[Chem. Pharm. Bull. **17**(3) 550—558 (1969)]

UDC 547.756.04.07

Thiation of Oxindoles[1]

TOHRU HINO,[2a] KAZUKO TSUNEOKA (née YAMADA),[2] MASAKO NAKAGAWA,[2a] and SANYA AKABOSHI[2]

Department of Pharmaceutical Sciences, National Institute of Radiological Sciences[2]

(Received August 13, 1968)

The thiation of methyl substituted oxindoles (I) with phosphorous pentasulfide gave the corresponding 2-indolinethiones (II). The 2-indolinethione (II) having more than one hydrogen at 3-position, however, were sensitive towards phosphorous pentasulfide to produce the indolic compounds such as III, IV, V and VI. On the other hand the 2-indolinethione (VIII) prepared from VII with phosphorous pentasulfide, was stable towards the reagent.

Reactivity of 2-indolinthione (IIb) was compared with the oxindole (Ib) in some reactions including the deuteration at 3-position in deuterochloroform-acetic acid-d_4.

Synthesis and chemical reactivity of oxindoles (I) have been intensively investigated especially in the field of indole alkaloids.[3] 2-Indolinethiones (II), however, draw a little attention up to present time.

Formation of 2-indolinethione was first reported in the reaction of indole Grignard reagent with sulfur,[4] in the Fischer indole synthesis,[5] and in the reduction of 2,2′-indolyl disulfide.[6] Thiation of oxindole with phosphorous pentasulfide (P_2S_5) was reported by Sugasawa, *et al.*[7] on oxindole (Ia) and by Brunner[8] on 3,3-dimethyloxindole (VII). Wieland and his coworkers,[6a] however, did not succeed to obtain IIc by the thiation of 3-methyloxindole with P_2S_5, but obtained 2,2′-indolyl disulfide besides sulfide and trisulfide. Furthermore Plieninger[9] reported that 3-benzyl-2-indolinethione obtained by thiation of the corresponding oxindole could not be purified but the crude reaction mixture afforded 3-benzylindole by hydrogenolysis with Raney-nickel. These results indicate that the thiation of oxindoles is not simple reaction as in cases of general carboxylic acid amides which give the corresponding thionamide smoothly with P_2S_5.[10] In the present paper we report that 2-indolinethione (II) can be prepared by the thiation of the corresponding oxindoles (I), however II was sensitive towards an excess P_2S_5 and gave indole derivatives, some of which contained sulfur atom.

When oxindole (Ia) was heated for 80 min in benzene with 0.2 mole equivalent of P_2S_5, 2-indolinethione (IIa), mp 148—150°, was obtained in 56% yield. Biindole (IIIa), and its

---

[1] A part of this paper was published as a preliminary report: T. Hino, K. Yamada, and S. Akaboshi, *Chem. Ind.* (London), 1967, 275.

[2] Location: *Anagawa 4-Chome, Chiba-shi*; *a*) Present Address: *Faculty of Pharmaceutical Sciences, University of Chiba, Yayoi-cho, Chiba-shi.*

[3] P.L. Julian, E.W. Meyer, and H.C. Printy, "Heterocyclic Compounds," Vol. 3, ed. by R.C. Elderfield, John Wiley & Sons, Inc., New York, 1952, Chapter I; R.H.F. Manske(ed.), "The Alkaloids" Vol VIII, Academic Press, New York, 1965.

[4] B. Oddo and Q. Mingoia, *Gazz. Chim. Ital.*, **62**, 299 (1932) [(*C.A.*, **29**, 7952 (1932)]; B. Oddo and L. Raffa, *ibid.*, **71**, 242 (1941) [(*C.A.*, 36,2854 (1942)].

[5] H. Wuyts and A. Laccourt, *Bull. Sci. Acad. Roy. Belg.*, **21**, 736 (1935) [(*C.A.*, **29**, 7952 (1935)].

[6] *a*) T. Wieland, O. Weiberg, E. Fischer, and G. Horlein, *Ann.*, **587**, 146 (1954); *b*) T. Wieland, O. Weiberg, and W. Dilger, *Ann.*, **592**, 69 (1955).

[7] S. Sugasawa, S. Satoda, and J. Yanagisawa, *Yakugaku Zasshi*, **58**, 29 (1938).

[8] K. Brunner, *Monatsh.*, **62**, 396 (1933); G.E. Fichen and J.D. Kendall, *J. Chem. Soc.*, **1960**, 1529.

[9] H. Plieninger and G. Werst, *Angew. Chem.*, **70**, 272 (1958).

[10] W. Walter and K.-D. Bode, *Angew. Chem.*, **78**, 517 (1966).

tetra sulfide (IVa) were isolated as by-products from the reaction mixture. The structure of IIIa[11] and IVa[12] were confirmed by direct comparison of authentic specimens. Intermediacy of IIb to the formation of IIIa and IVa was proved by the reaction of IIa with P_2S_5 from which IIIa and IVa were obtained. The yield of IIa was decreased under more vigorous reaction condition with increasing by-products.

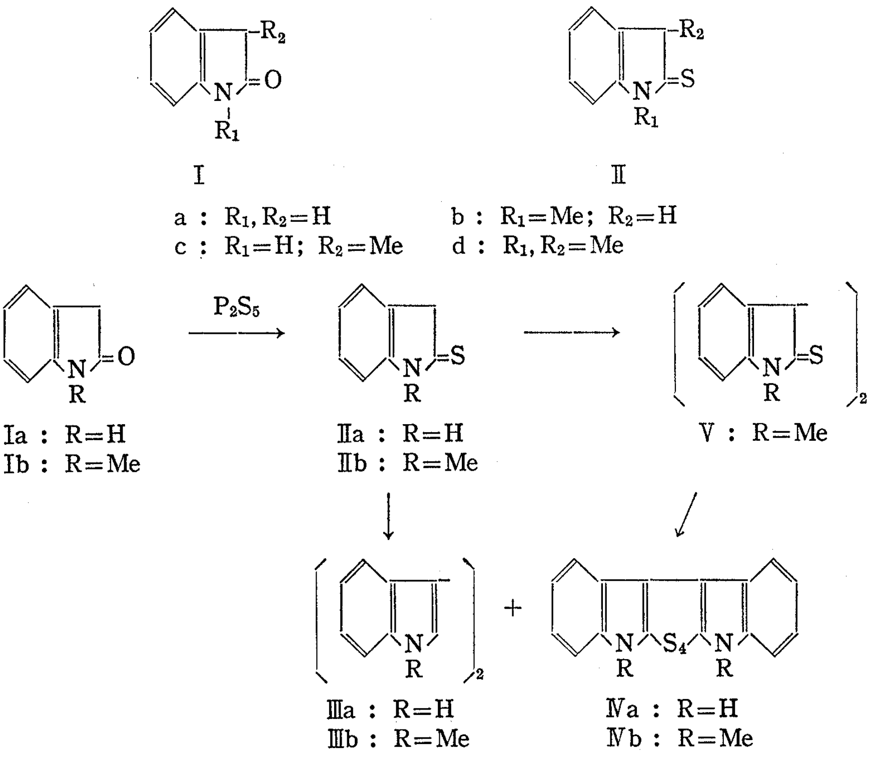


Chart 1

1-Methyl-2-indolinethione (IIb), mp 109—110°, was obtained in 67% yield when Ib was treated with 0.2 mole equivalent of P_2S_5 in xylene at 100°. Dimethylbiindole (IIIb) and its tetrasulfide (IVb) were isolated from the reaction mixture. The structures of IIIb and IVb were confirmed by the direct comparison with authentic samples. The authentic specimen of IIIb was prepared by the methylation of IIIa with methyl iodide in liquid ammonia in the presence of sodium amide. And the standard sample of IVb was prepared from the reaction of 1-methylindole with sulfur[12] in dimethylformamide. 1,1′-Dimethyl-3,3′-bis-2-indolinethione (V), mp 183—184°, was isolated from the reaction mixture as the third by-product. The corresponding desmethyl derivative of V could not be isolated in the thiation of Ia. The structure of V[13] was deduced by spectral data and confirmed by the direct comparison with the sample prepared by two different methods, namely by the thiation of 3,3′-bioxindole,[14] or by the oxidative dimerization of IIb with iodine in methanol. Thiation of Ib with 0.2 mole equivalent of P_2S_5 in boiling xylene gave IIIb as a main product, and IIb, IVb and Vb as minor products.

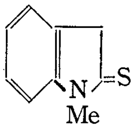
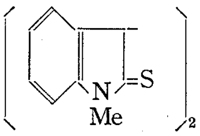
The stability of these compounds (IIb, IIIb, IVb and V) was examined under the thiation condition. The compounds (IIIb and IVb) were rather stable on refluxing in toluene with 0.2 mole equivalent of P_2S_5. However, the mixture of the products were obtained when IIb or V was heated in benzene or xylene in the presence or absence of P_2S_5. The approximate

---

[11] L. Raffa, *Gazz. Chim. Ital.*, **71**, 253 (1941) [*C.A.*, **36**, 2856 (1942)].
[12] W. Carpenter, M.S. Grant, and H.R. Snyder, *J. Am. Chem. Soc.*, **82**, 2739 (1960).
[13] The stereochemistry of V is not clear, but a sole isomer is obtained by the three methods.
[14] T. Hino, *Chem. Pharm. Bull.* (Tokyo), **12**, 979 (1961).

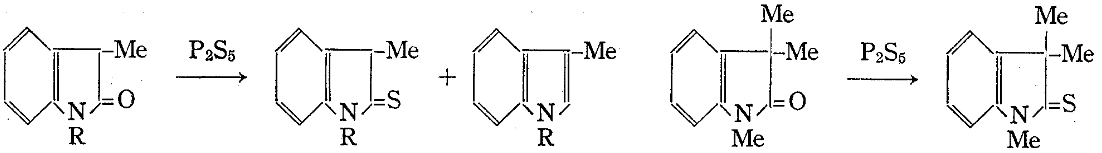
NII-Electronic Library Service

Table I. Stability of 1-Methyl-2-indolinethione (IIb) and 1,1'-Dimethyl-3,3'-bis-2-indolinethione (V)

Compound	Condition		Ratio of products			
			IIb	V	IIIb	IVb
 IIb	a) without P_2S_5 toluene reflux	2 hr		no change		
	b) with P_2S_5 benzene reflux	30 min	15	1	—	—
		2 hr	5.5	1.5	1	—
		4 hr	7	5	6.5	2
	xylene reflux	5 min	3	3	8.5	2.5
		2 hr	—	1.5	7.0	3.0
 V	a) without P_2S_5 xylene reflux	1 hr	3	5	3	3
		4 hr	2	1	6	7
	b) with P_2S_5 benzene reflux	1 hr	5	6	14	14
	xylene reflux	1 hr	—	2	9	16

ratios of the products estimated by the N-methyl signals[15] of the nuclear magnetic resonance (NMR) spectra of the mixture are shown in Table 1. The compound (V) decomposed to IIb, IIIb and IVb in boiling xylene without P_2S_5 in which condition IIb did not decomposed. The compound (IIb) transformed to V, IIIb and IVb in boiling xylene in the presence of P_2S_5. It is probable to assume that the compound (V) would be the intermediate of the transformation of IIb to IIIb and IVb, but another pathway of the formation of IIIb and IVb directly from IIb could not be excluded because the ratios of IIIb and IVb from IIb and V were not identical. Phosphorous pentasulfide could be considered to act as a dehydrogenation reagent in the formation of V from IIb, since the formation of V was not observed when IIb was refluxed in toluene without P_2S_5. Though the mechanism of the formation of IIIb and IVb from V is umbiguous, the process of thiation and its side reaction could be shown as chart 1.

Thiation of 3-methyloxindoles (Ic and d), which is not expected to produce biindoles such as III and IV, with P_2S_5 was carried out. The corresponding 2-indolinethiones (IIc and d) were obtained in moderate yield. 3-Methylindole (VIa or b) was isolated as one of the by-products from the reaction mixture. When IId was refluxed in toluene with P_2S_5, IId changed to VIb. On the other hand IId did not change to VIb in a boiling toluene without P_2S_5. The compound (IId) decomposed on storage to many products among which the presence of VIb was confirmed by thin-layer chromatography (TLC).



Ic : R=H IIc : R=H VIa : R=H VII VIII
Id : R=Me IId : R=Me VIb : R=Me

Chart 2

Thiation of 1,3,3-trimethyloxindole (VII), which can not produce indole derivative without rearrangement, was carried out with P_2S_5. The corresponding 2-indolinethione (VIII) was obtained as a sole product in good yield as reported[8] in boiling xylene with 0.4 mole equivalent of P_2S_5, which was more vigorous condition than those employed to other

---

[15] The chemical shift of N-methyl in IIb and V are very close each other, but could be assigned considering signals of 3-methylene or 3-methine.

oxindoles. The compound (VIII) was stable towards P_2S_5 in boiling xylene and recovered without decomposition.

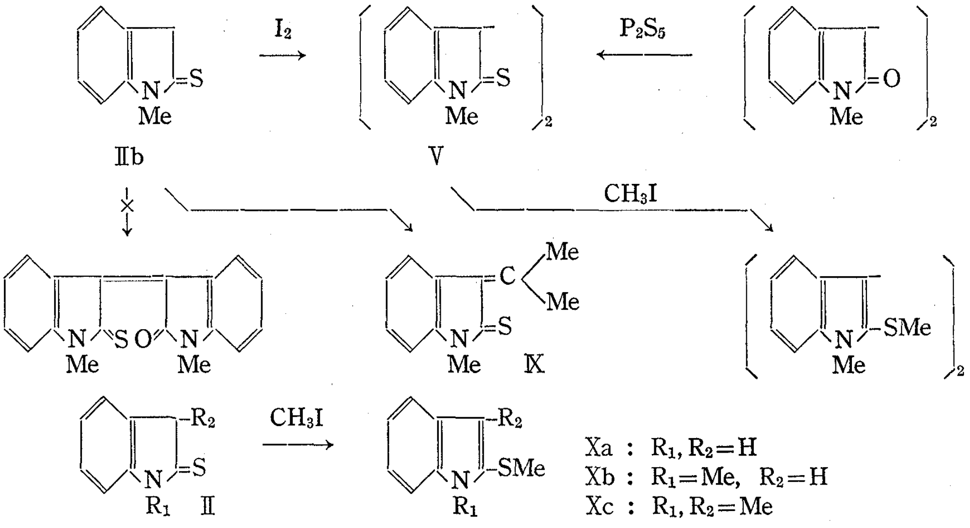
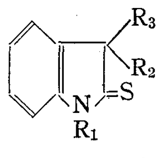


Chart 3

These results indicate that the main factor for the complicated result of thiation of the oxindole was due to the reactivity of the hydrogen at 3-position. Therefore, the reactivity of 3-position of 2-indolinethiones was compared with that of oxindoles which is also known to be reactive. As described above IIb gave V on iodine oxidation in methanol at room temperature in good yield, while the oxidation of Ib with iodine under the similar condition was slow and gave a small amount of 1,1′-dimethylisoindigotin instead of the bioxindole besides many other products. This reaction indicate the bioxindole is more sensitive to iodine oxidation than Ib while IIb is more reactive to iodine than V. On treatment with acetone in the presence of potassium carbonate or hydrochloric acid, IIb gave 3-isopropylidene compound (IX), mp 164—165°. The compound (Ib) gave 1,1′-dimethylisoindigotin[14] in good yield when Ib was treated with N-methylisatin in warmed acetic acid containing a few drops of hydrochloric acid. Under the similar condition IIb did not gave an isoindigotin type compound and the only compound isolated was unreacted N-methylisatin, and IIb could not be recovered. This indicate that IIb was unstable in warmed acetic acid and decomposed before the condensation. Oddo[4] reported that IIa did not react with isatin in the presence of hydrochloric acid.

To examine further the reactivity of 3-hydrogen of oxindoles and 2-indolinethiones, deuterium exchange reactions of IIb and IIc were carried out in a deuterochloroform solution in the presence of acetic acid-d_4. About 20% of 3-methylene group of IIb was deuterated

TABLE II. The UV and NMR Spectral Data of 2-Indolinethiones (II and VIII)

			UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ ($\varepsilon \times 10^{-4}$)	NMR (in $CDCl_3$, ppm from TMS)			
R_1	R_2	R_3		3-Me	N-Me	3-H	NH
H	H	H	317 (1.67), 293 (1.06), 228 (1.29)	—	—	4.08 (s)	11.04 (br)
Me	H	H	315 (1.66), 295 shoulder (1.13), 232 (1.40)	—	3.62 (s)	4.07 (s)	—
H	Me	H	318 (1.61), 293 shoulder (1.03), 230 (1.40)	1.64 (d)	—	3.84 (q)	10.65 (br)
Me	Me	H	315 (1.70), 295 shoulder (1.13), 230 (1.48)	1.63 (d)	3.64 (s)	3.79 (q)	—
Me	Me	Me	312 (1.90), 295 shoulder (1.30), 230 (1.40)	1.43 (s)	3.65 (s)	—	—

NII-Electronic Library Service

in the first two hours in a deuterochloroform-acetic acid-d_4 solution and nearly 70% of 3-methylene was deuterated after 24 hours at room temperature. Deuteration of IIc seemed to proceed more rapidly to give about 70% of 3-deuterated IIc within first 2 hours and the deuteration was nearly completed after 24 hours in a deuterochloroform-acetic acid-d_4 at room temperature. On the other hand, a very little or no deuteration was observed in Ib and Ic under the similar condition. These results clearly show the higher mobility of 3-hydrogen in 2-indolinethiones than that of oxindoles. Though these results can be considered as one of valuable indications of the presence of the equilibrium between the 2-indolinethione and the 2-mercaptoindole, the spectral data (UV and NMR) indicate that 2-indolinethiones prepared in this study are present mostly in the 2-indolinethione form.

Another difference in the reactivity of the oxindole and 2-indolinethione was observed in the alkylation reactions. The 2-indolinethiones give 2-methylthioindoles (X) in good yield when II was treated with methyl iodide in acetone in the presence of potassium carbonate at room temperature. S-Alkylation was preferencial to N-methylation in case of IIa as in cases of general thionamides. N-Methylation was observed in the reaction of oxindole with methyl iodide in boiling acetone in the presence of potassium carbonate.

The ultraviolet and nuclear magnetic resonance spectra of II were shown in Table II. The absorption maxima of 2-indolinethiones (IIa, b, c and d) are at 315 and 230 mμ, which are very close to those of VIII, and different from those of 2-methylthioindoles (X), which are 295 and 287 mμ. As far as the UV and NMR spectra concern, it is concluded that the 2-indolinethione in solution is present mostly in thione form and the 2-mercaptoindole form could not be detected.[16)]

The mass spectra and the solvent shift in NMR spectra as well as IR spectra or II and I will be discussed in the separate paper.

Further investigation of the reactivity of these 2-indolinethiones are now under progress.

Experimental[17)]

Thiation of Oxindole (Ia)——i) With 0.2 mole of P_2S_5. To a mixture of Ia (15.0 g) and sea sand (15 g) in benzene (300 ml) was added P_2S_5 (5.3 g, 0.2 mole equivalent) in portionwise. The whole mixture was heated to reflux with stirring for 80 min. After cooling benzene layer was decanted and insoluble materials were extracted with benzene and AcOEt. The benzene solution and benzene extracts were combined and evaporated *in vacuo* to leave a solid (11.5 g, 68.4% as crude IIa), mp 125—130°. Recrystallization from MeOH gave pale yellow crystals (7.4 g), mp 145—148°, which afforded analytical sample of IIa on further recrystallizations, mp 147—149° (reported mp 145°,[7)] 146—150°[4)]). *Anal.* Calcd. for C_8H_7NS: C, 64.39; H, 4.73; N, 9.39; S, 21.49. Found: C, 64.70; H, 4.13; N, 9.11; S, 21.71.

The mother liquors of the recrystallization and the AcOEt extracts (1.0 g) were combined and were chromatographed over silicagel column. From the benzene eluate biindolyl tetrasulfide (IVa, 15 mg), and biindole (IIIa, 94 mg) were isolated. These compounds were identical with the authentic samples in IR and TLC. The methyle chloridene eluate gave IIa (2.0 g). Total yield of IIa was 9.4 g (56%).

When Ia (7.5 g) was treated with 0.4 mole of P_2S_5 in boiling benzene for 1 hr, IIa was obtained in poor yield (175 mg), and IIIa (145 mg) and IVa (62 mg) were isolated from resinous reaction products. Other products were not isolated in pure state.

Formation of Biindole (IIIa) and Its Tetrasulfide (IVa) from IIa——A mixture of IIa (650 mg) and P_2S_5 (200 mg) in xylene (25 ml) was refluxed for 1 hr. After cool xylene layer was decanted and the residue was extracted with hot benzene and tetrahydrofuran. The combined extracts were evaporated *in vacuo* to leave a brown solid (660 mg), which was chromatographed over silica gel. From the benzene eluate crude IVa (69 mg) was obtained. On recrystallization from acetone gave IVa, mp 293—294° (decomp.), which was identical with the authentic sample[12)] prepared by our hand on admixture and in IR and UV spectra. Secondly crude biindole (IIIa, 230 mg) was eluted with the same solvent. Recrystallization from benzene

---

16) However, the NMR spectrum of IIc showed a small but sharp signal at 2.3 ppm which may consider the signal of the 3-methyl in 2-mercaptoindole. Investigation along this line is now under progress.

17) All melting points are uncorrected. The UV spectra were taken with a Cary Model 14 or Perkin-Elmer 202 spectrometer pectrometer, and NMR spectra with a Varian Associates HR-100 spectrometer. The chemical shifts were expressed by the δ values in ppm from TMS as an internal standard.

gave IIIa, mp 277—279° (decomp.), which showed no depression on mixed melting with the authentic sample.[11] IR and UV spectra were superimposable with those of the authentic sample.

Thiation of 1-Methyloxindole (Ib)——i) To a mixture of Ib (14.7 g) and sea sand (15.0 g) in xylene (150 ml) was added P_2S_5 (4.7 g, 0.2 mole equivalent) portionwise at 80° (bath temperature) with stirring. The whole mixture was heated at 100° (bath temperature) for 1 hr with stirring until the UV maximum of Ib had disappeared. After cool xylene layer was decanted and the residue was extracted with hot xylene. The combined extracts were evaporated *in vacuo* to leave a brown solid (13.2 g), mp 94—97°. Recrystallization from benzene–hexane twice gave pale yellow crystals of IIb (8.9 g), mp 108—110°, which showed a sole spot on thin-layer chromatogram. Recrystallizations from benzene gave analytical sample of IIb, mp 109—11°, as almost colorless crystals. *Anal.* Calcd. for C_9H_9NS: C, 66.22; H, 5.56; N, 8.58; S, 19.64. Found: C, 66.21; H, 5.33; N, 9.16; S, 19.73.

The mother liquors of recrystallization and methylene chloride soluble fraction of the residue of the reaction mixture were combined and evaporated *in vacuo*. The residue (4.7 g) was chromatographed on silica gel. From hexane–benzene (1:2) eluate curde IIIb (280 mg) was obtained. Recrystallization from benzene gave IIIb, mp 180—183°, which was identical with the authentic IIIb by direct comparison. From the benzene–methylene chloride (1:1)eluate IIb (2.0 g, total 10.9 g, 67% yield), mp 104—106°, was obtained. Elution with methylene chlorid gave crude V (320 mg). Recrystallizations from benzene–hexane gave pale yellow crystals, mp 182—184°, which was identical with the sample obtained by other methods (see below). The presence of IVb was recognized by TLC in the fraction eluted with hexane–benzene (2:1), but was unable to isolate in pure state.

ii) A mixture of Ib (7.36 g), sea sand (3.0 g) and P_2S_5 (2.35 g, 0.2 mole equivalent) in xylene (80 ml) was heated to reflux with stirring for 30 min. After cool xylene layer was decanted and the residue was extracted with xylene. The combined extracts were evaporated *in vacuo* to leave a dark brown solid (6.7 g). The NMR spectra showed the presence of IIIb, IVb, IIb and V in approximate ratio 7:1.5:1:0.4 by the estimation from N-methyl signals. The solid was chromatographed over silica gel. From the hexane–benzene (2:1) eluate yellow crystals (928 mg) was obtained which was recrystallized from hexane–benzene to afford yellow IVb, mp 260—262°. *Anal.* Calcd. for $C_{18}H_{14}N_2S_4$: C, 55.92; H, 3.65; N, 7.25. Found: C, 56.05; H, 3.24; N, 6.70. NMR (in $CDCl_3$, ppm from TMS): 3.99 (s, NMe), 7.01—7.51 (m, aromatic H). Mass: M^+ *m/e* 386. The compound was found to be identical with the sample prepared from 1-methylindole and sulfur in dimethylformamide following the procedure for IVa.[12]

From benzene–hexane (2:1) eluate IIIb (3.2 g, 49%) was obtained as a main product. Recrystallization from benzene gave colorless crystals of IIIb, mp 181—183°, which was identical with the sample obtained by the N-methylation of IIIa with methyl iodide in liquid ammonia in the presence of $NaNH_2$. *Anal.* Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 82.90; H, 6.15; N, 10.40. NMR (in $CDCl_3$, ppm from TMS): 3.82 (s, NMe), 7.05—7.87 (m, aromatic H). Mass: M^+ *m/e* 260.

From later fractions IIb (710 mg) and V (170 mg) were obtained and characterized.

Thiation of 1,3-Dimethyloxindole (Id)——A mixture of Id (9.67 g) and P_2S_5 (2.67 g) in toluene (150 ml) was refluxed for 2.5 hr. Toluene layer was decanted and the residue was extracted with toluene. The combined extracts were evaporated *in vacuo* to leave a brown oil (10.6 g). Thin-layer chromatogram of the oil on silica gel (developed by hexane–benzene (2:1), and spots were disclosed by I_2 vapor) showed 8 spots. The oil was chromatographed over silica gel column using hexane–benzene as eluting solvent. The compounds obtained from the column are shown below. Numbering of the compounds correspond the spot on TLC from the top.

Compound 1, 90 mg, mp 106—111°, colorless crystal.
Compound 2, 250 mg, a pale brown oil.
Compound 3, 250 mg, mp 218—230°, after two recrystallizations from benzene.
Compound 4, 4.0 g, pale yellow oil.
Compound 5, 78 mg, mp 205—215°.
Compound 6, 300 mg, mp 227—230°.
Compound 7, 170 mg, mp 137—150° after one recrystallization.
Compound 8, 2.0 g pale brown oil.

The compound 2 was identical with 1,3-dimethylindole by comparison of spectral data (IR, UV and NMR) with those of the standard sample. The compound 4 was solidified on standing, mp 42—43°, which was recrystallized from petr. ether to afford IId, mp 45—46°. *Anal.* Calcd. for $C_{10}H_{11}NS$: C, 67.75; H, 6.35; N, 7.90; S, 17.99. Found: C, 68.22; H, 5.91; N, 7.55; S, 17.99. The compound 8 corresponded to recovered Id identified by the comparison of spectral data. Other compounds were not investigated further. The compound (IId) was unstable and decomposed to a dark brown oil on long standing. The dark brown oil showed many spots on TLC, one of which had the *Rf* value corresponded to 1,3-dimethylindole.

Thiation of 3-Methyloxindole (Ic)——To a benzene solution (45 ml) in which Ic (5.89 g) was dissolved with heating was added dried sea sand (4.0 g) and P_2S_5 (1.78 g), and the reaction mixture was refluxed for 1.5 hr with vigourous stirring under a stream of N_2. The hot reaction mixture was decanted to remove sand, which was washed with hot benzene. On cooling, the benzene extracts were filtered to remove yellowish precipitates (3.9 g), mp >200°, which was not yet investigated. The filtrate was diluted with methylene chloride and neutralized with $NaHCO_3$, washed with H_2O and dried. Evaporation of the solvent gave an oil (3.9 g), which solidified upon standing, was column chromatographed on silicagel. Elution with benzene gave skatole (440 mg) which was recrystallized from benzene–hexane to give mp 92—93°, mixed mp 93—95° with an authentic specimen. Spectral data confirmed its identities in all regions as well as TLC. Elution with benzene–methylene chloride (3:1) furnished IIc (2.2 g, 23%), mp 115—116°, as pale yellow needles. Recrystallizations from benzene–hexane gave mp 118—119°, as a colorless needles. *Anal.* Calcd. for C_9H_9NS: C, 66.24; H, 5.56; N, 8.58; S, 19.61. Found: C, 66.59; H, 5.35; N, 8.53; S, 19.73.

The starting material (Ic, 1.2 g) was recovered from the elution with methylene chloride.

Thiation of 1,3,3-Trimethyloxindole (VII)——A mixture of VII (5.26 g) and P_2S_5 (2.67 g, 0.4 mole equivalent) in xylene (60 ml) was refluxed for 4 hr. The xylene layer was decanted and the residue was extracted with xylene. The combined extracts were evaporated *in vacuo* to leave a brown oil. The oil was distilled to give VIII (4.6 g, 81%), bp 137° 2 mmHg, (reported bp 102°, 0.3 mmHg), as a colorless viscous oil. Mercuric chloride complex, mp 198—199° (reported mp 200—200.5°). On heating VII with P_2S_5 (0.2 mole equivalent) in xylene for 2 hr, there was obtained a mixture of VII and VIII in ratio of 1:2. The compound (VIII) was stable towards P_2S_5 in boiling xylene and recovered unchanged.

Alternative Synthesis of V——i) Oxidative Dimerization of IIb: To a solution of IIb (1.06 g) in MeOH (40 ml) was added I_2 (1.65 g, 1 mole equivanlet) in MeOH (30 ml) dropwise during 25 min with stirring at room temperature. After each addition of I_2 solution color of I_2 faded rapidly, and crystals were precipitated. The mixture was further stirred at room temperature for 30 min by which time the spot of IIb on TLC had disappeared. The crystals were collected to give crude V (970 mg), mp 163—165°, which was purified through silicagel column to afford V (750 mg, 71%). Recrystallizations from benzene–hexane to give V, mp 182—184°. *Anal.* Calcd. for $C_{18}H_{16}N_2S_2$: C, 66.63; H, 4.97; N, 8.63; S, 19.76. Found: C, 67.00; H, 4.84; N, 8.73; S, 19.99. UV $\lambda_{\max}^{\mathrm{CCl_4}}$ mμ (ε): 330 (2.59×10^4), 299 (1.99×10^4), 293 shoulder (1.51×10^4). NMR (in $CDCl_3$, ppm from TMS): 3.64 (s, N–Me), 4.94 (s, 3–H), 6.74—7.33 (m, aromatic H). Mass: M^+ *m/e* 324 (direct inlet system).

ii) Thiation of 1,1′-Dimethyl-3,3′-bioxindole: A mixture of bioxindole (2.05 g) and P_2S_5 (780 mg) in benzene (20 ml) was refluxed for 3 hr under a stream of N_2. The benzene layer was decanted and the residue was extracted with benzene. The extracts were evaporated *in vacuo* to leave a resinous oil (2.29 g), which was chromatographed over silica gel column. From the benzene–hexane (2:1) eluate, crude IVb (195 mg) was obtained. Recrystallization from benzene twice gave IVb, mp 259—261°. IR spectra and TLC behaviour were identical with those of the authentic sample. The fraction eluted with benzene–hexane (1:1) gave crude IIIb (440 mg). Recrystallizations from benzene–hexane gave IIIb, mp 180—182°, whose IR spectra was superimposable with that of the authentic sample. The fraction eluted with benzene gave curde V (263 mg), which was recrystallized from benzene–hexane twice to give V, mp 180—182°, mixed mp 180.5—182° with the sample obtained by the method i). The fraction eluted with methylene chloride containing 2% MeOH gave the starting material (406 mg), mp 172—173°. Recrystallizations from benzene–hexane gave the bioxindole, mp 183—185°, whose IR spectrum was superimposable with that of the authentic sample.[14]

Reaction of IIb with P_2S_5——i) A solution of IIb (980 mg) and P_2S_5 (270 mg) in xylene (30 ml) was refluxed for 40 min. The benzene layer was decanted and evaporated *in vacuo* to leave a dark green resinous oil (950 mg), which was extracted with benzene and the extracts were evaporated to leave a brown resinous oil (650 mg). The oil was chromatographed over silica gel column. Crude IVb (95 mg), IIIb (240 mg) and IIb (30 mg) were obtained from the eluates. Each compounds were identified with standard samples after recrystallizations. The compound (V) was not isolated in pure state.

ii) By NMR. A mixture of IIb (980 mg), P_2S_5 (270 mg) and K_2S (400 mg) in benzene or xylene (30 ml) was refluxed. After appropriate period of the refluxing, a portion (about 1 ml) of the reaction mixture was taken out. The solvent was evaporated *in vacuo* and the residue was dried and dissolved in $CDCl_3$ (0.5 ml) to run the NMR spectrum analysis. Intensities of N-methyl signals of IIb, IIIb, IVb and V in the reaction mixture were estimated by an integrator. The results are shown in Table I.

Reaction of IId with P_2S_5——A mixture of IId (522 mg) and P_2S_5 (133 mg) in toluene (40 ml) was refluxed for 2 hr. The toluene was evaporated *in vacuo* and the residue was chromatographed over silica gel column. The starting material (IId, 120 mg) accompanied with dimethylindole (87 mg) were obtained besides other by-products which could not be isolated in pure state. The both compounds were identified with the standard samples by TLC as well as UV and IR spectra. Without P_2S_5 IId was stable in boiling toluene for 2 hr and recovered unchanged.

Reaction of IIb with Acetone: Formation of 3-Isopropylidene-1-methyl-2-indolinethione (IX)——A solution of IIb (500 mg) in acetone (20 ml) containing 3 drops of conc. HCl solution was stirred at room temperature for 3 days. Yellow crystalls were precipitated from the solution. The crystals (200 mg), mp 157—160°, were collected and recrystallized repeatedly from petr. benzine or hexane–benzene to give pure IX, mp 164—165°. *Anal.* Calcd. for $C_{12}H_{13}NS$: C, 70.89; H, 6.45; N, 6.89; S, 15.77. Found: C, 70.90; H, 6.07; N, 6.90; S, 15.64. NMR (in $CDCl_3$, ppm from TMS): 2.54 (s, Me), 2.96 (s, Me) 3.70 (s, N–Me), 6.97—7.69 (m, aromatic H).

NII-Electronic Library Service

Reaction of IIb with 1-Methylisatin——A mixture of IIb (506 mg) and 1-methylisatin (500 mg) in AcOH (20 ml) was heated at 95—100° (bath temperature) for 4.5 hr. Small amount of precipitate was filtered and the filtrate was evaporated *in vacuo* to leave a dark brown resinous oil, which showed many spots on TLC. The oil was chromatographed over silica gel column. From the fraction eluted with benzene–methylene chloride crude 1-methylisatin (370 mg) was recovered and was identified with the standard sample by mixed melting point and IR spectra. From the other fractions no pure compound was isolated.

Reaction of Ib with I_2——To a solution of Ib (515 mg) in MeOH (15 ml) was added I_2 (888 mg) in MeOH (15 ml) dropwise at room temperature. Decoloration of I_2 was slow compared with the case of IIb. On completion of the addition, the mixture was stirred at room temperature for 1 hr. Since the mixture still showed the presence of Ib, the mixture was stirred for 2 days at room temperature. The crystals (20 mg), mp 275—279°, were collected and were identified as N,N′-dimethylisoindigotin by the direct comparison with the authentic sample.14) The filtrate showed many spots on TLC, but none of which corresponded to 1,1,-dimethyl3.3-′-bioxindole on TLC.

Formation of IIb from V——A solution of V (520 mg) in xylene (50 ml) was refluxed for 5 hr. The xylene solution was evaporated to leave a brown resinous solid (550 mg) which was chromatographed over silicagel. Elution with hexane–benzene (1:1) gave crude IVb (154 mg), mp 248—252°. Recrystallization from hexane–benzene gave IVb, mp 254—255° which was identical with the standard sample in IR, and UV spectra as well as TLC. Elution with hexane–benzene (1:2) gave crude IIIb (73 mg). Recrystallizations from benzene–hexane gave IIIb, mp and mixed mp 182—184°, which was identical with the authentic sample in IR and UV spectra as well as TLC. Elution with benzene gave crude IIb (45 mg), mp 101—103°. Recrystallizations from benzene–hexane gave IIb, mp 102—104°, which was identical with the authentic sample in IR and UV spectra as well as TLC.

2-Methylthioindole (Xa)——A mixture of IIa (448 mg), CH_3I (1.28 g) and K_2CO_3 (553 mg) in acetone (20 ml) was stirred at room temperature for 4 hr. The mixture was filtered and the filtrate was evaporated to leavea brown oil, which was extracted with benzene. The benzene solution was evaporated *in vacuo* to leave a pale brown oil (450 mg) which was solidified on standing, mp 40—43°. The solid was purified through silica gel column to afford 2-methylthioindole (350 mg, 73%), mp 48—49°. *Anal.* Calcd. for C_9H_9NS: C, 66.22; H, 5.56; N, 8.56; S, 19.64. Found: C, 66.47; H, 5.54; N, 9.01; S, 19.94. IR ν_{max}^{KBr} 3420 cm^{-1} (NH). UV λ_{max}^{EtOH} mμ (log ε): 281 (4.08), 289 (4.10), 297 (4.05). NMR (in $CDCl_3$, ppm from T: MS): 2.44 (s, S–Me), 6.56 (d, 3–H), 7.95 (s, NH).

1-Methyl-2-methylthioindole (Xb)——A mixture of IIb (490 mg), CH_3I (640 mg) and K_2CO_3 (622 mg) in acetone (20 ml) was stirred at room temperature for 3 hr. The mixture was filtered and the filtrate was evaporated *in vacuo* to leave an oil which was extracted with abs. EtOH. The EtOH was evaporated *in vacuo* to give crude 1-methyl-2-methylthioindole (500 mg) as an pale yellow oil, which was solidified in a refrigerator and melted at room temperature. Its NMR spectrum showed two singlet methyls at 2.40 ppm (S-Me) and 3.74 (N-Me). And the signal for 3-hydrogen was observed at 6.54 ppm as singlet. UV λ_{max}^{EtOH} mμ (log ε): 293 (4.09), 287 (4.10), 222 (4.51). Picrate: Red crystals, mp 83—84° (from EtOH). *Anal.* Calcd. for $C_{16}H_{14}O_7N_4S$: C, 47.29; H, 3.47; S, 7.89. Found: C, 47.47; H, 3.33; S, 7.95.

1,3-Dimethyl-2-methylthioindole (Xc)——A mixture of IId (480 mg), CH_3I (700 mg) and K_2CO_3 (345 mg) in acetone (25 ml) was stirred at room temperature for 3 hr. The reaction mixture was found to show the presence of IId on TLC, an excess of CH_3I (700 mg) was added to the mixture and stirred at room temperature overnight. The mixture was filtered and the filtrate was evaporated *in vacuo* to leave an oil which was extracted with benzene. The benzene solution was evaporated *in vacuo* to leave a crude indole (485 mg) as a pale yellow oil. It was purified through silicagel column to afford colorless oil, which showed one spot on TLC. UV λ_{max}^{EtOH} mμ (log ε): 227 (4.53), 287 (4.04), 295 (4.03). NMR (in $CDCl_3$, ppm from TMS): 2.25, 2.45 (s, 3-Me and S-Me), 3.83 (s, N-Me).

1,1′-Dimethyl-2,2′-bismethylthio-3,3′-biindole——A mixture of V (324 mg), CH_3I (570 mg) and K_2CO_3 (276 mg) in acetone (20 ml) was refluxed for 1.5 hr. An excess of CH_3I (200 mg) was added to the mixture, and the mixture was further refluxed for 14 hr. The reaction mixture was filtered and the filtrate was evaporated *in vacuo* to leave a solid, which was extracted with benzene. The benzene was evaporated *in vacuo* to leave crude methylthioindole (390 mg), mp 183—184°. Repeated recrystallization from hexane–benzene gave pure sample, mp 186—187°, as colorless crystals. *Anal.* Calcd. for $C_{20}H_{20}N_2S_2$: C, 68.14; H, 5.72; N, 7.95; S, 18.19. Found: C, 68.09; H, 5.48; N, 8.32; S, 17.74. NMR (in $CDCl_3$, ppm from TMS): 2.15 (s, S-Me), 3.95 (s, N-Me), 6.93—7.42 (m, aromatic H). UV λ_{max}^{EtOH} mμ (log ε): 228 (5.24×10^4), 295 (2.04×10^4). Mass: M$^+$ *m/e* 352.

Deuteration of the Hydrogen at 3-Position of I and II——To a solution of I or II (20 mg) in $CDCl_3$ (0.5 ml) in a NMR sample tube was added CD_3COOD (0.1 ml). NMR spectrum analysis was run immediately after the mixing, 2 hr standing at room temperature (about 25°) and 24 hr standing. The extent of the deuteration was estimated from the ratio of intensities of N-methyl and 3-hydrogens. The results are shown below.

Compound	Extent of deuteration Immediately after	2 hr	24 hr
IIb	$\sim$0	20%	70%
IIc	$\sim$0	70%	$\sim$100%
Ib	little or no deuteration		
Ic			

Complete deuteration at 3-hydrogen of Ib was observed when Ib was refluxed for 1.5 hr in D_2O solution in the presence of K_2CO_3.

Acknowledgement The authors express their deep gratitudes to Prof. Emeritus S. Sugasawa for his valuable suggestions. The authors are indebted to Prof. S. Sakai, University of Chiba, for mass spectral data and to members of Analytical Centre of Tanabe Seiyaku Co., Ltd. for microanalytical data, and to Messrs T. Kondo and M. Uoji in this institute for spectral data.