Oxidation of 2-Ethylthioindoles with Hydrogen Peroxide. Oxidative Migration of the Ethylsulphonyl Group †

By **Tohru Hino,* Hitoshi Yamaguchi, Mamoru Endo,** and **Masako Nakagawa,** Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Chiba-shi 280, Japan

Oxidation of 2-ethylthioindoles (1) with three molar equivalents of hydrogen peroxide in acetic acid yielded the sulphones (6a, b, and d), the 3-ethylsulphonylindolin-2-ones (7a, b, and d), and the 3-hydroxyindolin-2-ones (8b and d); the sulphoxides (5a, b, d, and e) were the main products with one molar equivalent of hydrogen peroxide. Compounds (7) and (8) were also obtained by oxidation of 2-ethylsulphonylindoles (6) with one molar equivalent of hydrogen peroxide in acetic acid, indicating that oxidative migration of the ethylsulphonyl group was occurring.

We have reported that autoxidation of 2-ethylthio-3-methylindole (1a) [1] and 3-benzyl-2-ethylthioindole (1c) [2] in cyclohexane or chloroform yields the *S*-oxide (3) and the 3-hydroxy-3*H*-indole (4), formed by the reaction of the intermediate 3-hydroperoxy-3*H*-indole (2) with unchanged indole (1).[3] These results indicated that molecular oxygen attacks the indole ring more easily than the thioether group, whereas the hydroperoxide *S*-oxidizes the thioether system.

We have now examined the oxidation of 2-ethylthioindoles (1a, b, d, and e) with hydrogen peroxide in acetic acid, in order to compare the susceptibility of the thioether group and the indole ring. Thioethers are well known to be *S*-oxidized by hydrogen peroxide, and indoles are known to be oxidized to indoxyl, indolinone, and oxo-amide derivatives by hydrogen peroxide or peroxy-acids.[4]

The results of oxidation at room temperature are summarized in Table 1. With 1 mol. equiv. of hydrogen peroxide the sulphoxide (5) was obtained in high yield. However the reaction with 3 mol. equiv. of hydrogen peroxide yielded the sulphone (6) as the main product, together with the indolinones (7) and (8) suggesting that the indole ring is also oxidized after complete oxidation of the thioether.

TABLE 1

Oxidation of 2-ethylthioindoles (1) and 2-ethylsulphonyl indoles (6) with hydrogen peroxide in acetic acid at room temperature

Compd.	H_2O_2 (mol. equiv.)	Reaction time (h)	Products (% yield)
(1a)	1	12 [a]	(5a) (77),[c] (6a) (6)
	3	12 [a]	(6a) (62), (7a) 5)
(1b)	1	8 [a]	(5b) (77)
	3	15 [a]	(6b) (30), (7b) (30), (8b) (29) [d]
(1d)	1	24 [b]	(5d) (80)
	3	24 [b]	(6d) (88), (7d) (6), (8d) (3) [e]
(1e)	1	5 [a,f]	(5e) (62)
(6a)	1	24 [a]	(7a) (20), (6a) (76)
(6d)	1	48 [b]	(7d) (27), (8d) (6), (6d) (48)
	1 (at 65—70 °C)		

[a] Method A. [b] Method B. [c] Ref. 1. [d] P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.*, 1935, **57**, 539. [e] J. M. Bruce, *J. Chem. Soc.*, 1959, 2366; S. Inagaki, *Yakugaku Zasshi*, 1939, **59**, 5. [f] Two equiv. of trifluoroacetic acid added to the acetic acid solution before addition of hydrogen peroxide.

The structures of the sulphonylindolinones (7a, b, and

† Preliminary communication, T. Hino, H. Yamaguchi, and M. Nakagawa, *J.C.S. Chem. Comm.*, 1972, 473.

[1] M. Nakagawa and T. Hino, *Tetrahedron*, 1970, 4491; T. Hino, M. Nakagawa, and S. Akaboshi, *Chem. Comm.*, 1967, 656.

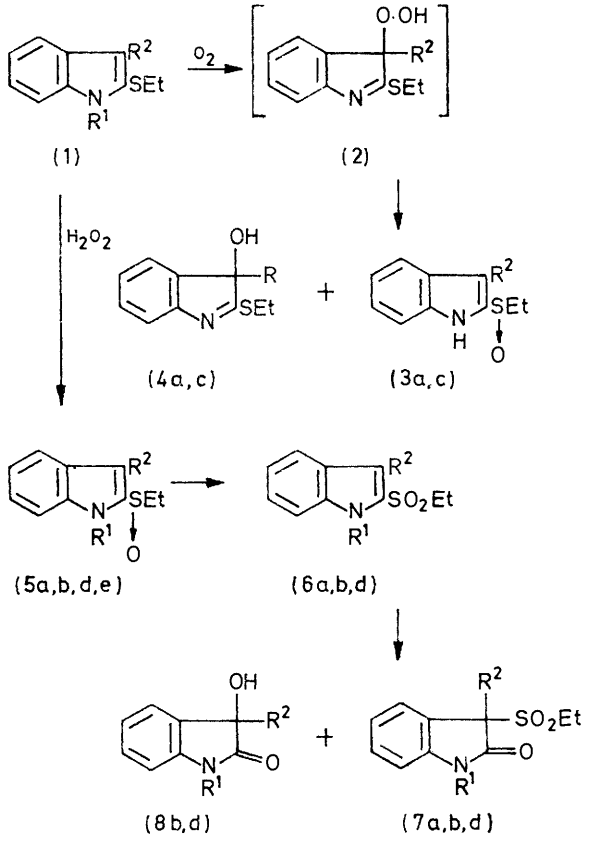
[2] T. Hino and M. Nakagawa, *J. Amer. Chem. Soc.*, 1969, **91**, 4598.

[3] M. Nakagawa, H. Yamaguchi, and T. Hino, *Tetrahedron Letters*, 1970, 4035; M. Nakagawa, T. Suzuki, T. Kawashima, and T. Hino, *Chem. and Pharm. Bull.* (*Japan*) 1972, **20**, 2413.

[4] B. Witkop, *Annalen*, 1947, **558**, 91, 98; *J. Amer. Chem. Soc.*, 1950, **72**, 2311; B. Witkop and J. B. Patrick, *ibid.*, 1951, **73**, 713; S. David and J. Monnier, *Bull. Soc. chim. France*, 1959, 1333; F. Piozzi and R. Langella, *Gazzetta*, 1963, **93**, 1373 (*Chem. Abs.*, 1964, **60**, 9232).

d) were confirmed by spectral data and elemental analyses (Tables 2 and 3), and by direct comparison of (7a) with a sample prepared by oxidation of 3-ethylthio-3-methylindolinone (9).[5]

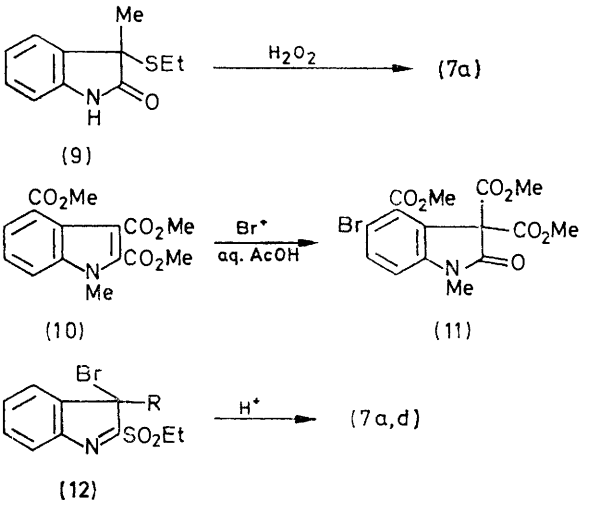
The fact that oxidation of the 2-ethylsulphonylindoles (6a and d) with 1 mol. equiv. of hydrogen peroxide in acetic acid yielded the indolinones (7a and d) and the hydroxyindolinone (8d) shows that oxidative migration



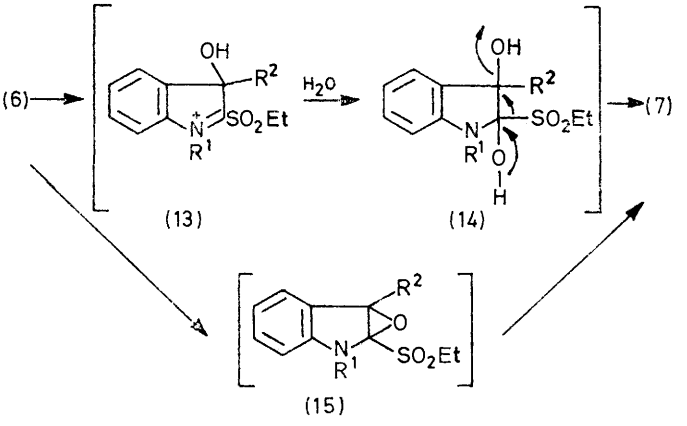
a; R^1=H, R^2=Me
b; R^1 = R^2 = Me
c; R^1=H, R^2 = CH_2Ph
d; R^1=H, R^2=Ph
e; R^1=H, R^2=$CH_2 \cdot CH_2 \cdot NMe_2$

SCHEME 1

of the ethylsulphonyl group in the 2-ethylsulphonylindole (6) is brought about by hydrogen peroxide. The migration of an alkoxycarbonyl group, *e.g.* in the reaction of compound (10) with bromine to give the indolinone (11), has been reported and reviewed by Acheson,[6] but the migration of an ethylsulphonyl group has no precedent. Recently we reported [7] that 3-bromo-3*H*-indoles (12), obtained by bromination of 2-ethylsulphonyl indoles (6) were converted into indolinones (7) on treatment with ethanolic hydrochloric acid. It therefore seems most likely that migration of the ethylsulphonyl group takes place *via* the intermediates (13) and (14), arising from the initial attack of OH^+ at the 3-position of



indole as in the case of the alkoxycarbonyl group.[6] However, the intervention of the epoxide (15) may not be excluded; products known to be obtained by oxidation of indoles with hydrogen peroxide or peroxy-acids can be interpreted in terms of an epoxide intermediate in spite of the lack of evidence for the presence of an epoxide.[8] It is noteworthy that hydrogen peroxide attacks the thioether group faster than it attacks the indole ring, but finally attacks the indole ring of a 2-ethylsuphonylindole (6), although the electron density of



SCHEME 2

2-ethylsuphonylindoles (6) would be expected to be lower than that of 2-ethylthioindoles (1).

EXPERIMENTAL

M.p.s. were taken with a Yamato capillary apparatus or a Yanagimoto hot-stage apparatus. I.r. spectra were recorded with a Hitachi G-3 spectrophotometer. U.v.

[5] T. Wieland and D. Grimm, *Chem. Ber.*, 1965, **98**, 1727.
[6] R. M. Acheson, R. M. Snaith, and J. M. Vernon, *J. Chem. Soc.*, 1964, 614; R. M. Acheson, *Accounts Chem. Res.*, 1971, **4**, 177.
[7] T. Hino, M. Endo, T. Tonozuka, and M. Nakagawa, *Heterocycles*, 1974, **2**, 505.
[8] D. M. Harrison, *J.C.S. Perkin I*, 1974, 2609.

spectra were recorded with a Hitachi 323 spectrophotometer. N.m.r. spectra were obtained with a JEOL 4H-100 or MH-100 spectrometer for solutions in deuteriochloroform with tetramethylsilane as an internal reference. Mass spectra were recorded with a Hitachi RMU-6E instrument.

dichloromethane, washed with aqueous sodium chloride, dried, and evaporated, and the residue was distilled *in vacuo* to remove the starting materials and chromatographed over silica gel with hexane to give the 2-*ethylthioindole* (1b) (6.9 g, 48%) as an oil, b.p. 106—114° at 0.08

TABLE 2

Analytical data *

Compd.	M.p. (°C) (recryst. solv)	Formula	%C	%H	%N
(6a)	77—78 [a] (Et_2O–C_6H_{14}, MeOH–H_2O)	$C_{11}H_{13}NO_2S$	59.2 (59.3)	5.85 (5.9)	6.3(6.3)
(5b)	97—97.5 (PhH–LP) †	$C_{12}H_{15}NOS$ [b]	65.1 (64.6)	6.85 (6.75)	6.35 (6.15)
(6b)	84—85 (EtOH–H_2O)	$C_{12}H_{15}NO_2S$	60.75 (60.85)	6.35 (6.45)	5.9 (5.9)
(5d)	161.5—162 ‡ (Me_2CO)	$C_{16}H_{15}NOS$	71.35 (71.25)	5.6 (5.65)	5.2 (5.05)
(6d)	156—157 (PhH)	$C_{16}H_{15}NO_2S$	67.1 (66.9)	5.3 (5.2)	4.9 (4.75)
(5e)	138—139 (PhH–LP)	$C_{14}H_{20}N_2OS$ [c]	63.6 (64.2)	7.65 (7.65)	10.6 (10.45)
(7a)	200—201.5 (EtOH–H_2O)	$C_{11}H_{13}NO_3S$	55.25 (55.15)	5.5 (5.5)	5.85 (5.85)
(7b)	129—130 (PhH–C_6H_{14})	$C_{12}H_{15}NO_3S$	56.9 (56.8)	5.95 (6.05)	5.55 (5.45)
(7d)	197—198 (Me_2CO)	$C_{16}H_{15}NO_3S$	63.75 (63.65)	5.0 (5.05)	4.65 (4.5)

[a] Lit. m.p. 113° (H. Faulstich and T. Wieland, *Annalen*, 1968, **713**, 186). [b] S: 14.45 (14.5). [c] S: 12.05 (12.15).

* Required values in parentheses. † LP = light petroleum. ‡ Decomp.

TABLE 3

Spectral data of oxidation products

Compd.	$\lambda_{max.}$(EtOH)/nm(ε)	δ($CDCl_3$)	*m/e*	$\nu_{max.}$(KBr)/cm^{-1}
(5b)	225 (27 500), 286 (14 200), 305sh (8 000)	1.18 (3 H, t, CH_3), 2.42 (3 H, s, 3-CH_3), 3.22 (2 H, m, CH_2), 4.02 (3 H, s, NMe), 7.0—7.8 (4 H, m, ArH)	221 (M^+, 39%), 192 (M − Et, 100), 176 (M − Et − O, 25)	1 025 (S–O)
(5d)	230sh (26 400), 235 (26 700), 289 (14 600)	1.16 (3 H, t, CH_3), 3.22 (2 H, q, CH_2), 7.0—7.8 (9 H, m, ArH), 11.34br (s, NH)	269 (M^+, 59%), 240 (M − Et, 100), 224 (M − Et − O, 30), 212 (73)	3 120—3 020 (NH), 1 030 (S–O)
(5e)	222 (26 400), 284 (14 600), 298sh (9 400)	1.20 (3 H, t, CH_3), 2.30 (6 H, s, NMe_2), 2.4—3.4 (6 H, m, CH_2), 11.05br (s, NH)	No M^+, 248 (M − O, 0.3), 247 (M − OH, 0.6), 187 (M − SOEt, 9.5), 58 (CH_2·NMe_2, 100)	3 200—3 020 (NH), 1 005 (S–O)
(6a)	222 (27 000), 279 (8 800), 296sh (5 000), 307sh (2 700)	1.28 (3 H, t, CH_3), 2.57 (3 H, s, 3-CH_3), 3.22 (2 H, q, CH_2), 7.05—7.7 (4 H, m, ArH), 9.16br (s, NH)	223 (M^+, 100%), 146 (49), 130 (M − SO_2Et, 56), 131 (M − SO_2·CH_2·CH_2, 30)	3 340 (NH), 1 150, 1 300 (SO_2)
(6b)	225 (37 800), 275sh (10 200), 282 (11 800), 305 (6 600), 315 (4 800)	1.28 (3 H, t, CH_3), 2.60 (3 H, s, 3-CH_3), 3 15 (2 H, q, CH_2), 3.95 (3 H, s, NMe), 7.05—7.7 (4 H, m, ArH)	237 (M^+, 99%), 144 (M − SO_2Et, 44), 143 (100)	1 130, 1 320 (SO_2)
(6d)	225 (34 200), 285 (14 800)	1.10 (3 H, t, CH_3), 2.95 (2 H, q, CH_2), 7.1—7.75 (9 H, m, ArH), 9.51br (s, NH)	285 (M^+, 100%), 193 (M − $SO_2CH_2CH_2$, 53), 192 (M − SO_2Et, 26), 191 (35)	3 320 (NH), 1 130, 1 300 (SO_2)
(7a)	255.5 (5 000), 266sh (3 700), 295 (1 400)	1.36 (3 H, t, CH_3), 1.88 (3 H, s, 3-CH_3), 3.22 (2 H, m, CH_2), 6.85—7.6 (4 H, m, ArH), 8.70br (s, NH)	239 (M^+, 6%), 146 (M − SO_2Et, 100)	3 275 (NH), 1 720 (C=O), 1 135, 1 300 (SO_2)
(7b)	259 (5 600), 269sh (4 100), 293 (1 200)	1.36 (3 H, t, CH_3), 1.85 (3 H, s, 3-CH_3), 2.95—3.55 (2 H, m, CH_2), 3.22 (3 H, s, NMe), 6.8—7.65 (4 H, m, ArH)	253 (M^+, 4%), 160 (M − SO_2Et, 100)	1 720 (C=O), 1 142, 1 306 (SO_2)
(7d)	216 (24 900), 259 (5 500), 269sh (4 200), 300 (2 000)	1.24 (3 H, t, CH_3), 2.80—3.64 (2 H, m, CH_2), 6.84—8.20 (9 H, m, ArH), 8.45br (s, NH)	301 (M^+, 1%), 208 (M − SO_2Et, 100)	3 320 (NH), 1 725 (C=O), 1 130, 1 305 (SO_2)

2-Ethylthio-1,3-dimethylindole (1b).—To a solution of 1,3-dimethylindole (10.0 g, 0.07 mol) in dry ether (40 ml) was added ethylsulphinyl chloride (7.5 g, 0.08 mol) in chloroform (50 ml) at 0 °C. The mixture was stirred overnight at room temperature, and neutralized with sodium hydrogen carbonate solution. The organic layer was diluted with

mmHg, $\lambda_{max.}$ (EtOH) 227 (ε 31 000), 288 (11 000), and 295 nm (11 000), δ 1.15 (3 H, t, CH_3), 2.41 (3 H, s, 3-CH_3), 2.62 (2 H, q, CH_2), 3.78 (3 H, s, NMe), and 7.0—7.6 (m, ArH), *m/e* 205 (M^+, 48%) and 176 (M − Et, 100) (Found: C, 69.35; H, 7.25; N, 6.65; S, 15.65. $C_{12}H_{15}NS$ requires C, 70.25; H, 7.35; N, 6.85; S, 15.6%); *picrate*, m.p. 73—74°

(from propan-2-ol), dark red needles (Found: C, 49.45; H, 4.4; N, 12.85. $C_{18}H_{18}N_4O_7S$ requires C, 49.75; H, 4.2; N, 12.9%).

2-Ethylthio-3-phenylindole (1d).—To a solution of 3-phenylindole (13.84 g, 0.071 mol) in dry ether (100 ml) cooled in ice was added ethylsulphinyl chloride (7.13 g, 0.075 mol) in dry dichloromethane (20 ml) during 20 min. The mixture was stirred for 20 h at room temperature and neutralized with aqueous sodium hydrogen carbonate. The organic layer was washed with water, dried, and evaporated. The residue (17.7 g) was chromatographed over silica gel (130 g). Elution with benzene–hexane (1 : 3) gave the *2-ethylthioindole* (1d) (10.39 g, 58%), and 3-phenylindole (2.91 g, 21%). Recrystallization of the crude 2-ethylthioindole from hexane gave material of m.p. 90—90.5°, $\lambda_{max.}$ (EtOH) 226 (ε 29 000), 253 (12 400), 284sh (13 800), 292 (14 900), and 301sh nm (13 900), δ 1.12 (3 H, t, CH_3), 2.66 (2 H, q, CH_2), 7.0—7.8 (9 H, m, ArH), and 8.12br (s, NH), *m/e* 253 (M^+, 58%), 225 ($M - CH_2{:}CH_2$, 100), and 224 (M – Et, 97) (Found: C, 75.85; H, 6.05; N, 5.5. $C_{16}H_{15}NS$ requires C, 75.85; H, 5.95; N, 5.55%).

3-(2-Dimethylaminoethyl)-2-ethylthioindole (1e).—To a solution of 3-(2-dimethylaminoethyl)indole (5.0 g, 0.027 mol) in dry dichloromethane (40 ml) was added ethylsulphinyl chloride (2.9 g, 0.03 mol) during 40 min at 0 °C. The mixture was stirred overnight at room temperature and evaporated. The residue was basified with 10% sodium hydroxide and extracted with dichloromethane. The extracts were washed with aqueous sodium chloride, dried, and evaporated. The residue was purified by passage through an alumina column to give the *2-ethylthioindole* (1e) (3.0 g, 47%). Recrystallizations from benzene–hexane gave a specimen of m.p. 89—91.5°, $\lambda_{max.}$ (EtOH) 224 (ε 32 200), 248sh (5 100), 283sh (11 500), 291 (13 300), and 300 nm (11 000), *m/e* 248 (M^+, 11%) and 58 ($CH_2{:}\overset{+}{N}Me_2$, 100), δ 1.23 (3 H, t, CH_3), 2.38 (6 H, s, NMe_2), 2.5—2.7 (2 H, m, CH_2), 2.76 (2 H, q, SCH_2), 3.0—3.2 (2 H, m, NCH_2), 7.0—7.7 (4 H, m, ArH), and 8.4br (s, NH) (Found: C, 68.1; H, 8.1; N, 11.25; S, 12.15. $C_{14}H_{20}N_2S$ requires C, 67.7; H, 8.1; N, 11.3; S, 12.9%).

Examples of General Procedures for Oxidation of 2-Ethylthioindoles (1) *or 2-Ethylsulphonylindoles* (6) *with Hydrogen Peroxide in Acetic Acid.—Method A. With 3 mol. equiv. of peroxide.* To a solution of the 2-ethylthioindole (1a) (574 mg, 3 mmol) in acetic acid (5 ml) was added 35% hydrogen peroxide (0.9 ml, 9 mmol) with stirring at room temperature. The mixture was stirred for 12 h at room temperature, evaporated *in vacuo* to a small volume below 40 °C, neutralized with 10% sodium hydroxide, and extracted with dichloromethane. The extracts were washed with saturated aqueous sodium chloride, dried, and evaporated. The residue was chromatographed on silica gel. Elution with benzene gave *2-ethylsulphonyl-3-methylindole* (6a) (413 mg, 62%), which was recrystallized from ether–hexane and then from methanol–water to give a specimen of m.p. 77—78°. Elution with benzene–acetone (5 : 1) gave *3-ethylsulphonyl-3-methylindolin-2-one* (7a) (39 mg, 5%), m.p. 193—198°. Further elution with the same solvent gave an unknown compound (34 mg).

Method B. With 3 mol. equiv. of peroxide. To a solution of the 2-ethylthioindole (1d) (2.53 g, 10 mmol) in acetic acid (30 ml) was added 35% hydrogen peroxide (3.0 ml, 30 mmol) at room temperature. The mixture was stirred at room temperature for 22 h and poured into a solution of sodium hydroxide (20 g) in water (100 ml) cooled in ice. The mixture was extracted with dichloromethane. The extracts were washed with water, dried, and evaporated. The residue was chromatographed over silica gel. Elution with dichloromethane gave *2-ethylsulphonyl-3-phenylindole* (6d) (2.52 g, 88%), *3-ethylsulphonyl-3-phenylindolin-2-one* (7d) (173 mg, 6%), and 3-hydroxy-3-phenylindolin-2-one (8d) (66 mg, 3%).

3-Ethylthio-3-methylindolin-2-one (9).—Compound (9) was prepared by the reaction of 3-bromoindolin-2-one with sodium ethanethiolate [5] and by the reaction of 3-methylindolin-2-one with ethylsulphinyl chloride.[5] The *product* in both cases melted at 111—112° (lit.,[5] m.p. 74°), $\lambda_{max.}$ (EtOH) 253 (ε 7 000) and 287 nm (1 300), $\nu_{max.}$ 3 150 (NH), and 1 715 and 1 680 cm^{-1} (C=O), *m/e* 207 (M^+, 3%) and 146 (M – SEt, 100), δ 1.05 (3 H, t, CH_3), 1.65 (3 H, 3-CH_3), 2.35 (2 H, m, SCH_2), 6.9—7.4 (m, ArH), and 9.36br (s, NH) (Found: C, 63.55; H, 6.2; N, 6.65; S, 15.1. $C_{11}H_{13}NOS$ requires C, 63.75; H, 6.3; N, 6.75; S, 15.45%).

Preparation of the Indolinone (7a) *from 3-Ethylthio-3-methylindolin-2-one* (9).—To a solution of the indolinone (9) (414 mg, 2 mmol) in acetic acid (10 ml) was added 35% hydrogen peroxide (0.6 ml, 6 mmol) at room temperature. The mixture was stirred at room temperature for 22 h and evaporated to a small volume *in vacuo*. The residue was recrystallized from ethanol–water to give the indolinone (7a) (389 mg, 81%). Further recrystallizations gave a specimen of m.p. 200—201.5°, identical with that obtained by the oxidation of the 2-ethylsuphonylindole (6a) (mixed m.p. and i.r.)

We thank the Naito Foundation and the Foundation for the Promotion of Research on Medicinal Resources for financial support. We are grateful to Mr. Y. Torisawa for technical assistance.

[5/1826 *Received, 22nd September,* 1975]