Heterocycles from Substituted Amides II. (Ia,b) Novel Behavior of a Reactive Thiophene in Some Cyclo- and Acyclo-addition Reactions

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N,N'-Diisopropyl-N,N'-diphenyl-2,4-thiophenediamine (1) has demonstrated its remarkable electron-donating abilities and atypical behavior as a thiophene, by its facile reaction with a number of electron deficient dienophiles. Thus, β-nitrostyrene, ethoxymethylene malononitrile, diethyl azodicarboxylate and dimethyl acetylenedicarboxylate undergo Michael-type addition at the 5-position of 1 to form adducts 2, 3, 4, and 5. Alternatively, the dienophiles, acrylonitrile, N-phenylmaleimide and phenyl-1,2,4-triazoline-3,5-dione gave novel cyclic materials 6, 9, and 11, not necessarily arising from simple Diels Alder addition. Structure proofs for the products as well as alternative mechanisms for their formation are discussed.

The behavior of N,N'-diisopropyl-N,N'-diphenyl-2,4-thiophenediamine towards electrophiles revealed the high reactivity of the 5-position. Normal electron enrichment of this "α"-position by adjacent sulfur is strongly reinforced by interaction with both anilino nitrogen atoms, perhaps to the extent of weakening normal thiophene aromaticity (2).

Of the three common 5-membered heterocycles, furan compounds readily undergo ($\pi^4 + \pi^2$) cyclo-additions (Diels Alder), pyrrole does so less readily, and then usually only with electrophilic dienophiles, where sometimes Michael addition occurs, while thiophene compounds are generally least reactive toward such cyclo-addition, because of their higher resonance energy (3a). A few examples of cyclizations from certain substituted thiophenes and dienophiles have been reported (3b-3e) although in only one case is the Diels Alder bicyclo-adduct actually isolated (3c).

In view of the increased nucleophilicity of 1 over usual thiophenes, coupled with its ability to apparently lose a degree of aromaticity on reaction with electrophiles, it became of interest to ascertain the behavior of this novel thiophene toward selected dienophiles.

Reaction of β-nitrostyrene, ethoxymethylene malononitrile, diethyl azodicarboxylate, and dimethyl acetylenedicarboxylate gave the Michael adducts 2, 3, 4, 5, respectively (Scheme 1), (Table 1).
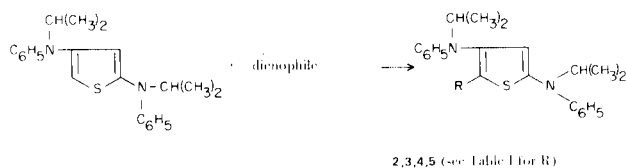
The nmr spectra of the acyclic adducts are characterized by the presence of the remaining thiophene proton as a singlet between 5.4-6.2 ppm (4). The asymmetry of 2 causes chirality of the isopropyl methyl groups, (4 doublets) while achiral isopropyl groups (two methyl doublets) are observed in 3, 4, and 5. Michael additions of alkoxymethylenemalononitrile are often accompanied by elimination of alcohol; 3 is no exception as shown by the presence of the olefinic side chain. In addition to the NH visible by nmr, the ir spectra of 4 clearly shows this moiety at 3400 cm^{-1}.

SCHEME II (a,b)
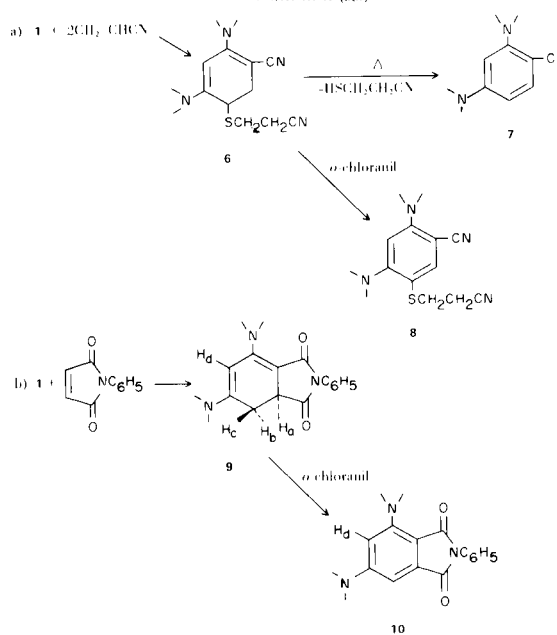
(a) Valences on nitrogen connected to isopropyl and phenyl groups respectively. (b) See Fig. 1 for sequential A-60 nmr spectra of these materials.
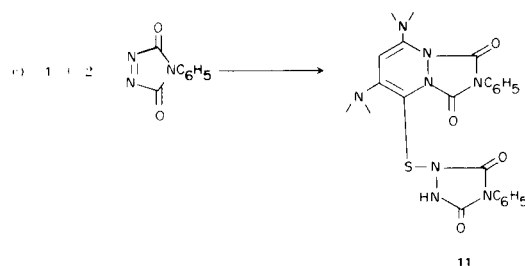
On the other hand, with the electrophilic olefins, acrylonitrile, N-phenylmaleimide, and phenyl-1,2,4-triazoline-3,5-dione more deep-seated transformations took place giving products arising from cyclo-addition (Scheme II, **6**, **9**, **11**, respectively).

(a) Valences on nitrogen connected to isopropyl and phenyl groups respectively.

(b) See Figure 1 for sequential A-60 nmr spectra of these materials.

Structure proofs for the adducts were verified by chemical transformations as well as characteristic spectral analyses (nmr, ir, uv, ms). Thus, **6** (Fig. 1) (5) displays chiral isopropyl methyl groups as two pairs of well-separated doublets at δ 0.88 and 0.93 (J = 6.6 Hz) and two other pairs of more closely spaced doublets at δ 1.24 and 1.27 (J = 6.6 Hz). The remainder of the spectra shows complex multiplets for the chiral ring and side-chain methylene protons and one methine proton (δ 2-3.3, 7 protons). Well-defined heptets for the two isopropyl methine protons are evident at 3.73 and 4.73 (J = 6.6 Hz), associated respectively with the high and low field isopropyl methyl groups (as determined by decoupling experiments). A single resonance (one proton) for the olefinic resonance appears at δ 4.53.

Transformation of **6** to aromatic achiral **8** led to considerable simplification. Two doublets only appear for the isopropyl methyl groups at δ 1.19 and 1.25 (J = 6.5 Hz), while the corresponding methine protons are both found as heptets at δ 4.37 (J = 6.5 Hz). A considerable lessening of both shielding and deshielding effects on these moieties are thus evident as compared with **6** (6). Multiplets centered at δ 2.49 and 2.95 (2 protons each; J_{ab} = 7.3 Hz) are characteristic of what would be expected from adjacent A_2B_2 methylene groups (7). The two benzonitrile protons are also quite evident as single resonance peaks at δ 6.93 and 7.49, thereby substantiating the 1,4-positioning of these aromatic protons.

The formation of **7** was apparent as the base peak in the mass spectrum of **6**. Material **7** was also prepared in macro amounts by thermolysis of **6**. In addition to 13 aromatic protons, only two isopropyl methine (δ 4.4) and six isopropyl methyl protons (two doublets at δ 1.18, 1.70) were evident.

TABLE I

Acyclic Adducts to N,N'-Diisopropyl-N,N'-diphenyl-2,4-thiophenediamine (1)

Product (Empirical Formula)	R	Yield	M.p.	Calcd. C	H	N	S	Found C	H	N	S	Thiophene β-proton	Isopropyl methyl groups	Protons in R side-chain
2 ($C_{30}H_{33}N_3O_2S$)	$C_6H_5CHCH_2NO_2$	21	119-121	72.11	6.66	8.41		71.77	6.56	8.15		6.2 (s)	1.13 (4 doublets)	multiplets 4.6-5.2 (3 protons)
3 ($C_{26}H_{26}N_4S$)	$(NC)_2C=CH-$	52	197 (222-228)	73.20	6.14	13.13	7.52	73.14	6.17	12.97	7.60	5.4 (s)	1.1, 1.26 (2 doublets)	6.7 (s, one proton)
4 ($C_{22}H_{36}N_4O_4S$)	$-N-CO_2Et$ / $NHCO_2Et$	---	125-127	64.10	6.92	10.68		64.02	7.01	10.77		5.80 (s)	(obscured by ethoxy triplets)	4.12 (two triplets OCH_2CH_3 6.4 (broad N-H))
5 ($C_{26}H_{32}N_2O_4S$)	$C-CO_2CH_3$ / $HC-CO_2CH_3$	49	131-132	68.27	6.55	5.69		68.11	5.96	5.18		5.54 (s)	1.2, 1.22 (2 doublets)	3.08, 3.72 (2s, OCH_3) 6.8 (s, =CH)

11

The ir and uv spectra established the double-bond conjugation in 6. Conjugated nitriles show more intense absorption at lower frequency than their saturated counterparts (8). Dinitrile 6 typically showed a strong intensity band at 2162 cm⁻¹ [shoulder at 2194 cm⁻¹ (chloroform)], and weaker absorption at 2256 cm⁻¹ (side-chain nitrile). The nitrile band in aromatized 8 was less intense at 2230 cm⁻¹ (shoulder at 2213 cm⁻¹), while the side-chain nitrile was essentially constant at 2254 cm⁻¹ (weak). Aromatized nitrile group in 7 showed a single high intensity absorption at 2218 cm⁻¹. The somewhat increased frequency and lowered intensity of the aromatic nitrile band in 7 and 8 would be expected, as full aromatization would lead to less resonance interactions than with the nitrile group in 6.

Uv (ethanol) for 8 shows maxima at 250 and 295 mμ (ϵ = 17,800 and 13,300 res.). These aromatic and conjugation bands are present in 6 (253, 306 mμ (ϵ = 13,500 and 14,200 respectively), but in addition, there is a strong maxima at 366 mμ (ϵ = 14,700), absent in 8, indicative of the conjugated double bond system present in this compound.

Alternative conjugative structures to 6 can be eliminated because they would not be expected to suffer facile loss of β-mercaptopropionitrile.

The structure of 9, the product from cyclo-addition of N-phenylmaleimide to 1, was likewise confirmed from both spectral and chemical properties. The chiral isopropyl methyl groups appeared as four doublets at δ 0.81, 0.91, 1.14, 1.26 (J = 6.7 Hz) (Fig. 1). The multiplets for the two isopropyl methine protons were found at δ 3.85 and 5.27 and, as in 6, coupled respectively to the high and low field isopropyl methyl groups.

Three saturated ring protons were found between δ 2-3.5. Using the 100 megacycle instrument, both the magnitude and sign of the chemical shifts and coupling constants were obtained as follows: H_a, δ 3.48; H_b, δ 2.47; H_c, δ 2.06; and J_{ac} = 15 Hz, J_{ab} = 6.3 Hz, J_{bc} = -16.7 Hz. The last negative coupling constant confirmed the geminal positioning of these two protons, while the first J value is indicative of trans (axial-axial) and the second J value of cis (equitorial-axial) orientation (9).

A single uncoupled proton resonance occurs at δ 4.29. Although this absorption is at somewhat higher field than normally found for olefinic protons, it is consistent with what would be expected for an olefinic proton (H_d) of a 1-enamine, situated between two nitrogens (10). The only diolefin structure consistent with both the geminal and vicinal coupling found here and the very high field uncoupled olefinic proton is that shown in Scheme II (11).

Like 6, 9 is easily aromatized to 10, with consequent simplification of spectra, displaying only two closely

spaced doublets at δ 1.14 and heptets at δ 4.1-4.9 for the two isopropyl groups (6). One of the aromatic protons (presumably H_d) appears as a doublet (J = 1.5 Hz) upfield at δ 5.88, entirely consistent with its structure as a meta-phenylenediamine (12).

Conjugation of the two olefinic bonds in 9 is confirmed by comparison of its uv spectra with 10. The former material possesses a strong absorption at 318 mμ (ϵ = 19,100), while the maxima (aromatic) for 10 occurs at 290 mμ (ϵ = 20,600).

Analogous to cyclo-addition with acrylonitrile, phenyl-1,2,4-triazoline-3,5-dione appears to react with 1 in a 2:1 ratio without loss of sulfur. Nmr indicates for 11 an ArH:$(CH_3)_2$CH ratio of 20:12 while an amidic N-H absorption is apparent at ca. δ 8, which vanishes on treatment with deuterium oxide. Uv shows very strong maxima at λ 355 (ϵ = 37,000) and λ 275 (ϵ = 27,000), the former indicative of conjugated double bonds.

Neutral dienophiles such as allyl alcohol and styrene failed to react with 1 while excessively electrophilic and powerful dienophiles such as maleic anhydride and tetracyanoethylene gave red complexes which could not be
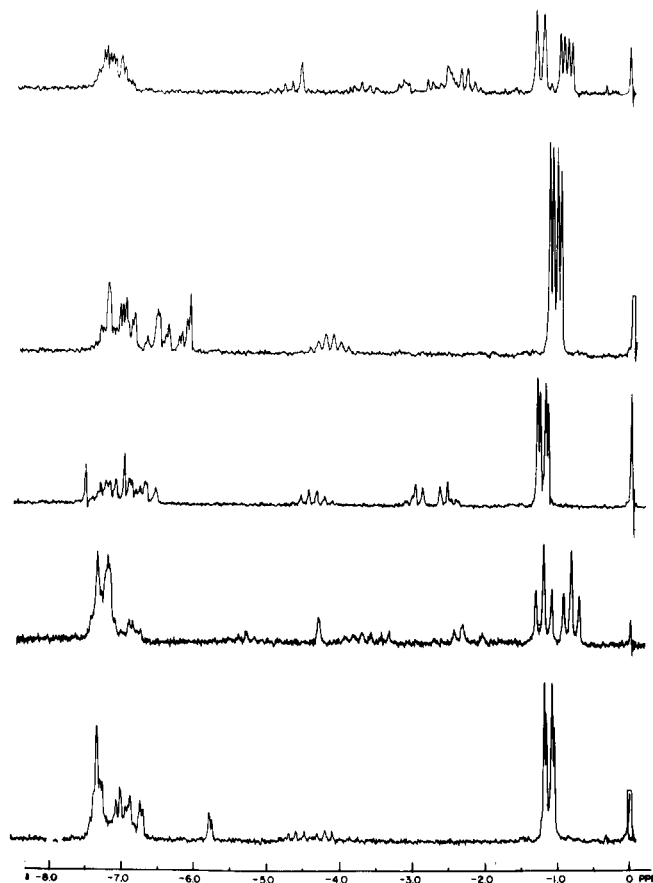

Figure 1. A-60 nmr (CDCl₃ or CCl₄) for materials (reading from top), 6, 7, 8, 9, 10.

disassociated without decomposition (13). Efforts to combine two electrophilic nucleophiles such as acrylonitrile and N-phenylmaleimide with 1 led to resin, or, as with a mixture of 1, acrylonitrile and ethoxymethylene malononitrile, gave only 3; no combinations of dienophiles yielded new isolable materials. Furthermore, reaction of other thiophenes, such as 3,4-diphenyl-2-thiophene-piperidine (14) with acrylonitrile gave back starting materials.

Alternative mechanistic pathways for both the cyclic and acyclic adducts have been diagrammed in Scheme III. Cyclo-addition could take place by a classical, concerted Diels Alder mechanism, a, or arise in stepwise fashion through d, f. Cyclo-products 6, 9, 11 would then be formed from the initial bicyclo adduct by carbon-sulfur cleavage (b,c), while acyclic adducts would form from the same intermediate by cleavage of the carbon-B bond (a,e,g,i).

Acyclic-products could alternatively arise from a classical Michael type addition (d,g,i), while the cyclic products could arise via path d, h, c, without going through an initial Diels Alder bicyclo adduct. In any event, much of the driving force for the reaction may be furnished by the propensity to form the resonance stabilized

SCHEME III (a)

bicyclo intermediate

Michael Products 2, 3, 4, 5

Cyclo Products, 6,9,11

(a) All structures shown are unstable intermediates except for diene 1 and starting dienophile (A–B).

vinylogous amidinium ion present in the several intermediates (15).

A final 1,4- addition in step c (to form 6, 11) must be rapid, to compete with sulfur loss (as in formation of 9). An indication that the final addition of mercaptan is indeed rapid, is the observation that with equimolar amounts of 1 and acrylonitrile, only 6 is formed, with 1 remaining. Hence step c must be substantially faster than the other preliminary steps.

EXPERIMENTAL (16)

2-(2-Nitro-1-phenylethyl)-N,N'-diisopropyl-N,N'-diphenyl-3,5-thiophenediamine (2).

The thiophenediamine 1 (1) (2 g., 0.057 mole) was placed in carbon tetrachloride and 0.06 mole (0.9 g.) of beta-nitrostyrene was added. Standing overnight did not produce crystals, although the nmr showed the disappearance of olefinic protons. The solvent was evaporated to give an oil which did not crystallize. The material was taken up in pentane and cooled externally with dry ice, causing solid to precipitate. The solid was collected on a precooled funnel, then dissolved in ether. The ether washings were evaporated to give a residual oil which on standing overnight gave crystals. Recrystallization from heptane gave 0.6 g. of white solid.

[3,5-Bis(N-isopropylanilino)-2-thenylidene]malononitrile (3).

The thiophenediamine 1 (1.7 g.) was placed in a mixture of carbon tetrachloride and chloroform, and 1.2 g. of ethoxymethylene malononitrile was added. The solution was permitted to stand overnight. A few solids were filtered off and the filtrate vacuum treated to remove solvent. The residual oil was triturated with pentane, whereupon the oil solidified (pentane extracts contained some ethoxymethylene malononitrile). The insoluble material (2.3 g.) was shown by nmr to be the product. This material was recrystallized from acetonitrile to give 1.2 g. of yellow crystals. The crystals melted at 197°, but solidified on the melting point block and remelted at 222-228°. Nmr of remelted material was identical to parent material and recrystallization from acetonitrile again gave crystals, m.p. 197° (with solidification).

[3,5-Bis[N-isopropylanilino)-2-thienyl]hydrazodicarboxylic Acid, Diethyl Ester (4).

The thiophenediamine 1 (3.5 g., 0.01 mole) in carbon tetrachloride was mixed with 1.8 g. of diethyl azobiscarboxylate. There was an exothermic reaction, but the material was allowed to stand for 54 hours to give crystals. The material was filtered off and recrystallized from ethanol. Additional crystals were obtained by recrystallization of the residue from evaporation of the carbon tetrachloride filtrate.

[3,5-Bis(N-isopropylanilino)-2-thienyl]maleic or Fumaric Acid, Dimethyl Ester (5).

The thiophenediamine 1 (3.5 g., 0.01 mole) was mixed in carbon tetrachloride with 1.9 g. of dimethyl acetylenedicarboxylate, to give an exothermic reaction. The mixture was allowed to stand overnight, then the material vacuum treated to remove solvent, and the residue triturated with pentane. After filtering off the solid, it was recrystallized twice from methylcyclohexane (charcoal) to give 2.4 g. of product.

2,4-Bis(N-isopropylanilino)-5-(2-cyanoethylthio)-1,3-cyclohexadiene-1-carbonitrile (6).

The thiophenediamine **1** (1.2 g., 0.0034 mole) was placed in benzene with 2.0 g. (0.038 mole) of acrylonitrile and refluxed overnight. The material was vacuum treated to remove benzene, and the residual oil solidified. Recrystallization from methylcyclohexane gave crystals, m.p. 132-136°, while a second recrystallization from 95% ethanol gave white crystals, m.p. 143-145°. Yields in subsequent runs were ca. 60%. When equimolar amounts of **1** and acrylonitrile were reacted in carbon tetrachloride, and the reaction monitored by nmr, the solid that was filtered from solution after 8 hours proved to be **6**, while the remaining carbon tetrachloride solution showed no trace of acrylonitrile, but did show unreacted **1**. See Figure 1 and Discussion for ms, ir, nmr and uv spectral features of **9** and sequential products **7** and **8**.

Anal. Calcd. for $C_{28}H_{32}N_4S$: C, 73.64; H, 7.06; N, 12.27; S, 7.02. Found: C, 73.78; H, 7.29; N, 12.08; S, 7.04.

2,4-Bis(N-isopropylanilino)benzonitrile (7).

Material **6**, when subjected to ms examination (high temperature probe), showed a prominent m/e = 369 with only a trace of higher m/e peaks. The ms of **6** also showed an appreciable m/e - 87. From this data it was concluded that the material broke down *via* elimination of H_2S and $CH_2=CHCN$ (or $HSCH_2$-CH_2CN), to give **7**. The reaction was carried out in macro amount by heating ca. 1.5 g. of **1** in an oil bath at 150-165°. The thick residual oil on cooling was taken up in ether, a small amount of solid material filtered off, and the ether evaporated. The residue was extracted with boiling pentane and the resulting tacky oil eluted through a silicic acid column with chloroform. The residual oil could not be crystallized, but nmr (Figure 1) and ms were consistent with structure, including an m/e peak at 369 and 89.

Anal. Calcd. for $C_{25}H_{27}N_3$: C, 81.26; H, 7.37. Found: C, 80.74; H, 7.38.

2,4-Bis(N-isopropylanilino)-5-(2-cyanoethylthio)benzonitrile (8).

Material **6** (0.9 g.) was placed in acetonitrile and dropwise, an acetonitrile solution of 0.5 g. of o-chloranil was added. The mixture was permitted to stand overnight, after what appeared to be an instantaneous reaction. The solution assumed a dark red hue. The acetonitrile was removed under vacuum and the residue eluted with pentane or carbon tetrachloride through Florisil® to give crystals which upon recrystallization from 95% ethanol possessed m.p. 122.5-123°.

Anal. Calcd. for $C_{28}H_{30}N_4S$: C, 73.97; H, 6.65; N, 12.32; S, 7.05. Found: C, 74.32; H, 6.74; N, 12.40; S, 6.82.

3,5-Bis(N-isopropylanilino)-N-phenyl-2,4-cyclohexadiene-1,2-dicarboximide (9).

Material **1** (1 g.) was dissolved in 20 ml. of ether and 0.5 g. of N-phenylmaleimide was added. The solution was permitted to stand overnight, then the ether cooled by means of dry ice-acetone bath to give crystals which were recrystallized twice from toluene-methylcyclohexane solution to give 0.5 g., m.p. 185-187°. See Discussion and Figure 1 for spectral features of **9** and **10**.

Anal. Calcd. for $C_{32}H_{33}N_3O_2$: C, 78.18; H, 6.77; N, 8.55; S, 0.0. Found: C, 78.08; H, 6.85; N, 8.51; S, 0.0.

3,5-Bis(N-isopropylanilino)-N-phenylphthalimide (10).

Material **9** was placed in acetonitrile with 0.25 g. of o-chloranil. There appeared to be an immediate reaction, with the imide dissolving in acetonitrile. The material was permitted to stand overnight, then vacuum treated to remove solvent. This material was dissolved in chloroform and eluted through a silicic acid column. The chloroform fractions were combined, vacuum

treated and the residual oil recrsytallized from hexane, while a second recrystallization afforded 0.3 g. of yellow needles from absolute methanol, m.p. 149-150°.

Anal. Calcd. for $C_{32}H_{31}N_3O_2$: C, 78.50; H, 6.38; N, 8.58. Found: C, 78.61; H, 6.34; N, 8.54.

3-(3,5-Dioxo-4-phenyl-1,2,4-triazolidin-1-ylthio)-4,6-bis(N-isopropylanilino)-N-phenyl-1,2-pyridazinedicarboximide (11).

N-Phenyltriazoline-3,5-dione (0.5 g.) was reacted in tetrahydrofuran with 1.1 g. of **1**. There was an immediate decoloration of the red azo compound. After standing overnight, the precipitate was filtered from the mixture, and triturated with ethyl acetate and ether to give 0.5 g., m.p. 166-168°. Spectral results are as follows: nmr (deuteriochloroform) δ 0.88-1.3 [two partially imposed doublets, 12 protons, J = 7 Hz, $CH(CH_3)_2$], 3.75 [s, 1, =C-H], 3.9 [m, 1, $CH(CH_3)_2$], 4.75 [s, 1, =CH], 5.20 [m, 1, $CH(CH_3)_2$], 6.8-7.8 [broad absorptions, 20 protons, ArH], 8.4 [broad, 1 proton, disappears on washing with D_2O, N-H]; ir (chloroform) 5.8μ (C=O), 6.1μ (C=O); uv (see Discussion).

Anal. Calcd. for $C_{38}H_{36}N_8O_4S$: C, 65.12; H, 5.18; N, 15.99; S, 4.58. Found: C, 64.36; H, 5.04; N, 15.57; S, 4.52.

Acknowledgment.

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(1a) For part I, see J. P. Chupp, *J. Heterocyclic Chem.*, 7, 285 (1970).

(1b) Presented at the 164th National ACS Meeting, New York City, August 1972, Abstract No. ORGN 52.

(2) Acyl derivatives substituted in the 5-position of **1** causes a dramatic upfield shift of the single thiophene ring proton from δ 6.2 to δ 5.4-5.6. This has been explained as due to diminished ring current (less aromaticity) in the acylated material, resulting from strong resonance interactions with the acyl group.

(3a) M. C. Kloetzel, "Organic Reactions," 4, Chapter 1, pp. 35-39.

(3b) D. B. Clapp, *J. Am. Chem. Soc.*, 61, 2733 (1939).

(3c) C. F. Allen and J. W. Gates, Jr., *ibid.*, 65, 1283 (1943).

(3d) R. Helder and H. Wynberg, *Tetrahedron Letters*, 605 (1972).

(3e) H. J. Kuhn and K. Gollnick, *ibid.*, 1909 (1972).

(4) Similar interactions to those found for the acyl derivatives (Ref. 2) are also evident with the unsaturated acyclic adducts discussed in this paper. (Compare the upfield chemical shifts of the thiophene proton in **3** and **5** with that of **2**).

(5) Both A-60 and HR-100 nmr (Varian Associates, Inc.) were employed in this study. The latter instrument was used for the decoupling experiments and to obtain precise chemical shifts and J values for materials **6**, **8**, and **9**; these are quoted in the Discussion. Elsewhere, nmr values are derived from the A-60 instrument.

(6) Upon aromatizing **6** (and **9**) the two anilino nuclei undoubtedly suffer spatial reorientation, thus affecting the anisotropic shielding of the isopropyl groups.

(7) Varian nmr Spectra Catalog, Vols. I and II. (Varian Associates, 1963).

(8) R. T. Conley, "Infrared Spectroscopy," p. 116, Allyn and Bacon, Inc., Boston, 1966.

(9) R. M. Silverstein, and G. C. Bassler, "Spectrometric

Identification of Organic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, 1967, pp. 131-132.

(10) S. K. Malhatra, "Enamines: Synthesis, Structure, and Reactions," Chapter 1, Edited by A. G. Cook, Marcel Dekker, N.Y., 1969.

(11) The formation of 9, in line with step c (Scheme III) would be as follows:

(sulfur loss)
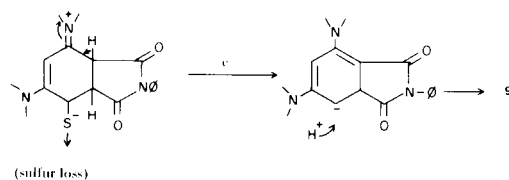
It would be difficult to similarly rationalize facile formation of **9a**, the only possible alternative structure for **9** which could conceivably possess the observed spectral characteristics.

9a
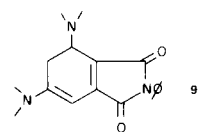
(12) Similar to the shielding observed for the 2-proton in m-phenylenediamine (δ 6.03), ref. 7, p. 458.

(13) This is reminiscent of the red complexes and subsequent multiple reactions that occur between tetracyanoethylene and N,N-dimethylaniline, see P. G. Farrell, R. K. Wojtowski, J. Chem. Soc. (C), 1390 (1970).

(14) H. Hartmann and R. Mayer, Z. Chem., 6, 28 (1966).

(15) A study involving cyclo- and acyclo-additions of cyano-acetylenes to a 2,4-bis(dimethylamino)pyridine has recently appeared, T. Sasaki, and A. Kojima, Tetrahedron Letters, 4593 (1971). Undoubtedly resonance stabilized vinylogous amindinium ion intermediates here also influence product formation, and similar to the alternative mechanisms shown in Scheme III, their postulated Diels Alder bicyclo adduct intermediate represents only one of several routes possible.

(16) Microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tennessee. Spectral analyses were performed on a Varian A-60 and HR-100 (nmr), Perkin-Elmer Infracord (ir), Bausch and Lomb Spectronic 505 (uv) and a CEC 21-04 mass spectrometer.