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OXIDATIVE CYCLIZATION OF N_b-DIMETHYLTRYPTAMINE, 3-INDOLEPROPANOL, AND 3-INDOLEPROPANETHIOL WITH N-BROMO- OR N-CHLOROSUCCINIMIDE

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The reaction of N_b-dimethyltryptamine(5b) with NBS in carbon tetrachloride yielded a quaternary salt of pyrrolo[2,3-b]indole(7b). The similar oxidative cyclization of 3-indolepropanol(5c) and 3-indolepropanethiol(5e) with NBS in methylene chloride gave pyrano- and thiopyranoindoles(7c and 7e). Further halogenation of 7c with NCS yielded a spirooxindole(12, Y=O) and a dichloride(13), whereas 7e with NBS gave 12(Y=S) and bromothiopyranoindole(14).

Ionic bromination of 3-alkylindole(1) with N-bromosuccinimide(NBS) has been known to proceed via 3-bromoindolenine intermediate(2) which collapsed to 2-bromoindoles(3) or oxindoles(4) depending on the reaction media[1]. When a nucleophilic group is present at an appropriate position in the 3-substituent, the nucleophile may attack to 2-position of the indolenine intermediate(2) to form a cyclic product. Witkop and his coworkers[2] have been reported the oxidative cyclization of N-acetyltryptamine(5a) and N-acetyltryptophan with NBS to give pyrroloindole(7a). We now report oxidative cyclization of

N_b-dimethyltryptamine(5b)[3], 3-indolepropanol(5c)[4], and 3-indolepropanethiol(5e)[5] which contain a nucleophilic center such as NMe_2, OH, or SH group in the 3-substituent.

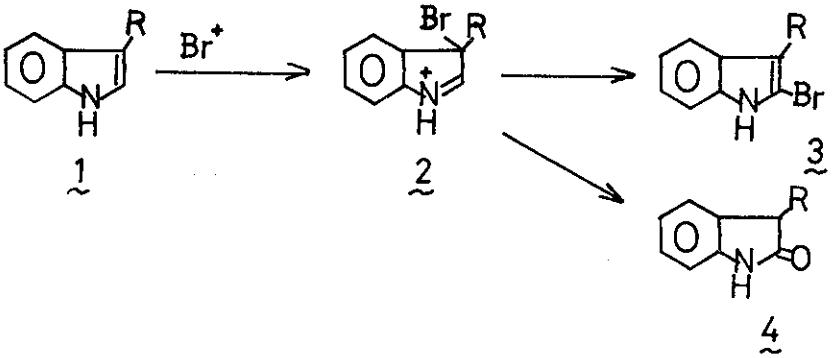
The reaction of 5b, 5c and 5e with NBS or N-chlorosuccinimide(NCS) were carried out under various conditions and the results are summarized in Table 1, indicating the superiority of NBS over NCS in oxidative cyclization.

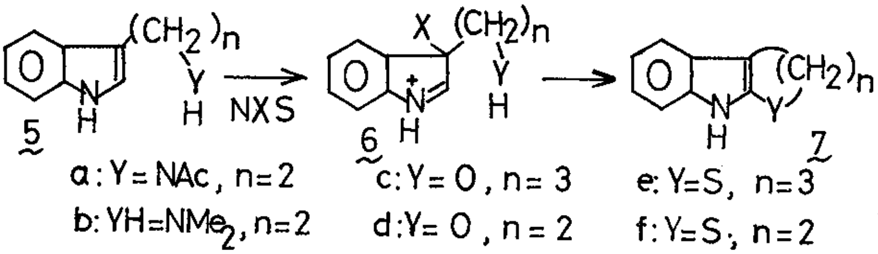
Table 1 Oxidative Cyclization of 5

Compd	Condition	Products(% yield)
5b	CCl_4-NBS, rm. temp	7b(65%)
5c	CH_2Cl_2-NBS, -14 - -18°	7c(57%)
	CH_2Cl_2-NCS, -14 - -16°	12(30%)
5e	CH_2Cl_2-NBS, -13- -10°	7e(80%)
	CH_2Cl_2-NCS, -50- -48°	7e(32%)

The structures of these cyclized products were confirmed by elemental analyses and spectral data which are summarized in Table 2. Pyranoindole(7c) was easily hydrolyzed by an acid to 3-(3-hydroxypropyl)oxindole, mp 105-105.5°[6].

On the other hand the expected cyclized products such as 7d or 7f have not been obtained by the reaction of 3-indoleethanol(5d) and 3-indoleethanethiol(5f) with NBS or NCS under various conditions. The reaction of 5d gave complicated products which included oxindolic products[7], while 5f yielded the corresponding disulfide(8) as major product. These results may suggest that a thiol group is more reactive than an indole ring towards NBS(NCS) and an intermediate of the cyclization of 5e to 7e would not be an indolenine(6e), but a spiroindolenine(10) which derived from a sulfenyl halide(9). The disulfide(8) may be


R
Br⁺
Br R
R
Br
R
O
1
2
3
4


(CH2)n
Y
H
NXS
X (CH2)n
5
6
7
a: Y=NAc, n=2
b: YH=NMe2, n=2
c: Y=O, n=3
d: Y=O, n=2
e: Y=S, n=3
f: Y=S, n=2

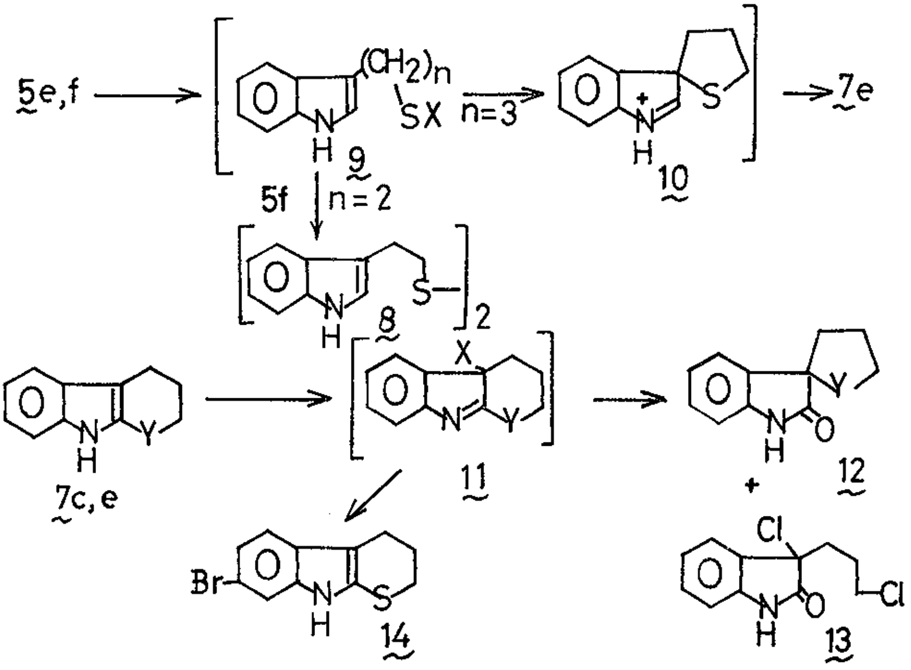
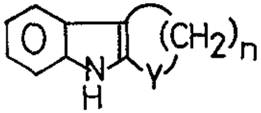

5e,f
(CH2)n
SX
n=3
S
7e
9
10
5f
n=2
S
2
8
7c, e
X
Y
11
Y
O
12
+
Cl
Cl
O
13
Br
S
14

Table 2 Spectral Data of 7



Compd No	mp	λ_{max}^{EtOH} nm(ϵ)	Nmr (δ-value)	Mass (m/e (rel.intens.))
7b Y=$\overset{+}{N}Me_2$, Br^- n= 2	275°(decomp)	263(6,900) 275^{s}(5,900) 278^{s}(5,400) 286(4,400)	in D_2O 3.24(t, 2H, 3-CH_2) 3.54(s, 6H, NMe) 4.61(t, 2H, 2-CH_2)	186(100, M^+- HBr)
7c Y=O, n=3	91.5-92.5°	219(22,200) 230(28,700) 275(7,700) 293(5,000)	in $CDCl_3$ 1.90-2.20(m,2H, 3-CH_2) 2.63(t, 2H, 4-CH_2) 4.30(t,2H, 2-CH_2) 7.50(br.s. NH)	173(M^+, 100) 145(M-CH_2=CH_2,75)
7e Y=S, n=3	147-148°	224(21,000) 238(28,000) 275^{s}(6,800) 286(9,300) 302(10,900)	in $CDCl_3$ 2.10-2.32(m, 2H, 3-CH_2) 2.7-2.9(m, 2H, 2-CH_2) 3.05-3.15(m, 2H, 4-CH_2) 8.50(br.s, NH)	189(M^+, 99) 161(M-CH_2=CH_2,100)

formed by the reaction of 5f and 9(n=2) due to the difficulty in intramolecular cyclization of 9 to form a four membered spiroindolenine as an intermediate to thienoindole[8].

Further halogenation of pyranoindole(7c) and thiopyranoindole(7e) was investigated in order to compare with our previous results obtained by bromination of 2-ethylthioindoles[9]. Treatment of 7c with NCS in methylene chloride at -5 - -10°[10], followed with an acid gave spirooxindole(12, Y=O), mp 97-98°, in 80% yield. On the other hand followed treatment of the reaction mixture with ammonium chloride in aqueous ethanol provided 12(Y=O, 36%) and dichloride(13, 7%), mp 111-112°, which were also obtained by the reaction of 5c with two moles of NCS in methylene chloride at -5 - 0°. Reaction of 7e with NBS in methylene chloride at room temperature gave unstable bromoindolenine(11, Y=S, X=Br)[11] which was readily converted to the spirooxindole(12(Y=S), mp 126-127°, by addition of an acid and to 7-bromo derivative(14), mp 152°, on heating. While the chloroindolenine(11,Y=S, X=Cl)[12] obtained by the reaction of 7e with NCS in carbon tetrachloride, was converted to the spirooxindole(12,Y=S) by addition of an acid , but 7-chloro derivative corresponding to 14 was not obtained on heating in carbon tetrachloride, suggesting that the reactivity of chloroindolenine and bromoindolenine may be different.

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6 All new compounds shown with mps gave correct elemental analyses and reasonable spectral data.

7 Oxidation of 3-indoleethanol with bromine in acetic acid was reported to give 3-(2-hydroxyethyl)oxindole. E.Wenkert,J.S.Bindra,C-J.Chang,D.W.Cochran, and D.E.Pearick, *J.Org.Chem.*, **39**, 1662(1974).

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10 An intermediate, probably an chloroindolenine(11, X=Cl, Y=O) was recognized in the reaction mixture by UV spectra(λ_{max} 298nm) and tlc, but was not isolated.

11 The bromoindolenine could not be isolated, but its presence was recognized by UV (λ_{max} 325 nm) which is similar to that of 3-bromo-2-ethylthio-3-methylindolenine[9].

12 The chloroindolenine was isolated as crystals, but decomposed on recrystallization. Mass m/e 223(M^+,42%). IR(KBr) 1520 cm^{-1}(C=N). λ_{max}^{EtOH} 228, 238, 325 nm.

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