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The Fragmentation of Some Oxindoles and 2-Indolinethiones induced by Electron Impact

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Fragmentation of methyl substituted oxindoles (I—V) and 2-indolinethiones (VI—X) induced by electron impact were investigated. Main fragments of the oxindoles are M-Me, M-CO, and M-HCO. M-1, M-S and M-SH are main fragments in the indolinethiones and M-CS is observed as a minor fragment.

Fragmentation of 1,1′-dimethyl-3,3′-bioxindole and its thione derivative are also discussed.

Mass spectra of the indole alkaloids have been widely utilized for the elucidation of their structures and for their identifications.[2] And the fragmentation of simple indole derivatives induced by electron impact has discussed by several workers.[3] The fragmentation of the simple oxindoles, however, had not been discussed until recently Powers,[3b] and Hodges[3c] have reported the mass spectra of a few oxindoles derivatives. During course of the study on the 2-indolinethione,[4] we have prepared methyl substituted 2-indolinethiones as well as the corresponding oxindoles. In the present paper we describe the fragmentation of the oxindoles and the 2-indolinethiones induced by electron impact.

Oxindoles

Mass spectra of the oxindole are shown in Fig. 1. The molecular ion peaks of all oxindoles are the base

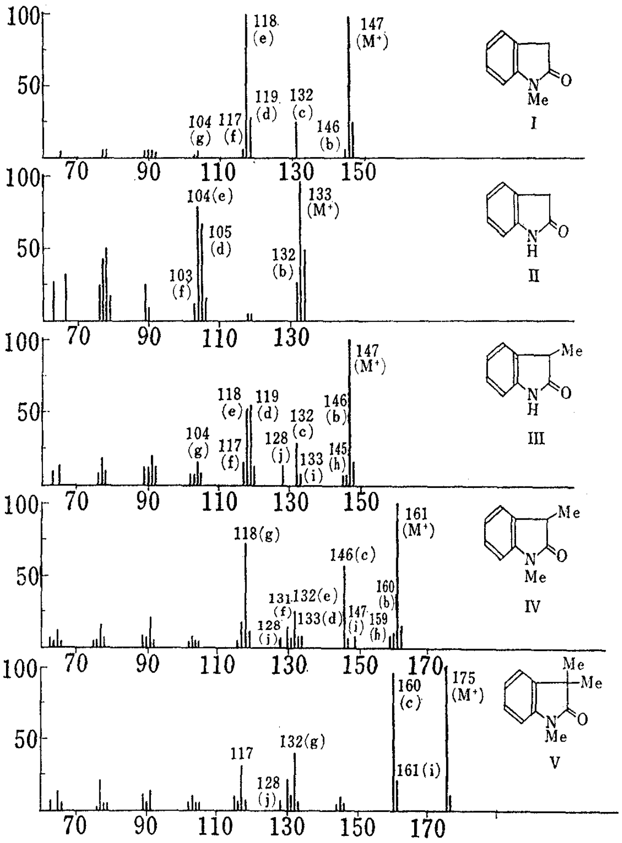

Fig. 1

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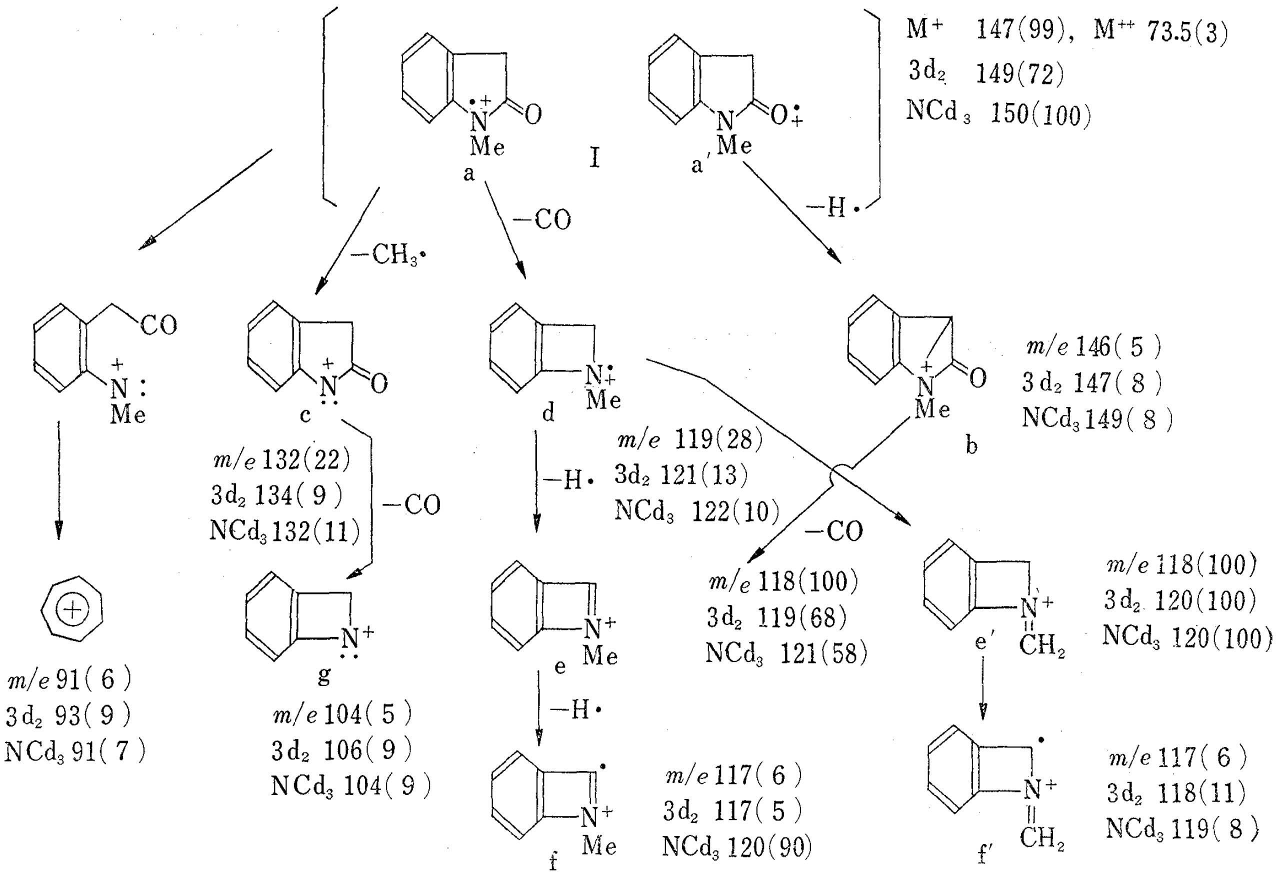
[1] Location: *a*) *Yayoi-cho, Chiba*; *b*) *Anagawa 4-Chome, Chiba.*

[2] H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Structural Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Holden-Day Inc., San Francisco, 1964.

[3] *a*) H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day Inc., San Francisco, 1967, p. 610; *b*) J.C. Powers, *J. Org. Chem.*, **33**, 2044 (1968); *c*) R. Hodges, J.S. Shannon, W.D. Tamieson, and A. Taylor, *Can. J. Chem.*, **46**, 2189 (1968).

[4] T. Hino, K. Yamada, and S. Akaboshi, *Chem. Ind.* (London), **1967**, 275; T. Hino, K. Tsuneoka, M. Nakagawa, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **17**, 550 (1969).



m/e (relative abundance)

Chart 1

peak or the next to that, and may be represented by Ia or Ia′ as in cases of simple lactams.[5] Doubly charged molecular ion peaks are clearly observed due to odd number in the molecular mass.

To interprete the genesis of principal fragments of N-methyloxindole, 3,3-d_2-N-methyloxindole and N-d_3-methyloxindole were prepared by the known method. The fragmentation pattern of N-methyloxindole and its deuterated compounds are shown in Chart 1. The fragment of mass 146 (M-1) in N-methyloxindole shifted to *m/e* 147 in 3,3-d_2-compound and to *m/e* 149 in N-d_3-compound. No loss of deuterium in N-d_3-methyloxindole suggested that

Table I. Main Fragments of Oxindoles (*m/e* (Relative Abundance, %))

Compound	M+ a	M-1 b	M-15 (M-Me) c	M-28 (M-CO) d	M-29 (M-HCO) e	M-30 (M-(2H+CO)) f	M-43 (M-(Me+CO)) g
I	147 (99)	146 (5)	132 (22)	119 (28)	118 (100)	117 (6)	104 (5)
II	133 (100)	132 (26)	— —	105 (68)	104 (76)	103 (12)	— —
III	147 (100)	146 (8)	132 (28)	119 (56)	118 (52)	117 (16)	104 (16)
IV	161 (100)	160 (9)	146 (57)	133 (7)	132 (25)	131 (7)	118 (71)
V	175 (100)	— —	160 (96)	— —	— —	— —	132 (41)

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[5] A.M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 5536 (1964).

the ion may be represented by Ib. The structure (Ib) was further supported by the finding that no M-1 peak was observed in 1,3,3-trimethyloxindole. The fragment at *m/e* 132 (M-15) shifted to 134 in 3,3-d_2-compound and remained unchanged in N-d_3-compound, and may be assigned structure Ic. The ion at *m/e* 119 (M-28) may arise from a loss of carbon monoxide from Ia, corresponding to Id, since the elimination of ethylene observed in N-methylpyrrolidone[5] is impossible in the oxindole. The base peak at *m/e* 118 (M-29) shifted to *m/e* 119 and 120 in 3,3-d_2-compound to *m/e* 120 and 121 in N-d_3-compound and may be represented by Ie or Ie′ produced by the loss of carbon monoxide from Ib or a loss of a hydrogen from Id. A metastable peak was observed at about *m/e* 96 which shifted to 98 in 3,3-d_2-compound and to 99 in N-d_3-compound, and correspond to Ia→Id (calcd. 96.3) and Ib→Ie (calcd. 95.4). Probable structures of other fragments of N-methyloxindole are shown in Chart 1.

The main fragments of other oxindole which were rationalized in N-methyloxindole are shown in Table I. The relative abundance of M-Me peak is increased with increasing methyl groups as expected. Thus (M-CO) ion (d) was not observed in 1,3,3-trimethyloxindole, but (M-(Me+CO)) (g) and M-(2×Me+CO) (*m/e* 117) peaks were predominant.

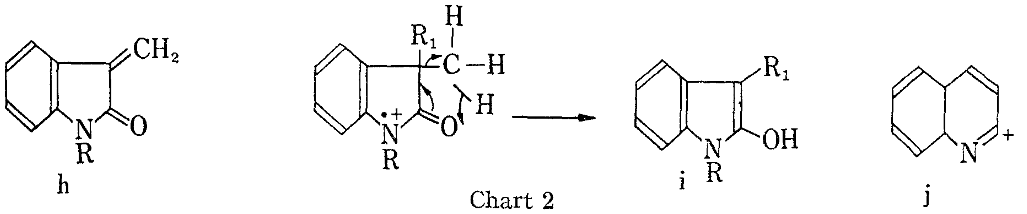

Chart 2

It is interesting to note that there are characteristic fragmentation which were not observed in N-methyloxindole but derived from the participation of 3-methyl group of III and IV. The loss of two hydrogens from the molecular ion was observed in III and IV having a methyl group at 3-position, may represented by structure h in Chart 2. The fragment of (M-14) which was observed in V as a prominent peak and in III and IV as amall peaks, may be assigned the structure i. A fragment at *m/e* 128 observed in III, IV and V may represented by j.

2-Indolinethiones

Lawrence and Waight[6] recently reported the fragmentation of 2-pyridones and 2-pyridthiones. The loss of carbon monosulfide from 2-pyridthione corresponding to the loss of carbon monoxide from 2-pyridones was observed. The important fragments in the 2-pyridthione are ions such as (M-SH) and (M-(H+HCN)).

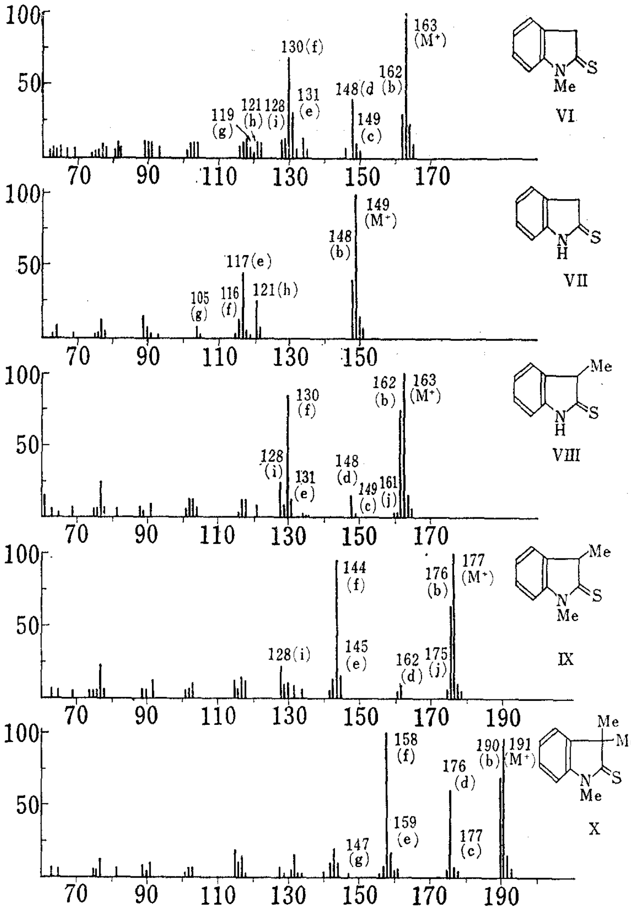

Fig. 2

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[6] R. Rawrence and E.S. Waight, *J. Chem. Soc.* (*B*), **1968, 1.**

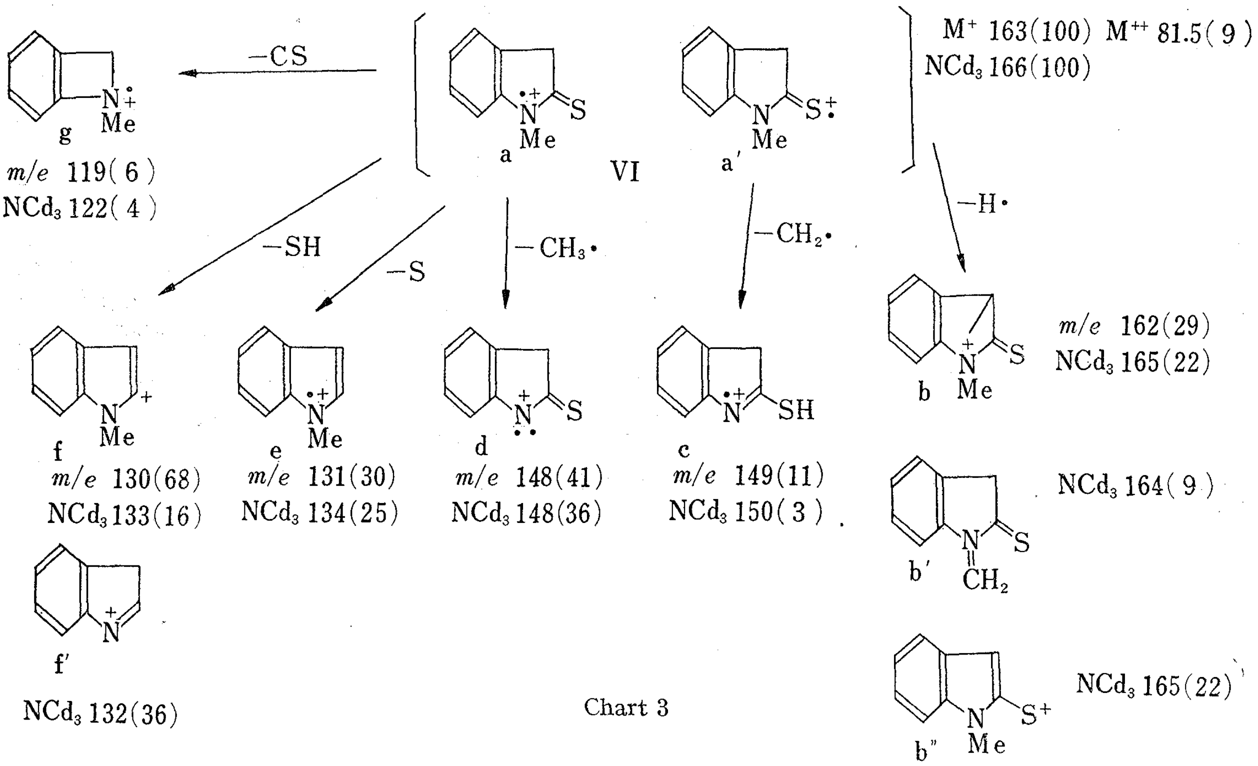


Chart 3

m/e (relative abundance)

The mass spectra of 2-indolinethiones are shown in Fig. 2 Fragmentation pattern of VI and N-d_3-compound are shown in Chart 3. The base peak in N-methyl-2-indolinthione (VI) is molecular ion (*m/e* 163) (a or a′) and its doubly charge ion (*m/e* 81.5) is recognized also. The fragment of *m/e* 162 (M-1) shifted to 164 and 165 in NCd_3-compound and represented by b,b′ and b″. This fact indicated that the loss of a hydrogen from N-methyl group which was not observed in oxygen analogue (I), may occur as a minor fragmentation. This was supported by the presence of the M-1 peak in X, which was not recognized in the oxygen analogue (V). The ion at *m/e* 149 (M-14) shifted partially to 150 in N-d_3-compound may be assigned structure c in which a hydrogen of SH group is partially derived from N-methyl group. The fragment at *m/e* 148 (M-15) mostly remained unchanged in NCd_3-compound may be represented by d. The fragment at *m/e* 131 (M-32) shifted to 134 in NCd_3-compound suggested a loss of a sulfur atom (e). The fragment at *m/e* 130 (M-33) (f or f′) shifted to 132 and 133 and indicated that a hydrogen of SH eliminated is largely derived from N-methyl group as shown in Chart 4. Metastable peaks for M^+- (M-S) (calcd. 105.3), and M^+- (M-SH) (calcd. 103.7) were

TABLE II. Main Fragments of 2-Indolinethiones (*m/e* (Relative Abundance, %))

Compound	M+ a	M-1 b	M-14 c	M-15 (M-Me) d	M-32 (M-S) e	M-33 (M-SH) f	M-44 (M-CS) g
VI	163 (100)	162 (29)	149 (11)	148 (41)	131 (30)	130 (68)	119 (6)
VII	149 (100)	148 (39)	— —	— —	117 (45)	116 (12)	105 (3)
VIII	163 (100)	162 (64)	149 (3)	148 (15)	131 (13)	130 (85)	119 (2)
IX	177 (100)	176 (64)	163 —	162 (10)	145 (15)	144 (93)	133 (2)
X	191 (95)	190 (70)	177 (7)	176 (60)	159 (18)	158 (100)	147 (3)

observed as a broad peak centered at *m/e* 103. The loss of carbon monosulfide (M-44) was recognized as a small peak.

The main fragmentation of other 2-indolinethiones are summarized in Table II. When the relative abundance of M-S peak was compared with that of M-SH peak, the latter peak was more intense than M-S peak except VI. This might indicate that a hydrogen of SH is derived from 3-methyl group as well as N-methyl group by the sequence shown in Chart 4.

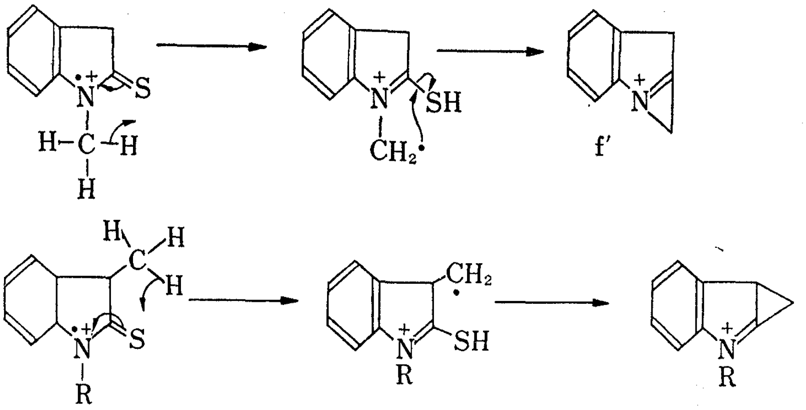
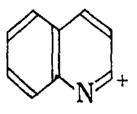
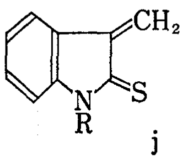


Chart 4



i



j

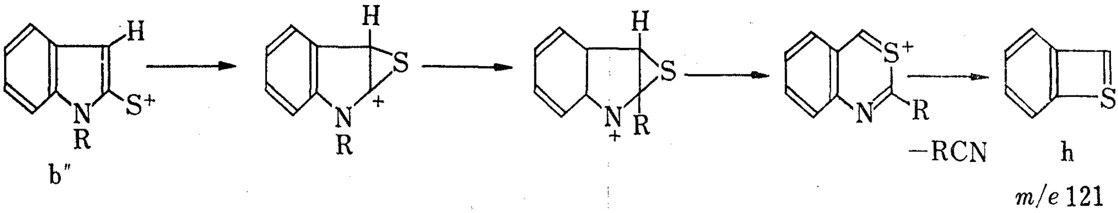


Chart 5

It may be valuable to note that some fragmentation in specific compound. The fragment at *m/e* 121 in VI (M-(H+CH_3CN)) and VII (M-(H+HCN)) might be assigned the structure h which was produced from the M-1 ion *via* benzothiazinium ion (Chart 5). The fragment at *m/e* 128 in VI,VIII and IX, may be represented by i. The fragment of M-2 peak in VIII and IX may be formulated as j.

Thus the characteristic fragmentation of the oxindole and the 2-indolinethione can be represented by loss of CO or HCO in the oxindole and S or SH in the 2-indolinethione. Facile elimination of SH in 2-indolinethione is further demonstrated in 1,3,3-trimethyl-2-indolinethione in which M-SH peak is more intense than M-Me peak though M-CO peak is not recognized in 1,3,3-trimethyloxindole due to easier elimination of the methyl group.

Bioxindole and Bis-2-indolinethione

The characteristic feature of the fragmentatiion of the oxindole and 2-indolinethione was further demonstrated in bioxindole and bis-2-indolinethione. The plausible fragmentation of N,N-dimethyl-3,3′-bioxindole and N,N-dimethyl-3,3′-bis(2-indolinethione) are shown in Chart 6 and 7.

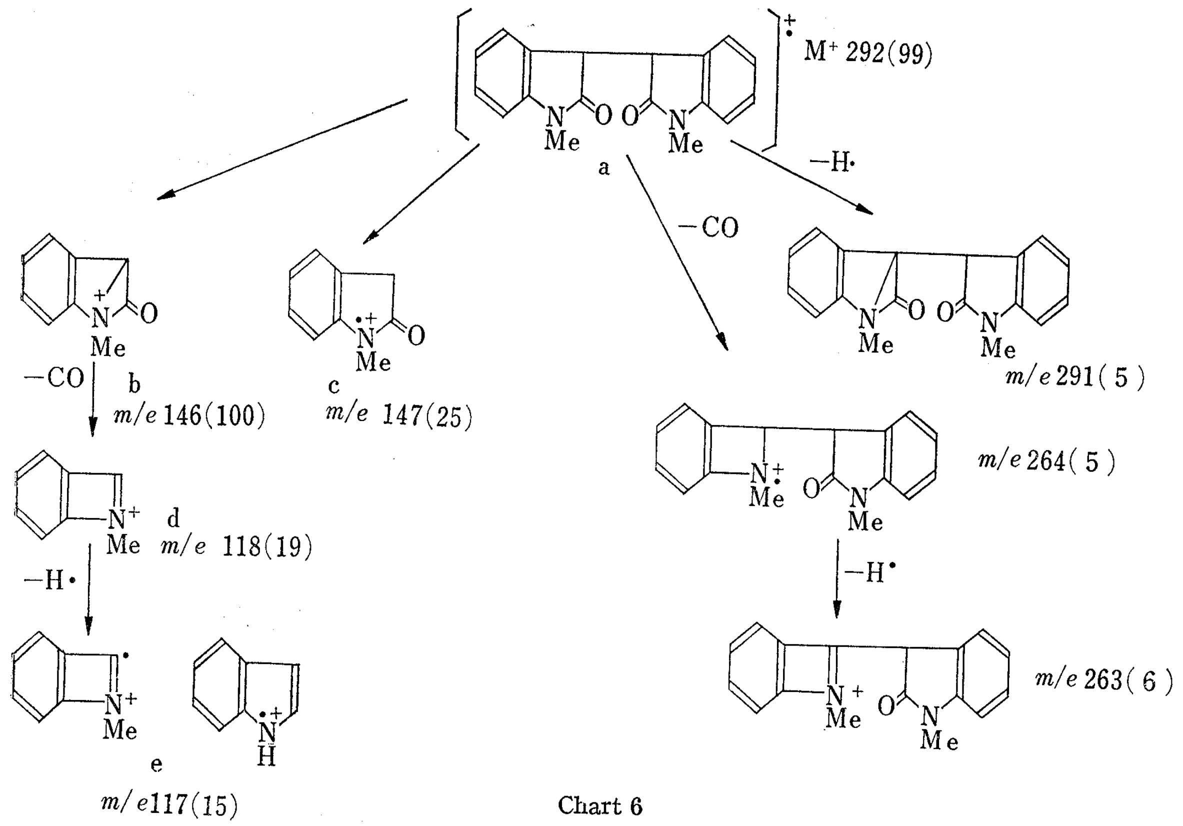


Chart 6

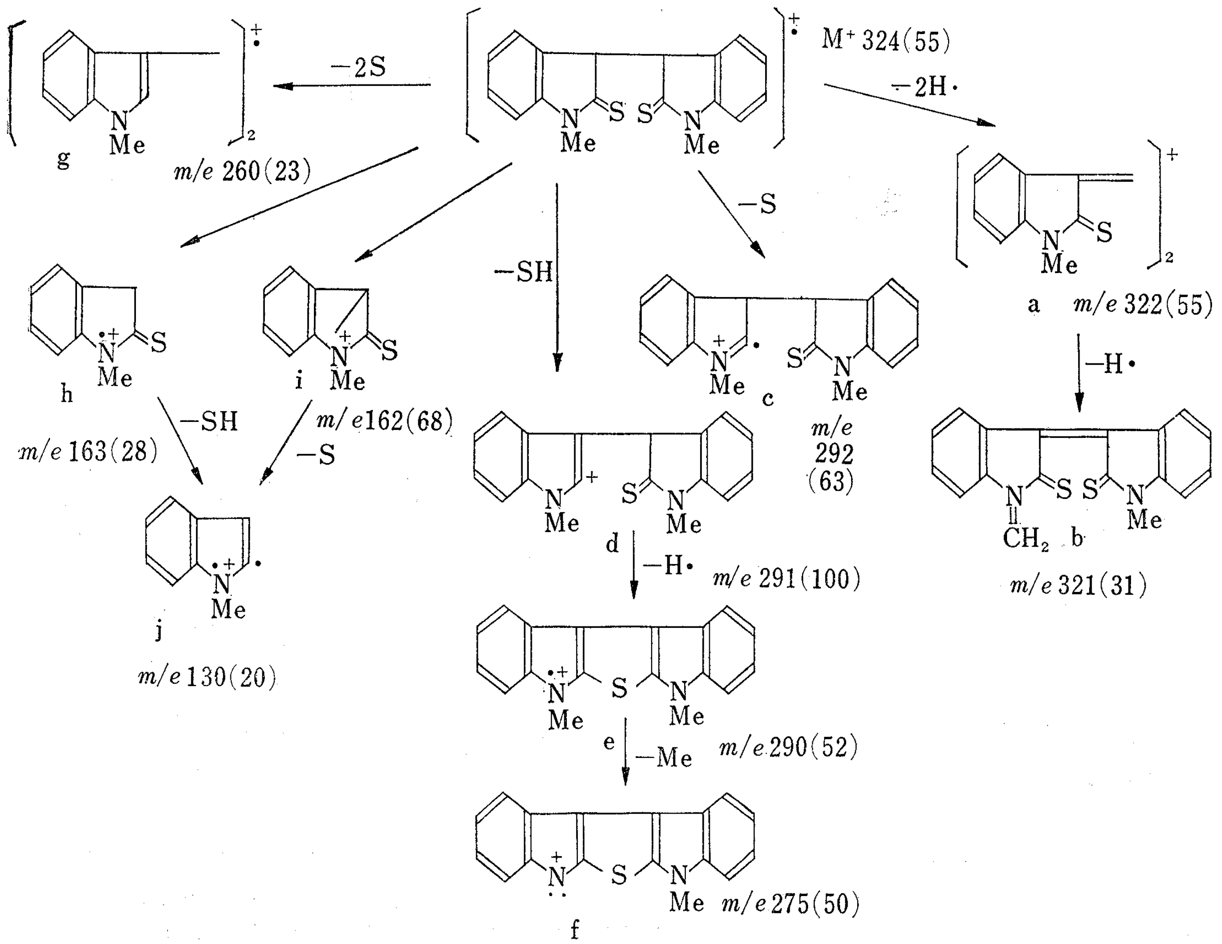
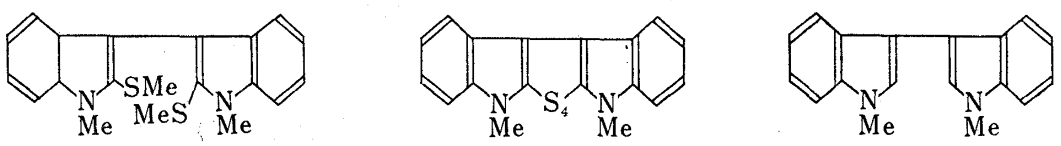


Chart 7

In the bioxindole molecular ion peak was very intense as the base peak, and M-1, M-CO and M-HCO peaks were observed as small peaks. Main fragments of the bioxindole were monomeric fragments such as b, c, d and e which derived from the removal of a oxindole ring from the molecular ion.



XI XII XIII

Chart 8

On the other hand the molecular ion peak was not so strong in bis-indolinethione but ions of M-S and M-SH were the base peak and the second from the base peak. Although monomeric fragments such as h, i, and j were recongnized, ions of M-2H(a), M-3H(b), M-S (c) and M-SH(d) were observed as prominent peaks. Fragments of *m/e* 290 and 275 may be represented by the structure of thienobiindole (e and f). The same fragments (*m/e* 290 and 275) are observed in the mass spectra of 2,2′-bis(methylthio)-N,N-dimethyl-,3,3′-biindole (XI) and N,N-dimethyl-3,3′-biindole-2,2′-tetrasulfide (XII) as main fragments. These results may indicate that the loss of S or SH from 2-indolinethione is more facile than that of CO or HCO from oxindole as already described in the case of 1,3,3-trimethyl derivatives. Mass spectrum of the bis-indolinethione by the heated inlet system did not show the molecular ion peak, and the major fragments corresponded to those of the mixture of XII,VI and N,N′-dimethylbiindole (XIII). Since the bis-2-indolinethione decomposed to XII,VI and XIII in boiling xylene,[4] the same decomposition occured in the heated inlet system.

Experimental

The mass spectra were measured with a Hitachi RMU-6E instrument using an ionizing energy of 70 eV. The heated inlet system was used for oxindoles and 2-indolinethiones and the direct inlet system was used for bioxindole and bis-2-indolinethione.

3,3-d_2-N-Methyloxindole——A mixture of 100 mg of N-methyloxindole and 100 mg of K_2CO_3 in 4 ml of D_2O was refluxed for 1.5 hr. On cooling separated crystals were collected and dried. Recrystallization from hexane gave colorless needles. Its NMR spectrum in $CDCl_3$ showed 90% of the two hydrogens at 3-position was deuterated.

NCd_3-Methyloxindole——A mixture of 600 mg of oxindole, 800 mg of CD_3I and 1.0 g of K_2CO_3 in 50 ml of dry acetone was refluxed for 2 hr with stirring. The whole mixture was stirred overnight at room temperature. The mixture was filtered and washed with acetone. The filtrate and the washings were combined and evaporated *in vacuo* to leave a brown semi-solid, which was extracted with benzene. The benzene extracts were washed with 1N NaOH four times to remove the starting material, and washed with H_2O and dried. The benzene was evaporated *in vacuo* to leave 240 mg of crystals which was recrystallized from hexane twice to give NCd_3-methyloxindole, mp 86—88°. Its NMR spectrum in $CDCl_3$ showed a singlet at 3.48 δ for 3-methylene group and no signal for N-methyl or NH was observed.

NCd_3-Methyl-2-indolinethione——A mixture of 360 mg of NCd_3-methyloxindole, 130 mg of P_2S_5, and 200 mg of K_2S in 5 ml of benzene was refluxed for 1 hr with stirring. The mixture was evaporated *in vacuo* to leave a solid which was extracted with benzene. The extracts were evaporated *in vacuo* to leave 350 mg of solid which was chromatographed over silica gel. Elution with hexane–benzene (1:3) gave 270 mg of crude NCd_3-methyl-2-indolinethione. Recrystallizations from benzene–hexane gave NCd_3-methyl-2-indolinethione, mp 108—109°, which showed a sole spot on TLC. Its NMR spectrum in $CDCl_3$ showed a singlet at 4.09 δ for 3-methylene group and no signal for N-methyl group.

Mass Spectrum of N,N′-Dimethyl-3,3′-bioxindole——(direct inlet system), *m/e* (relativeabu ndance), 293 (23), 292 (99, M^+), 291 (5), 263 (6), 249 (2), 248 (2), 247 (3), 234 (3), 219 (4), 204 (3), 190 (3), 165 (3), 147 (25, c), 146 (100, b), 119 (3), 118 (19, d), 117 (15, e), 92 (3), 91 (35), 90 (7), 89 (7), 77 (8), 65 (7).

Mass Spectrum of N,N′-Dimethyl-3,3′-bis-(2-indolinethione)——*m/e* (relative abundance), i) by direct inlet system: 326 (8), 325 (15), 324 (55, M^+), 323 (18), 322 (55, a), 321 (31, b), 307 (15), 294 (6), 293 (21), 292 (63, c), 291 (100, d), 290 (52, e), 289 (13), 288 (6), 278 (6), 277 (16), 276 (28), 275 (50, f), 274 (11), 273 (6), 262 (6), 261 (12), 260 (23), 259 (13), 258 (7), 257 (6), 250 (11), 247 (5), 246 (7), 245 (6), 243 (5), 242 (5), 233 (5), 229 (5), 218 (6), 217 (5), 216 (6), 215 (5), 203 (5), 201 (6), 190 (8), 189 (5), 176 (5), 175 (5), 164 (9), 163 (28, h), 162 (68, i), 161 (8), 160 (5), 148 (5), 146 (7), 145 (11), 138 (6), 131 (7), 130 (20, j), 129 (14), 128 (21), 118 (25), 117 (17), 103 (5), 102 (6), 91 (13), 90 (5), 89 (10), 77 (9).

ii) by heated inlet system: *m/e* (over 10% relative abundance), 306 (13), 292 (14), 291 (43), 290 (93), 277 (11), 276 (21), 275 (99), 261 (31), 260 (100), 259 (11), 246 (12), 245 (278), 190 (10), 164 (14), 163 (51), 161 (13), 149 (13), 148 (14), 145 (14), 131 (13), 130 (42), 121 (10), 118 (11), 117 (10).

Mass Spectrum of XI——(heated inlet system), *m/e* (relative abundance), 354 (10), 353 (22), 352 (89, M^+), 292 (10), 290 (100), 276 (13), 275 (56), 274 (5), 260 (11), 176 (7), 152 (5), 145 (20), 137.5 (7).

Mass Spectrum of XII——(direct inlet system), *m/e* (relative abundance), 386 (1.6, M^+), 321 (16), 320 (6), 291 (12), 290 (100), 276 (9), 275 (94), 260 (14), 155 (6), 145 (10), 141 (22), 77 (5), 64 (14), 57 (8), 55 (8).

Mass Spectrum of XIII——(heated inlet system), *m/e* (relative abundance), 261 (20), 260 (100, M^+), 259 (6), 246 (6), 245 (28), 243 (6), 229 (6), 203 (6), 130 (7), 129 (9), 122 (14), 121.5 (8), 115 (7), 108.5 (8), 78 (6), 77 (6), 51 (5).