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Preparation of 3-Substituted 2-Indolinethiones *via* Diindolyl Disulfides. The Reaction of 3-Substituted Indoles with Sulfur Monochloride

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The reaction of 3-alkylindoles (**1**) with sulfur monochloride in ether gave the corresponding 2-diindolyl disulfides (**2**) as the main product, and mono and tri-sulfides (**3**) as minor products. The similar reaction of 3-arylindoles (**6**) gave the disulfides (**7**) in good yields. 2-Chloro derivatives (**4** and **9**) were obtained as the minor products in the reaction of **1e** and **6d**. The reactions of **1e**, **6g** and **6h** with sulfur monochloride in ether were very slow, but proceeded rapidly in methylene chloride.

The reduction of these diindolyl disulfides (**11**) with sodium borohydride in ethanol afforded the 2-indolinethiones (**12**) in good yields. These reactions are a general method for the preparation of 3-substituted 2-indolinethiones from 3-substituted indoles.

We previously reported[2] the thiation of methyl substituted oxindoles with phosphorous pentasulfide. The preparation of 3-monosubstituted 2-indolinethiones by this method accompanied indoles as by-products. The reduction of the diindolyl disulfide to the corresponding thiones with zinc-acetic acid was reported by Wieland and his co-workers.[3]

We examined the reaction of various 3-substituted indoles with sulfur monochloride (S_2Cl_2) and the reduction of the resulted diindolyl disulfide by sodium borohydride and found that this method seems to be another general method for the preparation of 3-substituted 2-indolinethiones from 3-substituted indoles.

The Reaction of 3-Substituted Indoles with S_2Cl_2

Wieland and his co-workers[3] reported the reaction of 3-methyl, 3-phenyl- and 3-carboxymethylindoles with sulfur monochloride in ether. Following their procedure, several 3-alkylindoles were treated with S_2Cl_2 in ether.

The reaction of skatole (**1a**) with 0.5 mole of S_2Cl_2 at room temperature gave the disulfide (**2a**) as a main product and mono and trisulfides (**3a**, $n=1$ and 3) were obtained as minor products as reported. Under the similar reaction condition **1b** gave the disulfide (**2b**) which precipitated from the reaction mixture, and **3b** ($n=1$ or 3) could not be isolated as pure compounds. The reaction of 3-*tert.* butylindole (**1c**) with S_2Cl_2 gave the mixture of sulfides (**2c** and **3c**).

The reaction of 3-benzylindole (**1d**) with S_2Cl_2 in methylene chloride gave the disulfide (**2d**) and the monosulfide (**3d**, $n=1$) after careful chromatographic separation, but the trisulfide was not isolated. The reaction of N-acetylskatole (**1e**) with S_2Cl_2 in ether at room temperature did not proceed. However, the reaction proceeded smoothly in methylene chloride at room temperature to give **2e** in 54% yield. The 2-chloro derivative (**4**) was isolated as a minor product, but mono or trisulfide was not detected. On mild alkaline hydrolysis **2e** gave **2a**, and **4** gave the known compound, **5**. The reaction of **1e** with S_2Cl_2 in boiling dioxane gave **4** in low yield.

1) Location: *Yayoi-cho, Chiba-shi, 280, Japan.*
2) T. Hino, K. Tsuneoka, M. Nakagawa, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **17**, 550 (1969).
3) T. Wieland, O. Weiberg, E. Fischer, and G. Horlein, *Ann.*, **587**, 146 (1954).

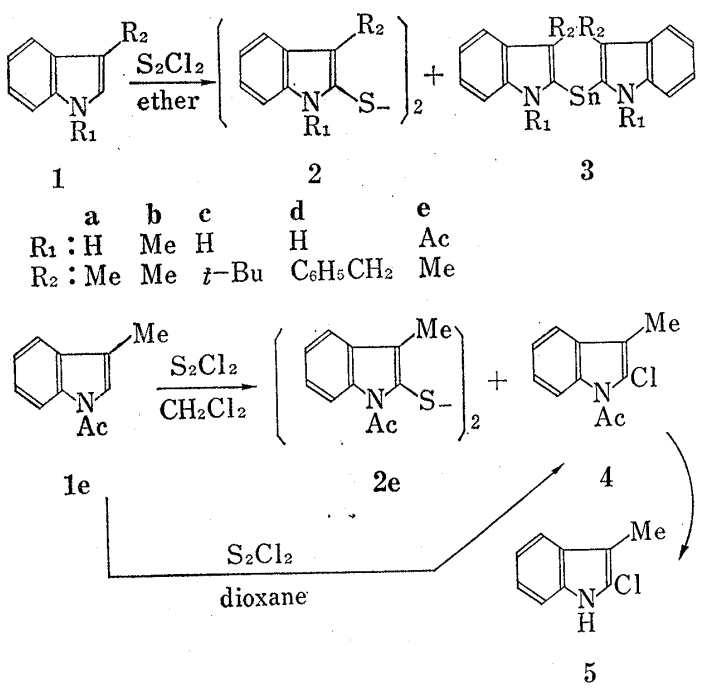


Chart 1

The various *p*-substituted 3-phenylindoles have also been treated in the similar manner. The preparation of the indoles will be described in the separate paper. The reaction of 3-phenyl indole (**6a**) with S_2Cl_2 in ether gave the disulfide (**7a**) in 60% yield. The presence of a small amount of the other sulfides (**8a**, n=1,3) was observed on thin-layer chromatography (TLC) of the reaction mixture, the separation did not however, succeeded. The compounds (**6b**, **c**, **e**, and **f**) similarly gave the disulfide as the main product. In the case of **6d**, 2-chloro derivative (**9**) was isolated in 10% yield besides the disulfide (**7d**). The structure of **9** was confirmed by the spectral data (see experimental) as well as the direct comparison with 2-chloro-3-(*p*-methoxyphenyl)indole obtained by the chlorination of **6d** with N-chlorosuccinimide in acetic acid. The acid hydrolysis of **9** produced the oxindole (**9a**), which was confirmed by the spectral data. The chlorination of **6d** gave a dimeric compound (**10**) beside **9**.

The reaction of **6g** with S_2Cl_2 in ether proceeded slowly and the most of **6g** remained unchanged even after refluxing of the ether solution. However, the reaction in methylene chloride proceeded rapidly to give the disulfide (**7g**) in good yield at room temperature and 2-chloro derivative was not obtained. The N-methyl derivative (**6h**) was similarly allowed

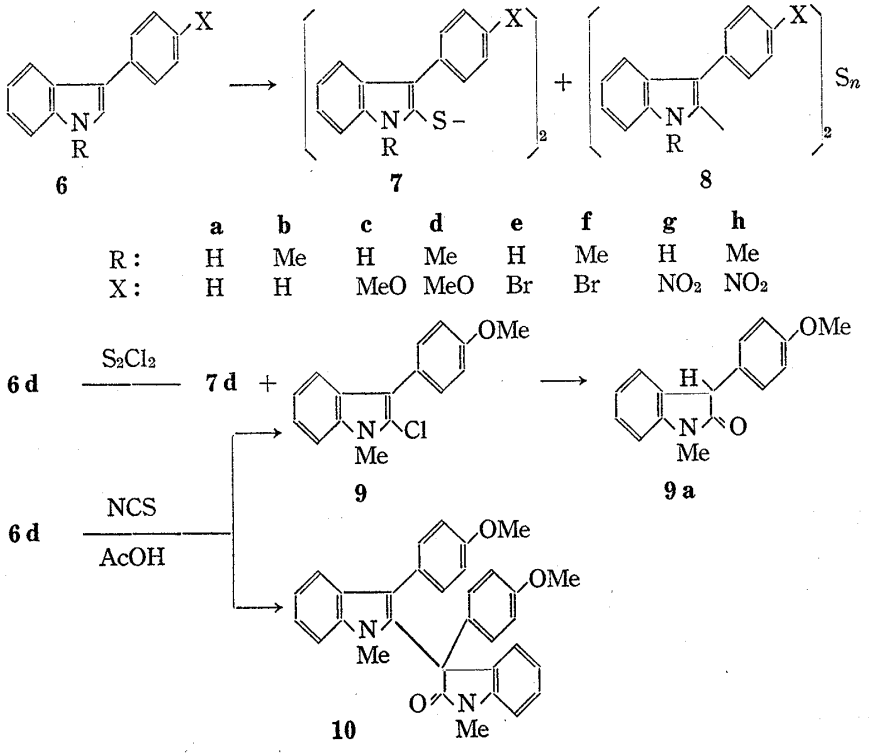


Chart 2

to react with S_2Cl_2 in methylene chloride to give the disulfide (**7h**). But the purification of the disulfide was not successfull due to its low solubility to various solvents.

The reaction of 3-substituted indoles with S_2Cl_2 can be considered as one of the electrophilic substitution reaction of indoles[4] and the reaction paths may be depicted as in Chart 3. The formation of 2-chloro derivative suggested that attack of S_2Cl^+ at 3-position had occurred to produce the indolenine derivative which was then attacked by Cl^- as shown in the chart.

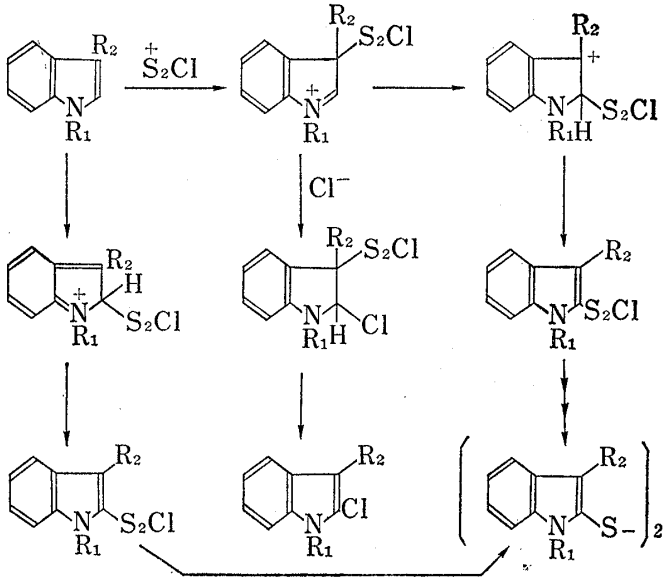
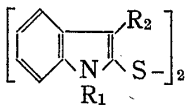


Chart 3

Methylene chloride was a good solvent for the indoles such as N-acetylskatole and 3-(*p*-nitrophenyl)-indole which were less reactive in ether. However, the reaction of 3-phenyl and 3-(*p*-methoxyphenyl)-indole with S_2Cl_2 in methylene chloride gave a complicated result in contrast to the reaction in ether, and monosulfides, unknown compounds, besides disulfide were obtained. These results might suggest that S_2Cl_2 in ether is less reactive than S_2Cl_2 in methylene chloride probably due to the formation of a complex with ether.

Table I. Diindolyl Disulfides

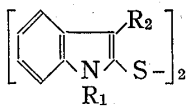


Compd No	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
11b	Me	Me	121—122	$C_{20}H_{20}N_2S_2$	68.18	5.72	7.95	—	68.09	5.88	7.79	—
11d	H	$C_6H_5CH_2$	150—151	$C_{30}H_{24}N_2S_2$	75.61	5.08	5.88	13.43	75.61	5.12	5.81	13.43
11f	Me	Ph	142.5—143	$C_{30}H_{24}N_2S_2$	75.61	5.08	5.88	—	75.22	5.12	5.66	—
11g	H	MeO-C$_6$H$_4$-	187—189	$C_{30}H_{24}O_2N_2S_2$	70.87	4.72	5.51	12.54	71.33	4.96	4.98	12.39
11h	Me	MeO-C$_6$H$_4$-	169—171	$C_{32}H_{28}O_2N_2S_2$	71.90	5.30	5.60	11.62	71.63	5.26	5.22	11.93
11i	H	Br-C$_6$H$_4$-	189—191	$C_{28}H_{18}N_2S_2Br_2$[a]	55.45	2.97	4.62	10.56	56.06	3.15	4.43	10.79
11j	Me	Br-C$_6$H$_4$-	194—196	$C_{30}H_{22}N_2S_2Br_2$[b]	56.78	3.47	4.40	10.09	56.45	3.68	4.32	9.78
11k	H	NO_2-C$_6$H$_4$-	253—255	$C_{28}H_{18}N_4S_2$	62.45	3.35	10.41	—	62.38	3.49	10.02	—
2e	Ac	Me	156—157	$C_{22}H_{20}O_4N_2S_2$	64.67	4.94	6.86	15.69	64.89	4.98	6.86	15.70

a) Br: Calcd. 26.40; Found 26.47. b) Br: Calcd. 25.24; Found 24.76.

4) R. J. Sundberg, "The Chemistry of Indoles," Academic press, New York, 1970, Chapter 1; W. J. Houlihan (ed), "Indoles" Part I, Wiley-Interscience, New York, 1972, Chapter 1.

Table II. Ultraviolet and Mass Spectral Data of Diindolyl Disulfide

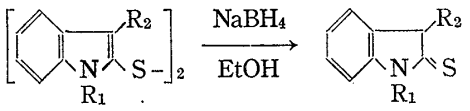


11

Compd No	R_1	R_2	UV λ_{max}^{EtOH} nm (ε)	Mass M^+ (relative abundance)
11 d	H	$CH_2C_6H_5$	299(12200), 340(13500)	476(1)
11 e	H	C_6H_5	ref. 3	448(10)
11 f	Me	C_6H_5	227(38900), 258(26700), 283^{sh}(15600), 360(10000)	476(21)
11 g	H	MeO-C$_6$H$_4$-	226(44600), 255(34300), 333(11200)	508(0)
11 h	Me	MeO-C$_6$H$_4$-	230(43100), 255^{sh}(33500), 331(10000)	536(5)
11 i	H	Br-C$_6$H$_4$-	222(46200), 261(27200), 333(10400)	608(0)
11 j	Me	Br-C$_6$H$_4$-	224(47300), 267(33200), 355(11700)	636(4)
11 k	H	NO_2-C$_6$H$_4$-	223, 275, 350	538(7)
11 l	Me	NO_2-C$_6$H$_4$-	225, 360	566(27)
2 e	Ac	Me	243, 273, 320	408(3)

The analytical data and the ultraviolet and mass spectral data of these disulfides are summarized in Table I and II. The ultraviolet (UV) spectra showed a broad maximum at between 320—360 nm and only minor effect of the substituent at 3-position was observed. The molecular ion peak of these disulfides in mass spectra are very weak and they were not observed in **11g** and **11i**. N-Methylation, however, seems to stabilize the molecular ion and gave fairly strong molecular ion peak. In most cases $M^+/2$ or $M^+/2+1$ peaks are prominent and the fragments below $M^+/2$ are similar to those of the corresponding 2-indolinethiones.

Table III. The Reduction of Diindolyl Disulfide to 2-Indolinethiones

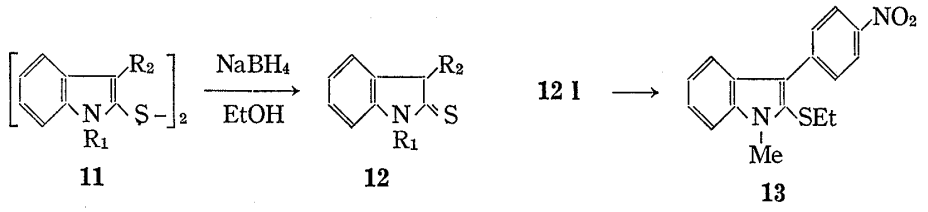


11 **12**

Compd. No.	R_1	R_2	Yield (%)	mp of **12** (°C)
12 a	H	Me	40(*)	118—119[2)]
12 b	Me	Me	60	45— 46[2)]
12 c	H	*t*-Bu	50(*)	117—118
12 d	H	$C_6H_5CH_2$	50(*)	144—145
12 e	H	C_6H_5	75	132—134
12 f	Me	C_6H_5	75	111—112
12 g	H	MeO-C$_6$H$_4$-	90	156—157
12 h	Me	MeO-C$_6$H$_4$-	80	126—127
12 i	H	Br-C$_6$H$_4$-	90	152—154
12 j	Me	Br-C$_6$H$_4$-	50(*)	142—144

The Reduction of the Disulfides

The disulfides (**11a** and **11e**) were reported[3] to produce the corresponding 2-indolinethiones (**12a** and **12e**) by the reduction with zinc-acetic acid. We found the disulfides were smoothly reduced to the 2-indolinethiones with sodium borohydride in ethanol at room temperature. The results are summarized in Table III. When the disulfide was difficult to isolate in pure form from the sulfide mixture, the mixture of sulfides was reduced with $NaBH_4$ in ethanol without any further purification, and the resulted 2-indolinethione and the monosulfide which was not reduced with $NaBH_4$ were separated by silica gel column. The yield % with asterisk in the Table III show the percentage from the indole by this procedure. The trisulfide (**3a**, $n=3$) could also be reduced with $NaBH_4$ in ethanol to afford the 2-indolinethione (**12a**) in 60% yield.



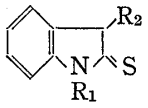
11 **12** **13**

	a	**b**	**c**	**d**	**e**	**f**
R_1:	H	Me	H	H	H	Me
R_2:	Me	Me	*t*-Bu	$C_6H_5CH_2$	C_6H_5	C_6H_5

	g	**h**	**i**	**j**	**k**	**l**
R_1:	H	Me	H	Me	H	Me
R_2:	-OMe	-OMe	-Br	-Br	$-NO_2$	$-NO_2$

Chart 4

TABLE IV. Analytical Data of 2-Indolinethiones



12

Compd No	R_1	R_2	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
12c	H	*t*-Bu	$C_{12}H_{15}NS$	70.22	7.37	6.86	15.59	69.91	7.43	6.77	15.99
12d	H	$C_6H_5CH_2$	$C_{15}H_{13}NS$	75.30	5.48	5.85	13.37	75.45	5.53	6.06	13.33
12f	Me	C_6H_5	$C_{15}H_{13}NS$	75.30	5.48	5.85	13.37	75.04	5.44	5.68	13.35
12g	H	MeO-	$C_{15}H_{13}ONS$	70.58	5.13	5.49	—	70.38	5.22	5.31	—
12h	Me	MeO-	$C_{16}H_{15}ONS$	71.36	5.61	5.20	11.88	71.10	5.55	5.45	11.70
12i	H	Br-	$C_{14}H_{10}NSBr$	—	—	4.61	—	—	—	4.30	—
12j	Me	Br-	$C_{15}H_{12}NSBr$[a]	56.60	3.77	4.40	10.06	56.65	3.78	4.37	9.85
12l	Me	NO_2-	$C_{15}H_{12}O_2N_2S$	—	—	9.86	11.26	—	—	9.49	10.86

a) Br: Calcd. 25.16; Found 25.30

The analytical data of these 2-indolinethiones are summarized in Table IV. 3-(*p*-Nitrophenyl)-2-indolinethione could not be purified due to facile air oxidation to the corresponding

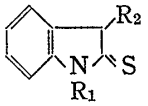
disulfide during recrystallization. Its N-methyl derivative (**12l**) can be recrystallized from benzene–hexane, but analytical sample was not obtained. Therefore, **12l** was treated with ethyl iodide in acetone–potassium carbonate to give S-ethyl derivative (**13**), mp 117—120.

The preparation of the 3-substituted 2-indolinethiones by this procedure seems to be a general method. However, this procedure was not applicable to the 2-indolinethiones which have no substituent at 3-position, since the reaction with S_2Cl_2 may produce 3-indolyl disulfide instead of 2-indolyl disulfide in these cases. Therefore thiation of the oxindole[2] remained as the useful method for the preparation of 2-indolinethiones which have no substituent at 3-position and 3,3-disubstituted 2-indolinethiones.

The mass spectral data of these 2-indolinethiones are summarized in Table V. The peaks, M–S and M–SH, which were the characteristic fragments observed in methyl substituted 2-indolinethiones,[5] were seen in 2-indolinethiones prepared. But other peaks were more complicated than those of methyl substituted 2-indolinethiones.

The air oxidation and the thione-thiol tautomerism of 2-indolinethiones will be discussed in the separate paper.

Table V. Mass Spectra of 2-Indolinethiones



R_1	R_2	M^+	M−1	M−S	M−SH	M−Me	*m/e* 165	Other peaks (over 10% of relative abundance)
H	$CH_2C_6H_5$	239 (100)	238 (20)	207 (15)	206 (41)	—	—	237(15), 236(33), 205(15), 204(23), 178(12), 176(10), 162(30), 161(62), 148(31), 130(10), 128(12), 121(15), 117(15), 102(15), 95(15), 91(90)
H	*t*-Bu	205 (10)	—	173 (2)	172 (0)	190 (7)	—	150(13), 149(100), 148(14), 121(10), 117(12), 77(10)
H	C_6H_5	225 (100)	224 (64)	193 (34)	192 (10)	—	165 (16)	223(89), 222(25), 196(10), 190(11), 152(10), 111.5(19)
Me	C_6H_5	239 (100)	238 (27)	207 (35)	206 (30)	224 (26)	165 (27)	223(28), 222(12), 205(10), 204(10), 178(10), 128(11), 78(11)
H	MeO-C$_6$H$_4$-	255 (100)	—	223 (40)	222 (22)	240 (53)	165 (5)	212(47), 210(35), 184(13), 180(17), 178(18), 152(30), 138(17), 78(25)
Me	MeO-C$_6$H$_4$-	269 (100)	—	237 (21)	236 (11)	254 (54)	165 (5)	226(12), 222(14), 210(8), 194(5), 193(5), 192(5), 152(11), 135(7), 127(6)
H	Br-C$_6$H$_4$-	303 (97)	—	276 (6)	—	—	165 (11)	305(M^++2, 100), 224(68), 223(90), 222(90), 190(11), 163(10), 152(9), 113(28), 112(55), 97(10)
Me	Br-C$_6$H$_4$-	317 (96)	—	285 (8)	—	302 (8)	165 (14)	319(M+2, 100), 287(8), 286(8), 238(30), 237(30), 223(29), 222(20), 204(10), 190(7), 118(23)

Experimental[6]

Purification of S_2Cl_2[7]——To a commercial S_2Cl_2 (50 g) was added sulfur (2 g) and active carbon (0.5 g), and the mixture was distilled at ordinary pressure to collect the fraction of bp 137—138°. The S_2Cl_2 was distilled *in vacuo* immediately before use, bp_{17-18} 36—37° (golden yellow liquid).

5) T. Hino, M. Nakagawa, K. Tsuneoka, S. Misawa, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), 17, 1651 (1969).

6) All melting points are uncorrected. The infrared (IR) spectra were recorded on a Hitachi G-3 model or 215 model. The UV spectra were recorded on a Hitachi EPS-3T spectrophotometer. The nuclear magnetic resonance (NMR) spectra wer etaken with a JEOL JNM-4H-100 spectrometer. The chemical shift was expressed as δ value using TMS as an internal standard. The mass spectra were measured with a Hitachi RMU-6E.

7) G. Brauer, "Handbook of preparative Inorganic Chemistry," Vol. 1, 372.

2,2′-Dithiobis(1,3-dimethylindole) (**2b**)——To a chilled solution of 1,3-dimethylindole (**1b**, 2.9 g, 0.02 mole) in ether (15 ml) was added dropwise freshly dilstilled S_2Cl_2 (1.35 g, 0.01 mole) in ether (15 ml) at 4—5° with stirring. When 2/3 S_2Cl_2 was added, yellow precipitates began to precipitate. After addition, the mixture was stirred at the same temperature for 30 min. Yellow precipitates were filtered and washed with chilled ether. The crude disulfide (2.1 g, 60%), mp 115—117°, showed λ_{max}^{EtOH} at 350 nm. Recrystallizations from petr. ether gave **2b**, mp 121—123°. NMR (in $CDCl_3$); 1.85 (s, 3-CH_3), 3.65 (s, N-CH_3), 7.0—7.45 (m, arom. H).

2,2′-Dithiobis(3-benzylindole) (**2d**). **Reaction of 3-Benzylindole with S_2Cl_2 in Methylene Chloride**——A solution of S_2Cl_2 (1.63 g) in CH_2Cl_2 (20 ml) was added dropwise at 0—5° to a solution of 3-benzylindole[8] (5.0 g) in CH_2Cl_2 (80 ml). After the addition the mixture was stirred for 1 hr at the same temperature and left overnight. The mixture was neutralized with aq. $NaHCO_3$. The CH_2Cl_2 solution was washed with H_2O and dried. The solvent was evaporated to leave a brown residue (5.61 g), which was chromatographed over silica gel column (40 g). From the fraction eluted with benzene–hexane (2: 8) the monosulfide (**3d**, $n=1$) (3.1 g, 59%), mp 115—140°, and disulfide (**2d**) (1.5 g, 27%), mp 120—139°, were obtained. From the fraction eluted with benzene an unknown compound (0.9 g), mp 127—132°, was obtained. These products were recrystallized from benzene. Monosulfide (**3d**, $n=1$), mp 178—179°, colorless crystals. UV λ_{max}^{EtOH} nm (ε); 293 (26400), 301 (27700). IR ν_{max}^{KBr} 3400 cm^{-1} (NH). NMR (in $CDCl_3$); 4.27 (s, CH_2), 6.75—7.58 (m, arom. H). Mass Spectrum *m/e*: 444 (M^+, 100). *Anal.* Calcd. for $C_{30}H_{24}N_2S$: C, 81.08; H, 5.44; N, 6.30; S, 7.20. Found: C, 81.51; H, 5.55; N, 6.35; S, 7.28. Disulfide (**2d**) ,mp 150—151°, yellow needles. NMR ($CDCl_3$); 3.95 (s, CH_2) 7.07—7.40 (m, arom. H), 7.93 (s, NH). Unknown compound, mp 137—138°, pale yellow plates.

The Reaction of 1-Acetyl-3-Methylindole with S_2Cl_2. Formation of 2e and 4——i) In Ether, with an Excess of S_2Cl_2: A solution of S_2Cl_2 (8.4 g) in ether (30 ml) was added to a solution of 1-acetylskatole[9] (5.0 g) in ether (60 ml) under ice cooling. After the addition the reaction mixture was refluxed for 1 hr. The reaction mixture was neutralized with aq. $NaHCO_3$, washed with H_2O and dried. The ethereal solution was evaporated to leave a residue (5.1 g) which was chromatographed over silica gel column. The crude disulfide (**2e**) (0.87 g, 13%), mp 155—157°, was obtained from the fraction eluted with benzene. Recrystallizations from benzene–hexane gave **2e**, mp 156—157°. The starting materials (**1e**) was recovered in 56% yield.

The reaction of **1e** with 0.5 mole of S_2Cl_2 in ether did not proceed and **1e** was recovered.

ii) In CH_2Cl_2: A solution of S_2Cl_2 (0.39 g) in CH_2Cl_2 (10 ml) was added to a solution of **1e** (1.0 g) in CH_2Cl_2 (20 ml) during 10 min at room temperature. After stirring for 2 hr at room temperature, the mixture was neutralized with $NaHCO_3$, washed with H_2O, and dried. The CH_2Cl_2 solution was evaporated to leave a residue (1.15 g), which, on chromatographic separation, gave a crude disulfide (**2e**. 0,64 g, 54%), mp 149—151°. Recrystallizations from benzene–hexane gave **2e** which was identical with the sample obtained above in mixed mp and IR spectra. From the less polar fraction a small amount of 1-acetyl-2-chloroskatole (**4**) was obtained. **2e**: NMR ($CDCl_3$): 1.55 (s, 3-CH_3), 2.80 (s, $COCH_3$), 7.2—7.5 (m, 3H, arom. H), 8.35 (d, 7-H). In benzene two singlets shifted to 1.45 and 2.52 ppm.

The reaction of **1e** (5.0 g) with S_2Cl_2 (5.0 ml) in CH_2Cl_2 gave **2e** in 68% yield and **4** in 5% yield.

iii) In Dioxane: A solution of S_2Cl_2 (2.03 g) in dioxane (30 ml) was added during 30 min to a solution of **1e** (5.0 g) in dioxane (60 ml) at room temperature. The mixture was refluxed for 10 hr and then the solvent was removed. The residue was dissolved in CH_2Cl_2, and neutralized with aq. $NaHCO_3$, washed with H_2O, and dried. The CH_2Cl_2 solution was Evaporated *in vacuo* to leave a residue (6.3 g) which was chromatographed over silica gel column. The fractions eluted with hexane–benzene (3: 1) gave sulfur (0.6 g). The fractions eluted with hexane–benzene (10: 7) gave 2-chloro derivative (**4**, 0.77 g, 12%), mp 40—43°. Recrystallizations from MeOH gave **4**, mp 47—48.5°, as colorless crystals. *Anal.* Calcd. for $C_{11}H_{10}ONCl$; C, 63.61; H, 4.86; N, 6.75; Cl, 17.08. Found: C, 63.76; H, 4.86; N, 6.56; Cl, 17.76. IR ν_{max}^{KBr} 1700 cm^{-1} (C=O). NMR ($CDCl_3$); 2.25 (s, 3-CH_3), 2.77 (s, $COCH_3$), 7.2—7.5 (m, arom. H), 8.2—8.4 (m, 7-H). Mass Spectrum: *m/e*: (relative abundance); 207 (M^+, 22), 209 (M+2, 8), 167 (32), 165 (M−CH_2=C=O, 100), 164 (59), 130 (*m/e* 165−Cl, 73).

The fraction eluted with benzene gave **1e** (3.48 g, 67%). The disulfide (**2e**) could not be isolated.

iv) Hydrolysis of **4** to **5**: A solution of **4** (60 mg) in EtOH (5 ml) and 2N NaOH (0.5 ml) was stirred at room temperature for 1 hr and the solvent was evaporated *in vacuo*. The residue was extracted with CH_2Cl_2 and the extracts were washed with H_2O, dried and evaporated to leave a residue which was purified through silica gel column to give crude 2-chloroskatole (**5**), mp 111—115°. Recrystallization from aq. AcOH gave **5** which was identical with the sample obtained by the chlorination[10] of skatole with N-chlorosuccinimide in AcOH (mix mp and IR).

vi) Hydrolysis of **2e** to **2a**: To a solution of **2e** (300 mg) in dioxane (30 ml) was added 2N NaOH (10 ml). The reaction mixture was stirred for 90 min at room temperature. The mixture was evaporated, neutralized

8) S. Swaminathan, S. Ranganathan, and S. Sulochana, *J. Org. Chem.*, **23**, 707 (1958).
9) T.A. Geissman and A. Armen, *J. Am. Chem. Soc.*, **74**, 3916 (1952).
10) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958) [*C.A.* **53**, 21867 g (1959)].

with 10% HCl, and extracted with CH_2Cl_2. The residue obtained upon evaporation was purified through silica gel column. The crude **2a** (100 mg) was recrystallized from benzene–hexane to give **2a**, mp 124—127°, whose IR spectra was identical with that of the authentic sample.

2,2′-Dithiobis(3-phenylindole) (**7a**)——An etheral solution of S_2Cl_2 (2.48 g, 0.018 mole, in 30 ml) was added dropwise to an ethereal solution of 3-phenylindole[11] (7.0 g, 0.036 mole, in 70 ml) at 0—1.5° during 20 min. After the addition, the reaction mixture was stirred for 1 hr at room temperature, then neutralized with aq. $NaOCH_3$, washed with H_2O and dried. The solvent was evaporated to leave a residue (8.33 g) which was recrystallized from benzene–hexane to give crude disulfide (**7a**, 4.83 g, 60%), mp 192—194°. Recrystallizations from the same solvent gave **7a**, mp 197—199° (reported mp 194—195°[3]), as orange crystals. NMR ($CDCl_3$) 7.0—7.6 (m, arom. H), 8.0 (br. s, NH).

2,2′-Dithiobis(1-methyl-3-phenylindole) (**7b**)——By the similar procedure as above **6b** (5.5 g) gave crude **7b** (6.69 g). Recrystallization from benzene–hexane gave **7b** (2.53 g, 40%), mp 137—140°. Further recrystallizations from the same solvent gave **7b**, mp 142—143°, as organe pillars. NMR ($CDCl_3$) 3.50 (s, NMe), 6.7—7.5 (m, arom. H).

2,2′-Dithiobis(3-*p*-methoxylindole) (**7c**)——To a solution of **6c**[12] (2.23 g, 0.01 mole) in ether (50 ml) was added S_2Cl_2 (0.68 g, 0.005 mole) in ether (10 ml) at −5° during 30 min. After the addition, the reaction mixture was stirred for 2 hr at room temperature. The mixture was washed with aq. $NaHCO_3$, H_2O, and dried. Evaporation of the solvent gave a residue (2.67 g) as a brown caramel which was chromatographed over silica gel. From the fraction eluted with benzene–hexane **7c** (2.0 g, 80%) was obtained as yellow solid. Recrystallizations from benzene gave **7c**, mp 187—189°, as yellow needles. IR ν_{max}^{KBr} 3400 cm^{-1} (NH). NMR ($CDCl_3$); 3.73 (s, OMe), 6.7—7.6 (m, arom. H), 8.0 (br. s, NH).

2,2′-Dithiobis(3-*p*-methoxylphenyl)-1-methylindole) (**7d**)——A solution of S_2Cl_2 (0.34 g, 2.5 mole) in ether (10 ml) was added dropwise to a solution of **6d**[12] (1.18 g, 5 mmole) in ether (15 ml) and CH_2Cl_2 (15 ml) at −5°. After the addition the mixture was stirred at room temperature for 5.5 hr, and washed with aq. $NaHCO_3$, H_2O, and dried. Evaporation of the solvent gave a solid (1.4 g), mp 138—152°. Recrystallizations from benzene–hexane gave **7d** (0.21 g), mp 169—171°, as yellow powder. The mother liquor of the recrystallization was chromatographed over silica gel. Fractions eluted with benzene–hexane gave 2-chloro derivative (**9**) (90 mg) and **7d** (850 mg, total 1.06 g, 70%). The crude **7d** gave analytical sample on recrystallizations from benzene, mp 169—171°. NMR ($CDCl_3$); 3.61 (s) and 3.73 (s) (NMe and OMe), 6.45 (d), 6.70 (d) (AB quartet of *p*-substituted benzene) 7.0—7.5 (m, arom. H). Recrystallizations of crude **9** from petr. ether gave colorless crystals, mp 90—92°. *Anal.* Calcd. for $C_{16}H_{14}ONCl$: C, 70.80; H, 5.16; N, 5.16; Cl, 12.91. Found: C, 70.70; H, 5.15; N, 5.50; Cl, 12.84. Mass Spectrum (*m/e* (relative intensity)); 273 (M^++2, 48), 271 (M^+, 97), 258(51), 257 (28), 256(100), 228(40), 192(29), 178(25). UV λ_{max}^{EtOH} nm (ε); 230(31400), 263(14800), 283sh(12000), 194sh(11700). NMR ($CDCl_3$) 3.78(s), 3.84(s) (NMe and OMe), 6.95—7.7 (m, arom. H).

The Reaction of 6d with N-Chlorosuccinimide——A solution of N-chlorosuccinimide (0.56 g, 4.2 mmole) in AcOH (20 ml) was added dropwise to a solution of **6d** (1.0 g, 4.2 mmoles) in AcOH (20 ml) and CH_2Cl_2 (5 ml) at 20° during 20 min. At the end of addition the mixture turned dark purple, but it gradually faded upon stirring for 2 hr at 20°. The reaction mixture was neutralized with aq. NaOH with cooling and the oil separated was extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to leave a pale yellow oil (1.0 g) which was chromatographed over silica gel (25 g). The fraction eluted with benzene–hexane (1:2) gave **9** (720 mg, 80%). Recrystallizations from petr. ether raised mp to 97—99°, which was identical with the sample obtained above (mixed mp and IR spectra). The fraction eluted with CH_2Cl_2–benzene (1:1) gave pale brown crystals (**10**, 214 mg, 20%). Recrystallizations from benzene–hexane gave **10**, mp 200—204°. Mass Spectrum (*m/e* (relative abundance)); 488 (M^+, 100), 473(11), 460(7), 459(15), 445 (3), 430(6), 353(26), 252(4). UV λ_{max}^{EtOH} 228 (23000), 286sh(7300). NMR ($CDCl_3$); 2.95(s, oxindolic NMe), 3.44(s, indolic NMe), 3.74(s), 3.78(s) (two OMe).

Hydrolysis of 9——A solution of **9** (500 mg) in dioxane (10 ml) and conc. HCl (15 ml) was refluxed for 2 hr until the TLC of the reaction mixture showed no starting material. The solution was diluted with H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated. The residue (518 mg) was chromatographed over silica gel (15 g). The fraction eluted with acetone–CH_2Cl_2 (1:5) gave crude 3-(*p*-methoxyphenyl)-1-methyloxindole (229 mg) which was recrystallized from ether–hexane to give the oxindole (**9a**), mp 90—91°, as colorless plates. *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.29; H, 5.95; N, 5.48. UV λ_{max}^{EtOH} nm (ε): 226(30800), 255(13600), 266sh(11100), 277sh(6000), 284(5000). Mass Specrtum (*m/e* (relative abundance)); 253(M^+, 100), 238(17), 210(24), 195(4), 181(9), 165(5), 152(7), 127(8). NMR ($CDCl_3$); 3.20 (s, NMe), 3.74(s, OMe), 4.50(s, 3-H), 6.75—7.4(m, arom. H).

2,2′-Dithiobis(3-(*p*-bromophenyl)indole) (**7e**)——To a solution of **6e**[12] (3.6 g, 0.0133 mole) in ether (50 ml) was added dropwise S_2Cl_2 (0.91 g, 0.0067 mole) in ether (10 ml) at −5°. After the addition the reaction mixture was stirred for 30 min at the same temperature and the for another 2 hr at room temperature. The

11) E. Fischer and T. Schmidt, *Ber*, **21**, 1072, 1811 (1888).
12) T. Hino, T. Suzuki, and M. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 2786 (1973).

solution was washed with aq. $NaHCO_3$, H_2O, and dried. The solvent was evaporated to leave a yellow residue (4.34 g) which was chromatographed over silica gel (50 g). Fractions eluted with benzene and CH_2Cl_2 gave the crude disulfide (4.0 g), mp 183—187°, which showed a minor spot besides the main spot on TLC. One recrystallization from hexane gave **7e** (3.3 g, 80%) which showed a single spot on TLC. Further recrystallizations from benzene gave **7e**, mp 189—191°, as orange crystals.

The residue obtained on evaporation of the mother liquor was subjected to a preparative layer chromatography. The less polar zone than **7e** gave 23 mmg of crystals, mp 200—205°, which was assiged to monosulfide (**8e**, $n=1$) from its spectral data. UV λ_{max}^{EtOH} 228, 290, 302sh nm. Mass Spectrum *m/e*: 572 (M^+, 5).

2,2′-Dithiobis(3-(*p*-nitrophenyl)indole) (7g)——To a solution of **6g**[12] (1.0 g) in CH_2Cl_2 (70 ml) was added dropwise S_2Cl_2 (0.29 g) in CH_2Cl_2 (30 ml) at −5° during 20 min. After the addition yellow precipitates began to separate. The yellow precipitates (670 mg, 60%), mp 242—246°, was recrystallized from benzene to give **7g**, mp 253—255°, as yellow crystals.

2,2′-Dithiobis(3-(*p*-nitrophenyl)-1-methylindole) (7h)——A solution of S_2Cl_2 (0.34 g) in CH_2Cl_2 (15 ml) was added to a solution of **6h**[12] (1.26 g) in CH_2Cl_2 (70 ml) at −5° during 10 min. The reaction mixture was stirred for 1 hr at the same temperature. The reaction mixture was washed aq. $NaHCO_3$, H_2O, and dried, and evaporated to leave a yellow solid (1.6 g), mp 276—278°, which was sparlingly soluble to most solvents.

1,3-Dimethyl-2-indolinethione (12b)——To a suspension of **11b** (100 mg) in EtOH (20 ml) was added $NaBH_4$ (30 mg) with stirring. The reaction mixture became colorless within 10 min and was evaporated. The residue was extracted with benzene after addition of AcOH (1 ml). The benzene solution was washed with H_2O, dried and evaporated. The residue (80 mg) showed the presence of small amount of **11b** besides **12b** on TLC. Recrystallizations from petr. ether gave **12b**, mp 43—45°, whose IR spectrum was identical with that of the authentic sample.[2]

3-*tert*-Butyl-2-indolinethione (12c)——A solution of S_2Cl_2 (0.78 g) in ether (10 ml) was added to a solution of **1c**[13] (2.0 g) in ether (40 ml) with ice cooling. After stirring for 2 hr at room temperature, the reaction mixture was neutralized with aq. $NaHCO_3$, washed with H_2O, and dried. The solvent was evaporated to leave a residue (2.32 g), which was found to be a mixture of sulfides by TLC, and the separation of each components was failed. The residue was dissolved in EtOH (20 ml) and $NaBH_4$ (260 mg) was added to the solution at room temperature with stirring. After stirring at room temperature for 50 min the mixture was evaporated. The residue was neutralized with AcOH and extracted with benzene. The benzene solution was washed with H_2O, dried and evaporated to leave a residue (2.2 g) which was chromatographed over silica gel (22 g). The fraction eluted with CH_2Cl_2–benzene–hexane (1 : 1 : 4) gave **12c** (1.24 g, 50%). Recrystallizations from hexane gave **12c**, mp 117—117.5°, as pale yellow crystals.

3-Benzyl-2-indolinethione (12d)——i) From the Disulfide: $NaBH_4$ (410 mg) was added at room temperature to a solution of **11d** (2.75 g) in EtOH (20 ml). After the addition, the mixture was stirred at room temperature for 1 hr, and the solvent was evaporated. The residue was neutralized with aq. AcOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated. The residue (2.36 g) was chromatographed over silica gel (23 g). The fraction eluted with benzene–hexane (1 : 1) gave the disulfide (1.14 g) which was probably obtained by the reoxidation of the thion during work up. The fraction eluted with benzene–hexane (8 : 2) gave crude thione (**12b**, 1.16 g, 53%), mp 129—134°. Recrystallizations from benzene gave **12d**, mp 144—145°, as colorless crystals.

ii) From **1d**, without Isolation of **11d**: 3-Benzylindole (10.0 g) was treated with S_2Cl_2 and $NaBH_4$ as in the case of 3-*tert*-butylindole as above. Upon chromatographic separation of the reaction mixture, **12d** (6.1 g, 53%), monosulfide (**3d**, $n=1$, 2.4 g, 22%), disulfide (**2d**, 1.9 g, 16%), and unknown compound (0.7 g), mp 144—148°, were obtained.

3-Phenyl-2-indolinethione (12e)——$NaBH_4$ (565 mg) was added portionwise to a solution of **11e** (4.65 g) in EtOH–ether (1 : 1, 100 ml) at room temperature. After 40 min stirring at room temperature $NaBH_4$ (240 mg) was added to the mixture and the solvent was evaporated. The residue was treated with aq. AcOH and extracted with benzene. The extracts were washed with H_2O, dried and evaporated. The residue was crystallized from benzene–hexane to give crude **12e** (3.88 g, 83%), mp 129—132°. Recrystallizations from the same solvent twice gave **12e**, mp 130—132.5° (reported mp 134—135°[3]).

Under the similar reaction condition, **11f, g, h, i, k,** and **l** gave the corresponding 2-indolinethiones.

3-(*p*-Bromophenyl)-1-methyl-2-indolinethione (12j)——S_2Cl_2 (200 mg) in ether was added at −5° to a solution of 3-(*p*-bromophenyl)-1-methylindole (**6f**, 840 mg) in ether (50 ml) during 20 min. After the addition the mixture was stirred at room temperature for 4 hr. The mixture was washed with $NaHCO_3$, H_2O, and dried. The solvent was evaporated to give a residue (940 mg) which showed three spots on TLC, and their separation was not successful and the residue (700 mg) was reduced with $NaBH_4$ (500 mg) in EtOH at room temperature. The similar work-up as above gave products (570 mg) which was chromatographed over silica gel to give the thione (**12j**, 490 mg, 53% from the indole). Recrystallizations from benzene–hexane gave **12j**, mp 142—144°, as pale yellow crystals.

The corresponding disulfide (**7f**) was obtained by the air oxidation of **12j** in EtOH.

13) G.F. Smith and A.E. Walters, *J. Chem. Soc.*, **1961**, 940.

3-(*p*-Nitrophenyl)-2-indolinethione (12k)——To a suspension of crude disulfide (**11k**, 1.73 g) in EtOH (60 ml) was added $NaBH_4$ (1.0 g) at room temperature. The mixture was stirred for 6 hr, and the solvent was evaporated. The residue was treated with aqueous AcOH to afford yellow powder which was collected and washed with H_2O and dried. Crude **12k** (1.2 g), mp 120—130°. This 2-indolinethione was easily oxidized with air. Recrystallization from benzene gave the disulfide (**11k**).

1-Methyl-3-(*p*-nitrophenyl)-2-indolinethione (12 l)——A suspension of the crude **11 l** (1.6 g) in EtOH (60 ml) was reduced with $NaBH_4$ (100 mg) at room temperature. After 5 hr stirring at room temperature $NaBH_4$ (50 mg) was added to the mixture, and the solvent was evaporated. The residue was acidified with aq. AcOH and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to give a residue (1.23 g). The residue was extracted with hot benzene and insoluble disulfide (**11 l**), was separated. The benzene solution was evaporated to leave a solid which was recrystallized from benzene–hexane to give **12 l**, mp 159—161°, as pale yellow crystals.

1-Methyl-2-ethylthio-3-(*p*-nitrophenyl)indole (13)——To a suspension of the disulfide (**11 l**, 250 mg) in EtOH (50 ml) was added $NaBH_4$ (100 mg) at room temperature. After stirring at room temperature for 3 hr, ethyl iodide (140 mg) was added to the mixture. After 3 hr stirring at room temperature the solvent was evaporated. The residue was acidified with aq. HCl and extractecd with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to give a crystalline solid (230 mg). This was subjected to silica gel chromatography and 210 mg of yellow crystals was obtained. Recrystallizations (from cyclohexane) gave **13**, mp 117—120°, as yellow needles. *Anal.* Calcd. for $C_{17}H_{16}O_2N_2S$: C, 65.38; H, 5.13; N, 8.97. Found: C, 65.44; H, 5.61; N, 8.96. UV λ_{max}^{EtOH} nm (ε): 228(16500), 292(6850), 380(5050). Mass Spectrum *m/e* (relative abundance); 312 (M^+, 97), 284(20), 266(11), 237(100), 222(29). NMR ($CDCl_3$): 1.00(t, $CH_2C\underline{H}_3$), 2.58(q, $C\underline{H}_2CH_3$), 3.91(s, NMe).

Reaction of 6a with S_2Cl_2 in CH_2Cl_2——To a solution of **6a**(1.5 g) in CH_2Cl_2 (50 ml) was added S_2Cl_2 (0.55 g) at −5° during 30 min. The mixture was stirred at the same temperature for 30 min, and at room temperature for 3.5 hr. The reaction mixture was washed with aq. $NaHCO_3$, H_2O, dried and evaporated to leave a yellow oil (1.94 g) which was chromatographed over silica gel. The fraction eluted with benzene gave an oil (800 mg) which was found to consist of a mixture of the disulfide and the monosulfide on TLC. The fraction eluted with CH_2Cl_2 gave 800 mg of unknown compounds.

Reaction of 6a with SCl_2——To a solution of **6a** (1.0 g) in dry ether (50 ml) was added SCl_2 (0.27 g) in dry ether (20 ml) at −3° during 30 min. The mixture was stirred for 30 min at the same temperature, then for another 4 hr at room temperature. The mixture was washed with aq. $NaHCO_3$, H_2O, and dried, and evaporated to leave a residue (1.07 g). A portion (100 mg) of the mixture was separated by preparative layer to give 15 mg of disulfide, 19 mg of **6a**, and 32 mg of the monosulfide (**8a**, $n=1$). Mass spectrum of the monosulfide *m/e* 416 (M^+, 96). UV λ_{max}^{EtOH} 226, 295, and 303 nm.

Reaction of 6c with S_2Cl_2 in CH_2Cl_2——A solution of S_2Cl_2 (0.34 g) in CH_2Cl_2 (20 ml) was added to a solution of **6c** (1.12 g) in CH_2Cl_2 at −5° during 30 min. The reaction mixture was stirred for 30 min at −5°, then for 5 hr at room temperature. The reaction mixture was washed with $NaHCO_3$, H_2O, and dried. The solvent was evaporated to leave a residue (1.45 g), which was chromatographed over silica gel. The fraction eluted with benzene–hexane (2: 1) yielded **7c** (200 mg, 20%). The fraction eluted with benzene gave the monosulfide (**8c**, $n=1$, 200 mg). The fraction eluted with CH_2Cl_2 containing a small amount of acetone gave orange crystals, mp 240—250°. Further purification of this substance has not been successful.

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