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Radiation-Protective Agents. V.[1] Synthesis and Hydrolysis of 2-(2-Aminoethylthio)indole Derivatives

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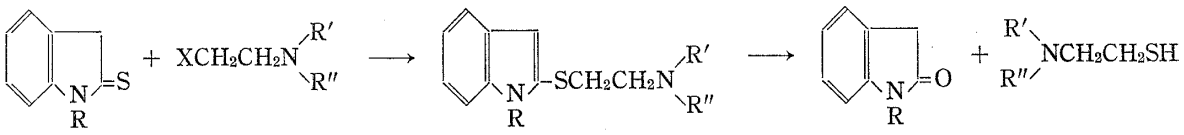
In the previous papers we have reported the synthesis of 2-aminoethylthiopseudoureas,[3] 2-aminothiazolines,[4] and tryptophanol derivatives[1] as potential radiation-protective agents. In this paper we describe the synthesis of derivatives (III) of cysteamine, one of the most strong radiation-protective agent hitherto known, from 2-indolinethiones. We have reported that 2-indolinethiones can be prepared by the thiation of oxindoles and give 2-methylthioindole derivatives by methylation with methyl iodide.[5]



I: a : R=H; b : R=Me

II: a : X=Cl, R′,R″=Me; b : X=Br, R′,R″=phthaloyl; c : X=Br, R′,R″=H

III:

	R	R′	R″
a :	H	Me	Me
b :	Me	Me	Me
c :	H	phthaloyl	
d :	Me	phthaloyl	
e :	H	H	H
f :	Me	H	H
g :	H	Ac	H
h :	Me	Ac	H

IV: a : R=H; b : R=Me

V: a : R′,R″=Me; b : R′,R″=phthaloyl

Chart 1

When 2-indolinethione (Ia) was treated with N,N-dimethylaminoethyl chloride (IIa) in dimethylformamide in the presence of potassium carbonate at room temperature, the compound (IIIa), mp 83—84°, was obtained in moderate yield. Under similar conditions IIIb, IIIc and IIId were prepared from Ia or Ib with IIa or IIb. In the case of aminoethyl bromide (IIc), IIIe and IIIf could not be purified and discolored during purification, but acetylation of the crude products gave stable acetyl derivatives. The properties of III are summarized in Table I and II.

To examine the possibility of the formation of thiol compounds (V) in the biological systems which might be essential for radiation protective effect, the compounds (IIIa, IIIb, and IIIc) were submitted to acid hydrolysis. Oxindoles (IV) and N-substituted cysteamine

1) Part IV: T. Hino, K. Uoji, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **18**, 384 (1970).
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3) T. Hino, K. Tanaami, K. Yamada, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1193 (1966).
4) T. Hino, K. Tanaami, K. Yamada, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1201 (1966).
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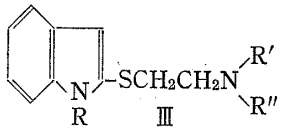
Table I. UV spetcra of III



III	R	R′	R″	mp (C°)	UV λ_{max}^{EtOH} mμ ($\varepsilon \times 10^{-4}$)
a	H	Me	Me	83— 84	298sh(1.00), 290(1.28), 281(1.25), 218(3.37)
b	Me	Me	Me	oil (HCl salt, 225—226)	294sh(1.18), 286(1.26), 222(3.43),
c	H	phthaloyl		167—169	298sh (0.99), 290(1.26), 281(1.22)
d	Me	phthaloyl		162.5—164	294sh (1.22), 286(1.25)
g	H	Ac	H	94 — 95	298sh (0.97), 290(1.28), 281(1.26), 218(3.45)
h	Me	Ac	H	83 — 84	294sh (1.21), 287(1.28), 220(3.43)

Table II. NMR Spectra of III (in $CDCl_3$, ppm from TMS)

Compound	1-Me	S-CH_2–	N–CH_2	N–Me	3H	Ind–NH
IIIa	—	2.71 m	2.93 m	2.38 s	6.56	9.49 s
IIIb	3.83 s	2.65 m	2.96 m	2.34 s	6.68 s	—
IIIc	—	3.04 t	3.92 t	—	6.71 s	9.57 s
IIId	3.81 s	3.14 t	3.97 t	—	—	—
IIIg	—	2.77 t	3.45 q	—	6.60 s	9.76 s
IIIh	3.77 s	2.80 t	3.37 q	—	6.68 s	—

s, singlet; m, multiplet; q, quartet

(V) were isolated in fair yield when IIIa, IIIb, and IIIc were refluxed in methanol-hydrochloric acid.

These results indicate that 2-indolinethiones could be the starting material for the preparation of thiol compounds and 2-indolyl group might be serve as a protective group of the thiol compounds.

Experimental[6]

2-(2-Dimethylaminoethylthio)indole (IIIa)——A mixture of 2-indolinethione (Ia, 895 mg), N,N-dimethylaminoethyl chloride-HCl (IIa-HCl, 1.73 g), K_2CO_3 (2.49 g) and KI (200 mg) in dimethylformamide (DMF, 20 ml) was stirred at room temperature for 24 hr. The mixture was added with H_2O (130 ml) and extracted with CH_2Cl_2 and dried. The CH_2Cl_2 solution was evaporated *in vacuo* to leave a purple oil (1.35 g), which was purified through alumina column to give a pale purple solid (0.59 g, 40.6%), mp 75—80°. The crude IIIa was further purified over alumina column. Fractions eluted with CH_2Cl_2–benzene (1:1) gave IIIa (280 mg), mp 79—80°, which was recrystallized from hexane–EtOH (30:1) to give pure IIIa, mp 83—84°, as colorless crystals. *Anal.* Calcd. for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.72; S, 14.55. Found: C, 65.38; H, 7.01; N, 12.46; S, 14.72.

Picrate, red crystals, mp 129—130° (from EtOH). *Anal.* Calcd. for $C_{18}H_{19}O_7N_5S$: C, 48.10; H, 4.26; N, 15.58; S, 7.13. Found: C, 48.46; H, 4.17; N, 15.33; S, 7.18.

2-(2-Dimethylaminoethylthio)-1-methylindole (IIIb)——A mixture of Ib (2.93 g), IIa-HCl (5.18 g), K_2CO_3 (7.46 g), and KI (0.9 g) in DMF (70 ml) was heated at 80° (bath temperature) for 3 hr with stirring. After cool, the mixture was added with H_2O (400 ml) and extracted with $CHCl_3$ and dried. The $CHCl_3$ solution was evaporated *in vacuo* to leave an orange red oil (4.1 g), which was purified through alumina column. The fractions eluted with $CHCl_3$–benzene (1:1) gave IIIb (2.32 g, 55%) as a pale yellow oil which was solidified under cooling with dryice–acetone, but melted at room temperature. Hydrochloride, mp 225—226° (from EtOH). *Anal.* Calcd. for $C_{13}H_{19}N_2SCl$: C, 57.65; H, 7.07; N, 10.34. Found: C, 57.77; H, 6.86; N, 10.12.

6) All melting points are uncorrected. NMR spectra were measured by a varian HR-100 spectrometer.

2-(2-Phthalimidoethylthio)indole (IIIc)——A mixture of Ia (2.09 g), N-(2-bromoethyl)phthalimide (IIb, 3.56 g) and K_2CO_3 (3.87 g) in DMF (60 ml) was stirred at room temperature for 2 hr. Some insoluble materials were removed by the filtration, and the filtrate was condensed to a half volume *in vacuo*. The solution was diluted with H_2O (100 ml) and a separated oil was soon solidified, which were collected and dried (4.4 g, 97%). The crude product was recrystallized from benzene to give IIIc, mp 167—169°, as pale yellow needles. *Anal.* Calcd. for $C_{18}H_{14}O_2N_2S$: C, 67.07; H, 4.38; N, 8.69; S, 9.95. Found: C, 67.81; H, 4.50; N, 8.50; S, 10.04.

2-(2-Phthalimidoethylthio)-1-methylindole (IIId)——The compound (IIId) was obtained by the similar procedure shown in IIIc from Ib (1.63 g), IIb (2.54 g) and K_2CO_3 (2.76 g) in DMF (40 ml). Crude IIId (3.1 g, 92%), mp 168—160°. Recrystallizations from benzene gave IIIc, mp 162.5—164°, as pale yellow crystals. *Anal.* Calcd. for $C_{19}H_{16}O_2N_2S$: C, 67.83; H, 4.79; N, 8.33; S, 9.53. Found: C, 67.84; H, 4.51; N, 8.01; S, 9.58.

2-(2-Acetoamidoethylthio)indole (IIIg) *via* IIIe——A mixture of Ia (1.79 g), IIc-HBr (4.92 g) and K_2CO_3 (4.98 g) in acetonitrile (35 ml) was stirred at room temperature for 40 min. Some insoluble materials were removed by filtration and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (80 ml) and washed with H_2O and dried. On evaporation of the solvent a purple crystalline solid (IIIe, 2.18 g, 94%), mp 100—103°, was obtained, but could not be purified. The crude IIIe was dissolved in pyridine (20 ml) and was added with Ac_2O (5.0 g). After stirring at room temperature for 1 hr the mixture was added with H_2O (120 ml) to separate a dark purple oil. The oil was extracted with benzene and the benzene solution was washed with 1N HCl and H_2O. The benzene solution was evaporated *in vacuo* after dry to give an oil (3.1 g), which was purified through alumina column. Fractions eluted with benzene–CH_2Cl_2 (4:1) gave IIIg (2.0 g, 75%). Recrystallizations from benzene gave IIIg, mp 94—95°, as colorless crystals. *Anal.* Calcd. for $C_{12}H_{14}ON_2S$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.76; H, 6.22; N, 11.62.

2-(2-Acetamidoethylthio)-1-methylindole (IIIh) *via* IIIf——A mixture of Ib (2.29 g), IIc-HBr (4.7 g) and K_2CO_3 (5.1 g) in DMF (60 ml) was warmed at 60° (bath temperature) for 3 hr with stirring. The mixture was condensed to a half volume *in vacuo* and was added to H_2O (150 ml). The mixture was extracted with CH_2Cl_2 and which was washed with H_2O and dried. On evaporation of the solvent pale brown oil (crude IIIf, 3.0 g) was obtained. The crude IIIf was acetylated with pyridine–Ac_2O as above to give crude IIIh (2.7 g), which was chromatographed over alumina column. Fractions eluted with benzene–CH_2Cl_2 (5:1) gave IIIf (1.8 g, 52% from Ib), 83—84°. Recrystallizations from hexane–benzene gave pure IIIf, mp 88—89°, as pale yellow crystals. *Anal.* Calcd. for $C_{13}H_{16}ON_2S$: C, 62.87; H, 6.49; N, 11.28. Found: C, 63.07; H, 6.55; N, 11.34.

Hydrolysis of IIa. Formation of Dimethylaminoethanethiol (Va) and Oxindole (IVa)——A solution of IIIa (500 mg) in MeOH (30 ml) and conc. HCl (5 ml) was refluxed for 1 hr. After cool the solvent were evaporated *in vacuo* to leave an oil. Benzene soluble part of the oil gave oxindole (140 mg, 46%), mp 106—107°. Recrystallizations from benzene–hexane raised the melting point to 125—127°. The sample was proved to be identical with oxindole on admixture and in IR spectra.

Benzene insoluble part was crystallized from EtOH–ether to give crude dimethylaminoethanethiol-HCl (190 mg, 59%). Repeated recrystallization from EtOH–ether gave Va-HCl, mp 157—159° (reported mp 156—157°[7]). NMR (HCl salt in D_2O, ppm from DSS); 2.84 (s, NMe), 2.84 (further splitted triplet, S–CH_2–), 3.28 (further splitted triplet, CH_2–N). Free base (in $CDCl_3$, ppm from TMS): 2.05 (broad s, SH), 2.25 (s, N–Me), 2.57 (m, N–CH_2CH_2S).

N-Methyloxindole (IVb) and Va-HCl were obtained when IIIb was refluxed in MeOH–HCl for 30 min.

Hydrolysis of IIIc. Formation of N-(2-Mercaptoethyl)phthalimide (Vb) and Oxindole (IVa)——A solution of IIIc (1.0 g) in MeOH (60 ml) and conc. HCl (10 ml) was refluxed for 3.5 hr. On cooling the solvent was evaporated *in vacuo*, and the residue was added with H_2O (2 ml) and extracted with CH_2Cl_2 and dried. The CH_2Cl_2 solution was evaporated *in vacuo* to leave a solid which showed positive test for SH by sodium nitroprusside. The solid was chromatographed over silicic acid column. Fractions eluted with benzene–CH_2Cl_2 (1:1) gave crude Vb (430 mg, 67%), which was recrystallized from benzene–hexane to give Vb, mp 77—78° (reported mp 76°,[8] 77—78°[9]), as pale yellow needles. IR ν_{max}^{KBr} 2560 cm^{-1} (SH). NMR (in $CDCl_3$, ppm from TMS): 1.41 (t, SH, J=8), 2.80 (sextet, S–CH_2–, J=8, J=7), 3.85 (t, N–CH_2–, J=7), 7.67—7.90 (aromatic H).

Fractions eluted with 5% MeOH in CH_2Cl_2 gave oxindole (310 mg, 75%), which was identical with the authentic sample on admixture and in IR spectra.

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