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Studies on Indole Derivatives. XXIV.[1] Reactions of Methyl 2-Cyano-3-(2-substituted indol-3-yl)thio-3-methylthioacrylates

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Reaction of methyl 2-cyano-3-(2-substituted indol-3-yl)thio-3-methylthioacrylates (III) with various nucleophilic reagents (amines, active methylene compounds) resulted in the formation of products by substitution of the methylthio or the indolylthio group. Treatment of these compounds (III, IVa, IVd) with 10% hydrochloric acid gave thieno-[3,2-*b*]indole derivatives 3-methoxycarbonyl-2-methylthiothieno[3,2-*b*]indole, 2-benzylamino-3-methoxycarbonylthieno[3,2-*b*]indole, 3-carbamoyl-2-(methylthio)thieno[3,2-*b*]-indole.

In a continuation of our previous studies of the ketenethioactals, we have synthesized several heterocyclic compounds using the displacement reaction of ketenethioacetals.[3]

The most versatile derivatives of ketenethiacetals are obtained by the reactions with amines or active methylene compounds. Although many reactions of these ketenethioacetals with S-alkyl group have been reported, the reactions of those with S-aryl group have not been reported as yet.

In this paper, we are going to report the synthesis of a new type ketenethioacetal with indole ring as S-aryl group and the application of their reaction gave thieno[3,2-*b*]indoles.

Recently, Harris[4] has reported the synthesis of thiouronium salts of indoles from indoles and thiourea in the presence of iodine and potassium iodide. This reaction is particularly interesting for the synthesis of indoline-3-thione derivatives.

The reaction of 3-iodoindole and sodium thiophenol, in aqueous methanol, gave 3-phenylthioindole in good yield. When the compounds other than phenylthioindole is desired, this reaction of 3-iodoindole is also successful. Generally, these compounds were obtained by Fischer indole synthesis such as shown in Chart 1.[5]

The reaction of sodium salt of methyl 2-cyano-3-mercapto-3-methylthioacrylate (IIa) with 3-iodoindoles, in the presence of sodium or potassium hydroxide, afforded new types of ketenethioacetal compounds (IIIa, b, c) in good yields.

Having one active methylthio group, these compounds were useful as synthetic intermediates of sulfur containing indoles. The chemical reactivity of methylthio or 3-indolylthio group of these ketenetioacetals (IIIa, b, c) can be revealed by the reaction between IIIa, b, and c and either amines or active methylene compounds.

1) Part XXIII: Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 2770 (1973).
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3) *a*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **91**, 203 (1971); *b*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **92**, 713 (1972); *c*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **92**, 1468 (1972); *d*) Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 1658 (1973); *e*) G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga, and M. Sone, *Yakugaku Zasshi*, **93**, 612 (1973); *f*) M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 1667 (1973).
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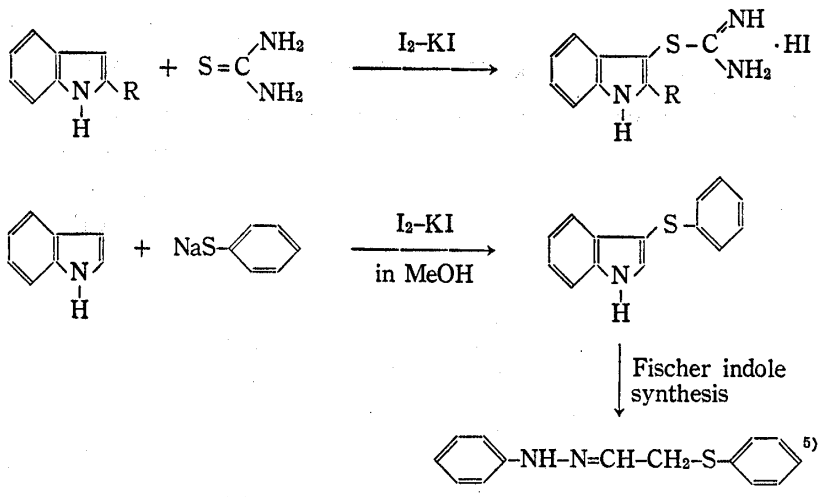

Chart 1

The reaction of IIIa, b, c with amines (benzylamine, aniline, morpholine) afforded amine derivatives, IVa—e, which were the replaced products of methylthio group of compounds IIIa—c. In these reactions, we did not obtain the replaced product of 3-indolylthio group. The infrared (IR) spectrum of IVa—c showed the absorption band due to the carbonyl group in the region between 1640 and 1660 cm^{-1}. This lower frequency shift from the usual position is clearly due to the hydrogen bond between the carbonyl group and the amino group. The results of the reaction are shown in Table II.

The reaction of the compound III with acetamidine hydrochloride in dimethyl formamide using sodium hydride or potassium carbonate was carried out and then acidification of the reaction mixture gave a pyrimidine derivative (VI), which was the replaced product of 3-indolylthio group, and bis(3-indolyl)disulfide (V). This pyrimidine derivative (VI) also was obtained from methyl 2-cyano-3,3-methylthioacrylate and acetamidine hydrochloride. Middelton reported that pyrimidine derivatives were obtained from 2-cyano-3,3-methylthioacrylonitrile and acetamidine hydrochloride.[6]

The reaction of III with active methylene compounds (methyl cyanoacetate, dimethyl malonate) occurred in the presence of potassium carbonate in dimethyl formamide or dimethyl sulfoxide, followed by treatment with 10% aqeuous hydrochloric acid to afford cyclized products, glutaconimide derivatives (VIIa, b). These were identical with the original samples which were synthesized by Kuwayama method.[7]

We reported that the treatment of ketenethioacetals IIIa, b, c with hydrochloric acid gave thiophene-2-spiro-3-(3*H*-indole) and thieno[3,2-*b*]indole derivatives.[8] To a solution of IIIa in methanol, 10% hydrochloric acid was added and the mixture was heated on a steam bath for 10 min, and then cooled. The red precipitate was collected by filtration and recrystallized from methanol to give red needles of mp 300° in good yield. This compound was 3-imino-4-methoxycarbonyl-5-(methylthio)thiophene-2-spiro-3-(3*H*-indole) (VIIIa).[8] In a similar manner the treatment of other compounds (IIIb, c) with 10% hydrochloric acid also gave spiro compounds (VIIIb, c). In other solvents (ethanol, isopropyl alcohol, dioxane) instead of methanol, these reaction gave the same spiro products.

Next, to a solution of 10% hydrochloric acid in methanol, VIIIa was added and the mixture was refluxed on a steam bath for 10 min, and then cooled. The precipitate was collected by filtration and recrystallized with methanol to give white needles of IXa in 80%

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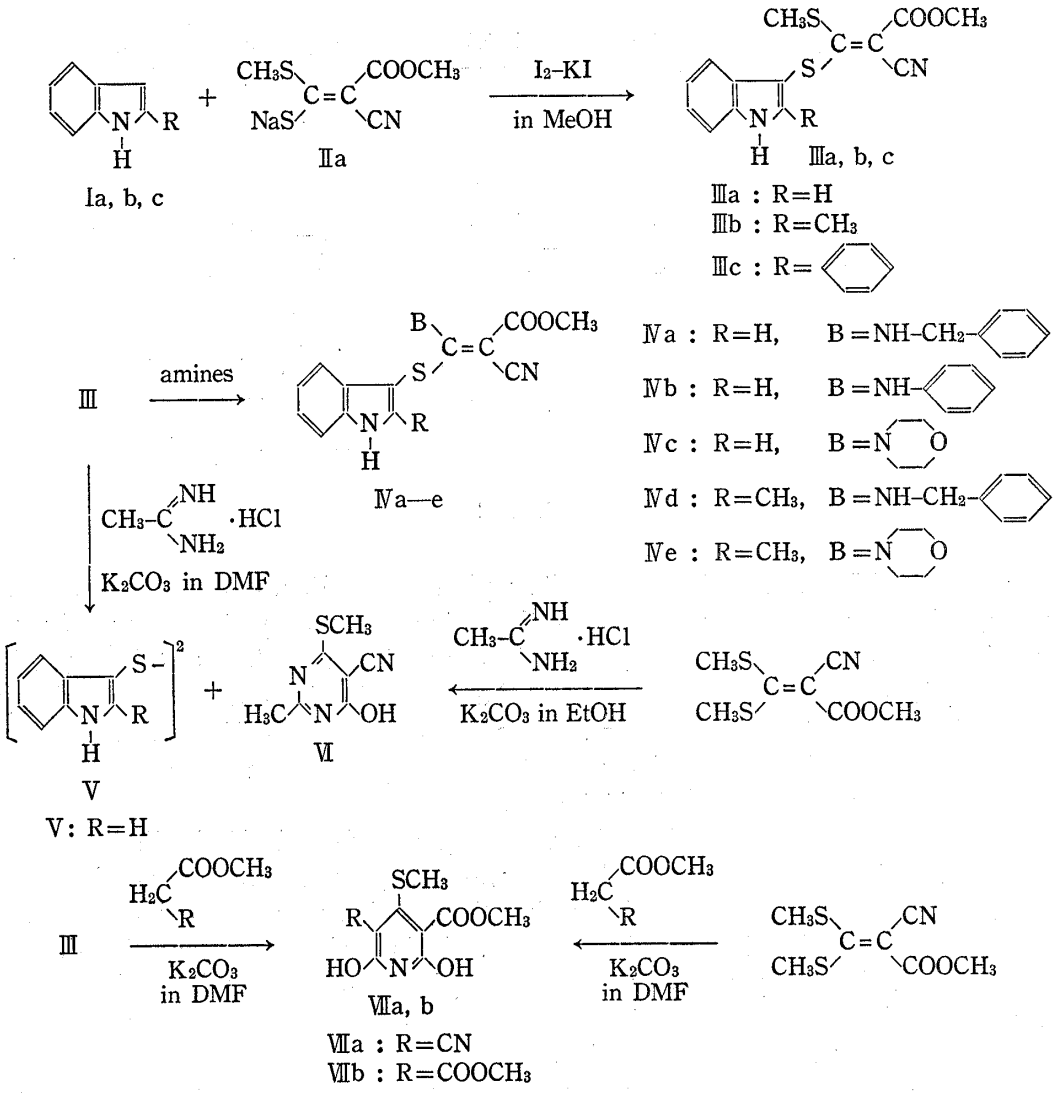
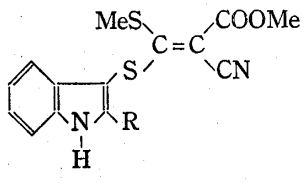


Chart 2

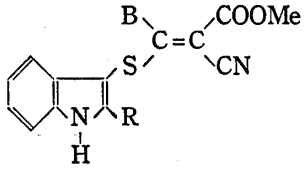
TABLE I.



No.	Yield (%)	mp (°C)	R	Formula	Analysis (%) Calcd.	Analysis (%) Found	UV λ_{max}^{EtOH} nm (log ε)	IR (KBr) cm^{-1}	NMR ($CDCl_3$) ppm
IIIa	65	154—156	H	$C_{14}H_{12}O_2N_2S_2$	C 55.26 H 3.99 N 9.21	C 55.30 H 4.19 N 8.64	287 (4.12) 325 (4.08)	C=O 1690 C≡N 2200 N-H 3340	S-Me 2.67 O-Me 3.99
IIIb	65	195—196	Me	$C_{15}H_{14}O_2N_2S_2$	C 56.60 H 4.33 N 8.80	C 56.94 H 4.39 N 8.86	288 (4.18) 326 (4.18)	C=O 1690 C≡N 2220 N-H 3340	C-Me 2.22 S-Me 2.50 O-Me 3.90
IIIc	51	157—158	Ph	$C_{20}H_{16}O_2N_2S_2$	C 63.15 H 4.27 N 7.44	C 62.96 H 4.17 N 7.15	243 (4.44) 312 (4.48)	C=O 1700 C≡N 2200 N-H 3360	——

Ph=phenyl

TABLE II.



No.	Yield (%)	mp (°C)	R	B	Formula	Analysis (%) Calcd.	Analysis (%) Found	UV λ_{max}^{EtOH} nm (log ε)	IR (KBr) cm^{-1}
Ⅳa	90	202	H	NHCH$_2$-	$C_{20}H_{17}O_2N_3S_2$	C 66.11 H 4.72 N 11.57	C 65.60 H 4.53 N 11.53	238 (4.26) 278 (4.02) 310 (4.17)	C=O 1640 C≡N 2200
Ⅳb	80	183	H	NH-	$C_{19}H_{15}O_2N_3S_2$	C 65.32 H 4.33 N 12.03	C 65.66 H 4.80 N 12.03	289 (4.25) 310 (4.24)	C=O 1663 C≡N 2206
Ⅳc	85	200	H	N O	$C_{15}H_{17}O_3N_3S_2$	C 59.47 H 4.99 N 12.24	C 59.75 H 5.09 N 11.49	280 (4.08) 336 (4.20)	C=O 1706 C≡N 2200
Ⅳd	92	230	Me	NHCH$_2$-	$C_{21}H_{19}O_2N_3S_2$	C 66.83 H 5.07 N 11.14	C 66.82 H 5.10 N 10.89	290 ([a])	C=O 1653 C≡N 2203
Ⅳe	83	196	Me	N O	$C_{16}H_{19}O_3N_3S_2$	C 60.49 H 5.36 N 11.76	C 60.00 H 5.36 N 11.13	288 (4.08) 333 (4.18)	C=O 1640 C≡N 2200

a) Concentration is unknown because of insufficient solubility.

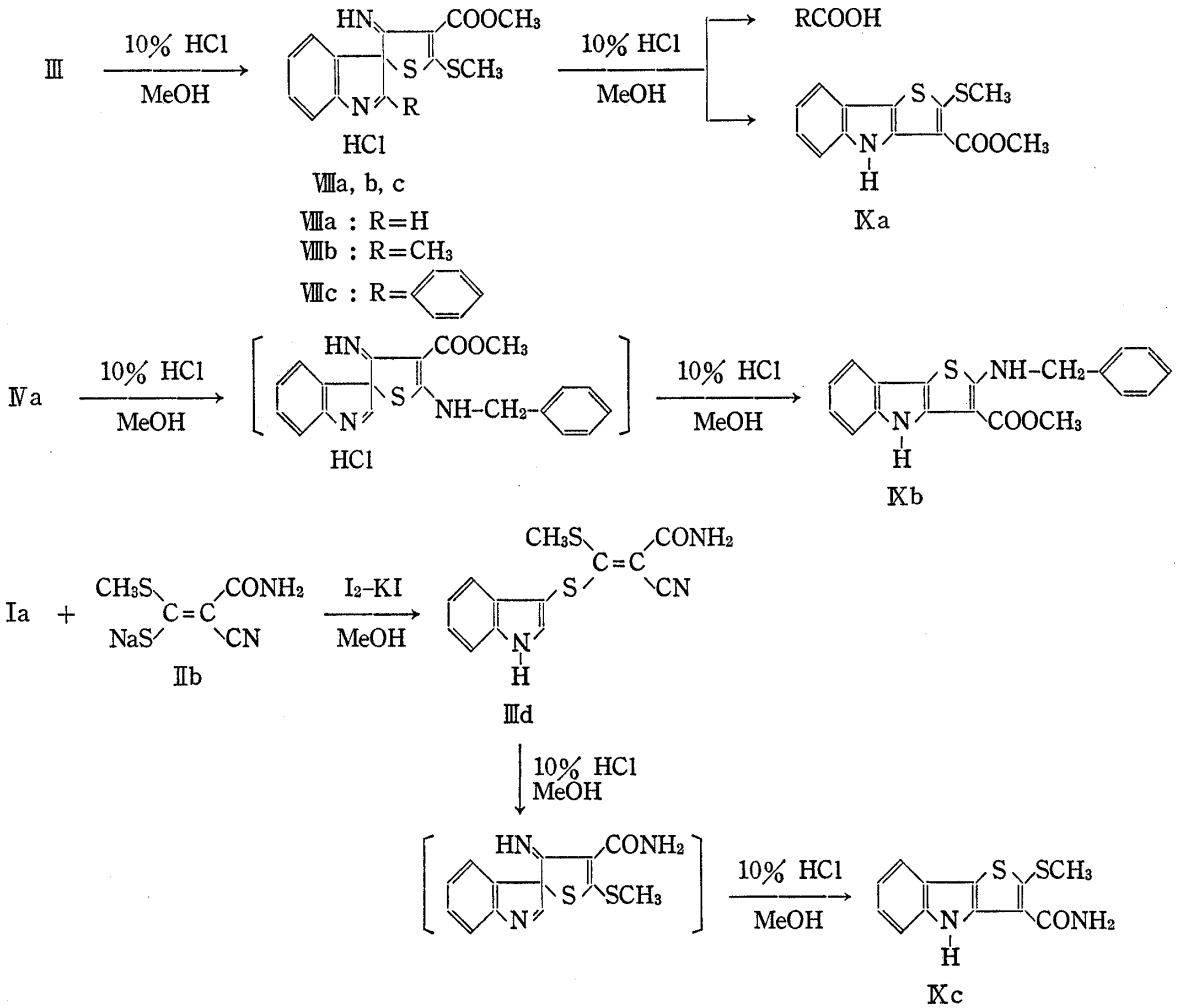
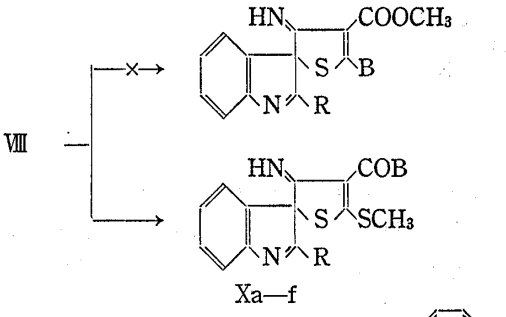


Chart 3



Xa—f

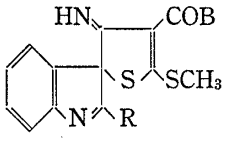
Xa : R=H, B=NHCH$_2$-
Xb : R=CH$_3$, B=NHCH$_2$-
Xc : R=CH$_3$, B=NHCH$_2$COOC$_2$H$_5$
Xd : R=CH$_3$, B=NHNH$_2$
Xe : R=CH$_3$, B=NH$_2$
Xf : R=-, B=NHCH$_2$-

Chart 4

yield (from VIIIa). This compound was 2-methyl-3-(methoxycarbonyl)thieno[3,2-*b*]indole (IXa), which was also obtained from either VIIIb or VIIIc. In the case of VIIIc, the reation time was required about 5 hr longer than that for other compounds, and benzoic acid also obtained simultaneously. In a similar manner, treatment of amino derivative (IVa) with 10% hydrochloric acid gave 2-benzylaminothieno[3,2-*b*]indole derivative (IXb). This reaction may be quite useful for the synthesis of 2-aminothieno[3,2-*b*]indole derivatives. The reaction of 3-iodoindole with other dithiocarboxylate, amide derivative (IIb), gave a ketenethioacetal derivative (IIId). Treatment of IIId with 10% hydrochloric acid gave 3-carbamoyl-2-methylthiothieno[3,2-*b*]indole (IXc), mp 161°.

The reaction of compound VIII with amines was carried out to examine the activity of the methylthio group. Although, the displacement product of methylthio group was not obtained, this reaction gave amide derivatives (X). The data of these amide derivatives are shown in Table III.

Table III.



No.	Yield (%)	mp (°C)	R	B	Formula	Analysis (%) Calcd.	Analysis (%) Found	UV λ_{max}^{EtOH} nm (log ε)	IR (KBr) cm^{-1}
Xa	87	150	H	NHCH$_2$-	$C_{19}H_{17}ON_3S_2$	C 63.32 H 4.52 N 11.08	C 63.79 H 4.65 N 11.18	233 (4.48) 273 (4.42) 283 (3.97)	C=O 1656
Xb	90	164	Me	NHCH$_2$-	$C_{20}H_{19}ON_3S_2$	C 64.11 H 4.87 N 10.68	C 64.50 H 4.89 N 10.84	232 (4.58) 274 (4.46) 384 (4.06)	C=O 1678
Xc	80	204	Me	NHCH$_2$COOEt	$C_{18}H_{19}O_3N_3S_2$	C 55.52 H 4.92 N 10.79	C 55.14 H 4.90 N 10.39	231 (4.48) 272 (4.38) 380 (3.98)	C=O 1673 1730
Xd	90	208	Me	NHNH$_2$	$C_{14}H_{14}ON_4S_2$	C 52.83 H 4.43 N 17.60	C 53.18 H 4.45 N 17.41	235 (4.53) 272 (4.31) 384 (4.03)	C=O 1670
Xe	90	283	Me	NH$_2$	$C_{14}H_{12}ON_3S_2$	C 55.44 H 4.32 N 13.86	C 54.85 H 4.22 N 13.75	231 (*a*) 270 ( ) 379 ( )	C=O 1675
Xf	85	206	Ph	NHCH$_2$-	$C_{26}H_{21}ON_3S_2$	C 68.56 H 4.65 N 9.23	C 68.46 H 4.48 N 9.32	233 (*a*) 280 ( ) 292 ( )	C=O 1670

Ph=phenyl
a) Concentration is unknown because of insufficient solubility.

Experimental

3-Phenylthioindole——To a mixture 1.1 g of indole in 20 ml MeOH and 1.3 g of thiophenol in 50 ml of 20% NaOH solution, a solution of 1.2 g of I_2 and 2 g of KI in 20 ml of H_2O was added dropwise during 10 min with stirring at room temperature and the mixture was stirred at the same temperature for 30 min. The mixture was poured into 10 ml of H_2O and precipitate was collected by filtration, washed with H_2O,

and recrystallized from MeOH to give 3-phenylthioindole of mp 147° in 85% yield. This compound was identical to the compound synthesized by Wieland (mp 147°). *Anal.* Calcd. for $C_{14}H_{11}NS$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.68; H, 4.91; N, 6.11. IR (KBr) cm^{-1}: 3470 (NH).

Methyl 2-Cyano-3-(2-substituted indol-3-yl)thio-3-methylthioacrylates (IIIa, b, c)——To a mixture 0.01 mole of indoles (Ia, b, c) in 20 ml of MeOH and 0.01 mole of methyl 2-cyano-3-mercapto-3-methylthioacrylate (IIa) in 50 ml of 20% KOH or NaOH solution, a solution of 1.2 g of I_2 and 2 g of KI in 20 ml of H_2O was added dropwise during 10 min with stirring at room temperature and the mixture was stirred at the same temperature for 20 min. After stirring about 10 min, the precipitate appeared. The precipitate was collected by filtration, washed with H_2O, and recrystallized from MeOH to give ketenethioacetal derivatives (IIIa, b, c). These results are shown in Table I.

Reaction of III with Amines——A mixture of 0.01 mole of III and 0.015 mole of amines in 50 ml of MeOH was refluxed on a steam bath for 1 hr. The solvent was evaporated and the residue was washed by 5% HCl solution. The precipitate was collected by filtration, washed with H_2O, and recrystallized from MeOH to give amine derivatives. The result are shown in Table II.

5-Cyano-6-hydroxy-2-methyl-4-(methylthio)pyrimidine (VI)——a) To a solution of 1 g acetamidine hydrochloride and 3 g of IIIa in 50 ml of dimethyl formamide, 3 g of K_2CO_3 was added and the mixture was heated on a steam bath for 10 hr. After cooling, the mixture was poured into 200 ml of H_2O and allowed to stand for 1 hr. The precipitate was collected by filtration, and recrystallized from MeOH to give bis-(3-indolyl)disulfide[4] of mp 229° in 45% yield. The filtrate was acidified with 10% HCl solution. The pecipitate was collected by filtration, washed with H_2O, and recrystallized from MeOH to give pyrimidine derivative (VI) in 30% yield.

b) To a solution of 1 g of acetamidine hydrochloride in 50 ml of EtOH, 3 g of K_2CO_3 and 2 g of methyl 2-cyano-3,3-bis(methylthio)acrylate were added and the mixture was refluxed on a steam bath for 5 hr. The solvent was evaporated and to the residue was added 100 ml of water and the solution was acidified with 10% HCl. The precipitate was collected by filtration and recrystallized from MeOH to give VI of mp 300° in 92% yield. *Anal.* Calcd. for $C_7H_7ON_3S$: C, 46.41; H, 3.90; N, 23.20. Found: C, 46.60; H, 4.11; N, 22.84. IR (KBr) cm^{-1}: 1656 (CO), 2210 (CN). UV λ_{max}^{EtOH} nm(log ε): 242 (4.38), 282 (4.03), 315 (3.98).

Reaction of III with Active Methylenes——To a solution 3 g of IIIa and 3 g of K_2CO_3 in 50 ml of dimethyl formamide, 0.02 mole of active methylene compounds (methyl cyanoacetate, dimethyl malonate) was added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into 100 ml of ice water and the solution was acidified with 10% HCl solution. After being stand for about 5 hr, the precipitate was collected by filtration and recrystallized from MeOH to glutaconimide derivatives (VIIa, b).[7]

3-Imino-4-methoxycarbonyl-5-(methylthio)thiophene-2-spiro-3-(3*H*-indoles) (VIIIa, b, c)——A solution of 0.01 mole of III in 50 ml of MeOH (or isopropylalcohol, dioxane) and 10 ml of 10% HCl solution was heated on a steam bath for 10 min. After cooling, the red precipitate was collected by filtration and recrystallized from MeOH to give red needles in good yield.[8]

3-Methoxycarbonyl-2-methylthiothieno[3,2-*b*]indole (IXa)——A solution of 1 g of VIIIa, b in 40 ml of MeOH and 10 ml of 10% HCl solution was refluxed on a steam bath for 10 min. (In the case of VIIIc, the solution was refluxed for 5 hr). After cooling, the white precipitate was collected by filtration and recrystallized from MeOH to give colorless needles of IXa, mp 188°, in 60—80% yield. *Anal.* Calcd. for $C_{13}H_{11}O_2NS$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.38; H, 3.90; N, 5.02.

2-Benzylamino-3-methoxycarbonylthieno[3,2-*b*]indole (IXb)——A solution of 1 g of IVa in 30 ml of MeOH and 10 ml of 10% HCl solution was refluxed on a steam bath for 1 hr. The solvent was evaporated and the residue was acidified with 5% HCl. The precipitate was collected by filtration, washed with H_2O, and recrystallized from MeOH to give colorless crystals of mp 151° in 73% yield. *Anal.* Calcd. for $C_{19}H_{10}O_2N_2S$: C, 67.85; H, 4.08; N, 8.33. Found: C, 67.79; H, 4.72; N, 8.15. IR (KBr) cm^{-1}: 3310, 3440 (NH), 1670 (CO). UV λ_{max}^{EtOH} nm(log ε): 247 (4.59), 292 (4.25), 319 (4.14).

3-Carbamoyl-2-(methylthio)thieno[3,2-*b*]indole (IXc)——To a mixture of 0.01 mole of indoles (Ia, b) in 20 ml of MeOH and 1.7 g of 2-cyano-3-mercapto-3-methylthioacrylamide (IIb) in 50 ml of 20% NaOH solution, a solution of 1.2 g of I_2 and 2 g of KI in 20 ml of H_2O was added dropwise during 10 min with stirring at room temperature and the mixture was stirred at the same temperature for 20 min. The precipitate was collected by filtration and washed with water. To a solution of this crude product in 50 ml of MeOH, 10 ml of 10% HCl solution was added and the mixture was refluxed on a steam bath for about 1 hr. After cooling, the white precipitate was collected by filtration and recrystallized from MeOH to give colorless crystals, mp 161°, in 65% yield. *Anal.* Calcd. for $C_{12}H_{10}ON_2S_2$: C, 54.96; H, 3.84; N, 10.68. Found: C, 55.13; H, 3.88; N, 10.49. IR (KBr) cm^{-1}: 3240, 3440 (NH), 1640 (CO). UV λ_{max}^{EtOH} nm(log ε): 229 (4.26), 330 (4.19).

Reaction of VIII with Amines——To a solution of 0.01 mole of VIII in 30 ml of MeOH, 0.03 mole of amine was added and the mixture was refluxed on a steam bath for 10 min. The solvent was evaporated and the residue was washed with petro. ether, the precipitate was collected by filtration and recrystallized from MeOH to give amide derivatives in good yield. The results are shown in Table III.