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Bromination of 2-Bromo, 2-Ethylthio, and 2-Ethylsulfonylindoles with N-Bromosuccinimide. Isolation and Reactions of 1-Bromoindoles and 3-Bromoindolenines[1]

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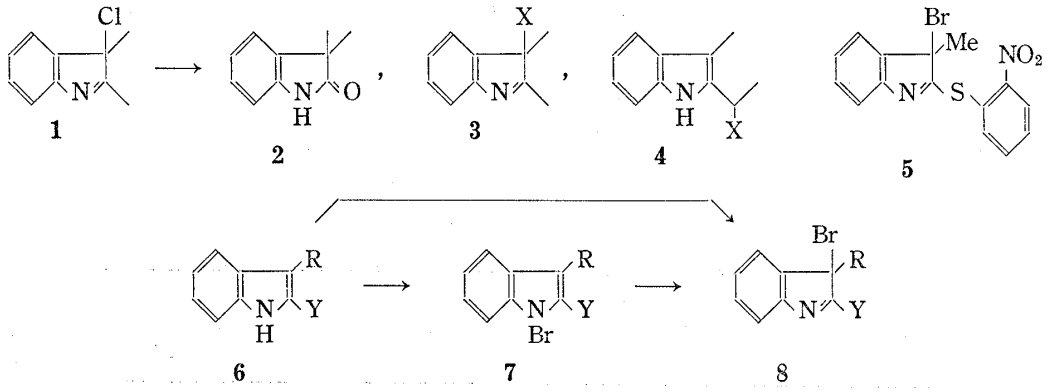
Bromination of 2-ethylthioindoles (**6a, c**) and 2-bromoindole (**6e**) with N-bromosuccinimide (NBS) in carbon tetrachloride gave 3-bromoindolenines (**8**). On the other hand, bromination of 2-ethylsulfonylindoles (**6b, d**) with NBS in methylene chloride gave 1-bromoindoles (**7b, d**) which were converted to **8** on heating. Both 1-bromoindoles and 3-bromoindolenines act as brominating agents for skatole or 3-phenylindole. Heating of 3-bromo-2-ethylthio-3-phenylindolenine (**8c**) in carbon tetrachloride gave the 6-bromoindole (**11**), while the 2-ethylsulfonyl derivative (**8d**) gave 5-bromoindole (**13**). However, 2,3-dibromo-3-phenylindolenine (**8e**) in acetic acid was converted to 6-bromo-(main) (**17**) and 5-bromoindole (**18**) (minor). 3-Bromoindolenines (**8a, b, d**) gave the oxindoles (**19**) accompanied with the migration of the 2-substituent on treatment with ethanolic hydrochloric acid, while some 3-alkoxyoxindoles (**21, 22, 23**) were obtained on treatment with alcohol and base. On the other hand, the 1-bromoindole (**7b**) was converted to the indole (**6b**) under various conditions.

Keywords——bromination; brominating agent; N-bromosuccinimide; 1-bromoindole; 3-bromoindolenine; migration of bromine; migration of ethylthio group; migration of ethylsulfonyl group; 2-ethylthioindole; 2-ethylsulfonylindole

Since Finch and Taylor[3] explored the transformation of yohimbine to its oxindole alkaloids *via* the 3-chloroindolenine derivatives, the chemistry of 3-chloroindolenines (**1**) has been investigated not only for the indole alkaloids[4] but also for simple indole derivatives.[5] Transformation of these highly reactive intermediates (**1**) has yielded a variety of products such as 3,3-disubstituted oxindoles (**2**), substituted indolenines (**3**), and substituted indoles (**4**), depending on the conditions used and the nature of the substituents. Although most of the 3-chloroindolenines are unstable at room temperature, some can be obtained as crystalline compounds. Gassman[5a] predicted the 1-chloroindole as the first intermediate to **1**, but did not confirm it. Recently Rosa[6] has reported the isolation of 1-chloroindole itself and its transformation to 3-chloroindole *via* 3-chloroindolenine. On the other hand, 3-bromoindolenine has been proposed to be an intermediate in the bromination of indole derivatives,[7] but its isolation

1) A part of this paper has been published as a communication; T. Hino, M. Endo, M. Tonozuka, and M. Nakagawa, *Heterocycles*, **2**, 565 (1974).
2) Location: *Yayoi-cho, Chiba-shi, 280, Japan.*
3) N. Finch and W.I. Taylor, *J. Am. Chem. Soc.*, **84**, 1318, 3871 (1962).
4) H. Zinnes and J. Shavel, *J. Org. Chem.*, **31**, 1765 (1966); G. Büchi and R.E. Manning, *J. Am. Chem. Soc.*, **88**, 2532 (1966); K.V. Lichman, *J. Chem. Soc. (C)*, **1971**, 2539; L.J. Dolby and G.W. Gribble, *J. Org. Chem.*, **32**, 1391 (1967).
5) *a*) P.G. Gassman, G.A. Campbell, and G. Mehta, *Tetrahedron*, **28**, 2749 (1972); *b*) A. Walser, J.F. Blout, and R.I. Fryer, *J. Org. Chem.*, **38**, 3077 (1973); *c*) R.J. Owellen, *J. Org. Chem.*, **39**, 69 (1974); R.J. Owellen and C.A. Hartke, *ibid.*, **41**, 102 (1976).
6) M.D. Rosa, *J.C.S. Chem. Commun.*, **1975**, 482.
7) *a*) W.B. Lawson and B. Witkop, *J. Am. Chem. Soc.*, **82**, 5918 (1960); *b*) R.L. Hinmann and C.P. Bauman, *J. Org. Chem.*, **29**, 1206 (1964); *c*) T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, and S. Yamada, *Tetrahedron*, **23**, 1441 (1967); *d*) T. Hino, M. Tonozuka, and M. Nakagawa, *Tetrahedron*, **30**, 2123 (1974); *e*) T. Hino, T. Nakamura, and M. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 2990 (1975); *f*) T. Hino, H. Miura, T. Nakamura, R. Murata, and M. Nakagawa, *Heterocycles*, **3**, 805 (1975).

and chemical behavior have not been reported, except a stable 3-bromoindolenine (**5**)[8] as a brominating reagent similar to N-bromosuccinimide(NBS).



a : R=Me, Y=SEt **d** : R=Ph, Y=SO_2Et
b : R=Me, Y=SO_2Et **e** : R=Ph, Y=Br
c : R=Ph, Y=SEt Ph=phenyl

Chart 1

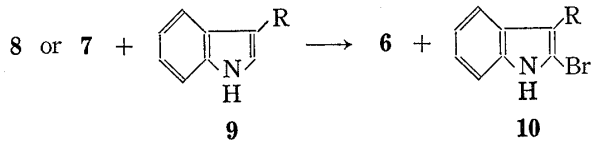
As an extension of our work on bromination of simple indole derivatives,[7a-f] we now report the isolation and reactivity of 3-bromoindolenine and 1-bromoindole, showing that the former is converted to 5- or 6-brominated indoles and oxindole derivatives. Bromination of 3-methyl- (**6a**) and 3-phenyl-2-ethylthioindole (**6c**) with NBS in boiling carbon tetrachloride for 10—15 min gave crystalline 3-bromoindolenines (**8a** and **8c**) in excellent yields. Under similar conditions 2-bromo-3-phenylindole (**6e**) gave 2,3-dibromo-3-phenylindolenine (**8e**) as an oil. Reaction of 2-ethylsulfonyl-3-phenylindole (**6d**) under the similar conditions proceeded slowly to give the corresponding 3-bromoindolenine (**8d**), but was accelerated by the addition of benzoyl peroxide. However, reaction of 2-ethylsulfonyl-3-methylindole (**6b**) with NBS in boiling carbon tetrachloride in the presence of benzoyl peroxide did not proceed and the starting materials were recovered. These 3-bromoindolenines are crystalline except **8e** and stable for a few days in a deep freezer, but decompose at room temperature. The structures of 3-bromoindolenines are confirmed by spectral data(see Tables) as well as elemental analysis. The spectral data of compound (**5**) (the methyl signal in its nuclear magnetic resonance (NMR) spectrum appeared at δ 2.08 and the C=N stretching band in its infrared (IR) spectrum appeared at 1520 cm^{-1})[9] agree with those of our compounds.

Bromination of **6b** with NBS in methylene chloride at room temperature for 1 hr, however, gave a crystalline compound (**7b**), mp 80—81°, in 92% yield. This compound was converted to another crystalline compound (**8b**), mp 96.5—97°, on heating in carbon tetrachloride for 8 hr. Spectral data of **8b** are similar to those of **8a**,**8c**, and **8d** (upfield shift of 3-methyl signal in its NMR spectrum (δ 1.88) and presence of C=N band at 1530 cm^{-1}), and it can be assigned to 3-bromo-2-ethylsulfonyl-3-methylindolenine (**8b**). On the other hand, the structure of **7b** was assigned to the 1-bromo derivative from the following evidence. Its NMR spectrum in $CDCl_3$ showed a singlet at δ 2.24 for the 3-methyl group which is shifted to upfield slightly from the starting material (**6b**, δ 2.57), but not so much as that of **8b**.[10] Its IR spectrum showed no NH band and no strong band at around 1500 cm^{-1} for C=N strecthing vibration. Similar

8) G.S. Omen, A. Fontana, and C.B. Anfinsen, *J. Biol. Chem.*, **245**, 1895 (1970).
9) These spectral data were communicated to us by Drs. B. Witkop and T.F. Spande of NIH, New Jersey, to whom the authors' thanks are due.
10) As the electronegativity of bromine is smaller than that of nitrogen, electron may be supplied from the bromine to the indole ring.

reaction of **6d** with NBS in methylene chloride at room temperature for 1.5 hr gave **7d**, mp 35—40°, in 36% yield which was transformed to **8d** on heating in carbon tetrachloride.

TABLE I. Bromination of Indoles (9) with 3-Bromoindolenines (8) or 1-Bromoindoles (7)



a: R=CH_3, **b**: R=Ph

Reagent	Substrate	Solvent	Yield(%) 6	Yield(%) 10
8a	**9b**	AcOH	—	56
8c	**9a**	CCl_4	37	36
8e	**9a**	AcOH	95	71
7b	**9b**	CH_2Cl_2	95	89
7d	**9b**	CH_2Cl_2	76	72

Ph=phenyl.

Since these 3-bromoindolenines and 1-bromoindoles showed a positive test with KI-starch as described by Gassman for 3-chloroindolenine, we examined the brominating power of these compounds. When **8a** was treated with 3-phenylindole (**9b**) in acetic acid at room temperature, 2-bromo-3-phenylindole(**10b**) was obtained in 56% yield. Similar reaction of **8c** with skatole (**9a**) in carbon tetrachloride at room temperature gave 2-bromoskatole (**10a**) and **6c** in 36% and 37% yields respectively besides the 6-bromo-2-ethylthio-3-phenylindole (**11**) in 30% yield. The other examples are summarized in Table I. The results indicate that 3-bromoindolenines and 1-bromoindoles behave as brominating agents in the same way as compound (**5**).

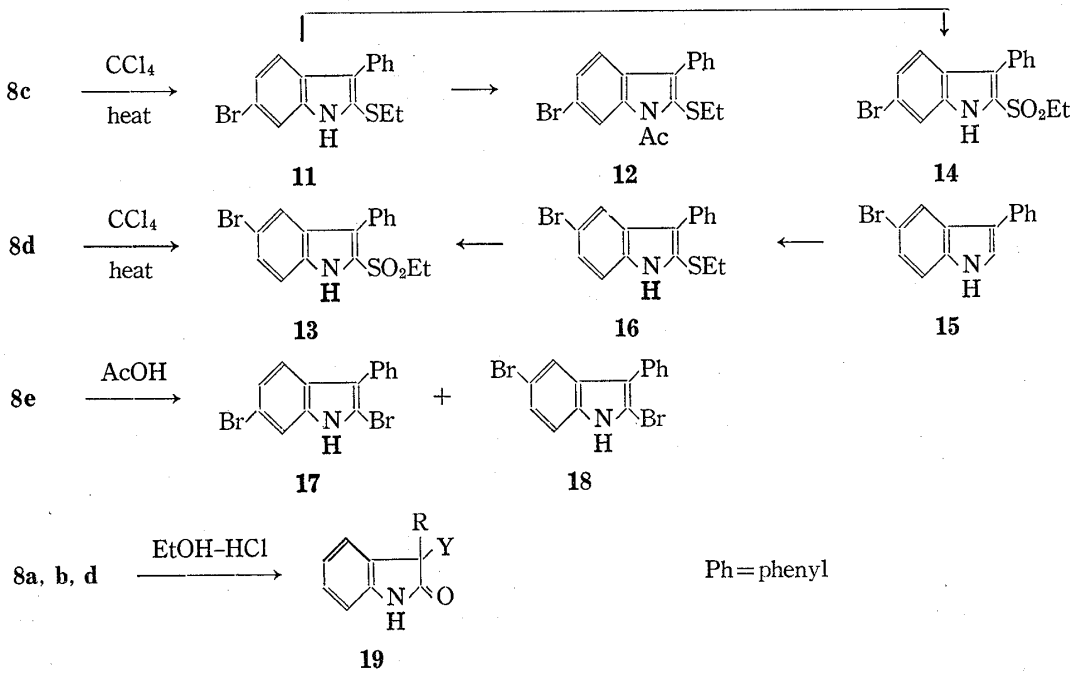
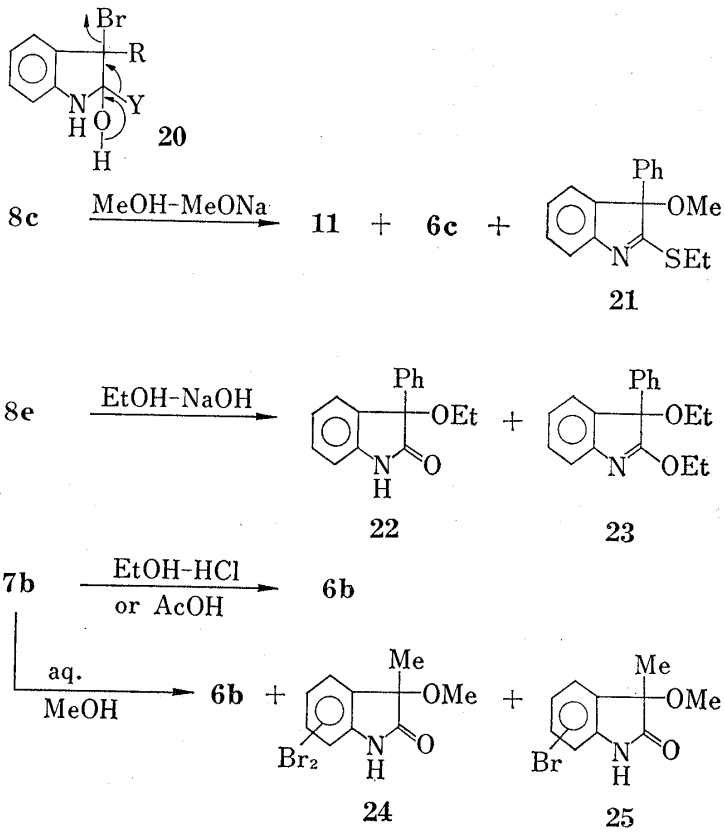


Chart 2

Formation of the 6-bromo derivative (**11**) in the above bromination suggests that the migration of bromine to the benzene ring may compete with bromination of another indole molecule. Thus when a solution of **8c** in carbon tetrachloride was refluxed for 2 hr, the 6-bromo derivative (**11**) was obtained in 92% yield. The position of bromine in **11** was confirmed by the NMR of the 1-acetyl derivative (**12**) which showed a down field finely split singlet for the 7-H without *ortho*-coupling.

On the other hand, heating of **8d** in carbon tetrachloride gave the 5-bromo derivative (**13**) in 69% yield. The structure of **13** was confirmed by the fact that it was not identical with 6-bromo-2-ethylsulfonyl-3-phenylindole (**14**) obtained by the oxidation of **11** with hydrogen peroxide but identical with an authentic sample prepared from 5-bromo-3-phenylindole (**15**)[7d] *via* 5-bromo-2-ethylthio-3-phenylindole (**16**). When a solution of **8e** in acetic acid was stood at room temperature for 24 hr, 2,5- (**18**) (minor) and 2,6-dibromo-3-phenylindole (**17**) (main) were obtained in excellent yield and the ratio of the isomers was the same as that



Ph=phenyl

Chart 3

Table II. Analytical Data of Brominated Indoles

Compound No.	mp	Formula	*Anal.* (Calcd./Found) C	H	N	Br
8a	36—37°	$C_{11}H_{12}BrNS$	48.89	4.49	5.19	29.57
			48.98	4.43	5.48	29.34
8b	96.5—97°	$C_{11}H_{12}BrNO_2S$	43.73	3.98	4.64	26.45
			43.89	3.90	4.76	26.21
8c	78.5—80.5°	$C_{16}H_{14}BrNS$	57.84	4.25	4.22	24.05
			57.87	4.24	4.21	24.21
8d	125—126.5°	$C_{16}H_{14}BrNO_2S$	52.76	3.87	3.85	—
			52.51	3.75	3.87	—
7b	80—81°	$C_{11}H_{12}BrNO_2S$	43.74	3.98	4.64	26.45
			43.94	4.06	4.78	26.35
11	87.5—88°	$C_{16}H_{14}BrNS$	57.84	4.22	4.25	24.05
			57.84	4.20	4.15	23.87
12	70.5—71.5°	$C_{17}H_{16}BrNOS$	57.76	4.31	3.74	21.35
			57.59	4.27	3.92	21.56
13	239—241°	$C_{16}H_{14}BrNO_2S$	52.76	3.87	3 85	21.94
			53.00	3.78	3.89	22.07
14	183.5—184.5°	$C_{16}H_{14}BrNO_2S$	52.76	3.87	3.85	21.94
			52.61	3.73	3.94	22.17

obtained by direct bromination in acetic acid.[7b] As the bromination of **6c** with NBS in acetic acid also gave **11** in 64% yield, 3-bromoindolenine can be assumed to be an intermediate to the 5- or 6-bromoindoles, though 3-bromoindolenine was not detected in the bromination of 3-phenylindole and **6c** in acetic acid. These results showed that the bromine atom in 3-bromoindolenines behaves as a bromonium ion, brominating the indole ring or migrating to the 5- or 6-position depending on the substituent at 2-position. These reactions were not found in the 3-chloroindolenine, but it is not clear if these reactions are characteristic for bromine or due to the substituents at 2-position.

When 3-bromo-2-ethylthio-3-methylindolenine (**8a**) was treated with ethanolic hydrochloric acid at room temperature, 3-ethylthio-3-methyloxindole (**19a**) was obtained in 81% yield as in the case of the 3-chloroindolenines. The structure of **19a** was confirmed by direct comparison with an authentic sample.[11] Similar results were obtained with **8b** and **8d**. However, the treatment of **8c** with ethanolic hydrochloric acid at room temperature did not

Table III. Spectral Data of Brominated Indoles

Compd. No.	UV(λ_{max}^{EtOH}nm($\varepsilon\times10^{-3}$))	IR(KBr) cm^{-1}	NMR($CDCl_3$) δ	MS(*m/e*(rel.intens.))
8a	245(17.0), 330(6.7)	1520(C=N)	1.93(3H,s,CH_3), 1.46(3H,t,CH_3) 3.33(2H,q,SCH_2) 7.0—7.7(m,arom.H)	271, 269(29) M^+ 191(55, M−Br+H) 190(67, M−Br) 162(100,M−CH_2=CH_2−Br)
8b	230(17.9), 235^s(16.4) 290(5.1)	1530(C=N) 1150(SO_2) 1530(SO_2)	1.12(3H,t,CH_3), 1.88(3H,s,3-CH_3) 2.48(2H,m,CH_2) 7.2—7.8(4H,m,arom.H)	303, 301(81, M^+) 223(25, M−Br+H) 211, 209(60, M−SO_2Et)
8c	240(17.2), 326(4.4)	1508(C=N)	1.49(3H,t,CH_3) 3.25(2H,m,SCH_2) 7.0—7.7(9H,m,arom. H)	333, 331(25, M^+) 253(88, M−Br+H) 252(88, M−Br) 224(100,M−Br−CH_2=CH_2)
8d	232(22.2), 261^s(3.9) 267^s(4.4), 273^s(3.6) 297(5.1)	1522(C=N) 1319(SO_2) 1143(SO_2)	1.20(3H,t,CH_3) 2.60(2H,m,CH_2) 7.3—7.9(9H,m,arom. H)	365, 363(3,M^+) 272, 270(100,M−SO_2Et) 190(49,M−SO_2Et−Br+H)
8e	239(18.0), 305(3.0)	1540(C=N) (neat)	7.17—7.60(m,arom. H)	353(3), 351(7), 349(3) M^+ 272, 270(100, M−Br)
7b	238(18.2), 312(4.3)	1330(SO_2) 1145(SO_2)	2.24(3H,s,3-CH_3),1.50(3H,t,CH_3) 3.60(2H,q,SO_2CH_2), 7.4—7.8(4H, m,arom. H)	303, 301(26, M^+) 223(35, M−Br+H) 210, 208(100,M−SO_2Et) 130(43,M−SO_2Et−Br+H)
11	236(29.5), 255(18.0) 287^s(12.5), 296(13.5) 305(13.7)	3400(NH)	1.80(3H,t,CH_3) 2.66(2H,q,CH_2) 7.10—7.78(8H,m,arom. H) 8.12(1H,bs,NH)	333, 331(42, M^+) 224(25, M−Br−CH_2CH_2) 223(100, M−Br−Et)
12	249(24.7), 303(14.7) 311^s(14.3),	1700(CO)	1.95(3H,t,CH_3) 2.48(2H,q,CH_2) 2.94(3H,s,$COCH_3$) 7.1—7.7(7H,m,arom. H) 8.53(1H,s,C_7-H)	375, 373(35, M^+) 332, 330(45, M−CH_3CO) 223(100, M−CH_2CO−Br−C_2H_5)
13	229(39.9), 234(38.5) 288(11.6), 307^s(7.8) 317(6.1)	3320(NH) 1320(SO_2) 1310(SO_2) 1140(SO_2)	1.10(3H,t,CH_3) 2.95(2H,q,CH_2) 7.16—7.78(8H,m,arom. H) 9.48(1H,bs,NH)	365, 363(100, M^+) 273,271(39,M−$SO_2CH_2CH_2$) 191(63, M−SO_2Et−Br)
14	233(57.3), 289^s(15.0) 297(16.5), 304^s(15.0)	3340(NH) 1320(SO_2) 1160(SO_2)	1.10(3H,t,CH_3) 2.96(2H,q,CH_2) 7.16—7.80(8H,m,arom. H) 9.64(1H,bs,NH)	365, 363(100, M^+) 273,271(48,M−$SO_2CH_2CH_2$) 191(74,M−SO_2Et−Br)

11) T. Hino, H. Yamaguchi, M. Endo, and M. Nakagawa, *JCS Perkin I*, **1976**, 745.

give the corresponding oxindole (**19c**), but gave the 6-bromo derivative (**11**) in 57% yield, besides some other products which were not characterized. These results demonstrated that the bromine atom in 3-bromoindolenine was removed as bromide ion as indicated in **20**, but the migration of bromine to the benzene ring is predominant in **8c**. To examine the reactivity of bromine in **8c** further, a methanolic solution containing sodium methoxide of **8c** was refluxed for 4 hr. Separation of the mixture gave 6-bromo derivative (**11**) (17%), **6c** (19%), and 3-methoxy derivative (**21**, 23%), mp 77—78°, indicating that nucleophilic substitution at 3-position did occur competing with bromine migration. Similar reaction of **8e** with ethanolic sodium hydroxide gave 3-ethoxyoxindole (**22**)[12] in 31% yield beside a small amount of 2,3-diethoxy-3-phenylindolenine (**23**).

On the other hand, reaction of 1-bromoindole (**7b**) with ethanolic hydrochloric acid or acetic acid at room temperature gave 2-ethylsulfonyl-3-methylindole (**6b**) in 88% and 43% yields respectively. Similar treatment of **7d** with ethanolic hydrochloric acid gave **6d** as major product. Unlike 3-bromoindolenine, 1-bromoindoles were not converted to oxindoles under acidic condition, but transformed to debrominated indoles. The 1-bromoindole (**7b**) was gradually transformed to **6b** in aqueous methanol concomitant with **24** and **25**. The formation of **24** and **25** might be rationalized by the steps: **7b**→**8b**→**19b**→**19**(R=Me, Y=OMe)→ **24**, **25**.

Experimental[13]

3-Bromo-2-ethylthio-3-methylindolenine (**8a**)——A mixture of **6a** (161 mg, 1 mmol) and NBS (178 mg, 1 mmol) in CCl_4 (60 ml) was refluxed for 10 min. The mixture was cooled to remove succinimide, and the filtrate was evaporated to give yellow oil (288 mg). The oil was purified through a short silica gel column to give **8a** (244 mg, 91%) which was recrystallized from pet. ether to give yellow needles, mp 36—37°. The same compound (**8a**) was obtained in 99% yield by the bromination of **6a** with NBS in acetic acid at room temperature for 20 min.

3-Bromo-2-ethylthio-3-phenylindolenine (**8c**)——A mixture of **6c** (253 mg, 1 mmol) and NBS (178 mg, 1 mmol) in CCl_4 (30 ml) was refluxed for 15 min. The mixture was cooled to remove succinimide and the filtrate was evaporated to give a yellow solid (**8c**, 337 mg, 100%) which showed a single spot on thin-layer chromatography (TLC). Recrystallizations of the solid from hexane gave minute yellow needles, mp 78.5—80.5°.

3-Bromo-2-ethylsulfonyl-3-phenylindolenine (**8d**)——A mixture of **6d** (285 mg, 1 mmol), NBS (178 mg, 1 mmol) and benzoyl peroxide (3 mg) in CCl_4 (40 ml) was refluxed for 1 hr. Work-up as above gave **8d** (350 mg, quantitative), mp 121—124°. Recrystallization from benzene-hexane gave colorless needles, mp 125—126.5°. Without benzoyl peroxide the reaction took 5 hr.

1-Bromo-2-ethylsulfonyl-3-methylindole (**7b**)——To a solution of **6b** (200 mg, 0.9 mmol) in CH_2Cl_2 (10 ml) was added NBS (160 mg, 0.9 mmol) in CH_2Cl_2 (10 ml) at room temperature during 5 min. The mixture was stirred for 1 hr at room temperature and the solvent was evaporated. The residue was separated by preparative TLC (silica gel/CH_2Cl_2) to give **7b** (250 mg, 92%). Recrystallizations from benzene-hexane gave pale yellow plates, mp 80—81°. Bromination of **6b** with NBS in boiling CCl_4 with or without benzoyl peroxide did not proceed, and the starting materials were recovered. However, reaction in CCl_4 containing MeOH (20: 5) at room temperature gave **7b** in 73% yield.

3-Bromo-2-ethylsulfonyl-3-methylindolenine (**8b**)——A solution of **7b** (220 mg) in CCl_4 (20 ml) was refluxed for 8 hr and the solvent was evaporated to give **8b** (220 mg, quantitative), mp 95—97°.

1-Bromo-2-ethylsulfonyl-3-phenylindole (**7d**)——A solution of **6d** (285 mg, 1 mmol) and NBS (178 mg, 1 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 1.5 hr. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with benzene–hexane (3: 1) gave **7d** (130 mg, 36%), mp 35—40°, which showed a single spot on TLC and was not purified further. UV λ_{max}^{EtOH}: 324 and 252 nm. IR (neat): 1330, 1150 cm^{-1} (SO_2); no NH and C=N band. Refluxing a solution of **7d** (75 mg) in CCl_4 (20 ml) for 2 hr gave **8d** quantitatively, identified by its IR spectrum.

12) J.M. Bruce and F.K. Sutcliffe, *J. Chem. Soc.*, **1957**, 4789.

13) All melting points are uncorrected. Ultraviolet (UV) spectra were recorded with a Hitachi 3T or 323 spectrophotometer. IR spectra were recorded with a Hitachi G-3 spectrophotometer. NMR spectra were obtained with a JEOL 4H-100 or MH-100 spectrometer for solutions in deuteriochloroform with tetramethylsilane as an internal reference. MS recorded with a Hitachi RMU-6E instrument.

2,3-Dibromo-3-phenylindolenine (8e)——A mixture of **6e** (544 mg, 2 mmol), NBS (356 mg, 2 mmol), and benzoyl peroxide (2 mg) in CCl_4 (15 ml) was refluxed for 1 hr. The mixture was cooled to removed succinimide, and the filtrate was evaporated to give **8e** (706 mg, quantitative) as an oil which showed a single spot on TLC.

Bromination of 3-Phenylindole (9b) with 8a——To a solution of **8a** (239 mg, 0.89 mmol) in AcOH (30 ml) was added **9b** (170 mg, 0.89 mmol) in AcOH (10 ml) at room temperature during 20 min. The mixture was stirred at room temperature for 1.5 hr, and poured into aqueous NaOH (NaOH (40 g) in H_2O (100 ml)). The mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 solution was washed with H_2O, dried, and evaporated. The residue (387 mg) was separated by preparative TLC (silica gel/benzene–hexane (1: 1)) to give **10b** (133 mg, 56%) and **9b** (58 mg, 34%). Only a trace amount of **6a** was recovered due to its decomposition during the isolation.

Bromination of Skatole (9a) with 8c——A mixture of **6c** (253 mg, 1 mmol) and NBS (178 mg, 1 mmol) in CCl_4 (30 ml) was refluxed for 15 min and was cooled to remove succinimide. To the filtrate which was found to contain **8c** as the sole product by TLC was added **9a** (131 mg, 1 mmol). The mixture was stirred at room temperature for 30 min, and evaporated. The residue was chromatographed over silica gel column (15 g). Elution with hexane–benzene (4: 1) gave **10a** (76 mg, 36%), **6c** (94 mg, 37%) and **11** (87 mg, 30%).

Bromination of 9b with 7b——To a solution of **7b** (200 mg, 0.66 mmol) in CH_2Cl_2 (30 ml) was added **9b** (129 mg, 0.66 mmol) in CH_2Cl_2 (10 ml) at room temperature. The mixture was stirred at room temperature for 50 min and evaporated. The residue was separated by preparative TLC (silica gel/benzene–hexane (1: 1)) to give **10b** (162 mg, 89%) and **6b** (139 mg, 95%).

Bromination of 9a with 8e——To a solution of **9a** (350 mg) in AcOH (20 ml) was added **8e** (1.0 g) in AcOH (5 ml) at room temperature. The mixture was stirred at room temperature for 1 hr and poured into aqueous NaOH (NaOH (17 g) in H_2O (100 ml)), and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated. The residue (1.26 g) was chromatographed over silica gel column (20 g). Elution with benzene–hexane (1: 9) gave **10a** (402 mg, 71%) and **6e** (710 mg, 95%).

Bromination of 9b with 7d——To a solution of **7d** (214 mg, 0.59 mmol) in CH_2Cl_2 (30 ml) was added **9b** (114 mg, 0.59 mmol) in CH_2Cl_2 (20 ml) at room temperature. The mixture was stirred at room temperature for 3 hr and evaporated. The residue (330 mg) was separated by preparative TLC (silica gel/benzene–hexane (1: 1)) to give **10b** (116 mg, 72%) and **6d** (128 mg 76%).

Transformation of 8c to 6-Bromo-2-ethylthio-3-phenylindole (11)——A mixture of **6c** (1.52 g, 6 mmol) and NBS (1.07 g, 6 mmol) in CCl_4 (50 ml) was refluxed for 15 min. The TLC of the mixture showed complete conversion of **6c** to **8c**. The mixture was again refluxed for 2 hr and cooled to remove succinimide. The filtrate was evaporated and the residue (2.31 g) was chromatographed on silica gel (60 g). Elution with benzene gave **11** (1.84 g, 93% from **6c**), mp 81—83°. Recrystallizations from hexane gave pale yellow needles, mp 87.5—88°. Heating of **11** in AcOH–AcONa for 4.5 hr gave 1-acetyl derivative (**12**), mp 70.5—71.5° (from pet. ether), as colorless prisms.

Bromination of 6c with NBS in Acetic Acid——To a solution of **6c** (253 mg, 1 mmol) in AcOH (20 ml) was added NBS (178 mg, 1 mmol) in AcOH (10 ml) at room temperature. The mixture was stirred at room temperature for 2 hr and poured into NaOH solution (12 g of NaOH in 100 ml of H_2O) under ice-cooling. The mixture was extracted with CH_2Cl_2 and the extracts were washed with H_2O dried, and evaporated. The residue (319 mg) was chromatographed over silica gel column (30 g). Elution with hexane–benzene (2: 1) gave **11** (201 mg, 64%), **6c** (27 mg), and structure unknown compound (37 mg). The IR spectrum of **11** was identical with that of the sample obtained above.

Transformation of 8d to 5-Bromo-2-ethylsulfonyl-3-phenylindole (13)——A solution of **8d** (717 mg) in cyclohexane (20 ml) was refluxed for 30 min. The mixture was evaporated and the residue was chromatographed over silica gel (20 g). Elution with benzene gave an unknown compound (40 mg) and **13** (540 mg, 69%). Recrystallization of crude **13** from benzene gave colorless crystals, mp 239—241°.

6-Bromo-2-ethylsulfonyl-3-phenylindole (14)——To a solution of **11** (890 mg, 2.7 mmol) in AcOH (10 ml) was added 30% H_2O_2 (0.5 ml). The mixture was stirred at 30—40° (bath temperature) for 15 hr and poured into aqueous NaOH (NaOH (16 g) in H_2O (50 ml)) under cooling. The mixture was extracted with CH_2Cl_2 and the extracts were washed with H_2O, dried, and evaporated to give pale brown solid (884 mg, 90%), mp 173—178°. Recrystallizations from benzene gave **14**, mp 183.5—184.5°, as colorless crystals.

5-Bromo-2-ethylsulfonyl-3-phenylindole (13) from 5-Bromo-3-phenylindole (15)——i) Preparation of 5-Bromo-2-ethylthio-3-phenylindole (**16**): To a chilled solution of **15** (5.24 g)[7d] in ether (40 ml) was added ethylsulfenyl chloride (3.86 g, 2 mol equiv.) in CH_2Cl_2 (14 ml) at −16° during 30 min. The mixture was stirred at room temperature for 20 hr and diluted with CH_2Cl_2. The solution was washed with $NaHCO_3$, H_2O, dried and evaporated to leave a residue (7.38 g) which was chromatographed over silica gel. Elution with benzene–hexane (1: 2) gave **16** (3.75 g, 56%) which showed a single spot on TLC and solidified in a refrigerator. UV λ_{max}^{EtOH} nm: 230, 256^s, 292, 300 310^s. NMR ($CDCl_3$) δ: 1.10 (t, 3H, CH_3), 2.66 (q, 2H, CH_2), 7.0—7.8 (m, arom H), 8.1 (b.s. NH). MS *m/e* (rel. intens.): 334, 332 (70, M^+), 223 (100, $M-C_2H_5-Br$).

ii) H_2O_2 oxidation of **16**: To a solution of **16** (1.0 g) in AcOH (12 ml) was added 35% H_2O_2 (874 mg, 3 mol equiv.) at room temperature. The mixture was stirred at room temperature for 24 hr, and poured into aqueous NaOH. The mixture was extracted with CH_2Cl_2 and the extracts were washed with H_2O,

dried, and evaporated. The residue (1.0 g) was chromatographed over silica gel (30 g). Elution with CH_2Cl_2 gave **14** (519 mg, 44%), mp 237—239°, which was recrystallized from benzene to give colorless crystals, mp 240—241°. This was identical with the sample obtained above (mixed mp, IR).

Transformation of 8 to 19——A solution of **8a** (200 mg) in EtOH (60 ml) and 10% HCl (3 ml) was stirred at room temperature for 3 hr. Usual work-up and separation by preparative TLC (silica gel/CH_2Cl_2) gave **19a** (124 mg, 81%), mp 111—112°, which was identical with known sample[11] (mixed mp and IR).

The similar treatment of **8b** gave **19b** (79%), mp 197—199°, which was identical with known sample[11] (mixed mp and IR). Similarly **8d** gave **19d** (94%), mp 195—197°, which was identical with known sample[11] (mixed mp and IR).

Reaction of 7b——i) EtOH–HCl: A solution of **7b** (94 mg) in EtOH (20 ml) and 5% HCl (0.1 ml) was stirred at room temperature for 10 hr. Usual work-up gave **6b** (59 mg, 89%), mp 99—115°.

ii) In AcOH: A solution of **7b** (348 mg) in AcOH (30 ml) was stirred at room temperature for 5.5 hr. The TLC of the mixture showed the absence of **7b** but the mixture still showed a positive test with KI. The mixture was poured into aqueous NaOH (NaOH (20 g) in H_2O (100 ml)) under cooling and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and evaporated to give pale yellow oil (181 mg), which was separated by preparative TLC (silica gel/CH_2Cl_2–acetone (10: 1)). 2-Ethylsulfonyl-3-methylindole (**6b**, 112 mg, 43%) was obtained with some other unknown compounds.

iii) In Aqueous MeOH: A solution of **7b** (2.5 g, 8.3 mmol) in MeOH (50 ml) and H_2O (5 ml) was stirred at room temperature for 17 hr. The reaction mixture became acidic (pH about 1) and showed negative test with KI. The solvent was evaporated and the residue was extracted with CH_2Cl_2–H_2O. The CH_2Cl_2 solution was dried and evaporated to give pale yellow oil (1.98 g). The oil was chromatographed on a silica gel column (60 g). Elution with CH_2Cl_2 gave **6b** (1.24 g, 68%), **24** (158 mg, 5.7%) and **25** (237 mg, 11%). **24**: mp 173—175° (from benzene). *Anal.* Calcd. for $C_{10}H_9Br_2NO_2$: C, 35.85; H, 2.71; N, 4.31; Br; 47.71. Found: C, 35.94; H, 2.68; N, 4.31; Br, 47.58. UV λ_{max}^{EtOH} nm (ε): 219 (24800), 263 (10700), 272 (8800), 309 (2200). IR (KBr): 1740 cm^{-1}. NMR ($CDCl_3$) δ: 1.58 (s, 3H, 3-CH_3), 3.13 (s, 3H, O–Me), 7.40 (d, 1H, arom. H), 7.60 (d, 1H, arom. H), 8.55 (b.s, 1H, NH). MS *m/e* (rel. intens.): 337 (38), 335 (79), 333 (39, M^+), 309 (31), 307 (86), 305 (81, M−CO, M−2×CH_3), 294 (52), 292 (100), 290 (57, M−CO−CH_3). **25**: mp 168—169° (from EtOH). *Anal.* Calcd. for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.95; N, 5.47; Br, 31.20. Found: C, 46.70; H, 3.97; N, 5.60; Br, 31.59. UV λ_{max}^{EtOH} nm (ε): 260 (11200), 301 (1600). IR (KBr): 1740, 1715 cm^{-1} (C=O). NMR ($CDCl_3$) δ: 1.60 (s, 3H, 3-CH_3), 3.13 (s, 3H, O–Me), 6.86 (d, 1H, arom. H), 7.30—7.50 (m, 2H, arom. H), 9.42 (b.s. NH). MS *m/e* (rel. intens.): 257, 255 (56, M^+), 229 (60), 227 (100), 225 (48, M−CO, M−2×CH_3), 214, 212 (88, M−CO−CH_3).

iv) In CH_2Cl_2–H_2O: To a solution of **7b** (prepared from 223 mg of **6b** and NBS (178 mg)) in CH_2Cl_2 (40 ml) was added H_2O (0.1 ml) and the mixture was stirred at room temperature for 24 hr and evaporated. The residue was separated by preparative TLC (silica gel/CH_2Cl_2) to give 5-bromo-2-ethylsulfonyl-3-methylindole (150 mg, 50%), mp 143—144° (from MeOH–H_2O). *Anal.* Calcd. for $C_{11}H_{12}BrNO_2S$: C, 43.73; H, 3.98; N, 4.64. Found: C, 43.78; H, 3.98; N, 4.74. UV λ_{max}^{EtOH} nm (ε): 227 (50600), 283 (11700), 304 (6300), 316 (3900). IR (KBr): 3280 (NH), 1320, 1145, 1135 (SO_2) cm^{-1}. NMR ($CDCl_3$) δ: 1.28 (t, 3H, CH_3), 2.50 (s, 3H, 3-CH_3), 3.22 (q, 2H, CH_2), 7.30—7.52 (m, 2H, arom. H), 7.76 (s, 1H, arom. H), 9.18 (b.s., NH).

Reaction of 8c——i) In EtOH–HCl: A solution of **8c** (332 mg) in EtOH (10 ml) and 10% HCl (1 ml) was stirred at room temperature for 24 hr. Usual work-up and separation by preparative TLC (silica gel) gave the 6-bromo derivative (**11**) (188 mg, 57%), mp 82—84°, beside some other unidentified compounds.

ii) In MeOH–MeONa: A solution of **8c** (332 mg) in MeOH–MeONa (26 mg of Na and 10 ml of MeOH) was refluxed for 4 hr and evaporated. The residue was chromatographed on a silica gel column (25 g). Elution with hexane–benzene (5: 1) gave **11** (57 mg, 17%) and **6c** (49 mg, 19%), which were identical with known samples (IR). Elution with CH_2Cl_2 gave **21** (100 mg) which was further purified by preparative TLC to give colorless crystals (**21**, 65 mg, 23%), mp 77—78°. UV λ_{max}^{EtOH} nm: 234, 248^s, 277^s, 286, 298, 311. IR (KBr): 1520 (C=N) cm^{-1}. NMR ($CDCl_3$) δ: 1.38 (t, 3H, CH_3), 3.0—3.4 (m, 2H, CH_2), 3.12 (s, 3H, OCH_3), 7.04—7.60 (m, 9H, arom. H). MS *m/e* (rel. intens.): 283 (29, M^+), 254 (100, M−C_2H_5).

Reaction of 8e——i) In AcOH: A solution of **8e** (1.0 g) in AcOH (40 ml) was stirred at room temperature for 24 hr, and poured into aqueous NaOH (27 g of NaOH in 150 ml of H_2O) with cooling. The mixture was extracted with CH_2Cl_2 and the extracts were washed with H_2O, dried, and evaporated to leave a residue (940 mg), which was chromatographed over silica gel (15 g). Elution with benzene–hexane (3: 2) gave a mixture of **17** and **18** (870 mg, 87%). Acetylation with Ac_2O–AcONa gave a mixture of acetylated compounds which consisted of a 6: 1 mixture of the 2,6- and 2,5-dibrominated derivatives determined by comparison of the NMR spectrum of known mixture.[7d]

ii) EtOH–NaOH: A solution of **8e** (1.0 g) in EtOH (50 ml) and 10% NaOH (30 ml) was stirred at room temperature for 16 hr and evaporated. The residue was extracted with CH_2Cl_2 and the extracts were washed with H_2O, dried, and evaporated to leave a residue (700 mg) which was chromatographed over silica gel column (15 g). Elution with CH_2Cl_2 gave **23** (104 mg) which was further purified by preparative TLC to give **23** (55 mg, 7%), mp 60—65°. Further elution with CH_2Cl_2 gave **22** (210 mg, 31%), mp 145—160°. Recrystallization from EtOH gave pure **22**, mp 167—169°, (reported[12] mp 169°). **23**: UV λ_{max}^{EtOH} nm: 259^s, 265^s, 278^s, 295^s. IR (KBr): 1580 (C=N) cm^{-1}. NMR ($CDCl_3$) δ: 1.23 (t, 3H, CH_3), 1.37 (t, 3H, CH_3), 3.29

(q, 2H, CH_2), 4.47 (m, 2H, CH_2), 7.0—7.4 (m, 9H, arom. H). MS *m/e* (rel. intens.): 281 (33, M^+), 252 (72, M−Et), 224 (60, M−Et−CH_2CH_2), 146 (100). **22**: UV λ_{max}^{EtOH} nm: 257, 295. IR (KBr): 1730 (C=O), 3215 (NH) cm^{-1}. NMR ($CDCl_3$) δ: 1.26 (t, 3H, CH_3), 3.41 (m, 2H, CH_2), 6.8—7.5 (m, 9H, arom. H), 9.28 (b.s, 1H, NH). MS *m/e* (rel. intens.): 253 (28, M^+), 224 (93, M−Et), 209 (74, M−EtO), 196 (100).

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