[Chem. Pharm. Bull. 20(1) 76 — 81 (1972)]

UDC 547.751.04 : 546.23.04

Oxidation of 2,3-Disubstituted Indole Derivatives with Selenium Dioxide

Shin-ichiro Sakai, Akinori Kubo, Kimio Katsuura, Kyoko Mochinaga and Mayumi Ezaki

Faculty of Pharmaceutical Sciences, Chiba University[1]

(Received June 4, 1971)

The action of selenium dioxide on several 2,3-disubstituted indole derivatives was found to give the corresponding 2-acylindoles as shown in Table I. In the case of tricyclic amides, (VI and VII), this oxidation reaction resulted in the formation of α-vinylindoles and organoselenium compounds. On the basis of these products, the mechanism of the oxidation with selenium dioxide is discussed.

Many oxidation reactions of indole derivatives have been studied, for example, the oxidations with air,[2] *t*-butylhypochlorite,[3] lead tetraacetate,[3] or periodic acid.[4] Furthermore, it was recently reported that a reaction of indole derivatives with selenium dioxide gave organoselenium compounds,[5] as shown in Chart 1. But to date no result has been reported regarding the oxidation of 2,3-disubstituted indole derivatives with this reagent.

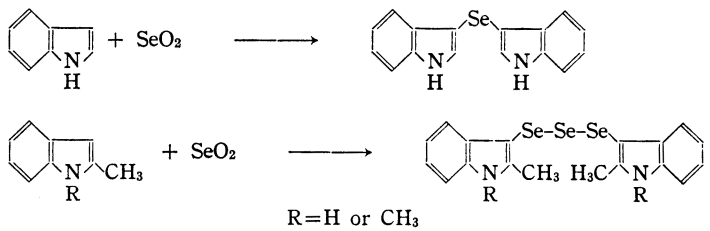

Chart 1

We have found that 2,3-disubstituted indole derivatives on similar oxidation with selenium dioxide gave no selenium compounds and that the major products were 2-acylindoles as shown in Table I. A similar selective oxidation of 2-alkylated indole derivatives to 2-acylindoles using periodic acid has been reported by Dolby and Booth.[4]

Table I[a]

Starting material	Product (%, yield)
2,3-Dimethylindole	2-formyl-3-methylindole (22), unknown compound (I) (2) 3-methylindole-2-carboxylic acid (7)
1,2,3,4-Tetrahydrocarbazole	1-ketotetrahydrocarbazole (44)
N-Methyl-1,2,3,4-tetrahydrocarbazole	N-methyl-1-keto-1,2,3,4-tetrahydrocarbazole(24) N-methylcarbazole (16), unknown selenium compound (4)

a) reaction conditions: ethyl acetate at 50° for 4 hr

1) Locatin: *1-Yayoi cho, Chiba.*
2) H.H. Wasserman and M.B. Floyd, *Tetrahedron Letters*, **29**, 2009 (1963); F. Ying-Hsiuch Chen and E. Leete, *Tetrahedron Letters*, **29**, 2013 (1963).
3) N. Finch and W.I. Taylor, *J. Am. Chem. Soc.*, **84**, 3871 (1962).
4) L.J. Dolby and D. Booth, *J. Am. Chem. Soc.*, **88**, 1050 (1966).
5) J.F.K. Wilshire, *Aust. J. Chem.*, **20**, 359 (1967).

The structure of a minor product, mp 192—196° (I), shown in Table I, was deduced to be 5,6,11b,12-tetrahydro-11b,13-dimethyl-pyrido[1,2-*a*: 5,4-*b'*]di-indole-6-one from the following spectral data. The infrared (IR) spectrum of this compound (I) showed $\nu_{C=O}$1695 cm^{-1} and no $\nu_{OH\ or\ NH}$ band in $CHCl_3$. The nuclear magnetic resonance (NMR) spectrum of I showed peaks at 6.45 τ (doublet, J=15 Hz, 1H), 7.50 τ (doublet, J=15 Hz, 1H) [by decoupling, these signals (AB type) were firmly assigned to the hydrogens at C_{12}], 7.75 τ (singlet, methyl group at C_{13}, 3H) and 8.63 τ (singlet, methyl group at C_{11b}, 3H).

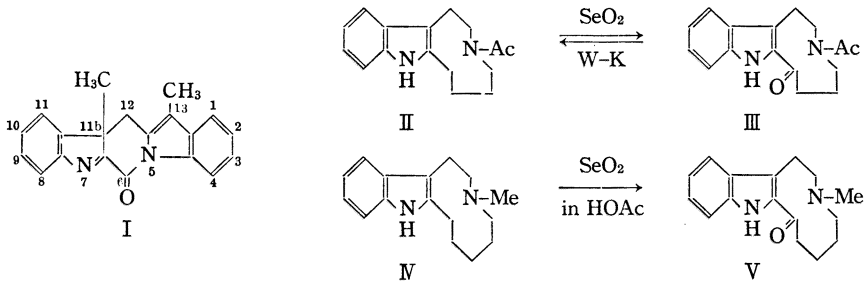

Chart 2

Under the same oxidation conditions, 4-acetyl-4,11b-seco-2,3,5,6,11,11b-hexahydro-1H-indolo[3,2-*g*]indolizine (II), synthesized from 4-acetyl-4,11b-seco-2,3,5,6,11,11b-hexahydro-1H-indolo[3,1-*g*]indolizine-11b-one (III)[6] by Wolff–Kishner reduction, was oxidized to the tricyclic ketone(III). In the case of 5-methyl-5,12b-seco-1,2,3,4,6,7,12,12b-octahydroindolo[2,-3-*a*] quinolizine (IV), its selenium salt gradually precipitated from the reaction mixture and the starting material (IV) was recovered unchanged. Under acidic conditions in 80% aqueous acetic acid with SeO_2 at 110—120°, the tricyclic base (IV) was oxidized into the tricyclic ketone (V), 5-methyl-5,12b-seco-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-12b-one in low yield (11%). This tricyclic ketone (V) was identified by comparison with an authentic sample.[7]

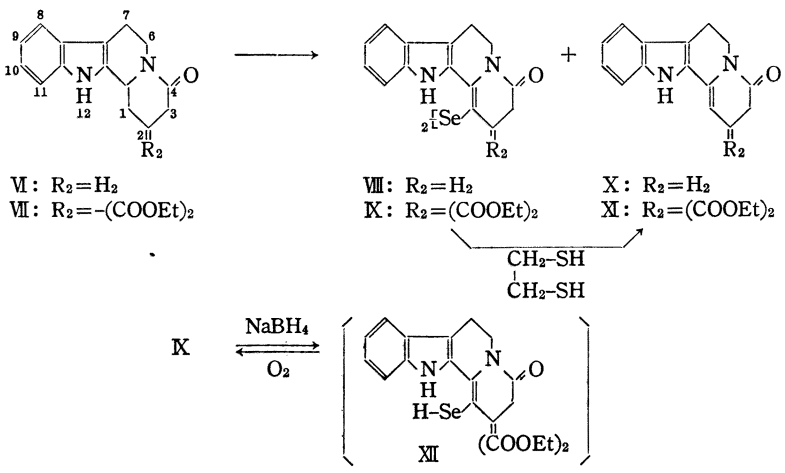

Chart 3

6) J. Harley-Mason, *Chem. Commun.*, **1967**, 21.
7) L.J. Dolby and G.W. Gribble, *J. Org. Chem.*, **32**, 1391 (1967). We are indebted to Professor Lloyd J. Dolby, University of Oregon, for providing us an authentic sample of V.

TABLE II. The NMR Spectral Data of the Tetracyclic Lactams[a)]

Compound	12 (NH)	1 (=CH-)	2 (CH_2)	3 (CH_2)	6 (CH_2)	7 (CH_2)
IX	−0.97[b)]	—	—	6.72 (s)	—	—
XI	1.47[c)]	4.25 (s)[c)]	—	6.90 (s)	5.95 (t)	7.11 (t)
VIII	−0.14[b)]	—	7.10 (m)	7.60 (m)	6.22 (t)[d)]	7.45 (m)[d)]
X	1.85[c)]	4.51 (t)[c,e)]	7.55 (m)[e)]	7.45 (m)	5.91 (t)	7.10 (t)

a) τ-value of H on the ring carbon numbered
b) not exchanged with D_2O,
c) exchanged with D_2O,
d, *e*) each of two peaks were detected by the decoupling method

When this method was applied to non-basic tetracyclic compounds such as 1,2,3,4,6,7,-12,12b-octahydroindolo[2,3-*a*]quinolizine-4-one (VI) and 2,2-diethoxycarbonyl-1,2,3,4,6,7,12,-12b-octahydroindolo[2,3-*a*]quinolizine-4-one (VII),[8)] selenium derivatives were obtained. Thus the compound (VI) gave rise to 1,1'-diseleno-bis-[2,3,4,6,7,12-hexahydroindolo[2,3-*a*]-quinolizine-4-one] (VIII). Similarly, the compound (VII) afforded the corresponding selenium compound 1,1'-diseleno-bis-[2,2-diethoxycarbonyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]-quinolizine-4-one] (IX) as well as the oxidation product, 2,2-diethoxycarbonyl-2,3,4,6,7,-12-hexahydroindolo[2,3-*a*]quinolizine-4-one (XI). Selenium derivatives, (VIII) and (IX), were characterized by their NMR spectra (Table II), and by molecular weight determinations. These compounds were reduced to the corresponding non-selenium compounds, 2,3,4,6,7,-12-hexahydroindolo[2,3-*a*]quinolizine-4-ones, (X and XI), by the action of 1,2-ethanedithiol. Very interestingly, selenium compound (IX) was reduced to 1-hydroseleno-2,2-diethoxycarbonyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine-4-one (XII) with $NaBH_4$ in methanol solution. Thus, by addition of the reagent, the red reaction mixture was decolored and became homogeneous within half an hour and after a few hours the red crystalline starting material (IX) was deposited. The decolored solution showed the same ultraviolet (UV) spectrum as that of non-selenium compound (XI). This observation can be reasonably explained if one considers $NaBH_4$ reduction and air oxidation reaction taking place between the compounds (IX) and (XII) as shown in Chart 3.

The lactam (XI) was reduced to the starting lactam (VII) by catalytic hydrogenation with palladium on carbon. By $Pb(OAc)_4$ oxidation,[9)] the tetracyclic lactam (VI) gave rise to the expected product, 7a-acetoxy-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-*a*]quinolizine-4-one (XIII), which then rearranged easily to the vinyl lactam (X) in an acetic acid medium as shown in Chart 4.

In order to elucidate the mechanism of the selenium dioxide oxidation, the tetracyclic vinyl lactam (XI) was again subjected to the oxidation reaction with selenium dioxide under the same conditions. Though reaction was obviously very slow, in the presence of large excess of selenium dioxide and after a prolonged reaction time (23 hr), organoselenium compound (IX) was obtained in 34% yield.

Generally, indole derivatives suffer initial oxidation at the β-position to the nitrogen atom with reagents such as $Pb(OAc)_4$ and *t*-BuOCl. Thus, the indole alkaloid, gardnerine (XIV) was easily oxidized to indolenine ether (XV) with *t*-BuOCl or by Jones oxidation.[10)] However the same alkaloid was recovered unchanged from the oxidation with selenium dioxide (Chart 5). Considering the above results together with the fact that α-picoline gives rise to α-picolylaldehyde on selenium dioxide oxidation,[11)] the mechanism shown in Chart 6

8) S. Sakai, A. Kubo, T. Hamamoto and C. Ueda, *Yakugaku Zasshi*, **86**, 760 (1966).
9) The results of this oxidation and a subsequent rearrangement reaction will be published in another paper.
10) S. Sakai, A. Kubo and J. Haginiwa, *Tetrahedron Letters*, **1969**, 1485.
11) M. Henze, *Chem. Ber.*, **67**, 750 (1934); W. Borsche and H. Hartmann, *Chem. Ber.*, **73**, 839 (1940).

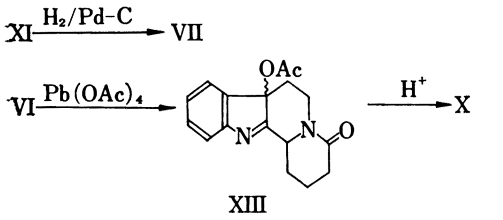

Chart 4

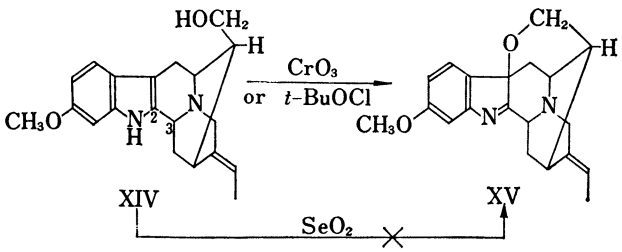

Chart 5

can be proposed for the present reactions. The inertness of gardnerine (XIV) to the oxidation may be due to the impossibility of intermediary formation of C_2-C_3 double bond, which is ruled out by Bredt's rule.

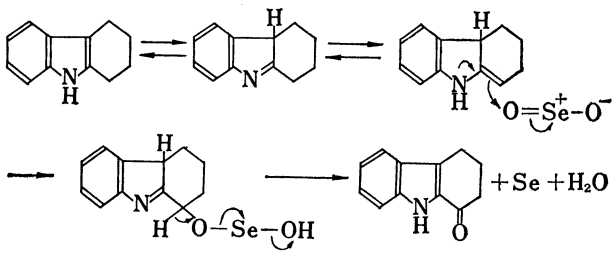

Chart 6

The tetracyclic lactams (VI and VII) gave rise to the vinyl lactams (X and XI), respectively, *via* the corresponding enamine intermediates, and selenium (II) oxide, formed during the reaction, may attack each species to give organoselenium derivatives (VIII and IX) in a manner similar to the oxidation of olefins with selenium dioxide[12] (Chart 7).

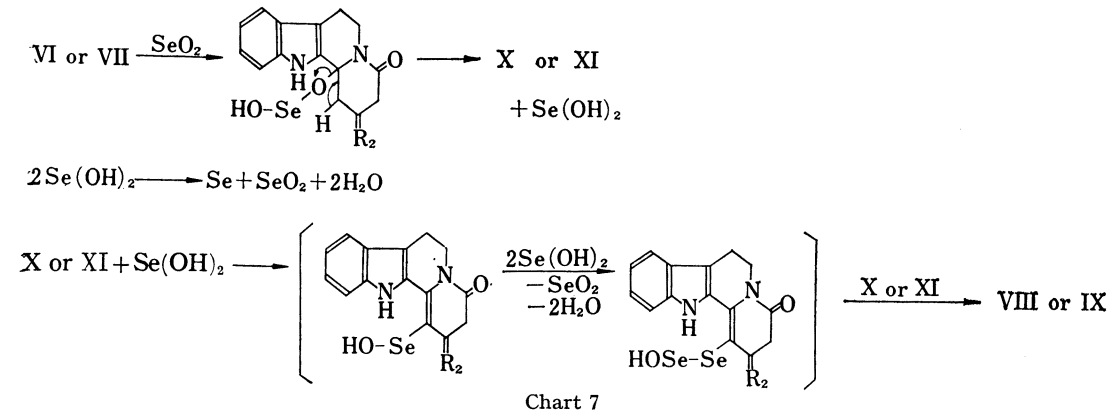

Chart 7

Experimental

Melting points are uncorrected. UV spectra were measured in methanol solutions using a Hitachi EPS-3T spectrophotometer and IR spectra were determined with a Hitachi EPI-G31 spectrophotometer. NMR spectra were measured on a JEOL HA-100 spectrometer. Chemical shifts are reported as τ-value with tetramethylsilane as internal standard. Deuteriochloroform was used as solvent and the abbreviations of (s), (d), (t) and (m) show singlet, doublet, triplet and multiplet signals respectively. Mass spectra were measured with a Hitachi RMU-7 mass spectrometer.

4-Acetyl-4,11b-seco-2,3,5,6,11,11b-hexahydro(1H)indolo[3,2-*g*]indolizine (II)——A mixture of 150 mg of tricyclic ketone (III), 1.35 g of potassium hydroxide and 4.5 ml of 100% hydrazine hydrate in 12 ml of diethylene glycol was heated at 180° for 3 hr under nitrogen. The cooled solution was diluted with 4 volumes

12) E.J. Corey and J.P. Schaefer, *J. Am. Chem. Soc.*, **82**, 918 (1960); J.P. Schaefer, *J. Am. Chem. Soc.*, **84**, 713, 717 (1962); J.L. Hugnet, "Oxidation of Organic Compound," Vol II., ed. by F.R. Mayo, Advances in Chemistry Series 76, *Am. Chem. Soc.*, Washington, D.C., 1968, p. 345.

of water and extracted with ether. A residue from ether solution was purified by Al_2O_3 column chromatography to give II: mp 189—190° (from ether and *n*-hexane), 71 mg (49%). *Anal.* Calcd. for $C_{16}H_{20}ON_2$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.89; H, 7.99; N, 10.89.

Oxidation of 2,3-Dimethylindole with SeO_2——Selenium dioxide (614 mg, 5.5 mmoles) was added to a solution of 2,3-dimethylindole (726 mg, 5 mmoles) in ethylacetate (10 ml) and the reaction mixture was heated at 50° for 4 hr with stirring. The cooled solution was filtrated to remove Selenium. The filtrate was evaporated under a reduced pressure and the residue was chromatographed on a column of silica gel (40 g). The column was eluted with benzene containing increasing amounts of chloroform and methanol, the fractions (each 50 ml) eluted with benzene: chloroform (1:1) and chloroform alone giving a solid (358 mg). Recrystallization from benzene–*n*-hexane gave 2-formyl-3-methylindole (175 mg, 22% yield) as colorless plates mp 139°. UV λ_{max}^{MeOH} mμ: 239 and 313, IR cm^{-1}: $\nu_{C=O}$ 1650 ($CHCl_3$). This aldehyde was oxidized with silver nitrate and aqueous NaOH in EtOH solution to a 2-carboxylic acid derivative mp 161°, which was identified by comparison with an authentic sample of 3-methylindole-2-carboxylic acid. The fractions eluted from the column with 1% MeOH–$CHCl_3$ were evaporated and the residue taken up in benzene and extracted with 5% aqueous NaOH solution. The acidic fraction gave rise to 3-methylindole-2-carboxylic acid, mp 163—164° (62 mg, 7% yield). The benzene layer was dried and evaporated. It gave rise to pale yellow crystals, mp 197—200° (16 mg, 2% yield) after recrystallized from benzene–*n*-hexane. *Anal.* Calcd. for $C_{20}H_{16}ON_2$: C, 79.98; H, 5.37; N, 9.33. Molecular Weight, 300. Found: C, 79.57; H, 5.48; N, 8.92. *m/e*: 300 (by mass spectrometry).

Oxidation of 1,2,3,4-Tetrahydrocarbazole with SeO_2——Under the same reaction conditions as the above experiment, 1,2,3,4-tetrahydrocarbazole, 514 mg (3 mmoles) and SeO_2, 382 mg (3.4 mmoles) in EtOAc 6 ml were treated at 50° for 3 hr. After separation of Se metal by filtration, the solvent was evaporated and the residue was sublimated under a reduced pressure to give a solid, 343 mg. The sublimate was filtrated through an alumina column (10 g) with benzene: $CHCl_3$ (1:1). Recrystallization of the eluted compound from benzene gave 244 mg of pale yellow prisms, mp 166—167° (44% yield). The product was identical to an authentic sample of 1-keto-1,2,3,4-tetrahydrocarbazole.

Oxidation of N-Methyl-1,2,3,4-tetrahydrocarbazole with SeO_2——In the same manner as in the above experiment, N-methyl-1,2,3,4-tetrahydrocarbazole, 925 mg (5 mmoles) and SeO_2 625 mg (5.6 mmoles) in EtOAc (10 ml) were treated at 50° for 3 hr. After separation of Se metal by filtration, the solvent was evaporated and the residue was chromatographed on a column of silica gel (40 g). Initial elution with benzene gave 352 mg of a crude gum (A). Further elution with benzene–$CHCl_3$ gave 293 mg of oil (B). The oil (B) gave rise to colorless crystals, mp 100—100.5°, 241 mg (24% yield) after recrystallized from benzene. The product was identical to an authentic sample of N-methyl-1-keto-1,2,3,4-tetrahydrocarbazole. Rechromatography of the crude gum (A) through alumina (15 g) using hexane gave 145 mg (16% yield) of pure N-methylcarbazole, mp 88° as the first fraction. Mixture melting point and IR spectrum were identical with those of authentic N-methylcarbazole. The second fraction which was eluted with benzene: *n*-hexane (1:1) gave 47 mg (4% yield) of orange crystals (recrystallization from benzene), mp 164—166° (unknown compound). *Anal.* Found: C, 54.49; 55.05; H, 3.44; 3.44; N, 5.11.

Oxidation of II——A solution of N-acetyl compound (II), 60 mg in EtOAc, 10 ml, was oxidized with SeO_2 (35 mg) in the same manner as in the above experiment. After the removal of EtOAc, the residue was chromatographed on 10 g of alumina. Elution with benzene: $CHCl_3$ (3:1) and methylenechloride gave starting meterial (II) (15 mg) and 12 mg (26% yield) of the tricyclic ketone (III), mp 209—210°. Infrared spectrum and mixture melting point were identical with those of the authentic ketone (III).

Oxidation of IV——A solution of tetracyclic amine (IV), 100 mg (0.413 mmoles) in 80% aq. acetic acid 5 ml was refluxed with SeO_2 460 mg (4.13 mmoles) for 3 hr under N_2 atmosphere. The cooled solution was filtrated to remove Se metal and evaporated under a reduced pressure. The residue was shaken with benzene (200 ml×3) and 5% aq. NaOH. The organic layer was separated, dried and evaporated to give a yellow oil, 37 mg. This oil was chromatographed over 5 g of alumina. Elution with $CHCl_3$ and 1% MeOH–$CHCl_3$ gave 21 mg of a crystalline fraction. Recrystallization from EtOH–ether gave 12 mg (11.3% yield) of the pure tricyclic ketone (V), mp 131—133°, which showed no depression of the melting point on admixture with an authentic sample.

Oxidation of VI——Selenium dioxide, 370 mg (3.3 mmoles) was added to a solution of tetracyclic lactam (VI), 720 mg (3 mmoles) in EtOAc (70 ml) and the solution was refluxed for 2 hr. After removal of the solvent, the residue was chromatographed over 100 g of alumina. Elution with $CHCl_3$ gave a red crystalline material.

Recrystallization from $CHCl_3$–EtOH gave 506 mg (63% yield) of red prisms (VIII), mp 223° (decomp.). *Anal.* Calcd. for $C_{30}H_{26}O_2N_4Se_2$: Melecular Weight, 636; C, 56.61; H, 4.75; N, 8.80; Se, 25.00. Found: MW, 567 (Vapor pressure method in $CHCl_3$); C, 56.23; H, 4.20; N, 8.77, Se, 23.03, 26.57. The mother liquor from the recrystallization gave 113 mg of the starting lactam (VI).

Reduction of VIII with 1,2-Ethanedithiol——Solutions of the organo-selenium compound (VIII), 120 mg in $CHCl_3$ (15 ml) and 1,2-ethanedithiol (0.5 ml) in AcOH 1 ml were mixed at room temperature. The color of reaction mixture turned from red to yellow after 10 hr. The solution was treated with excess $CHCl_3$ and 5% aq. NaOH and the chloroform layer was washed with water, dried, and concentrated to give an oil.

Filtration through alumina with $CHCl_3$: benzene (1:1) elution afforded 57 mg (63% yield) of pale yellow prisms of X, mp 239—240° (lit.[13] mp 237—238°). The IR spectrum (KBr) showed peaks at 3220 and 1630 cm^{-1}; the UV spectrum showed λ_{max}^{MeOH}: 233, 310 and 321 mμ [(lit.[13] 232 (ε: 30000), 308 (ε: 22200) and 319 (ε: 20500)], and the mass spectrum showed molecular ion at 238 (Calcd. for $C_{15}H_{14}ON_2$: 238).

Oxidation of VII with SeO_2——Selenium dioxide 270 mg (2.4 mmoles) was added to a solution of tetracyclic lactam (VII), 710 mg (1.83 mmoles) in EtOAc 20 ml and the solution was refluxed for 2.5 hr. After the removal of the solvent, the residue was chromatographed over 50 g alumina. Elution with $CHCl_3$ gave a red crystalline material, which was recrystallized from MeOH to give 526 mg (62% yield) of red needles of IX, mp 187—188°. *Anal.* Calcd. for $C_{42}H_{42}O_{10}N_4Se_2$: MW, 920; C, 54.78; H, 4.52; N, 6.09; Se, 17.17. Found: MW, 780 (Vapor pressure method in $CHCl_3$); C, 54.72; H, 4.98; N, 6.09; Se, 16.69. The IR spectrum (in $CHCl_3$) showed peaks at 3350, 1728, 1675, 1565 cm^{-1}, the UV spectrum showed λ_{max}^{MeOH} mμ (ε): 222 (42600), 310 (31300), 336 (23500 sh) and 420 (7800). The mother solution from the above recrystallization gave 178 mg (25% yield) of pale yellow prisms (XI), mp 172° after recrystallization from benzene–*n*-hexane. The IR spectrum showed λ_{max}^{MeOH} mμ (ε): 229 (27100) and 318 (18100). *Anal.* Calcd. for $C_{21}H_{22}O_5N_2$: MW, 382, C, 65.95; H, 5.80; N, 7.33. Found: *m/e* 382 (M^+, by mass spectrometry), C, 65.61; H, 5.81; N, 7.06.

Reduction of IX with 1,2-Ethanedithiol——A solution of organoselenium compound, IX (50 mg) in a mixture of HOAc (2 ml), BF_3-etherate (0.2 ml) and 1,2-ethanedithiol (0.12 ml) was kept at room temperature for 18 hr. The solution was treated with 10% aq. Na_2CO_3 and the ether layer was washed with water, and then dried over sodium sulfate. After removal of the ether, the residue afforded 37 mg (89% yield) of pure pale yellow prisms (mp 171—172°, from benzene–*n*-hexane). Mixture melting point and the comparison of UV and IR spectra with an authentic sample (XI) assured the identity of both compounds.

Reoxidation to IX from XI——Selenium dioxide 90 mg (0.81 mmoles) was added to the solution of compound (XI), [62 mg (0.16 mmoles)] in EtOAc (5 ml) and the solution was refluxed for 23 hr. The cooled solution was filtrated and evaporated. The resulting residue was chromatographed on SiO_2 (10 g) and elution with benzene: $CHCl_3$ (1:1) afforded a solid, 70 mg. It was recrystallized from MeOH to give 28 mg (37.5% yield) of the organoselenium compound (IX), mp 182—184°. The mother solution of the above recrystallization gave 15 mg (24% yield) of starting material (XI) mp 170—171.5°, after recrystallization from benzene–*n*-hexane. The mother solution of the latter recrystallization showed only the presence of the unchanged vinyl compound (XI) by thin-layer chromatography.

13) G.C. Morrison, W. Cetenko and J. Shavel, Jr, *J. Org. Chem.*, **29**, 2771 (1964).