3-HALOINDOLENINES ——— VERSATILE INTERMEDIATES IN THE INDOLE CHEMISTRY

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Abstract — This review summarized the preparation and synthetic use of 3-haloindolenines. Some of the factors which affect the reactivity of this interesting intermediates are also discussed.

1. Introduction

Since the first introduction in 1956,[1] 3-haloindolenines 1* have become popular as versatile synthetic intermediates in the indole chemistry. Besides use in the classical transformation to oxindoles, they can also be successfully utilized in the synthesis and transformation reactions of various indole alkaloids. In this brief survey, we have tried to evaluate the usefulness of this reactive, interesting intermediates. Although 3-haloindolenines also play an important role as possible intermediates in the halogenation of indoles,[2] this subject will generally not be included.

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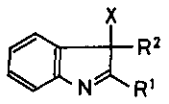
* 3-Haloindolenines are named as "3-halo-3H-indoles" in Chemical Abstracts.

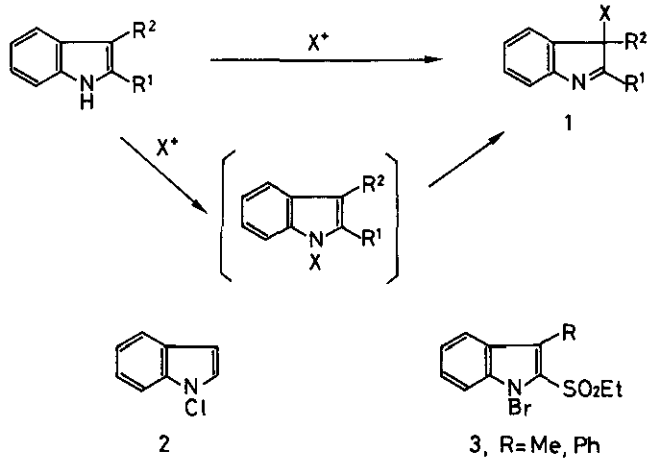


1 (X=Cl, Br, I)

2. Preparation and Characterization

The most commonly used method for the preparation of 3-chloroindolenines involves reaction of the indole with tert-butyl hypochlorite in aprotic solvents such as methylene chloride or benzene in the presence of triethylamine at low temperature. The yields are generally high.[1,3] Other chlorinating agents such as metal hypochlorite,[4] N-chlorosuccinimide,[5] and 1-chlorobenzotriazole[6] have also been used. The last one has been recommended for the preparation of chloroindolenines of some indole alkaloids. For preparing 3-bromoindolenines, N-bromosuccinimide (NBS) is the reagent of choice.[7,8] So far, 3-iodoindolenines have not been isolated.

The mechanism for the formation of 3-haloindolenines 1 has received considerable attention in recent years. The major question is whether initial halogenation occurs at the 1-position or at the 3-position of the indole nucleus. Gassman et al.[4] suggested that the initial attack would be on nitrogen, followed by rapid migration of the chlorine atom from the nitrogen to the 3-position. This suggestion is analogous to the known intermediacy of N-chloroanilines in the chlorination of aniline derivatives. Recently, De Rosa[9] has reported the first direct evidence for the existence of 1-chloroindole (2) and its transformation to 3-chloroindole. Hino



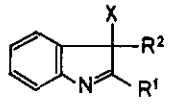
2

3, R=Me, Ph

et al.[8] have succeeded to isolate stable 1-bromoindoles 3 and showed that they rearrange to 3-bromoindolenines. The above evidence implicates that 1-haloindoles are involved as intermediates in the formation of 3-haloindolenines, at least in these specific cases.

The stability of 3-haloindolenines varies from extreme instability to isolable compounds. These compounds are characterized not only by the disappearance of an N-H stretching band and the presence of a C=N stretching band at 1500-1600 cm^{-1} in the IR spectra, but also by the UV absorption bands typical of an indolenine structure which shows two characteristic maxima (see Table 1). The NMR spectra are

Table 1. Physical Data of Some Representative 3-Haloindolenines



R^1	R^2	X	mp (°C)	UV [nm (log ε)]	IR(C=N)cm^{-1}	Ref.
Me	Me	Cl	unisolable	266(ca. 3.70),292 sh[a]	—	4
-$(CH_2)_4$-		Cl	unstable oil	235(4.14),264(3.56)[a]	1590(CCl_4)	10,15
-$CH_2NMe(CH_2)_2$-		Cl	unstable solid	226(3.94),286(3.04)[b]	1600(CCl_4)	22
Ph	Ph	Cl	127-128	225(4.22),328(3.88)[a]	1530(KCl)	27
CO_2Me	CO_2Me	Cl	102-103	240(3.92),300(3.49)[a]	1560(KCl)	27
Ph	Ph	Br	131-132	260(4.03),318(3.70)[a]	1530(KCl)	27
SEt	Me	Br	36-37	243(4.23),330(3.82)[b]	1510(KBr)	8
SO_2Et	Me	Br	96.5-97	230(4.25),290(3.71)[b]	1530(KBr)	8

a In methylene chloride. b In ethanol.

sometimes useful for characterization; the signal of 3-methyl group of 3-halo-3-methylindolenines shifts to the higher field compared to that of the corresponding 3-methylindoles. Formation of 3-haloindolenines can often be judged by a low temperature iodometric titration.[4]

3. Reactions

3-Haloindolenines are capable of reacting in a number of ways to lead to:

(a) 2-alkoxyindolenines, oxindoles, and 2-alkylideneindolines by skeletal

rearrangement,

(b) 3-substituted indolenines by nucleophilic substitution at the 3-position,

(c) indole derivatives substituted at the 2-methylene group by initial tautomerization to the enamine structures followed by nucleophilic substitution with an allylic rearrangement,

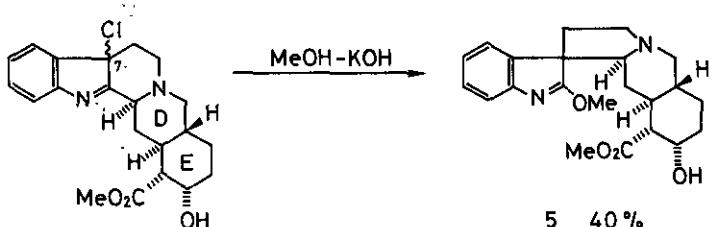
(d) furo- and pyrrolo-indoles and related compounds by intramolecular cyclization, and

(e) regeneration of indoles by attack of nucleophiles on halogen atom.

These reaction courses are highly dependent on several factors such as the structural features of the haloindolenines, the solvent, temperature, and other reaction conditions.

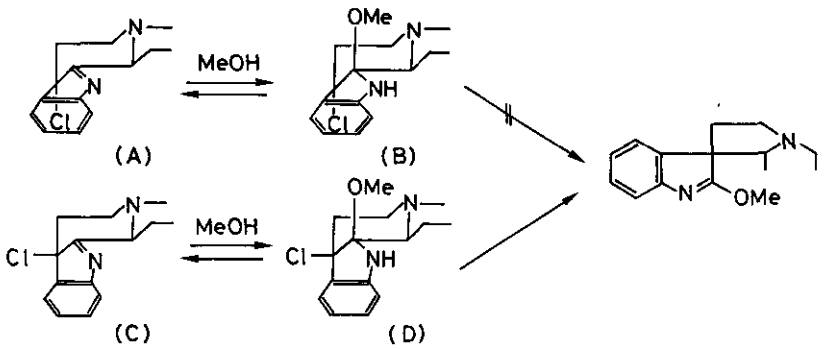
3.1. Formation of 2-Alkoxyindolenines

Upon treatment with alkali in refluxing alcohol, 3-chloroindolenines undergo rearrangement to 2-alkoxyindolenines. Since the latter are easily hydrolyzed with acid to oxindoles, the sequence of reactions can be employed for a conversion of indoles to the corresponding oxindoles.

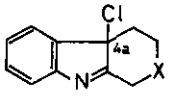


4 5 40%

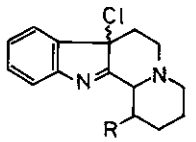
This reaction, first discovered in 1962 by Finch and Taylor,[3] was successfully applied to the chloroindolenines 4 derived from D/E trans yohimbine alkaloids, but failed with D/E cis yohimbine alkaloids. The difference in reactivity between the trans-DE and cis-DE yohimbines is explained as follows. The rearrangement can proceed only when the chlorine atom and the migrating carbon-carbon are properly oriented to allow inversion. This requires cis stereochemistry of the chlorine atom and the methoxyl group in the intermediate [i.e., (D)]. In the trans-DE case, the two theoretically possible chloroindolenines (A) and (C) are formed in equal amounts, and only the equatorially oriented chlorine atom has the correct stereochemistry to permit coplanality of the atoms involved in the rearrangement. In the cis-DE case, where one chloroindolenine predominates, the chlorine must be axially oriented [i.e., (A)].



More recently several simple chloroindolenines 6,[10] 7,[11] 8,[11] and 9a[12] were converted into the corresponding 2-methoxyindolenines. The rearrangement of 6 was studied in methanol with two kinds of alkali (sodium hydroxide and sodium methoxide) and over a range of temperatures (-10~60°). This rearrangement competes with displacement reaction at the C_{4a} which affords the 4a-methoxy derivatives (see Section 3.4.). At higher temperature (60°C) in the presence of sodium hydroxide the rearranged product increased in proportion to the displacement product.[10]



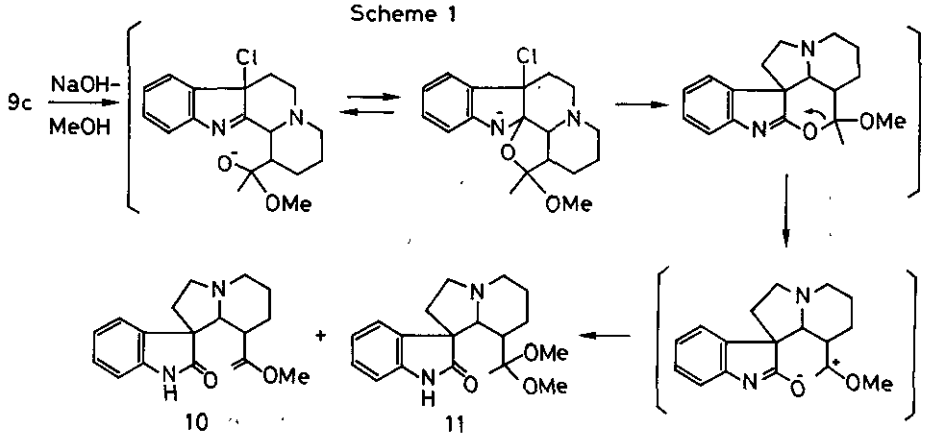
6, X=CH_2
7, X=NMe
8, X=NCH_2Ph



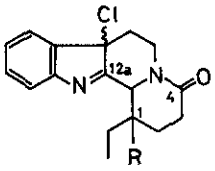
9a, R=H
9b, R=Et
9c, R=Ac

In the case of 9c in which the carbonyl group is held in close proximity to the C=N group, two oxindoles 10 and 11 were obtained.[13] A proposed mechanism involves initial attack of methoxide ion to the carbonyl group followed by addition of the resulting hemiketal to the imino group, rearrangement, and ring opening to lead to the observed products (Scheme 1). No reaction took place with 9b.

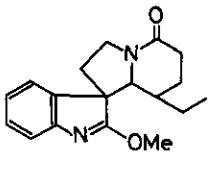
Scheme 1



The lactam 12a gave the expected product 13 in only 16% yield; 14 (25%) and 15a (14%) were obtained as by-products. Compounds 12b,c gave only 15b,c, respectively.[14] The C_{12a}-position of these chloroindolenines is hindered to approach of methoxide ion by the bulky C_1-substituent.



12a, R=H
12b, R=Et
12c, R=$(CH_2)_2CO_2Me$



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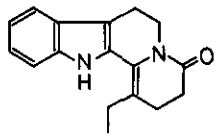

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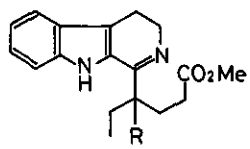
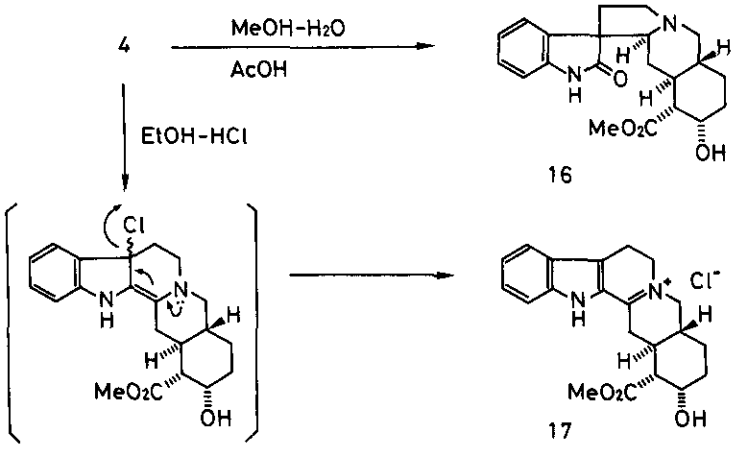


15a, R=H
15b, R=Et
15c, R=$(CH_2)_2CO_2Me$

Recently, it has been reported that the conversion of 6 to the corresponding 2-ethoxyindolenine can be effected by treating with thallium ethoxide in refluxing benzene.[15]

3.2. Formation of Oxindoles

In 1962 Zinnes and Shavel, Jr.[16] discovered that the chloroindolenines derived from various yohimbine alkaloids (e.g., 4) give directly the corresponding oxindoles 16 by refluxing in aqueous methanolic solution adjusted to pH 6.* It

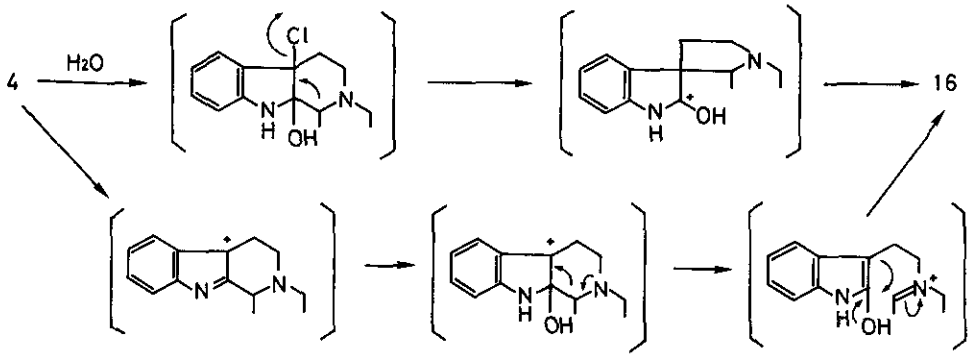


Scheme 2

* However, the same chloroindolenine 4, upon treatment with ethanolic hydrogen chloride, afforded 3-dehydro salt 17. This reaction has been postulated to proceed as depicted in Scheme 2.[1]

should be noted that this procedure can be applied to both the D/E trans- and D/E cis-yohimbine alkaloids,[16,17] in contrast to the procedure by Finch and Taylor (see Section 3.1.).

Several mechanisms for the formation of the oxindoles have been proposed, and two of them[16] are shown in Scheme 3.



Scheme 3

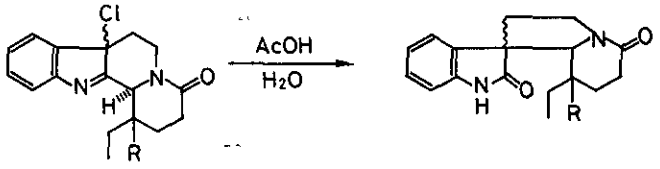
More recently, a variety of 3-haloindolenines have been shown to rearrange to oxindoles. Some of the typical examples are summarized in Table 2. Exceptionally, 2-acetyl and 2-carboxyl groups were eliminated under the reaction conditions.

Table 2. Preparation of Oxindoles[a]

R^1	R^2	X	Conditions	Yield (%)	Ref.
Ph	Ph	Cl	AcOH, r.t.	quant.	18
SEt	Me	Br	EtOH-HCl, r.t.	81	8
SO_2Et	Me	Br	"	79	8
SO_2Et	Ph	Br	"	94	8
$-O(CH_2)_2-$	CH_2-	Cl	"	89	19
$-S(CH_2)_2-$	CH_2-	Cl	"	56	19
CON	Me	Cl	EtOH, reflux	75	20

a For more examples, see ref. 20.

The lactams 12a-c also rearranged to oxindoles 18a-c in diluted acetic acid at 60°.[14] The oxindole 18c has already been transformed to vincadifformine and aspidospermidine.[21]



12a-c

a, R=H
b, R=Et
c, R=$(CH_2)_2CO_2Me$

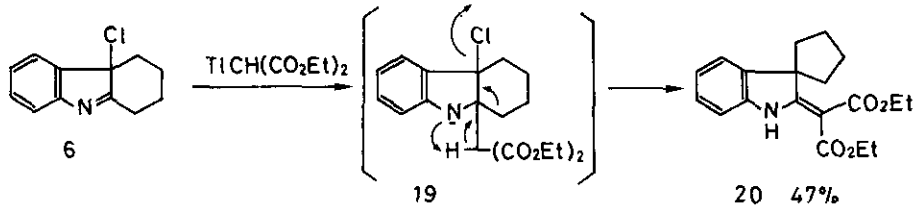
18a-c

22% + 14 (21%)
35% + 12.5%[a)]
36% + 12%[a)]

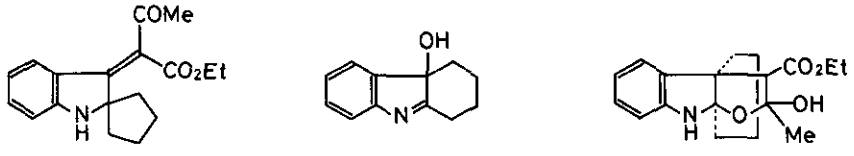
a) diastereoisomer

3.3. Formation of 2-Alkylideneindolines

Kuehne et al.[15] have observed that the chloroindolenine 6 reacts with thallium diethyl malonate to give 3-spiro-2-alkylideneindolines 20. Interestingly, with thallium ethyl acetoacetate 2-spiro-3-alkylideneindoline 21 and the unrearranged O- and C-alkylation products 22 and 23 were formed. Use of sodium diethyl malonate or sodium ethyl acetoacetate in these reactions gave only tetrahydrocarbazole. The mechanism for the formation of 20 is not clear but suggested to occur via intermediate 19.



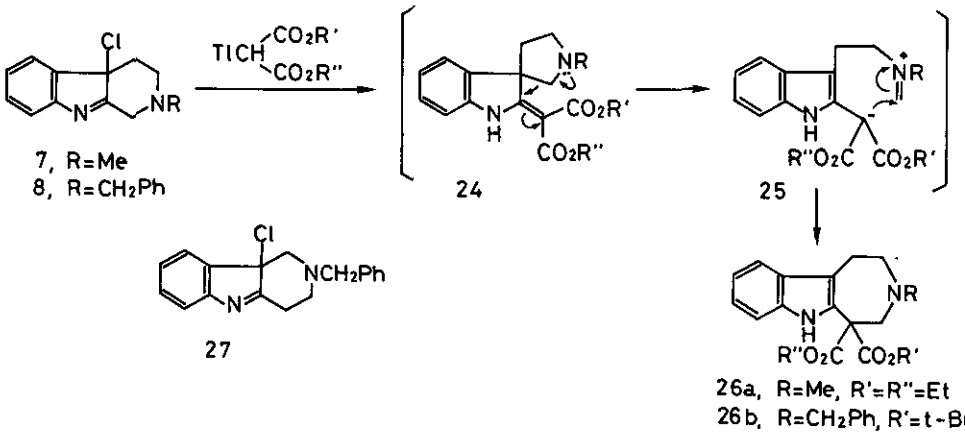
6 19 20 47%



21 22 23

An extension of this reaction to the chloroindolenines 7 and 8 of tetrahydro-β-carbolines resulted in the formation of the respective indoleazepines 26a and 26b.[22] The latter was transformed into vincadifformine after several further steps. The formation of 26 is believed to proceed through 3-spiro-2-alkylideneindoline 24 which would undergo fragmentation to a zwitterionic immonium ion 25 followed by cyclization. A similar rearrangement took place with the chloroindolenine 27. The

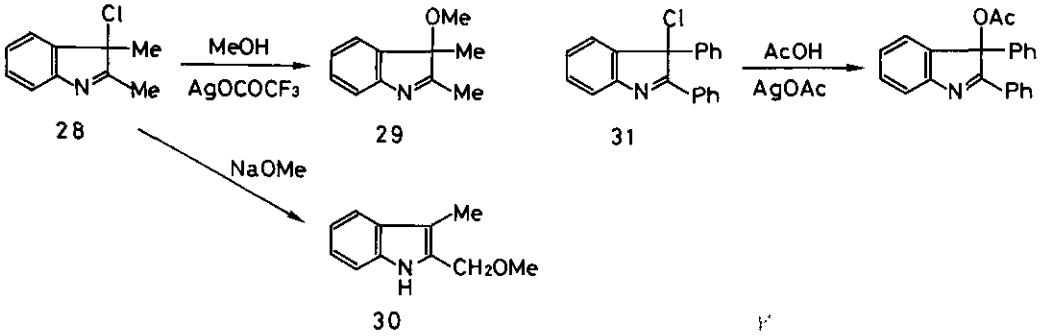
proposed intermediate 24 was isolated from the reaction of 27.



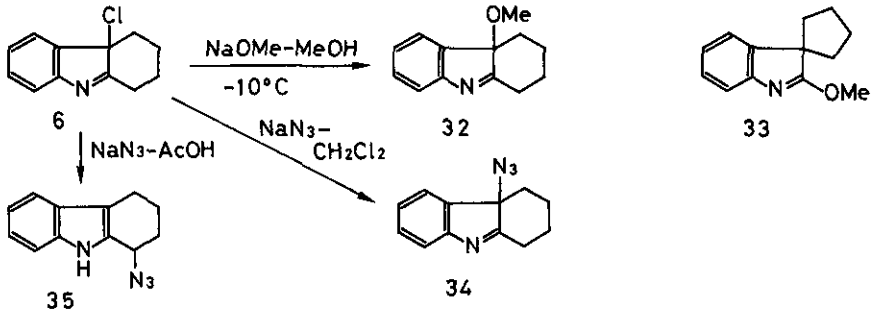
3.4. Formation of 3-Substituted Indolenines

3-Haloindolenines undergo somewhat erratic substitution reactions at the 3-position with some nucleophiles. The success of the reactions may depend on the reaction conditions, the nature of nuecleophiles, and the structures of the substrate. Despite the limited number of examples, some tentative generalizations appear valid.

Clearly, substitution reaction by alkoxy and acetoxy groups are best achieved in the presence of silver ion at low temperature. Even thermally labile 2,3-dimethyl-3-chloroindolenine (28) reacted with silver trifluoroacetate in methanol at -10° to give 3-methoxyindolenine 29 in 94% yield, while the same 3-chloroindolenine, upon treatment with sodium methoxide at 15°, gave 2-methoxymethylindole 30[4] (see Section 3.5.). Acetoxylation of chloroindolenine 31 proceeded poorly with sodium acetate (52% yield after 70 hr) but quantitatively with silver acetate (the reaction completed within 2 hr).[18]

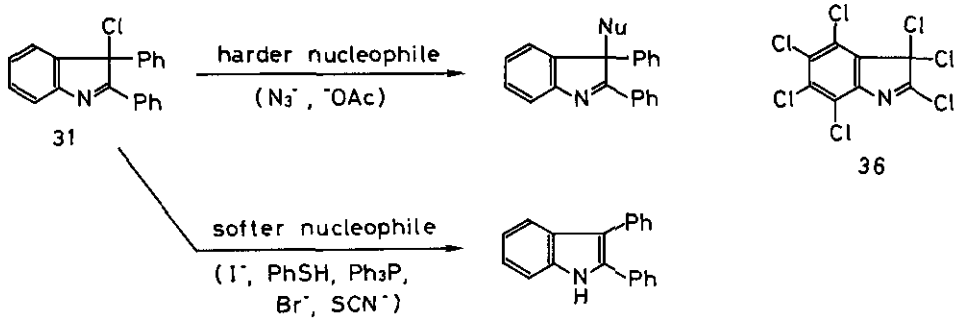


Chloroindolenine 6, when allowed to react with sodium methoxide at -10°, gave 32 in 88% yield, whereas reaction with sodium hydroxide in methanol under reflux gave 2-methoxyindolenine 33 in 82% yield. The relative proportion of 32 and 33 was dependent upon both base and temperature[10] (see Section 3.1.).



The same chloroindolenine 6 reacted with azide anion to give the *normal* product 34 in methylene chloride but the rearranged product 35 in acetic acid.[18] The formation of the latter will be discussed in Section 3.5.

In contrast to successful substitution of chlorine atom of 3-chloroindolenine 31 by AcO^- and N_3^-, some nucleophiles such as I^-, Ph_3P, PhSH, Br^-, SCN^- reverted 31 to the parent indoles by attack on chlorine atom. [Bromine and thiocyanogen (or their equivalents) thus formed underwent further electrophilic attack at the 6-position of the indoles to give ultimately 6-bromo- and 6-thiocyanato-indoles, respectively (see Section 3.7.)]. These results are discussed in terms of the HSAB (hard and soft acids and bases) principle of Pearson;[24] the harder nucleophiles (AcO^- and N_3^-) tend to undergo irreversible nucleophilic attack on the harder carbon atom at the 3-position, while the softer nucleophiles (I^-, PhSH, Ph_3P, Br^-, and SCN^-) attack on the softer chlorine atom. Similar results have been reported with a chloroindolenine 36,[25] which reacted with potassium isopropoxide, methylamine, and dimethylamine to give the corresponding ether and amines (the structures



were not specified), while treatment with sodiomalonic ester, butyllithium or sodium benzenethiolate led only to reduction, giving 2,3,4,5,6,7-hexachloroindole.[25]

Finally, it should be noted that the azide group can be introduced at the 3-position in high yields directly from the indoles by using iodine azide or bromine azide.[26,27] This reaction is believed to proceed via 3-haloindolenine intermediates.

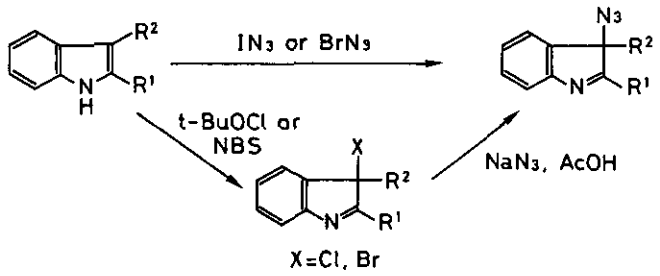


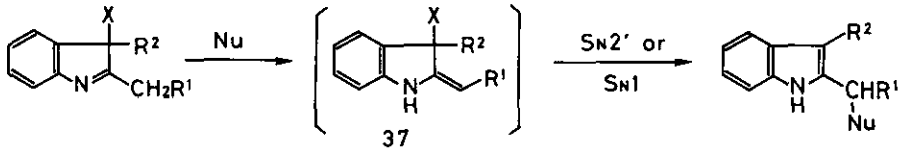
Table 3. Preparation of 3-Azidoindolenines

		Yield (%)	
R^1	R^2	By IN_3	via 3-Chloro-indolenines
Ph	Ph	100(98)[a]	100(100)[b]
Ph	Me	100(98)[a]	100(100)[b]
CO_2Et	Me	85	100
CO_2Me	CO_2Me	r.t.	74

a) By BrN_3. b) via 3-Bromoindolenines.

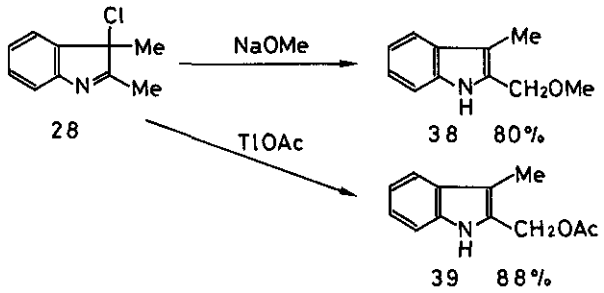
3.5. Formation of Indole Derivatives Substituted at 2-Methylene Group

3-Haloindolenines derived from indoles bearing 2-methyl or methylene group can undergo substitution reactions at the 2-alkyl group. The currently accepted mechanistic hypothesis[28] for this reaction involves the intermediacy of the tautomeric enamines 37, which may undergo substitution at the 2-methylene group by S_N2' or S_N1 mechanism. The isomerization of 3-haloindolenines to enamines 37 is promoted by a variety of factors; structure of the substrate and reaction conditions

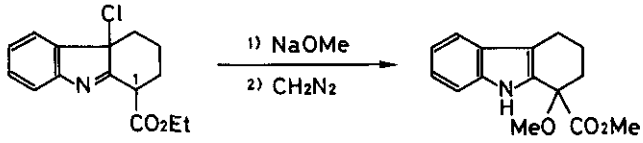


(e.g., temperature, and acid or base).

After 2,3-dimethylindole was chlorinated at -78°, the reaction mixture was quickly warmed to 15° and then treated with sodium methoxide or thallium acetate to give 38 and 39, respectively.[4] The 3-chloroindolenine 28 may undergo thermal isomerization of the double bond (Gassman[4] has also suggested other possibilities).



As described earlier (Section 3.4.), the chloroindolenine 6 gave the substitution product 32 when treated with sodium methoxide, and the rearranged product 33 when treated with sodium hydroxide in refluxing methanol; 1-methoxytetrahydrocarbazole was not found in any of these reactions. However, when the chloroindolenine 40 was treated with sodium methoxide at room temperature followed by esterification, it formed 41.[29] The different reactivities of 6 and 40 are rationalized on the basis that the electron-withdrawing 1-carbethoxy group makes the α-proton more acidic than normal and promotes a facile tautomerization to the enamine structure.



40 41

Treatment of 3-chloroindolenines 43 with sodium azide in acetic acid produced 2-azidomethylindole derivatives 44 in high yields.[30] Under the acidic conditions the isomerization of 43 to the enamine form appears to be facilitated.* The same compounds were obtained directly from the reaction of indoles 42 with iodine azide.

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* An alternative mechanism for the formation of 44 would involve the initial nucleophilic substitution by azide anion at the 3-position followed by the isomerization of the C-N double bond and then [3,3]sigmatropic rearrangement of the azide group to the observed products.[30]

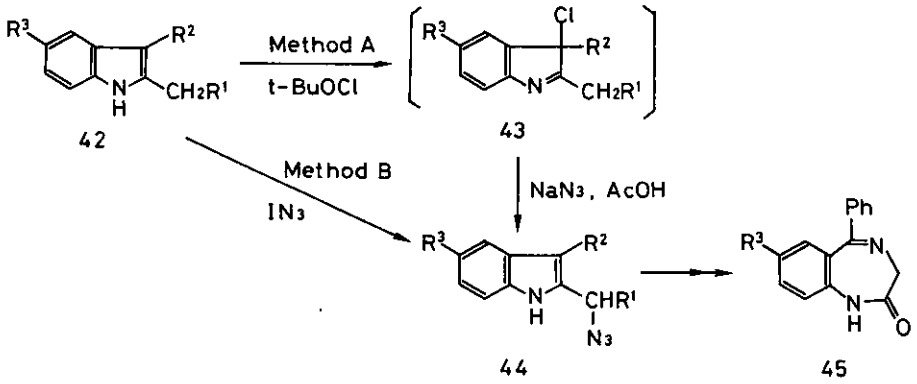
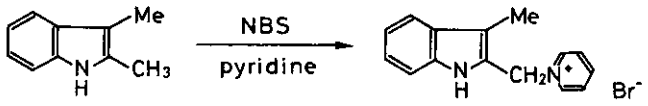


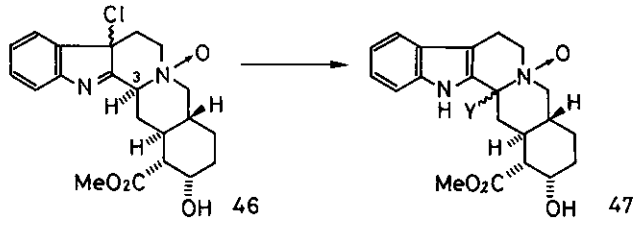
Table 4. Preparation of 2-Azidomethylindoles

R^1	R^2	R^3	Yield (%) Method A	Yield (%) Method B
H	Me	H	93	94
Me	Me	H	94	91
H	Ph	H	72	quant.
H	Ph	Cl	quant.	93
$-(CH_2)_4-$		H	92	89



Compounds 44 have been converted into 1,4-benzodiazepines 45 after 2 steps. An analogous reaction has been observed in bromination of 2,3-dimethylindole or tetrahydrocarbazole with NBS in the presence of pyridine.[31,10]

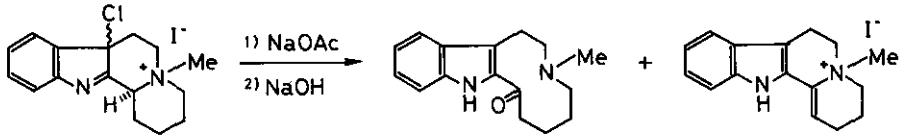
In contrast to chloroindolenines of yohimibine alkaloids which, upon treatment with sodium methoxide in methanol, rearranged to 2-methoxyindolenines (see Section 3.1.), the corresponding N-oxides 46 reacted with a variety of nucleophiles at the



Conditions	Y
KOH-EtOH	OH
NaOMe-MeOH	OMe
KCN-MeOH	CN
$KCH(CO_2Et)_2$-t-BuOH	$CH(CO_2Et)_2$

3-position to give 47.[32] This may reflect the increase of the acidity of C_3 proton by the N-oxide group.

A similar effect can be expected by quarternization of Nb. Dolby et al.[12] obtained 49 from chloroindolenines 48a and 48b, along with 50, by treating with sodium acetate in aqueous ethanol followed by sodium hydroxide.

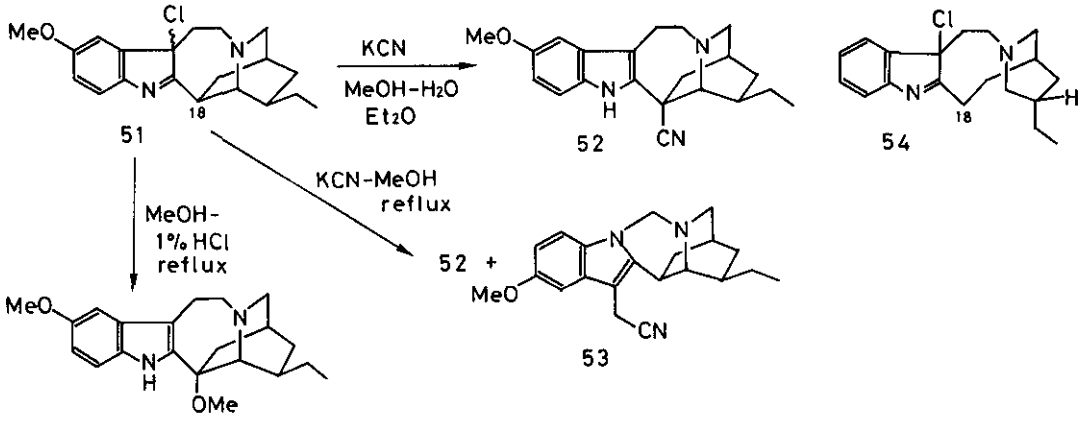


48a, α-Cl
48b, β-Cl

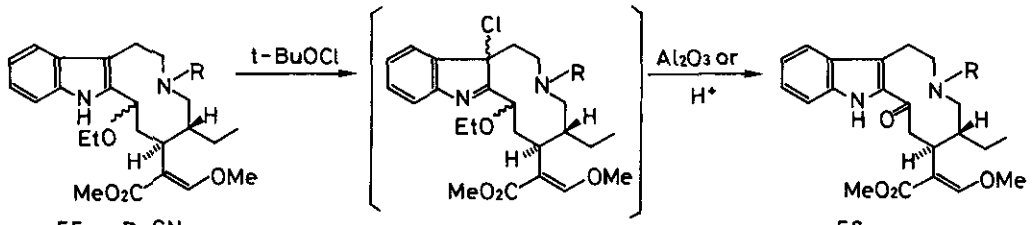
49

50

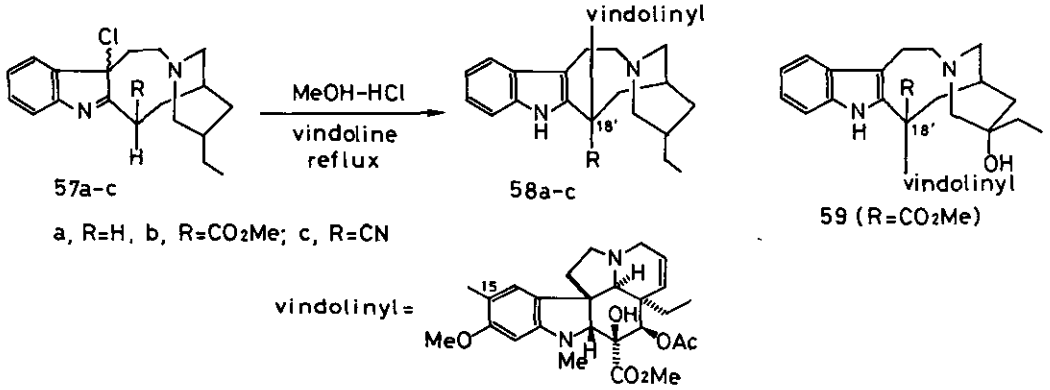
Increase of the ring size at C_2 and C_3 of the indole ring appears to facilitate the isomerization of the double bond of the indolenine. For example, the chloroindolenine 51 of ibogaine racted with potassium cyanide to give 18-cyanoibogaine 52 and a rearranged product 53.[33] Methoxyl and hydroxyl groups could also be introduced at the C_{18} position. Similarly, the chloroindolenine 54 of dihydrocleavamine reacted with cyanide ion to give the 18-cyano derivative, although in low yield.[34]



Sakai et al.[35,36] used this reaction for conversion of 55 to 2-acylindole derivatives 56.

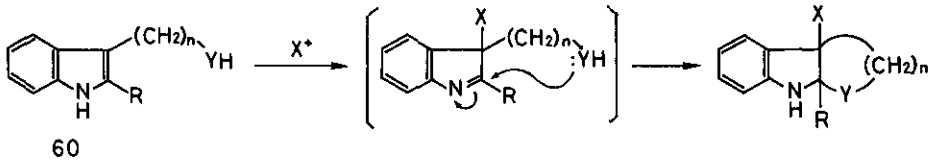


One of the most important applications may be the synthesis of the anti-tumor dimeric indole alkaloid such as vinblastine 59 and related compounds. If vindoline acts as a nucleophile at C_{15}, the reaction with chloroindolenines might provide a general route to these dimeric alkaloids. This approach was first realized by Neuss et al.,[37] who succeeded to couple chloroindolenine 57a with hydrazide of deacetylvindoline. Later, Kutney et al.[38,39,5] extended this coupling reaction to chloroindolenines 57a-c with vindoline and the related compounds. Unfortunately the dimeric compounds 58b,c obtained by this reaction possessed the unnatural configuration at $C_{18'}$.

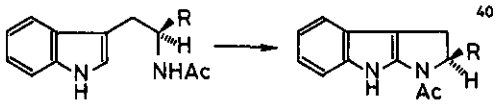


3.6. Intramolecular Cyclization

When some indole derivatives 60 bearing a nucleophilic group at the 3-position, e.g., derivatives of tryptophan, tryptamine, and tryptophol, were treated with halogenating agents, tricyclic pyrrolo- or furo-indole derivatives were directly formed.[40] In the case that R=H dehydrohalogenation was followed. It is suggested that the reactions occur via 3-haloindolenine intermediates. Reaction of tryptophol (60, R=H, Y=O, n=2) with NBS or NCS gave complex mixtures.[19]



60



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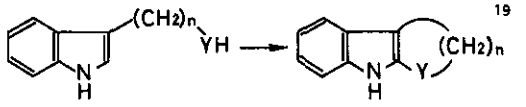


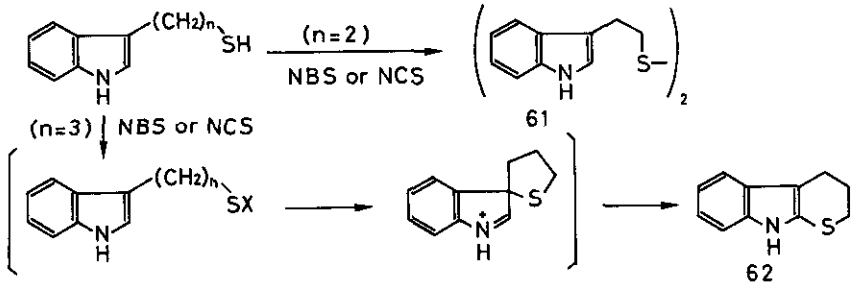
19

R	Conditions	Yield (%)
H	t-BuOCl,Et_3N,CH_2Cl_2	63
CO_2Me	t-BuOCl,Et_3N,CH_2Cl_2	78
CO_2Et	t-BuOCl,Et_3N,CH_2Cl_2	80
$CONH_2$	NBS,pH8-9,r.t.	30

YH	n	Conditions	Yield (%)
NMe	2	NBS,CCl_4,r.t.	65[a]
OH	3	NBS,CH_2Cl_2,-15∿-17°	57[b]

a) Obtained as a quaternary salt ($Y=\overset{+}{N}Me\ ,Br^-$)
b) Accompanied by the formation of 3-(3-hydroxypropyl)oxindole (9%)

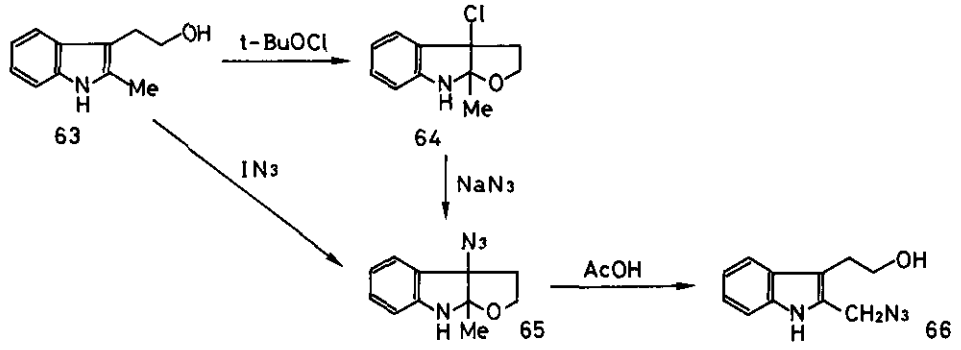
An extension of this reaction to indole-ethanethiol and propanethiol gave disulfide 61 and thiopyranothiol 62, respectively.[19] These reactions are suggested to proceed through halogenation of sulfur atom rather than via 3-haloindolenine intermediates.



61

62

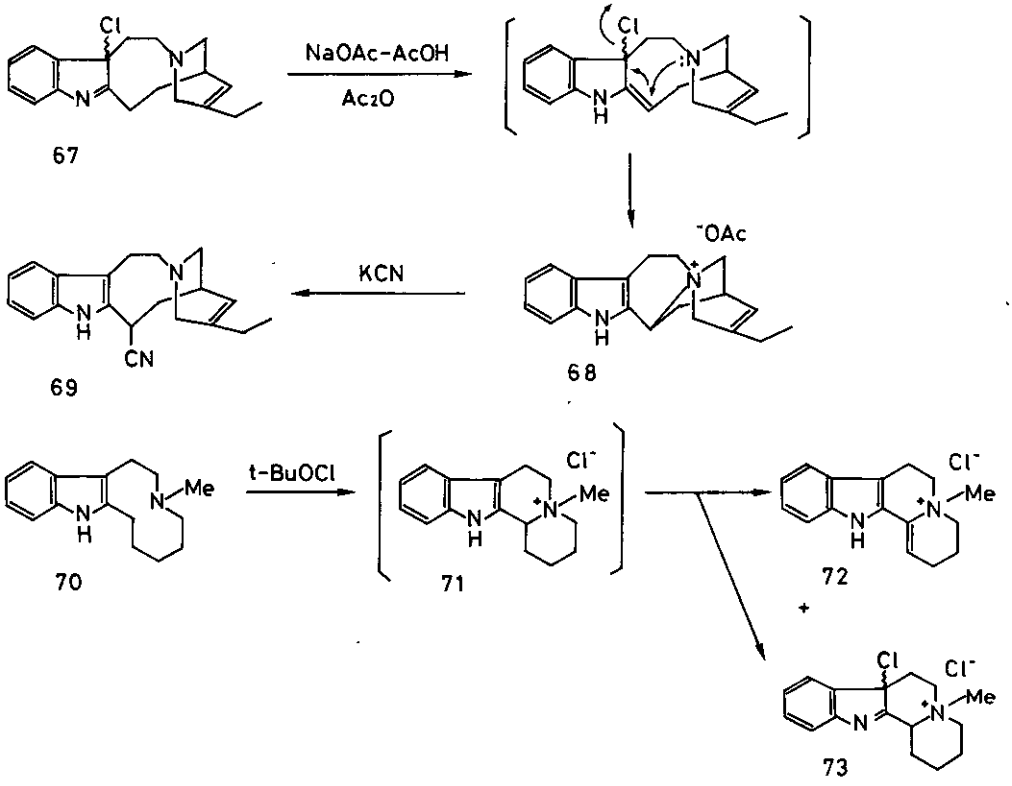
Reaction of 2-methyltryptophol (63) with 1 equiv of tert-butyl hypochlorite gave unstable 64, which was transformed into 65 by treating with sodium azide. It



63 64 65 66

should be noted that 65 was directly obtained from the reaction of 63 with iodine azide. Compound 65 rearranged to 66 in acetic acid at room temperature.[41]

Another type of cyclization has been reported. When 67 was treated with sodium acetate in acetic acid, 68 was obtained. This compound was converted into 69 by reacting with potassium cyanide.[34,42] Reaction of 70 with tert-butyl hypochlorite gave a mixture of 72 and 73. The formation of 72 and 73 is explicable as secondary products from unisolable intermediate 71.[12]

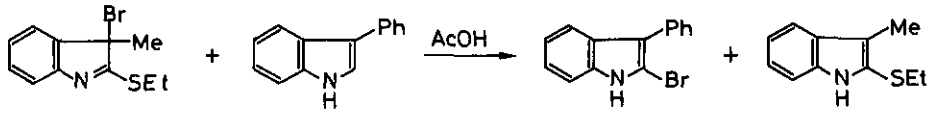


3.7. Regeneration of Indoles and Introduction of Halogen on the Benzene Ring

The C-X bond of 3-haloindolenines can be cleaved, in the formal sense, in three different manners; (i) heterolytic fission to halide anions (X^-) and indolenyl cations, (ii) heterolytic fission to halonium cations (X^+) and indolenyl anions, and (iii) homolytic fission to halogen atom ($X^\cdot$) and indolenyl radicals.

However, all the reactions described so far are categorized into the type (i). In this section the reactions of the types (ii) and (iii) are discussed.

As described earlier (Section 3.4.), 3-haloindolenines react with I^-, phosphines, thiols, and carbanions to give the indoles by attack of these nucleophiles on the halogen atom.[18,25] 3-Bromoindolenines can brominate some reactive compounds such as 3-phenylindole.[7,8]



The reaction of 3-chloro-2,3-diphenylindolenine (31) with sodium bromide or sodium thiocyanate in acetic acid gave 6-bromo- and 6-thiocyanato-indoles, respectively. In principle, two mechanisms can be considered: (a) direct nucleophilic substitution of 31 at the 6-position by bromide or thiocyanate ion, and (b) initial generation of the indoles and bromine or thiocyanogen (or their equivalents) followed by electrophilic substitution of the indoles by Br^+ of SCN^+. Trapping experiments of Br^+ and SCN^+ ions using N,N-dimethylaniline, together with the fact that direct bromination (by bromine) and thiocyanation[43] (by thiocyanogen) of 74 gave 6-substituted indoles, suggest the mechanism (b) for the formation of 6-bromo- and 6-thiocyanato-indoles.[18] Other examples are shown in Table 5.

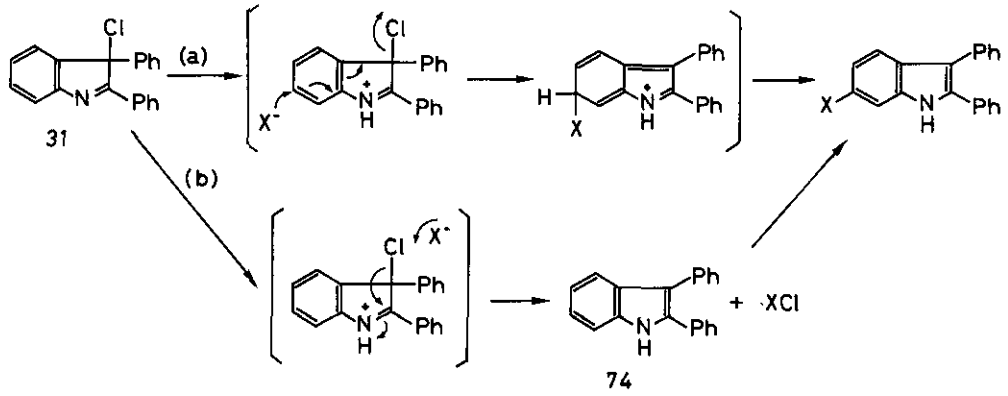
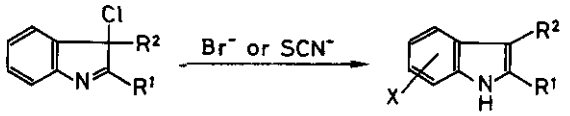


Table 5. Formation of Bromo- and Thiocyanato-indoles

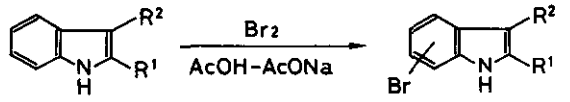


X = Br, SCN

R^1	R^2	Anion	Product	Yield(%)
Ph	Me	Br^-	6-bromo-	quant.
Ph	Me	SCN^-	6-thiocyanato-	quant.
Ph	Ph	Br^-	6-bromo-	quant.
Ph	Ph	SCN^-	6-thiocyanato-	quant.
CO_2Et	Me	Br^-	5-bromo-	60

In this connection it is of interest to see which position can be brominated by direct bromination of 2,3-disubstituted indoles. The results of bromination in acetic acid in the presence of sodium acetate[44] are summarized in Table 6. These data clearly indicate that the substituent at the 2-position determined the position of bromination: the indoles with the electron-donating group at the 2-position are brominated at the 6-position and ones with the electron-withdrawing group at the 5-position. The nature of the substituent at the 3-position appears to be not so important.

Table 6. Bromination of 2,3-Disubstituted Indoles[44]



R^1	R^2	Position of Bromination	Yield(%)
Ph	Ph	6	90
Ph	Me	6	92
Ph	NO_2	6	59
Ph	COMe	6[a)]	78
Ph	CN	6	75
$-(CH_2)_3-CO-$		6	76
CO_2Et	Me	5	69
CO_2Me	CO_2Me	5	92

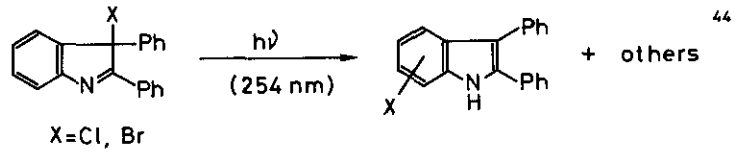
a) The originally assigned structure (5-bromo derivative)* was found to be incorrect[44]; [* G. Buchmann, D. Rosner, J. Prakt. Chem., 1964, 22, 117]

Hino et al.[8] demonstrated that 3-bromoindolenines rearrange to 5- and 6-bromoindoles by heat or acid. The mechanism of this reaction is not studied in detail, but the fact that the position of bromination is in good agreement with that predicted by the general rule described above suggests that the reaction is ionic in nature.

Table 7. Formation of Bromoindoles from 3-Bromoindolenines

R^1	R^2	Conditions	Position of Bromination	Yield(%)	Ref.
SEt	Ph	EtOH-HCl	6	56	8
SEt	Ph	CCl_4, reflux	6	92	8
SO_2Et	Ph	CCl_4, reflux	5	69	8
Br	Ph	AcOH, r.t.	6 + 5	87(6:1)	8
Ph	Ph	$Cl_2CHCHCl_2$,reflux	6	quant.	44
Ph	Ph	AcOH, r.t.	6	quant.	44

3-Haloindolenines also rearranged under photolytic conditions to give 4-, 5-, 6-, and 7-haloindoles with other unidentified products, among which 4- and 7-haloindoles were relatively predominant.[44,45] *A radical mechanism is suggested.*



REFERENCES

1. W.O. Godtfredsen and S. Vangedal, Acta Chem. Scand., 1956, 10, 1414. However, the originally assigned structure was incorrect.
2. J.C. Powers, "The Chemistry of Heterocyclic Compounds", Vol. 25, W.J. Houlihan, Ed., 1972, John Wiley, New York, p. 127.
3. a) N. Finch and W.I. Taylor, J. Am. Chem. Soc., 1962, 84, 1318; ibid., 1962, 84, 3871; b) D. Herlem and F. Khuong-Huu, Tetrahedron, 1979, 35, 633.

4. P.G. Gassman, G.A. Campbell, and G. Mehta, Tetrahedron, 1972, 28, 2749.
5. J.P. Kutney, J. Beck, F. Bylsma, J. Cook, W.J. Cretney, K. Fuji, R. Imhof, and A.M. Treasurywala, Helv. Chim. Acta , 1975, 58, 1690.
6. K.V. Lichman, J. Chem. Soc. C, 1971, 2539.
7. G.S. Omenn, A. Fontana, and C.B. Anfinsen, J. Biol. Chim., 1970, 245, 1895.
8. T. Hino, M. Endo, M. Tonozuka, Y. Hashimoto, and M. Nakagawa, Heterocycles, 1974, 2, 565; Chem. Pharm. Bull. (Tokyo), 1977, 25, 2350.
9. a) M. De Rosa, J. Chem. Soc. Chem. Commun., 1975, 482; b) M. De Rosa and J.L.T. Alonsa, J. Org. Chem., 1978, 43, 2639.
10. R.J. Owellen, J. Org. Chem., 1974, 39, 69.
11. F.M. Hershenson, K.A. Prodan, R.L. Kochman, J.L. Bloss, and C.R. Mackerer, J. Med. Chem., 1977, 20, 1448.
12. L.J. Dolby and G.W. Gribble, J. Org. Chem., 1967, 32, 1391.
13. E. Wenkert, J.S. Bindra, C.-J. Chang, D.W. Cochran, and D.E. Rearick, J. Org. Chem., 1974, 39, 1662.
14. J.-Y. Laronze, J. Laronze, D. Royer, J. Lévy, and J. Le Men, Bull. Soc. Chim. France, 1977, 1215.
15. M.E. Kuehne and R. Hafter, J. Org. Chem., 1978, 43, 3702.
16. H. Zinnes and J. Shavel, Jr., J. Am. Chem. Soc., 1962, 84, 1320; J. Org. Chem., 1966, 31, 1765.
17. A.J. Gaskall, H.-E. Radunz, and E. Winterfeldt, Tetrahedron, 1970, 26, 5353.
18. Y. Tamura, M.W. Chun, H. Nishida, and M. Ikeda, Heterocycles, 1977, 8, 313.
19. T. Hino, H. Miura, T. Nakamura, R. Murata, and M. Nakagawa, Heterocycles, 1975, 3, 805; Chem. Pharm. Bull. (Tokyo), 1978, 26, 3695.
20. A. Walser, J.F. Blount, and R.I. Fryer, J. Org. Chem., 1973, 38, 3077.
21. J.-Y. Laronze, J. Laronze, J. Lévy, and J. Le Men, Tetrahedron Lett., 1974, 491.
22. M.E. Kuehne, D.M. Roland, and R. Hafter, J. Org. Chem., 1978, 43, 3705.
23. M.E. Kuehne, T.H. Matsko, J.C. Bohnert, and C.L. Kirkemo, J. Org. Chem., 1979, 44, 1063.
24. T.-L. Ho, "Hard and Soft Acids and Bases Principle in Orgnic Chemistry", 1977; Academic Press, New York.
25. G.M. Brooke, R.D. Chambers, W.K.R. Musgrave, A.A. Storey, and J. Yeadon, J. Chem. Soc. Perkin I, 1976, 162.

26. M. Ikeda, F. Tabusa, Y. Nishimura, S. Kwon, and Y. Tamura, Tetrahedron Lett., 1976, 2347.

27. Y. Tamura, M.W. Chun, H. Nishida, S. Kwon, and M. Ikeda, Chem. Pharm. Bull. (Tokyo), 1978, 26, 2866.

28. W.I. Taylor, Proc. Chem. Soc., 1962, 247.

29. R.J. Owellen and C.A. Hartke, J. Org. Chem., 1976, 41, 102.

30. Y. Tamura, M.W. Chun, K. Ohno, S. Kwon, and M. Ikeda, Chem. Pharm. Bull. (Tokyo), 1978, 26, 2874.

31. H. Sakakibara and T. Kobayashi, Tetrahedron, 1966, 22, 2475.

32. a) N. Aimi, Y. Asada, S. Tsuge, T. Kohmoto, K. Mogi, and S. Sakai, Heterocycles, 1976, 5, 267; b) N. Aimi, E. Yamanaka, M. Ogawa, T. Kohmoto, K. Mogi, and S. Sakai, Heterocycles, 1978, 10, 73.

33. G. Büchi and R.E. Manning, J. Am. Chem. Soc., 1966, 88, 2532.

34. J.P. Kutney, W.J. Cretney, P.Le Quesne, B. McKague, and E. Piers, J. Am. Chem. Soc., 1966, 88, 4756; ibid., 1970, 92, 1712.

35) a) S. Sakai, A. Kubo, K. Katano, N. Shinma, and K. Sasago, J. Pharm. Soc. Japan, 1973, 93, 1165; b) S. Sakai, E. Yamanaka, and L.J. Dolby, ibid., 1977, 97, 309.

36. S. Sakai and N. Shinma, J. Pharm. Soc. Japan, 1978, 98, 950.

37. N. Neuss, M. Gorman, N. Cone, and L.L. Huckstep, Tetrahedron Lett., 1968, 783.

38. J.P. Kutney, J. Beck, F.B. Bysma, and W.J. Cretney, J. Am. Chem. Soc., 1968, 90, 4504.

39. J.P. Kutney, J. Cook, K. Fuji, A.M. Treasurywala, J. Clardy, J. Fayos, and H. Wright, Heterocycles, 1975, 3, 205.

40. M. Ono, T.S. Stande, and B. Witkop, J. Am. Chem. Soc., 1968, 90, 6521; ibid., 1970, 92, 343.

41. M. Ikeda, K. Ohno, M. Katsura, M.W. Chun, and Y. Tamura, J. Chem. Soc. Perkin I, 1979, 3061.

42. J.P. Kutney and F.B. Bylsma, J. Am. Chem. Soc., 1970, 92, 6090; Helv. Chim. Acta, 1975, 58, 1672.

43. Y. Tamura, S. Kwon, M.W. Chun, and M. Ikeda, J. Heterocyclic Chem., 1978, 15, 425.

44. Y. Tamura, H. Nishida, T. Uno, and M. Ikeda, unpublished data.

45. C. Kaneko, R. Kitamura, A. Yamamoto, H. Fujii, and M. Somei, Abstracts of the 10th Congress of Heterocyclic Chemistry, Tsukuba, Japan, 1976, p. 26.

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