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Pyranoindole and Thiopyranoindole. Oxidative Cyclization of 3-Indolepropanol and 3-Indolepropanethiol with N-Bromosuccinimide, N-Chlorosuccinimide, and Singlet Oxygen[1]

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Oxidative cyclization of 3-indolepropanethiol (**6**) and 3-indolepropanol (**9**) with N-bromosuccinimide or N-chlorosuccinimide (NCS) gave the corresponding thiopyrano-[2,3-*b*]indole (**7**) and pyrano[2,3-*b*]indole (**10**) in good yields. Reaction of **7** with NCS in carbon tetrachloride gave an unstable chloroindolenine (**18**) which transformed to a spirooxindole (**19**) on treatment with ethanolic hydrochloric acid. Reaction of **7** with NBS in carbon tetrachloride gave 7-bromo derivative (**20**) *via* the 3-bromoindolenine. Similarly pyranoindole (**10**) gave a spirooxindole (**23**) in good yield on treatment with NCS in methylene chloride followed by the addition of ethanolic hydrochloric acid. On the other hand reaction of **9** with two equivalents of NCS gave **23** and dichlorooxindole (**24**). Dye-sensitized photooxygenation of 3-indolepropanol (**9**) in benzene gave 4a-hydroxy-pyrano[2,3-*b*]indole instead of **10**.

Keywords——N-bromosuccinimide; N-chlorosuccinimide; 3-substituted indoles; halogenation; oxidative cyclization; thiopyranoindole; pyranoindole; 3-haloindolenine; dye-sensitized oxygenation

3-Bromoindolenine (**2**) has been known as the intermediate in the bromination of 3-alkylindole (**1**) to 2-bromoindole (**3**).[3] Presence of the intermediate was proved by the isolation of the 1-(2-skatyl)pyridinium bromide (**4**) in the bromination of skatole with dioxane dibromide in the presence of pyridine.[4] Furthermore, we have isolated 3-bromoindolenine derivatives

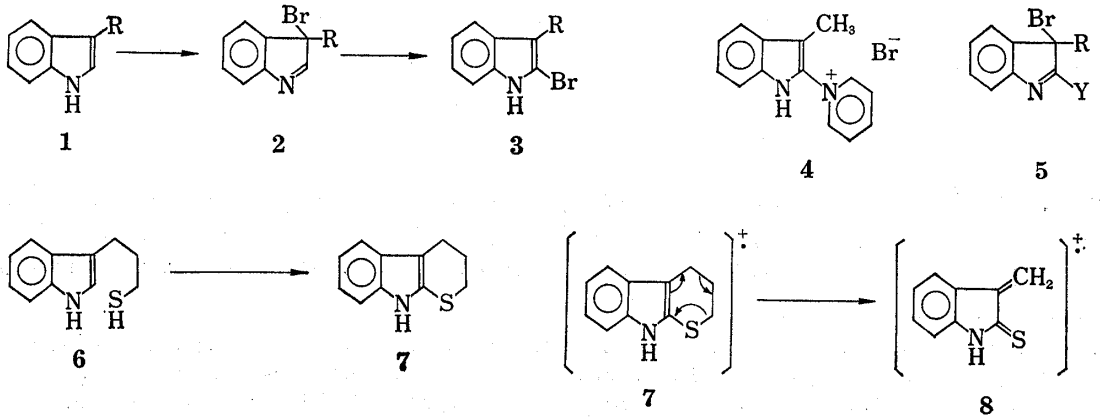

Chart 1

1) A part of this paper was published as a communication: T. Hino, H. Miura, T. Nakamura, R. Murata, and M. Nakagawa, *Heterocycles*, **3**, 805 (1975).
2) Location: *Yayoi-cho, Chiba-shi, 280, Japan.*
3) R.L. Hinman and C.P. Bauman, *J. Org. Chem.*, **29**, 1206 (1964); W.B. Lawson, A. Patchornik, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 5918 (1960); R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1971.
4) T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, and S. Yamada, *Tetrahedron*, **23**, 1441 (1967).

(**5**) as crystalline form.[5] Several 3-chloroindolenine derivatives were also isolated.[6] As 2-position of the indolenine is known to be reactive towards nucleophiles, a cyclized product may be obtained when 3-substituent of the indolenine contains a nucleophilic center at appropriate position. Witkop group has reported that N-acetyltryptamine and tryptophan esters cyclized to give pyrroloindole derivatives on treatment with N-bromosuccinimide (NBS) or *tert.* butyl hypochlorite.[7]

As an extension of our studies on the halogenation of indole derivatives,[4,5,8] we have studied the halogenation of indole derivatives which have a nucleophilic center such as a thiol or a hydroxy group in the substituents at 3-position.

When N-chlorosuccinimide (NCS) was added to a solution of 3-indolepropanethiol (**6**),[9] prepared from 3-indolepropanol (**9**),[10] in methylene chloride at −40——50°, the expected thiopyranoindole (**7**), mp 147—148°, was obtained in 32—34% yield along with a dimeric product. The similar reaction of **6** at higher temperature gave **7** in decreased yield. The yield of thiopyranoindole (**7**) increased up to 80% when NBS was added to **6** in methylene chloride at −10——15°. The structure of **7** was confirmed by the spectral data as well as elemental analysis (see Table I and II). The mass spectrum showed a molecular ion peak at *m/e* 191 and a base peak at *m/e* 161 which was assigned to have the structure (**8**) obtained by the loss of ethylene from the molecular ion. The nuclear magnetic resonance (NMR) spectrum of **7** showed disappearance of the protons of 2-position and SH group observed in **6**.

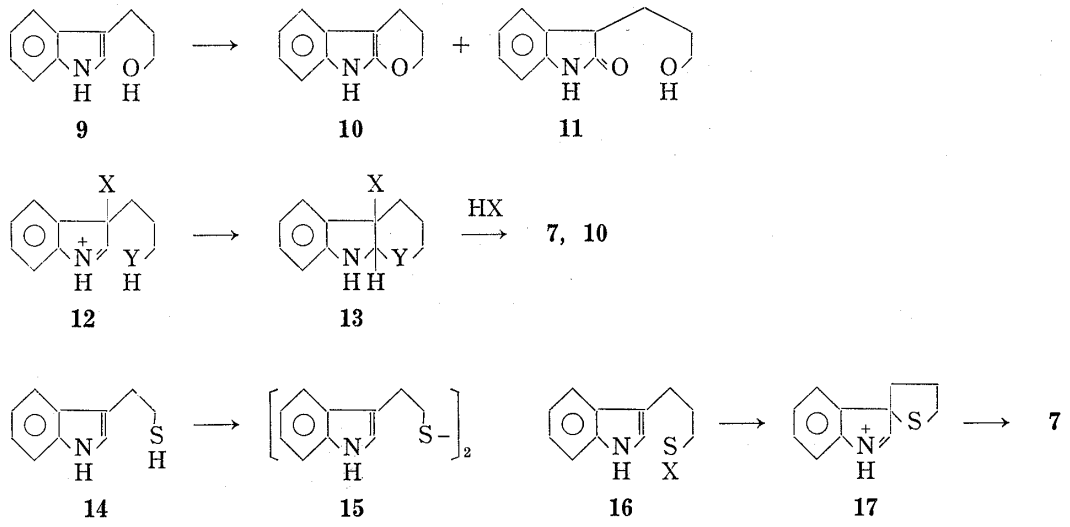

Chart 2

Addition of NBS to 3-indolepropanol (**9**) in methylene chloride at −15——17° similarly gave pyranoindole (**10**) in 57% yield and 3-(3-hydroxypropyl)-oxindole (**11**) in 9% yield. On the other hand, reaction of **9** with NCS in methylene chloride at −5° gave the spiroox-

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10) F. Lingens and K.H. Weiler, *Ann.*, **662**, 139 (1963).

indole (**23**), and **10** was not obtained (*vide infra*). The structures of **10** and **11** were confirmed by the spectral data and elemental analysis. The pyranoindole (**10**) was sensitive to acid and converted to the oxindole (**11**) on treatment with ethanolic hydrochloric acid at room temperature. The ultraviolet (UV) spectrum of **10** in ethanol, λ_{max} 230, 275 and 293 nm, gradually changed to that of **11**, λ_{max} 250, 282^{s}, and 293^{s} nm, with two isosbestic points at 240 and 260 nm, on the addition of hydrochloric acid.

These results indicate that the expected attack of nucleophilic center (OH or SH) to the 2-position of the indolenine intermediate (**12**) takes place to form **13** which readily converts to **7** or **10**. However, it is necessary to consider another mechanism for the formation of **7** *via* **16** and **17**, as the reaction of thiols with NBS or NCS has been known to give sulfenyl halides. In order to examine these points, the reaction of indoleethanethiol (**14**), lower homolog of **6**, with NBS was carried out. Thus, when NBS was added to **14** in methylene chloride at —10——13°, under which conditions **6** gave **7** in excellent yield, the corresponding disulfide (**15**) was isolated in 48% yield and the thienoindole was not obtained. The similar result was obtained by chlorination of **14** with NCS, giving **15** as the major product. These results suggest that the disulfide (**15**) may be produced by the reaction of **14** with the sulfenyl halide which is difficult to react with the indole ring intramolecularly due to involvement of a four membered spiroindolenine intermediate, and the thiopyranoindole (**7**) may be formed from **6** *via* **16** and **17**.

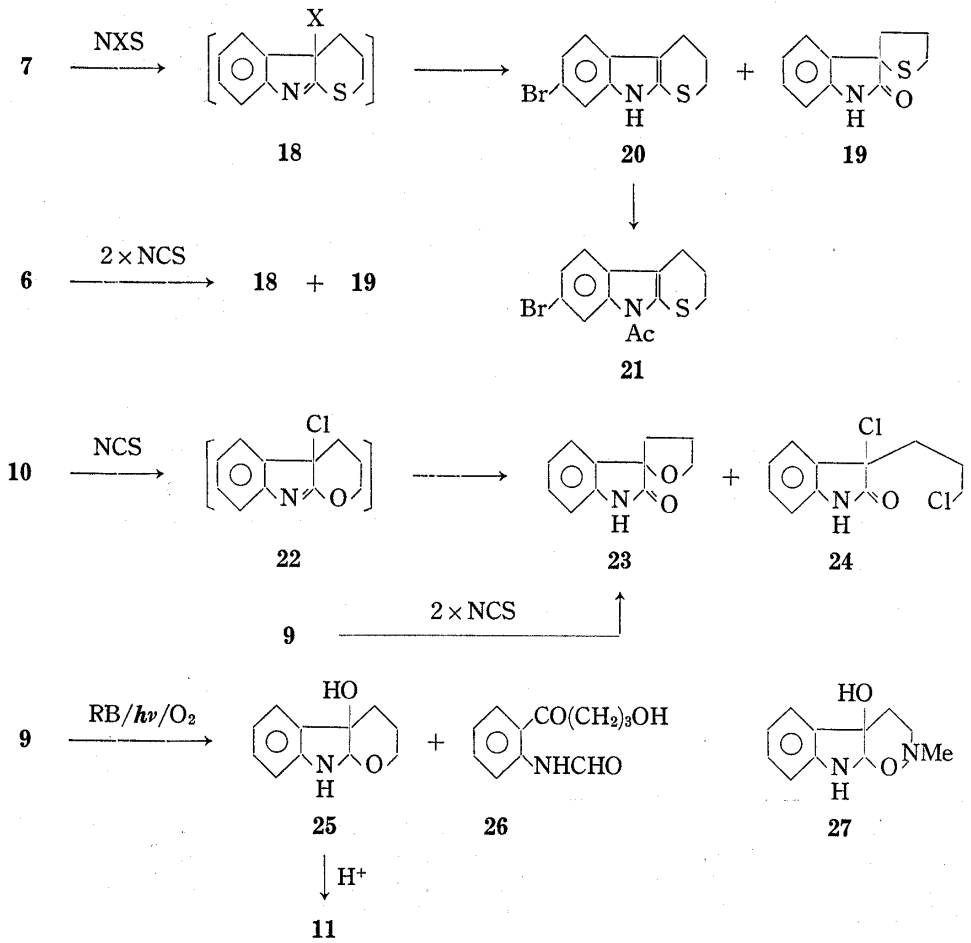

Chart 3

Further halogenation of thiopyranoindole (**7**) obtained above was examined, as the compound (**7**) was a cyclic analog of 3-substituted 2-ethylthioindoles which afforded stable 3-bromoindolenine derivatives.[5] When **7** was treated with NCS in carbon tetrachloride at

room temperature, 3-chloroindolenine (**18**, X=Cl) and the spirooxindole (**19**) were obtained in 39% and 37% yields respectively. The chloroindolenine (**18**) was unstable to be purified, but its structure was assumed by spectral data. On treatment with ethanol containing hydrochloric acid at room temperature the compound **18** (X=Cl) was converted to **19**. The compounds (**18** and **19**) were obtained by the reaction of **6** with two equivalents of NCS in methylene chloride at −5——10°. On the contrary to 3-bromoindolenines,[5] the chloroindolenine (**18**, X=Cl) showed negative test with KI starch and did not transformed to 7-chlorothiopyranoindole (**20**, Cl instead of Br) by heating in carbon tetrachloride. On the other hand, the reaction of **7** with NBS in carbon tetrachloride at room temperature gave an unstable 3-bromoindolenine, the presence of which was detected by the UV spectrum (λ_{max} 320 nm) and thin-layer chromatography (TLC) of the reaction mixture, but it decomposed during isolation. When **7** was stirred with NBS in carbon tetrachloride at room temperature for 45 min and then refluxed for 30 min, an transient intermediate disappeared and 7-bromothiopyranoindole (**20**) was obtained in 30% yield. As the separation of **20** from **7** was difficult, the pure sample of **20** was prepared *via* 1-acetyl derivative (**21**). On the other hand, when ethanolic hydrochloric acid was added to the mixture obtained by the reaction of **7** with NBS in carbon tetrachloride at room temperature, the oxindole (**19**) was obtained in 10% yield along with **20** (7%). The bromoindolenine (**18**, X=Br) is unstable to isolate, but behaves like as 3-bromo-2-ethylthio-3-methylindoles.[5]

Reaction of the pyranoindole (**10**) with NCS in methylene chloride at −5——10° followed by the addition of ethanolic hydrochloric acid gave a spirooxindole (**23**), mp 97—98°, in 89% yield. On the other hand, the same reaction followed by the addition of aqueous ammonium chloride gave dichlorooxindole (**24**) in 7% yield along with **23** (37%). In this reaction the presence of 3-chloroindolenine as an intermediate was recognized by the TLC and the UV spectrum (λ_{max} 298 nm) of the reaction mixture. The reaction of 3-indolepropanol (**9**) with two equivalents of NCS in methylene chloride at 0° gave **23** (63%). On the other hand the similar reaction in carbon tetrachloride at 50° gave **24** (45%) and **23** (5%). The compound (**24**) may be formed by the nucleophilic attack of chloride ion to 2-position of the intermediate (**22**), while addition of water to the C=N of **22** and followed by the rearrangement may give **23**.

As described above the reaction of 3-indolepropanol (**9**) with NBS (one equivalent) in methylene chloride at −15° gave pyranoindole (**10**). However, the reaction of **9** with NCS (one equivalent) in methylene chloride at −5—0° gave the spirooxindole (**23**, 27%) along with recovered **9** (26%). Although the former spirooxindole (**23**) is assumed to be derived from pyranoindole (**10**), the different reactivity of NBS and NCS could not be explained clearly.

Table I. Analytical Data

Compd. No.	mp	Formulae	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
7	147—148°	$C_{11}H_{11}NS$	69.80	5.86	7.40		69.66	5.82	7.40	
10	91.5—92.5°	$C_{11}H_{11}NO$	76.27	6.40	8.09		76.17	6.45	8.14	
11	105—105.5°	$C_{11}H_{13}NO_2$	69.09	6.85	7.33		69.04	6.88	7.36	
20	152.5—153.5° (dec.)	$C_{11}H_{10}BrNS$	49.26	3.76	5.22		49.65	3.74	5.40	
21	158.5—160°	$C_{13}H_{12}BrNOS$	50.33	3.90	4.51		50.10	3.81	4.61	
19	126—127°	$C_{11}H_{11}NOS$	64.36	5.40	6.82		64.32	5.40	6.76	
23	97—98°	$C_{11}H_{11}NO_2$	69.83	5.86	7.40		69.89	5.91	7.40	
24	111—112°	$C_{11}H_{11}Cl_2NO$	54.12	4.54	5.74	29.28	54.24	4.50	5.85	29.28
25	114.5—115°	$C_{11}H_{13}NO_2$	69.09	6.85	7.33		68.98	6.88	7.34	

As an application of our studies on dye-sensitized photooxygenation of tryptamine and tryptophan derivatives,[11] we examined dye-sensitized oxygenation of 3-indolepropanol (**9**). Extensive study of dye-sensitized photooxygenation of tryptophol has been reported by Matsuura's group.[12]

Table II. Spectral Data

Compd. No.	UV: λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$)	IR (KBr, cm^{-1})	NMR (δ in $CDCl_3$)	Ms (*m/e* (rel.intens.))
7	224^s (20.9), 238.5(28.0), 286.5(9.28), 302(10.9)	3380(NH)	2.05—2.40 (2H, m, C-CH_2-C) 2.80 (2H, t, SCH_2) 3.0—3.20 (2H, m, ind-CH_2) 6.95—7.43 (4H, m, arom. H) 8.50 (1H, brs, NH)	191 (6, M+2) 189 (99, M) 188 (20, M−1) 162 (15) 161 (100, M−CH_2=CH_2)
10	219^s (22.2), 230.5(28.7), 275(7.6), 293.5(5.0)	3370(NH)	1.90—2.20 (2H, m, CCH_2C) 2.63 (2H, t, ind-CH_2) 4.30 (2H, t, OCH_2) 7.50 (1H, brs, NH)[a]	173 (100, M) 145 (75, M−CH_2=CH_2) 117 (44)
11	250.5(8.42), 282^s (1.38), 293^s (0.73)	3175—3420 (NH, OH) 1685—1715 (C=O)	1.40—1.80 (2H, m, CCH_2C) 1.90—2.20 (2H, m, CCH_2C) 2.68 (1H, s, OH)[a] 3.50 (1H, t, 3-H) 3.62 (2H, t, CH_2O) 6.80—7.26 (4H, m, arom. H) 9.20 (1H, brs, NH)[a]	191 (65, M) 173 (55, M−H_2O) 146 (100, M−CH_2CH_2OH) 145 (90)
20	228.5^s (19.1), 245(35.5), 280^s (6.74), 291.5(9.57), 312.5(12.2)	3395(NH)	2.0—2.4 (2H, m, CCH_2C) 2.72 (2H, t, SCH_2) 3.0—3.2 (2H, m, ind-CH_2) 7.0—7.4 (3H, m, arom. H) 7.40 (1H, brs, NH)[a]	269 (98, M+2) 267 (100, M) 241 (71) 239 (61, M−CH_2=CH_2)
21	212(26.4), 239(17.2), 268^s (7.57), 306(16.6)	1695(C=O)	2.0—2.35 (2H, m, CCH_2C) 2.65 (3H, s, Ac) 2.65 (2H, t, SCH_2) 2.85—3.10 (2H, m, 4-CH_2) 7.08 (1H, d, (J=7 Hz), 5-H) 7.28 (1H, d-d (J=7 and 1 Hz), 6-H) 7.96 (1H, d, (J=1 Hz) 8-H)	311 (67, M+2) 309 (60, M) 269 (100, M−CH_2=C=O) 267 (100, M−CH_2=C=O) 241 (30, 269−CH_2=CH_2) 239 (30, 267−CH_2=CH_2)
19	254(6.83), 289(1.41)	3280(NH) 1730—1690 (C=O)	2.0—2.9 (4H, m, CCH_2CH_2C) 3.25 (2H, t, CH_2S) 6.9—7.4 (4H, m, arom. H) 9.41 (1H, brs, NH)	207 (3, M+2) 205 (57, M) 149 (48) 145 (100, M−C$_4$H$_3$S)
23	250(5.15), 268^s (2.83), 295(1.01)	3150(NH) 1710(C=O)	2.05—2.55 (4H, m, CCH_2CH_2C) 4.13—4.27 (2H, m, OCH_2) 6.76—7.30 (4H, m, arom. H) 8.74 (1H, brs, NH)[a]	189 (100, M) 162 (72, M−CO) 160 (29) 146 (20) 145 (29)
24	217(17.9), 259(3.0), 305^s (0.9)	3200(NH) 1720(C=O)	1.60—1.93 (2H, m, CCH_2C) 2.34—2.50 (2H, m, $ClCCH_2$) 3.50 (2H, t, Cl-CH_2) 6.90—7.45 (4H, m, arom. H) 9.15 (1H, brs, NH)	245 (25, M+2) 243 (41, M) 208 (100, M−Cl)
25	241(7.44), 294(2.35)	3180—3450 (NH, OH)	1.20—2.40 (4H, m, CCH_2CH_2C) 3.20—3.80 (4H, m, OCH_2, NH, OH) 4.68 (1H, s, NCH-O) 6.60—7.32 (4H, m, arom. H)	191 (100, M) 173 (10, M−H_2O) 149 (46, M−CH_2=C=O)

Abbreviation in NMR: *a*) exchange with D_2O; s, singlet, t, triplet, m, multiplet, brs, broad singlet; ind-; 3-indolyl-.

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When **9** was irradiated in benzene with 500 W halogen lamp for 5 hr in the presence of rose bengal under a stream of oxygen and ice-cooling, 4a-hydroxypyranoindole (**25**), mp 114—115°, and the ketoamide (**26**) were obtained in 9—12% and 8—20% yield respectively. The structure of **25** was confirmed by the elemental analysis and the following spectral data. The UV spectrum showed an indoline type chromophor, λ_{max} 241 and 294 nm. The mass spectrum showed a strong molecular ion peak at *m/e* 191. The NMR spectrum in $CDCl_3$ showed a characteristic singlet at δ 4.68 for N–CH–O which shifted to δ 5.29 in pyridine-d_5, corresponding to N–CH–O in the 1,2-oxazinoindole (**27**) (δ 5.37 in pyridine-d_5).[11] The compound **26** could not be purified as crystalline and its structure was confirmed by the spectral data (see experimental). Treatment of **25** with ethanolic hydrochloric acid at room temperature gave the oxindole (**11**) in 80% yield. The UV spectrum of **25** in ethanol changed to that of **11** with an isosbestic point at 287 nm on the addition of a drop of 10% hydrochloric acid within 30 min. On the addition of one drop of 5% hydrochloric acid, however, the UV spectrum gradually changed to that of pyranoindole (**10**) contaminated with that of **11**. Therefore, transformation of **25** to **11** may proceed *via* **10**. Oxidative cyclization of **9** with NBS gave pyranoindole (**10**), while hydroxypyranoindole (**25**) was obtained with dye-sensitized oxygenation. These results indicate that 4a-halopyranoindole (**13**) initially formed in the reaction of **9** with NBS was easily dehydrobrominated to form **10** under reaction condition but 4a-hydroxypyranoindole (**25**) obtained by dye-sensitized oxygenation of **9** was not dehydrated under reaction condition. The similar results were obtained for the oxidative cyclization of tryptamine derivatives with NBS[7] and dye-sensitized oxygenation.[11]

Experimental[13]

Preparation of 3-Indolepropanethiol (6) from 3-Indolepropanol (9)[9]——To a boiling solution of 3-indolepropanol (**9**)[10] (24.0 g, 0.136 mol) in benzene (650 ml) containing pyridine (13 ml) was added PBr_3 (20.7 g, 0.0764 mol) in benzene (200 ml) during 35 min. The mixture was refluxed for 6.5 hr. The benzene solution was decanted from the insoluble residue and washed with $NaHCO_3$ solution and H_2O, and dried. Evaporation of the solvent gave crude 3-indolepropyl bromide (26.3 g). To the crude bromide (20.3 g) in ethanol (300 ml) was added thiourea (98.0 g) in ethanol (300 ml) during 45 min. The mixture was refluxed for 7 hr and evaporated. The crude isothiuronium bromide (36.8 g) thus obtained, was dissolved in ethanol (250 ml) and 15% NaOH (200 ml) and the mixture was refluxed for 7.5 hr under N_2. The mixture was neutralized with conc. HCl and poured into ice-water (250 ml). Separated oil was extracted with CH_2Cl_2 and the extracts were washed with H_2O and dried. The solvent was evaporated and the residue was distilled *in vacuo* under N_2 to give 3-indolepropanethiol (**6**) as yellow oil (12.8 g, 48% from **9**), bp 170—173°/1 mmHg. IR (neat) cm^{-1}: 3440 (NH), 2550 (SH, weak). NMR ($CDCl_3$) δ: 1.22 (1H, t, SH), 1.80 (2H, m, CCH_2C), 2.26 (2H, q, SCH_2), 2.64 (2H, t, skatyl CH_2), 6.52 (1H, finely splitted s, 2-H), 6.90—7.60 (4H, m, arom. H), 7.25 (1H, br.s, NH). Ms *m/e*: 191 (M^+).

2,3,4,9-Tetrahydrothiopyrano[2,3-*b*]indole (7)——i) Reaction of **6** with NCS: To a chilled solution of **6** (384 mg, 2 mmol) in CH_2Cl_2 (20 ml) was added a suspension of NCS (273 mg, 2 mmol) in CH_2Cl_2 (80 ml) at −48——−42° (dryice–ice) during 105 min under N_2. The TLC of the mixture showed the presence of an intermediate. The reaction mixture was stirred at −40——−20° for 30 min, when the intermediate disappeared and new spots appeared on TLC of the mixture. Saturated $NaHCO_3$ solution (50 ml) was added to the mixture at 0——5°, and the CH_2Cl_2 solution was washed with H_2O and dried. Evaporation of the solvent gave a pale yellow solid (411 mg) which was chromatographed on silica gel (25 g) column. Elution with benzene–hexane (1: 1) gave thiopyranoindole (**7**) (129 mg, 34%), mp 140—142°, and starting material (58 mg). Recrystallization of **7** from benzene–hexane gave colorless crystals, mp 147—148° (Table I, II). Elution with CH_2Cl_2 gave a dimeric product (128 mg) as a colorless caramel which showed a single spot on TLC, but could not be purified further due to low solubility. Mass *m/e* (rel. intens.): 378 (13), 376 (100), 348 (45), 320 (20). IR (KBr) cm^{-1}: 3200—3400, 1510. UV λ_{max}^{EtOH} nm: 216, 240, 267. Similar reaction at −5——10° gave **7** (10%) and the dimeric product (7%).

13) All melting points are not corrected. Infrared (IR) and ultraviolet spectra were recorded on a Hitachi G-3 and Hitachi-323 spectrophotometers, respectively. NMR spectra were obtained using a JEOL MH-100 spectrometer and are recorded in ppm down field of the internal standard of tetramethylsilane. Mass spectra were obtained on a Hitachi RMU-6 spectrometer.

(ii) Reaction of **6** with NBS: To a chilled solution of **6** (4.58 g, 0.024 mol) in CH_2Cl_2 (1200 ml) was added NBS (4.27 g, 0.024 mol) in CH_2Cl_2 (300 ml) at −12——14° (ice-salt) during 190 min with stirring under N_2. The mixture was stirred without cooling bath, and saturated $NaHCO_3$ solution (200 ml) was added to the mixture at −5°. The CH_2Cl_2 solution was washed with H_2O, dried, and evaporated to leave a yellow solid (4.2 g) which was chromatographed on silica gel column (10 g). Elution with benzene gave **7** (3.02 g, 79%), which was identical with the sample obtained above (IR). Elution with CH_2Cl_2 gave brown oil (210 mg) which showed many spots on TLC and was not investigated further. The similar reaction at −42——30° gave **7** (48%) and the dimeric product (30%).

2,3,4,9-Tetrahydropyrano[2,3-*b*]indole (10). Reaction of 3-indolepropanol (9) with NBS——To a chilled solution of **9** (4.0 g, 22.8 mmol) in CH_2Cl_2 (1000 ml) was added NBS (4.08 g, 22.8 mmol) in CH_2Cl_2 (400 ml) at −14——16° during 75 min under N_2. Saturated $NaHCO_3$ solution (200 ml) was added to the mixture at around −5°. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated to leave a pale yellow oil (3.5 g), which was chromatographed on alumina column (110 g). Elution with benzene gave **10** (2.25 g, 67%), mp 88—92°. Recrystallization from aqueous MeOH gave colorless pillars, mp 91.5—92.5° (Table I, and II). Elution with CH_2Cl_2–MeOH (20: 1) gave oxindole (**11**, 386 mg, 8.8%) which was identical with a standard sample (IR, mmp).

3-Hydroxypropyloxindole (11). Hydrolysis of 10——A solution of **10** (565 mg, 3.25 mmol) in EtOH (30 ml) and 5% HCl (2 ml) was stirred at room temperature for 5 min. The mixture was evaporated and the residue was extracted with CH_2Cl_2–H_2O. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated to give the oxindole (**11**) (590 mg, 95%). Recrystallization from AcOEt–hexane gave colorless needles, mp 105—105.5°.

Reaction of 9 with NCS (1 Equivalent). Formation of Spirooxindole (23)——To a chilled solution of **9** (517 mg, 2.95 mmol) in CH_2Cl_2 (30 ml) was added a suspension of NCS (380 mg, 2.95 mmol) in CH_2Cl_2 (30 ml) during 30 min at −5—0°. The mixture showed the presence of **9** and **22** on TLC. The mixture was stirred at room temperature for 30 min. Saturated $NaHCO_3$ solution (50 ml) and CH_2Cl_2 (100 ml) were added to the mixture and the CH_2Cl_2 solution was washed with H_2O and dried. The CH_2Cl_2 solution was evaporated and the residue (460 mg) was chromatographed on silica gel (10 g). Elution with benzene–CH_2Cl_2 (10: 1) gave **23** (78 mg) and a mixture (223 mg) of **23** and **9**. The latter fraction was separated by preparative TLC to give **23** (44 mg, total 122 mg, 27%) and **9** (112 mg). Elution with benzene–CH_2Cl_2 (5: 1) gave **9** (24 mg, total 136 mg, 26%). Recrystallization of **23** from benzene–hexane gave colorless plate, mp 97—98° (Table I and II).

Reaction of 3-Indoleethanethiol (14) with NBS——To a chilled solution of **14** (400 mg, 2.26 mmol) in CH_2Cl_2 (150 ml) was added NBS (410 mg, 2.26 mmol) in CH_2Cl_2 (50 ml) at −11——15° during 40 min with stirring. Saturated $NaHCO_3$ solution (80 ml) was added to the mixture when the temperature rose to −5°. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated to leave a yellow caramel (354 mg), which was chromatographed on silica gel column (7 g). Elution with benzene–hexane (1: 5) gave (**14**) (32 mg, 8%). Elution with benzene–hexane (1: 1) gave a disulfide (189 mg, 48%), mp 122—123°,[9] which was identical with the sample prepared by the autoxidation of **14** in alkaline media (IR, mmp). Elution with CH_2Cl_2 gave yellow oil (84 mg) which showed a carbonyl band in its IR spectrum. Its UV spectrum was not a simple oxindolic type.

Reaction of 7——1. Reaction with NCS in CCl_4: i) Isolation of Chloroindolenine (**18**): A mixture of **7** (100 mg, 0.512 mmol) and NCS (72 mg, 0.512 mmol) in CCl_4 (10 ml) was stirred at room temperature for 1 hr under N_2. The mixture was filtered to remove succinimide, and the filtrate was evaporated to give a pale yellow caramel (102 mg), which was chromatographed on silica gel column (2 g). Elution with benzene gave **7** (15 mg, 15%). Further elution with benzene gave **18** (X=Cl, 45 mg, 38%) as colorless oil which showed a single spot on TLC and negative test with KI-starch. The oil solidified on standing, but could not be purified further. UV λ_{max}^{EtOH} 228, 238, and 325 nm. IR (KBr) 1520 cm^{-1} (C=N). NMR ($CDCl_3$) δ: 1.60—2.20 (2H, m), 2.40—2.90 (2H, m), 2.95—3.20 (2H, m), 7.20—7.60 (4H, m, arom.). Mass *m/e* (rel. intens): 225 (13, M+2), 223 (42, M^+), 195 (52), 189 (100), 188 (56, M–Cl), 186 (36), 161 (80), 141 (29), 118 (29). Elution with benzene–MeOH (20: 1) gave spirooxindole (**19**) (40 mg, 37%) as a colorless oil. Recrystallization from AcOEt–hexane gave **19**, mp 126—127°, which was identical with a standard sample (IR).

When a mixture of **7** (100 mg) and NCS (72 mg) in CCl_4 (10 ml) was refluxed for 3 hr, **7** (18 mg), **18** (21 mg, 18%), and **19** (22 mg, 21%) were obtained by chromatographic separation of the mixture as above.

ii) Isolation of Spirooxindole (**19**): A mixture of **7** (1.0 g, 5.30 mmol) and NCS (720 mg, 5.3 mmol) in CCl_4 (100 ml) was stirred at room temperature for 1 hr under N_2. The TLC of the mixture showed the presence of **18**. The mixture was filtered to remove succinimide and the filtrate was evaporated. The residue was dissolved in EtOH (50 ml) and 10% HCl (1 ml) and the mixture was stirred at room temperature for 5 min. The mixture was evaporated and the residue was extracted with CH_2Cl_2–H_2O. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated to leave a pale yellow caramel (780 mg) which was chromatographed on silica gel column (16 g). Elution with benzene recovered **7** (93 mg, 9.3%). Elution with benzene–MeOH (20: 1) gave **19** (610 mg, 56%) as a colorless oil. Recrystallization from hexane–AcOEt gave colorless pillars, mp 126—127° (Table I, II).

2. Reaction with NBS in CCl_4: i) A mixture of **7** (300 mg, 1.58 mmol) and NBS (285 mg, 1.58 mmol) in CCl_4 (15 ml) was stirred at room temperature for 50 min under N_2. The mixture showed the presence of **18** (X=Br) by TLC and UV (λ_{max} 320 nm). The mixture was filtered to remove succinimide, and the filtrate was mixed with EtOH–HCl. The mixture was stirred for 5 min at room temperature and showed negative test for KI. The mixture was evaporated to leave a residue (223 mg), which was separated by preparative TLC (silica gel/benzene–acetone (3:1)). 7-Bromo derivative (**20**) (30 mg, 7%), dimer (41 mg, 13%) and spirooxindole (**19**, 36 mg, 11%) were obtained and identified with standard samples.

ii) Formation of **20**: A mixture of **7** (1.0 g, 5.3 mmol), NBS (1.036 g, 5.3 mmol) in CCl_4 (100 ml) was stirred at room temperature for 45 min. An intermediate was observed in the mixture (TLC and UV (320 nm)). Benzoyl peroxide (trace amount) was added to the mixture and the whole mixture was refluxed for 30 min. The mixture was filtered to remove succinimide, and the filtrate was evaporated to leave a residue (822 mg) which showed the presence of 7-bromo derivative (**20**) and small amount of **7**. The residue was dissolved in Ac_2O (30 ml) and AcONa (1.04 g) and the mixture was refluxed for 3.5 hr. The mixture was filtered to remove some insoluble materials and the filtrate was evaporated *in vacuo* to leave a residue which was extracted with CH_2Cl_2–H_2O. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated to leave a pale yellow solid (610 mg). Recrystallization from benzene–pet. ether gave N-acetyl-7-bromo derivative (**21**, 298 mg), mp 155—159°. Separation of the mother liquor by preparative TLC (silica gel/benzene-acetone (3:1)) gave further **21** (184 mg, total 428 mg, 29% from **7**) and N-acetylthiopyranoindole (36 mg). Recrystallization of **21** from benzene–pet. ether gave colorless crystals, mp 158.5—160°. Hydrolysis of **21** (450 mg) with EtOH–10% NaOH at room temperature gave **20** (351 mg, 92%), which was recrystallized from benzene–pet. ether to give colorless crystals, mp 153° (dec.) (Table I and II).

Reaction of 6 with Two Moles of NCS——To a solution of **6** (384 mg, 2.0 mmol) in CH_2Cl_2 (30 ml) was added NCS (346 mg, 4.0 mmol) in CH_2Cl_2 (80 ml) at −5——10° during 90 min under N_2. The mixture was stirred at room temperature for 30 min. Saturated $NaHCO_3$ solution was added to the mixture and the CH_2Cl_2 solution was washed with H_2O, dried and evaporated to leave a residue (403 mg) which was chromatographed on silica gel column (15 g). Elution with benzene gave **18** (X=Cl, 124 mg, 27%). Further elution with benzene gave a dimer (24 mg) and spirooxindole (**19**, 31 mg, 7%).

Reaction of 10——i) NCS–CH_2Cl_2/EtOH–HCl: To a chilled solution of pyranoindole (**10**, 100 mg, 0.575 mmol) in CH_2Cl_2 (10 ml) was added NCS (77 mg, 0.575 mmol) in CH_2Cl_2 (10 ml) at −5—0° during 20 min under N_2. The mixture showed the presence of an intermediate (**22**) (TLC, UV (298 nm)). After stirring at room temperature for 20 min, EtOH (20 ml) and 10% HCl (10 ml) were added to the mixture. The mixture was further stirred at room temperature for 1 hr and evaporated. The residue was extracted with CH_2Cl_2–H_2O. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated to give spirooxindole (**23**, 97 mg, 89%), which showed a single spot on TLC. Recrystallizations from hexane gave pure compound, mp 97—98°, which was identical with a standard sample (IR, mmp).

ii) NCS–CH_2Cl_2/NH_4Cl: To a solution of **10** (90 mg, 0.518 mmol) in CH_2Cl_2 (10 ml) was added NCS (69 mg, 0.518 mmol) in CH_2Cl_2 (10 ml) at −5—0° during 20 min under N_2. The mixture was stirred at room temperature for 30 min and added with saturated aqueous NH_4Cl (10 ml) and EtOH (20 ml). The whole mixture was stirred at room temperature overnight, and evaporated. The residue was extracted with CH_2Cl_2–H_2O. The CH_2Cl_2 solution was washed with H_2O, dried and evaporated to leave a residue. Separation by preparative TLC (silica gel/benzene–acetone (3:1)) gave dichlorooxindole (**24**, 9 mg), and spirooxindole (**23**, 36 mg) which were identical with standard samples (IR).

Reaction of 9 with Two Moles of NCS——i) In CCl_4: A mixture of **9** (500 mg, 2.84 mmol) and NCS (760 mg, 5.76 mmol) in CCl_4 (50 ml) was stirred at room temperature for 1 hr under N_2. The mixture was warmed at 50° for 30 min. The mixture was filtered to remove succinimide and the filtrate was evaporated to leave a residue (780 mg) which was chromatographed on silica gel column (21 g). Elution with CH_2Cl_2 gave dichlorooxindole (**24**, 305 mg, 45%) and spirooxindole (**23**, 26 mg, 5%). Recrystallization of **24** from benzene–hexane gave colorless needles, mp 111—112°.

ii) In CH_2Cl_2: To a chilled solution of **9** (500 mg, 2.84 mmol) in CH_2Cl_2 (30 ml) was added a suspension of NCS (780 mg, 5.67 mmol) in CH_2Cl_2 (50 ml) during 45 min at −5—0°. The mixture was stirred for 1 hr at room temperature. The mixture showed a single spot of **22** on TLC. The mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel column. Elution with benzene–CH_2Cl_2 (2:1) gave **23** (337 mg, 63%) which was identical with the standard sample (IR, mmp).

4a-Hydroxy-2,3,4,4a,9,9a-hexahydropyrano[2,3-*b*]indole (25). Dye-sensitized Photooxygenation of 9——A solution of **9** (2.0 g) in benzene (500 ml) containing rose bengal (810 mg) in MeOH (25 ml) was irradiated in an ice bath by a 500 W halogen lamp for 5.0 hr, while a stream of oxygen was bubbled through the reaction vessel. The mixture was filtered to remove insoluble materials and evaporated to leave a residue. The same photooxygenation was repeated again. The combined residue (obtained from 4 g of **9**) was chromatographed on alumina (10 g). Elution with CH_2Cl_2 gave a mixture of **9**, **25** and **26** (fraction A, 2.1 g). Elution with CH_2Cl_2–MeOH (20:1) gave a brown caramel (fraction B, 2.8 g). Fraction A was separated by silica gel column and preparative TLC to **25** (480 mg, 11%) and **26** (510 mg). Recrystallization of **25** from benzene–hexane gave colorless needles, mp 114.5—115° (Table I and II). The ketoamide (**26**) was recrystallized from benzene–hexane to give crystals, mp 68—71°, but seems to be decomposed on standing. The following

spectral data suggested the structure. UV λ_{max}^{EtOH} 231, 236, 255^{s}, 262, 268, and 322 nm. NMR (in $CDCl_3$) δ: 2.0 (2H, m, CCH_2C), 3.15 (2H, t, $COCH_2$), 2.40 (1H, br. s, OH, exchangable), 3.72 (2H, t, CH_2O), 7.0—8.8 (4H, m, arom. H), 8.5 (s, CHO), 11.50 (1H, br. s, NH). IR (KBr): 3400, 3150 (NH, OH), 1650 (broad, C=O) cm^{-1}. MS *m/e*: 207 (20, M^+). Fraction B showed many spots on TLC, some of which seemed to have oxindolic nature, but was not investigated further.

When a solution of **25** (50 mg) in EtOH (5 ml) and 5% HCl (0.5 ml) was warmed on a water-bath for 5 min, 3-oxindolylpropanol (**11**) was obtained in 80% yield.

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