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Halogenation of 1-Substituted Skatoles. Preparation of 3-Bromomethylindoles*

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Halogenation of skatole (**1a**) and 1-acetyl (**1b**), 1-benzenesulfonyl (**1c**), and 1-tosylskatole (**1d**) with N-bromosuccinimide (NBS) N-chlorosuccinimide (NCS), N-iodosuccinimide (NIS) in acetic acid or carbon tetrachloride has been studied. Bromination of **1a** with NBS in carbon tetrachloride in the presence of benzoyl peroxide yielded 2-bromoskatole (**2a**) in 85% yield. Reaction of **1b** with NBS (NCS) in acetic acid or in carbon tetrachloride yielded 1-acetyl-2-(1-acetyl-3-indolylmethyl)-3-methylindole (**7b**) and 2-halo derivative (**2b**). The reaction of **2b** (X=Br) with skatole or 3-methyloxindole gave 1-acetylskatole (**1b**). Bromination of **1c** (**1d**) with NBS in carbon tetrachloride yielded 3-bromomethyl derivative (**6c** or **6d**). On the other hand the reaction of (**1c** or **1d**) with NBS in acetic acid gave 2-bromo derivative (**2c** or **2d**) and the 3-bromo-oxindole (**5c** or **5d**). Mechanism of the formation of **7b** and other products has been discussed.

Bromination of skatole with N-bromosuccinimide (NBS) in acetic acid yielded a 2-bromoskatole.[2] Further reaction with NBS resulted in the 2,6-dibromoskatole.[2,3] Bromination in aqueous solvent yielded 3-methyloxindole and further bromination yielded 5-bromo-3-methyloxindole,[3] while in *tert*-butanol the bromination gave the 3-methyloxindole and 3-bromo-3-methyloxindole.[2] Bromination of skatole with bromine in ether at −70° yielded also 2-bromoskatole,[4] and with dioxane-dibromide[5] or NBS[6] in the presence of pyridine yielded 1-(3-methyl-2-indolyl)pyridinium bromide. Chlorination of skatole with sulfuryl chloride, chlorine, and N-chlorosuccinimide (NCS) in various solvents yielded oxindolic products.[7] However, neither halogenation of skatole under radical condition nor halogenation of 1-substituted skatoles has been studied so far.

We describe in this paper halogenation of skatol (**1a**), 1-acetyl (**1b**), 1-benzenesulfonyl (**1c**), and 1-tosyl (**1d**) skatoles in order to investigate the reactivity of 3-methyl group of skatole under various conditions, including ionic and radical conditions, using NBS, NCS, and N-iodosuccinimide (NIS). The results are summarized in Table I and Chart 1.

The reaction of skatole (**1a**) with NIS in acetic acid (run 1) was slow at 20° in contrast to the reaction with NBS.[2] However, the reaction proceeded at 40° to give a dimeric compound, 2-(3-methyl-3-oxindolyl)-3-methylindole (**8a**), as the main product and 2-acetylskatole and 1-acetylskatole (**1b**) were obtained as minor products. Bromination of **1a** with NBS in boiling carbon tetrachloride in the presence of benzoyl peroxide (BPO) (run 3)[8] yielded 2-bromoskatole (**2a**, X=Br) in 85% yield which is found to be the best method for the preparation of **2a** (X=Br). However, 3-bromomethyl derivative (**6a**) was not obtained in contrast

* Dedicated to the memory of Prof. Eiji Ochiai.

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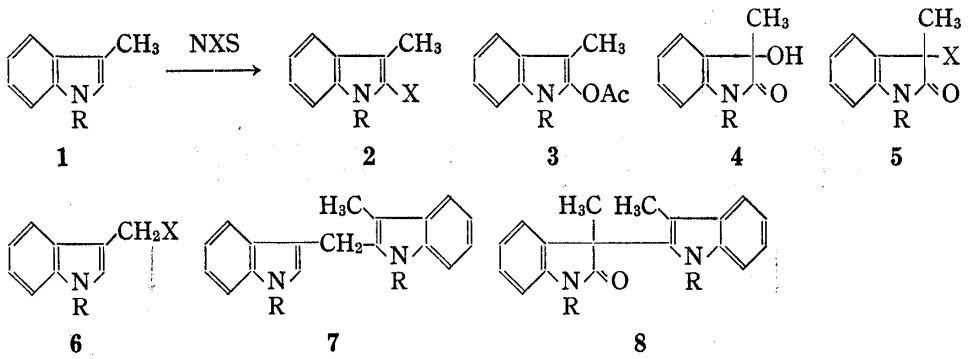
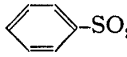
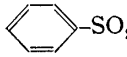
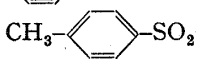
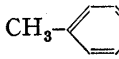


a: R=H, **b**: R=CH_3CO, **c**: R=$C_6H_5SO_2$, **d**: R=Ts

X=Cl or Br

Chart 1

TABLE I. Halogenation of 1-Substituted Skatoles

Run	1-Substituent	Condition	Products (yield %)
1	H (**1a**)	NIS–AcOH, 40°, 2 hr	**8a** (33), SM (7)[a]
2	H	NCS–BPO–CCl_4, reflux, 5 hr	**2a** (43), **4a** (17)
3	H	NBS–BPO–CCl_4, reflux, 4.5 hr	**2a** (85)
4	CH_3CO (**1b**)	NCS–AcOH, 40°, 5 hr	**2b** (61), **3b** (7), **7b** (8)
5	CH_3CO	NBS–AcOH, 20°, 4 hr	**2b** (2), **5b** (26), **7b** (19) SM (26)
6	CH_3CO	NIS–AcOH, 40°, 2 hr	**3b** (6), **8b** (5), SM (73)
7	CH_3CO	NCS–BPO–CCl_4 reflux, 6 hr	**2b** (2), **7b** (9), SM (79)
8	CH_3CO	NBS–BPO–CCl_4 reflux, 4 hr	**2b** (61), **7b** (22), SM (1)
9	 (**1c**)	NBS–AcOH, 20°, 4 hr	**2c** (39), **5c** (21), **7c** (4.5) SM (24)
10		NBS–BPO–CCl_4, reflux, 4.5 hr	**6c** (88)
11	 (**1d**)	NBS–AcOH, 20°, 4.5 hr	**2d** (31), **5d** (23), SM (23)
12		NBS–BPO–CCl_4, reflux, 4 hr	**6d** (75)

a) SM: starting material

to the bromination of 3-methylbenzothiophen[9] and 3-methylbenzofuran[10] under similar conditions which have been reported to form 3-bromomethyl derivatives. Chlorination of **1a** under similar conditions (run 2) gave a mixture of **2a** (X=Cl) and 3-methyldioxindole (**4a**).

Bromination of 1-acetylskatole (**1b**)[11] with NBS in acetic acid (run 5) yielded 1-acetyl-3-bromo-3-methyloxindole (**5b**, X=Br), a dimeric compound, 1-acetyl-2-(1-acetyl-3-indolylmethyl)-3-methylindole (**7b**), and a trace of 1-acetyl-2-bromoskatole (**2b**, X=Br), while skatole (**1a**) was reported to give only **2a** under similar conditions.[2] On the other hand, the reaction of **1b** with NCS in acetic acid (run 4) was slow at 20°, but at 40° the reaction proceeded to give **2b** (X=Cl) as main product besides **3b** and **7b** as minor products, and an oxindolic compound (**5b**, X=Cl) was not obtained. Furthermore, bromination of **1b** under radical condition (run 8) yielded **2b** (X=Br) and **7b**, showing a marked contrast to that of 1-acetyl-3-phenylindole[8] which did not proceed under similar conditions. Chlorination of **1b** under radical condition (run 7), however, proceeded slowly and gave small amount of **2b** (X=Cl) and **7b** with recovering the most of starting materials even after refluxing for 6 hr. Although the bromomethyl

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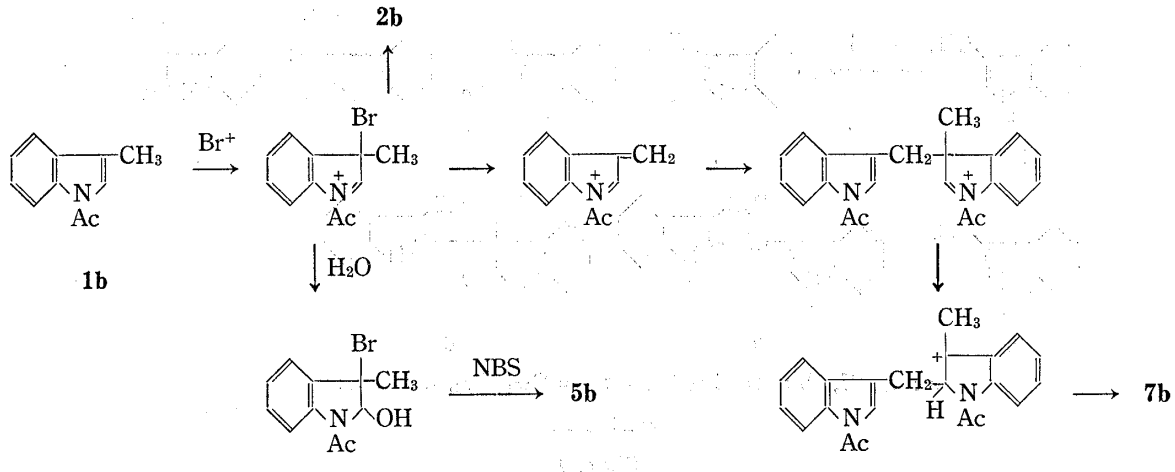

Chart 2

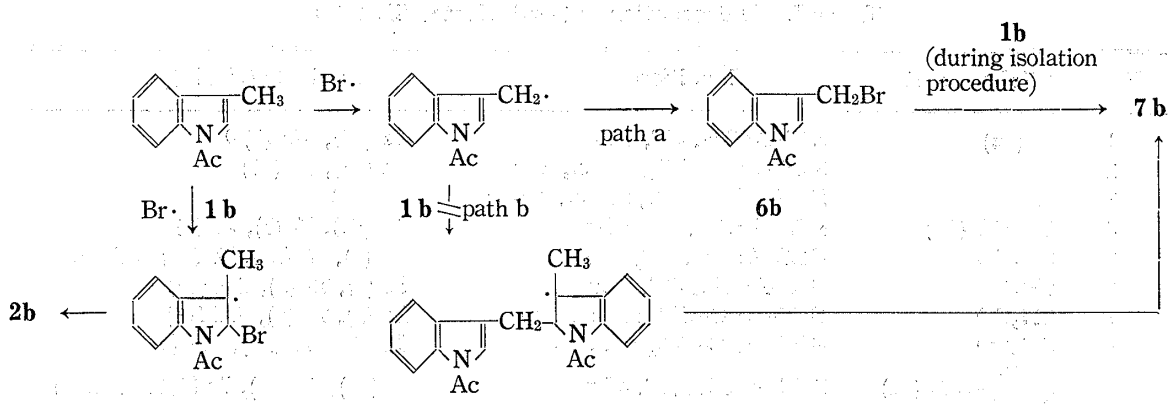

Chart 3

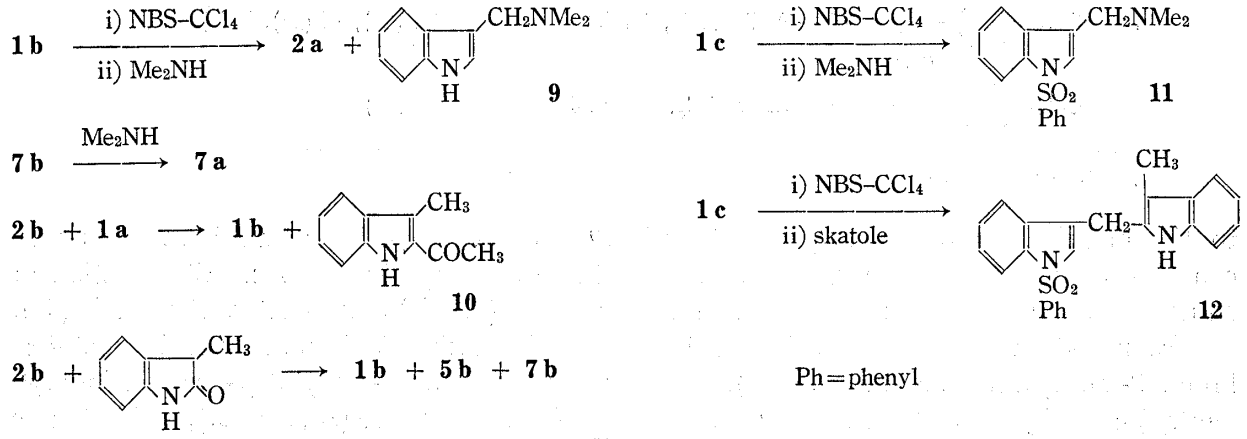

Chart 4

derivative (**6b**) was not obtained from the reaction mixture, the formation of **7b** indicated involvement of 3-methyl group in the bromination.

The mechanism of the reaction is best interpreted by the sequences of steps shown in Chart 2 (for ionic condition) and Chart 3 (for radical condition). According to the mechanism proposed in Chart 3 the dimeric compound (**7b**) would originate from 3-bromomethyl derivative (**6b**). In order to show the presence of the intermediate, 3-bromomethyl-1-acetylindole (**6b**), under radical condition, dimethylamine gas was introduced to the reaction mixture after removal of succinimide. Separation of the mixture gave **2a** (X=Br) (31%), gramine (38%), and skatole (8%), the dimer was not isolated. On the other hand, the reaction of **7b** with dimethylamine in carbon tetrachloride yielded only the deacetyl derivative (**7a**). Therefore,

the dimer (**7b**) obtained in run 8 would not be the primary product of the reaction, but may derived from the reaction of the unreacted **1b** with unstable **6b** during isolation procedure. These results ruled out the path b for the formation of **7b**.

It is worthwhile to note that **2b** (X=Br) is more labile than 2-bromoskatole (**2a**, X=Br) and decomposed during the isolation by silica gel column at hight temperature (>20°). Pure **2b** decomposed on standing at room temperature in an open air to many products among which **5b** (X=Br), **1b**, and **7b** were isolated and identified. However, a solution of **2b** (X=Br) in acetic acid was stable until at 100°, but decomposed rapidly at the refluxing temperature. To examine a mode of decomposition, the reaction of **2b** (X=Br) with skatole in acetic acid was carried out. Vigorous reaction occurred at about 100° and yielded **1b** (94%) and 2-acetylskatole (**10**, 18%) with recovering skatole (22%). The similar reaction of **2b** with 3-methyloxindole in acetic acid yielded **1b** (81%), **5b** (X=Br, 4.7%), and **7b** (8%) with recovered oxindole (44%). These results indicated that **2b** was reactive and predicted to behave as a brominating agent.

The above results indicate that 1-acetylation of skatole increased the reactivity of 3-methyl group in the bromination with NBS under radical condition and **6b** (X=Br) was formed as well as **2b** (X=Br) which presumed to be formed by direct addition of bromine at 2-position. As reported previously,[8] we have found 1-acetylation of 3-phenylindole inhibited the direct bromine addition to 2-position under radical condition due to the steric hindrance. In the case of 1-acetylskatole (**1b**), 2-position may not be so hindered towards to the attack of bromine due to the smaller substituent at 3-position. Therefore, bromination of 1-benzenesulfonyl (**1c**) and 1-tosyl skatole (**1d**) which have balkier substituents than acetyl at 1-position, were carried out under radical condition. Bromination of **1c** and **1d** under radical conditions (run 10 and 12) yielded expected 3-bromomethyl derivatives (**6c** and **6d**) in good yields, and 2-bromo derivatives (**2c** and **2d**) were not obtained. The both bromomethyl derivatives are unstable and decomposed during purification by silica gel column, but **6c** and **6d** were obtained by direct recrystallizations of the reaction mixture as stable crystals. The reaction of **6c** with an excess of dimethylamine in carbon tetrachloride yielded the gramine derivative (**11**) and benzenesulfonyl group was not removed under this condition. When **6c** was treated with skatole, the expected mixed dimer (**12**) was obtained. These results support the reaction path for the formation of **7b** as shown in Chart 3.

Table II. Analytical Data of Substituted Skatoles

Compound No.	X	mp	Recryst. solvents	Formula	Analytical calculated				Found			
					C	H	N	X	C	H	N	X
2b	Cl	47 — 48.5°	MeOH	$C_{11}H_{10}ONCl$	63.61	4.86	6.75		63.76	4.86	6.56	
2b	Br	49 — 50.5°	EtOH	$C_{11}H_{10}ONBr$	52.38	3.97	5.56		52.36	3.98	5.60	
2c	Br	129.5—131°	EtOH	$C_{15}H_{12}O_2NSBr$	51.44	3.45	4.00	22.60	51.67	3.50	4.16	22.60
2d	Br	140 —141.5°	EtOH	$C_{16}H_{14}O_2NSBr$	52.71	3.87	3.85	21.94	52.86	3.87	3.91	21.86
3b	—	82 — 83.5°	hexane	$C_{13}H_{13}O_3N$	67.52	5.67	6.06		67.47	5.71	5.96	
5b	Br	112 —113.°	benzene	$C_{11}H_{10}O_2NBr$	49.28	3.76	5.22		49.62	3.76	5.54	
5c	Br	127 —128°	EtOH	$C_{15}H_{12}O_3NSBr$	49.18	3.30	3.82	21.81	49.34	3.26	3.89	22.06
5d	Br	157 —159°	benzene–hexane	$C_{16}H_{14}O_3NSBr$	50.54	3.71	3.69	21.01	50.48	3.68	3.60	21.07
6c	Br	136 —138°	benzene	$C_{15}H_{12}O_2NSBr$	51.44	3.45	4.00	22.82	51.84	3.87	4.07	22.60
6d	Br	145.5—146.5°	benzene	$C_{16}H_{14}O_2NSBr$	52.76	3.87	3.85	21.94	52.64	3.62	3.88	22.18
7a	—	170 —171.5°	benzene	$C_{18}H_{16}N_2$	83.08	6.15	10.77		82.74	6.20	10.50	
7b	—	164 —165°	benzene–hexane	$C_{22}H_{20}O_2N_2$	76.71	5.88	8.13		76.95	5.81	7.99	
11	—	77 — 79°	iso-PrOH-iso-Pr_2O	$C_{17}H_{18}O_2N_2S$	64.94	5.77	8.91		64.47	5.81	8.65	
12	—	182 —183°	benzene	$C_{24}H_{20}O_2N_2S$	71.98	5.03	7.00		71.91	5.07	6.66	

Table III. Ultraviolet and Mass Spectra

Compound No.	X	UV λ_{max}^{EtOH} nm($\varepsilon \times 10^{-3}$)	Mass: M^+ (rel. int)	Mass: Base peak
2a	Cl	222, 274, 280, 290 (37.1) (8.9) (8.8) (6.9)	167(34) 165(100)	M^+
2b	Br	234.5, 273.5, 279^s, 292^s 302	253(16) 251(16)	130 (M–Br–CH_2CO)
2c	Br	218, 257 (23.2) (15.1)	351(63) 349(63)	210, 208 (M–SO_2Ph)
2d	Br	221, 254 (24.2) (16.4)	365(57) 363(57)	210, 208 (M–Ts)
3b	—	241, 264^s, 275^s, 292 (17.9) (9.4) (7.5) (4.9) 300^s (4.8)	231(6)	147 (M–Ac–CH_2CO)
5b	Br	232, 275^s, 283^s (15.3) (1.6) (1.4)	269(5) 267(5)	146 (M–Br–CH_2CO)
5c	Br	235, 267^s, 275 (14.5) (4.0) (3.0)	367(5) 365(5)	286 (M–Br)
5d	Br	234, 276^s (18.1) (2.1)	381(4) 379(4)	300 (M–Br)
6c	Br	211, 253, 284^s, 291^s (27.6) (12.3) (3.0) (2.8)	351(8) 349(8)	270 (M–Br)
6d	Br	213, 252, 276^s, 283 (27.4) (14.8) (4.8) (4.3) 291^s (4.0)	365(4) 363(4)	284 (M–Br)
7a	—	228, 275^s, 283, 291 (94.1) (12.9) (14.2) (12.8)	260(100)	M^+
7b	—	242, 272, 292, 301 (35.0) (18.9) (13.0) (13.0)	344(32)	259 (M–CH_2CO–CH_3CO)
11	—	254, 284, 292^s (11.9) (3.3) (3.1)	314(32)	270 (M–NMe_2)
12	—	225, 259, 284, 292^s (63.9) (15.3) (12.2) (11.3)	400(100)	M^+

Ph=phenyl

Table IV. NMR Spectra

Compound No.	X	NMR ($CDCl_3$) δ-Value
2a	Cl	2.24(s, 3-CH_3), 7.76(br. s. NH)
2b	Br	2.28(s, 3-CH_3), 2.83(s, Ac), 8.25(m, 7-H)
2c	Br	2.16(s, 3-CH_3), 8.24(m, 7-H)
2d	Br	2.17(s, CH_3), 2.33(s, CH_3), 8.22(m, 7-H)
3b	—	2.05(s, 3-CH_3), 2.37(s, Ac), 2.53(s, Ac)
5b	Br	2.08(s, 3-CH_3), 2.67(s, Ac), 8.18(d-d, 7-H)
5c	Br	1.99(s, 3-CH_3)
5d	Br	1.97(s, 3-CH_3), 2.43(s. Ar–CH_3)
6c	Br	4.63(s, CH_2)
6d	Br	2.31(s, Ar–CH_3), 4.59(s, CH_2)
7a	—	2.32(s, 3-CH_3), 4.16(s, CH_2), 6.88(s, 2-H) 7.85(br. s., NH)
7b	—	2.32(s, 3-CH_3), 2.48(s, Ac), 2.65(s, Ac), 4.47(s, CH_2) 6.92(s, 2-H), 7.87(m, 7-H), 8.40(m, 7-H)
11	—	2.22(s, NMe), 3.52(s, CH_2)
12	—	2.28(s, 3-CH_3), 4.08(s, CH_2)

On the other hand bromination of **1c** and **1d** in acetic acid (run 9 and 11) gave 2-bromoindoles (**2c** and **2d**, X=Br) and 3-bromooxindoles (**5c** and **5d**, X=Br). Small amount of **7c** was obtained in the bromination of **1c**, but **7d** was not isolated in the bromination of **1d**.[12] These results may provide further evidence for the mechanism of bromination of 1,3-disubstituted indoles; namely bromine radical may attack at the 2-position, while brominium ion may attack at 3-position of the indoles.

Analytical and spectral data of the compounds obtained by halogenation of 1-substituted skatoles are summarized in Table II, III, and IV.

Experimental[13]

Reaction of 1a with NIS-AcOH (Run 1)——To a solution of **1a** (1.31 g, 10 mM) in AcOH (20 ml) was added NIS (2.25 g, 10 mM) in AcOH (40 ml) during 20 min at 20° under N_2. The mixture was stirred at 20° for 4 hr and then at 40° for 2 hr, and neutralized with 40% NaOH under cooling and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to leave a residue (1.6 g) which was chromatographed over silica gel. Elution with benzene–hexane (2: 1) gave **1a** (96 mg, 7.3%). Elution with benzene–CH_2Cl_2 (20: 1) gave 1-acetylskatole (**1b** 45 mg, 2.6%). Elution with benzene–CH_2Cl_2 (1: 1) gave 2-acetylskatole (147 mg, 8.5%), mp 135—140°, which was identical with a standard sample[14] (IR). Elution with CH_2Cl_2–MeOH (20: 1) gave **8a** (456 mg, 33%), mp 204—212°. Recrystallization from benzene gave mp 221—223° (reported mp 224—225°[7]).

Reaction of 1a with NCS-CCl_4-BPO (Run 2)——A mixture of **1a** (1.31 g, 10 mM), NCS (1.34 g, 10 mM), and BPO (7 mg) in CCl_4 (40 ml) was refluxed for 2 hr under N_2. Further BPO (7 mg) was added to the cooled mixture and the mixture was refluxed for 3 hr. After cooling insoluble succinimide was removed and the filtrate was evaporated to leave a residue (1.73 g) which was chromatographed over silica gel (30 g). Elution with benzene–hexane (1: 1) gave 2-chloroskatole (**2a**, X=Cl) (704 mg, 42.6%), mp 105—112°. Recrystallizations from aqueous AcOH gave pure sample, mp 114.5—115.5° (reported mp 113.5°[15]). Elution with CH_2Cl_2–MeOH (10: 1) gave a mixture (537 mg). Further separation of the mixture gave **4a** (281 mg, 17%) which was identical with a standard sample (IR, and TLC).

Reaction of 1a with NBS-CCl_4-BPO (Run 3)——A mixture of **1a** (1.31 g, 10 mM), NBS (1.78 g, 10 mM), and BPO (7 mg) in CCl_4 (40 ml) was refluxed for 2 hr under N_2 further BPO (7 mg) was added and the mixture was further refluxed for 2.5 hr. The cooled mixture was filtered to remove succinimide and the filtrate was evaporated to leave a residue (2.1 g) which was chromatographed over silica gel (40 g). Elution with benzene–hexane (1: 1) gave **2a** (X=Br), mp 94—95.5° (1.79 g, 85%). Recrystallization from aqueous AcOH gave pure **2a**, mp 102—104°, which was identical with a standard sample (IR and TLC).

Reaction of 1b with NCS-AcOH (Run 4)——To a solution of **1b** (2.6 g, 15 mM) in AcOH (50 ml) was added NCS (2.00 g, 15 mM) in AcOH (30 ml) during 20 min at room temperature under N_2. The mixture was stirred at 40° for 5 hr and condensed to 20 ml *in vacuo*. The mixture was diluted with ice-water (30 ml) and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to leave a residue (3.6 g) which was chromatographed over silica gel (50 g). Elution with benzene–hexane (3: 10) gave **2b** (X=Cl) (1.91 g, 61%), mp 44—46°. Elution with benzene recovered **1b** (200 mg, 7.7%). Elution with benzene–CH_2Cl_2 (10: 1) gave **3b** (235 mg, 7%). Elution with benzene–CH_2Cl_2 (1: 1) gave **7b** (203 mg, 8%).

Reaction of 1b with NBS-AcOH (Run 5)——To a solution of **1b** (1.73 g, 10 mM) in AcOH (25 ml) was added NBS (1.78 g, 10 mM) in AcOH (65 ml) during 20 min at 20° under N_2. The mixture was stirred at 20° for 4 hr. The mixture was neutralized to pH 6 with 20% NaOH under cooling and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to leave a residue (2.19 g) which was chromatographed over silica gel. Elution with benzene–hexane (5: 1) gave **2b** (41 mg, 2%), mp 47—49°. The second elution with the same solvent gave **5b** (701 mg, 26%). Elution with benzene–CH_2Cl_2 (1: 1) gave **1b** (459 mg, 27%). Elution with CH_2Cl_2 gave **7b** (337 mg, 20%) and small amount of brominated **7b**, probably 1-acetyl-2-(1-acetyl-2-bromo-3-indolylmethyl)-3-methylindole, mp 119—121° (from CH_2Cl_2–MeOH). *Anal.* Calcd. for $C_{22}H_{19}O_2N_2Br$; C, 62.41; H, 4.49; N, 6.62. Found: C, 61.99; H, 4.49; N, 6.54. IR (KBr); 1710, 1700 cm^{-1}. UV: λ_{max}^{EtOH} 244, 271^s,, 293^s, 301^s nm. Mass Spectrum: (*m/e* (rel. int)); 424, 422 (5, M^+), 343 (100, M–Br).

12) In acetic acid 1-benzenesulfonyl or 1-tosyl group, stronger electron withdrawing group than 1-acetyl, may prevent the dimerization path shown in Chart 2.

13) All melting points are not corrected. Ultraviolet (UV) spectra were recorded on a Hitachi 3T or 323 spectrophotometer. Infrared (IR) spectra were measured with a Hitachi G3 spectrometer. NMR spectra were taken with a JEOL 4H-100 or MH-100. Mass spectra were recorded on a Hitachi RMU-6E.

14) K. Ishizumi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 863 (1967); **15**, 1010 (1967).

15) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958) [*Chem. Abstr.*, **53**, 21876*g* (1959)].

NMR ($CDCl_3$); 2.32 (s, 3H, CH_3), 2.60 (s, 3H, Ac), 2.84 (s, 3H, Ac), 4.50 (s, 2H, CH_2), 6.8—7.4 (m, arom.H), 7.7 (m, 1H, 7-H), 8.23 (m, 1H, 7-H).

Alternative Synthesis of 5b (X=Br)——To a boiling solution of 1-acetyl-3-methyloxindole[16] (800 mg, 4 mM) in CCl_4 (50 ml) was added dropwise Br_2 (0.672 g, 4 mM). After addition the mixture was refluxed for 8 hr and evaporated to leave a crystalline solid (1.15 g). Recrystallization from benzene gave **5b** (541 mg, 51%), mp 111—113°. Further recrystallization from benzene gave pure sample, mp 112—113°, which was identical with the sample obtained in run 5.

Reaction of 1b with NBS-CCl_4-BPO (Run 8)——A mixture of **1b** (6.05 g, 35 mM), NBS (6.23 g, 35 mM), and BPO (25 mg) in CCl_4 (150 ml) was refluxed for 4 hr under N_2. The cooled mixture was filtered to remove succinimide and evaporated *in vacuo* to leave a residue (9.9 g) which was chromatographed over silica gel (100 g). Elution with benzene–hexane (2: 1) gave **2b** (X=Br) (5.40 g, 61.3%), mp 48—50°. Elution with benzene gave **1b** (80 mg, 1%). Elution with CH_2Cl_2 gave **7b** (1.35 g, 22%). Isolation of **2b** (X=Br) was successful only in winter time.

The similar reaction of **1b** with NCS–CCl_4–BPO gave **2b** (X=Cl) and **7b** in low yield (run 7).

Reaction of 6b with Dimethylamine——A mixture of **1b** (1.73 g, 10 mM), NBS (1.78 g, 10 mM), and BPO (7 mg) in CCl_4 (40 ml) was refluxed for 4.5 hr under N_2. The cooled mixture was filtered to remove succinimide. Dimethylamine gas was introduced to the filtrate during 2 hr with stirring at room temperature. The mixture was left overnight and diluted with CH_2Cl_2. The solution was washed with H_2O, 10% HCl, H_2O, dried, and evaporated *in vacuo* to leave a dark red powder (904 mg) which was chromatographed over silica gel (20 g). Elution with benzene–hexane (1: 1) gave **2a** (645 mg, 31%) which was recrystallized from aqueous AcOH to give pure **2a**, mp 91—95°. Elution with benzene gave **1a** (102 mg, 7.7%). The HCl extracts were basified with 10% NaOH under cooling, and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to leave a dark red oil (1.02 g) which was chromatographed over silica gel. Elution with CH_2Cl_2 and CH_2Cl_2–MeOH (5: 1) gave **9** (653 mg, 38%) which was recrystallized from acetone to give **9**, mp 126—130° (reported mp 134—138°[17]). It was identical with a standard gramine (IR and TLC). Small amount of 2-bromogramine, mp 115—120°, was isolated from the same fraction. Purification of this compound was not successfull, but its structure was assumed from the spectral data of the sample which showed a single spot on TLC. UV λ_{max}^{EtOH} 220, 273^s, 283, 290 nm. Mass Spectrum (*m/e* (rel. int.)); 254, 252 (41, M^+), 210, 208 (100, M–NMe_2). NMR ($CDCl_3$); δ 2.32 (s, 6H, NMe), 3.62 (s, 2H, CH_2), 7.02—7.56 (m, 4H, arom.H), 9.38 (br.s, 1H, NH).

Reaction of 7b with Dimethylamine——To a solution of **7b** (700 mg) in CCl_4 (70 ml) was bubbled dimethylamine gas for 5 hr at room temperature. The mixture was left overnight and washed with H_2O, dried, and evaporated to give a dark brown oil (993 mg). Separation by silica gel column and preparative TLC gave **7a** (325 mg, 62.5%) which was recrystallized from benzene to give colorless needles, mp 170—171.5°. A trace of gramine was detected by TLC, but could not be isolated.

Reaction of 1-Acetyl-2-bromoskatole (2b, X=Br)——i) In AcOH: A solution of **2b** (X=Br, 156 mg) in AcOH (30 ml) was refluxed for 2 hr under N_2. The dark purple mixture was neutralized with 20% NaOH to pH 6—7 under cooling and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to leave a dark purple oil (167 mg) which was separated by preparative TLC (silica gel/CH_2Cl_2–hexane (1: 1)). The least polar zone gave **1b** (42 mg, 39%). The second zone gave **7b** (8 mg, 7.4%). The both compounds were identical with standard samples. (IR).

ii) With Skatole: A solution of **2b** (X=Br, 500 mg, 2 mM) and **1a** (262 mg, 2 mM) in AcOH (30 ml) was stirred at room temperature for 3 hr under N_2. Since TLC of the mixture showed only starting materials to be present, the mixture was warmed up to 105° (bath temperature). The mixture was turned to dark purple which showed many spots on TLC. Worked-up and separation as above gave **1b** (331 mg, 94%), 2-acetylskatole (38 mg, 12%), **1a** (57 mg, 22%), and other unidentified compounds.

iii) With 3-Methyloxindole: A solution of **2b** (X=Br, 200 mg, 0.79 mM) and 3-methyloxindole (117 mg, 0.79 mM) in AcOH (40 ml) was heated at 115° (bath temperature). The dark purple mixture was treated as above. 1-Acetylskatole (**1b**, 111 mg, 81%), **5b** (10 mg, 4.7%), and **7b** (10 mg, 8%) were isolated and identified with standard samples (IR and TLC).

iv) With Silica Gel: A mixture of **2b** (195 mg) and silica gel (2 g) in CH_2Cl_2 (5 ml) was evaporated *in vacuo*. The residue was warmed at 70° (bath temperature) for 1 hr, and extracted with CH_2Cl_2. Evaporation of the solvent gave a dark purple oil (158 mg) which was separated by preparative TLC (silica gel/CH_2Cl_2–hexane (2: 1)). 1-Acetylskatole (**1b**, 57 mg, 43%), **5b** (4 mg, 2%), and **7b** (14 mg, 10%) were isolated and identified with standard samples (IR).

1-Benzenesulfonylskatole (1c)——To a suspension of NaH (3.85 g (80 mM) of a 50% dispersion in mineral oil) in THF (50 ml) was added skatole (10.34 g, 80 mM) in THF (30 ml). The mixture was refluxed for 30 min. Benzenesulfonyl chloride (14.13 g, 80 mM) in THF (100 ml) was added to the cooled mixture during 30 min at room temperature. The mixture was refluxed for 2.5 hr and evaporated to leave a residue. Water was

16) K. Brunner, *Monatsh.*, **18**, 536 (1897).
17) H. Kuhn and O. Stein, *Chem. Ber.*, **70**, 567 (1937).

added to the residue and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to give a pale brown solid (21.8 g). Recrystallization from benzene gave **1c** (18.95 g, 87.5%), mp 118—120.5°. Further recrystallizations from benzene gave colorless needles, mp 120—121°. *Anal.* Calcd. for $C_{15}H_{13}O_2NS$; C, 66.40; H, 4.83; N, 5.16. Found: C, 66.35; H, 4.81; N, 5.12. IR (KBr); 1375, 1180, 1190 (SO_2), 760, 750 cm^{-1}. UV: λ_{max}^{EtOH} nm (ε); 214 (26000), 254.5 (12800), 285^s, (3700), 293^s (3600); λ_{min} 233 (8600), 282 (3700), 290 (3600). Mass Spectrum (*m/e* (rel. int.)); 273 (15, M+2), 271 (43, M^+), 130 (100, M–$C_6H_5SO_2$). NMR ($CDCl_3$) δ 2.21 (s, 3H, CH_3), 7.00—8.00 (m, arom H).

The similar reaction of **1a** with tosyl chloride gave **1d**, (80%), mp 114—115.5° (reported mp 114.5—115°[18]).

Reaction of 1c with NBS-CCl_4-BPO (Run 10)——A mixture of **1c** (2.00 g, 7 mM), NBS (1.32 g, 7 mM), and BPO (7 mg) in CCl_4 (100 ml) was refluxed for 4.5 hr under N_2. Cooled mixture was filtered to remove succinimide and condensed to a half volume. The separated crystals (**6c**, 1.752 g), mp 122—136°, were collected and the filtrate was further condensed to give the second crop of **6c** (512 mg, total 2.264 g, 87.7%). Recrystallizations from benzene gave analytical specimen.

The similar reaction of **1d** (run 12) gave **6d.**

Reaction of 6c with Dimethylamine——A mixture of **1c** (2.00 g, 7 mM), NBS (1.32 g, 7 mM), and BPO (7 mg) in CCl_4 (100 ml) was refluxed for 4 hr under N_2. The cooled mixture was filtered to remove succinimide and dimethylamine gas was bubbled for 4 hr to the filtrate at room temperature. The mixture was kept overnight and washed with H_2O and 5% HCl. The HCl solution was basified with 10% NaOH (to pH 11) and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to leave a brown oil (1.427 g, 61%) which showed a single spot on TLC. Recrystallizations from iso-PrOH–iso-Pr_2O gave **11**, mp 77—79, as pale brown needles. The CCl_4 solution was washed with H_2O, dried and evaporated to leave a yellow oil (714 mg). Chromatography over silica gel gave **1c** (264 mg, 12.3%).

Reaction of 6c with Skatole——A mixture of **1c** (1.626 g, 6 mM), NBS (1.068 g, 6 mM), and BPO (7 mg) in CCl_4 (100 ml) was refluxed for 4 hr under N_2. To the cooled mixture was added skatole (787 mg, 6 mM) at room temperature. The mixture was stirred at room temperature for 2 hr and filtered to remove succinimide. The filtrate was evaporated to give dark brown oil (2 g) which was chromatographed over silica gel (40 g). Elution with benzene–hexane (1: 2) gave recovered skatole (11 mg, 1.4%). The second elution with the same solvent gave recovered **1c** (176 mg, 11%). Elution with benzene–hexane (3: 1) gave **12** (816 mg, 34%), mp 187—189°.

Reaction of 1c with NBS-AcOH (Run 9)——To a solution of **1c** (2.0 g, 7.4 mM) in AcOH (30 ml) was added NBS (1.32 g, 7.4 mM) in AcOH (50 ml) at 20° during 20 min under N_2. The mixture was stirred at 20° for 4 hr, neutralized with 30% NaOH under ice-cooling, and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to leave a solid (2.69 g) which was chromatographed over silica gel (40 g). Elution with benzene–hexane (2: 1) gave **2c** (X=Br) (1.02 g, 39%), mp 127—130°. Further elution with the same solvent gave **1c** (486 mg, 24%). Elution with benzene and benzene–CH_2Cl_2 (2: 1) gave **5c** (579 mg, 21%). Elution with benzene–CH_2Cl_2 (1: 5) gave **7c** (122 mg, 4.5%).

The similar reaction of **1d** gave **2d** and **5d** (run 11).

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18) M. Natsume and I. Utsunomiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 1595 (1972)