

substrate and solvent, should be informative (e.g., in naphthyl azoxy series in which there is evidence for two mechanisms). Systematic study is needed of the course of reaction, and acidity dependence, of unsymmetrically substituted azoxybenzene derivatives.⁴⁹ Finally, heteroaromatic substrates have not yet been studied, and little is known about the rear-

(49) B. T. Newbold in "The Chemistry of the Hydrazo, Azo, and Azoxy Groups," S. Patai, Ed., Wiley, New York, N.Y., 1975.

angement of aliphatic azoxy compounds. Thus one may look to future investigations of the Wallach rearrangement to provide some of the clues which have thus far not been revealed.

My thanks go to my most able coworkers, R. A. Cox, A. Dolenko, B. T. Lawton, K. Mahendran, and W. M. J. Strachan, for their enthusiasm in pursuing the research, and to the National Research Council of Canada for providing financial support.

Nonclassical Condensed Thiophenes

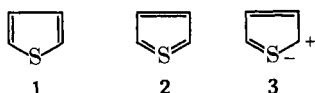
M. P. Cava* and M. V. Lakshmikantham

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19174

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The great chemical stability of thiophene (1) as compared with either pyrrole or furan has long been known to organic chemists.

In 1939, Schomaker and Pauling suggested that an expansion of the sulfur octet could be a special factor in stabilization of the thiophene molecule. In resonance terminology, this concept can be represented by including structures with tetravalent sulfur (2) as well as related dipolar structures (i.e., 3) in which the sulfur atom bears a negative charge.¹



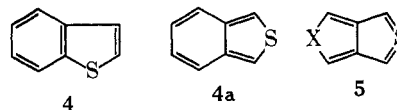
Longuet-Higgins later developed this concept in molecular orbital terms, showing that the mixing of sulfur $3p_z$, $3d_{xz}$ and $3d_{yz}$ orbitals would provide three pd^2 hybrid orbitals, two of which are nonorthogonal and capable of π overlap.² In this way, sulfur heteroatoms can be treated as structurally analogous to $-\text{CH}=\text{CH}-$ units in conjugated systems. This formulation has been expressed in quantitative terms and used in Hückel-type calculations on thiophene and other sulfur heterocycles.³

Critics of this model contend that there is no reason to suppose on the basis of stability alone that d-orbital participation is significant.^{4a} Mangini and Zauli, for example, have argued that sulfur pd^2 orbitals would be of too high energy and cause too much angle strain to participate effectively.^{4b}

Many molecular orbital calculations have been carried out on thiophene in recent years. The sophis-

ticated studies of Clark, and those of Dewar and Trinajstić, are particularly noteworthy. They have led to the general conclusion that sulfur d-orbital participation is insignificant in the thiophene molecule.⁵

Fusion of thiophene to a benzene nucleus gives rise to either of the well-known heterocycles benzo[*b*]thiophene (4) or benzo[*c*]thiophene (4a); both of these are examples of classical condensed thiophenes, and can be represented by the usual Kekulé structures. It is possible, however, to conceive of condensed thiophene heterocycles (i.e., general structure 5) for which no uncharged singlet structure can be



written other than one containing a tetravalent sulfur as part of a thiophene ring. Such systems represent novel structures in which one may consider the sulfur atom as being coaxed to the maximum, so to speak, into using pd hybrid orbitals, even if this type of participation is negligible in thiophene itself.

In this Account, we review the chemistry of compounds of this type, which we shall refer to as nonclassical condensed thiophenes, and which have been the object of chemical investigation only since 1967.⁶

(1) V. Schomaker and L. Pauling, *J. Am. Chem. Soc.*, 61, 1769 (1939).

(2) H. C. Longuet-Higgins, *Trans. Faraday Soc.*, 45, 173 (1949).

(3) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N.Y., 1961.

(4) (a) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N.Y., 1969; (b) A. Mangini and C. Zauli, *J. Chem. Soc.*, 2210 (1960).

(5) (a) D. T. Clark, *Tetrahedron*, 24, 2663 (1968); (b) M. J. S. Dewar and N. Trinajstić, *J. Am. Chem. Soc.*, 92, 1453 (1970).

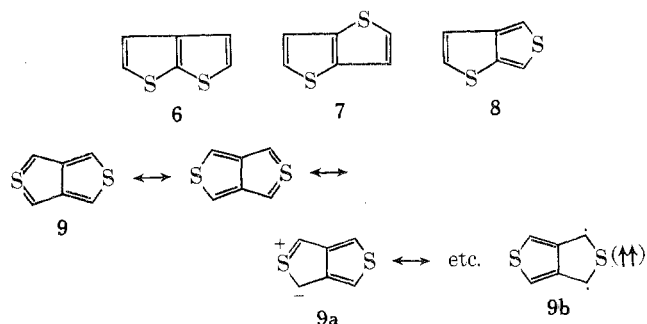
(6) For an earlier review of this subject, see M. P. Cava, *Int. J. Sulfur Chem., Part C*, 7, 55 (1972). For the synthesis of some nonclassical six-membered sulfur heterocycles, see (a) M. P. Cava, N. M. Pollack, and D. A. Repella, *J. Am. Chem. Soc.*, 89, 3640 (1967); (b) R. H. Schlessinger and I. S. Ponticello, *ibid.*, 89, 3641 (1967); (c) I. S. Ponticello and R. H. Schlessinger, *ibid.*, 90, 4190 (1968); (d) J. M. Hoffman, Jr., and R. H. Schlessinger, *ibid.*, 91, 3953 (1969).

Michael P. Cava is Professor of Chemistry at the University of Pennsylvania. He was born in Brooklyn, N.Y., and received the Ph.D. from the University of Michigan in 1951. His research interests are divided among the areas of benzylisoquinoline alkaloids, cyclobutadienoid compounds, and organic sulfur and selenium compounds.

M. V. Lakshmikantham is a native of Madras, India, where she received the Ph.D. from the University of Madras in 1958. She has worked mainly in natural products and organosulfur chemistry, and is presently a research associate with Professor Cava.

Thieno[3,4-*c*]thiophene

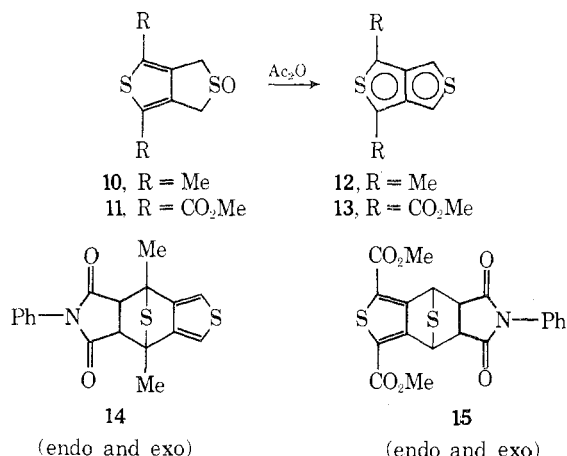
Two thiophene rings can be fused together in four different ways, giving rise to the four isomeric thienothiophenes, 6-9. Isomers 6-8 have classical



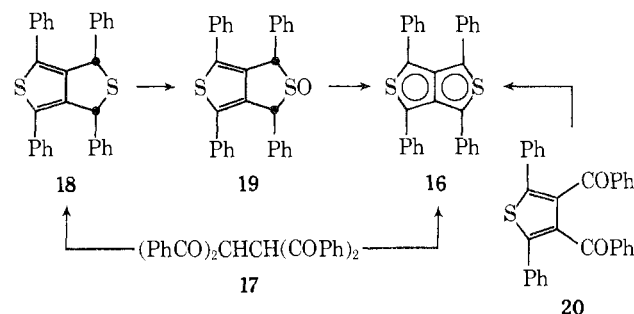
structures and are known, isolable compounds.⁷ Isomer 9, thieno[3,4-*c*]thiophene, has a nonclassical structure by our definition. The symmetry of the molecule, which allows both sulfurs to have partial tetravalent character, would appear to make 9 a particularly favorable molecule for sulfur d-orbital participation. In the absence of such participation, the molecule must either have the character of a thiocarbonyl ylide (9a) or a diradical (9b).

The first evidence for the existence of a derivative of 9 was reported in 1967.⁸ Attempts to dehydrate sulfoxide 10 to give 1,3-dimethylthieno[3,4-*c*]thiophene (12) led to no isolable product. However, dehydration of 10 in the presence of *N*-phenylmaleimide showed that 12 was produced as a transient intermediate, since both the endo and exo adducts 14 were isolated in reasonable yield.^{8,9} In a related study, dehydration of sulfoxide 11 in acetic anhydride afforded a nonpolar orange product, presumably 1,3-dicarbomethoxythieno[3,4-*c*]thiophene (13), which proved too sensitive to light and air to permit isolation.

The trapping of 13 by *N*-phenylmaleimide succeeded in good yield to give a mixture of endo and exo adducts 15. In accord with the assumption that thieno[3,4-*c*]thiophene is a delocalized system, dienophile addition of both 12 and 13 takes place as expected at the ring of highest electron density.⁹

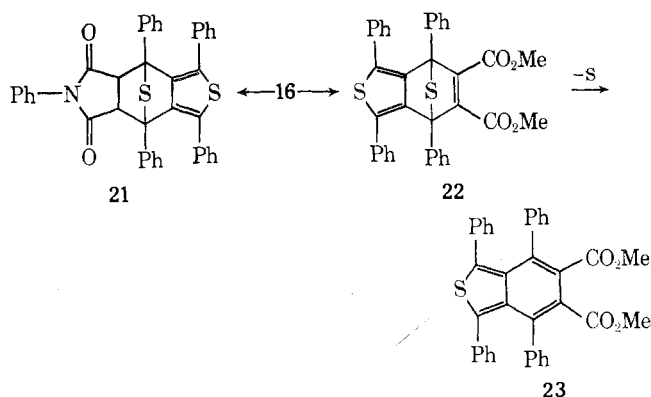


Tetraphenylthieno[3,4-*c*]thiophene (16), first reported in 1969, was the first example of an isolable nonclassical condensed thiophene.¹⁰ The original synthesis involved condensed reaction of tetrabenzoylthane (17) with P₄S₁₀ in hot xylene to give the *cis* dihydro sulfide 18 (as well as some of the *trans* sulfide), periodate oxidation of 18 to the sulfoxide 19, and acetic anhydride dehydration of 19 to 16.^{10,11} Recent improved syntheses of 16 consist of the reaction of P₄S₁₀ in pyridine with either 2,5-diphenyl-3,4-dibenzoylthiophene (20)¹² or tetrabenzoylthane (17).¹³



The thienothiophene 16 forms purple crystals, mp 257-258°, which are stable indefinitely in the solid state. The purple color is due to a strong visible band at 553 nm (log ϵ 4.04). The nonpolar nature of 16 is reflected by its crystallizability from hexane and the fact that it is not adsorbed strongly on basic alumina. Its benzene solution gives no esr signal, showing it to have a singlet ground state.¹¹

The chemistry of 16 is characterized by a general tendency of reagents to add to the 1,3 positions of the molecule. As with the unstable analogs 12 and 13, *N*-phenylmaleimide adds to give a mixture of endo and exo adducts 21; addition occurs only slowly, however, and the adducts revert to 16 at their melting points. Dimethyl acetylenedicarboxylate also adds slowly in refluxing xylene; the initial adduct 22 is not isolable, but loses elemental sulfur to give the fully aromatic isothianaphthene 23.¹¹



Catalytic reduction over palladium converts 16 to the *cis* sulfide 18. Reduction of 16 to 18 also takes place when 16 is refluxed with xylene and P₄S₁₀; the P₄S₁₀ is essential for this reaction, which is probably free radical in nature.¹¹

(7) (a) H. Wynberg and D. T. Zwanenburg, *Tetrahedron Lett.*, 761 (1967); (b) F. Challenger, *Sci. Prog.*, 41, 593 (1953).

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

(9) M. P. Cava, N. M. Pollack, and G. A. Dieterle, *J. Am. Chem. Soc.*, 95, 2558 (1973).

(10) M. P. Cava and G. E. M. Husbands, *J. Am. Chem. Soc.*, 91, 3952 (1969).

(11) M. P. Cava, M. Behforouz, G. E. M. Husbands, and M. Srinivasan, *J. Am. Chem. Soc.*, 95, 2561 (1973).

(12) K. T. Potts and D. McKeough, *J. Am. Chem. Soc.*, 95, 2750 (1973).

(13) M. V. Lakshmikantham, unpublished observations.

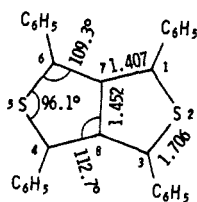
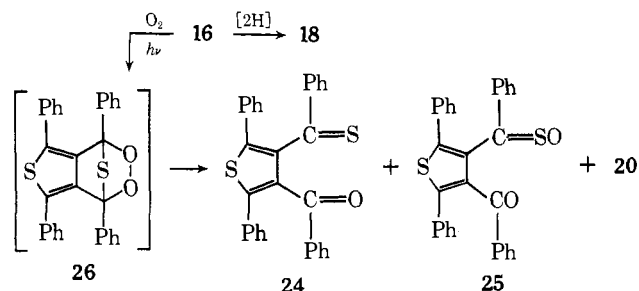
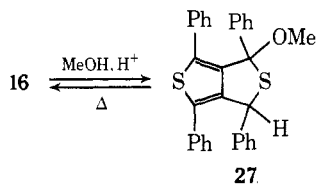


Figure 1.

Benzene solutions of **16** are unusually stable photochemically in the absence of oxygen. In the presence of air, photooxidation occurs readily to give a mixture of thioketone **24**, thioketone *S*-oxide **25**, and diketone **20**. The formation of these products suggests that an unstable thioozonide of structure **26** is produced initially from **16**.¹¹



Methanol does not add to **16** under basic conditions; acid-catalyzed addition occurs rather easily to give the methoxy sulfide **27**. The latter is surprisingly unstable, and easily reverts to **16** on heating.¹¹

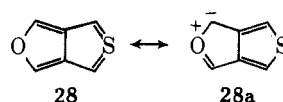


The structure of **16** has been confirmed by an X-ray crystallographic analysis, which also reveals some interesting structural features (Figure 1).¹⁴ As expected, the thienothiophene nucleus is planar, the two thiophene units being identical. The C-S bond length (1.706 Å) is relatively short, while the C_α-C_β bond length (1.407 Å) and C_β-C_β bond length (1.452 Å) are relatively long, compared to the corresponding values for thiophene (1.714, 1.370, and 1.423 Å, respectively). The phenyl substituents are rotated out of the plane of the bicyclic nucleus to a surprising extent, namely 39.6° for those at C-1 and C-4 and 58.4° for those at C-3 and C-6. The lack of coplanarity of the phenyls and the nucleus and the fact that the C-phenyl bond (1.48 Å) corresponds approximately to an sp²-sp² single bond preclude major electronic stabilization of the thienothiophene system by the substituents and suggest that their stabilizing effect must be at least partially steric in nature.

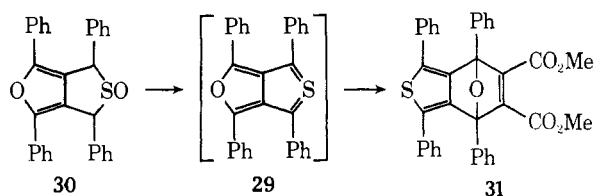
Thieno[3,4-*c*]furan

Replacement of one of the sulfur atoms of thieno[3,4-*c*]thiophene (**9**) by an oxygen results in a loss of symmetry. In the resulting thieno[3,4-*c*]furan

there is only one nonclassical canonical form (**28**), although *p* orbital conjugation of the oxygen gives rise to dipolar carbonyl ylide forms such as **28a**.

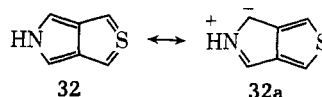


The predicted decrease in the stability of thieno[3,4-*c*]furan as compared to **9** was demonstrated experimentally by the generation of its tetraphenyl derivative **29**, the analog of the stable thienothiophene **16**. The acetic anhydride dehydration of sulfoxide **30** afforded no isolable product. When the dehydration of **30** was carried out in the presence of dimethyl acetylenedicarboxylate, however, the transient intermediate **29** was trapped efficiently to give a single adduct (**31**) in which addition had taken place to the furan ring.^{15,16}

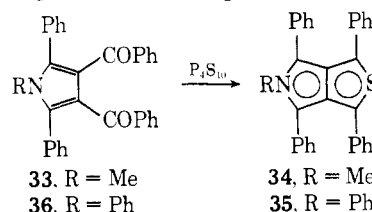


Bicyclic Nonclassical Thiophenes Containing Nitrogen

The direct nitrogen analog of furan **28** is thieno[3,4-*c*]pyrrole (**32**), a system which might be expected to be more stabilized than **28** by dipolar ylide forms (i.e., **32a**) in view of the greater basicity of nitrogen compared to oxygen.



Indeed, two phenylated derivatives of **32** have been synthesized and found to be isolable crystalline compounds.¹⁵⁻¹⁷ Reaction of the pyrrole diketone **33** with P₄S₁₀, best in pyridine solution,¹⁷ affords the bright red microcrystalline *N*-methyltetraphenylthieno[3,4-*c*]pyrrole (**34**), mp 210-214°. Solutions of **34** showed a visible absorption maximum at 533 nm and gave no ESR signal, indicating a singlet ground state for the molecule. Compared to thienothiophene **16**, **34** is considerably more polar in nature, being only very slightly soluble in benzene. It is also much more sensitive to light and air and could not be successfully chromatographed and recrystallized.^{15,16} The *N*-phenyl analog **35**, prepared from diketone **36** and P₄S₁₀, is more stable and crystallizes from acetic anhydride as long red needles, mp 212-214°.¹⁶



(15) M. P. Cava and M. A. Sprecker, *J. Am. Chem. Soc.*, **94**, 6214 (1972).

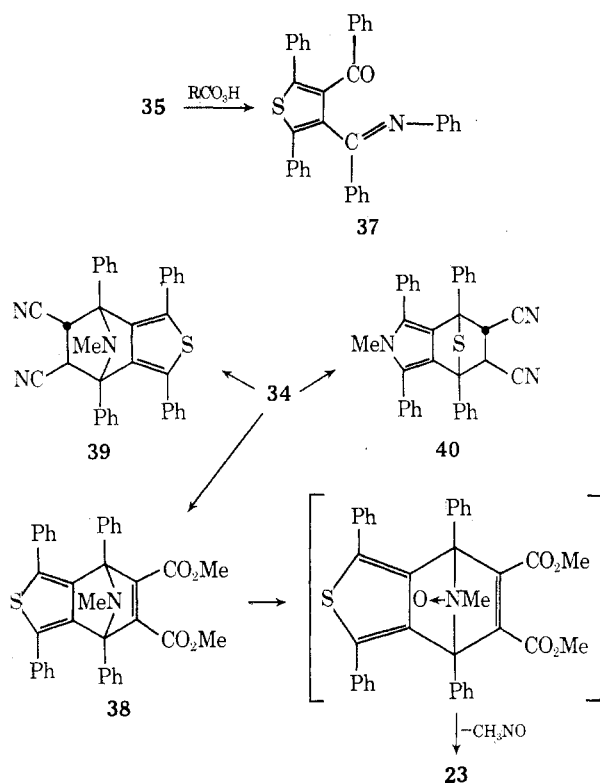
(16) M. P. Cava, M. A. Sprecker, and W. R. Hall, *J. Am. Chem. Soc.*, **96**, 1817 (1974).

(17) K. T. Potts and D. McKeough, *J. Am. Chem. Soc.*, **95**, 2749 (1973); **96**, 4268 (1974).

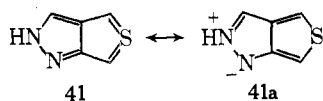
(14) M. D. Glick and R. E. Cook, *Acta Crystallogr., Sect. B*, **28**, 1336 (1972).

Peracetic acid oxidation of the pentaphenyl derivative 35 results in attack on the pyrrole ring and formation of the imine 37 as the major product.¹⁶

Cycloaddition reactions also occur most rapidly at the pyrrole portion of the thieno[3,4-*c*]pyrrole system. For example, the *N*-methyl derivative 34 adds dimethyl acetylenedicarboxylate rapidly in the cold to give the nitrogen-bridged adduct 38; peracid oxidation of 38 gives an *N*-oxide which immediately loses nitrosomethane to give the fully aromatic isothianaphthene diester 23.¹⁶ Similarly, fumaronitrile in refluxing benzene (80°) gives the analogous adduct 39 as the exclusive product; when the same reaction is carried out in refluxing toluene (110°), however, the isomeric adduct 40 is the major reaction product. These experiments indicate that cycloaddition to either ring of a thieno[3,4-*c*]pyrrole is possible, addition to the pyrrole ring being kinetically favored and addition to the thiophene ring being thermodynamically favored.¹⁷

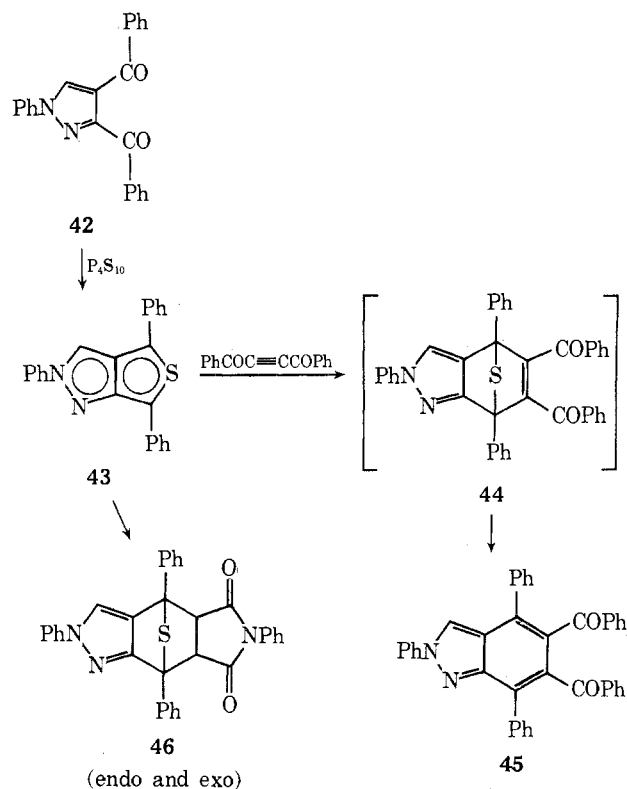


The thieno[3,4-*c*]pyrrole system (41) should be more stabilized by dipolar resonance than its pyrrole analog 32, since a nitrogen atom bears the negative charge in canonical form 41a.

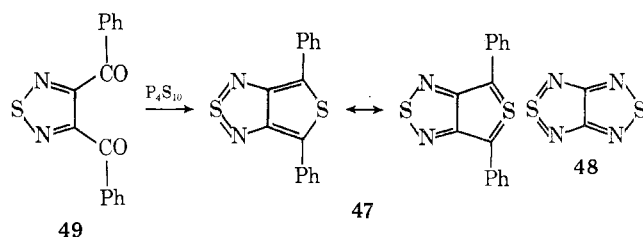


Indeed, reaction of P_4S_{10} with the pyrazole diketone 42 affords 2,4,6-triphenylthieno[3,4-*c*]pyrrole (43) as stable brick-red needles, mp 200–202°. Compound 43, which can be crystallized from acetic anhydride, shows a visible absorption maximum at 497 nm; its mass spectrum, like that of thienothiophene 16, is indicative of a very stable molecule which is resistant to fragmentation. Cycloadditions take place exclusively at the thiophene ring of 43. For example, dibenzoylacetylene gives, *via* the nonisolable inter-

mediate 44, the benzo[*c*]pyrazole 45. Similarly, *N*-phenylmaleimide adds to 43 to give a mixture of the *exo* and *endo* adducts 46 in which the *exo* isomer predominates.¹⁸



Finally, the reported synthesis of diphenylthieno[3,4-*c*]-1,2,5-thiadiazole (47)¹⁹ is of considerable interest, since 47 stands structurally between the stable purple thienothiophene 16 and the equally stable colorless 1,2,5-thiadiazolo[3,4-*c*]-1,2,5-thiadiazole (48).²⁰ Compound 47 (prepared from P_4S_{10} and diketone 49) forms purple needles, mp 146°; its longest wavelength absorption maximum is at 558 nm, almost identical with that (553 nm) of thienothiophene 16. The nmr of 47 shows that all four ortho phenyl protons are deshielded ($\delta \sim 8.2$), suggesting that the phenyls are coplanar with the bicyclic nucleus. The mass spectrum shows the molecular ion to be the base peak, but an important fragment (30%) corresponds to $\text{C}_7\text{H}_5\text{S}$.



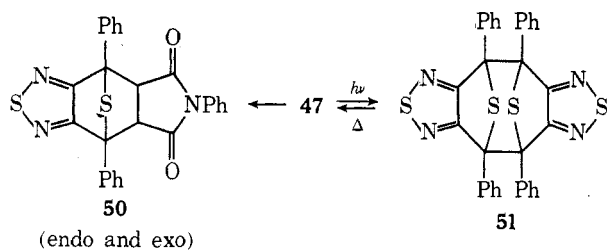
Compound 47, like 16, reacts slowly on heating with *N*-phenylmaleimide, giving a mixture of *exo* and *endo* isomers 50. Unlike 16, 47 gives a photodimer, 51, of uncertain stereochemistry. The photodi-

(18) K. T. Potts and D. McKeough, *J. Am. Chem. Soc.*, **94**, 6215 (1972); **96**, 4276 (1974).

(19) J. D. Bower and R. H. Schlessinger, *J. Am. Chem. Soc.*, **91**, 6891 (1969).

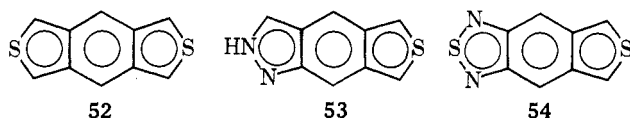
(20) M. Carmack, R. W. Street, and R. Y. Wero, 158th National Meeting of the American Chemical Society, New York, N.Y., Sept 1969, Abstract ORGN-54.

mer is thermally unstable and reverts to 47 on gentle heating in a variety of solvents.¹⁹

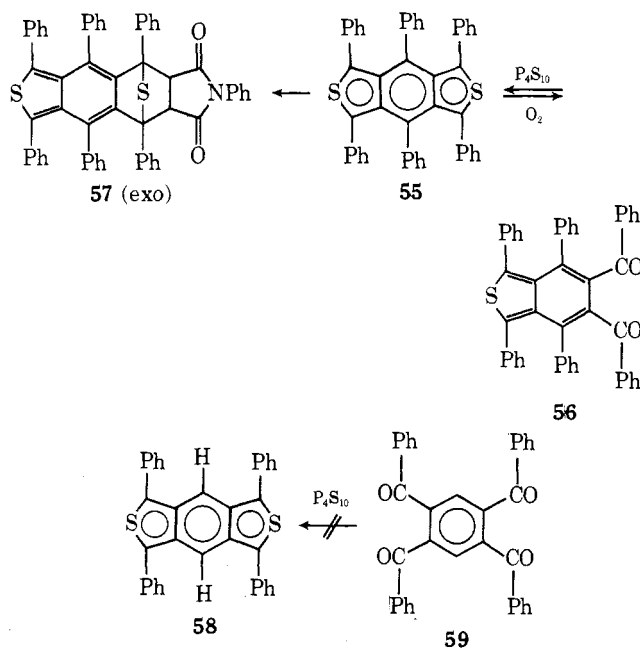


Tricyclic Nonclassical Thiophenes

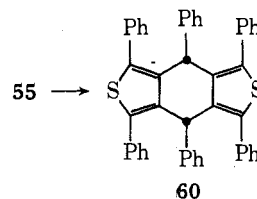
The insertion of a benzene ring in a linear manner between the thiophene ring and the second heterocyclic nucleus of a nonclassical condensed thiophene gives rise to a corresponding tricyclic benzolog. For example, thieno[3,4-*c*]thiophene, thieno[3,4-*c*]pyrazole, and thieno[3,4-*c*]-[1,2,5]-thiadiazole give rise to the tricyclic systems 52, 53, and 54. Derivatives of all three of these systems have been synthesized. The chemistry of these compounds, which is reviewed briefly below, indicates that annelation of this type produces systems which are more reactive than their bicyclic counterparts.



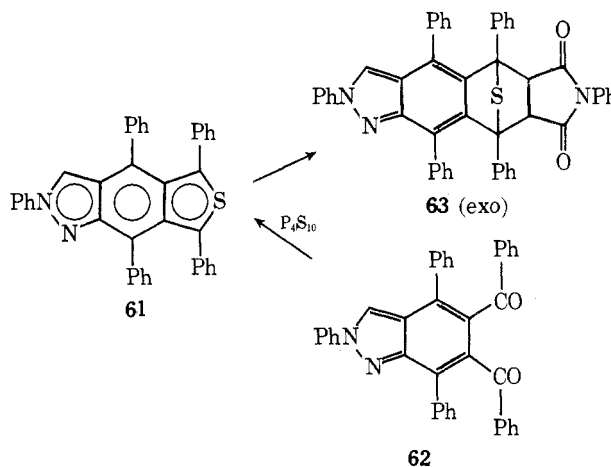
Hexaphenylthieno[3,4-*f*]benzo[*c*]thiophene (55), produced from P_4S_{10} and diketone 56 in pyridine, forms fine blue needles, mp 348–350°; it shows strong visible maxima at 793 and 877 nm. *N*-Phenylmaleimide in hot xylene adds to one of the thiophene rings to give the exo adduct 57.¹² Compound 55 is extremely susceptible to oxidation in solution; air at room temperature in the dark reconverts it to diketone 56. The two central phenyls of 55 seem to be necessary for the stabilization of the molecule; the corresponding tetraphenyl derivative 58 could not be prepared by the reaction of P_4S_{10} with the tetraketone 59.²¹



Although oxygen and dienophile additions occur at a thiophene ring, 55 is reduced at the central benzene nucleus when heated with P_4S_{10} and xylene, affording the dihydro derivative 60.²¹ Since both oxygen and dienophile addition to the central nucleus are potentially reversible reactions, it is tempting to speculate that all additions of 55 are kinetically favored at the central nucleus; 56 and 60 would then represent products of irreversible reactions, while adduct 57 would be a product of thermodynamic control.



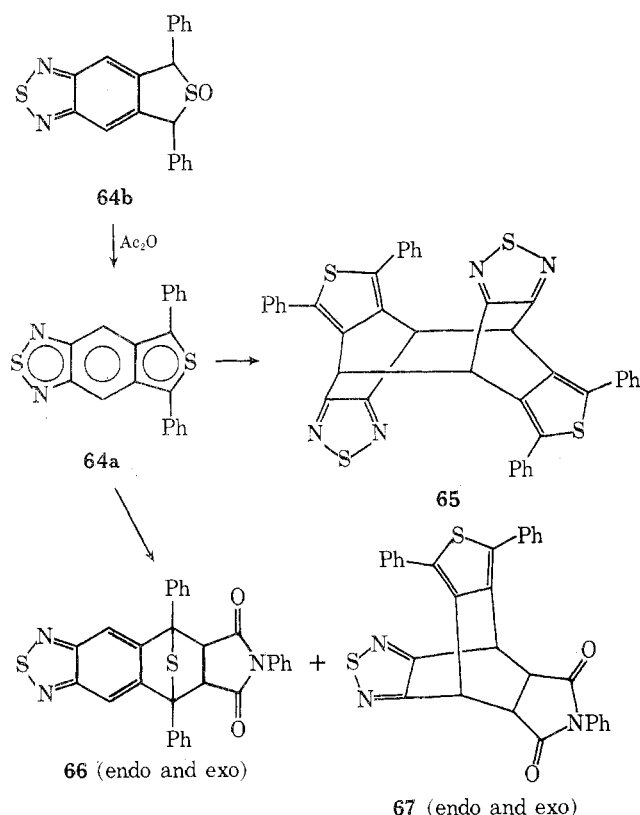
Pentaphenylthieno[3,4-*f*]benzo[*c*]pyrazole (61), obtained in the usual manner from diketone 62, crystallizes from acetonitrile as blue-black needles, mp 238–240°, and shows a visible maximum at 602 nm. As with 55, compound 61 adds *N*-phenylmaleimide to the thiophene ring to give exo adduct 63.¹⁷ The relative reactivity of 61 as compared to its bicyclic analog 43 cannot be judged from the literature data.



1,3-Diphenylthieno[3,4-*f*]benzo[*c*]-[1,2,5]-thiadiazole 64a is generated by the acetic anhydride dehydration of sulfoxide 64b and has a blue color caused by an absorption band at 645 nm. In contrast to the stable bicyclic analog 47, compound 64a was too reactive to permit isolation and readily dimerized at the benzene nucleus to give a dimer of probable structure 65. Solutions of 64a reacted with *N*-phenylmaleimide, addition taking place at both the benzene ring and the thiophene ring to give stereoisomeric mixtures of adducts 66 and 67.¹⁹ On the basis of the known chemistry of the dithiophene system 52, one may predict that phenyl substitution at the central ring of 64a would result in considerable stabilization of the molecule.

Electronic Structure of the Nonclassical Thiophenes

We pointed out above that recent refined molecular orbital calculations have shown that sulfur d-or-



bital participation is insignificant in the thiophene molecule; in qualitative terms, this means that the tetravalent sulfur contributor 5 may be ignored. On the basis of this conclusion, MO calculations for all of the isomeric thienothiophenes and thienopyrroles were carried out, neglecting sulfur d-orbital participation. It was concluded that thieno[3,4-*c*]thiophene (9) would have a triplet ground state and would be extremely unstable compared to its classical isomers 6, 7, and 8;^{6b,22} indeed, one study predicted that, compared to the most stable isomer 6, the lowest triplet of 9 would be 46.0 kcal greater in energy, and the lowest singlet would be 48.5 kcal greater in energy.²² Similar calculations for the isomeric thienopyrroles predicted that thieno[3,4-*c*]pyrrole (32) would be much less stable than its isomers and that it would have a triplet ground state.²³

After the synthesis of stable derivatives of 9 and 32 had been achieved, it seemed desirable to carry out a theoretical study of 9 and 32, as well as the related

(22) D. T. Clark, *Tetrahedron*, **24**, 2567 (1968).

(23) L. Klasinc and N. Trinajstić, *Tetrahedron*, **27**, 4045 (1971).

thieno[3,4-*c*]furan 28. The CNDO/2 method was used, considering all valence electrons as well as sulfur d orbitals. In this study, 9, 32, and 28 are all predicted to have singlet ground states. The thienothiophene 9 is calculated to have substantial π character in the C-S bonds, about 55% of which is in fact due to p_{π} - d_{π} overlap; there is very little overlap between the central bridging carbons. The calculated dipole moment of 9 is 0.00 D. The observed properties of the tetraphenylthienothiophene 16, both chemical and physical, seem to fit best for this theoretical model of the parent system.

The related furan and pyrrole systems 28 and 32 are also predicted to have C-S bonds in which p_{π} - d_{π} overlap is an important factor. The predicted dipole moments of 28 and 32 are 0.15 and 3.21 D, respectively, with the highest electron densities being on the carbons adjacent to oxygen or nitrogen. In simple resonance terminology, dipolar contributors 28a and 32a are important canonical forms. Again, the observed properties of the stable derivatives of the highly dipolar 32 fit nicely with this theoretical description of the parent system.¹⁶

The same type of CNDO/2 study of the benzodithiophene system 52 predicts that, as compared to the related 9, 52 will be more dipolar in nature, the excess electron density being distributed at the non-bridgehead carbons. It will, nevertheless, have a singlet ground state and about as much tetravalency as the related bicyclic 9.²⁴ These predictions are in accord with the isolability of the perphenyl derivative (55) of 52 and with its higher reactivity as compared to its bicyclic analog 16.

In conclusion, the nature of the sulfur bonding in the "nonclassical" condensed thiophenes remains a matter of some controversy, despite the physical availability of some highly phenylated derivatives. Further insight into this problem will best be gained, in our opinion, not by polemics but by new experimental work. A particular challenge is to find ways of synthesizing, at low temperatures, unsubstituted and therefore unperturbed parent systems (i.e., 9 itself) so that direct spectroscopic observations of these can be made and compared with theory.

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(24) M. A. Sprecker, Ph.D. Dissertation, University of Pennsylvania, 1973.