2-mercapto-1,2-dicyanovinyl) disulfide (**5**) with thionyl chloride and the spontaneous conversion of 1,2,3-trithiole-2-oxide (**4**) in ether solvents to tetracyano-1,4-dithiin (**2**) proceed *via* the intermediate dicyano-1,2-dithiete (**3**). If ethyl vinyl ether was present during these reactions, only a low yield of dithiin **2** resulted, and the major product was 2,3-dicyano-5-ethoxy-5,6-dihydro-1,4-dithiin (**6**).[1c] This result was interpreted as trapping of the fleetingly formed **3** by the vinyl ether in a reaction resembling Diels–Alder addition.



Substituted 2,3-Dicyano-5,6-dihydro-1,4-dithiins.—The addition of transiently formed dicyano-1,2-dithiete (**3**) to electron-rich olefins is a convenient synthesis of substituted 2,3-dicyano-5,6-dihydro-1,4-dithiins. Dihydrodithiins have been obtained by (1) oxidation of salt **1** in the presence of olefins, (2) oxidation of salt **5** in the presence of olefins, (3) oxidation of sodium cyanodithioformate[1c] in the presence of olefins, (4) reaction of trithiole oxide **4** with olefins, and (5) metathetical reactions of salt **1** with certain 1,2-dihaloethanes. The most general and practical paths are 1, 3 and 5, the latter metathetical reactions having been studied previously.[1,3]

A brief study was made of the synthetic utility of some of these methods. Many oxidizing reagents were unsuitable (*e.g.*, chlorine, iodine) since the oxidant reacted with the substituted olefins. For synthetic purposes it was convenient to use the systems thionyl chloride in DME and potassium ferricyanide in water. Generally the yields in the former system were higher, and the reactions were simply carried out by addition of the oxidizing agent at 0° to a stirred mixture of salt **1**, the olefin and solvent. Some typical examples of electron-rich olefins used under these conditions are presented in Table I.

In general, the yields were higher with olefins which contained an electron-donating group conjugated with the double bond. Small amounts of dithiin **2** were usually isolated as by-product. With electron-poor olefins, such as acrylonitrile, the rate of addition of dithiete **3** is depressed so that dimerization of **3** with sulfur loss competes effectively to give dithiin **2**. This is illustrated by oxidation of **1** in the presence of methyl vinyl ether and acrylonitrile. In latter case only dithiin **2** was isolated and none of the expected adduct was detected.



Although yields were lower, the trapping of dithiete **3** from the direct oxidation[1c] of the sodium cyanide–carbon disulfide adduct, sodium cyanodithioformate,[1b] could be demonstrated. This pro-

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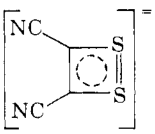
[1] (a) I, H. E. Simmons, R. D. Vest, D. C. Blomstrom, J. R. Roland and T. L. Cairns, *J. Am. Chem. Soc.*, **84**, 4746 (1962); (b) II, H. E. Simmons, D. C. Blomstrom and R. D. Vest, *ibid.*, **84**, 4772 (1962); (c) III, H. E. Simmons, D. C. Blomstrom and R. D. Vest, *ibid.*, **84**, 4756 (1962).

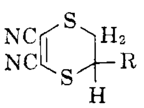
[2] It was suggested in ref. 1b that *cis*-**1** is stabilized by contributions from states in which sulfur–sulfur covalent bonding is important. Although **1** may be best represented as

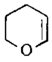
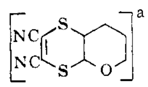
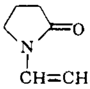
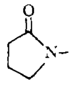


we will continue to employ the classical dimercaptide structure **1** until the electronic structure is entirely clear.

[3] A. van Schoor, E. Jacobi, S. Lust and H. Flemming, German Patent 1,060,655 (E. Merck), 1959; A. van Schoor, E. Jacobi, S. Lust and D. Erdmann, German Patent 1,077,915 (E. Merck), 1960.

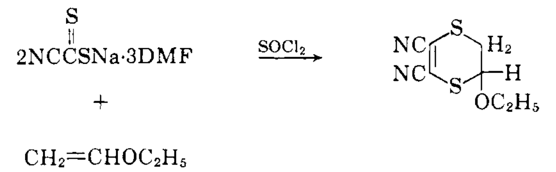
TABLE I

SUBSTITUTED 2,3-DICYANO-5,6-DIHYDRO-1,4-DITHIINS 

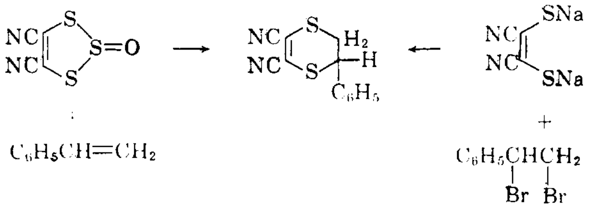
Olefin	Oxidant	Yield, %[b]	Product, R =
p-$CH_3OC_6H_4CH{=}CH_2$	$K_3Fe(CN)_6$ in H_2O	11	p-$CH_3OC_6H_4$–
$CH_3OCH{=}CH_2$	$SOCl_2$ in DME	36–60	CH_3O–
$C_2H_5OCH{=}CH_2$	$K_3Fe(CN)_6$ in H_2O	25	C_2H_5O–
	$SOCl_2$ in DME	63	
	$K_3Fe(CN)_6$ in H_2O	28	 [a]
	$SOCl_2$ in DME	29	

[a] Product isolated. [b] No attempts were made to maximize the yields.

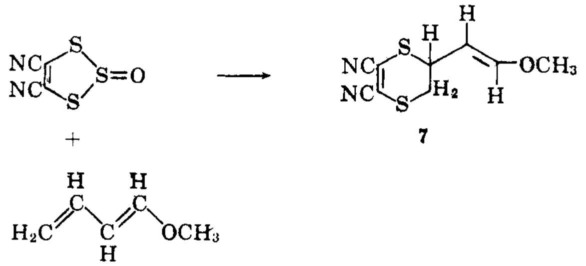
cedure is very easily carried out in one step: sodium cyanide and carbon disulfide are mixed in dimethylformamide solution, the vinyl ether and a co-solvent are added, and the oxidizing agent is introduced. When cyanodithioformate ion was oxidized in this manner by thionyl chloride in acetonitrile solution in the presence of ethyl vinyl ether, the dihydro adduct 6 was isolated in 34% yield.[1c]



Dicyanodihydrodithiins could also be prepared by decomposing trithiole oxide 4 in the presence of olefins. When 4 was added to a hot xylene solution of styrene, there was obtained in 31% yield 2,3-dicyano-5-phenyl-5,6-dihydro-1,4-dithiin, which was synthesized independently by the metathetical reaction of salt 1 with dibromostyrene.[3] When 4 was allowed to react with 1-methoxybutadiene in DME solution at 25°, addition occurred at the unsubstituted double bond to give 7 in 14% yield.



Evidence for the structure of 7 is given in the Experimental Section, and none of the other possible adduct was detected. It is not known whether



styrene and 1-methoxybutadiene react directly with trithiole oxide 4 to give the observed products, but previous kinetic studies[1c] suggest that dithiete 3 is an intermediate. The qualitative results indicate that dithiete 3 is an electrophile with respect to its addition reactions, and both steric and polarizability effects make the mode of addition to 1-methoxybutadiene plausible.

Adduct of Thionyl Chloride and Ethyl Vinyl Ether.—In the oxidation of salt 1 with thionyl chloride in DME containing ethyl vinyl ether, the vinyl ether was assumed to function solely as a scavenger for dithiete 3 in the formation of adduct 6. It has been found that ethyl vinyl ether undergoes a slow addition reaction with thionyl chloride under the oxidation conditions; however, this finding has been shown not to alter the previous conclusions concerning the mechanism.

Although salt 1 reacts with thionyl chloride at a much greater rate than thionyl chloride adds to vinyl ethers,[1c] this aspect of the oxidation system was clarified. Thionyl chloride adds to ethyl vinyl ether in DME solution at 25° to give a saturated adduct, 2-chloro-2-ethoxyethanesulfinyl chloride (8). Spectral characterization of 8 was in

$$C_2H_5OCH{=}CH_2 + SOCl_2 \longrightarrow \underset{\mathbf{8}}{C_2H_5OCHClCH_2SOCl}$$

accord with the addition of Cl and SOCl to the double bond, and the direction of addition was assigned on the basis of additions of thionyl chloride to other olefins. 1,1-Diphenylethylene is known to react with thionyl chloride to give, after hydrolysis, 2,2-diphenylethylenesulfinic acid.[4]

This finding suggested that 2,3-dicyano-5-ethoxy-5,6-dihydro-1,4-dithiin (6) may arise simply from a metathetical reaction of sulfinyl chloride 8 with salt 1. That this possibility was incorrect was shown by treating salt (1) (1 mole) with sulfinyl chloride (8) (1 mole). *trans-trans*-5 was isolated in >90% yield along with 7% of the ethoxy derivative 6. When *trans-trans*-5 (1 mole) was treated with sulfinyl chloride 8 (1 mole), the major product was dithiin 2 (62%), and only 15% of adduct 6 was detected. It seemed likely that 8 acted simply as an oxidizing agent through the sulfinyl chloride function to give dithiete 3, the usual precursor of 2, and that the small amount of 6 resulted from re-

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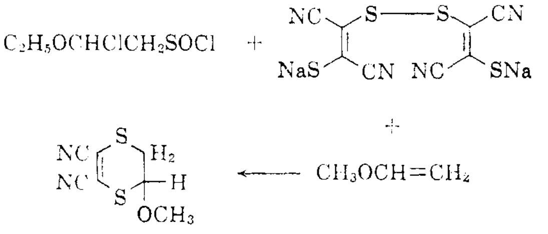
(4) S. Patai and A. Patchornik, *J. Am. Chem. Soc.*, **74**, 4494 (1952).

action of **3** with ethyl vinyl ether liberated in the oxidation. That this interpretation is essentially correct was shown by treating *trans-trans*-**5** with sulfinyl chloride **8** in the presence of *methyl* vinyl ether. The major product isolated was the *methoxy* derivative **9** which must have been formed by trapping of dithiete **3**, generated from **5** and **8**, by methyl vinyl ether. Only traces of the corresponding ethoxy derivative were detected. The mechanism of the oxidation of salts **1** and **5** with **8** is probably similar to that previously described for the thionyl chloride oxidation.[1c]



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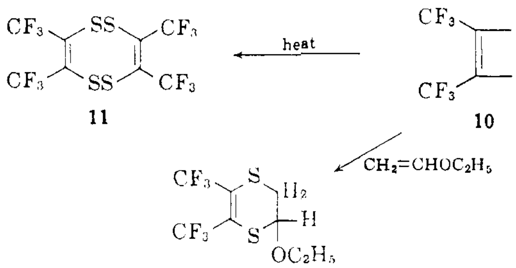
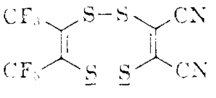
Dicyano-1,2-dithiete (3).—Attempts to isolate dithiete **3** have not yet been successful. Evidence for its existence was sought fruitlessly by examining the ultraviolet and infrared spectra at low temperatures of systems in which salt **1** was being oxidized.

In other experiments it was found that trithiole oxide **4** is converted both thermally in the melt and in ether solvents at 25° to dithiin **2**, sulfur and sulfur dioxide. The solution studies indicated[1c] that dimerization of **3** was so rapid even at low temperatures that isolation was not feasible. Pyrolysis of **4** using rapid quenching techniques were no more successful. When **4** was passed through a quartz tube at 200–250° and the products were quenched on a liquid-nitrogen-cooled surface, a solid was obtained, which upon warming to 25° exhibited only the spectrum of dithiin **2**. In another experiment the exit gases were allowed to impinge on a surface of frozen ethyl vinyl ether. The surface was warmed to room temperature slowly and the ultraviolet spectrum was taken. The product was largely dithiin **2**, although a weak band at 342 $m\mu$, characteristic of the adduct **6**, was also observed. It cannot be concluded unequivocally that dithiete **3** was trapped in the vinyl ether matrix, since traces of **4** were known to have passed unchanged onto the frozen surface in control experiments. It can be concluded, however, that if thermolysis of **4** occurs with expulsion of sulfur monoxide to give **3**, then the dimerization of **3** with sulfur loss is a very rapid reaction even at relatively low temperatures.

The neutral intermediate $(NC)_2C_2S_2$, formed by oxidation of salt **1**, is formally similar to the product obtained from the reaction of hexafluorobutyne-2 with sulfur, $(CF_3)_2C_2S_2$, characterized as bis-(trifluoromethyl)-1,2-dithiete (**10**),[5] although alternative structures were not unequivocally ruled out. Dithiete **10**, an isolable liquid, was easily dimerized without sulfur loss by heat or tertiary amines to the eight-membered ring structure **11**.[6] Electron-rich olefins, *e.g.*, ethyl vinyl ether, add to dithiete **10** below room temperature to give 2,3-bis-(trifluoromethyl)-5-ethoxy-5,6-dihydro-1,4-dithiin.[6]



In this work dithiete **10** was allowed to react with salt **1** in DME solution in an attempt to prepare a mixed salt **13**, analogous to salt **5**. A rapid reaction occurred below room temperature, and the only product isolated was tricyano-1,4-dithiino[c]isothiazole (**14**). Isothiazole **14** is often found in oxidation reactions of salt **1** and has been shown to arise in a subsequent insertion reaction of dithiin **2** with sulfur.[1a] Apparently, salt **1** was oxidized by **10**, but attempts to isolate the presumed reduction product, salt **15**, were not successful. The presence of fluoride ion among the reaction products may reflect the instability of **15** under these conditions.



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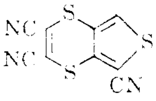

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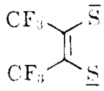

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Trithiole oxide **4** was allowed to decompose in DME solution in the presence of dithiete **10** in an attempt to prepare a mixed dithiin derived from dicyano-1,2-dithiete and bis-(trifluoromethyl)-1,2-dithiete. Tetracyano-1,4-dithiin (**2**) was the only product isolated (87%).

Bis-(trifluoromethyl)-1,2-dithiete (**10**) is thus similar in its chemical behavior to the intermediate **3** postulated[1c] to occur in oxidation reactions of salt **1**. Both **3** and **10** undergo formal Diels–Alder reactions with electron-rich olefins and self-condensation reactions, although **10** gives predominantly eight-membered ring dimer.[6]

Polarographic studies[1b] have given some information on the formation of dithiete **3**. Salt **1** ($E_{p/2}$ = +0.08 v.) was more readily oxidized than *trans-trans*-**5** ($E_{p/2}$ = +0.43 v.) in aqueous solutions at pH $\sim$5. Moreover, salt **1** showed a second wave at $E_{p/2}$ = +0.43 v. corresponding to that of **5**. These results can be interpreted in terms of a highly reactive anion-radical **16**[1c] formed in the one-electron oxidation, followed by rapid dimerization to **5** (A). The one-electron wave at +0.43 v. presumably corresponds to process B. Conclusions such as these are tenuous when considering polarographic processes at solid electrodes, and the

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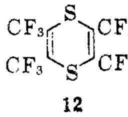
(5) C. G. Krespan, B. C. McKusick and T. L. Cairns, *J. Am. Chem. Soc.*, **82**, 1515 (1960).

(6) Observations by Dr. C. G. Krespan have indicated that tetrakis-(trifluoromethyl)-1,4-dithiin (**12**) may be formed when solutions of dithiete **10** in ethanol were allowed to stand several hours.



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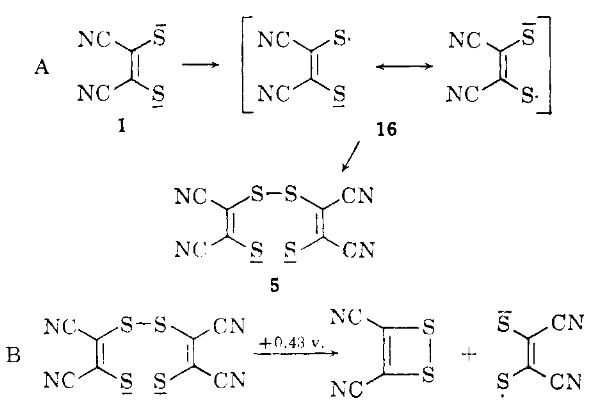
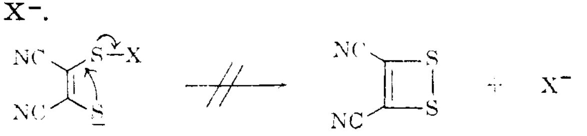


above suggestion requires rapid diffusion and dimerization of the anion-radical **16** to **5**.

Little literature is available on the polarographic oxidation of mercaptide ions, but the above results may be compared with oxidation–reduction potentials (E_0) obtained at a normal hydrogen electrode by Calvin[7] under conditions similar to those reported here. Both E_0 (N.H.E.)[7] and $E_{p/2}$ (S.C.E.) are probably *p*H dependent, and our $E_{p/2}$ values show some concentration dependence. For these reasons comparison of E_0 and $E_{p/2}$ is difficult. In aqueous solution at *p*H 4.5 mercaptoacetic acid and ethyl mercaptan have $E_0 = -0.24$ and -0.16 v., respectively. In 70% ethanol thiophenol shows $E_0 = -0.40$ v. and mercaptans are generally found to lie in the range $E_0 = -0.06$ to -0.40 v.[7] A rough comparison can be made from the relation $E_{p/2} = E_0 - 0.25$, so that the range of $E_{p/2}$ for typical mercaptans is $E_{p/2} = -0.31$ to -0.65 v. It is thus seen that salt **1** is oxidized ($E_{p/2} = +0.08$ v.) with nearly the ease of aliphatic mercaptans; however, the removal of the second electron ($E_{p/2} = +0.43$ v.) requires more energy than is normally observed. It is to be expected that mercaptans conjugated with cyano groups are more difficultly oxidized than aliphatic or aromatic mercaptans. The above interpretation then suggests that anion-radical **16** is formed readily but that no significant driving force is evident in the formation of dithiete **3**. This is in accord with the finding[1c] that salts of structure **17** (X = -SOCl, Br) do not readily expel X^-.



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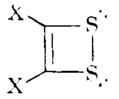
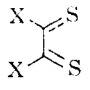
In summary, these considerations suggest that aromatic sextet stabilization is not an important driving force during formation of dithiete **3**. The extent of such stabilization is difficult to estimate, and in the following section the electronic factors which influence the stability of the 1,2-dithiete ring are discussed.

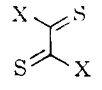
Structure of 1,2-Dithietes.—The first example of an isolable 1,2-dithiete was provided by the characterization of bis-(trifluoromethyl)-1,2-dithiete (**10**).[5] The question immediately is raised concerning the structure of the two carbon–two sulfur function, which conceivably can exist as the 6π-electron dithiete **18-A** and as the 4 π-electron bis-(thiocarbonyl) isomer **18-B** (or **18-C**). Presumably 1,2-dithietes are stabilized by resonance



18-A



18-B



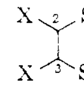
18-C

with the *s-cis* structure (**18-A**↔ **18-B**). If $(X)_2$-C_2S_2 were a bis-(thiocarbonyl) derivative, steric and electrical effects might be expected to favor the *s-trans* form (**18-C**).[8]

Theory provides a partial answer to the question of what electronic factors stabilize the cyclic and open structures when symmetrically substituted derivatives are considered. Qualitative LCAO-MO calculations were carried out for structure **18-A** and **B**, where X = $(CH_3)_2N$, CH_3, CF_3, CN, in order to assess the effects of substituents that are conjugative donors, inductive acceptors and conjugative acceptors. The formal neglect of overlap was invoked, and heteroatoms were treated in the usual manner as perturbations in a carbon skeleton.[9] The parameter values for coulomb ($\alpha_i = \alpha_0 + \delta_i\beta_0$) and resonance ($\beta_{ij} = \eta_{ij}\beta_0$) integrals were selected in part from those determined in these laboratories[1b] for nitrogen and in part from the observations of Janssen[10] on sulfur in similar systems. No effort was made to study the effects of inclusion of the sulfur d-orbitals in the calculations, which would be hardly profitable at this stage. The d-orbitals of sulfur may be only weakly popu-

TABLE II

LCAO-MO PARAMETERS[a]



X^b	i	δ_i	ij	η_{ij}
$(CH_3)_2N$	1	0.2	12	0.6
	2	0.0	23	1.0
	5	1.0	25	1.0
			14	0.3^c
CH_3	1	0.2	12	0.6
	2	0.0	23	1.0
			14	0.3^c
CF_3	1	0.2	12	0.6
	2	0.5	23	1.0
			14	0.3^c
$\overset{6}{N}\equiv\overset{5}{C}-$	1	0.2	12	0.6
	2	0.0	23	1.0
	5	0.0	14	0.3^c
	6	1.5	25	1.0
			56	1.2

[a] $\alpha_i = \alpha_0 + \delta_i\beta_0$, $\beta_{ij} = \eta_{ij}\beta_0$ where α_0 and β_0 refer to an ethylenic carbon atom. [b] Since the molecules are symmetrically substituted, values are given only for one set of non-identical atoms and bonds. [c] Value in 1,2-dithiete structure, zero otherwise.

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[7] M. Calvin, University of California Radiation Laboratory Report 2438, 1954.

[8] It is also conceivable that valence tautomerism dictates an equilibrium such as **18-A** $\rightleftarrows$ **18-B**, **C**.

[9] R. Daudel, R. Lefebvre and C. Moser, "Quantum Chemistry," Interscience Publishers, Inc., New York, N. Y., 1959, p. 70.

[10] M. J. Janssen, *Rec. trav. chim.*, **79**, 454, 464, 1066 (1960).

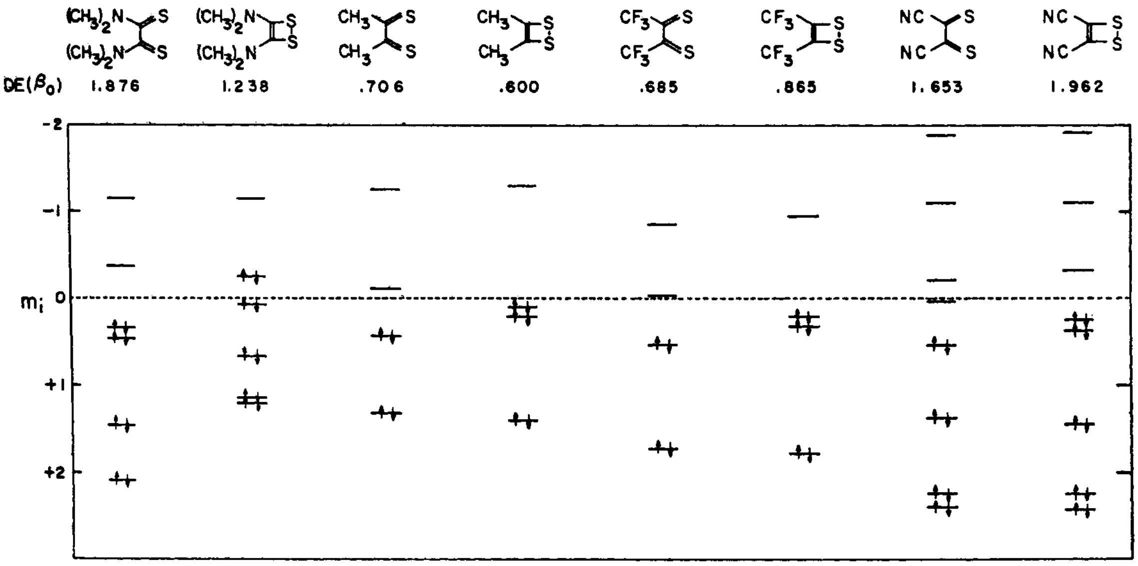

Fig. 1.—Orbital energy levels expressed in conventional form $\epsilon_i = \alpha_0 + m\beta_0$.

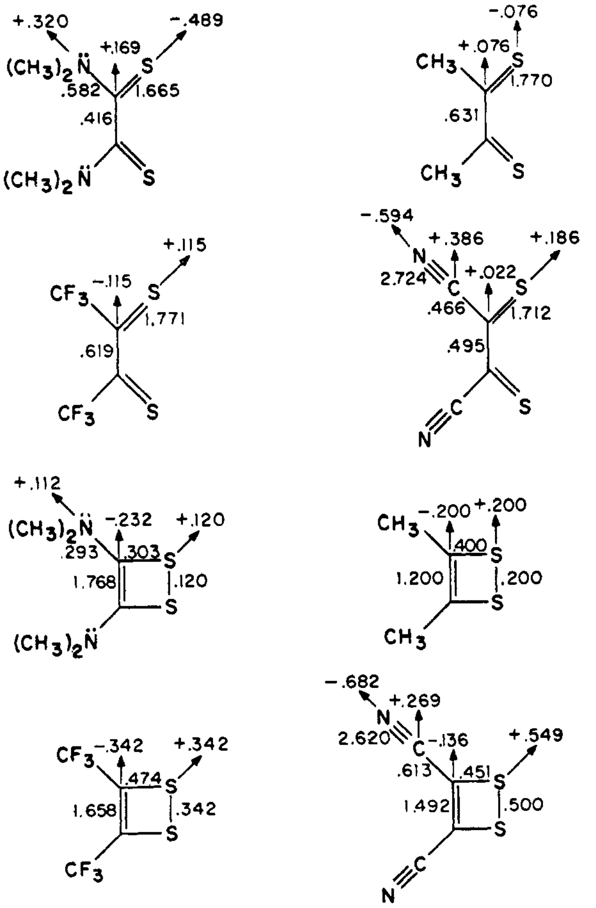

Fig. 2.—Molecular diagrams of bond orders and charge densities.

lated in simple sulfide and thiocarbonyl environments, but the occurrence of dp-hybrids of π-character in the 1,2-dithiete ring may be significant. It was assumed, however, that only 3pπ-orbitals on sulfur are used in bonding in both thiocarbonyl and 1,2-dithiete structures and that the σ-bonds in the 1,2-dithiete structures are formed by 3pσ-orbitals on sulfur. The latter approximation is probably not too serious in view of the geometry known for dimethyl trisulfide (∠CSS = 104 ± 5°).[11] In other words, sulfur "fits" comfortably in four-membered rings.

The parameter values used in the calculations are collected in Table II. Pilot calculations using other values were carried out and it was determined that the results were not very sensitive to the absolute values chosen for the parameters, even in the case of β_{SS}. The significant features of the calculations which predict the trend in stabilization of the cyclic or open structures are sensibly independent of the parameter values, as long as values are employed that reflect the known relative donor or acceptor capacities of the substituents X. The methyl and trifluoromethyl groups were treated as perturbations on the atoms to which they are bonded. The parameters allow for both inductive and resonance contributions for the dimethylamino and cyano groups.

It is well known that LCAO–MO calculations in the Hückel approximation give unreliable information on the *total* energy of conjugated structures, so the substituted 1,2-dithietes and their bis-(thiocarbonyl) analogs were compared in terms of their delocalization energies. However, this poses serious problems in the choice of models for the canonical structure of the uninteracted ground state. The models chosen here cannot be rigorously justified, but it is felt that they are reliable regarding trends in delocalization energy as the substituent is changed, since consistent criteria were used in selecting the models. The energies of isolated groups were determined by resolution of the simple secular equations involved (*e.g.*, the cyano group) or by definition from the assumed coulomb parameters. The group energy contributions are summarized in Table III. For example, the summation of energy contributions for **18-A** (X =

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[11] "Tables of Interatomic Distances," Special Publication No. 11, The Chemical Society, London, 1958, p. M140.

$((CH_3)_2N)$ is $\Sigma\epsilon = 10\alpha_0 + 6.80000\beta_0$. When this quantity is subtracted from the total energy obtained by diagonalizing the energy matrix for this structure ($10\alpha_0 + 8.03774\beta_0$), the resulting calculated delocalization energy for this model is $1.23774\beta_0$. The delocalization energies and orbital energies of the various structures are given in Fig. 2.

TABLE III

GROUP CONTRIBUTIONS TO ENERGIES OF ASSUMED MODELS[a]

Structure	Substituent	(C=C)	(C=S)	$(\ddot{S})$	$((CH_3)_2\ddot{N})$	$(\ddot{N}\equiv C)$
18-A	$(CH_3)_2\ddot{N}$	2.0000		0.4000	2.0000	
	CH_3	2.0000		.4000		
	CF_3	3.0000		.4000		
	CN	2.0000		.4000		4.3302
18-B	$(CH_3)_2\ddot{N}$		1.4166		2.0000	
	CH_3		1.4166			
	CF_3		1.9369			
	CN		1.4166			4.3302

[a] Energies refer to two electrons on $(\ddot{S})$ and $((CH_3)_2\ddot{N})$ and two electrons in all multiple bonds; units are β_0.

The calculations indicate quite clearly that conjugative electron release by the substituent X stabilizes the bis-(thiocarbonyl) structure **18-B** relative to the 1,2-dithiete structure **18-A**, while both conjugative and inductive electron-withdrawing substituents stabilize the cyclic structure with respect to the open form. Tetramethyldithioöxamide (**18-A**, X = $(CH_3)_2N$) is predicted to be more stable than the corresponding 1,2-dithiete by $0.638\ \beta_0$ (~ 0.9 e.v.), whereas dicyano-1,2-dithiete (**18-A**, X = CN) should be more stable than the corresponding bis-(thiocarbonyl) structure by $0.309\ \beta_0$ (~ 0.4 e.v.). It is also of interest that this set of parameters predicts bis-(trifluoromethyl)-1,2-dithiete to be stabilized by ~ 0.25 e.v. relative to bis-(trifluoromethyl)-dithione (**18-B**, X = CF_3). The general appearance of the orbital energy level diagrams also reflects the destabilizing effect of electron-donating groups on the ring structures. As the substituent is varied from $(CH_3)_2N \rightarrow CH_3 \rightarrow CF_3 \rightarrow CN$, the highest filled orbital, which is anti-bonding when X = $(CH_3)_2N$, is smoothly depressed in the 1,2-dithiete structure **18-A**, whereas this orbital is practically unaffected in this sequence in **18-B**. From the other point of view, the highest bonding orbital of **18-B** (X = CN) is unfilled, whereas all bonding orbitals are filled in **18-A** (X = CN).

It is important to note that the effects caused by substituents of varying electrical character, as determined by delocalization energies, are operative in a manner that is essentially independent of the absolute values of δ and η, so long as the basic electrical character (inductive or resonance, electron-attracting or -donating) of the substituents is reflected in the values chosen.[12]

The charge densities in Fig. 2 refer only to π-electron density and the bond orders are given in terms of the contribution of π-electrons to the various bonds. As expected, the carbon–sulfur double bond in **18-B** (X = $(CH_3)_2N$) has a very low order and reflects the strong contribution of thioamide resonance structures. In structure **18-A** the curious effect is observed that as more strongly electron-withdrawing groups are substituted on the ring, the sulfur–sulfur bond order increases from $p_\pi = 0.120$ (X = $(CH_3)_2N$) to $p_\pi = 0.500$ (X = CN). The effect of electron-withdrawing substituents on the 1,2-dithiete structure is thus clearly manifested and averages out the π-electron distribution in the ring. This may be seen qualitatively by averaging the bond orders over the four ring bonds giving p_π (av.) = 0.624, 0.550, 0.737 and 0.724 for X = $(CH_3)_2N$, CH_3, CF_3, CN, respectively. The "normal" distribution of 6 π-electrons in a four-membered ring may be estimated as p_π (av.) = $0.500 \times 6/4 = 0.750$. It can thus be seen that electron-withdrawing groups, such as CF_3 and CN, are more effective in providing and distributing the proper number of π-electrons in the 1,2-dithiete ring to produce the appearance of aromatic sextet stabilization. The increase in bond order of the sulfur–sulfur bond as more electronegative groups are substituted on the ring could hardly have been anticipated on classical grounds. The total number of π-electrons in the ring is 6.224, 6.000, 6.000, 5.174, respectively, for the above series in accord with the expectation of simple resonance considerations; however, the distribution is apparently a purely quantum mechanical effect.

Various criteria, such as free valence and frontier electron density, were applied to these molecules in an attempt to rationalize the observed preference for dimerization to the eight-membered ring dimer by **18-A** (X = CF_3) compared to the preferred formation of the six-membered ring product by **18-A** (X = CN). The results were in general accord with observation, but it is felt that these calculations for systems containing hetereoatoms are unreliable. The high reactivity of dicyano-1,2-dithiete is most easily seen in the high partial positive charges carried by the sulfur atoms compared to that in any of the other substituted dithietes. An estimate of the activation energy for formation of the eight-membered ring dimer can be made by considering the process

TS

The geometry of the transition state (TS) is such that maximum p-orbital overlap occurs. We may then consider each half of TS to be a bis-(thiocarbonyl) type (**18-B**) containing 6 π-electrons exclusive of those of the substituent. In this manner $(E_{TS})_{CF_3} = 12\alpha_0 + 9.25520\beta_0$ and the energy of the ground state is twice that of **18-A** (X = CF_3) or $(E_G)_{CF_3} = 12\alpha_0 + 9.32988\beta_0$. This corresponds to an "activation energy" of $(E_{TS})_{CF_3}-(E_G)_{CF_3} = -0.07468\beta_0$ (a positive energy since β_0 is negative). Similarly for **18-A** (X = CN), $(E_{TS})_{CN} = 20\alpha_0 + 26.37060\beta_0$, $(E_G)_{CN} = 20\alpha_0 + 26.84380\beta_0$ and $(E_{TS})_{CN} = -0.47320\beta_0$. Thus,

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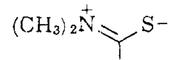
[12] Calculations were carried out in which $\delta = -0.2$ and $+0.5$ for sulfur, and the same pattern of results was obtained. When β_{CS} was similarly given, different values in the dithiete and bis-(thiocarbonyl) structures to reflect the presumed higher bond order in the latter structures, the qualitative influence of substituents on **18-A** and **18-B** was invariant.

it can be concluded that dimerization to eight-membered ring dimer is energetically more favorable when X = CF_3 than when X = CN, which is in agreement with observation.

The general conclusions derived from the theoretical calculations are in accord with experience. The simplest dithioöxamide, rubeanic acid, is well known as a stable, red crystalline substance whose structure is stabilized by strong hydrogen bonding. Tetrasubstituted derivatives, such as tetramethyldithioöxamide (**18-B**, X = $(CH_3)_2N$),[13] are high-melting, stable, white crystalline compounds whose properties and spectra are in agreement with the open structure **18-B** or **C**. The loss of color through strong thioamide resonance is well known and this molecule is probably best represented as



This formulation is in good accord with the theoretical calculations of delocalization energy and bond orders. On the other hand, the only other known member of the series, bis-(trifluoromethyl)-1,2-dithiete (**18-A**, X = CF_3), is believed[5] to exist as the ring structure, again in agreement with the calculations. It is felt that the success in correlation of the influence of substituents on the structures under consideration provides justification for representing the intermediate obtained by oxidation of salt 1 as dicyano-1,2-dithiete.

Experimental[14]

Substituted 2,3-Dicyano-5,6-dihydro-1,4-dithiins.—The following general procedures were employed for the oxidation of disodium dimercaptomaleonitrile (1) in the presence of olefin acceptors. No effort was made to obtain optimum yields and the procedures are given only to demonstrate the reactions.

N-Vinyl-2-pyrrolidone–Thionyl Chloride.—A suspension of salt 1 (5.0 g., 0.027 mole) in a solution of N-vinyl-2-pyrrolidone (6.0 g., 0.054 mole) in DME (30 ml.) was stirred and cooled in an ice-bath while a solution of thionyl chloride (3.2 g., 0.027 mole) in DME (7 ml.) was added over 15 minutes. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The resulting red sirup was dissolved in methylene chloride, and the solution was filtered. The solution was chilled in Dry Ice for several days, during which time a gray-green solid crystallized. There was obtained 1.95 g. (29%) of **2,3-dicyano-5-(N-2-pyrrolidonyl)-5,6-dihydro-1,4-dithiin**. Two recrystallizations from methylene chloride–methylcyclohexane (Darco) gave prisms with a slight lavender tint, m.p. 131–132.5°. The ultraviolet and infrared spectra were in accord with the assigned dihydrodithiin structure.

Anal. Calcd. for $C_{10}H_9N_3OS_2$: C, 47.79; H, 3.61; N, 16.72. Found: C, 47.93; H, 3.67; N, 16.43.

Dihydropyran–Potassium Ferricyanide.—Dihydropyran (6.8 g., 0.081 mole) was stirred vigorously with a solution of potassium ferricyanide (17.7 g., 0.054 mole) in water (100 ml.) and dioxane (10 ml.) while the mixture was cooled in an ice-bath. A solution of salt 1 (5.0 g., 0.027 mole) in water (25 ml.) was added over 40 minutes. A red-orange color developed and a brown tar slowly separated. The reaction mixture was extracted twice with ether and once with chloroform, and the combined extracts were evaporated *in vacuo* to a red sirup. The residue was chromatographed on a 2 × 15-cm. column of Florex using 50:50 benzene–cyclohexane as solvent. Elution with benzene gave a series of yellow oils which crystallized on standing. The combined solid fractions were recrystallized from ether to give 1.69 g. (28%) of **2,3-dicyano-1,4-dithiino[b]tetrahydropyran** as pale yellow crystals, m.p. 99.5–100.5°. The infrared spectrum of the product was very similar to that of the vinyl ether product[1c] in the (C≡N), (C=C) and (C—O) stretching regions.

Anal. Calcd. for $C_9H_8N_2OS_2$: C, 48.19; H, 3.60; N, 12.49. Found: C, 48.36; H, 3.82; N, 12.45.

***p*-Methoxystyrene–Potassium Ferricyanide.**—In the same manner described for dihydropyran, employing *p*-methoxystyrene and potassium ferricyanide, there was obtained an 11% yield of **2,3-dicyano-5-(*p*-methoxyphenyl)-5,6-dihydro-1,4-dithiin** as off-white leaflets from methylene chloride–cyclohexane; m.p. 126–127.5°.

Anal. Calcd. for $C_{13}H_{10}N_2OS_2$: C, 56.76; H, 3.93; N, 10.18. Found: C, 56.49; H, 3.86; N, 10.26.

Methyl Vinyl Ether–Thionyl Chloride.—A mixture of salt 1 (10.0 g., 0.054 mole), methyl vinyl ether (10.0 g., 0.172 mole) and DME (60 ml.) was stirred and cooled in an ice-bath. A solution of thionyl chloride (6.4 g., 0.054 mole) in DME (15 ml.) was added over 20 minutes. The reaction mixture was worked up in the manner previously described to give 1.90 g. (36%) of **2,3-dicyano-5-methoxy-5,6-dihydro-1,4-dithiin**, m.p. 78–79°, as colorless crystals from methylene chloride–methylcyclohexane. The infrared spectrum was in accord with that expected of the assigned structure.

Anal. Calcd. for $C_7H_6N_2OS_2$: C, 42.40; H, 3.05; N, 14.13. Found: C, 42.74; H, 3.21; N, 14.09.

A similar experiment was carried out under the identical conditions employing acrylonitrile. The only product isolated was dithiin 2 (80%); none of the expected dihydro adduct was detected under these conditions.

2,3-Dicyano-5-phenyl-5,6-dihydro-1,4-dithiin.—The procedure employed was similar to that described in the literature.[3] Styrene dibromide (5.30 g., 0.020 mole) and salt 1 (5.20 g., 0.028 mole) were heated under reflux with stirring in DME (50 ml.) for 24 hours. The cooled mixture was poured into water, filtered, and the solid was washed well with water. The dried solid was extracted with three 25-ml. portions of hot carbon tetrachloride. The combined extracts deposited crystals on evaporation *in vacuo*. One recrystallization from carbon tetrachloride gave 1.60 g. (33%) of **2,3-dicyano-5-phenyl-5,6-dihydro-1,4-dithiin** as buff colored leaflets, m.p. 124.5–125°. The structure was assigned by analogy with the many simple displacement reactions known for salt 1.[1,3]

Anal. Calcd. for $C_{12}H_8N_2S_2$: C, 58.99; H, 3.30; N, 11.47. Found: C, 58.79; H, 3.33; N, 11.32.

Reaction of Trithiole Oxide 4 with Styrene.—Xylene (12 ml.) was heated to 135° and distilled styrene (3.6 g., 0.035 mole) was added. At 120°, trithiole oxide 4 (0.10 g., 0.00053 mole) was added in small portions over 3 minutes. After 10 minutes the yellow-orange solution was cooled and evaporated *in vacuo* to a brown sirup. The residue was chromatographed on a column of acid-washed alumina using ether as eluent. There was obtained 0.045 g. (31%) of pale yellow plates, m.p. 124–125°. There was no depression of melting point on admixture with an authentic sample of 2,3-dicyano-5-phenyl-5,6-dihydro-1,4-dithiin.

Reaction of Trithiole Oxide 4 with 1-Methoxybutadiene.—A solution of trithiole oxide 4 (0.40 g., 0.0021 mole) and 1-methoxybutadiene (1.0 g., 0.012 mole) in DME (10 ml.) was allowed to stand 2 hours at 25°. The solvent was removed *in vacuo*, and the residue was chromatographed on acid-washed alumina using ether–methylene chloride (50:50) as eluent. After two recrystallizations from ether there was obtained 0.07 g. (14%) of **2,3-dicyano-5-(2-methoxyvinyl)-5,6-dihydro-1,4-dithiin**, m.p. 73–75°.

Anal. Calcd. for $C_9H_8N_2OS_2$: C, 48.19; H, 3.60; N, 12.49. Found: C, 48.34; H, 3.72; N, 12.12.

The near infrared spectrum of the product showed no terminal methylene at 1.63 μ, a highly characteristic absorption for this function. Furthermore, the ring protons of the product exhibited an n.m.r. spectrum that was characteristic of monosubstitution on the 2,3-dicyano-5,6-dihydro-1,4-dithiin. It was thus concluded that addition occurred at the terminal double bond of 1-methoxybutadiene.

Reaction of Ethyl Vinyl Ether with Thionyl Chloride.—A solution of thionyl chloride (6.00 g., 0.051 mole) in tetra-

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[13] Substituted dithioöxamides are described by C. L. Levesque, U. S. Patents 2,525,075 and 2,525,416 (1950). Other examples have been prepared and characterized in these laboratories.

[14] Melting points are corrected and boiling points are uncorrected. Physical and spectral characterizations were carried out on the apparatus described previously.[1]

hydrofuran (20 ml.) was stirred and cooled while ethyl vinyl ether (3.67 g., 0.051 mole) was added over 10 minutes. The temperature rose spontaneously to 35°, where it was checked by slight external cooling. Fifteen minutes after addition was complete the solvent was removed under reduced pressure and the product was distilled through a 25-cm. Vigreux column; b.p. 74–75° (3.5 mm.), $n^{25}\mathrm{D}$ 1.4978. Much tar formation occurred in the still-pot during distillation. The yield of faintly pink **2-chloro-2-ethoxyethanesulfinyl chloride** was 4.57 g. (48%). The product was stored at Dry Ice temperature. The infrared spectrum shows bands at 3.40, 3.45, 3.50, 6.82, 6.98, 7.26, 7.33, 7.50, 7.91, 8.26, 8.60–9.10, 9.65, 10.08, 10.90, 11.25, 12.15 and 13.44 μ. The broad unresolved band at 8.60–9.10 μ probably consists both of (C—O—C) and (S=O). The (S=O) band was found at 8.55–8.75 μ in two aliphatic sulfinyl chlorides in this Laboratory.

Anal. Calcd. for $C_4H_8Cl_2O_2S$: C, 25.14; H, 4.22; Cl, 37.11. Found: C, 25.81; H, 4.40; Cl, 37.21.

Reaction of Sulfinyl Chloride 8 with Salt 1.—A solution of sulfinyl chloride 8 (0.52 g., 0.0027 mole) in DME (5 ml.) was added over 10 minutes to a suspension of salt 1 (1.00 g., 0.0054 mole) in DME (12 ml.). After 30 minutes the mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The resulting sirup was stirred with methylene chloride (100 ml.). The hygroscopic orange solid which deposited was collected by filtration under nitrogen. The solid weighed 0.91 g. (104% crude yield) and the infrared spectrum showed it to consist of a mixture of *cis-cis*-5 and *trans-trans*-5.[1a] The methylene chloride extract was chromatographed on a 1 × 10-cm. column of acid-washed alumina. There was thus obtained 0.08 g. (7%) of 2,3-dicyano-5-ethoxy-5,6-dihydro-1,4-dithiin, which was identified by the infrared spectrum.

Reaction of Disodium *trans-trans*-5 with Sulfinyl Chloride 8.—A solution of sulfinyl chloride 8 (0.58 g., 0.0030 mole) in DME (4 ml.) was added over 10 minutes to a solution of disodium *trans-trans*-5 (1.00 g., 0.0032 mole) in DME (12 ml.). The temperature was maintained at 0° by an ice-bath. After 10 minutes the mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was extracted twice with boiling ether and once with cold methylene chloride. The insoluble solid remaining weighed 0.41 g. (62%), and the infrared spectrum showed it to be slightly impure dithiin 2. The combined ether and methylene chloride extracts were concentrated and chromatographed on a 1 × 10-cm. column of acid-washed alumina. There was thus obtained 0.02 g. (15%) of 2,3-dicyano-5-ethoxy-5,6-dihydro-1,4-dithiin which was identified spectrally.

Reaction of Disodium *trans-trans*-5 with Sulfinyl Chloride 8 in the Presence of Methyl Vinyl Ether.—A solution of sulfinyl chloride 8 (0.59 g., 0.0031 mole) in DME (5 ml.) was added at 0° to a solution of disodium *trans-trans*-5 (1.00 g., 0.0031 mole) and methyl vinyl ether (1.50 g., 0.026 mole) in DME (10 ml.). After 5 minutes the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was chromatographed on a 1 × 20-cm. column of acid-washed alumina. Elution with 50:50 methylene chloride–ether gave 0.75 g. (62%) of crude product whose infrared spectrum showed it to be methoxy adduct 9 contaminated with a small amount of ethoxy adduct 6. The product was submitted to a second chromatographic purification from which 0.53 g. (44%) of essentially pure methoxy adduct 9 was isolated.

Pyrolysis of Trithiole Oxide 4.—A Pyrex tube (0.5″ i.d.) was packed to a depth of 1.5″ with small quartz cylinders and brought to a temperature of 250°. The internal pressure was adjusted to about 10 mm. while a slow stream of nitrogen was passed through the apparatus. Over 15 minutes a freshly prepared sample of pure trithiole oxide 4 (0.20 g., 0.00106 mole) was fed into the top of the tube. A liquid nitrogen trap was attached directly to the outlet to quench volatile products. Under these conditions little material reached the trap, and most of the product condensed at the base of the pyrolysis tube just below the furnace. The solid was collected (0.1 g.) and the infrared spectrum showed it to be essentially pure dithiin 2 contaminated with traces of 4.

A similar experiment was run in which ethyl vinyl ether (~ 2 g.) was condensed on the walls of the liquid nitrogen trap before the pyrolysis began. The pyrolysis was carried out at 200°, and the addition of 4 (0.15 g., 0.00080 mole) required 5 minutes. The trap was allowed to warm to 25°. The "infrared" spectrum of the small amount of solid formed in the trap showed it to be essentially pure dithiin 2. The ultraviolet spectrum of the product was indicative of dithiin 2, but a sizable shoulder at 342 mμ was observed which is characteristic of the ethoxy adduct 6. The product was not further investigated.

Reaction of Salt 1 with Bis-(trifluoromethyl)-1,2-dithiete (10).—A suspension of salt 1 (1.98 g., 0.0106 mole) in DME (20 ml.) was stirred and cooled at 0° in an ice-bath. Bis-(trifluoromethyl)-1,2-dithiete (10)[6] (2.41 g., 0.0106 mole) was added dropwise over 5 minutes. A deep red color developed as soon as the addition was begun. The mixture was allowed to stir for 3 hours at 0° and then 3 hours at 25°. The solvent was evaporated in a stream of dry nitrogen and the residue was extracted with hot benzene. From the benzene extract was isolated 0.6 g. of tricyano-1,4-dithiino[c]-isothiazole (14),[1a] m.p. 173.4–174.5°. The infrared spectrum of the product was identical with that of an authentic sample of 14.[1a]

Reaction of Trithiole Oxide 4 with Bis-(Trifluoromethyl)-1,2-dithiete (10).—Over 3 minutes trithiole oxide 4 (0.100 g., 0.00053 mole) was added in small portions to a freshly prepared solution of diethiete **10**[6] (0.120 g., 0.00053 mole) in DME (3 ml.). After 30 minutes a small precipitate of sulfur had deposited. The solution was evaporated *in vacuo* after 2 hours to a light yellow residue which was extracted with two 25-ml. portions of boiling petroleum ether. The insoluble portion weighed 0.05 g. (87%), m.p. 194–199° dec., and the infrared spectrum showed it to be almost pure dithiin 2. From the petroleum ether extract was obtained 0.065 g. of tan needles, m.p. 50°, whose infrared spectrum indicated it was an isomer of 2,3,4a,6,7,8a-hexakis-(trifluoromethyl)-4a,8a-dihydro-1,4-dithiino[2,3-b]-1,4-dithiin, a known product of self condensation of **10**.[6]

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, THE UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, N. C.]

Chemistry of Aliphatic Disulfides. IV. Studies on the Synthesis of Open-chain Unsymmetrical Cystine Derivatives[1,2]

BY RICHARD G. HISKEY AND WILLIAM P. TUCKER[3,4]

RECEIVED JULY 18, 1962

The sulfenyl thiocyanate method for the preparation of unsymmetrical disulfides has been applied to several unsymmetrical cystine derivatives. Unsymmetrical disulfides can also be obtained directly from the appropriate S-(2-tetrahydropropyranyl) thioether by treatment with thiocyanogen followed by a second mercaptan.

The importance of combined cystine in the stabilization of secondary and tertiary protein structure is generally recognized although little understood.[5] For example, fission of the disulfide

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[1] Supported in part by research grant A-3416 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, United States Public Health Service.

[2] Part III of this series, R. G. Hiskey and F. I. Carroll, *J. Am. Chem. Soc.*, **83**, 4647 (1961).

[3] R. J. Reynolds Tobacco Co. Fellow, 1959.

[4] Abstracted in part from a dissertation submitted by W. P. Tucker to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, August, 1962.

[5] P. D. Boyer in "The Enzymes," P. D. Boyer, H. Lardy and K.