was mostly evaporated *in vacuo*, 10 ml of fresh D_2O was added to the residue. The reaction mixture was warmed at 95° for another 5 hours. 2-Trideuterio-5-methyl-6-deuteriopyridine 1-oxide, which was obtained by extraction of the reaction mixture with $CHCl_3$, was purified by vacuum distillation (120°/5 mmHg). D-Atom content was more than 95 D-atom %.

4-^{15}N-Nitro-2-trideuterio-5-methyl-6-deuteriopyridine (IV)——In 4 ml of conc. H_2SO_4 was dissolved 300 mg of the partly deuterated lutidine 1-oxide obtained as the above and 300 mg of $K^{15}NO_3$ was added to this solution, which was warmed at 95° for 10 hours. The reaction mixture was poured into ice–water and made alkaline by addition of Na_2CO_3. From the $CHCl_3$ extract, 167 mg of 2-trideuteriomethyl-4-^{15}N-nitro-5-methyl-6-deuteriopyridine 1-oxide (IV) was obtained.

2,6-Di-trideuteriomethylpyridine 1-Oxide——Two grams of 2,6-lutidine 1-oxide was dissolved in 10 ml of 2% NaOD–D_2O and warmed in a sealed tube at 95° for 2 hours. After the solvent was evaporated *in vacuo* upto about 1/10 volume, 10 ml of fresh D_2O was added and the reaction mixture was sealed in a tube again. It was warmed at 95° for another 2 hours and extracted with $CHCl_3$. 2,6-Di-trideuteriomethylpyridine 1-oxide was purified by destillation *in vacuo* (100°/4 mmHg) in an almost quantitative yield. Isotope purity was proved to be satisfactory by NMR spectroscopy.

2,6-Di-trideuteriomethyl-4-^{15}N-Nitropyridine 1-Oxide (V)——In 5 ml of conc. H_2SO_4 was dissolved 300 mg of 2,6-di-trideuteriomethylpyridine 1-oxide and 300 mg of $K^{15}NO_3$ was added. After the reaction mixture was maintained at 80° for 10 hours, it was poured into ice–water, and made alkaline with Na_2CO_3 and extracted with ether. 4-^{15}N-Nitro derivative (V) was purified by recrystallization from ether to give 100 mg of the product (V), whose chemical and isotopic purities was proved to be satisfactory by NMR spectroscopy.

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Radiation-Protective Agents. IV.[1] Synthesis of Tetrahydro-β-carbolines and 2-Aminothiazoline Derivative from Tryptophanols

Tohru Hino,[2a] Katsuko Uoji (née Tanaami), and Sanya Akaboshi[2]

Department of Pharmaceutical Sciences, National Institute of Radiological Sciences[2]

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5-Hydroxytryptophan, 5-hydroxytryptamine, and tryptamine are known to have strong radiation protective effect.[3] A number of derivatives of tryptamine and tryptophan have been examined their radiation-protective effects,[4] but tryptophanol and its derivatives are not yet investigated.

Yamada, *et al.*[5] reported that amino acids ester hydrochloride can be reduced to the corresponding aminoalcohol by sodium borohydride. DL-Tryptophanol (IIa) and 5-methoxy-tryptophanol (IIb) were prepared by this method in good yields.

When IIa hydrochloride was treated with formaline at 90° following the procedure for tryptamine by Spaeth,[6] a β-carboline (IIIa) was obtained. The compound (IIIa), mp 189°,

1) Part III: K. Uoji, K. Tsuneoko, A. Hanaki, and S. Akaboshi, *Chem. Pharm. Bull* (Tokyo), **17**, 1742 (1969).
2) Location: *Anagawa 4-Chome, Chiba-shi*; *a*) Present address: *Faculty of Pharmaceutical Sciences, University of Chiba, Yayoi-cho, Chiba-shi.*
3) J.F. Thomas, "Radiation Protection in Mamals" Chapman and Hall, 1962.
4) R. Huber and E. Spode, "Biologisch-Chemischer Strahlenschutz," Ein Übersicht in Tabellen I, II, III und IV, Akademie-Verlag, 1961 and 1964.
5) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 995 (1965).
6) E. Spath and E. Lederer, *Ber.*, **63**, 2102 (1930).

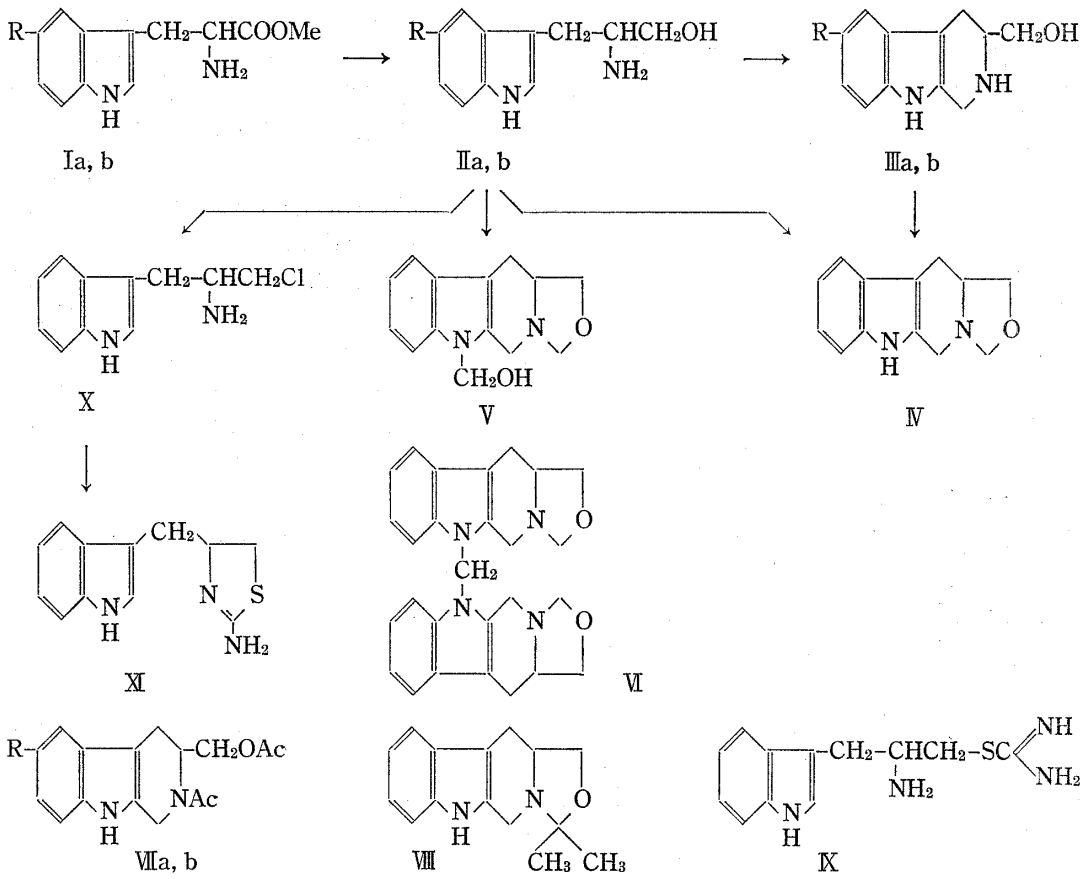

Chart 1

was identical with the sample prepared from tetrahydro-β-carboline-3-carboxylic acid methyl ester by the reduction with sodium borohydride.[7] The yield of IIIa was increased to 57% when IIa hydrochloride was stirred with one mole equivalent of formaline at room temperature for 24 hr. An oxazolocarboline derivative (IV) was obtained as a by-product. The same compound (IV) was obtained by refluxing IIIa with formaline in the presence of hydrochloric acid. Another oxazoline derivative (VIII) was obtained when IIIa was refuxed with acetone, indicating the facile formation of oxazoline ring from IIIa. When IIa hydrochloride was treated with 2.5 moles of formaline at room temperature, two compounds (V and VI) were isolated by fractional recrystallization besides IV. The structure of V was confirmed by spec-

Table I. Mass Spectra of IV, V and VIII
(m/e (relative abundance, %), direct inlet system)

Compound	Fragments						
IV	214(45, M^+),	183(8)[a],	156(17),	155(10),	154(14),	144(70)[b],	143(100)[c], 140(10)
	130(18),	129(9),	128(18),	116(10),	115(34)[d],	102(11),	77(10)
V	244(60, M^+),	214(32),	183(25)[a],	181(13),	174(41)[e],	173(100)[f],	158(32), 157(15)
	156(38),	155(21),	154(28),	145(18),	144(100)[b],	143(100)[c],	142(45), 141(10)
	140(18),	130(48),	129(22),	128(35),	127(20),	117(15),	116(27), 115(60)[d]
	103(10),	102(22),	101(12),	89(12),	78(12),	77(26),	51(12)
VIII	242(10, M^+),	229(22),	182(6),	169(6),	167(6),	154(6),	144(35)[b], 143(100)[c]
	142(6),	129 (6),	115(10)[d],	84(12),	77(5),	56(5),	

Probable structures of a,b,c,d,e, and f are shown in Chart 2.

7) The sample was donated by Dr. T. Shioiri of University of Tokyo to whom the authors thanks are due.

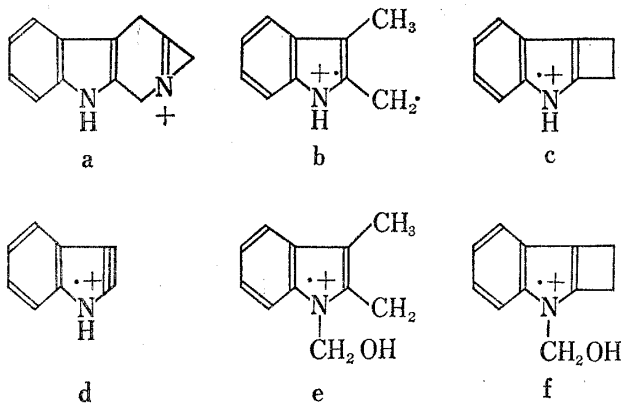

Chart 2

tral data as well as elemental analysis. The nuclear magnetic resonance (NMR) spectrum of V in pyridine-d_5 showed a singlet at 5.70 ppm for N-CH_2-OH and other signals were very close to those of IV except a signal for indolic NH was absent. Mass spectrum of V showed a molecular ion peak at *m/e* 244. Main fragmentations for IV, V and VIII are shown in Table I and Chart 2. The structure of the minor product (VI) was tentatively assigned to VI from mass spectra (M^+ *m/e* 440).

6-Methoxycarboline derivative (IIIb), mp 181—182°, was obtained by treating IIb with one mole of formaline at room temperature, and the corresponding oxazolocarboline could not be isolated in this case. The both carboline alcohols (IIIa and b) gave diacetates (VII a and b) by pyridine and acetic anhydride.

Tryptophanol (IIa) might be considered to be a good starting material to synthesize the compound (IX), which possesses both tryptamine moiety and aminoethylpseudothiourea moiety, another famous radiation protective agent. Although chlorination with thionyl chloride did not succeed, IIa was chlorinated with phosphor oxychloride to give X which was obtained as an amorphous powder and characterized as a picrate. When X-hydrochloride was heated with thiourea in a boiling butanol, an 2-amino-2-thiazoline (XI), mp 127—128° was obtained instead of IX. The NMR spectra of XI in deuterochloroform showed a multiplet at between 2.78 and 3.40 ppm for skatyl methylene and methylene at 5-position in the thiazoline ring, a further splitted quintet at 4.56 ppm for methine at 4-position of the thiazoline, broad singlet at 3.65 and 8.16 ppm for NH_2 and indolic NH. The overlapped signals for two methylene separated to a doublet at 3.18 ppm for skatyl methylene and octet at 3.52 ppm for methylene at 5-position by the addition of trifluoroacetic acid. The methine proton also shifted to 4.71 ppm. Mass spectrum of XI showed small molecular ion peak at *m/e* 231 and strong peaks at *m/e* 131, 130, 101, structures of which might be assigned to a, b, and c, in Chart 3, indicating facil cleavage between skatyl and the thiazoline ring.

The formation of XI was probably due to the rearrangement of IX produced during the reaction. The same rearrangement was observed in simple 2-aminoethylpseudothioureas.[8]

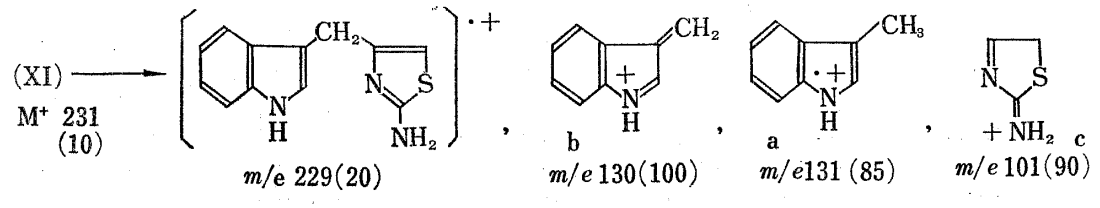

Chart 3. Fragmentation of XI

8) T. Hino, K. Tana-ami, K. Yamada, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1201 (1966).

Experimental[9]

DL-Tryptophanol Hydrochloride (IIa-HCl)——The hydrochloride was prepared from DL-tryptophanol.[5,10] Colorless crystals, mp 178—179° (EtOH–ether). *Anal.* Calcd. for $C_{11}H_{14}ON_2HCl$: C, 58.28; H, 6.67; N, 12.36; Cl, 15.64. Found: C, 58.35; H, 6.74; N, 11.80; Cl, 15.69. NMR (in D_2O, ppm from DSS): 3.17 (d, 2H, $\underline{CH_2}$–CH–), 3.78 (m, 3H, –CH–$\underline{CH_2}$–OH), 7.15–7.70 (m, aromatic H)

DL-5-Methoxytryptophanol (IIb)——i) DL-5-Methoxytryptophan Methylester Hydrochloride: The hydrochloride was prepared from 5-methoxytryptophan.[11] Colorless crystals, mp 214—218° (decomp.) (from MeOH–iso-Pr_2O). *Anal.* Calcd. for $C_{13}H_{16}O_3N_2HCl$: C, 54.83; H, 6.02; N, 9.84; Cl, 12.45. Found: C, 55.12; H, 5.78; N, 9.67; Cl, 12.45.

ii) DL-5-Methoxytryptophanol: To a suspension of $NaBH_4$ (1.17 g) in 75% EtOH (20 ml) was added dropwise the methylester hydrochloride (2.2 g) in 75% EtOH (40 ml) under cooling. The mixture was then refluxed for 3 hr. On cooling the reaction mixture was evaporated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated after dry *in vacuo* to leave a crude tryptophanol (1.32 g, 77.7%), mp 130°. Recrystallizations from benzene gave DL-5-methoxytryptophanol, mp 134°, as colorless crystals. *Anal.* Calcd. for $C_{12}H_{16}O_2N_2$: C, 65.43; H, 7.32, N, 12.72. Found: C, 65.40; H, 7.31; N, 12.77. Hydrochloride, mp 175° (from EtOH–iso-Pr_2O). *Anal.* Calcd. for $C_{12}H_{16}O_2N_2HCl$: C, 56.14; H, 6.67; N, 10.91. Found: C, 56.45; H, 6.58; N, 10.91.

NMR (Hydrochloride in D_2O, ppm from DSS): 3.09 (d, 2H, $\underline{CH_2}$–CH–CH_2OH), 3.62—3.95 (m, 3H, CH_2–$\underline{CH}$(NH$_2$)–$\underline{CH_2}$OH), 3.90 (s, 3H, MeO), 6.97 (dd, 1H, 6-H, $J_{67}=8.4$ cps), 7.21 (d, 1H, 4-H, $J_{46}=2$ cps), 7.34 (s, 1H, 2H), 7.48 (d, 1H, 7-H), IR (free base); ν_{max}^{KBr} cm^{-1}: 3400 (indolic NH), 3300, 3200 (NH, OH), 1055 (C–O).

Reaction of Tryptophanol with 1 mole of Formaline——i) At 90°[6]: To a solution of tryptophanol HCl (6.8 g) in H_2O (100 ml) was added 40% formaline (3 ml) under cooling. The mixture was warmed at 90° (bath temperature) for 30 min. On cooling the mixture was basified with 10% NaOH and was extracted with $CHCl_3$. The $CHCl_3$ solution was evaporated *in vacuo* to leave a solid (5.5 g). The residue was dissolved in dilute H_2SO_4(H_2SO_4:H_2O=12:250, 500 ml) and refluxed for 1 hr. On cooling the solution was basified with 20% NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was evaporated *in vacuo* to leave a crude carboline alcohol (IIIa, 1.55 g, 25.6%), mp 155—160°. Recrystallizations from EtOH gave pure IIIa, mp 189°. The sample was proved to be identical with the sample obtained from 1,2,3,4-tetrahydrocarboline-3-carboxylic acid methyl ester by the reduction with $NaBH_4$,[7] on admixture and in NMR spectra in pyridine–d_5 and DMSO–d_6. O,N-Biacetate, mp 154—155° (from benzene–hexane). *Anal.* Calcd. for $C_{16}H_{18}O_3N_2$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.24; H, 6.19; N, 9.80. NMR (in $CDCl_3$, ppm from TMS): 2.02 (s, 3H, $COCH_3$), 2.24 (s, 3H, $COCH_3$), 2.70—3.20 (m, 2H, 4-CH_2), 3.90—4.34 (m, 3H, 3-H and CH_2–O), 4.49—4.69 (q, 2H, 1-CH_2).

ii) At Room Temperature: Tryptophanol HCl (1.31 g) was added to 40% formaline (0.5 ml) in H_2O (20 ml). The mixture was stirred at room temperature for 24 hr. The mixture was basified with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was evaporated *in vacuo* to leave a crude IIIa (670 mg, 57%) which gave pure IIIa, mp 189°, on recrystallization from EtOH. The sample was identical with the specimen obtained above on admixture.

An oil which was not extracted with $CHCl_3$ was separated from alkaline solution and dissolved in EtOH. The ethanolic solution was evaporated *in vacuo* to leave a solid (202 mg). The residue was recrystallized from ethanol to give IV, mp 238° (decomp.), which was proved to be identical with the sample obtained from IIIa (vide infra) in IR spectra.

3,3a,4,10-Tetrahydro-1H-oxazolo[3,4-*b*]-β-carboline (IV) and (VIII)——To a suspension of IIIa (974 mg) in H_2O (15 ml) and 1N HCl (5 ml) was added 40% formaline (0.36 ml). The mixture was refluxed for 1 hr to give clear solution. On cooling the mixture was made alkaline with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was dried and evaporated *in vacuo* to leave a crude IV (1.0 g). Recrystallizations from EtOH gave pure IV, mp 237° (decomp.). *Anal.* Calcd. for $C_{13}H_{14}ON_2$: N, 13.08. Found: N, 12.96. NMR (in pyridine–d_5, ppm from TMS): 2.68—3.07 (m, 3H, >N–$\underline{CH_2}$–$\underline{CH}$–), 3.46—3.82 (m, 2H, 10-CH_2), 4.04—4.24 (m, 3H, 3-CH_2– and 1-CH), 5.05 (d, 1H, 1-CH), 11.78 (broad s, 1H, NH).

When IIIa was recrystallized from acetone repeatedly, VIII, mp 193—194°, was obtained. *Anal.* Calcd. for $C_{15}H_{18}ON_2$: N, 11.56. Found: N, 11.51. NMR (in pyridine–d_5, ppm from TMS): 1.21 (s, 3H,

9) All melting points are uncorrected. NMR spectra were measured with a Varian HR-100 spectrometer, and Mass spectra were measured with a Hitachi RMU-6E instrument.

10) P. Karrer and P. Portmann, *Helv. Chim. Acta*, **32**, 1034 (1949).

11) J.W. Cook, J.D. Loudon, and P. MClosky, *J. Chem. Soc.*, **1951**, 1203.

CH_3), 1.45 (s, 3H, CH_3), 11.66 (broad s, NH).

Reaction of Tryptophanol with 2.5 moles Equivalent of Formaline——A solution of IIa HCl (2.27 g) in 40% formaline (2 ml) and H_2O (30 ml) was stirred at room temperature for 110 hr. The solution was made alkaline with 10% NaOH and extracted with $CHCl_3$ ten times. The $CHCl_3$ solution was evaporated *in vacuo* to leave a white solid (2.0 g). On repeated fractional recrystallizations from ethanol gave two compounds: A, mp 241—242° (106 mg) and B, mp 225° (540 mg). From the mother liquor another crystals were obtained (C), mp 152—153° (from benzene) (950 mg). The compound B was proved to be IV by comparison of IR and NMR spectra. The compound A was assigned to be VI. *Anal.* Calcd. for $C_{27}H_{28}O_2N_4$: N, 12.71. Found: N, 12.40. Mass *m/e* 440 (M^+).

The compound C was proved to be V. *Anal.* Calcd. for $C_{14}H_{16}O_2N_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.70; H, 6.77; N, 11.74. NMR (in pyridine-d_5, ppm from TMS), 5.70 (s, 2H, N-CH_2OH).

3-Hydroxymethyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline (IIIb)——5-Methoxytryptophanol HCl (IIb HCl) (1.54 g) was dissolved in 40% formaline (0.45 ml) and H_2O (20 ml). The solution was stirred at room temperature and white crystals began to separate after 7.5 hr. After 24 hr stirring separated crystals were collected (619 mg, 38%), mp 260—270°. Recrystallizations from EtOH gave IIIb HCl, mp 265—270° (decomp.), as colorless crystals. *Anal.* Calcd. for $C_{13}H_{16}O_2N_2HCl$: C, 58.10; H, 6.38; N, 10.42; Cl, 13.19. Found: C, 57.98; H, 6.50; N, 10.30; Cl, 12.97.

Free base, mp 181—182° (EtOH). *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; H, 12.06. Found: C, 67.34; H, 7.18; N, 12.07. Mass (*m/e* (relative abundance)); 232 (M^+, 25), 201 (31), 173 (100), 158 (51).

O,N-Diacetate, mp 121° (from benzene). *Anal.* Calcd. for $C_{17}H_{20}O_4N_2$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.35; H, 6.41; N, 9.00.

The filtrate was made alkaline with 10% NaOH and extracted with $CHCl_3$ ten times. The $CHCl_3$ solution was dried and evaporated to leave a solid (731 mg) which was chromatographed over silica gel. Fractions eluted with MeOH–CH_2Cl_2 (20% MeOH) gave further IIIb (250 mg).

α-Chloromethyltryptamine (X)——Phosphor oxychloride (30 ml) was added to IIa (3.0 g) under 5° with cooling. The suspension was warmed gradually to 74°, and the resulting clear solution was heated further for 3 hr at the same temperature. After standing at room temperature over night, the reaction mixture was evaporated *in vacuo*. The residue was washed with ether and the insoluble residue was made alkaline with 10% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and evaporated to leave an oil (1.75 g, 63%). The oil was treated with EtOH saturated with HCl gas to give hydrochloride (2.0 g) as amorphous powder. The free base and the hydrochloride could not be crystallize.

Picrates, mp 166—167° (from H_2O). *Anal.* Calcd. for $C_{17}H_{16}O_7N_5Cl$: C, 46.64; H, 3.68; N, 16.00. Found: C, 46.03; H, 3.90; N, 15.84.

2-Amino-4-(3-indolylmethyl)-2-thiazoline (XI)——To a solution of X–HCl (590 mg) in BuOH (10 ml) was added thiourea (182 mg). The mixture was refluxed for 10 hr. After cool the reaction mixture was filtered to remove some inorganic material and the filtrate was evaporated *in vacuo*. The residue was basified with 10% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried and evaporated *in vacuo* to leave a solid (360 mg) which was chromatographed over silicic acid. Fractions eluted with CH_2Cl_2–EtOH (10:2) gave crude XI (194 mg, 35%). Recrystallizations from benzene gave pure XI, mp 127—128°, as colorless crystals. *Anal.* Calcd. for $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N, 18.17; S, 13.86. Found: C, 62.59; H, 5.59; N, 17.72; S, 13.90. NMR (in $CDCl_3$, ppm from TMS): 2.78—3.40 (m, 4H, $-\underline{CH_2}-\underset{\underset{N}{|}}{CH}-\underline{\underset{\underset{S}{|}}{CH_2}}$), 3.64 (s, NH_2), 4.56 (quintet, 1H, 4–CH), 8.16 (broad s, 1H, indolic NH). (in $CDCl_3$–F_3CCOOH) 3.18 (d, 2H, skatyl CH_2), 3.52 (octet, 2H, 5–CH_2 of thiazoline), 4.71 (quintet, 1H, 4–CH of thiazoline).

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