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1,4-Cycloaddition Reaction of Enaminodithiocarboxylate Derivatives with Dimethyl Acetylenedicarboxylate*

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The reaction of enaminodithiocarboxylates, which have a conjugated thiocarbonyl-diene system, with dimethyl acetylenedicarboxylate as a dienophile resulted in a 1,4-cycloaddition to afford various thiapyrane derivatives and spiro(benzothiazoline) and thiazolinecyclopentadiene derivatives by the monodesulfurization. The reaction of thioamide derivatives of lepidine and 4-picoline gave benzoazocine and azocine derivatives.

A few alkyl enaminodithiocarboxylate of heterocyclic compounds have been prepared and their chemical properties were studied.[2] The treatment of these enaminodithiocarboxylates with alkyl reagents such as methyl iodide or dimethyl sulfate produces the ketenethioacetal (β,β-bismethylthiovinyl) derivatives which react with the nucleophiles to give the corresponding substituted product of methylthio group.[3] In 1971, Smutny[4] reported the Diels-Alder reaction of the enaminodithiocarboxylate which had a diene system containing the thiocarbonyl group, with maleic anhydride to afford a thiapyrane derivatives. We found that the Diels-Alder reaction of methyl 3-indoledithiocarboxylates afforded the Diels-Alder reaction products, 4a-substituted 5-methyl-1-methylthio-3,4-dimethoxycarbonyl-4aH-thiapyrano[4,3-*b*]indole in a good yield.[5] These reactions are also thought to be a 1,4-dipolar cycloaddition, reported by Huisgen.[6] It has also been reported that the analogous 1,4-cycloaddition reaction of a diene of the conjugated thioketone, obtained by the reaction of 1,3-dipolar reaction of trithione derivatives with dipolarophiles,[7] with various dienophiles gave the corresponding thiapyrane derivatives.

We recently reported briefly that the reaction of 1-methyl-2-methylene-1,2-dihydropyridine-α-dithiocarboxylate (Ia) with dimethyl acetylenedicarboxylate (DMAD) afforded a product which the pyridine ring opened, 3-formyl-2-methylthio-5,6-dimethoxy-carbonylbut-2-enolidene (4*H*) thiapyrane (III), in 15% yield.[8]

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* Dedicated to the memory of Prof. Eiji Ochiai.

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2) *a*) R. Gompper, B. Wetzel, and W. Elser, *Tetrahedron Letters*, **1968**, 5519; *b*) E.B. Knott, *J. Chem. Soc.*, **1955**, 949; *c*) K. Mizuyama, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **94**, 702 (1974).

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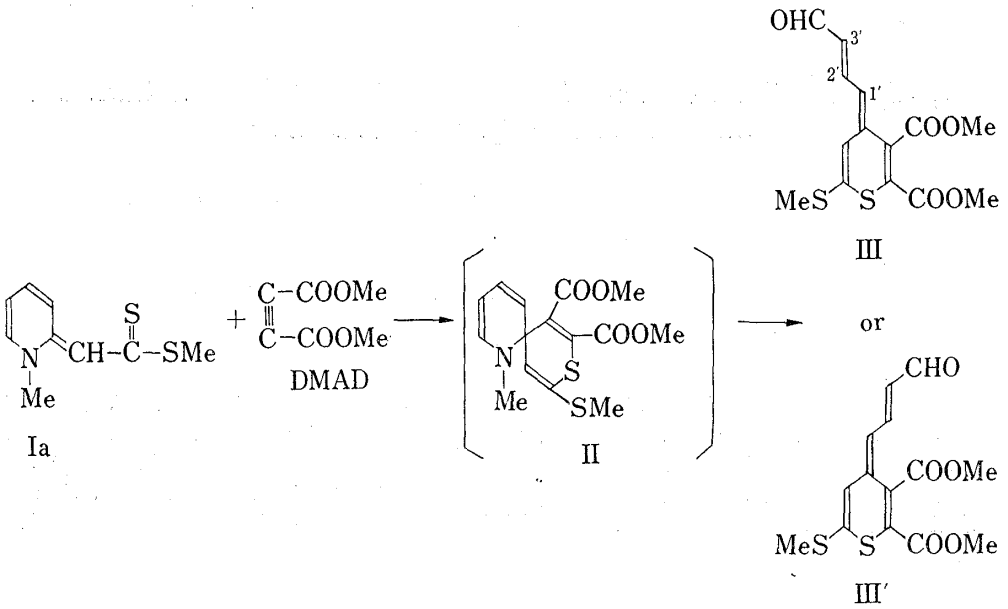


Chart 1

The formation of III can be explained by assuming the spiro-compound as a key intermediate which might be the usual Diels-Alder reaction product of the above reaction. This reaction is also the first example of the ring-opening of a spiro-pyridine derivative, although ring opening reactions of other pyridinium[9] and N-alkoxypyridinium salts[10] and betaines[11] are well known. Powers[12] reported that the reaction of indole with cyanogen bromide and excess pyridine gave 5-(3-indolyl)-2,4-pentadienal.[12] Very recently, Boyle[13] also reported that pyridine undergoes ring scission when treated with thiophosgene and barium carbonate to give the *trans*, *cis*- and *trans*, *trans*-5-isothiocyanatopenta-2,4-dienals. Cleavage of the intermediate spiro compound of 1,4-cycloadduct gave the aldehyde III, similar to the reactions of Katritzky, Powers, Boyle, and others, and to the formation of glutaconic dialdehyde derivatives by ring cleavage of pyridinium salts by nucleophiles.[10,14] The structure of our ring-opened product is supported a trans-aldehyde system (III or III') from the nuclear magnetic resonance (NMR) spectrum. In deuteriochloroform, the formyl proton gave a sharp doublet at 9.64 ppm (1H, J=8 Hz) due to the coupling to H-3', which gave a four-line pattern centered at 6.50 ppm (1H, J=8.0 and 12 Hz). The 1-proton gave a doublet at 5.95 ppm (1H, J=12 Hz) showing coupling to H-2', which also gave a four-line pattern centered at 8.04 ppm (1H, J=12 and 12 Hz). The latter coupling is characteristic of a transoid arrangment of protons on a double bond.

In a similar manner as the reaction Ia with DMAD, the reaction of methyl 1-methyl-2-methylene- 1,2-dihydroquinoline-α-dithiocarboxylate (Ib)[2c] with DMAD gave a brown oil in 75% yield. Elemental analysis of the oil agreed with $C_{19}H_{19}O_4NS_2$. The NMR spectrum of IV

9) TH. Zincke, *Ann.*, **338**, 107 (1905).
10) *a*) R. Eisenthal and A. R. Katritzky, *Tetrahedron*, **21**, 2205 (1965); *b*) A.R. Katritzky and E. Lunt, *Tetrahedron*, **25**, 4291 (1969); *c*) J. Schnekenburger and D. Heber, *Chem. Ber.*, **107**, 3408 (1974); *d*) U. Fritzche and S. Hunig, *Ann.*, **1974**, 1407; *e*) P. Schiess, C. Monnier, P. Ringele, and E. Sendi, *Helv. Chim. Acta.*, **57**, 1676 (1974); *f*) V. Boekelheide and W. Feely, *J. Am. Chem. Soc.*, **80**, 2217 (1958); *g*) V. Boekelheide and R. Scharrer, *J. Org. Chem.*, **26**, 3802 (1961); *h*) R. Eisenthal, A.R. Katritzky, and E. Lunt, *Tetrahedron*, **23**, 2775 (1967).
11) P. Baumgarten, *Ber. Dtsch. Chem. Ges.*, **59**, 1166 (1926).
12) J.E. Powers, *J. Org. Chem.*, **30**, 2534 (1965).
13) *a*) R. Hull, *J. Chem. Soc., Perkin I*, **1973**, 2911; *b*) F.T. Boyle and R. Hull, *J. Chem. Soc., Perkin I*, **1974**, 1541.
14) J.N. Gardner and A.R. Katritzky, *J. Chem. Soc.*, **1957**, 4375.

displayed four sharp singlets due to methyl protons at 2.40 (3H, SCH_3), 2.75 (3H, NCH_3), 3.47 (3H, OCH_3), and 3.78 ppm (3H, OCH_3), and a singlet at 6.08 ppm (1H, –CH=C–) due to a vinyl proton. The infrared (IR) spectrum of IV showed an absorption at 1715 cm^{-1} due to carbonyl groups of the ester groups. The ultraviolet (UV) spectrum of IV revealed maxima at 223 and 260 nm. These spectral data and elemental analysis indicated that the Diels-Alder reaction had the structure of spiro[1-methyl-1,2-dihydroquinoline-2,4′-2′,3′-dimethoxycarbonyl-6-methylthio (4*H*) thiapyrane)] (IV). In this condition, this reaction did not give a ring-opened product of a spiro compound (IV).

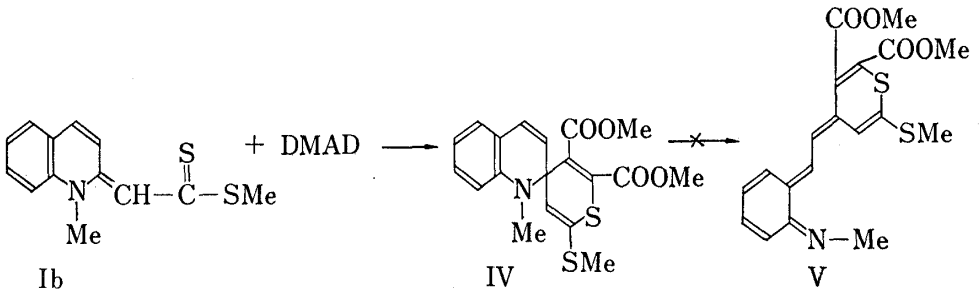


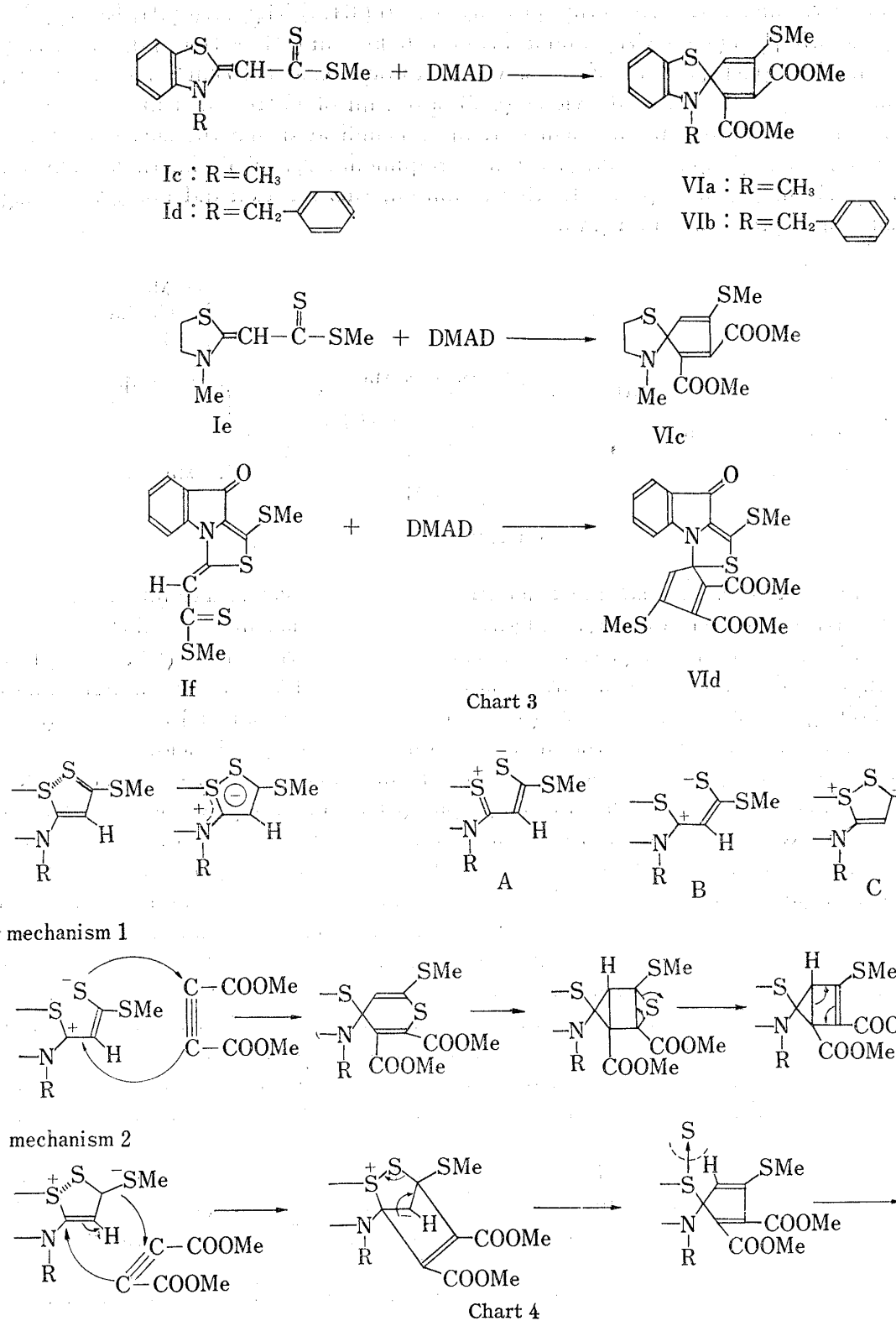
Chart 2

We also reported recently that the reaction methyl 2-methylenethiazoline-α-dithiocarboxylate derivatives, methyl 3-methyl-2-methylene(3*H*)benzothiazoline-α-dithiocarboxylate (Ic), methyl 3-benzyl-2-methylene(3*H*)benzothiazoline-α-dithiocarboxylate (Id), methyl 3-methyl-2-methylenethiazolidine-α-dithiocarboxylate (Ie) with DMAD in dimethylformamide (DMF) on a boiling water bath gave spiro (benzothiazolinecyclopentadiene) and spiro (thiazolinecyclopentadiene) derivatives by the mono-desulfurization in a good yield.[15] The reaction of methyl 1-methylthio-3-methylene-9-oxo (9*H*) thiazolo[3,4-*a*]indole-α-dithiocarboxylate,[16] with DMAD in DMF also occurred to form spiro (thiazolinecyclopentadiene) derivative (VId) in a good yield. This compound came as orange crystals of mp 203°. These desulfurization are thought to be due to the characteristic structure, a strong S·····S interaction.

Several investigation on the S·····O, S·····S, S·····N, and S·····Se interaction have been reported in a range of molecules for 1,6,6a-6^{IV}-trithiapentalenes and related structures.[17] The enaminodithiocarboxylate having a thiazoline ring may have a characteristic structure which is contributions to Ic, d, e from dipolar forms A—C. This 1,3-dipole or 1,4-dipole would be expected to undergo analogous 1,3-dipolar cycloaddition reaction as those observed with mesoionic compounds or 1,4-cycloaddition reaction to enaminodithiocarboxylate of indole, quinaldine, and 2-picoline. Since mentioned above, other mechanism must be thought different from 1,4-cycloaddition reaction. The mechanisms of two routes are thought as shown in Chart 4.

The reaction of methyl 1-methyl-4-methylene-1,4-dihydroquinoline-α-dithiocarboxylate (Ig) with DMAD in dioxane on a boiling water bath gave yellow crystals (VII) of mp 178° in 72% yield. This reaction in dioxane carried out by refluxing for 36 hr, did not give VII but afforded two 1,2-cycloadducts; pale yellow crystals (VIII) of mp 205—207° and yellow needles (IX) of mp 159—161°, in 30% and 60% yield, respectively. Elemental analyses of VII, VIII, and IX agreed with the same molecular formula of $C_{25}H_{25}O_8NS_2$. The molecular weight of

15) G. Kobayashi, Y. Matsuda, Y. Tominaga, and K. Mizuyama, *Heterocycles*, **2**, 309 (1974).
16) Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **95**, 880 (1975).
17) *a*) T.R. Lynch, I.P. Mellor, and S.C. Nyburg, *Acta Cryst.*, B **27**, 1948 (1971); *b*) H. Buzlaff, K. Hartke, and R. Salamon, *Chem. Ber.*, **103**, 156 (1970); *c*) I.P. Mellor and S.C. Nyburg, *Acta Cryst.*, B **27**, 1954 (1971); *d*) M. Mami, R. Bardi, G. Traverso, and S. Bezzi, *Nature*, **192**, 1282 (1961); *e*) S. Sato, T. Kinoshita, T. Hata, and C. Yamura, Collected Abst., 9-Int. Congr. Crystallogr., 25 (1972); *f*) A.R. Katritzky and A.J. Boulton, *Adv. Heterocycl. Chem.*, **13**, 161 (1971).



these compounds were also supported by mass spectra (M^+ 531). These results showed addition of 2 moles of DMAD to the enaminodithiocarboxylate derivative, Ig. The compound IX was also obtained in excellent yield by heating of VII at 200° for 5 min but this reaction did not give VIII which did not also convert into VII and IX. The UV spectra of VII, VIII, and IX are shown in Fig. 1. The UV spectrum of VII was similar to that of VIII but the spectrum of VII showed absorption different from that of IX. The IR spectrum of VII showed absorption at 1735, 1720, 1710, and 1640 cm^{-1} due to the ester carbonyl groups. The absorption

at 1640 cm^{-1} did not appear in the spectra of VIII and IX, and also of VI. The NMR spectrum of VIII in deuteriochloroform displayed six sharp singlets due to methyl protons at 2.40 (3H, SCH_3), 2.98 (3H, NCH_3), 3.40 (3H, OCH_3), 3.68 (3H, OCH_3), 3.73 (3H, OCH_3), and 3.76 ppm (3H, OCH_3), two doublets due to two protons of Ha and Hb in the quinoline ring at 4.30 (1H, J=4.2 Hz) and 4.42 ppm (1H, J=4.2 Hz), and one vinyl proton of thiapyrane ring (Hc) at 6.00 ppm (1H, singlet). In trifluoroacetic acid, the methy. protons of methyoxy groups gave two sharp singlets at 3.85 ppm (6H, $2\times OCH_3$) and 4.00 ppm (6H, $2\times OCH_3$), two protons of Ha and Hb in the quinoline ring at 4.62 ppm (1H, J=4.2 Hz) and 5.40 (1H, J=4.2 Hz), and Hc proton at 4.16 ppm (1H, singlet). In NMR spectrum of IX two Ha and Hb protons gave two doublets at 2.98 ppm (1H, Ha, J=12.2 Hz) and 2.66 ppm (1H, Hb, J=12.2 Hz). This coupling constant of 12.2 Hz indicated a trans configuration. From these spectral data and elemental analyses, these compounds were assigned to be endo-form (VII) and exo-form (VIII), respectively, shown in Chart 5. These results are explained by the double cycloaddition reaction of 1,4- and 1,2-cycloaddition of usual thiocarbonyl-diene and cyclic enamine with DMAD. The compound IX was assumed to be the intramolecular Walden inversion product of VII. This interesting phenomenon also supports the configuration of VII as endo-form and mutually opposite orientation of dimethoxycarbonylethylene groups. The compound IX was shown to be the Walden inversion product of VII with simultaneous double ring expansion, in which the vinyl anion of cyclobutene ring directly attached to an asymmetric carbon atom 4-position of quinoline ring is replaced by another vinyl anion of thiapyrane ring.

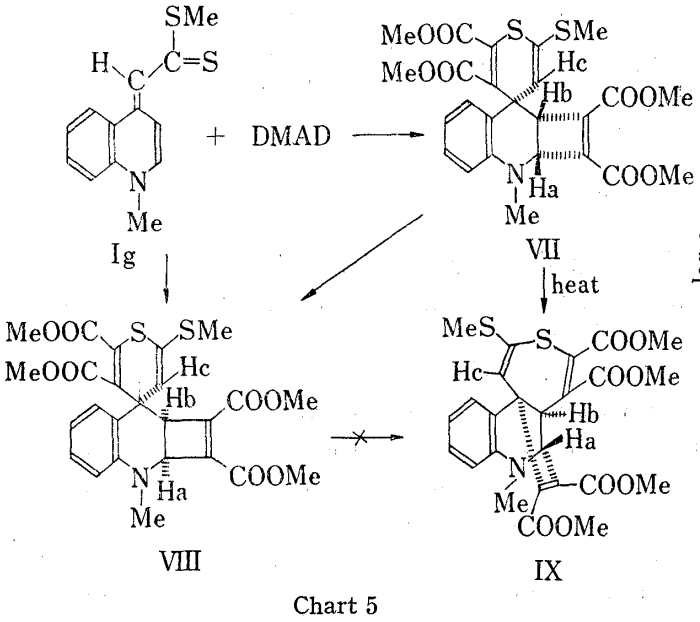


Chart 5

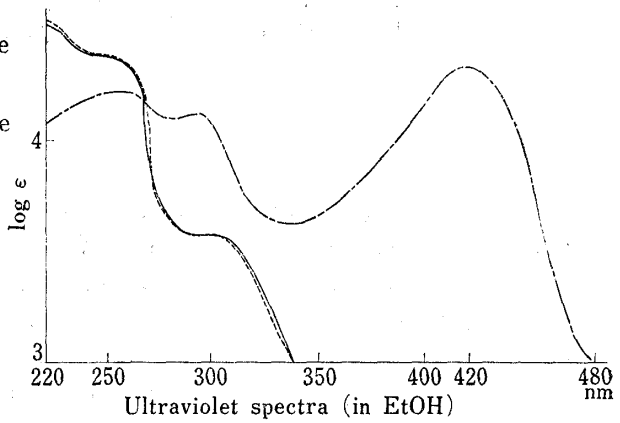


Fig. 1

———: VII
----------: VIII
———: IX

It was found that the thiocarbonylmethylene derivatives reacted with DMAD giving the corresponding 1,4-cycloaddition reaction product, spiro (thiapyrane) and pentadienal derivatives. Methyl 2-methyl-1-oxo-1,2-dihydroisoquinoline-4-dithiocarboxylate (Ih) would be expected to undergo analogous 1,4-cycloaddition reactions as those observed with the enaminodithiocarboxylates of methyl indole-3-dithiocarboxylates because of having a conjugated thiocarbonyl-diene system in the thiocarbonyl of its dithiocarboxylate and a double bond between 3 and 4 positions of the isoquinoline ring. The compound (Ih) was obtained by the treatment of 2-methyl-4-(methylthio)thiocarbonylisoquinolinium iodide, which was prepared by the reaction of 2-methylisoquinolinium iodide with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide, alkylation with methyl iodide, and oxidation with potassium ferricyanide in the presence of sodium hydroxide. In a similar manner as above, Ih

also reacted with DMAD in dioxane by refluxing for 10 hr to give the corresponding 1,4-cycloaddition reaction product, 5-methyl-3,4-dimethoxycarbonyl-1-methylthio-4a,5,6-trihydrothiapyrano[4,3-*c*]isoquinolin-6-one (X) as colorless needles, mp 167°, in 65% yield.

This thiocarbonyl-diene system also reacted with other dienophile, N-phenylmaleinimide, to afford 1,4-cycloaddition product in a good yield. This result shows that enaminodithiocarboxylate can react with other dienophiles. We have now a plan to study the reaction of enaminodithiocarboxylates with various dienophiles and also of other thiocarbonyl-dienes with DMAD.

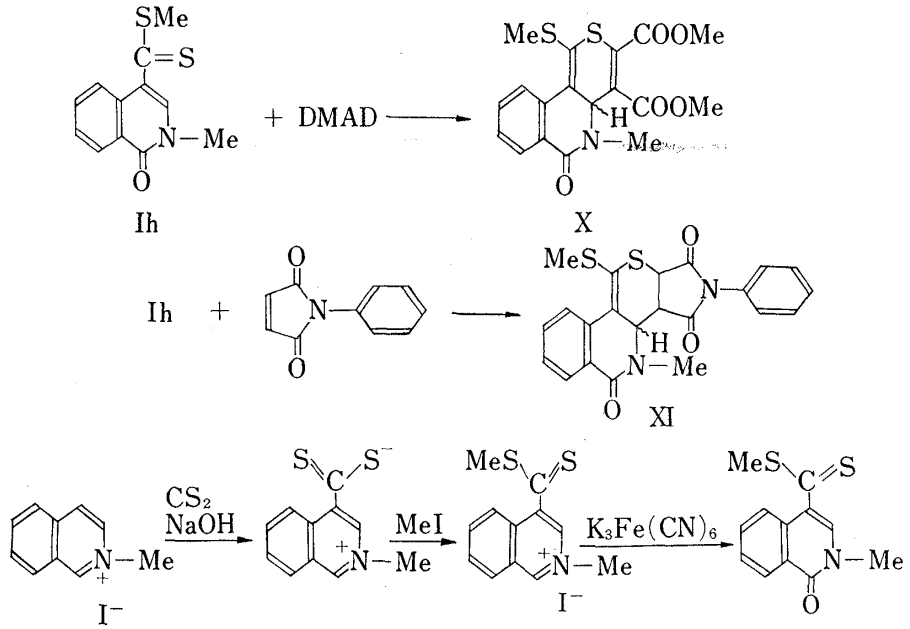


Chart 6

The thiocarbonyl-diene of thioamide derivatives did not react with DMAD under a similar condition. However, the reaction of the thioamide, Ih, obtained by the reaction of methyl 1-methyl-4-methylene-1,4-dihydroquinoline-α-dithiocarboxylate with morpholine, with DMAD afforded a red violet needles of mp 243° in 53% yield. Elemental analysis of this compound agreed with $C_{22}H_{24}O_5N_2S$ (mol. wt. 428.43) and its molecular weight was also supported by mass spectroscopy (M^+ 428). These results showed the product being the 1: 1 adduct of DMAD and Ii. The NMR spectrum (in trifluoroacetic acid) of this compound showed the signals due to methoxy protons as singlets at 3.86 (3H) and 4.40 ppm (3H), and olefin protons as singlets at 9.12, 8.00, and 8.60 ppm. Its UV spectrum revealed maxima at 229, 275, and 450 nm, and its IR spectrum showed the absorption of carbonyl groups of methyl esters at 1695 and 1660 cm^{-1}. The structure of this compound was found to be benzoazocine derivative (XIIa) which was derived from the direct cleavage of cyclobutene ring. This cyclobutene compound of 1,2-cycloaddition reaction was not isolated but the compound was thought to be an intermediate. Similarly, the reaction of other thioamide compounds (piperidine and pyrrolidine derivatives) with DMAD gave the corresponding benzoazocine derivatives (XIIb, c) in 40% and 45% yield, respectively. This reaction was also applied to thiocarbamoylmethylene of 4-picolines (II, m), which were obtained by the reaction of methyl N-benzyl-4-methylene-1,4-dihydropyridine- α-dithiocarboxylate with secondary amines (morpholine, piperidine), with DMAD in dioxane on a boiling water bath gave the corresponding 1,6-dihydroazocine derivatives (XIIIa,b) in 70— 80% yield.

Many workers reported that the enamines react with electrophilic alkynes to form cyclobutene adducts which undergo stepwise ring opening under mild thermal conditions to afford

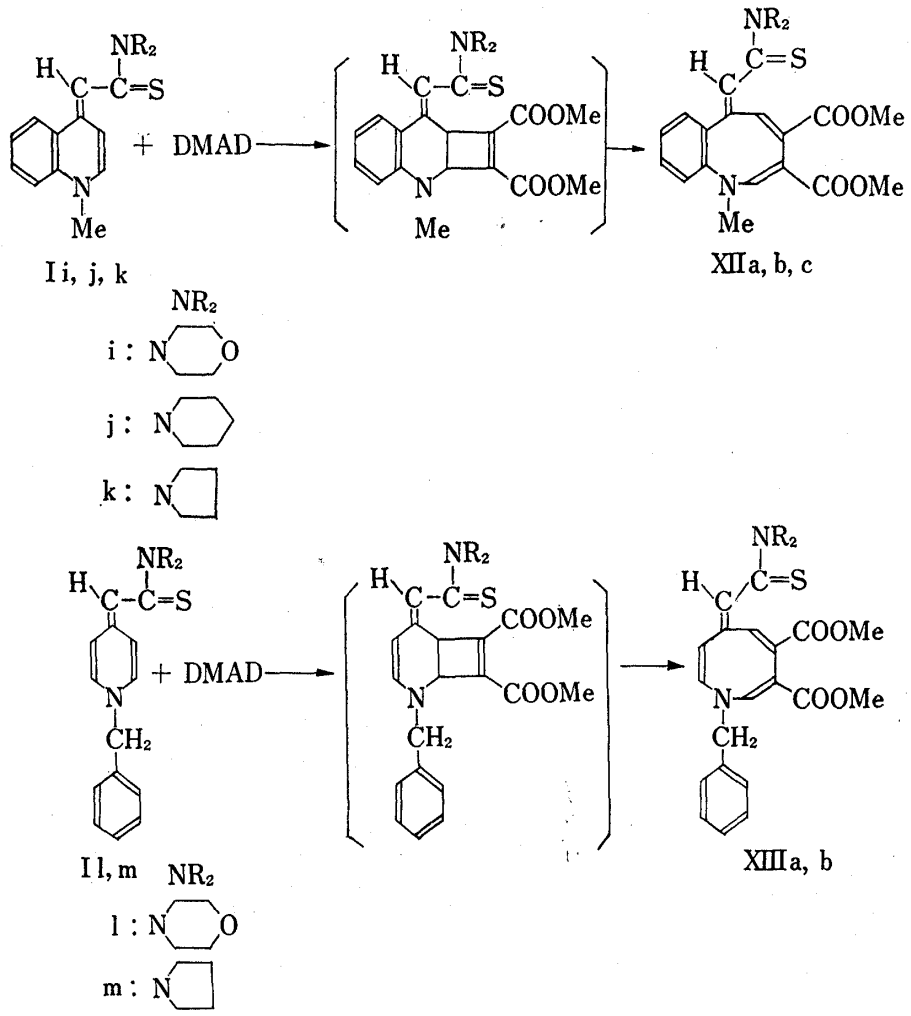


Chart 7

ring expanded dienamines. 1-Alkyl-1,6-dihydro-1-benzoazocine[18] and 1,2-dihydroazocine[19] derivatives were synthesized by the application of cyclic enamine (1-alkyl-1,4-dihydroquinoline, 1,2-dihydropyridine) with DMAD. However, the cyclobutene adducts[20] from certain 1,3-disubstituted 1,4-dihydropyridines and DMAD do not undergo thermal ring expansion. Our synthetic methods for 1,4-dihydrobenzoazocine and 1,6-dihydroazocine derivatives by the cycloaddition of DMAD are useful and interesting, and can be applied to the synthesis of various methylenazocine derivatives.

Experimental

All melting points were determined in a capillary and are uncorrected. The IR spectra were recorded in KBr pellets on a Nippon-Bunko IRA-2 spectrometer. The UV absorption spectra were determined on a Hitachi EP-S2 spectrometer in 95% EtOH. The NMR spectra were obtained using a JNM-ps-100 (100 MHz) spectrometer with tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were recorded on a JEOL JMS-01SG double focus mass spectrometer, using all case a direct sample insertion into the ion source.

Reaction of Methyl 1-Methyl-2-methylene-1,2-dihydropyridine-α-dithiocarboxylate (Ia) with DMAD—a) A mixture of 1.5 g of DMAD and 1.97 g of Ia was heated on a boiling water bath for 3 hr. When cooled, the resultant solid was treated with a small amount of petroleum ether and chromatographed over Al_2O_3

18) P.G. Lehman, *Tetrahedron Letters.*, **1972**, 4863.
19) *a*) R.M. Acheson, G. Paglietti, *J. Chem. Soc. Chem. Commun.*, **1973**, 665; *b*) R.M. Acheson, G. Paglietti, and P.A. Tasker, *J. Chem. Soc. Perkin I*, **1974**, 2496.
20) R.M. Acheson and N.D. Wright, *J. Chem. Soc. Chem. Commun.*, **1971**, 1421.

with benzene to give red violet needles of mp 128° in 10% yield and brown oil which may be an intermediate of spiro thiapyrane derivative of 1,4-cycloadducts.

b) A solution of 1.5 g of DMAD and 1.97 g of Ia in 50 ml of DMF was heated on a boiling water bath for 2 hr. The solvent was removed over under reduced pressure. The residue was chromatographed over Al_2O_3 with benzene to give red violet needles of mp 128° in 15% yield.

Spiro[1-methyl-1,2-dihydroquinoline-2,4′-(2′,3′-dimethoxycarbonyl-6′-methylthio(4*H*)thiapyrane)] (IV)——A solution of 2.47 g of Ib and 1.6 g of DMAD in 50 ml of dioxane was heated on a boiling water bath for 2 hr. The initially light red solution slowly changed color, ending up in an intense dark brown. The solvent was removed under a reduced pressure. The residue was chromatographed over Al_2O_3 with benzene and repeated gave pure light brown oil in 65% yield. *Anal.* Calcd. for $C_{19}H_{19}O_4NS_2$: C, 58.61; H, 4.92; N, 3.60. Found: C, 58.81; H, 4.93; N, 3.44. IR (KBr): 1715 cm^{-1} (C=O of methyl ester). NMR (δ in $CDCl_3$) ppm: 2.40 (3H, singlet, SCH_3), 3.78 (3H, singlet, OCH_3), 6.09 (1H, singlet, vinyl proton on the pyrane ring).

Reaction of Methyl 3-Methyl or Benzyl-2-methylene (3*H*)-benzothiazoline-α-dithiocarboxylates (Ic, d) with DMAD——a) A solution of 2.1 g of DMAD and 2.5 g of Ic in 30 ml of DMF was heated in a boiling water bath for 5 hr. (Yellow needles separated out within about 3 hr.) When cooled, the precipitate was isolated by filtration and recrystallized from acetone. The yield of this product, spiro[3-methylbenzothiazoline-2(3*H*), 1′-(2′,3′-dimethoxycarbonyl-4′-methylthio(2,4)cyclopentadiene)] (VIa), was 95%.

b) Spiro[3-benzylbenzothiazoline-2 (3*H*), 1′-(2′,3′-dimethoxycarbonyl-4′-methylthio (2,4) cyclopentadiene)] (VIb) was obtained by the reaction of Id with DMAD in same manner on 90% yield.

Spiro [3-methyl-1,2-dihydrothiazoline-2,1′-(2′,3′-dimethoxycarbonyl-4′-methylthio (2,4) cyclopentadiene)] (VIc)——A solution of 2.1 g of DMAD and 2.1 g of Ie in 20 ml of DMF was heated on a boiling water bath. After cooling, the precipitate was collected by filtration, and recrystallized from acetone to yellow needles of mp 185—186° in 85% yield.

Spiro[1-methylthio-9-oxo(3*H*, 9*H*)thiazolo[1,5-*a*]indole-3,1′-(2′,3′-dimethoxycarbonyl-4′-methylthio(2,4)-cyclopentadiene) (VId)——A solution of 0.16 g of DMAD and 0.34 g of If in 20 ml of DMF was heated on a boiling water bath for 10 hr. The reaction mixture was poured into 100 ml of ice-wateh, and the mixture was extracted with benzene. After removal of benzene, the residure was recrystallized from acetone to orange crystals of mp 202—203° in 70% yield. *Anal.* Calcd. for $C_{20}H_{17}O_5NS_3$: C, 53.70; H, 3.83; N, 3.13. Found: C, 53.42; H, 3.72; N, 2.79. Mass Spectrum *m/e*: 447 (M^+), 388, 387 (base peak), 355, 313. IR(KBr): 1740 cm^{-1} (ester carbonyl), 1665 cm^{-1} (C=O of indolinone). UV λ_{max}^{EtOH} nm (log ε): 220 (4.26), 244 (4.19), 280(4.28), 305 (4.27), 340 (4.31), 450 (4.13). NMR (δ in $CDCl_3$) ppm: 2.64 (3H, singlet, SCH_3), 2.72 (3H, singlet, SCH_3), 3.57 (3H, singlet, OCH_3), 3.85 (3H, singlet, OCH_3), 6.54 (1H, singlet, 1H, on cyclopentadiene).

Methyl 1-Methyl-4-methyene-1,4-dihydroquinoline-α-dithiocarboxylate (Ig)——To a suspension of 1 g of NaH (50% in oil) and 2.85 g of 1,2-dimethylquinolinium iodide in 50 ml of tetrahydrofuran, 2 g of CS_2 was added and the mixture was then refluxed for 2 hr on a boiling water bath. After cooling, the separated solid was collected on a filter, washed with ether, and dissolved in 100 ml of water. The solution was stirred for 20 min, 1.7 g of Me_2SO_4 was added dropwise to that solution with cooling over a period of 20 min, and the reaction mixture was stirred for 1 hr. The precipitate was collected by filtration and recrystallized from benzene to give red needles of mp 193° in 85% yield. *Anal.* Calcd. for $C_{13}H_{13}NS_2$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.60; H, 5.30; N, 5.89. UV λ_{max}^{EtOH} nm (log ε): 220 (4.25), 235 (4.42), 288 (3.79), 370 (3.68), 525 (4.41).

Reaction of Methyl 1-Methyl-4-methylene-1,4-dihydroquinoline-α-dithiocarboxylate (Ig) with DMAD——A solution of 0.59 g of DMAD and 0.5 g of Ig in 30 ml of dioxane was heated on a boiling water bath for 4 hr, cooled, and poured into ice-water. The colorless precipitate was collected by filtration and recrystallized from acetone to give pale yellow crystals of mp 178° in 72% yield. *Anal.* Calcd. for $C_{25}H_{25}O_8NS_2$ (mol. wt., 531.46): C, 56.66; H, 4.75; N, 2.64. Found: C, 56.61; H, 4.75; N, 3.00. IR(KBr): 1735, 1720, 1710, 1640 cm^{-1} (C=O of ester carbonyl). UV λ_{max}^{EtOH} nm (log ε): 220 (4.55), 250 (4.40), 300 (3.69). Mass Spectrum *m/e*: 531 (M^+), 485, 484, 472, 449, 426, 412, 356, 341, NMR (δ in $CDCl_3$) ppm: 2.40 (3H, singlet, SCH_3), 2.93 (3H, singlet, NCH_3), 3.40 ,3.68, 3.73, 3.76 (all singlets, OCH_3 of methyl esters on the cyclobutadiene and thiapyrane), 4.30 (1H, J=4.2 Hz), 4.42 (1H, J=4.2 Hz), 6.00 (1H).

Spiro[1a,2a,3,8-tetrahydro-1,2-dimethoxycarbonyl-exo-cyclobut-1-eno[1,2-*b*]quinoline-8,4′-(2′,3′-dimethoxy carbonyl-6′-methylthio(4*H*)thiapyrane)] (VIII)——A solution of 1.3 g of VII in 30 ml of dioxane was refluxed for 24 hr. After removal of the solvent, the residue was recrystallized from acetone to give pale yellow prisms of mp 205—207° in 65% yield. *Anal.* Calcd. for $C_{25}H_{25}O_8NS_2$ (mol. wt., 531.46): C, 56.66; H, 4.75; N, 2.64. Found: C, 56.48; H, 4.70; N, 2.49. IR(KBr): 1710 cm^{-1} (C=O of methyl ester groups). UV λ_{max}^{EtOH} nm (log ε): 220 (4.60), 250 (4.41), 300 (3.61). NMR (δ in $CDCl_3$) ppm: 2.25 (3H, singlet, SCH_3), 3.40 (3H, singlet, NCH_3), 3.72 (6H, singlet, OCH_3), 3.90 (6H, singlet, OCH_3), 4.20 (1H, doublet, J=4.2 Hz), 5.32 (1H, doublet, J=4.2 Hz), 6.81 (1H). Mass Spectrum *m/e*: 531 (M^+), 484 (base peak), 452, 424, 367.

Walden Inversion of VII——The compound VII (2 g) was heated at 200° for 5 min. When cooled, the solid was recrystallized from MeOH to yellow needles, mp 159—161°, in 92% yield. *Anal.* Calcd. for $C_{25}H_{25}O_8NS_2$ (mol. wt., 531.46): C, 56.66; H, 4.75; N, 2.64. Found: C, 56.35; H, 4.77; N, 2.57. IR (KBr): 1720 cm^{-1} (C=O of methyl ester groups). UV λ_{max}^{EtOH} nm (log ε): 220 (4.20), 256 (4.25), 290 (4.13), 420 (4.34). NMR

(δ in $CDCl_3$) ppm: 2.35 (3H, singlet, SCH_3), 2.69 (1H, doublet, $J=12$ Hz), 3.02 (1H, doublet, $J=12$ Hz), 3.28 (3H, singlet, NCH_3), 3.72, 3.80, 3.82 (3H, 6H, 3H, three singlets, OCH_3 of methyl ester groups). Mass Spectrum *m/e*: 531 (M^+), 484, 472, 449, 412, 356 (base peak).

2-Methylisoquinolinium 4-Dithiocarboxylate——To a suspension of 1 g of powder NaOH in 50 ml of Me_2SO, 2.7 g of 2-methylisoquinolinium iodide was added slowly under stirring while the temperature of the mixture was maintained at 5—10° and 1.5 g of CS_2 was then added dropwise with cooling over a period of 30 min. The reaction mixture was stirred for 10 hr and poured into ice-water. The precipitate was collected by filtration and recrystallized from DMF to orange needles of mp 280° in 60% yield. *Anal.* Calcd. for $C_{11}H_9NS_2$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.16; H, 4.27; N, 6.39.

2-Methyl-4-(methylthio)thiocarbonylisoquinolinium Iodide——A mixture of 1.1 g of 2-methylisoquinolinium 4-dithiocarboxylate, 30 ml of MeOH, and 0.8 ml of MeI was refluxed for about 20 min until this compound dissolved. The solvent was evaporated about 15 ml. The concentrated solution was allowed to stand at room temperature for several hours, the precipitated red crystals were collected on a filter, and recrystallized from MeOH to give red prisms of mp 187—188° in 90% yield. *Anal.* Calcd. for $C_{12}H_{12}NIS_2$: C, 39.89; H, 3.35; N, 3.68. Found: C, 39.87; H, 3.21; N, 3.78. UV λ_{max}^{EtOH} nm (log ε): 223 (4.41), 322 (4.14). NMR (δ in CF_3COOH) ppm: 2.96 (3H, singlet, SCH_3), 4.68 (3H, singlet, NCH_3), 9.70 (1H, singlet).

Methyl 2-Methyl-1-oxo-1,2-dihydroisoquinoline-4-dithiocarboxylate (Ih)——To a solution of 3.61 g of 2-methyl-4-(methylthio)thiocarbonylisoquinolinium iodide in 50 ml of acetone, 10 g of $K_3Fe(CN)_6$ and 5 ml of 50% NaOH solution were added with stirring during 30 min. The reaction mixture was poured into 200 ml of ice-water, the yellow precipitate was collected by filtration, and recrystallized from acetone to give yellow needles of mp 144° in 85% yield. *Anal.* Calcd. for $C_{12}H_{11}ONS_2$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.54; H, 4.40; N, 5.55. IR(KBr): 1660 cm^{-1} (C=O). UV λ_{max}^{EtOH} nm (log ε): 220 (4.32), 228 (4.33), 317 (4.13), 340 (3.97). NMR (δ in $CDCl_3$) ppm: 2.80 (3JH, singlet, SCH_3), 3.67 (3H, singlet, NCH_3).

3,4-Dimethoxycarbonyl-5-methyl-1-methylthio-6-oxo-4a,5-dihydrothiapyrano[4,3-c]isoquinoline (X)——A solution of 1.25 g of Ih and 0.7 g of DMAD in 30 ml of diocxane was refluxed for 24 hr, cooled, and poured into 100 ml of ice-water. The precipitate was collected by filtration and recrystallized from MeOH to give colorless needles of mp 167° in 72% yield. *Anal.* Calcd. for $C_{18}H_{17}O_5NS_2$: C, 55.24; H, 4.38; N, 3.58. Found: C, 55.02; H, 4.39; N, 3.60. IR(KBr): 1715, 1650 cm^{-1} (C=O). UV λ_{max}^{EtOH} nm (log ε): 220 (4.49), 251 (4.40), 336 (4.06). NMR (δ in $CDCl_3$) ppm: 2.45 (3H, singlet, SCH_3), 3.17 (3H, singlet, NCH_3), 3.71 (3H, singlet, OCH_3), 3.84 (3H, singlet, OCH_3).

Reaction of Methyl 2-Methyl-1-oxo(1*H*)isoquinoline-4-dithiocarboxylate(Ih) with N-Phenylmaleinimide——A solution of 1.25 g of Ih and 0.87 g of N-phenylmaleinimide in 50 ml of dioxane was refluxed for 7 hr, cooled, and poured into 200 ml of ice-water. The precipitate was collected by filtration and recrystallized from acetone to give colorless crystals mp 151—152° in 75% yield. *Anal.* Calcd. for $C_{22}H_{18}O_3N_2S_2$ (mol. wt., 422.38): C, 62.56; H, 4.30; N, 6.63. Found: C, 62.32; H, 4.60; N, 6.18. IR(KBr): 1772, 1710 cm^{-1} (C=O). UV λ_{max}^{EtOH} nm: 316 (Concentration is unknown because of insufficient solubility).

Thioamide Derivatives (Ii, j, k, l, m)——A mixture of methyl 1-methyl-4-methylene-1,4-dihydroquinoline-α-dithiocarboxylate or methyl 1-benzyl-4-methylene-1,4-dihydropyridine-α-dithiocarboxylate and and excess secondary amine (morpholine, piperidine, pyrrolidine) was heated at 150° for 24 hr. The cexcess amine was evaporated and the precipitate was collected by filtration and recrystallized from benzene to give thioamide derivatives (Ii, j, k, l, m) in a good yield. These results are shown in Table I.

Azocine Derivatives (XIIa, b, c, XIIIa, b)——A mixture of 0.01 mole of thioamide compound (Ii, j, k, l, m) and 0.02 mole of DMAD in 50 ml of dioxane was heated on a boiling water bath for 1—2 hr, cooled, and poured into ice-water under vigorous stirring. The precipitate was collected by filtration and recrystallized from benzene to give the corresponding azocine derivatives. These results are shown in Table II.

TABLE I

	NR_2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	UV λ_{max}^{EtOH} nm (log ε)
Ii		96	150	$C_{16}H_{18}ON_2S$	67.11 (67.01)	6.34 (6.50)	9.78 (9.81)	228(4.55), 276(4.10), 314(3.94), 470(4.42), 490(4.42)
Ij		95	146—147	$C_{17}H_{20}N_2S$	71.80 (72.01)	7.09 (7.12)	9.85 (9.75)	220(4.40), 228(4.45), 275(4.12), 315(3.85), 465(4.25)
Ik		97	215—216	$C_{16}H_{18}N_2S$	71.09 (70.95)	6.71 (6.76)	10.36 (10.15)	220(4.48), 229(4.59), 270(4.04), 308(3.99), 465(4.41), 485(4.43)
Il		90	190—191	$C_{18}H_{20}ON_2S$	69.21 (68.97)	6.45 (6.39)	8.97 (8.54)	220(4.25), 279(4.15), 445(4.16)
Im		92	208—210	$C_{18}H_{20}N_2S$	72.95 (72.98)	6.80 (6.77)	9.47 (9.26)	220(4.20), 270(4.01), 320(3.97), 437(4.42)

Table II

	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR(KBr) cm^{-1} >C=O	UV λ_{max}^{EtOH} nm (log ε)
XIIa	55	243	$C_{22}H_{24}O_5N_2S$	61.67 (62.10)	5.65 (5.81)	6.54 (6.29)	1695 1660	220,[a] 275, 450
XIIb	40	211	$C_{23}H_{26}O_4N_2S$	64.77 (64.75)	6.15 (6.15)	6.57 (6.47)	1690 1660	220(4.50), 228(4.59), 272(4.18), 445(4.14)
XIIc	45	232—233	$C_{22}H_{24}O_4N_2S$	64.06 (64.03)	5.87 (5.83)	6.79 (6.64)	1695 1660	220(4.67), 227(4.74), 270(4.25), 470(4.21)
XIIIa	67	148—150	$C_{24}H_{26}O_5N_2S$	63.42 (63.06)	5.77 (5.75)	6.16 (5.96)	1700 1675	220(4.41), 380(4.55)
XIIIb	75	198	$C_{24}H_{26}O_4N_2S$	65.74 (65.70)	5.98 (5.97)	6.39 (6.36)	1725 1665	220(4.14), 280(4.10), 445(4.53)

a) Concentration is unknown because of insufficient solubility.

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