BROMINATION OF 3-SUBSTITUTED INDOLES. ISOLATION AND PROPERTIES OF 3-BROMOINDOLENINES.

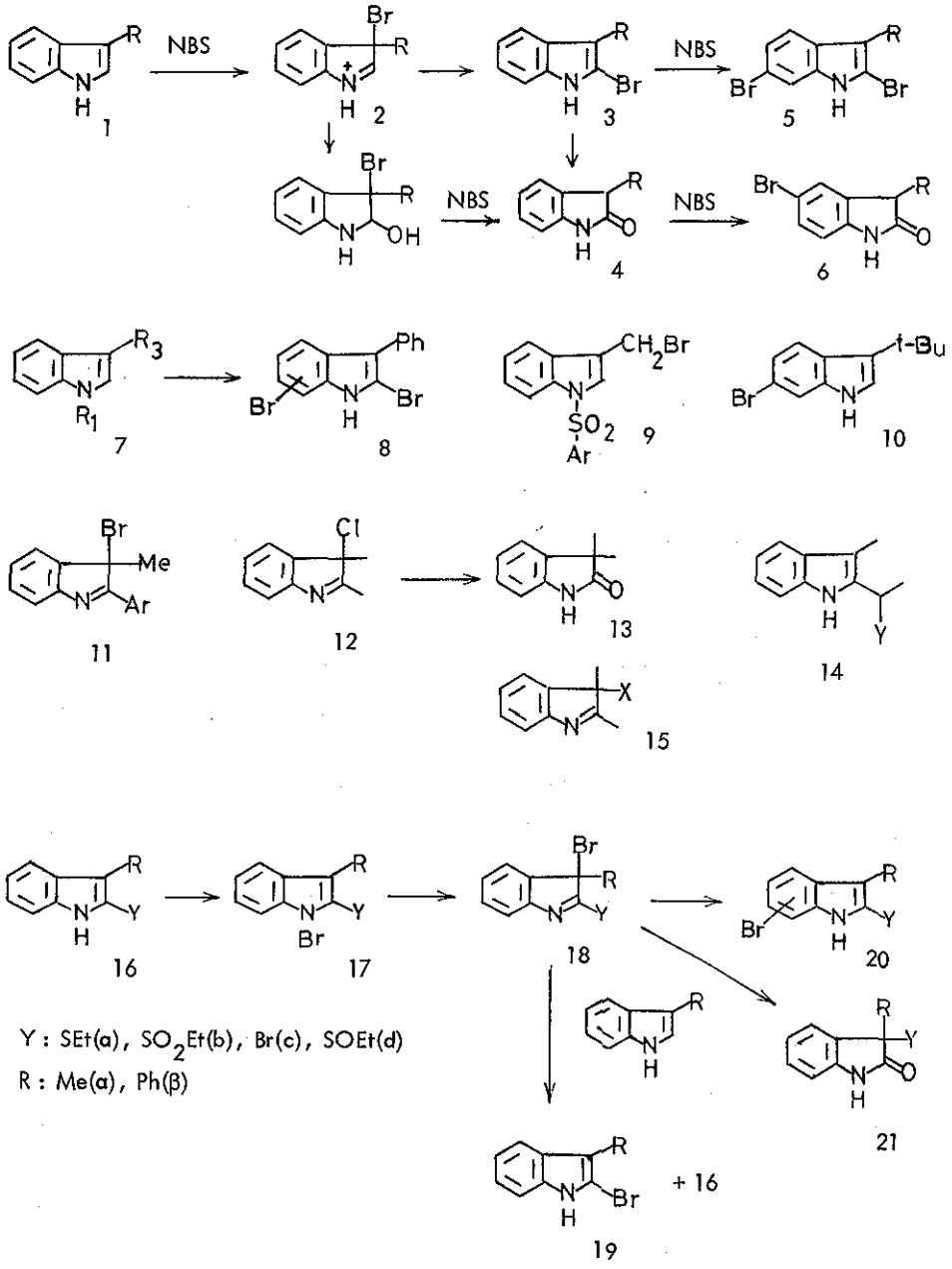
Tohru Hino and Masako Nakagawa

Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Chiba-shi 280

Bromination of 3-alkylindoles(1) with N-bromosuccinimide(NBS) has been reported by Witkop and Hinmann in early 1960's to give 2-bromoindoles(3) in anhydrous media or oxindoles(4) in aqueous media. With two moles of NBS 3-alkylindoles give 2,6-dibromo-*indole(5) or 5-bromooxindole(6)*. *They suggested* that the bromination would proceed via the 3-bromoindolenine(2) obtained by the electrophilic attack of bromonium ion at 3-position of the indole. We have shown the presence of the 3-bromoindolenine by isolating of N-(3-methyl-2-indolyl)pyridinium bromide in the reaction of skatole with dioxane-dibromide in dioxane-pyridine. Further information about the intermediate of the brominatio of indoles has been obtained by Witkop and by us. More recently we have studied the effect of substituents at 1- and 3-positions on the bromination of indoles, and reaction conditions. Reaction of 3-phenylindole with two moles of NBS in AcOH gave 2,6-dibromo-(major) and 2,5-dibromoindole(minor)[1]. Bromination of 1-arylsulfonylskatole with NBS in boiling CCl_4 gave 3-bromomethyl derivative(9)[2]. Reaction of 3-tert butylindole with NBS in AcOH gave 6-bromoindole(10) besides 2-bromo derivative, indicating attack of bromonium ion at 3-position is prevented and thereby 6-position was brominated[3]. In this paper we summarize our results on the isolation and properties of 3-bromoindolenines.

---

1. T.Hino, M.Tonozuka, and M.Nakagawa, Tetrahedron, 30, 2123(1974). And earlier references are cited therein.
2. T.Hino, T.Nakamura, and M.Nakagawa, Chem.Pharm.Bull., 23, 2990(1975).
3. T.Hino, M.Tonozuka, Y.Ishii, and M.Nakagawa, ibid., 25, 354(1977).
4. T.Hino, M.Endo, M.Tonozuka, and M.Nakagawa, Heterocycles, 2, 565(1975). And references cited herein. Idem , Chem.Pharm.Bull., 25, in press(1977).


NBS
NBS
NBS
NBS
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
+ 16
Y : SEt(a), SO2Et(b), Br(c), SOEt(d)
R : Me(α), Ph(β)

1. Isolation and reactivity of 1-bromoindoles and 3-bromoindolenines[4].

As described above the 3-bromoindolenine has been presumed to be the first intermediate of the bromination of indole derivatives. However, the 3-bromoindolenine has not been isolated as a stable form, except 3-bromo-2-(o-nitrophenyl)-3-methylindolenine (11) which is unusually stable crystalline solid and known as a brominating agent. On the other hand, 3-chloroindolenines are first isolated as an intermediate of the transformation of indole alkaloids with tert. butyl hypochlorite to oxindole alkaloids by Finch and Taylor. Later several groups investigated the chemistry of 3-chloroindolenines, some of which were isolated as crystalline form, and disclosed the various transformations of this highly reactive intermediate to 13,14, and 15. Recently Rosa[5] has succeeded in isolating of 1-chloroindole itself and found it transforms to 3-chloroindole via 3-chloroindolenine. As an extension of the bromination of indole derivatives, we examined the bromination of 2-bromo-, 2-ethylthio-, and 2-ethylsulfonyl-3-substituted indoles(16) with NBS.

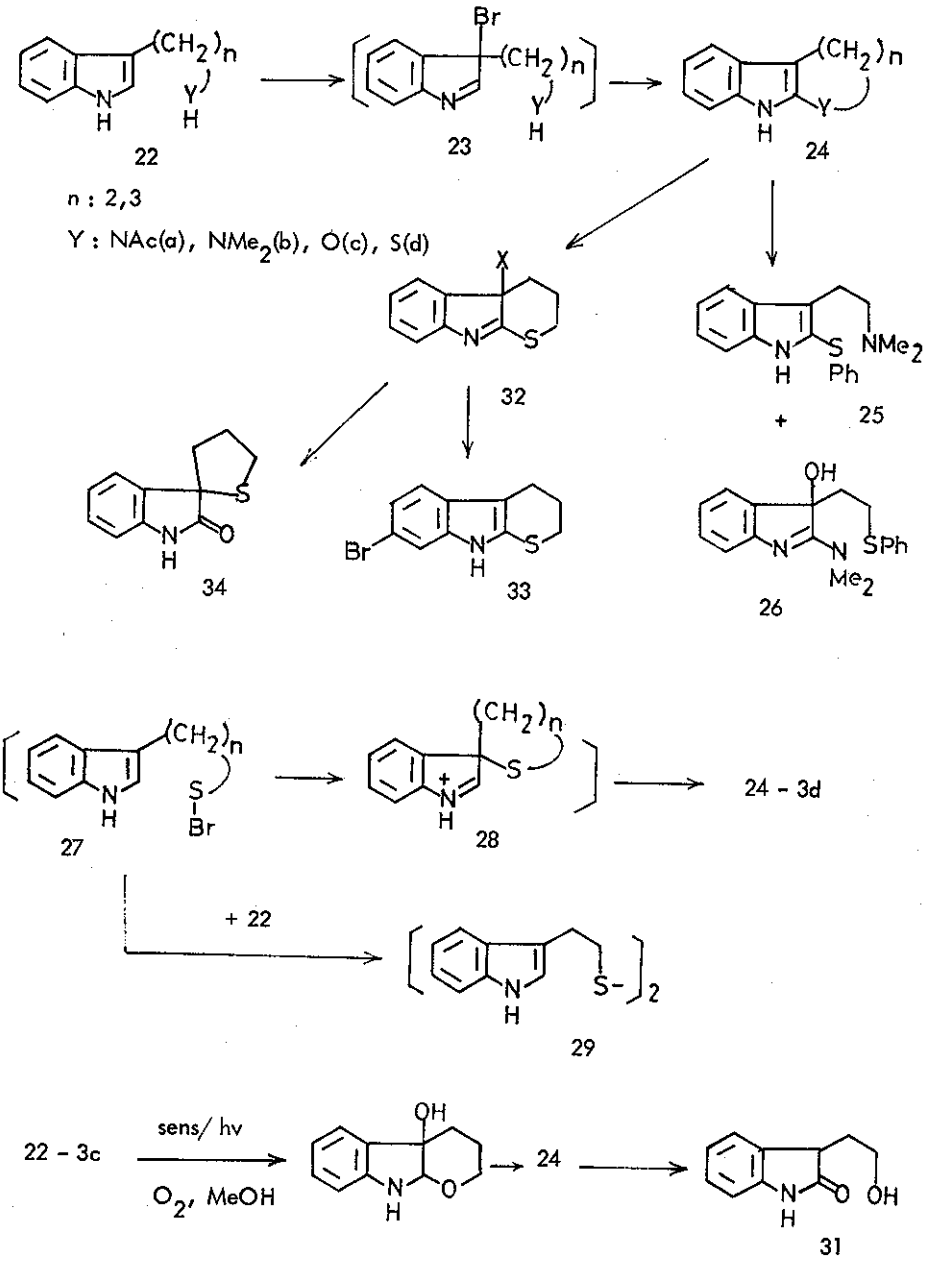
Bromination of 16aα,16aβ, and 16cβ with NBS in boiling CCl_4 for a short time was found to give 3-bromoindolenines(18) in excellent yields as crystals except 2-bromo derivative. Bromination of 16bβ under similar conditions proceeded slowly to give the corresponding 3-bromoindolenine(18), but was accelerated by the addition of benzoyl peroxide. These 3-bromoindolenines showed a positive test with KI-starch as described by Gassman for 3-chloroindolenine, and can brominate indole derivatives such as skatole or 3-phenylindole to give 2-bromo derivatives. A characteristic reaction of 3-bromoindolenines is the migration of the bromine to the benzene ring(intramolecular or intermolecular) when refluxed in CCl_4 or in AcOH at room temperature. The 2-substituents affect the migrating position of the bromine in benzene ring. 2-Ethylthio derivative gave 6-bromo isomer, 2-bromo derivative gave a mixture of 6- and 5-bromo isomers, predominant in the former, and 2-ethylsulfonyl derivative gave 5-bromo isomer.

As in cases of 3-chloroindolenines, 18aα and 18bβ converted to oxindoles on treatment with EtOH-HCl. However, 18aβ rearranged to 6-bromo isomer under similar conditions, indicating preferential migration of bromine. These results suggest that the bromine atom in 3-bromoindolenine behaves as a brominating agent and also as a good leaving

---

5. M.D.Rosa, J.C.S.Chem.Comm., 1975, 482.

6. T.Hino, Y.Torisawa, and M.Nakagawa, Unpublished observations.


22
23
24
n : 2,3
Y : NAc(a), NMe2(b), O(c), S(d)
32
25
34
33
26
27
28
24 - 3d
+ 22
29
22 - 3c
sens/ hv
O2, MeOH
24
31

group in the nucleophilic substitution. The reaction of 2-ethylsulfonyl-3-methylindole with NBS in boiling CCl_4 in the presence of benzoyl peroxide did not proceed, but the bromination did occur with NBS in CH_2Cl_2 at room temperature. A crystalline compound isolated was not 3-bromoindolenine, but 1-bromoindole(17bα). Heating in CCl_4 for 8 hr 17bβ converted to another crystalline compound (18bα) which showed characteristic feature for the 3-bromoindolenine. Similar reaction of 16bβ with NBS-CH_2Cl_2 gave 1-bromo derivative(17bβ) which is converted to 18bβ on heating in CCl_4. These 1-bromoindoles showed positive test with KI-starch and act as brominating agents, but on treatment with EtOH-HCl reverted to 16 and not to the oxindoles. In these reactions effect of the 2-substituents was prominent in the bromination and in the reactivity of 3-bromoindolenines. Therefore, reaction of 2-ethylsulfinyl-3-phenylindole(16dβ) with NBS was carried out[6]. Under both conditions, NBS-CCl_4-BPO and NBS-CH_2Cl_2, the product isolated was 2-bromo-3-phenylindole and neither 3-bromoindolenine nor 1-bromoindole was isolated. Though mechanism of the substitution was not clear, it showed that the sulfoxide group behaves quite differently from the thioether or the sulfone.

2. Oxidative cyclization of 3-alkylindoles having a nucleophilic center with NBS[7].

As the 2-position of 3-bromo-3-alkylindolenines is susceptable to nucleophilic attack, the 3-bromoindolenine which has a nucleophilic center at appropriate position of 3-alkyl group may cyclize to 2-position. Witkop group has reported that the reaction of Nb-acyltryptamine with NBS gave pyrroloindole derivatives. Reaction of Nb-dimethyltryptamine (22-2b) with NBS in CCl_4 at room temperature gave pyrroloindole derivative(24-2b) in 65% yield. The quaternary salt gave 25 and 26 on treatment with thiophenoxide[8]. The latter compound may derive from 2-dimethylamino-3-phenylthioethylindole by autoxidation. 1,Nb-Trimethyltryptamine gave similar results. Reaction of 22-3c and 22-3d with NBS in CH_2Cl_2 at below -10° gave the pyranoindole(24-3c) and thiopyranoindole(24-3d) in 57% and 80% yield respectively. On the other hand reactions of tryptophol with NBS in CH_2Cl_2 gave complicated results and none of pure compound was isolated.

---

7. T.Hino,H.Miura,T.Nakamura,R.Murata, and M.Nakagawa , Heterocycles, 3, 805 (1975). And references cited herein.

8. T.Hino,M.Nakamura, and M.Nakagawa, Unpublished observations.

However 3-indoleethanethiol gave the corresponding disulfide as major product under similar conditions. These results indicate that tryptamines and 3-indolepropanol gave the cyclized products via 3-bromoindolenines, but another pathway may be possible for 3-indolepropanethiol. As the thiol group is known to be sensitive to NBS to form sulfenyl bromide, the thiol group in 3-indolepropanethiol may convert to sulfenyl bromide(27) with NBS. It is known that sulfenyl halide can react with indole derivatives to form thioethers. So the sulfenyl bromide(27) may cyclize at 3-position to 28 and then rearrange to the product. In case of 22-2d sulfenyl bromide formed may difficult to form four membered ring and converted to the disulfide on the reaction with unreacted thiol.

It is interesting to note that the photosensitized oxygenation of 3-indolepropanol in MeOH gave hydroxypyranoindole(30), instead of pyranoindole(24-3c)[9]. The same situation was observed in acetyltryptamine[10]. Hydroxypyranoindole and pyranoindole converted to 3-hydroxypropyloxindole on treatment with EtOH-HCl at room temperature in good yield, and intermediacy of pyranoindole was observed by UV spectral change of the hydrolysis of hydroxypyranoindole with dilute HCl[9].

Bromination of thiopyranoindole with NBS in CCl_4 at room temperature gave 7-bromothiopyranoindole(33) in 20% yield. UV spectral change indicate the presence of 3-bromoindolenine(32) as an intermediate, though it could not be isolated. On the other hand, chlorination of thiopyranoindole with NCS in CCl_4 at room temperature gave 3-chloroindolenine besides spirooxindole(34). The chloroindolenine which showed negative test with KI-starch did not transform to 7-chloro derivative, although it was converted to 34 by addition of acid. Although the evidence is not sufficient, migration of 3-halo atom in 3-haloindolenines to the benzene ring may be restricted to bromine compounds.

---

9. T.Hino, H.Miura, and M.Nakagawa, Unpublished observations.

10. M.Nakagawa, H.Okajima, and T.Hino, J.Am.Chem.Soc., 98, 635(1976); M.Nakagawa and T.Hino, J.Synth.Org.Chem., 35, 42(1977).