Synthesis of Heterocyclic Compounds Using Carbon Disulfide and Their Products

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Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

This review described developments in the synthesis of heterocyclic compounds using carbon disulfide and their products.

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Contents.

I. Introduction.

The use of carbon disulfide as a solvent in the Friedel-Crafts and other reactions or as a solvent for spectroscopy is well known. Carbon disulfide should also be considered as a versatile reagent in synthetic chemistry as well, finding use as a starting material for the synthesis of heterocyclic compounds, dithiocarboxylic acid deriatives, and ketene dithioacetals. These reactions are easily run on both small and large scales. A few reviews regarding condensation reactions of carbon disulfide with various types of nucelophiles have appeared in the literature [1-4]. Our re-

search deals with the effective use of carbon disulfide as a starting material for the synthesis of heterocyclic compounds with biological activity. These compounds find use as agricultural, medicinal, and pharmacological substances. This review describes the synthetic use of carbon disulfide in the preparation of heterocyclic compounds and the reactions of these products.

II. Indole Derivatives.

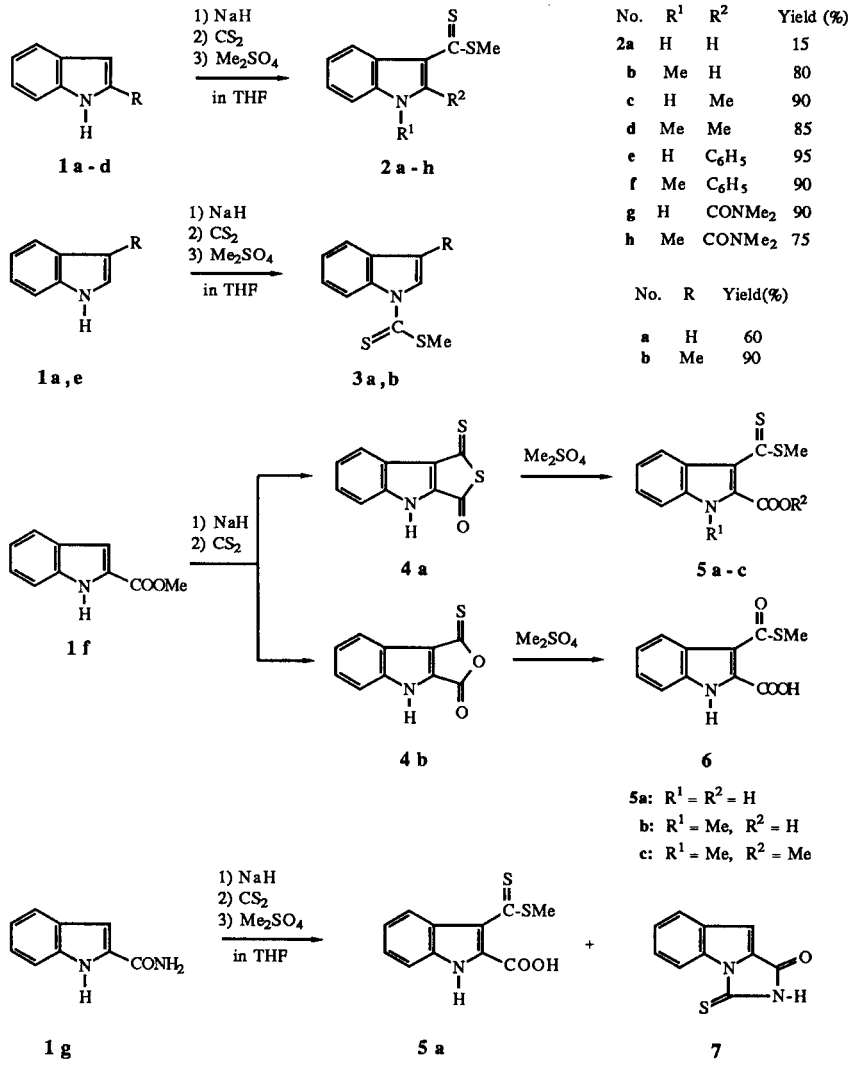
A. Reaction of Indole Derivatives with Carbon Disulfide.

Generally, electrophilic substitution of indole derivatives occurs at the 1-position or the 3-position on the indole nucleus [5]. Introduction of carbon disulfide into indole is a commonly used Grignard reaction [6]. The author devised a simple preparation of methyl indoledithiocarboxylate by the condensation of indole with carbon disulfide [7]. Namely, methyl indole-3-dithiocarboxylate derivatives **2a-h** are prepared by the condensation of indole derivatives **1a-d** with carbon disulfide in the presence of sodium hydride in tetrahydrofuran followed by treatment with dimethyl sulfate [7]. In the case of **1a** and **1e**, this reaction gave the corresponding methyl indole-1-dithiocarboxylates **3a,b**.

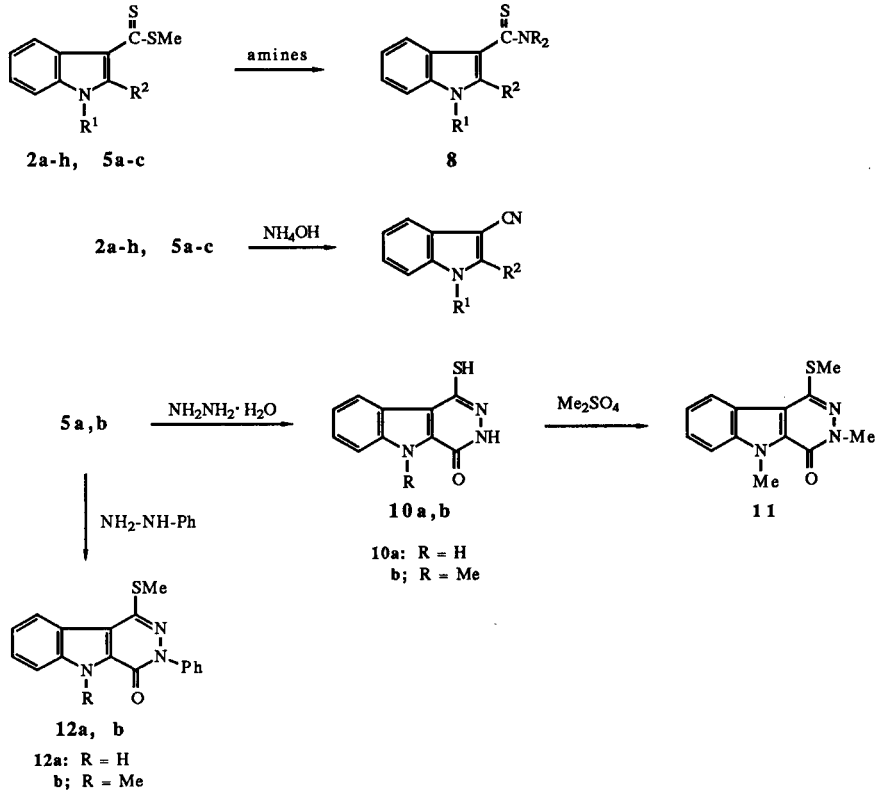
Application of this reaction to indole derivatives **1f,g** having an electron withdrawing group in the 2-position of the indole ring afforded methyl indole-3-dithiocarboxylates **5a-c**, indole-3-thioloesters **6**, and imidazo[3,4-*a*]indole derivatives **7** [8].

Nucleophilic substitution of the methylthio group in these dithio ester compounds and various amines gave thioamides **8** [7-9]. Methyl indole-3-dithiocarboxylates **2a-h** can be converted to indole-3-carbonitriles **9** by treatment with concentrated ammonia under heating in a sealed tube at 180° [9]. Reaction of these dithiocarboxylates **5a,b** with hydrazine affords the pyridazino[4,5-*b*]indole derivatives **10a,b,11**. Reaction of **5a,b** with phenylhydrazine results in a new type of specific reaction

Scheme 1



Scheme 2

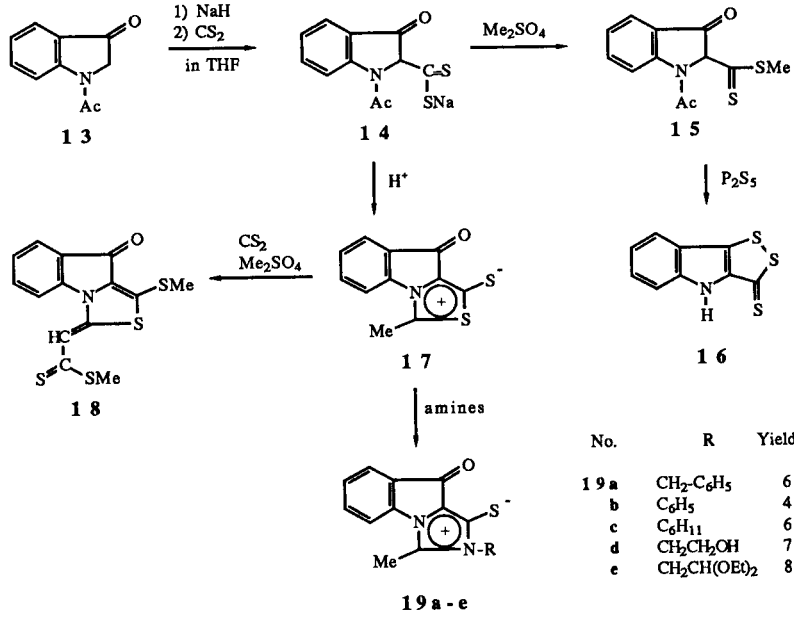


of phenylhydrazine with the thiocarbonyl group of dithiocarboxylates to give **12a,b** in good yields [8,9].

B. Reaction of 1-Acetylindoxyl with Carbon Disulfide.

Indoxyl is an interesting heterocyclic system which contains an active methylene carbon. Few reports have appeared in the literature regarding the synthetic use of this carbon atom. We have reported the reaction of 1-acetylindoxyl (**13**) with ketene dithioacetals to prepare pyrrolo[1,2-*a*]indolinone derivatives [11-12]. The reaction of 1-acetyl-3-indolinone (**13**) with carbon disulfide in the presence of sodium hydride gives a new type of mesoionic

Scheme 3



No.	R	Yield (%)
19a	CH_2-C_6H_5	60
b	C_6H_5	45
c	C_6H_{11}	60
d	CH_2CH_2OH	75
e	$CH_2CH(OEt)_2$	85

compound **17** [13]. Use of excess carbon disulfide and sodium hydroxide, followed by treatment with dimethyl sulfate gives **18**. Condensation of **13** with carbon disulfide in the presence of dimethyl sulfate gives dithiocarboxylate **15** which is converted to the trithione derivative **16** by treatment with phosphorus pentasulfide [13].

Reaction of **17** with primary amines results in the formation of mesoionic compounds **19a-e** having an imidazo-[1,5-*a*]indolium ring system [13,18].

Mesoionic compounds have received considerable interest because of their lack of bond valency [14]. X-Ray crystal structure analysis of this type of mesoionic compounds of the sydonone type, was first done by Schmidt [15]. More detailed structural analysis of 3-(*p*-bromo)sydnone, and 4,4-dichloro-3-ethylenebis(sydnone) were published by Barnighausen [16] and Thiessen [17]. Other mesoionic compounds have a thiazolium ring system in the main structure. These compounds, containing the imidazolium ring, are of interest due to the nature of their molecular plane and the conjugation system [18]. In order to confirm the detailed structure, compound **19a** was subjected to an X-ray structural analysis [18]. The mesoionic imidazolium ring system is almost planar. The C-S bond of 1.678 Å agrees well with the accepted vale 1.78 Å. The ethyl group of 1.44 Å attached to the an imidazolium ring indicates some double bond character [18]. Together with the bond lengths and planarity in five membered rings, it would be concluded that the π-electrons in this ring system are considerably delocarized. Thus, the cannonical forms may be written in the form of I-VI contributed to the resonance hybrid.

Scheme 4

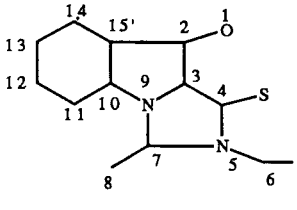


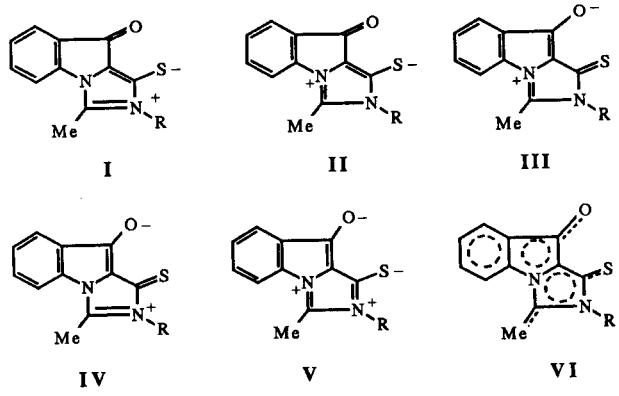
Table 1. Bond lengths(Å)

Bond	length
O-C2	1.241
C2-C3	1.440
C2-C15	1.499
C3-C4	1.378
C3-N9	1.385
C4-N5	1.415
N5-N6	1.449
N5-C7	1.347
C7-C8	1.449
C7-N9	1.323
N9-C10	1.418
C10-C15	1.404

Table 2. Bond angles (θ)

Bond	(θ)
O1-C2-C3	127.99
O1-C2-C15	126.81
C3-C2-C15	104.78
C2-C3-C4	143.58
C4-C3-N9	107.15
C2-C3-N9	108.98
S -C4-C3	132.20
S -C4-N5	123.60
C3-C4-N5	104.18
C4-N5-C6	124.31
C4-N5-C7	111.10
C6-N5-C7	124.52
N5-C6-C16	111.25
N5-C7-C8	126.18
N5-C7-N9	106.08

Scheme 5



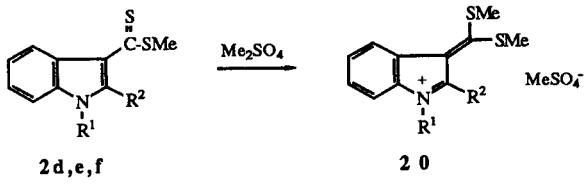
C. Synthesis and Reaction of 3-Indolyldithiolium Salts and 3-Indolylthiolonium Salts.

Carbonium ions containing three hetero atoms situated *a* to the ionic carbon atom have received much attention in the past decade and stable trihetero substituted carbonium ions have been used extensively in the synthesis of heterocyclic compounds. Thiolium salts of two substituted carbonium ions also exhibit interesting chemical behavior. 3-Indolyl dithiolium salts **20** are structures having two additional carbon atoms between the carbonium substituted sulfur atoms of the dithiocarboxylates and the nitrogen atom in the indole ring. The above compounds **20** also have a [bis(methylthio)methylene]indolenine structure, considered to be a pseudo ketene dithioacetal bearing an electon withdrawing quaternary nitrogen atom. group.

3-[α,α-Bis(methylthio)methylene]indolenium methyl sulfates (**20**), which are prepared by the reaction of methyl indole-3-dithiocarboxylates **2d,e,f** with dimethyl sulfate, react with active methylene compounds to form 3-(methylthio)vinylindole derivatives **21a-d** in good yields [19].

When allowed to react with nucleophilic reagents such as amines, active methylene compounds, and cyano anions compounds **21a-d** give the corresponding displacement products **22**, **25**, and **26** in good yields [20,21]. Reaction of **21a-d** with amidines or hydrazine hydrate gives the corre-

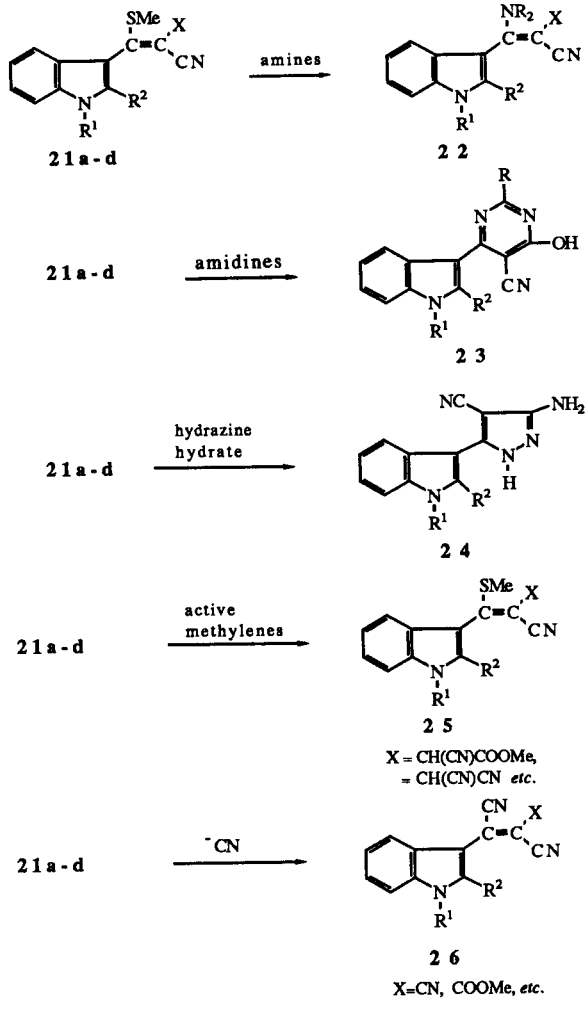
Scheme 6



2d,e,f 20 21a-d

No.	R^1	R^2	X	Yield (%)
21a	Me	Me	CN	90
b	Me	Me	COOMe	75
c	Me	C_6H_5	CN	90
d	H	C_6H_5	CN	90

Scheme 7



21a-d 22 23 24 25 26

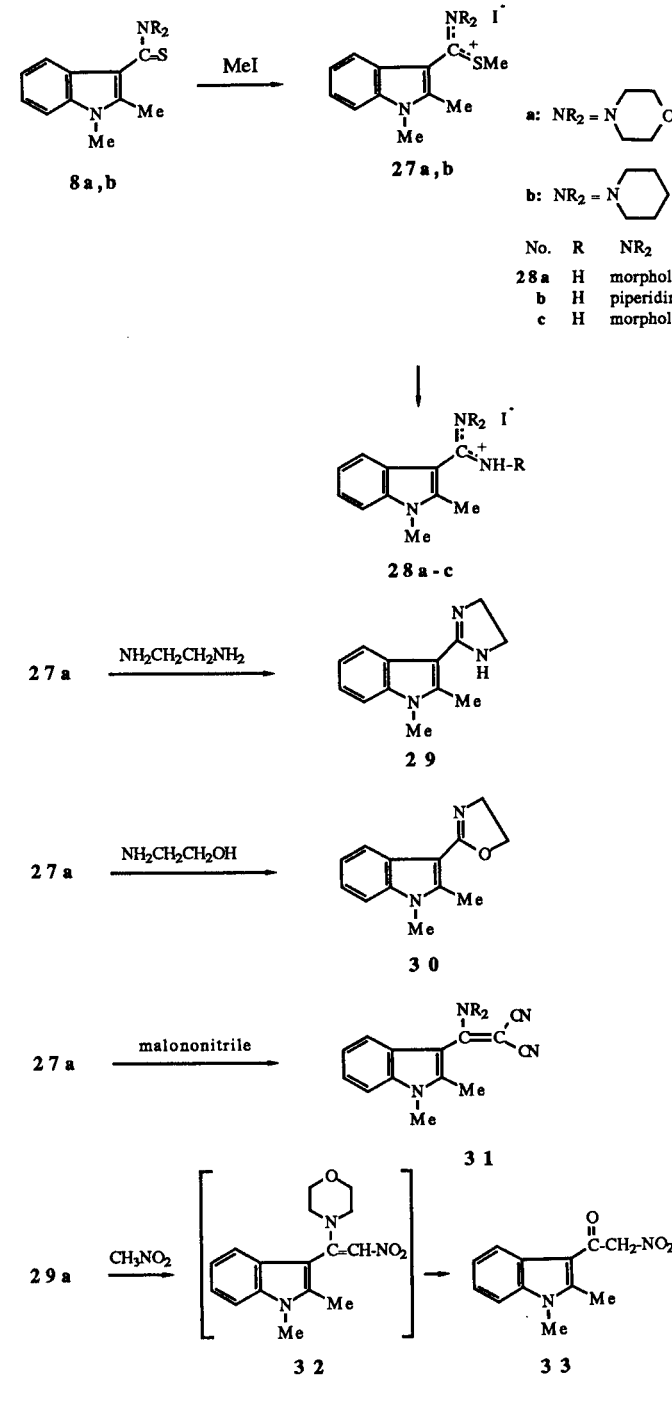
X = CH(CN)COOMe, = CH(CN)CN *etc.*

X=CN, COOMe, *etc.*

sponding pyrimidine **23** and pyrazole **24** derivatives in good yields [19].

Similarly, substitution of the methylthio or amino groups in (α-amino-α-methylthio)methyleneindolenium iodides **27a,b**, prepared by the reaction of thioamide derivatives **8a,b** with methyl iodide, with active methylene compounds or amines gives the corresponding substituted compounds **28a-c**, **29**, **30**, **31**, and **33** [19].

Scheme 8



8a,b 27a,b 28a-c 29 30 31 32 33

a: NR_2 = morpholino

b: NR_2 = piperidino

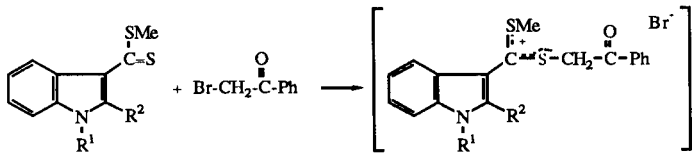
No.	R	NR_2
28a	H	morpholino
b	H	piperidino
c	H	morpholino

d. Synthesis and Reactions of 3-Indolyl-1,3-oxathiolium Salts.

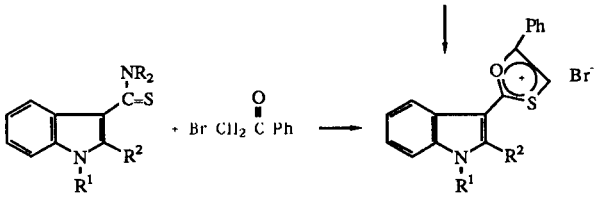
Many 1,3-oxathiolium compounds substituted with stabilizing groups have been reported. These compounds are attacked by a variety of nucleophiles exclusively at the 2-position, resulting in a number of possible products depending on the nature of the nucleophiles [22,23].

The reaction of methyl indole-3-dithiocarboxylates **2c,d,e,f** with phenacyl bromide in acetone gives 2-indol-3-yl-1,3-oxathiolium bromides **35a-d** in good yields [24]. The compounds **35a** and **b** are also obtained by the reaction of thioamides **8c,d,** and **f** with phenacyl bromide using Hartman's method [25-27]. Although some syntheses of 1,3-oxathiolium salts from thioamides or thioloester and a few synthesis of 1,3-dithiolium salts from dithiocarboxylates have been reported, there is no reported synthesis of 1,3-oxathiolium salts from dithiocarboxylates [24].

Scheme 9



2,c,d,e,f **34**



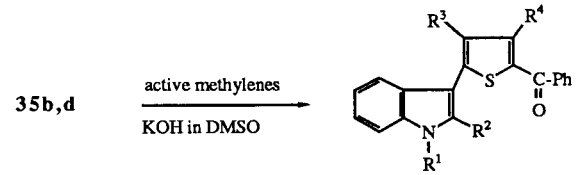
8c,d,f **35a-d**

8c, R^1 = H, NR_2 =morpholino
d, R^1 = Me, NR_2 =morpholino
e, R^1 = H, NR_2 = piperidino

No.	R^1	R^2
35a	H	Me
b	Me	Me
c	H	Ph
d	Me	Ph

Reaction of **35b** and **d** with active methylene compounds (malononitrile, ethyl acetoacetate, and acetylacetone) affords 5-benzoyl-2-indol-3-ylthiophene derivatives **36a-d** in 50-80% yields [24]. Hirai and Ishiba have reported the reaction of 1-aryl-1,3-oxathiolium salts with active methylene compounds to form thiophene derivatives [22]. Our results confirm this work.

Scheme 10

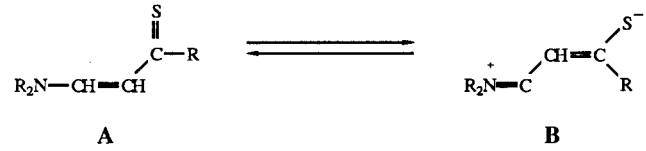


36a-d

No.	R^1	R^2	R^3	R^2
36a	Me	Me	CN	NH_2
b	Me	Ph	CN	NH_2
c	Me	Ph	COOEt	Me
d	Me	Ph	CN	Me

II. Reaction and Synthesis of Aromatic Enaminodithiocarboxylates.

Despite numerous reports concerning the utility of enamine compounds in organic synthesis [28], little research regarding enamino dithiocarboxylates has been published. The preparation of thiophene derivatives by Smutny, *et al.*, [29] is an exception. Smutny has reported a simple preparation of a new class of compounds, dithoiacylate esters, and amides, from trithione. All of these compounds show a prominent band or series of bands in the infrared between 1660 and 1570 cm^{-1}. This strong absorption is assigned to the polarized double bond, which conjugates the electron-donating nitrogen and electron-accepting sulfur (**A**↔**B**). He has discovered a new synthesis of substituted thiophene in testing his hypothesis [30].



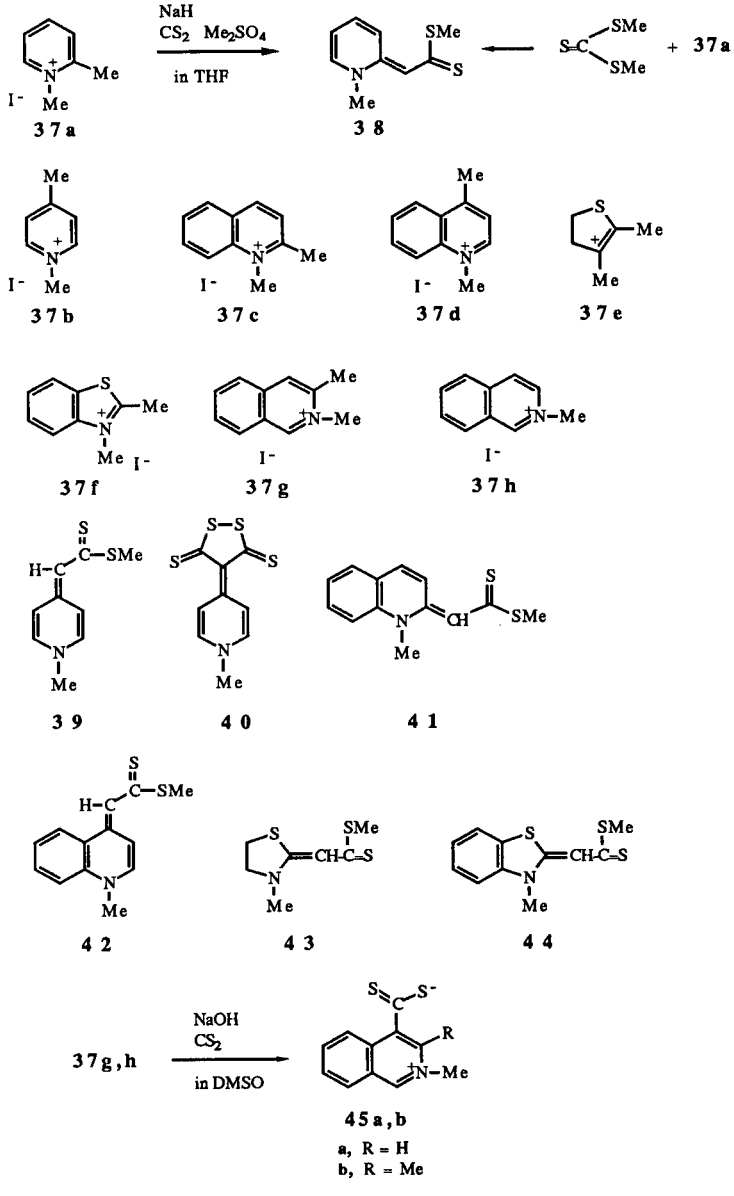
A **B**

A. Synthesis of Enaminodithiocarboxylic Acid Derivatives.

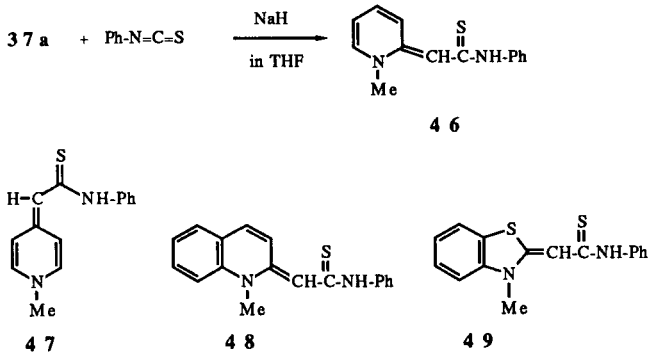
Enaminodithiocarboxylates **38-44** are prepared by reaction of carbon disulfide with 1,2-dimethylpyridinium iodide (**37a**), 1,4-dimethylpyridinium iodide (**37b**), 1,2-dimethylquinolinium iodide (**37c**), 1,4-dimethylquinolinium iodide (**37d**), and 4,5-dihydro-2,3-dimethylthiazolium iodide (**37e**), and 2,3-dimethylbenzothiazolium iodide (**37f**), respectively, in the presence of sodium hydride as a base in tetrahydrofuran [31]. Treatment of **37b** with carbon disulfide in the presence of sodium hydroxide, introduced 2 equivalents of carbon disulfide into the methyl group at 4-position to produce 1,4-dihydro-1-methyl-4-(3,5-dithioxo-1,2-dithiolan-4-ylidene)pyridine (**40**). Alternatively, compounds **38-44** are synthesized by reaction of the corresponding quntanary amines **37a-f** with trithiocarboxylic acid dimethylester in good yields. Reaction of 2,3-dimethylisoquinolinium iodide (**37g**) with carbon disulfide gives 2,3-dimethylisoquinolinium-4-dithiocarboxylate (**45b**), which is a betaine structure [31]. Reaction of 2-methylisoquinolinium iodie (**37h**) with carbon disulfide also gives a betaine product **45a**. In a similar manner, thioamide derivatives **46-49** are obtained by the reaction of **37a,b,c,f** with phenylisothiocyanate in good yields.

The dithiocarboxylates (**38**, **39**, **41**, and **44**) are treated with methyl iodide or dimethyl sulfate to give the corresponding ketene dithioacetal derivatives **50-53** in good yields [31].

Scheme 11

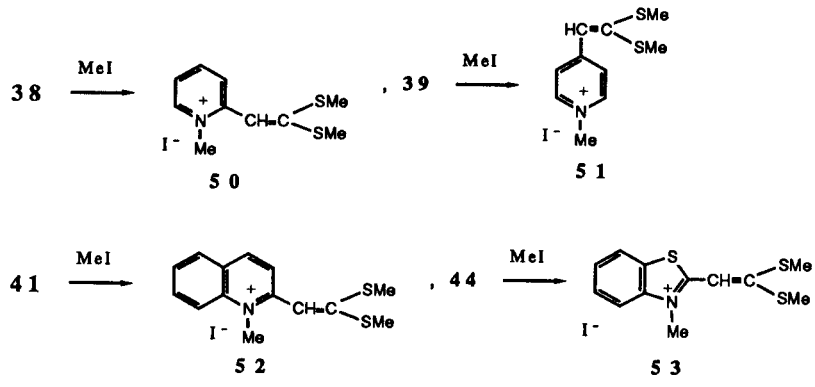


Scheme 12

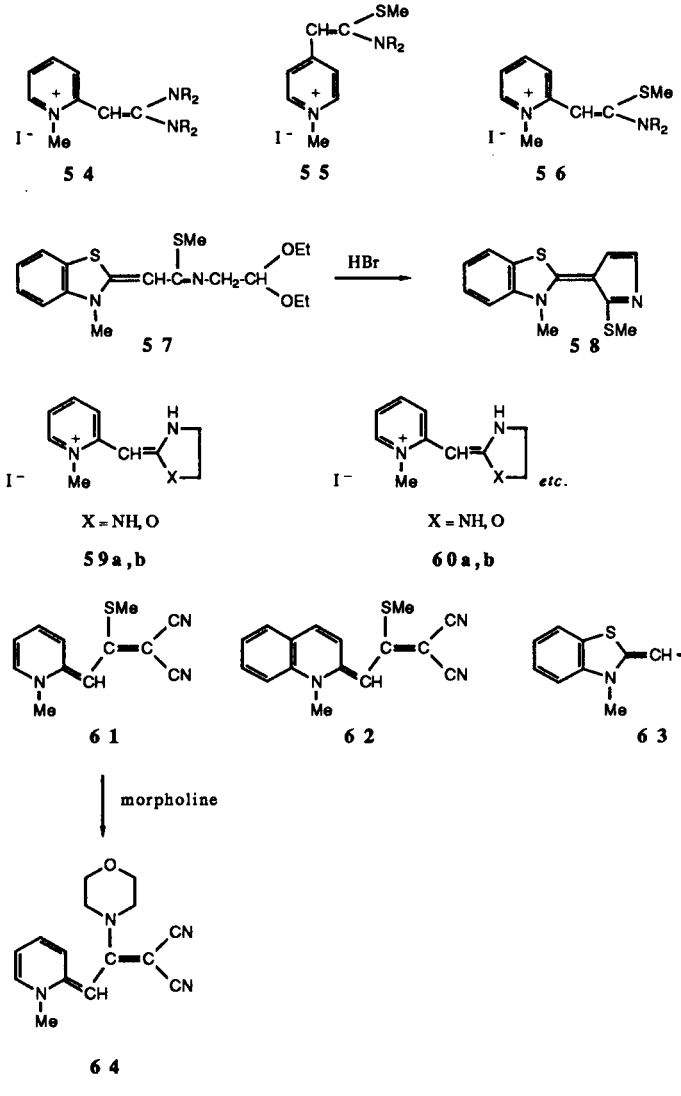


The reaction of heterocyclic ketene dithioacetal derivatives containing an electron withdrawing quaternary nitrogen group with nucleophilic reagents such as amine or active methylene compounds gives the corresponding substituted compounds **54-57**, and **61-63**. By the application of these reactions, fulvalene **58**, imidazolines **59a,b**, and oxazolines **60a,b** derivatives are obtained. Reaction of **50**, **52**, or **53** with malononitrile in the presence of potassium carbonate gives the corresponding γ-cyanopropylidene derivatives **61-63** in good yields. Substitution reaction of **61-63** with nucleophiles like amines or active methylene compounds, occurs smoothly to give replacement of the methylthio group in good yield. For example, reaction of **61** with morpholine gives the corresponding amine product **64** [31].

Scheme 13



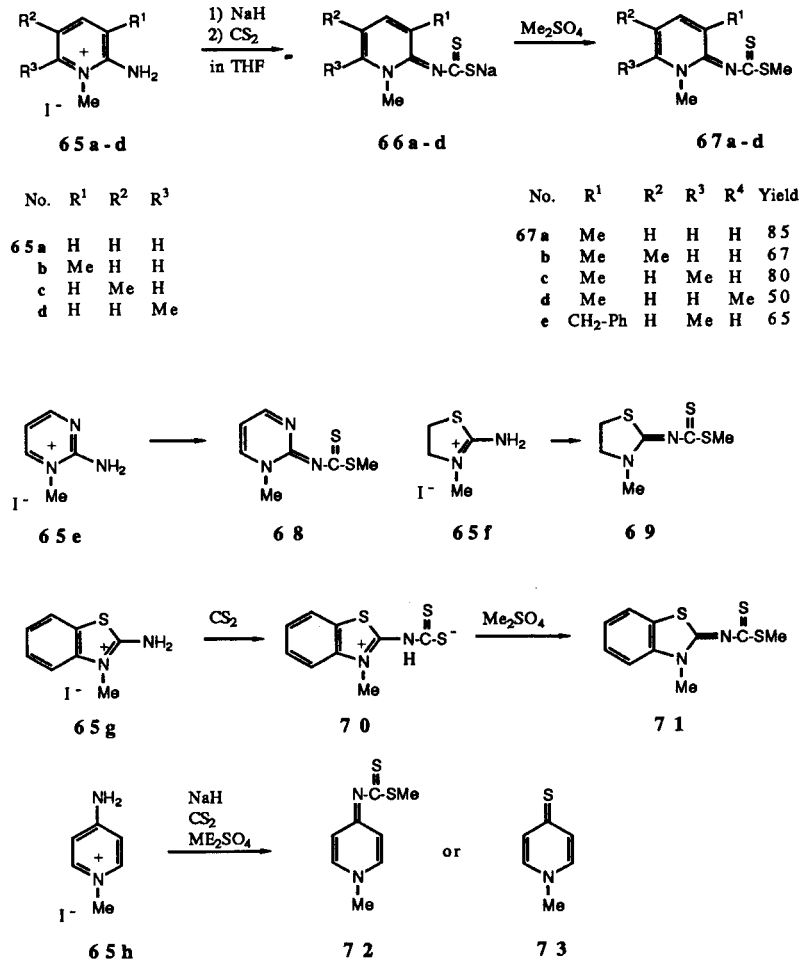
Scheme 14



B. Synthesis and Reaction of Heterocyclic Dithiocarbamates.

Dithiocarbamates are important and versatile intermediates for organic synthesis, particularly in the prepara-

Scheme 15



No.	R^1	R^2	R^3
65a	H	H	H
b	Me	H	H
c	H	Me	H
d	H	H	Me

No.	R^1	R^2	R^3	R^4	Yield
67a	Me	H	H	H	85
b	Me	Me	H	H	67
c	Me	H	Me	H	80
d	Me	H	H	Me	50
e	CH_2-Ph	H	Me	H	65

tion of biologically active compounds. Many synthetic reports concerning dithiocarbamates deal with the preparation of thioureas, isothiocyanates, and some heterocycles [33]. Reports concerning the reaction of heteroaromatic amines with carbon disulfide are not so prevalent, although the derived dithiocarbamate products are very useful intermediates for the preparation of a fused heterocyclic compounds. My compelling interest in these chemical reactions led to research to develop the chemisty of dithiocarbamates for the synthesis of heterocycles. In this section of the review, 2-amino- or 4-amino heterocyclic compounds are used as starting materials. Comparisons with the corresponding enamino dithiocarboxylates can be made.

Synthesis of Alkyl Dithiocarbamates.

The reaction of 2-amino-1-methylpyridinium iodide **65a-d** with carbon disulfide in the presence of sodium hydride in tetrahydrofuran gives the sodium dithiocarbamate **66a-d**, which is methylated with dimethyl sulfate to afford 1-methyl-2-(methylthio)thiocarbonylimino-1,2-dihydropyridines **67a-d**. Using benzyl chloride instead of dimethyl sulfate as the alkylating reagent in the reaction of **65d** with carbon disulfide, benzylthio derivatives **67e** was obtained. Similarly, other heterocyclic dithiocarbamate **68,69** are prepared by the reaction of 2-amino-1-methylpyrimidinium iodide (**65e**) and 2-amino-3-methylthiazolium iodide (**65f**) with carbon disulfide in good yields. The reaction of 2-amino-3-methylbenzothiazolium iodide (**65g**) with carbon disulfide under similar reaction conditions afford the stable dithiocarboxylic acid derivatives **70**. It is very interesting that **70** is quite stable and shows no acid character, presumably because of the betaine structure **70**. Methylation of **70** with dimethylsulfate in the presence of potassium carbonate in dimethyl sulfoxide yields the methyl dithiocarbamate **71**. When 4-amino-1-methylpyridinium iodide (**65h**) is reacted with carbon disulfide in a similar manner, 1-methyl-4-thioxo-1,4-dihydropyridine (**73**) is obtained. On the other hand, when a mixture of carbon disulfide and dimethyl sulfate in DMSO is added to a solu-

tion of **65h** and potassium carbonate in DMSO, **72** is obtained. The formation of **72** is a result of the attack of the dithiocarbamate anion, because of the preferential methylation of the dithiocarbamic acid group by dimethyl sulfate co-existing in the reaction mixture [34].

C. Methylation and The Reaction of Methyl Dithiocarbamate.

Treatment of **67a**, **68**, and **71** with methyl iodide gives **74-76** in good yields. The chemical reactivity of the methyltho group in **74-76** can be investigated by reaction of with amines or active methylene compounds. Reaction of **74** with morpholine gives the dimorpholino derivatives **77**. In a similar manner, reaction of **74** with ethylenediamine or ethanolamine gives the corresponding imidazoline **78a** and oxazoline **78b** derivaties in good yields. The reaction of **75** and **76** with these amines also afford the corresponding the displacement products in good yields. Compounds **74** and **76** readily react with active methylene compounds (malononitrile, methyl cyanoacetate, nitromethane, oxindole, acetylacetone, rhodanine) to give the corresponding methylthio substituted products in good yields [34]. Reaction of **74** with malononitrile gives the corresponding displacement product **79** [34].

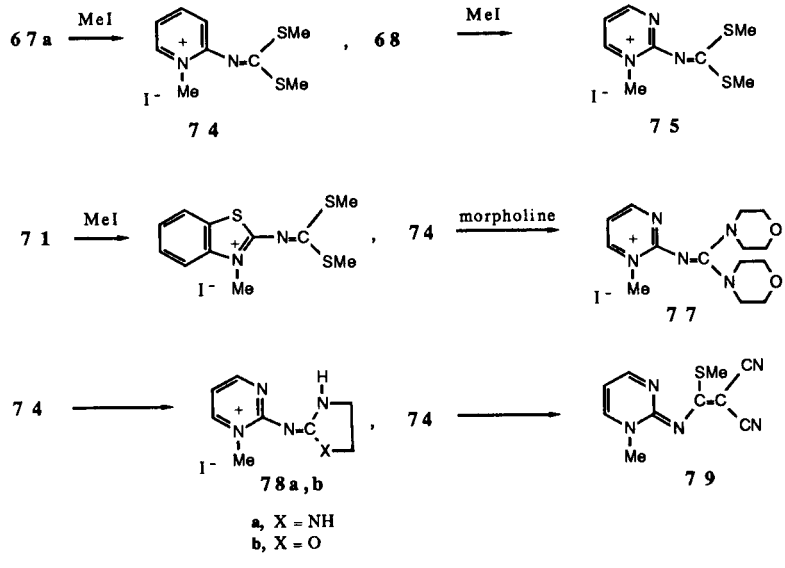
D. Diels-Alder Reaction of Dithiocarboxylates.

Non-enethiolizable dithiocarboxylates in particular undergo interesting addition reactions with a variety of compounds containing either a polarized multiple bond or some other sort of dipolar fragment to yield otherwise unattainable heterocyclic compounds. Some thioketones also behave as dienophiles in Diels-Alder reactions, being several orders of magnitude more reactive than the corresponding carbonyl compounds [35-37]. Enaminothioketones may act as the "Diene" in Diels-Alder reactions with appropriate alkenes, affording either 4-amino-2,3-dihydro-4*H*-thiapyranes or 2*H*-thiapyranes, depending on the nature of the substituents [38]. Easton has reported the Diels-Alder reaction of DMAD with conjugated thioketones, affording 1,3-dipolar cycloaddition reaction of trithione compounds with DMAD [39]. Diels-Alder reactions have been reported by other groups [40-43]. We attempted to apply the above reaction to the Diels-Alder reaction of methyl indoledithiocarboxylate derivatives with DMAD [44]. When our investigation of these Diels-Alder reaction was nearly complete [44], Kalish reported the Diels-Alder reaction of enaminodithiocarboxylate with maleic anhydride to give the corresponding the thiapyrane derivatives [45].

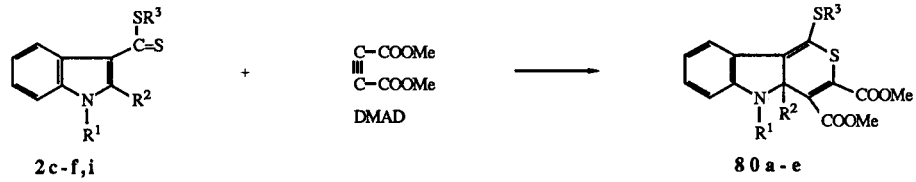
Methyl 3-indoledithiocarboxylates and these thioamides have a diene system in the thiocarbonyl group of their dithiocarboxylic acid and a double bond between the α- and β-position of indole. Reaction of methyl 3-indoledithiocarboxylates **2c-f,i** with dimethyl actylenedicarboxylate (DMAD) gives the corresponding Diels-Alder reaction products **80a-e** in good yields. In a similar manner, reaction of the 3-morpholino **8a** and 3-piperidino **8b** derivatives also gives the Diels-Alder reaction products **81a,b** in good yields.

Treatment of **80a,b,c** with methanolic acid gives 2,3-bis-(methoxycarbonyl)thiopyrano[2,3-*b*]indole salt derivatives **83a-c** in good yields. Most ring opening reactions of indoles are initiated by protonation or other electrophilic attack at the α-position, generating a 3*H*-indolenium ion. The conversion of **80a-c** into a ring opened intermediate in acidic solution occurs readily. Namely, treatment of **80** with an acidic solution would give an intermediate cation **82** (Scheme 18) having an amino group which might attach

Scheme 16

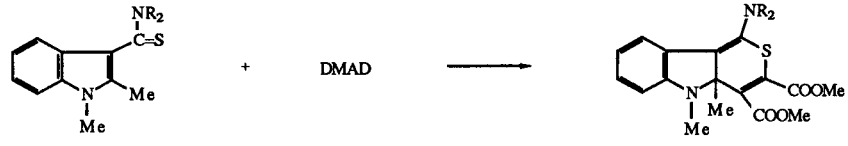


Scheme 17

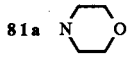
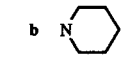


2c-f,i 80a-e

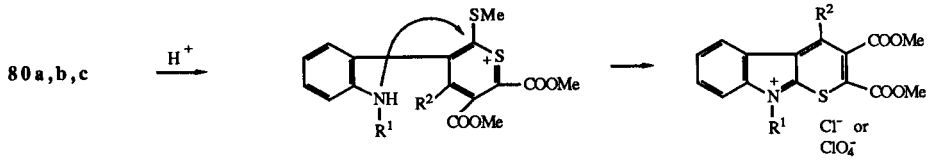
No.	R^1	R^2	R^3	Yield
80a	H	Me	Me	95
b	Me	Me	Me	85
c	H	Ph	Me	70
d	Me	Ph	Me	65
e	H	Me	CH_2CN	80



8a,b 81a,b

No.	NR_2	Yield (%)
81a		70
b		70

Scheme 18



82 83a-c

No.	R^1	R^2
83a	H	Me
b	Me	Me
c	H	Ph

to the carbon atom bearing the methylthio function [44].

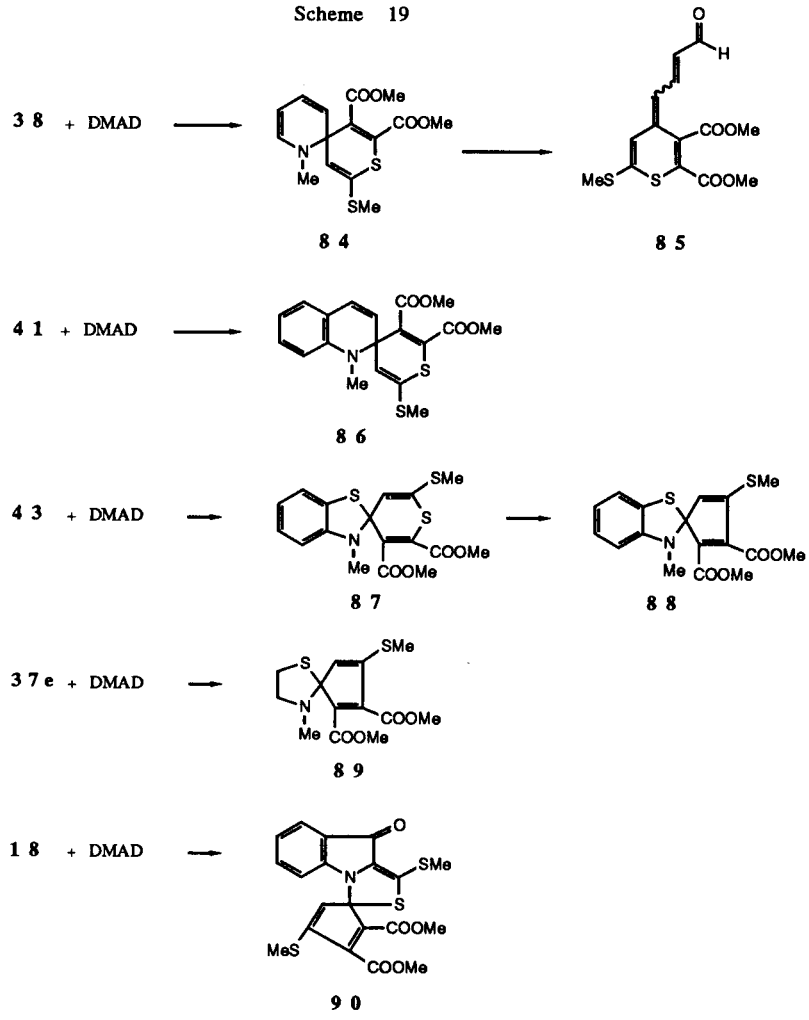
The reaction of methyl 1-methyl-2-methylene-1,2-dihydro-α-dithiocarboxylate (**38**) with DMAD affords a product with the pyridine ring opened, 2-methylthio-5,6-dimethoxycarbonylbut-2-enolidenethiapyran (**85**) [46]. The formation of **85** can be explained by assuming the spiro compound **84** is a key intermediate. This compound might be the usual Diels-Alder reaction product of the above reaction. The structure of the ring-opened product is supported by the all *trans*-aldehyde system from the nuclear magnetic resonance (nmr) spectrum. In a similar manner, the reaction of **41** with DMAD give a spirocompound **86** in good yield [47].

We also reported that the reaction of **43** with DMAD in DMF gives spiro(benzothiazolinecyclopentadiene) **88** by monodesulfurization in a good yield. The reaction of **37e** or **18** with DMAD also occurs to form spiro(thiazolinepentadiene) derivatives **89** and **90** [48].

The reaction of **41** with DMAD in dioxane gives two products **91** and **92** which are formed by double cycloaddition reactions, 1,4-cycloaddition and 1,2-cycloaddition [47].

Methyl 2,3-dimethyl-1-oxo-1,2-dihydroisoquinoline-4-dithiocarboxylate (**93**) also reacts with DMAD to give the corresponding 1,4-cycloaddition product **94**. This thiocarbonyl-diene system also reacts with *N*-phenylmaleimide to afford the 1,4-cycloaddition product **95** in a good yield [47]. Compound **93** is prepared by methylation of **45b** with

Scheme 19



methyl iodide followed by oxidation with potassium ferrocyanate.

Reaction of **45b** with DMAD gives **96** which might result from both cycloaddition reactions, simultanious a typical 1,4-dipolar cycloaddition and the usual Diels-Alder reaction [47].

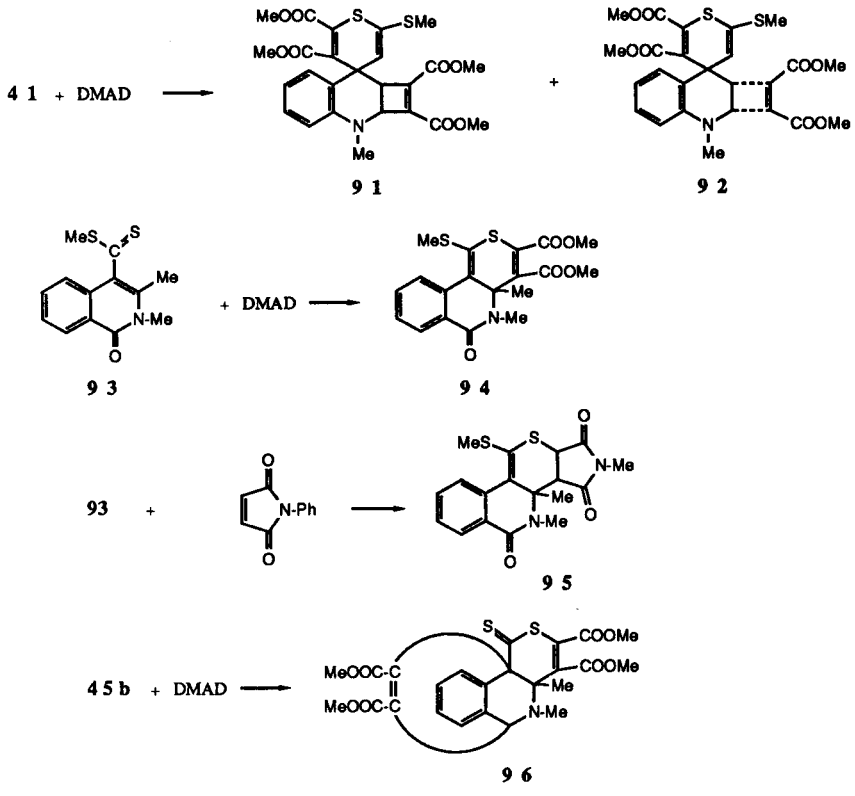
The thiocarbonyl-diene of thioamide derivatives do not react with DMAD under similar condition except in the case of indole-3-thiomorpholides. However, reaction of thioamides, **97a-c** with DMAD gives the benzazocine derivatives **99a-c**. This reaction when applied to reaction of the thiocarbamoyl methylene of 4-picolines **100a,b** with DMAD, yielded the corresponding 1,6-dihydroazocine derivatives **102a,b** in good yields. Many workers report that the enamines react with electrophilic alkynes to form cyclobutene adducts. These undergo stepwise ring opening under mild thermal conditions to afford ring expanded dienamines. 1-Alkyl-1,6-dihydro-1-benzazocine and 1,2-dihydroazocine derivatives are synthesized by cycloaddition of the cyclic enamine 1-alkyl-1,4-dihydroquinoline or 1,2-dihydropyridine with DMAD [47]. However, the cyclobutene adducts from certain 1,3-disubstituted 1,4-dihydropyridines and DMAD do not undergo thermal ring expansion. Our methods to prepare 1,4-dihydrobenzazocine and 1,6-dihydroazocine derivatives by cycloaddition are quite useful. They can be applied to the synthesis of various methyleneazocine derivatives [47].

Reaction of **38** with tetracyanoethylene (**103**) gives **62** *via* 1,2-cycloaddition reaction products **104** in good yield [52].

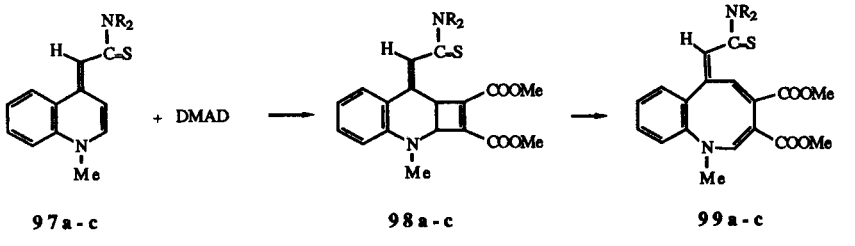
E. 1,4-Cycloaddition Reaction of Dithiocarbamates.

Conjugated dienes and their heteroanalogs have been thoroughly investigated in organic chemistry. However, few studies have been reported on diheterodienes having a thiocarbonyl group and a carbon-nitrogen double bond [49]. The methyl dithiocarbamate derivatives described above have a conjugated diheterodiene system.

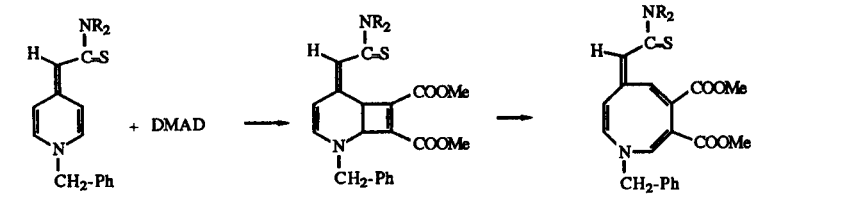
Scheme 20



Scheme 21

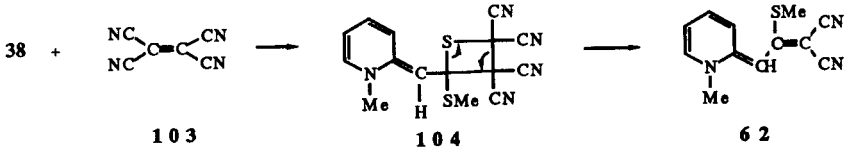


a: NR_2 = morpholino
b: NR_2 = piperidino
c: NR_2 = pyrrolidino

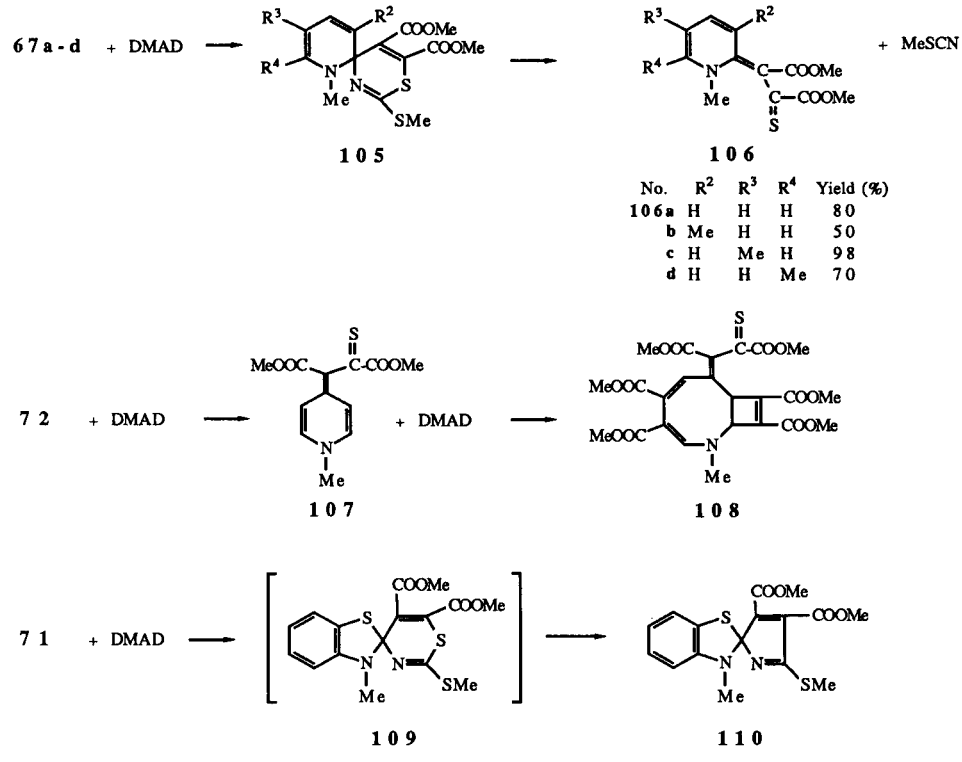


a: NR_2 = morpholino
b: NR_4 = pyrrolidino

Scheme 22



Scheme 23



No.	R^2	R^3	R^4	Yield (%)
106a	H	H	H	80
b	Me	H	H	50
c	H	Me	H	98
d	H	H	Me	70

Reaction of **67a** with DMAD gave 1-methyl-2-[1,2-bis-(methoxycarbonyl)-2-thiooxoethylidene]-1,2-dihydropyridine (**106a**). In a similar manner, treatment of other methyl dithiocarbamate derivatives **67b-d** and **72** with DMAD afforded the corresponding 2-(2-thiooxoethylidene)-1,2- **106b-d** or 1,4-dihydropyridine derivatives **107**, accompanied by the elimination of methylthiocyanate, in fairly good yields. Reaction of **107** with DMAD affords cyclobuta[*b*]azocine derivative **108**. The reaction of **71** with DMAD affords 3-methyl-2,3-dihydrobenzothiaole-2-spiro-2′-[3′,4′-di(methoxycarbonyl)-5′-methylthio-2*H*-pyrrole] (**110**). This reaction did not give the 1,4-cycloaddition product at room temperature. It has been reported that the analogous 1,4-cycloaddition reaction of an enaminodithiocarboxylate with DMAD gives the corresponding spiro-(benzothiazoline-cyclopentadiene) derivative by mono-desulfurization (Scheme 19) [50,52].

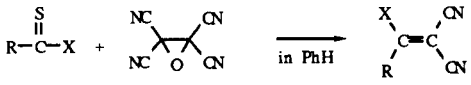
F. 1,3-Dipolar Cyclization Reaction of Dithioester and Thioamides with Tetracyanoethylene Oxide.

Non-enethiolizable thioketones behave as dienophiles or dipolarophiles in Diels-Alder or 1,3-dipolar reactions, being several orders of magnitude more reactive than the corresponding carbonyl compounds.

Ethylenes having electron-donating groups of an olefinic carbon atom and electron-accepting groups on the other olefinic carbon atom are important and interesting compounds from both synthetic and theoretical points of view [53]. Among these compounds, for example, ketene dithioacetals [54,55], ethoxymethylene compounds [56], and aminomethylene compounds [57] are widely used for the preparation of heterocycles. The reaction of thiocarbonyl derivatives with tetracyanoethylene oxide to give stable thiocarbonyl ylides, thiazoles, and dicyanomethylene compounds has been reported [58,59]. Preparation of the polarized ethylenes using dicyanomethylenation with tetracyanoethylene oxide was unknown prior to our research. We have recently discovered a novel and simple preparation of polarized ethylenes bearing push-pull substituents (an amino and a methylthio, and two cyano groups on each of the olefinic carbon atoms, respectively) by the reaction of thioamides or methyl dithiocarboxylates with tetracyanoethylene oxide [60]. Thioamides **111** are allowed to react with tetracyanoethylene oxide (**112**) at room temperature in benzene with stirring to readily give the corresponding dicyanoethylene compounds **113a-j** very smoothly. Moreover the reaction of methyl dithiocarboxylates **111k-s** with **112** also occurred under similar conditions to yield the corresponding 2-methylthio-1,1-dicyanoethylene derivatives **113k-s** in good yields [60].

It is well known that the reaction of polarized ethylenes, such as ketene dithioacetals, with bifunctionalized amines, such as hydrazine or amidine derivatives, gives the corresponding pyrazole or pyrimidine derivatives [61-64]. The

Scheme 24

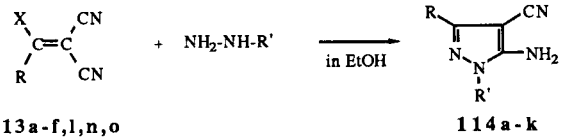


111 112 113a-s

Product	R	X	Yield (%)
113a	C_6H_5	morpholino	69
b	o-MeO-C_6H_4	morpholino	91
c	p-MeO-C_6H_4	morpholino	84
d	p-Cl-C_6H_4	morpholino	85
e	3,4-$(MeO)_2$-C_6H_3	morpholino	90
f	3,4-O-CH_2-O-C_6H_3	morpholino	82
g	2-thienyl	morpholino	88
h	C_6H_5-CH_2	morpholino	77
i	p-Me-C_6H_4-CH_2	morpholino	75
j	C_6H_5-CH_2CH_2	morpholino	79
k	methylthio	morpholino	62
l	C_6H_5	methylthio	78
m	o-MeO-C_6H_4	methylthio	67
n	p-MeO-C_6H_4	methylthio	72
o	p-Cl-C_6H_4	methylthio	82
p	p-Me_2N-C_6H_4	methylthio	91
q	2-thienyl	methylthio	78
r	C_6H_5-CH_2	methylthio	68
s	2-pyrrolyl	methylthio	88

heterocyclic compounds thus obtained exhibit interesting biological activities and are also important and useful as starting materials for conversion to other heterocyclic compounds. Therefore, we attempted to prepare pyrazole and pyrimidine derivatives using **112a-r**. Reactions of **113a-f,h,i** with hydrazine hydrate give the corresponding 3-substituted 5-amino-4-cyanopyrazole derivatives **114a-h** in good yield on heating at 100° for 5 hours. By contrast, reactions of morpholino compounds **113a-k** with phenylhydrazine did not occur under the similar conditions. However, reaction occurs when methylthioethylenic compounds **113l,n,o** are used instead of **113a-k**, since dicyanoethylenes methylthiogroup substitution are generally more reactive toward nucleophiles than those substituted with the morpholino group. For example, reactions of **113l,n,o** with phenylhydrazine at reflux for 1 hour in ethanol give the corresponding 5-amino-1-aryl-4-cyanopyrazoles **114i-k** in good yields [60].

Scheme 25

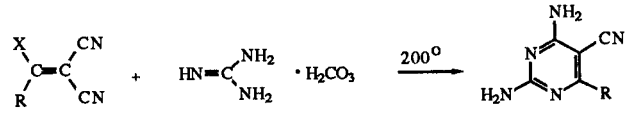


113a-f,l,n,o 114a-k

No.	R	R'	Yield (%)
114a	C_6H_5	H	74
b	o-MeO-C_6H_4	H	88
c	p-MeO-C_6H_4	H	69
d	p-Cl-C_6H_4	H	82
e	3,4-O-CH_2-O-C_6H_3	H	65
f	3,4-$(MeO)_2$-C_6H_3	H	51
g	C_6H_5-CH_2	H	98
h	p-Me-C_6H_4-CH_2	H	98
i	C_6H_5	C_6H_5	46
j	p-MeO-C_6H_4	C_6H_5	43
k	p-Cl-C_6H_4	C_6H_5	64

Reactions of **113a-d,g,** and **h** with guanidine carbonate on heating at 200° for 2 hours give the corresponding 2,4-diamino-5-cyanopyrimidine derivatives **115a-f** in 52-96% yields [60].

Scheme 26

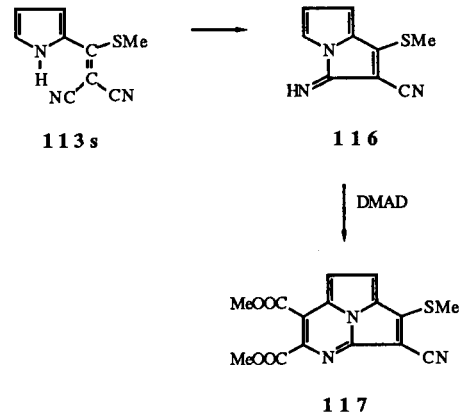


113 115a-f

No.	R	Yield (%)
115a	C_6H_5	85
b	p-MeO-C_6H_4	83
c	p-Cl-C_6H_4	90
d	C_6H_5-CH_2	70
e	2-thienyl	71
f	C_6H_5-CH_2	52

These polarized ethylenes are used to synthesize a 5-azacycl[3.2.2]azine derivative. Namely, intermolecular cyclization of **113s** under heating at 80° in the presence of triethylamine gives 3-imino-3*H*-pyrrolo[1,2-*a*]pyrrole **116**. Reaction of this fused pyrrole with dimethyl acetylenedicarboxylate in the presence of palladium-on-charcoal as a dehydrogenation catalyst yields the corresponding cyclized product, dimethyl 4-cyano-3-methylthio-5-azacycl-[3.2.2]azine-6,7-dicarboxylate (**117**) [52].

Scheme 27



113s 116 117

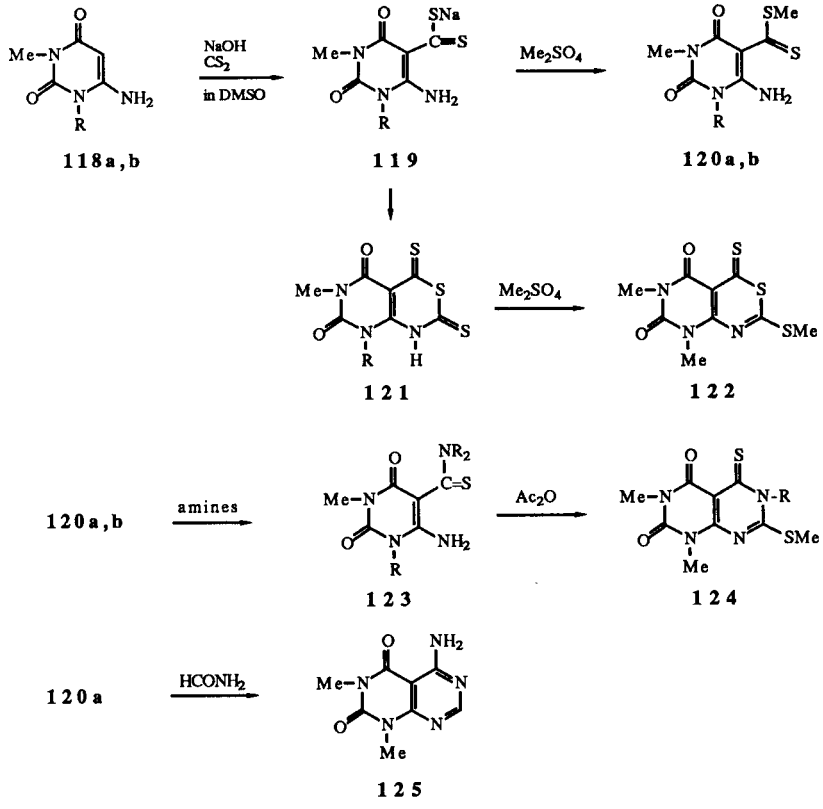
IV. Reaction of Enaminones with Carbon Disulfide.

A. Synthesis and Reactions of Methyl 6-Aminouracil-5-carbodithioates.

Enaminones are very useful and versatile in organic synthesis [28].

Reaction of 6-aminouracils (**118a,b**) with carbon disulfide and dimethyl sulfate in the presence of sodium hydride in dimethylsulfoxide gives methyl 6-aminouracil-5-carbodithioates **120a,b**. Using an excess of carbon disulfide, the above reaction affords pyrimido[4,5-*d*][1,3]thiazine derivatives **121** in good yields. Methylation of **121**

Scheme 28



with dimethyl sulfate gives **122**. Compound **120a,b** reacts with amines to give the corresponding 6-amino-5-substituted thiocarbamoyluracils **123** in good yields. The reaction of **111a** with formamide gives 5-amino-1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**125**) [65,66]. Other pyrimido[4,5-*d*]pyrimidine derivatives **124** are also obtained by treatment of **123** with acetic anhydride.

B. Synthesis and Reaction of 3-(Methylthio)isothiazolo-[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione.

Recently Niss [67] and Furukawa [68] have reported the reaction of 6-aminouracils with alkyl or aryl isothiocyanate to give 5-substituted thiocarbamoyl-6-aminouracils and its subsequent oxidation with bromine or hydrogen peroxide yields 3-substituted aminoisothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione. We have reported a new synthesis of 3-methylthioisothiazolo[3,4-*d*]pyrimidines [69]. Oxidation of **120a** with iodine in dimethyl sulfoxide gives 5,7-dimethyl-3-methylthioisothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**126a**). In a similar manner, **126b** is synthesized from compound **120b**.

It is well known that the methylthio group on a heterocyclic ring reacts with nucleophilic reagents to give the corresponding substituted products. However, prior to our work, there was no report on substitution reactions of the methylthio group on fused isothiazole rings [70]. Substitution of the methylthio group in compounds **126a,b** with amines (methylamine, benzylamine, cyclohexylamine, isopropanolamine, piperidine, morpholine, pyrrolidine) occurs easily. The corresponding 3-aminoisothiazolo[3,4-*d*]-pyridine-4,6(5*H*,7*H*)-diones **127a-i** are obtained in good yields. Alternatively, these amino derivatives **127** are obtained by iodine or bromine promoted oxidative cyclization of 5-substituted thiocarbamoyl-6-aminouracils **123**, prepared by the reaction of **120a** and **b** with amines (methylamine, benzylamine, morpholine) [69].

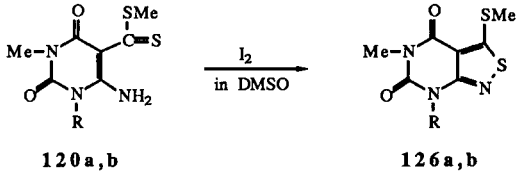
Reaction of **126a** with *p*-toluenesulfonamide or *p*-acetylaminophenylsulfonamide in the presence of potassium carbonate in sulfurane affords 5,7-dimethyl-3-*p*-tolysulfylamino- or *p*-acetylaminophenylsulfonylisothiaolo[3,4-*d*]-pyrimidine-4,6(5*H*,7*H*)-dione **128a,b** [69, 71].

The reaction of **126a** and **b** with active methylene compounds (methyl cyanoacetate, phenylsulfonylacetonitrile) in the presence of potassium carbonate gives the corresponding substituted products **129a,b,c** [69, 71].

C. Reaction of 6-Arylaminouracils with Carbon Disulfide.

The reaction of 6-arylamino-1,3-dimethyluracils **130a-e** with excess carbon disulfide in the presence of sodium hydroxide and subsequent methylation with dimethyl sulfate

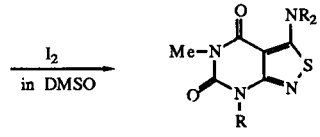
Scheme 29



120a,b 126a,b

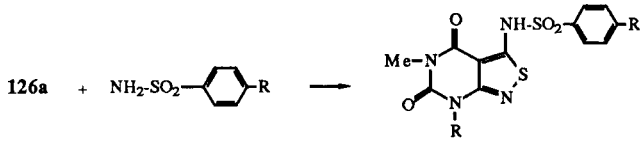
amines

123



127a-i

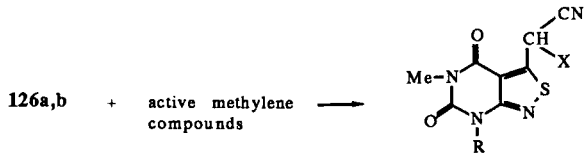
No.	R	NR_2	Yield (%)
127a	Me	NH-Me	75
b	Me	NH-CH_2Ph	61
c	Me	NH-CH_2CH(OH)Me	45
d	Me	N⟨⟩	63
e	Me	N⟨⟩O	77
f	Me	N⟨⟩	95
g	Me	NH-⟨⟩H	56
h	Ph	N⟨⟩	80
i	Ph	NH-CH_2Ph	47



128a,b

a: R = Me, Yield 27%
b: R = NH-Ac, Yield 56%

Scheme 30



129a-c

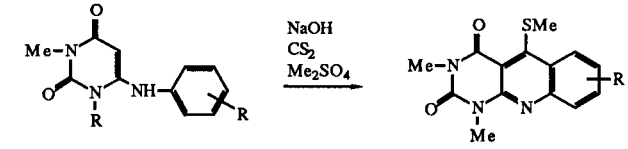
No.	R	X	Yield (%)
129a	Me	COOMe	62
b	Ph	COOMe	51
c	Me	SO_2Ph	56

gives the corresponding 1,3-dimethyl-5-methylthiopyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **131a-e** [72].

When a solution of sodium hydroxide is added to a solution of **130a**, carbon disulfide, and dimethyl sulfate in dimethyl sulfoxide, methyl *N*-phenyl-*N*-(1,3-dimethyl-6-uracilyl)dithiocarbamate (**132**) is obtained. Heating **132** in diphenyl ether at 250° for 20 minutes gives a cyclized product **133** [72]. This cyclization is a new reaction and will become of a convenient method for the preparation of quinoline derivatives.

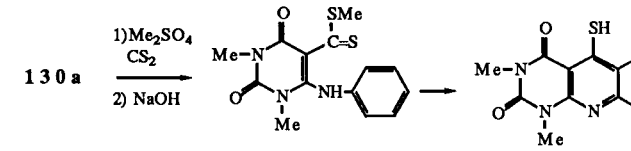
Raney-nickel desulfurization of **131a-d** affords 1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **134a-d** in good yields. Treatment of **131a,c** with hydrogen peroxide in acetic acid gives 5-hydroxy derivatives **135a,b** [72].

Scheme 31

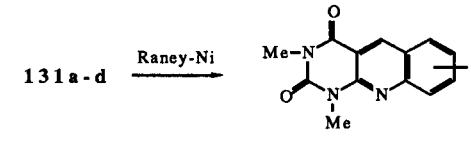


130a-e 131a-e

No.	R	Yield (%)
131a	H	18
b	7-Me	25
c	7-OMe	31
d	8-OMe	23
e	9-OMe	26

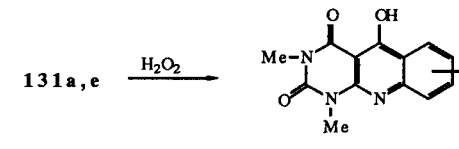


132 133



134a-d

No.	R	Yield (%)
134a	H	78
b	7-Me	72
c	7-OMe	78
d	8-OMe	70



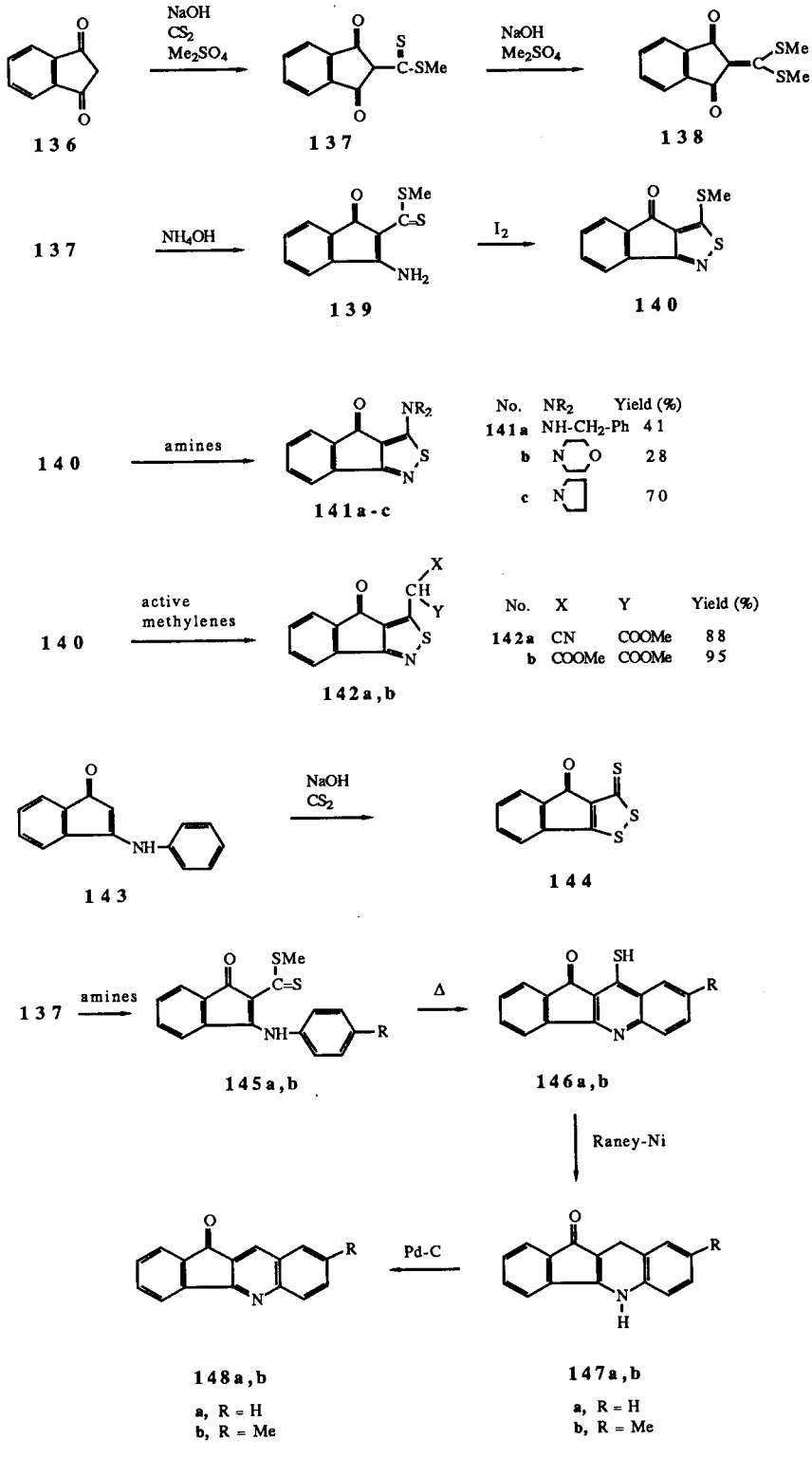
135a,b

No.	R	Yield (%)
135a	H	63
b	9-OMe	40

D. Synthesis and Reaction of Methyl 1,3-Dioxoindan-2-dithiocarboxylate.

The reaction of indan-1,3-dione (**136**) with carbon disulfide followed by methylation with dimethyl sulfate or methyl iodide in the presence of sodium hydroxide gives

Scheme 32



2-[bis(methylthio)methylidene]indane-1,3-dione (**138**) and methyl indan-1,3-dione-2-dithiocarboxylate (**137**) [73,74]. Compound **137** reacts with ammonia to give methyl 3-amino-1-oxoindan-2-dithiocarboxylate (**139**), which is converted to 3-methylthioindeno[1,2-*c*]isothiazol-4(4*H*)-one (**140**) by treatment with iodine in dimethyl sulfoxide [74]. Compound **140** reacts with amines or active methylene compounds giving the corresponding displacement pro-

duces (**141a-c**, and **142a,b**) of a methylthio group.

The reaction of 1-anilino-3-indanone (**143**) with carbon disulfide gives a dithione derivative **144** in good yield. In this reaction, the corresponding dithiocarboxylate is not detected. In a similar synthesis of **139**, reaction of **137** with aniline derivatives gives the corresponding methyl 1-anilino-3-oxainda-2-dithiocarboxylates **145a,b** which are converted to indenoquinoline derivatives **146a,b** under refluxing in diphenyl ether [52]. Desulfurization of **146a,b** with Raney-nickel gives dihydroindenoquinolines (**147a,b**) which are aromatized with palladium on charcoal to give **148a,b** in good yields [52].

Another enamino dithiocarboxylate **150**, which is prepared by the condensation of **149** with carbon disulfide followed by methylation with dimethyl sulfate, is cyclized in diphenyl ether to give the acridine derivative **151**. Compound **153** is prepared by dehydration of **152**, which is obtained by the desulfurization of **151** with Raney-nickel, in a manner similar to the described synthesis of **148** [52].

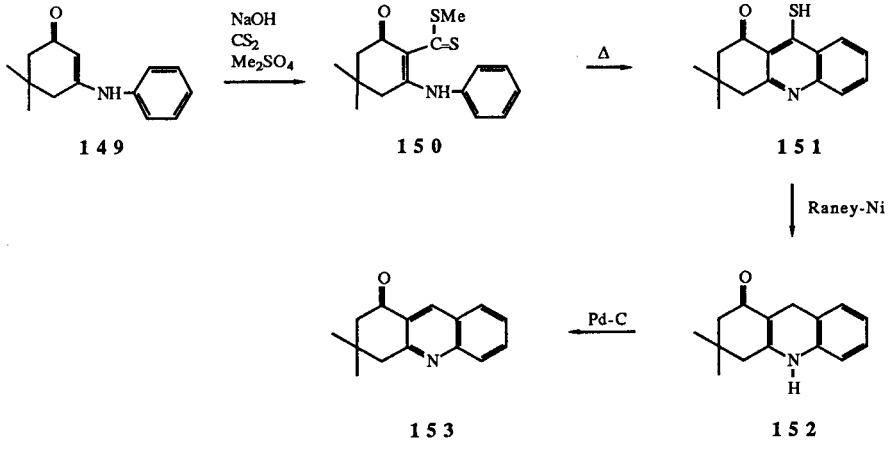
E. Reaction of 2-Aminonaphthoquinone with Carbon Disulfide.

Reaction of 2-aminonaphthoquinone (**154**) with carbon disulfide in the presence of sodium hydroxide, followed by methylation with dimethyl sulfate, affords 2-methyltho-4,9-dihydronaphtho[2,3-*d*]thiazole-4,9-dione (**155**). Reaction of **155** with amines or active methylene compounds gives the corresponding substituted products **156a-c** and **157a,b** of the methylthio group in **155** in good yields [75].

V. Aromatic *N*-Ylides.

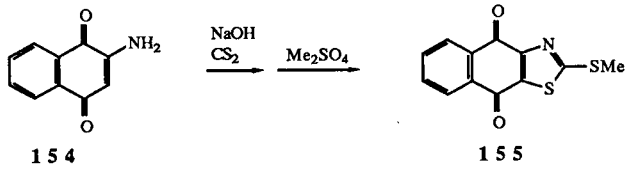
A. Synthesis of Ketene Dithioacetals Having Pyridinium Salts.

Scheme 33

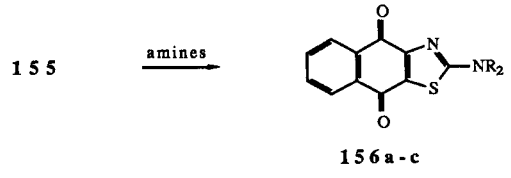


149 150 151 153 152

Scheme 34

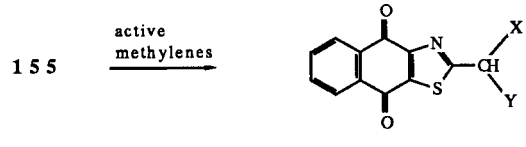


154 155



156a-c

No.	NR_2	Yield (%)
156a	NH-CH_2-Ph	91
b		87
c		91

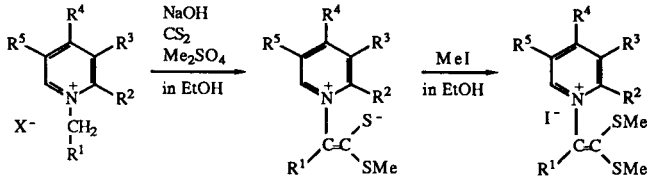


157a,b

No.	X	Y	Yield (%)
157a	CN	COOMe	92
b	COOMe	COOMe	88

It is well known that the ketene dithioacetals undergo nucleophilic attack by amines or active methylenes, replacing either one or two methylthio groups attached to the same carbon atom [54,55,76]. In this section, chapter, the reaction of heterocyclic ketene dithioacetals, containing an electron withdrawing aromatic quaternary nitrogen, are described. These above ketene dithioacetal derivatives, 1-[2,2-bis(methylthio)ethenyl]pyridinium iodides **160a-m**, are prepared by the alkylation of sulfur-containing pyridinium ylides **159a-m** with methyl iodide. These ylides are prepared by the reaction of pyridinium salts **158a-k** with carbon disulfide in the presence of sodium hydroxide [77].

Scheme 35



158a-k 159a-m 160a-m

No.	R^1	R^2	R^3	R^4	R^5	Yield (%)
160a	H	H	H	H	H	-
b	COPh	H	H	H	H	54
c	COPh	Me	H	H	H	63
d	COPh	H	Me	H	H	66
e	COPh	H	H	Me	H	68
f	COPh	Me	H	Me	H	39
g	COOEt	H	H	H	H	57
h	COOEt	Me	H	H	H	39
i	COOEt	H	Me	H	H	64
j	COOEt	H	H	Me	H	64
k	COOEt	H	Me	H	Me	80
l	$CONH_2$	H	H	H	H	36
m	CN	H	H	H	H	64

Although considerable research has been carried out on the synthetic chemistry of these betaine compounds, little has been published concerning their crystal structures. The pyridinium betaine N^+-C(5) bond length is 1.470 Å. The intermolecular S^-....N^+ distance is 2.937 Å [78].

The 2,6-Dimethylpyridinium salt (**158n**) is allowed to react with carbon disulfide in the presence of sodium hydroxide and subsequently methylated with dimethylsulfate to give methyl 5-methyl-2-hydroxyindolizine-3-dithiocarboxylate (**161**). Similarly, methyl 2-hydroxyimidazo[1,2-*a*]-pyridine-3-dithiocarboxylate (**162**) is prepared by reaction of the corresponding 2-aminopyridinium salts **158o** with carbon disulfide followed by methylation with dimethylsulfate in 90% yield [79].

The reaction of **160e, g-j** with active methylene compounds (malononitrile, methyl cyanoacetate) in the presence of triethylamine as a base gives the corresponding pyridinium allylides **163a-h** in good yields, accompanied with ring opened byproducts [80,81]. We have also reported that the ketene dithioacetals bis(methylthio)methylenemalononate or methyl bis(methylthio)methylenecyanoacetate yield the corresponding pyridinium allylides, (**163**) when allowed to react with a pyridinium *N*-ylide [82].

Scheme 36

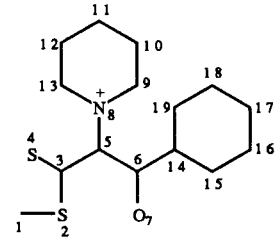


Table 3. Bond lengths (Å)
Standard deviations are in parentheses.

C(1)-S(2)	1.802(3)	C(9)-C(10)	1.374(5)
S(2)-C(3)	1.767(3)	C(10)-C(11)	1.382(6)
C(3)-S(4)	1.686(3)	C(11)-C(12)	1.378(6)
C(3)-C(5)	1.405(3)	C(12)-C(13)	1.374(5)
C(5)-C(6)	1.414(5)	C(14)-C(15)	1.385(5)
C(5)-N(8)	1.470(3)	C(14)-C(19)	1.392(5)
C(6)-O(7)	1.246(4)	C(15)-C(16)	1.394(5)
C(6)-C(14)	1.516(4)	C(16)-C(17)	1.369(6)
N(8)-C(9)	1.357(4)	C(17)-C(18)	1.375(6)
N(8)-C(13)	1.347(4)	C(18)-C(19)	1.393(4)

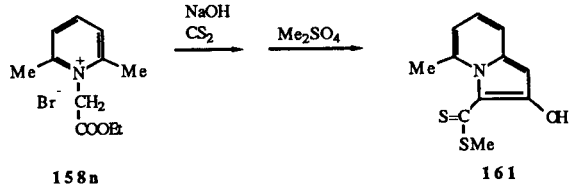
Table 4. Bond angles (°)
Standard deviations are in parentheses.

C(1)-S(2)-C(3)	103.1(O)	N(8)-C(9)-C(10)	120.7(3)
S(2)-C(3)-S(4)	121.2(2)	C(9)-C(10)-C(11)	118.9(3)
S(2)-C(3)-S(4)	116.1(2)	C(10)-C(11)-C(12)	119.7(3)
S(4)-C(3)-C(5)	122.8(2)	C(11)-C(12)-C(13)	120.0(3)
C(3)-C(5)-C(6)	127.7(3)	N(8)-C(13)-C(12)	119.9(3)
C(3)-C(5)-N(8)	114.7(2)	C(6)-C(14)-C(15)	119.6(2)
C(6)-C(5)-N(8)	117.4(2)	C(6)-C(14)-C(19)	120.6(3)
C(5)-C(6)-O(7)	122.2(3)	C(15)-C(14)-C(19)	119.3(3)
C(5)-C(6)-C(14)	120.5(2)	C(14)-C(15)-C(16)	119.9(3)
O(7)-C(6)-C(14)	117.3(3)	C(15)-C(16)-C(17)	120.6(4)
C(5)-N(8)-C(13)	120.5(2)	C(16)-C(17)-C(18)	119.8(3)
C(5)-N(8)-C(9)	118.2(2)	C(17)-C(18)-C(19)	120.4(3)
C(9)-N(8)-C(13)	120.8(2)	C(14)-C(19)-C(18)	119.9(4)

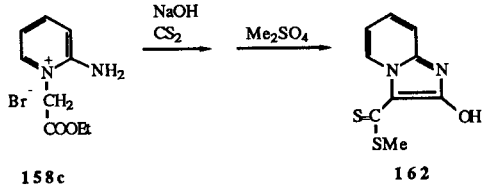
Table 5. Deviations (Å) from least-squares planes
Deviations of atoms not included in the calculations are given in parentheses.

	Plane A	Plane B	Plane C
C(1)	(-0.189)		
S(2)	-0.028		
C(3)	0.027	(1.512)	
S(4)	0.099		
C(5)	0.005	(0.175)	(0.900)
C(6)	0.007	(-0.992)	(-0.185)
O(7)	-0.039		(-1.320)
N(8)	-0.108	-0.001	
C(9)	(-1.348)	-0.002	
C(10)		-0.002	
C(11)		-0.008	
C(12)		-0.011	
C(13)	(0.993)	-0.007	
C(14)	0.065		-0.001
C(15)	(-1.057)		-0.007
C(16)			-0.008
C(17)			-0.002
C(18)			-0.007
C(19)	(1.274)		-0.008

Scheme 37

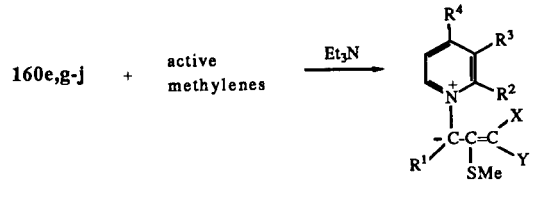


158n 161



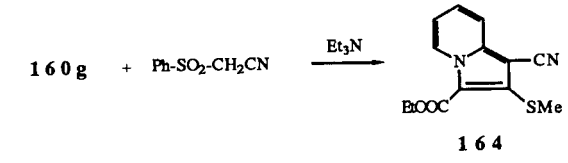
158c 162

Scheme 38

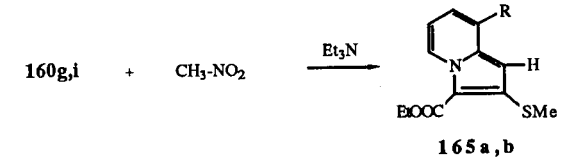


163a-h

No.	R^1	R^2	R^3	R^4	X	Y	Yield (%)
163a	COPh	H	H	H	CN	CN	61
b	COPh	H	H	H	CN	COOMe	45
c	COPh	H	H	Me	CN	CN	67
d	COOEt	H	H	H	CN	CN	91
e	COOEt	Me	H	H	CN	CN	73
f	COOEt	H	Me	H	CN	CN	93
g	COOEt	H	H	Me	CN	CN	62
h	COPh	Me	H	Me	CN	CN	36

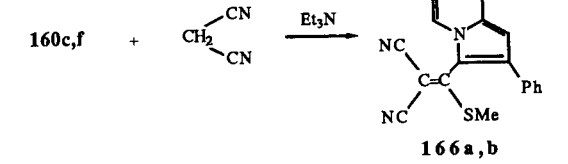


164



165a,b

a: R = H, b = Me



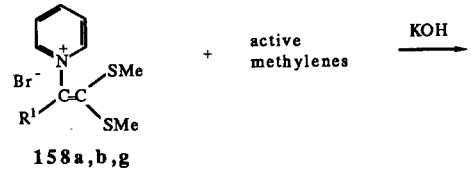
166a,b

a: R = H, b = Me

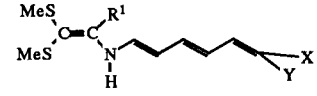
The reaction of **160g** with phenylsulfonylacetonitrile or nitromethane gives indolizine derivatives **164** and **165a,b** which are also prepared by the reaction of sulfonyl of nitro ketene dithioacetals with the corresponding pyridinium salts **158** in the presence of triethylamine as a base [82]. The reaction of 1-[1-benzoyl-2,2-bis(methylthio)ethenyl]-2-methylpyridinium iodides **160c,f** with active methylene compounds (malononitrile, methyl cyanoacetate, phenylsulfonylacetonitrile) gives the corresponding 3-vinylindolizine derivatives **166a,b**.

If potassium hydroxide is used instead of triethylamine when ketene dithioacetals are allowed to react with active methylene compounds (malononitrile, methyl cyanoacetate, cyanoacetamide, phenylsulfonylacetonitrile) only the corresponding ring-opened products **167a-j** are formed in excellent yields [81].

Scheme 39



158a,b,g



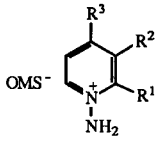
167a-j

No.	R^1	X	Y	Yeild (%)
167a	H	CN	CN	95
b	H	CN	$CONH_2$	87
c	H	CN	COOMe	45
d	H	CN	SO_2-Ph	99
e	COPh	CN	CN	93
f	COPh	CN	COOEt	45
g	COOEt	CN	CN	67
h	COOEt	CN	COPh	65
i	COOEt	CN	SO_2-Ph	84
j	COOEt	CN	$CONH_2$	87

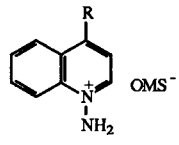
The reaction of **160b-k,m** with 1-aminopyridinium mesitylenesulfonates **168a-n**, **169a,b**, and **170** in the presence of triethylamine as a base in ethanol gives the corresponding 2-methylthiopyrazolo[1,5-*a*]pyridines **172a-d** and 2-methylthioimidazo[1,2-*a*]pyridine **173a-e** in a ratio as shown in Scheme 41. A possible reation mechanism for the formation of **172** and **173** is shown in Scheme 44. The reaction of benzoyl compound **160b** with the *N*-imine **168a** under the same conditions gives only 3-benzoyl-2-methylthioimidazol[1,2-*a*]pyridine **173b** [83,84].

The reaction of ketene dithioacetals **160b,g,m** with substituted pyridinium *N*-imines **168g,h,i,l,m,n**, substituted with electron withdrawing groups (CN, $CONH_2$, $CONEt_2$, COOMe) on the pyridine ring, gives only pyrazolo[1,5-*a*]-pyridine derivatives **174-k** in good yields. This is due to more efficient electron withdrawing the 2-position on the

Scheme 40

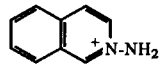


168a-n

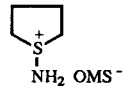


169a,b

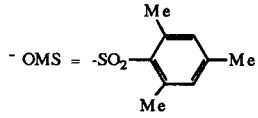
a: R = H
b: R = Me



170



171



No.	R^1	R^2	R^3
168a	H	H	H
b	Me	H	H
c	H	Me	H
d	H	H	Me
e	H	OH	H
f	H	NH_2	H
g	H	$CONH_2$	H
h	H	$CONET_2$	H
i	H	CN	H
j	H	COOMe	H
k	H	COOEt	H
l	H	H	$CONH_2$
m	H	H	COOEt
n	H	H	CN

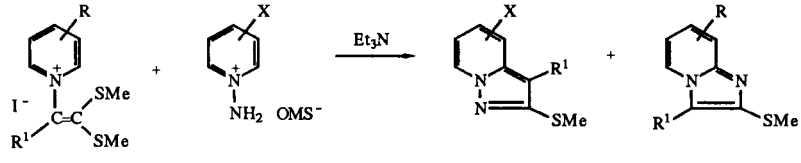
pyridine ring.

The reaction of **160k** with **169a** gives only pyrazolo[1,5-*a*]quinoline derivatives **175** in 87% yield. Under the same conditions the reaction of **160k** with **170** also affords pyrazolo[5,1-*a*]isoquinoline **176** in 94% yield.

In an attempt to obtain only the imidazo[1,2-*a*]pyridines, we tried to use the *S*-imine derivatives as an inset component nitrogen atom. Reaction of ketene dithioacetals **160g,i,k,m** with various *S*-imines (**171**) gives imidazo[1,2-*a*]pyridines **173a,d,e,f.** The 1,5-dipolar cyclization of pyridinium ketene dithioacetals with *S*-imines offers a direct and efficient synthesis of imidazo[1,2-*a*]pyridine derivatives and opens the way to the various annelated imidazoles [84].

1-Azacycl[3.2.2]azine is an aromatic compound involving delocalized 10π-electrons similarly to cycl[3.2.2]azines [85-87]. The synthesis of cycl[3.2.2]azines by the [2 + 8] cycloaddition reaction of indolizines with various acetylenic compounds is a particularly convenient and general method; it has recently been disclosed that di-

Scheme 41

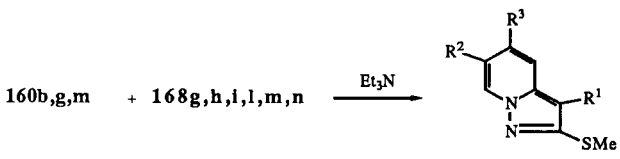


160 168 172a-d 173a-e

Entry	Starting material KDTA	NI	Product	R^1	M	X	R	Ratio PP IP (Yield %)
1	160	168a	172a + 173a	COOEt		H	H	81:19 (83)
2	160b	168a	172b + 173b	COPh		H	H	0:100 (53)
3	160m	168a	172c + 173c	CN		H	H	50:50 (93)
4	160g	168e	172d + 173d	COOEt		4-OH	H	42:58 ( )
5	160k	168e	172e + 173d	COOEt		4-OH	6,8-Me_2	68:32 (42)
6	160g	168f	172e + 173a	COOEt		4-NH_2	H	45:55
7	160k	168f	172e + 173d	COOEt		4-NH_2	6,8-Me_2	68:32 (37)
8	160g	168d	172f + 173a	COOEt		5-Me	H	57:43
9	160j	168a	172a + 173e	COOEt		H	7-Me	98:2 (65)
10	160k	168a	172a + 173d	COOEt		H	6,8-Me_2	99:1 (91)

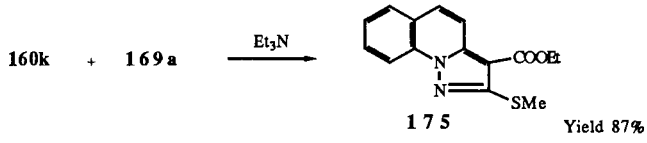
pp: Pyrazolo[1,5-*a*]pyridine; Ip: Imidazo[1,2-*a*]pyridine; KDTA: Ketene dithioacetal; NI: *N*-Imine product ratio determined by glc; ( ) Isolated yield.

Scheme 42

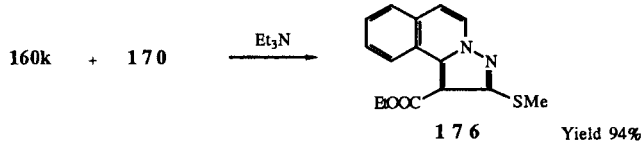


174a-k

No.	R^1	R^2	R^3	Yield (%)
174a	COOEt	H	$CONH_2$	52
b	COOEt	H	CN	40
c	COPh	H	COOEt	44
d	COOEt	$CONH_2$	H	86
e	COOEt	CN	H	61
f	COOEt	$CONEt_2$	H	64
g	CN	$CONH_2$	H	64
h	COPh	$CONH_2$	H	27

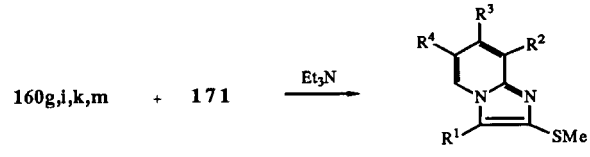


175 Yield 87%



176 Yield 94%

Scheme 43



173a,d,e,f

No.	R^1	R^2	R^3	R^4	Yield (%)
173a	COOEt	H	H	H	25
d	COOEt	Me	H	Me	6
e	COOEt	H	Me	H	24
f	CN	H	H	H	32

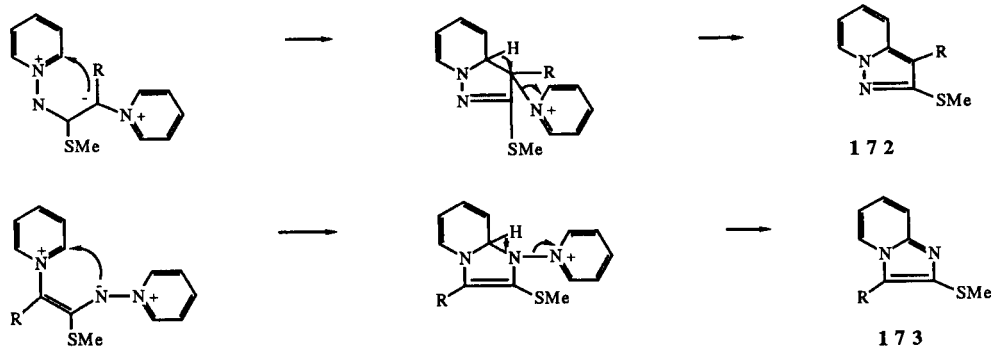
methyl acetylenedicarboxylate (DMAD) reacts with iodolizines in the presence of a dehydrogenating reagent to give cycl[3.2.2]azine derivaties [87]. Some azacycl[3.2.2]azines derivatives are also prepared by a [2 + 8] cycloaddition reaction [88]. However, the reaction of DMAD with azaindolizines, which are not substituted on the five-membered ring, does not give the desired cyclazine derivatives. This limits the above reaction. Therefore, in an extension of this cycloaddition reaction, appropriate 2-substituted imidazo[1,2-*a*]pyridine derivatives with substituents which may be removed after the cycloaddition reaction should be chosen. Thus 2-methylthioimidazo[1,2-*a*]pyridine is the most suitable starting material for the synthesis of 1-azacycl[3.2.2]azines.

Deesterification of **173a,d** using sodium hydroxide in methanol followed by treatment with polyphosphoric acid (PPA) gives the corresponding 2-methylthioimidazo[1,2-*a*]-pyridine **177a,b** in good yield. The reaction of **177a,b** with DMAD in boiling toluene in the presence of palladium on charcoal gives a cyclized product, dimethyl 2-methylthio-1-azacycl[3.2.2]azine-3,4-dicarboxylate (**178a**), in 36% yield. Hydrolysis of **178a** using sodium hydroxide in methanol followed by acidification with 10% hydrogen chloride gives the corresponding diacid. Decarboxylation of the diacid is conducted by copper chromate in boiling diphenyl ether to afford 2-methylthio-1-azacycl[3.2.2]azine (**179a**) in 42% yield. The desulfurization of **179a** with Raney-nickel in ethanol solution occurs smoothly to give the desired parent 1-azacycl[3.2.2]azine (**180a**) in 34% yield. 5,6-Dimethyl-1-azacycl[3.2.2]azine (**180b**) is also synthesized in good yield from 2-methylthio-6,8-dimethylimidazo[1,2-*a*]pyridine (**173b**) in a similar manner to that described for **180a**. This compound forms a very stable yellow needles, mp 106° [89].

B. Synthesis and Reactions of Ketone Dithioacetals Having Isoquinolinium Salts.

Ketene dithioacetal, 2-[1-ethoxycarbonyl-2,2-bis(methylthio)ethenyl]isoquinolinium iodides **183a,b** are prepared

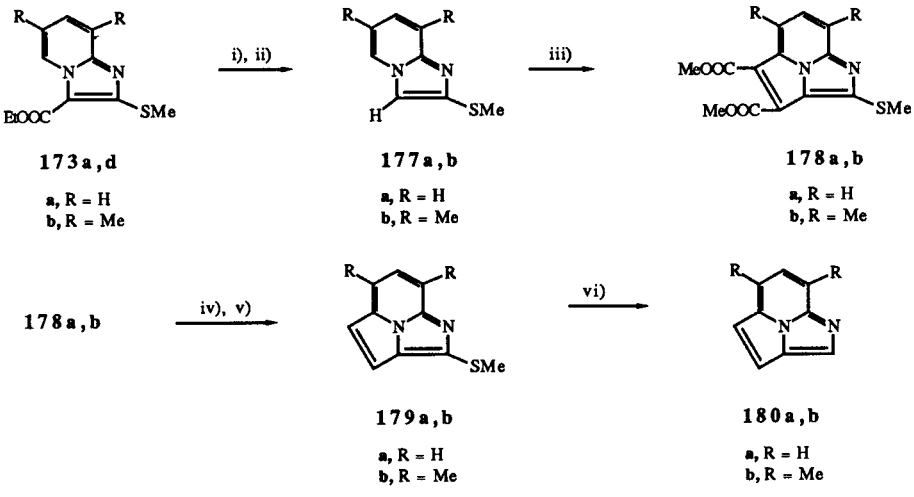
Scheme 44



172

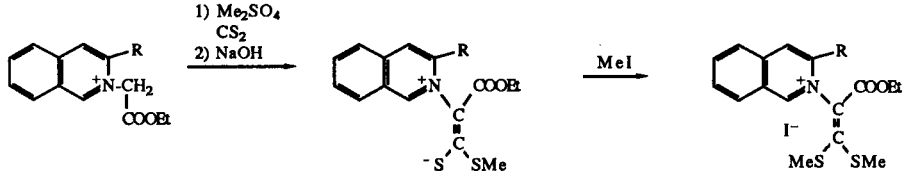
173

Scheme 45

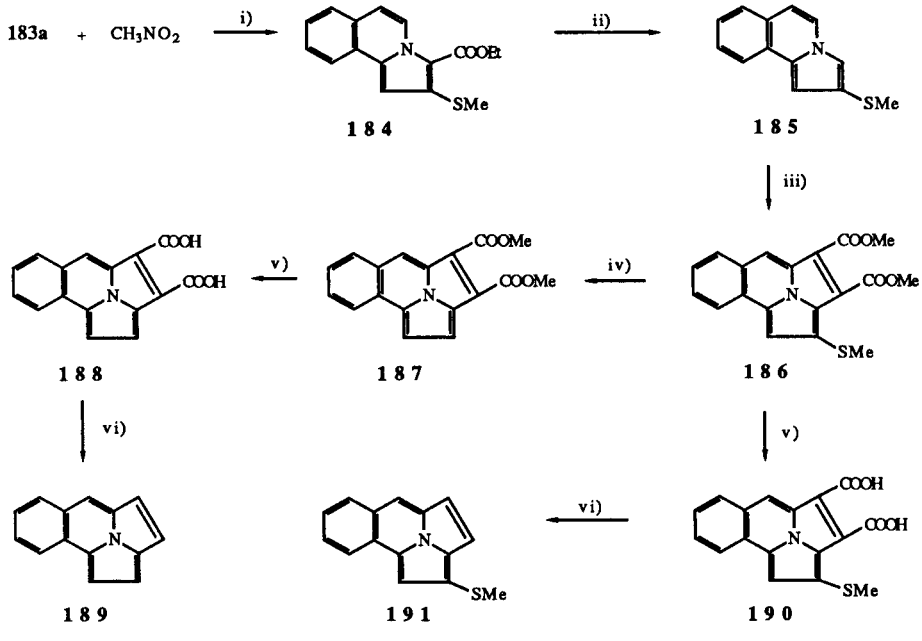


i) NaOH; ii) PPA; iii) DMAD; iv) NaOH, HCl; v) $CuCrO_4$; vi) Raney-nickel in ethanol.

Scheme 46



Scheme 47



i) Et_3N; ii) NaOH, PPA; iii) DMAD, 5% Pd-C; iv) Raney-Ni; v) NaOH; vi) $CuCrO_4$.

from the corresponding isoquinolinium salts **181a,b** as follows: a solution of sodium hydroxide is added portionwise to a solution of the 2-ethoxycarbonylmethylisoquinolinium bromide **181a,b**, an excess of carbon disulfide, and dimethyl sulfate in ethanol at room temperature under stirring to yield the corresponding methyl dithiocarboxylate derivatives **18a,b**. The methylation of **182a,b** with methyl iodide in ethanol gives the desired ketene dithioacetal **183a,b** in good yields [89,90].

C. Synthesis of Benzo[*g*]cycl[3.2.2]azine and 1-Azabenzo[*h*]cycl[3.2.2]azine.

Recently, considerable effort has been made to rationalize the effects of benzo-fusion on aromatic annulenes. It is generally recognized that benzannelation reduces the diatropicity or papratropicity of the macrocyclic system. The reasons for this are explained in terms of increased bond localizations in the macrocyclic ring [91-93].

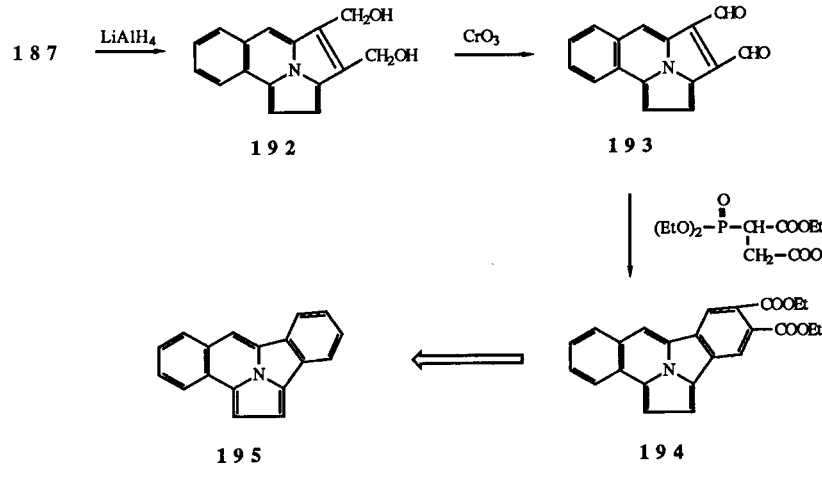
The reaction of **183a** with nitromethane in the presence of triethylamine as a base in ethanol gives the corresponding ethyl 2-methylthiopyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**184**). Hydrolysis and subsequent decarboxylation of **184** occurred smoothly to give **185**, a key intermediate for the synthesis of **189**, in 91% yield. The [2 + 8] cycloaddition reaction of **185** with DMAD in the presence of a 5% palladium-on-charcoal as a dehydrogenation catalyst under refluxing for 30 hours in toluene gives an expected cyclized product in 27% yield. The desulfurization of **186** with Raney-nickel occurs readily to give dimethylbenzo[*g*]cycl[3.2.2]azine-3,4-dicarboxylate (**187**) in 44% yield. Hydrolysis of the diester **187** with 10% sodium hydroxide proceeds essentially quantitatively. Decarboxylation of the diacid using copper chromate in quinoline occurs smoothly to produce the desired benzo[*b*]cycl[3.2.2]azine (**189**) in 45% yield. Similarly, 2-methylthiobenzo[*b*]cycl[3.2.2]-azines (**191**) is synthesized from **190** in 22% yield. The benzocyclazine **189** and **191** have a sweet smell like naphthalene and are a stable crystalline solids of bright yellow leaflets [90,94].

The Wittig reaction of compound **193**, which is prepared by the reduction of **187** with lithium aluminum hydride followed by oxidation with chrominium oxide-pyridine complex, with diethyl (diethoxyphosphinyl)succinate gives diethyl dibenzo[*a,g*]cycl[3.2.2]azine-4,5-dicarboxylate (**194**). The decarboxylation of **194** may give the corresponding parent dibenzo[*a,g*]cycl[3.2.2]azine (**195**) [52].

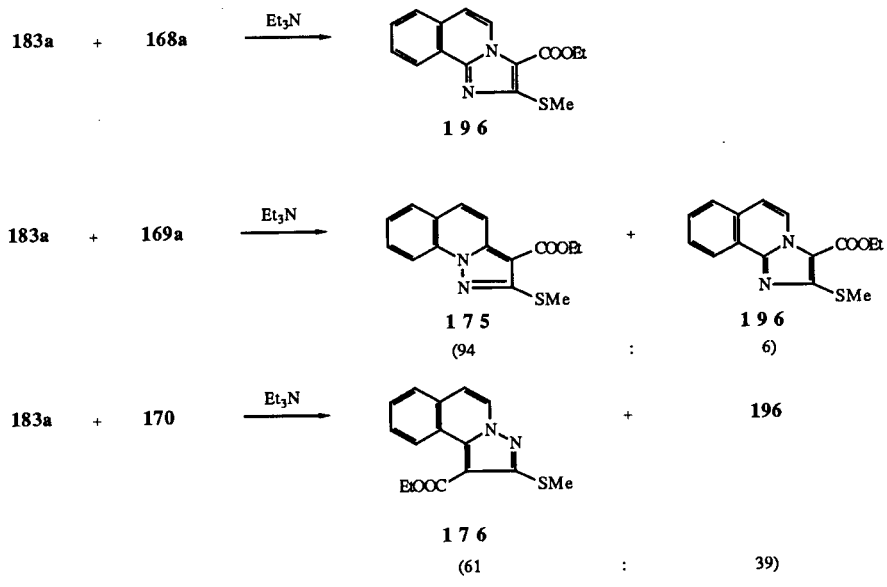
Reaction of **183a** with *N*-imine (**168a**) gives only the corresponding only imidazo[2,1-*a*]isoquinoline (**196**) in 66% yield. The corresponding pyrazolo[1,5-*a*]pyridine is not obtained in this reaction. It is suggested that the 1-position of the isoquinolinium ring are more reactive than the 2-position of the pyridinium ring. The reaction of **183a** with **169a** gives the corresponding two products, **175** and **196**, in a ratio of 94:6. When **183a** reacts with isoquinolinium *N*-imine **170**, a mixture of **176** and **196** is obtained in a ratio of 61:39 [84].

Hydrolysis of **196** with sodium hydroxide in methanol to give the corresponding carboxylic acid and subsequent decarboxylation of the diacid by heating in polyphosphoric acid gives the desired compound **197**. A solution of **197** and DMAD in toluene is refluxed for 30 hours using 5% palladium-on-charcoal as a dehydrogenation catalyst to give the expected product (**198**). Hydrolysis of **198** with 10% sodium hydroxide gives the corresponding diacid **199** almost quantitatively. Decarboxylation of **199** occurs smoothly on heating with copper chromate in diphenyl ether to produce 2-methylthio-1-azabenzo[*h*]cycl[3.2.2]-azine (**200**) in 34% yield. Finally, the desulfurization of **200** is easily effected with Raney-nickel to afford the desired parent compound, **201** in 15% yield. Compounds **200** and **201** are typical aromatic compounds [95].

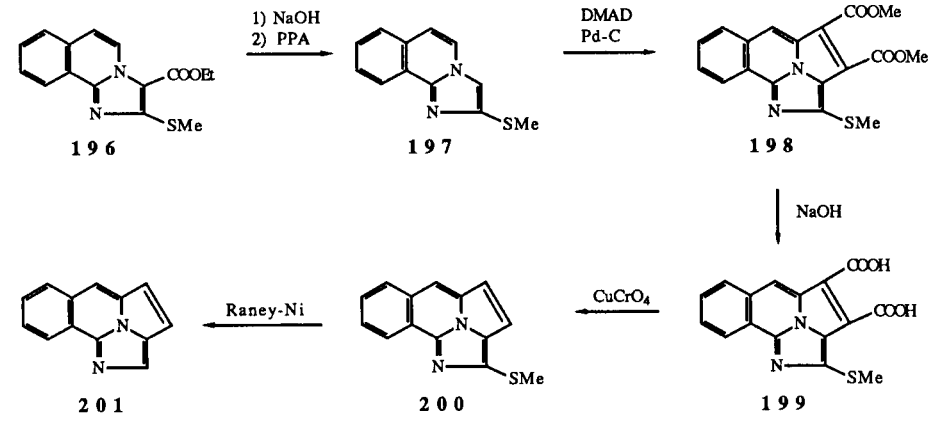
Scheme 48



Scheme 49



Scheme 50



D. Synthesis and Reaction of 3-Ethoxycarbonyl-2-methylthiothiazolo[2,3-*a*]isoquinolinium Sulfate.

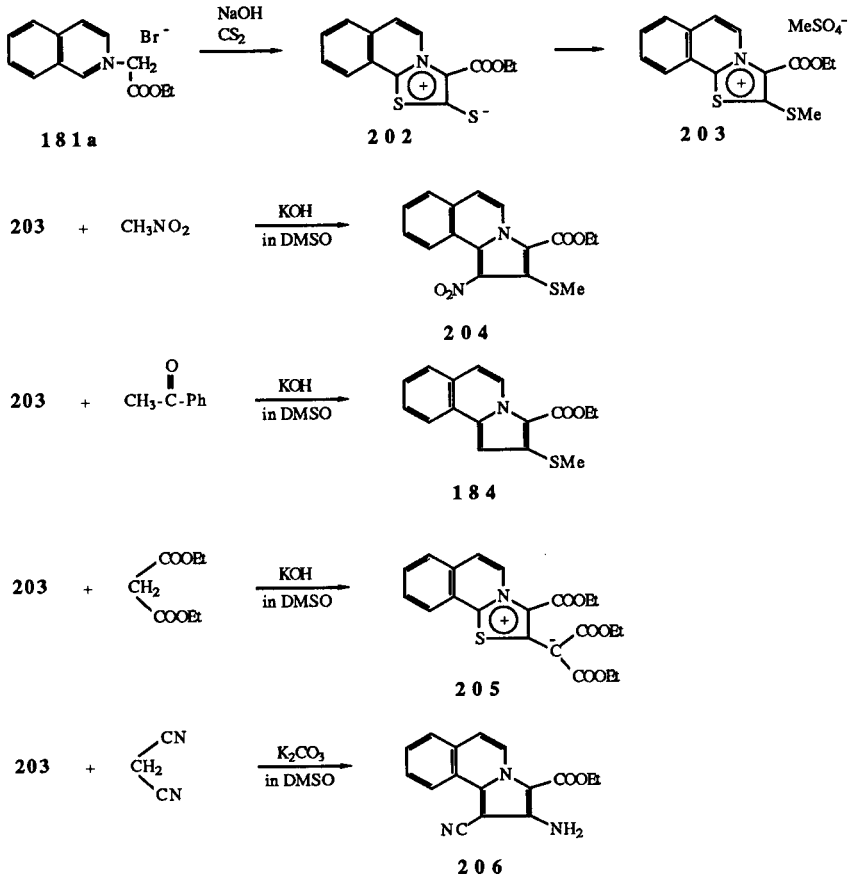
There have been many reports on the syntheses and reactions of mesoionic compounds since Earl and Mackney found that treatment of *N*-nitroso-*N*-phenylglycine with acetic anhydride gives an anhydro compound, sydnone, by intramolecular dehydration [96]. A review of these results was published by Ohta and Kato [97].

Concerning the synthesis of 3-acylthiazolo[2,3-*a*]isoquinolium-2-thione, Krohnke, *et al.* [98], had already reported a method of treatment of *N*-acylisoquinolinium salts with carbon disulfide in the presence of a base and also the alkylation of mesoionic compounds. It has been reported that the reaction of 3-(*p*-nitrophenyl)-2-methylthiothiazolo-[2,3*a*]isoquinolinium iodide with amines produced mesoionic imidazo[2,1-*a*]isoquinoliniumthiones, substituted with a methylthio group [99]. However, there was no report on the reaction of 3-acyl-2-methylthiothiazolo-[2,3-*a*]isoquinolinium salt with active methyl and methylene compounds except for the analogous reaction of 2-methylthio-1,3,4-triazolo[5,1-*a*]isoquinolinium iodide with active methylene compounds.

N-Ethoxycarbonylmethyleneisoquinolinium bromide (**181a**) is allowed to react with carbon disulfide to give 3-ethoxycarbonylthiazolo[2,3-*a*]isoquinolinium-2-thione (**202**). Treatment of **202** with dimethylsulfate gives 3-ethoxycarbonyl-2-methylthiothiazolo[2,3-*a*]isoquinolinium sulfate hydrate (**203**) in 95% yield [100,101].

The reaction of **203** with active methylene compounds such as nitromethane and acetophenone in the presence of

Scheme 51

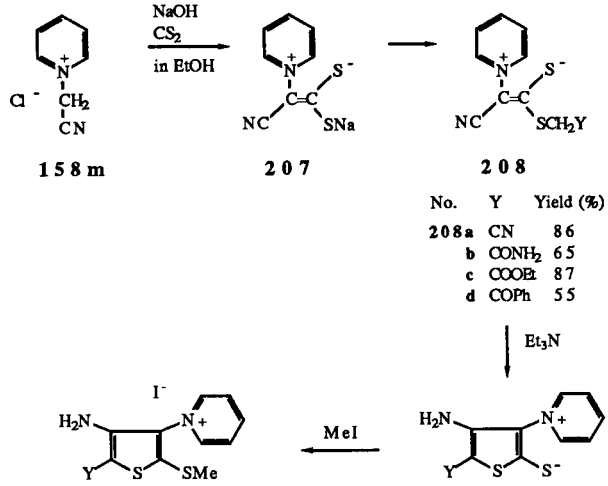


powdered potassium hydroxide produced ethyl 2-methylthio-1-nitropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**204**) and ethyl 2-methylthiopyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**184**) with opening of the thiazole ring and formation of a pyrrole ring. In a similar reaction, treatment of **203** with diethyl malonate gives the mesoionic compound (**205**), which is substituted with a methylthio group at the 2-position of **203**. The reaction of **203** with malononitrile in the presence of potassium carbonate in dimethyl sulfate afforded in a similar cyclized product, 2-amino-1-cyano-3-ethoxycarbonylpyrrolo[2,1-*a*]isoquinoline (**206**) [102].

E. Synthesis of 3,4-Diaminothiophenes.

Aromatic *o*-diamines are useful synthetic intermediates [102]. They are easily tranformed into a variety of condensed heterocyclic systems. We have reported the synthesis of heterocyclic diamines, 3,4-diaminothiophenes, by using the ring opening reaction of the pyridine ring in 3-aminotrien-4-ylpyridinium iodides [103,104]. Generally, 3,4-diaminothiophenes are obtained by the reduction of 3,4-dinitrothiophenes as very labile compounds. Gompper has reported the synthesis of thiophene using ketene di-

Scheme 52

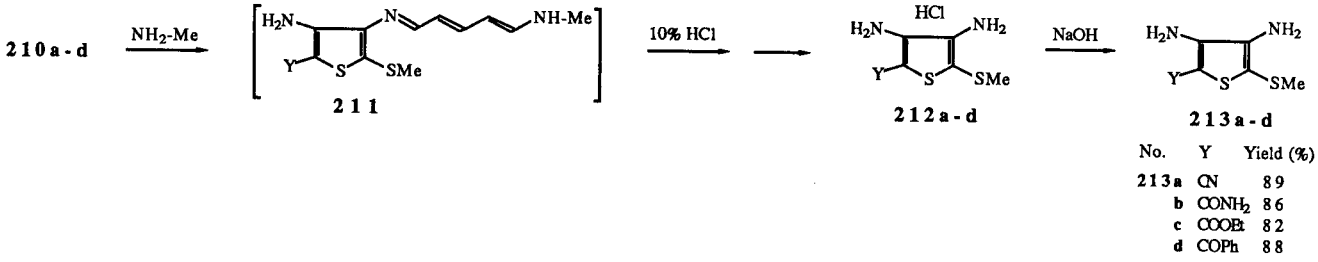


No.	Y	Yield (%)
208a	CN	86
b	$CONH_2$	65
c	COOEt	87
d	COPh	55

No.	Y	Yield (%)
210a	CN	86
b	$CONH_2$	88
c	COOEt	82
d	COPh	88

No.	Y	Yield (%)
209a	CN	87
b	$CONH_2$	77
c	COOEt	95
d	COPh	90

Scheme 53



No.	Y	Yield (%)
213a	CN	89
b	$CONH_2$	86
c	COOEt	82
d	COPh	88

thioacetals as an intemediate. We have reported that the reaction of a pyridinium ylide with carbon disulfide afforded various stable pyridinium ylides containing (methylthio)thiocarbonyl group in good yield as shown in this chapter. The synthesis of 3,4-diaminothiophene is accomplished by the application of Gompper's and our own methods.

Condensation of 1-cyanomethylpyridinium chloride (**158m**) with carbon disulfide in the presence of sodium hydroxide in ethanol yielded a sodium salt of the dithiocarboxylate **207** which reacts with 1 molar equivalent of chloroacetonitrile to give **208a**. This compound undergoes a Thorp-Ziegler cyclization by refluxing in the presence of triethylamine in ethanol to give 4-amino-5-cyano-3-(1-pyridinio)thiophene-2-thiolate (**209a**) in 85% yield. Similarly, treatment of **207** with other alkylating agents (α-chloroacetamide, ethyl α-bromoacetate, or α-bromoacetophenone) produced the dithiocarboxylates **208b-d** which undergo the Thorp-Ziegler type cyclization to give thiophene derivatives **209b-d** in a good yield. Compound **209a-d** are easily methylated with methyl iodides to yield the pyridinium salts **210a-d** in good yields [103,104].

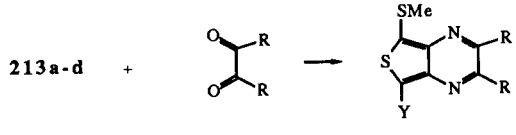
A number of ring-opening reactions of the pyridine ring by amines have been reported [105]. We examined the synthesis of 3,4-diaminothiophenes by ring cleavage of pyridinium salts by methylamine. Pyridinium salts **210a-d** react with methylamine. Treatment of the reaction mixture with 10% hydrochloric acid solution gives 3,4-diamino-2-(methylthio)thiophene mono hydrochlorides **212a-d**, which are neutralized by alkali to yield free 3,4-diaminothiophenes **213a-d** in good yield [103-104].

A variety of quinoxaline derivatives have been prepared for the characterization of aromatic *o*-diamines [106]. This method is widely used because product formation generally takes place very readily in good yield, and the products are readily isolated as crystalline compounds.

Imoto reported the synthesis of 2,3-diphenylthieno-[3,4-*b*]pyrazine by the condensation of 3,4-diaminothiophenes, which are obtained from 3,4-dinitrothiophenes by reduction with tin and hydrochloric acid, with benzil [107]. We examined the synthesis of thieno[3,4-*b*]pyrazine out of synthetic and pharmaceutical interest. Namely, 2-(methylthio)thieno[3,4-*b*]pyrazines **214a-g** are prepared in good yield by the condensation of 3,4-diamino-2-(methylthio)-thiophenes **213a-d** with 1,2-dicarbonyl compounds (glyoxal, diactyl, benzil). The reaction progresses very smoothly by refluxing in ethanol or heating at 100°.

The reaction of 5-substituted (a = CN, b = COOEt, c = COPh, d = $CONH_2$) 3,4-diamino-2-methylthiothiophenes **213a** with 1,3-dicarbonyl compounds (methyl acetoacetate, diethyl acetonedicarboxylate, diketene, ethyl benzoylacetate) gives the corresponding thieno[3,4-*b*][1,4]-diazepine derivatives **216**, **217**, and **218**. The condensation of **213** with ketene dithioacetal derivatives [2-bis-(methylthio)methylene-1,3-indandione, 3,3-bis(methylthio)-1-(*p*-substituted-phenyl)-2-propen-1-one (**219a** = *p*-H, **b** = *p*-Cl, **c** = *p*-Br) affords the corresponding diazepine derivatives **220a-c** as shown in Scheme 53 [108, 109].

Scheme 54

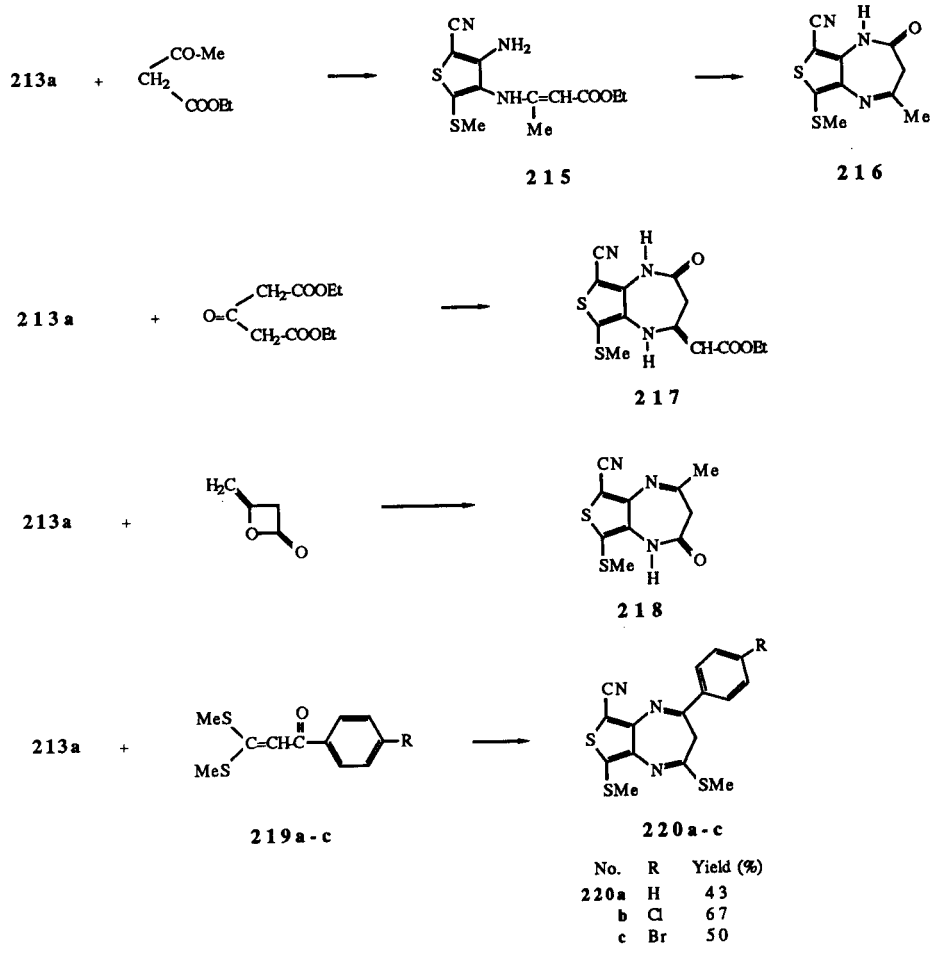


No.	Y	R	Yield (%)
214a	CN	H	97
b	CN	Me	64
c	CN	Ph	56
d	COOEt	H	95
e	COOEt	Ph	52
f	COPh	H	89
g	$CONH_2$	H	67

VI. Reaction of Cyanomethyl Heterocyclic Compounds with Carbon Disulfide.

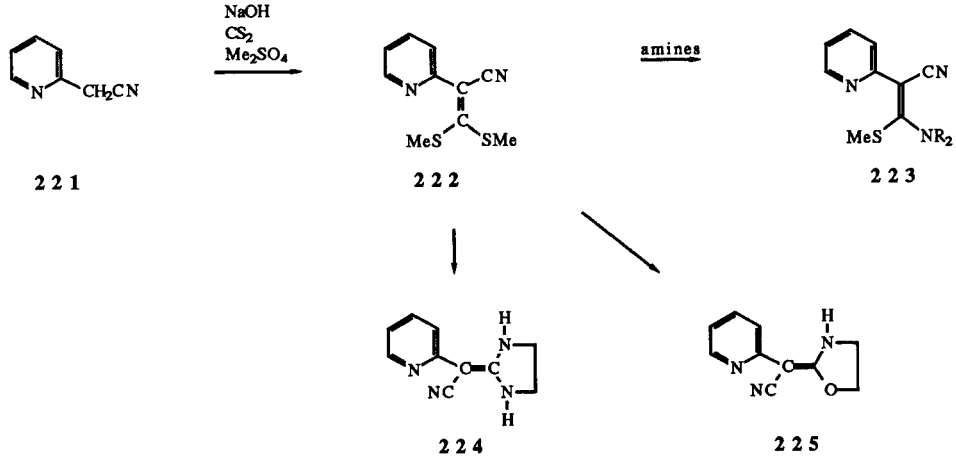
It is well known that the reaction of active methylene compounds with carbon disulfide followed by methylation with alkyl reagents in the presence of the appropriate base gives the corresponding ketone dithioacetals. These are versatile reagents for the synthesis of heterocyclic compounds [54,55,76]. Arylacetonitrile also reacts with carbon disulfide to give the corresponding β-aryl ketene dithioacetals. However, these ketene dithioacetals do not react as readily with nucleophilic reagents such as active methylene compounds. Displacement with hydrazine hydrate

Scheme 55



No.	R	Yield (%)
220a	H	43
b	Cl	67
c	Br	50

Scheme 56



gives the pyrazole derivatives [110]. However, some β-cyano-β-heteroarylketene dithioacetal derivatives react readily the nucleophiles such as amine or active methylene compounds.

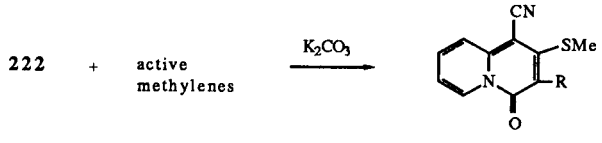
A. Synthesis and Reactions of Bis(methylthio)methylene-2-pyridylacetonitrile.

Bis(methylthio)methylene-2-pyridylacetonitrile (**222**) is prepared by the reaction of 2-pyridylacetonitrile (**221**) with

carbon disulfide in the presence of sodium hydride followed by methylation with dimethyl sulfate. This compound **222** reacts with amines to give the corresponding replacement products (**223**, **224**, and **225**) of one or two methylthio groups in good yield [111].

Compound **222** is allowed to react with active methylene compounds (methyl cyanoacetate, ethyl acetoacetate, dimethyl malonate, diethyl malonate ethyl 2-pyridineacetate, ethyl benzylacetate, dimethyl homophthalate, ethyl *o*-toluenesulfonylacetate, and methyl *o*-nitrophenylacetate) to give 2-methylthio-4*H*-quinolizin-4-one derivatives **226a-i**, in 40-85% yields [112]. Ethyl 2-methylthio-3-cyano-4-oxoquinolizine-1-carboxylate is used as starting material for a new method of synthesis of allomatridine [113].

Scheme 57

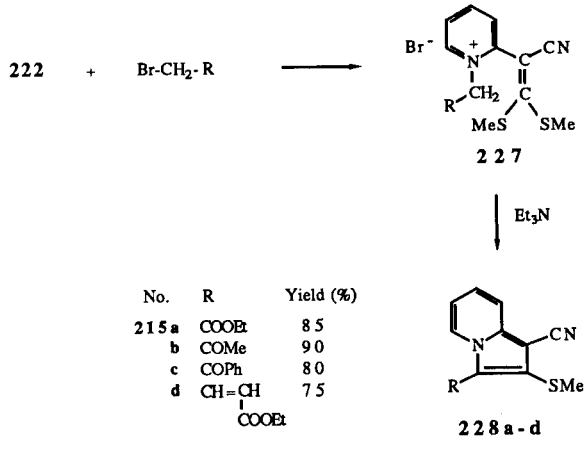


226a-i

No.	R	Yield (%)
226a	CN	61
b	COMe	45
c	COOMe	85
d	COOEt	70
e	2-pyridyl	50
f	COPh	40
g	Ph-COOMe(*o*)	50
h	SO_2-Ph-Me(*o*)	60
i	Ph-NO_2(*o*)	60

When compound **222** is allowed to react with ethyl bromoacetoacetate, followed by treatment with triethylamine, 1-cyano-3-ethoxycarbonyl-3-methylthioindolizine (**228a**) is formed in 85% yield. Other indolizine derivatives **228b-d** are synthesized by the reaction of **222** with corresponding bromo methyl compounds as shown in Scheme 58 [114].

Scheme 58



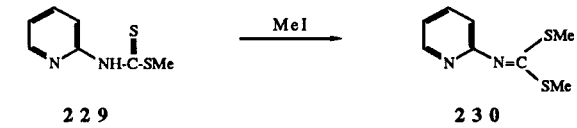
227

228a-d

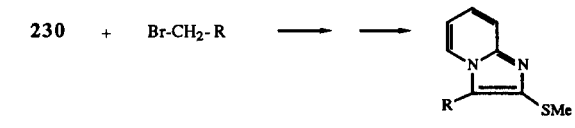
No.	R	Yield (%)
215a	COOEt	85
b	COMe	90
c	COPh	80
d	CH=CH (COOEt)	75

Similarly imidazo[2,1-*a*]pyridine derivatives **173a** and **231a-c**) are prepared from *N*-bis(methylthio)methyl-2-aminopyridine (**230**) with the corresponding bromomethyl compounds in 40-85% yields [114,115]. These imidazo-[2,1-*a*]pyridines are useful intermediates for the synthesis of 1-azacycl[3.2.2]azines [89,116].

Scheme 59



229 **230**

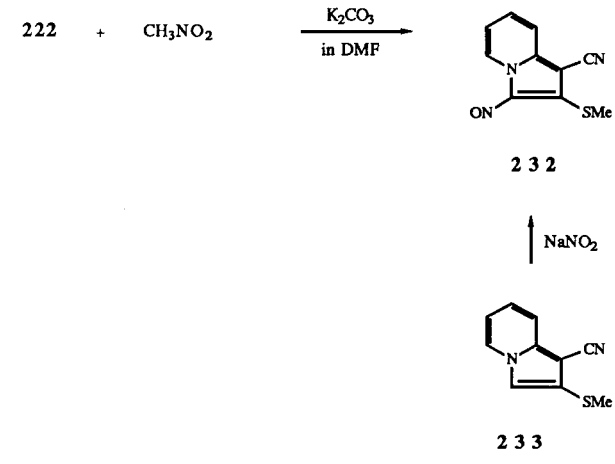


173a, 231a-c

No.	R	Yield (%)
173a	COOEt	80
231a	COMe	85
b	COPh	75
c	CH=CH (COOEt)	75

Reaction of **222** with nitromethane affords 1-cyano-2-methylthio-3-nitrosoindolizine (**232**), which is alternatively synthesized by the nitrosozation of 1-cyano-2-methylthioindolizine (**233**) with sodium nitrate [114].

Scheme 60



232

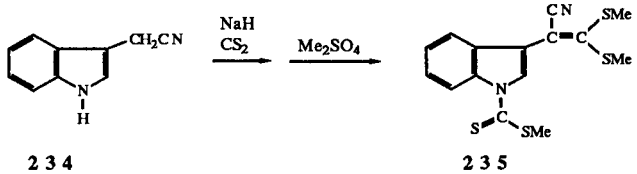
233

B. Reaction of 3-Cyanomethylindole with Carbon Disulfide.

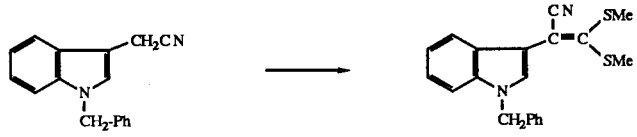
3-Cyanomethylindole (**234**) is allowed to react with carbon disulfide followed by methylation with dimethyl sulfate in the presence of sodium hydride to give 2-[1-methyl-

thio)thiocarbonyl-3-indolyl]-3-bis(methylthio)acrylonitrile (**235**). When 1-benzyl-3-cyanomethylindole (**236**) reacts with carbon disulfide and dimethyl sulfate to yield 1-benzylketene dithioacetal derivatives **237** are formed [117].

Scheme 61



234 **235**

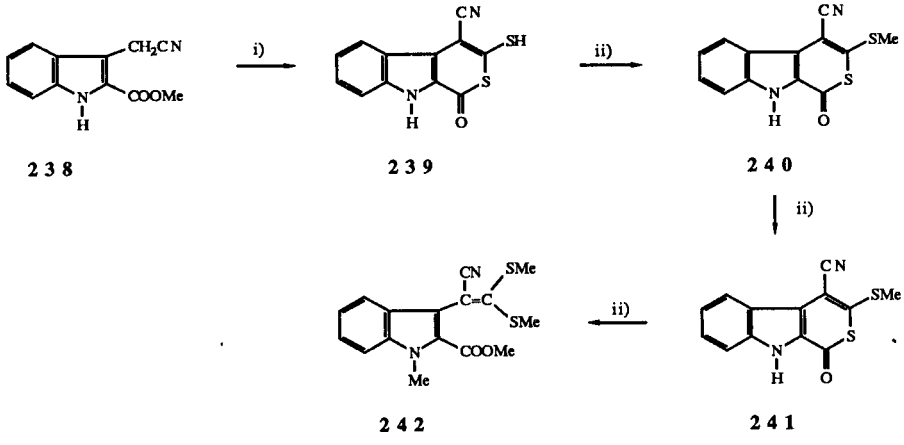


236 **237**

Reaction of methyl 3-cyanomethylindole-2-carboxylate (**238**) with carbon disulfide in the presence of sodium hydroxide gives 4-cyano-3-mercapto-1-oxo-9*H*-thiapyrano-[3,4-*b*]indole (**239**). Methylation with dimethyl sulfate yields 4-cyano-3-methylthio-1-oxo-9*H*-thiapyrano[3,4-*b*]indole (**240**) and the corresponding 9-methyl derivative **241** [118]. Compound **240** is alternatively prepared by the condensation of **238** with trithiocarboxylic acid dimethylester in good yield. Compound **241** is allowed to react with sodium hydroxide to give a ring cleaved product. Methylation with dimethyl sulfate gives ketene dithioacetal, methyl 3-[1-cyano-2,2-bis(methylthio)vinyl]-1-methylindole-2-carboxylate (**242**) in good yield [118].

In the reaction of **240** and **241** with hydrazine hydrate, the ring-cleaved products **243a,b** are formed. Treatment of these with ketones or aldehydes affords cyclized products, 4-cyano-3-mercaptopyrido[3,4-*d*]indole derivatives **245**, which are methylated with dimethyl sulfate to yield 3-methylthio derivatives (**246**). Treatment of **243** with car-

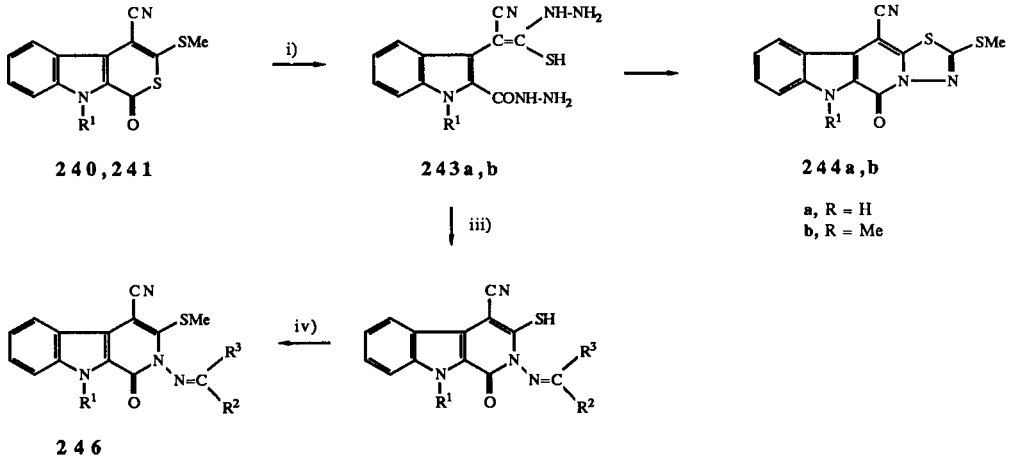
Scheme 62



238 **239** **240** **241** **242**

i) NaOH, CS_2; ii) NaOH, Me_2SO_4.

Scheme 63



240,241 **243a,b** **244a,b**

a, R = H
b, R = Me

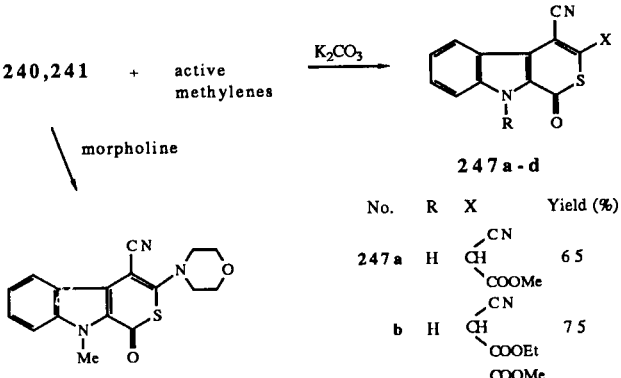
246

i) NH_2-NH_2; ii) NaOH, CS_2; iii) aldehyde or ketones; iv) NaOH, Me_2SO_4.

bon disulfide and dimethyl sulfate results in the formation of a compound with a thiadiazole ring, 11-cyano-2-methylthio-5-oxo-5,6-dihydro-1,3,4-thiazolo[2,3-*b*]harmans (**244a,b**) [118].

Reaction of cyclic ketene dithioacetal **240** or **241** with active methylene compounds (methyl cyanoacetate, ethyl cyanoacetate, and dimethyl malonate) or amine derivatives has been carried out; the corresponding products **247a-d** and **248** are obtained [118].

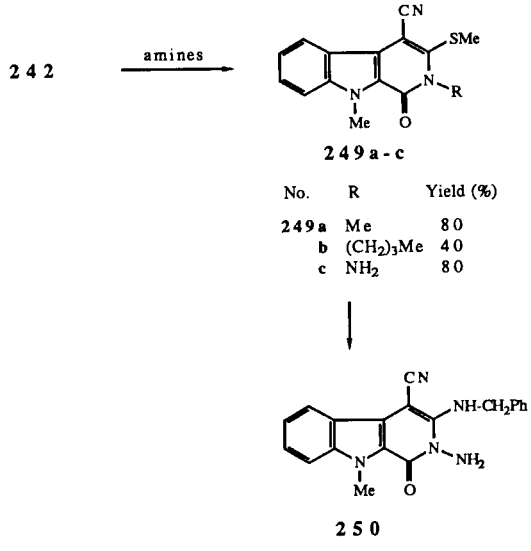
Scheme 64



No.	R	X	Yield (%)
247a	H	CH(CN)COOMe	65
b	H	CH(CN)COOEt	75
c	H	CH(COOMe)COOMe	45
d	Me	CH(CN)COOMe	60
e	Me	CH(CN)COOMe	70

The reaction of **242** with amines (methylamine, butylamine, and hydrazine hydrate) affords β-carboline derivatives **249a-c**. Compound **249c** reacts with benzylamine to yield replacement product **250** of the methylthio group [120].

Scheme 65



No.	R	Yield (%)
249a	Me	80
b	$(CH_2)_3Me$	40
c	NH_2	80

Compound **242** is treated with polyphosphoric acid to give the cyclized, 1,3-dioxo-β-carboline derivative **251**, which is allowed to react with cyclohexylamine to give the corresponding replacement product (**252**). Methylation of **251** with dimethyl sulfate gives **253** which is also obtained by the carbon disulfide treatment of the 1,3-dioxo-β-carboline **254** in the presence of sodium hydride and subsequent alkylation with dimethyl sulfate [120].

C. Synthesis of 3-Methylthio-4-cyanothioisocoumarin Derivatives and Their Reactions.

Carbon disulfide treatment of *o*-methoxycarbonylphenylacetonitrile (**255a**) or dimethyl homophthalate (**255b**), in the presence of sodium hydride, affords mercaptothioisocoumarins **256a,b**. Reaction of **255a,b** with carbon disulfide followed by methylation with dimethyl sulfate, in the presence of sodium hydride, gives 3-methylthioisocoumarins **257a,b**. Reaction of **257** with ethylenediamine, gives the 3-aziridino-4-cyanothioisocoumarin (**258**), which is also formed by the reaction of **244** with diethylaminoethylamine or aminoacetal [120]. Reaction of **257a** with secondary amines (morpholine, piperidine, and pyrrolidine) results in exchange of the methylthio group with an amino group. Further addition of 1 mole of the amine to the cyano group produces 4-iminothioisocoumarins **260** [120]. Cleavage of the thioisocoumarin ring occurs in the reaction of **257a** with hydrazine hydrate. This cleaved compound **261** reacted to form cyclized products **262** and **263** on treatment with alkali, or acetone, or on methylation.

VII. Bis(methylthio)methylene Heterocyclic Compounds.

In a manner similar to the reactivity of ketene dithioacetals, bis(methylthio)methylene substituted heterocyclic compounds are attacked by nucleophilic reagents. Replacement of either one or two methylthio groups attached to the same carbon atoms occurs with such nucleophiles as amines or active methylene compounds. Therefore, these compounds are also very useful for the synthesis of heterocyclic compounds.

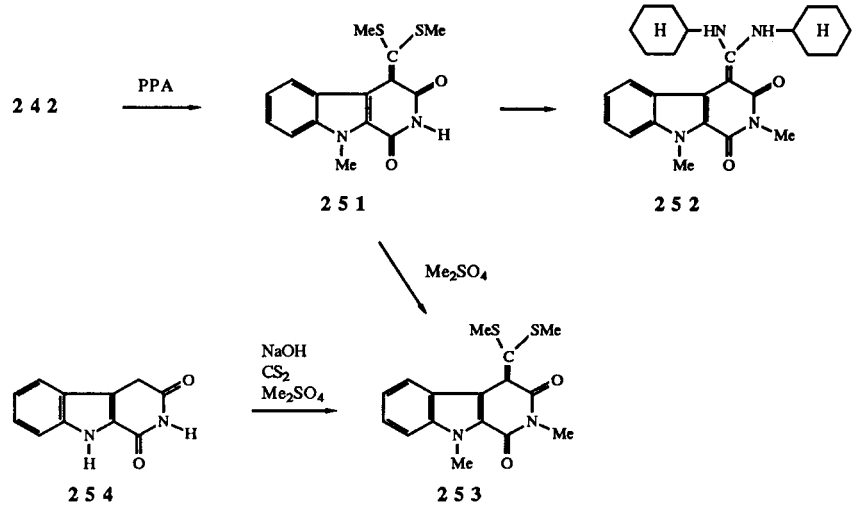
A. Synthesis.

Generally, these bis(methylthio)methylene compounds are prepared by treating the parent compounds in an appropriate solvent with carbon disulfide, followed by methylation with dimethyl sulfate or methyl iodide in the presence of a base such as sodium hydroxide. We have synthesized the following compounds **264-272** [121-128]. Compounds **273-278** have been prepared by other groups [129-134].

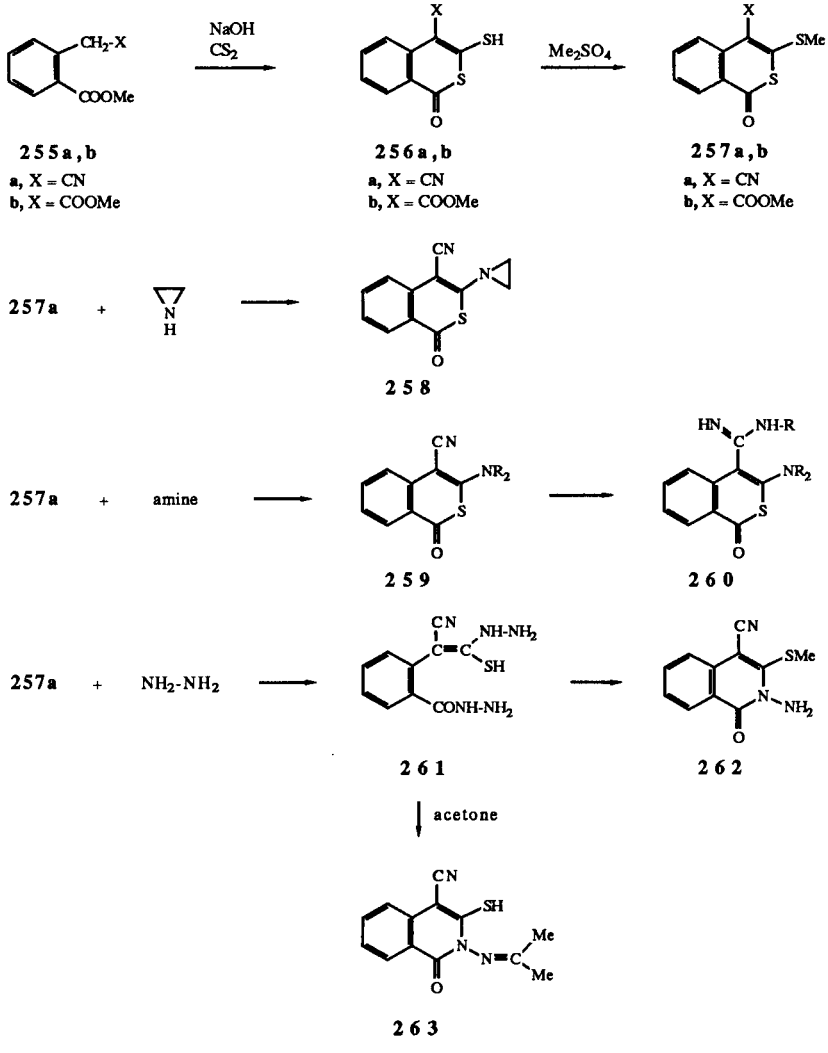
B. Reactions.

These bis(methylthio)methylene derivatives readily react with amines or active methylene compounds to give

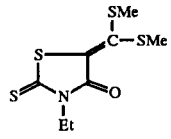
Scheme 66



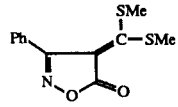
Scheme 67



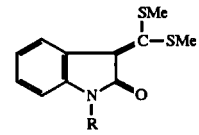
Scheme 68



264

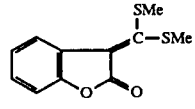


265

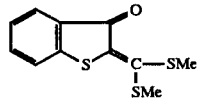


266a,b

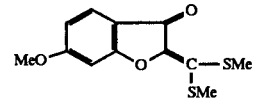
a, R = H
b, R = Me



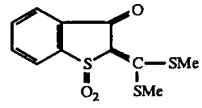
267



268

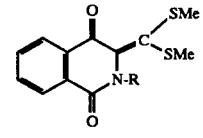


269

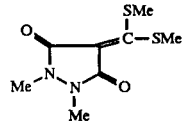


270

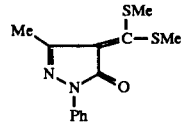
271



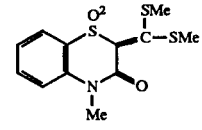
272



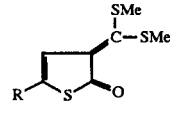
273



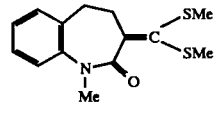
274



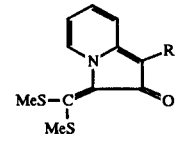
275



276



277



278

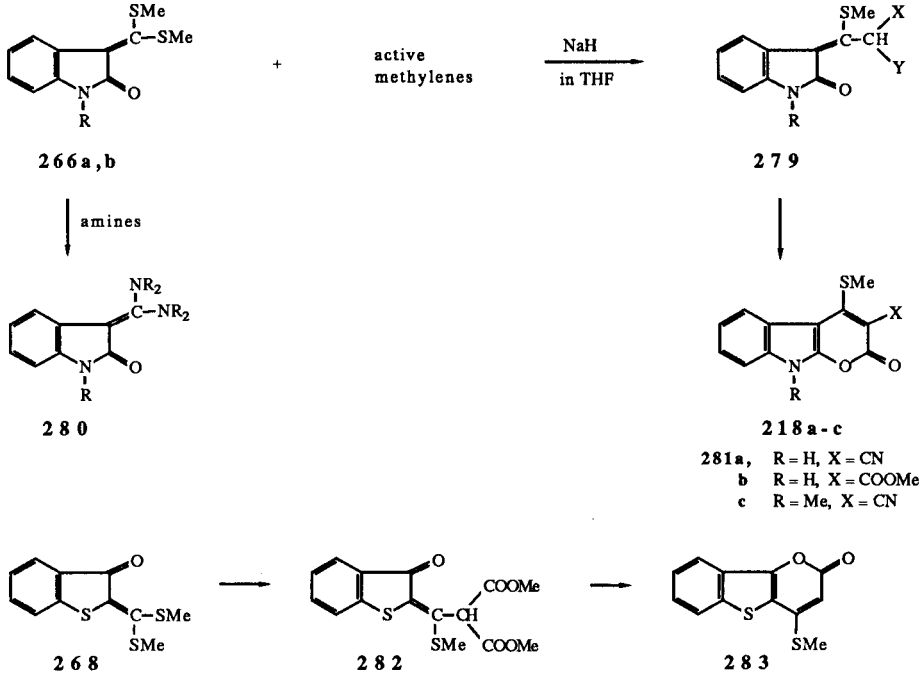
displacement of one or two methylthio groups in good yields. For example, the reaction of **266a** with methyl cyanoacetate in the presence of sodium hydride in THF gives the corresponding displacement product of **279a** in good yield. When heated at 200°, this compound gives the cyclized pyrano[2,3-*b*]indole derivatives **281a-c** [121]. Similarly, fused 2-pyrone derivatives **283** is prepared by this method [122].

Treatment of **266a,b**, and **268** with phosphorus pentasulfide gives the corresponding trithione derivatives **283** and **286**, which undergo 1,3-dipolar cyclization with such dipolarophiles as dimethyl acetylenedicarboxylate to give the corresponding 1,3-dipolar products **285** and **287** in good yields [122, 123].

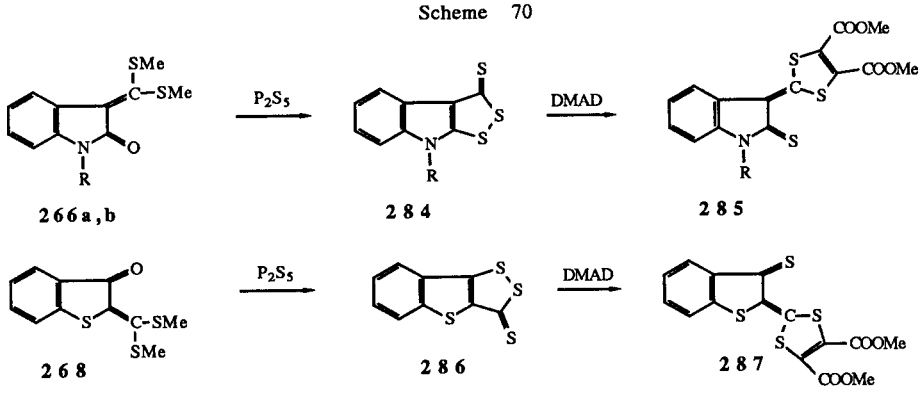
The reaction of **266a** with cyanide anion gives the (α-cyano-α-methylthio)methylene derivatives **288**, which readily displaces with methyl cyanoacetate to give the 3-pyrrolideneoxindole derivatives **289** [128]. Similarly, 2-(α-cyano-α-methylthio)methylenebenzo[*b*]thiophene 1,1-dioxide (**291**) is synthesized by the reaction of **270** with sodium cyanide in dimethyl sulfoxide. Compound **291** is allowed to react with *N,N*-dimethylaniline to give **292** which has a brilliant green color [124].

The synthesis of pyrimidine derivatives using ketene dithioacetals similar to ethoxy methylene compounds, is one of the most widely used in ketene dithioacetals chemistry. However, synthesis of pyrimidine derivatives using the above bis(methylthio)methylene heterocyclic compounds is unreported except for our studies. Reaction of **268** with guanidine carbonate as amidines (**268**) gives the corresponding fused pyrimidine derivatives (**293**). 2-Amino-4-methylthio[1]benzothieno[3,2-*d*]pyrimidine 5,5-dioxide (**294**) is also obtained by the reaction of **270** with guanidine carbonae [52].

Scheme 69



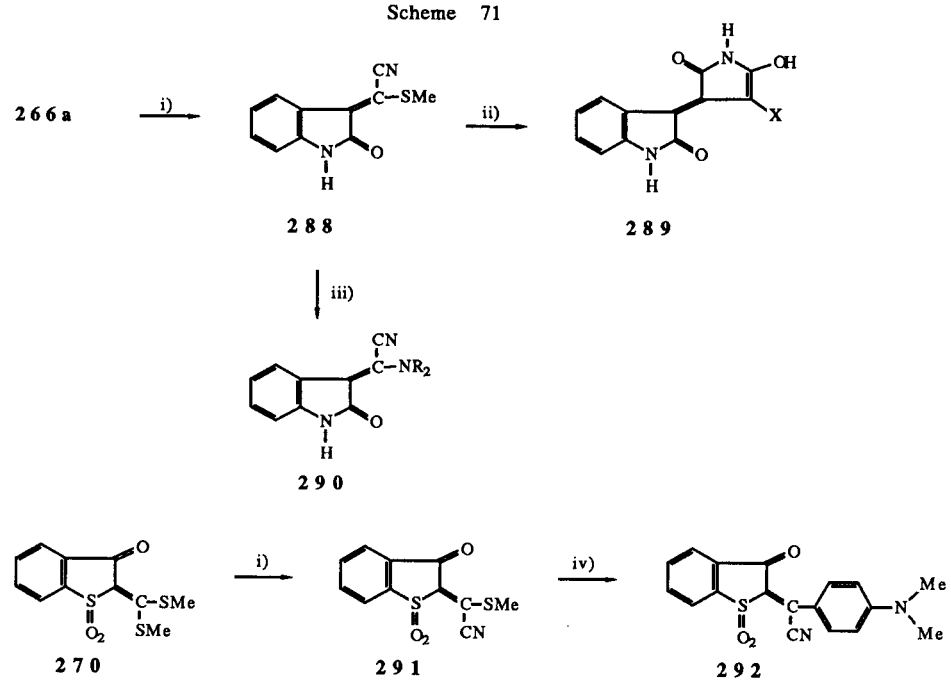
Scheme 70



Compound **270** is used for the synthesis of fused thiabenzene oxides and azathiabenzene oxide. In recent years, the synthesis of monocyclic 1-methylthiabenzene 1-oxides and 1-methyl-2-azathiabenzene 1-oxides by the reaction of ketene dithioacetals has been reported by Furukawa and Rudorf, and in our own laboratory [135-138].

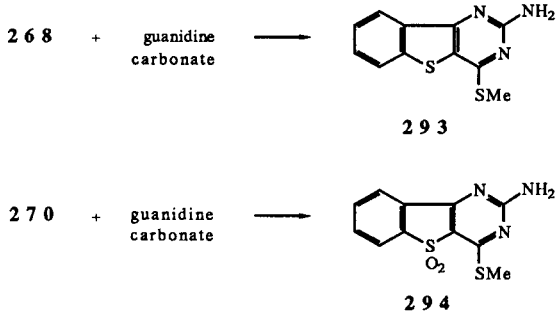
The reaction of **270** with trimethylsulfoxonium iodide in the presence of sodium hydride under reflux in tetrahydrofuran for 4 hours gives thiabenzene oxide, **295**. Treatment of an *N*-substituted dimethyl sulfoximine **296** which is prepared by the reaction of **270** with dimethylsulfoximine, with sodium hydride in tetrahydrofuran affords an azathiabenzene oxide, **297** [139].

Scheme 71

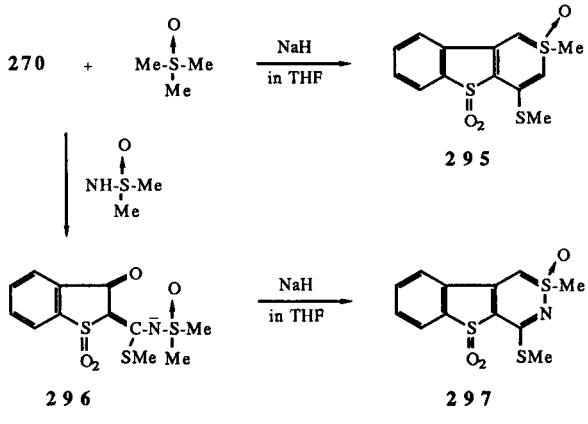


i) NaCN in DMSO; ii) K_2CO_3, $MeOOCCH_2CN$; iii) amines; iv) *p-N,N*-dimethylaniline in acetic acid.

Scheme 72



Scheme 73



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