BROMINATION OF 2-ETHYLTHIO- AND 2-ETHANESULFONYL-3-SUBSTITUTED INDOLES WITH N-BROMOSUCCINIMIDE. ISOLATION AND REACTIVITIES OF 1-BROMOINDOLES AND 3-BROMOINDOLENINES

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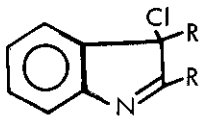
1-Bromoindole(4) and 3-bromoindolenines(5) were obtained by the reaction of 3 with NBS. Both compounds could brominate a 3-substituted indole to give the 2-bromo derivative. The bromine at the 3-position of 5 migrated to the 5- or 6-position on heating in an aprotic solvent.

The reaction of 2,3-disubstituted indoles with hypochlorite and other chlorinating agents to yield 3-chloroindolenines(1) is a well known reaction.[1-6] Transformation of these highly reactive intermediates has yielded a variety of products such as 3,3-disubstituted oxindoles or substituted indolenines depending on the conditions used and on the nature of the substituents. Gassman[4] has failed to prove the initial formation of 1-chloroindole in the chlorination of 2,3-dimethylindole to the 3-chloroindolenine. On the other hand Omen[7] has reported the preparation of a stable 3-bromoindolenine(2) which has similar oxidizing power to NBS.

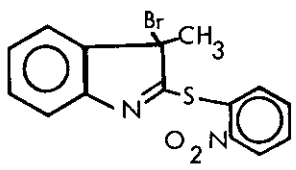
We report here the isolation of crystalline 3-bromoindolenines(5) and 1-bromoindole(4) which was shown to be an intermediate to 5, and some reactions of 4 and 5 which have not been previously investigated.

The reaction of 3a and 3b with NBS in boiling carbon tetrachloride gave 5a and 5b, respectively, in quantitative yields as pale yellow crystals which decompose rapidly at room temperature, but which are relatively stable in a deep freezer. Similar reaction of 3d to give 5d was slow, but when benzoyl peroxide was added as a catalyst, the reaction was complete within 1 hr. These 3-bromoindolenines showed a positive test with KI-starch, as described by Gassman for 3-chloroindolenine.[4] The characteristic features of these 3-bromoindolenines are summarized in Table 1.

On the contrary the reaction of 3c with NBS in boiling carbon tetrachloride did not proceed. But the reaction of 3c with NBS in dichloromethane at room temperature yielded pale yellow crystals(4c, 92%), mp 80-81°; uv(EtOH) 238(18,200),312 (4,300) nm; m/e (relative abundance); 303,301(28, M^+), 210,208(100, M^+-SO_2Et), 129(63, M^+-SO_2Et-Br). The compound showed a correct elemental analysis for $C_{11}H_{12}O_2NSBr$ and a positive test with KI-starch. However, its ir spectrum did not show any strong band for C=N between 1500-1550 cm^{-1}, and its nmr spectrum (in $CDCl_3$) showed a singlet at 2.44 ppm for 3-CH_3, which is down field in compaison with that of 5a(1.93 ppm). Furthermore, the compound(4c) was transformed into a new compound(5c), mp 96.5-97°, in quantitative yield when refluxed in carbon tetrachloride for 8 hr. The compound(5c) also showed a correct elemental analysis and gave a positive test with KI-starch. The spectral data(Table 1) of 5c are in agreement with those of other 3-bromoindolenines. These facts indicate that the structure of 4c is 1-bromo-2-ethanesulfonyl-3-methylindole, the first example of a 1-bromoindole. The reaction of 3d with NBS in dichloromethane at room temperature similarly gave 4d, which was converted to 5d in boiling carbon tetrachloride. The



1



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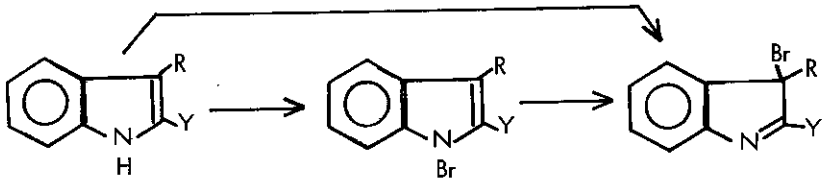
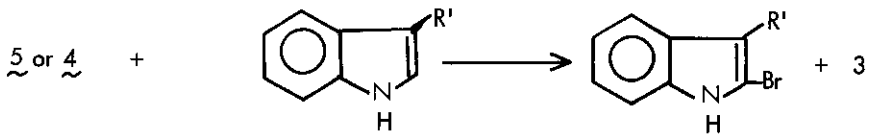


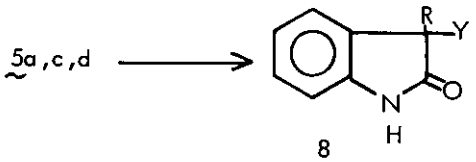
3 a-e 4c,d 5a-e

	a	b	c	d	e
R	Me	Ph	Me	Ph	Ph
Y	SEt	SEt	SO_2Et	SO_2Et	Br

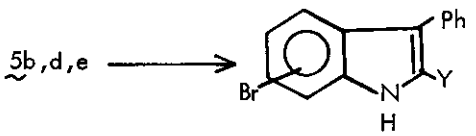


5 or 4 + 6 → 7 + 3

a; R'= CH_3 b; R'= Ph



5a,c,d → 8



5b,d,e → 9

a : Y= SEt; 6-Br

b : Y=SO_2Et; 5-Br

c : Y=Br ; 6- and 5-Br

stability of 4c and 4d is probably due to the presence of an electron withdrawing group at the 2-position.

In order to examine the brominating power of 1-bromoindoles and 3-bromoindolenines, the reaction of 6b with 5a in acetic acid was carried out at room temperature and 7b[8] was obtained in 56% yield, whereas that of 6a with 5b in carbon tetrachloride at room temperature gave 7a(36%), 3b(37%), and the 6-bromo derivative(9a)(30%). The reactions of 6b with 4c or 4d in dichloromethane at room temperature gave 7b (89% and 72%), and 3c(95%) or 3d(76%), respectively.

When 5(a, c, and d) were treated with ethanolic HCl at room temperature, migration of the 2-substituent occurred as observed in the 3-chloroindolenines, and oxindoles(8a, c, and d)[9] were obtained. However the reaction of 5b with ethanolic HCl at room temperature gave the 6-bromo derivative(9a,56%), mp 87.5-88°, instead of the oxindole, which was formed in 93% yield when 5b was refluxed in carbon tetrachloride for 2 hr. The position of the bromine in 9a was confirmed by the nmr spectrum of its 1-acetyl derivative, mp 70.5-71.5°. This is the first example of the bromine migration in 3-bromoindolenines. However, the 5-bromo derivative(9b), mp 239-241°, was obtained in 70% yield when 5d was refluxed in cyclohexane for 1 hr. On the other hand the reaction of 1-bromoindole(4c) with ethanolic HCl at room temperature gave 3c in 88% yield.

The characteristic properties of these 3-bromoindolenines, their brominating power and the migration of the bromine to the benzene ring, were not restricted to 2-ethylthio and 2-ethanesulfonylindoles. 2,3-Dibromo-3-phenylindolenine(5e), prepared by the reaction of 3e with NBS in boiling carbon tetrachloride, brominated 6a to give 7a. On the other hand, 5e was converted to a mixture of 2,6-(main)

Table 1 3-Bromoindolenines

Compd No	mp	UV λ_{max}^{EtOH} nm($\varepsilon \times 10^{-3}$)	IR(KBr) $\nu_{C=N}$ cm^{-1}	Mass M^+	Mass Base peak
5a [a]	36-37°	243(17.0), 330(6.7)	1510	271,269, (29) (29)	162 ($M-C_2H_4-Br$)
5b	78.5-80.5°	240(17.2), 326(4.4)	1508	333, 331 (24) (24)	224 ($M-C_2H_4-Br$)
5c [b]	96.5-97°	230(17.9), 290(5.1)	1530	303, 301, (81) (81)	210, 208 ($M-SO_2Et$)
5d	125-126.5°	232(22.2), 297(5.1)	1522	365,363, (3) (3)	272, 270 ($M-SO_2Et$)
5e	oil	239(18.0), 305(3.0)	1540	353,351,349, (3.5)(7) (3.5)	272, 270 (M-Br)

a) nmr (in $CDCl_3$); 1.93 ppm (s, 3-CH_3)

b) nmr (in $CDCl_3$); 1.88 ppm (s, 3-CH_3)

and 2,5-dibromo-3-phenylindole(9c) in good yield when stirred in acetic acid at room temperature.

These results indicate that the bromine at the 3-position of an indolenine can dissociate either as bromo cation(Br^+) or as bromide anion(Br^-) depending on the conditions used and the nature of the other substituents. Further details will be discussed in a full paper.

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References

1 N.Finch and W.I.Taylor, J.Am.Chem.Soc., 84, 3871(1962).

2 H.Zinnes and J.Shavel, J.Org.Chem., 31, 1765(1966).

3 G.Buchi and R.E.Manning, J.Am.Chem.Soc., 88, 2532(1966)

4 P.G.Gassman, G.A.Campbell, and G.Melta, Tetrahedron, 28, 2749 (1972).

5 A.Walser, J.F.Blount, and R.I.Fryer, J.Org.Chem., 38, 3077(1973).

6 R.J.Owellen, J.Org.Chem., 39, 69(1974).

7 G.S.Omen, A.Fontana, and C.B.Anfinsen, J.Biol.Chem., 245, 1895(1970).

8 T.Hino, M.Tonozuka, and M.Nakagawa, Tetrahedron, 30, in press (1974).

9 T.Hino, H.Yamaguchi, and M.Nakagawa, Chem.Commun., 1972, 473.

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