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Synthetic Studies on Pyridoxine Derivatives. II.[1] Synthesis of 3-(3-Hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methyl-4-methyl-5-substitutedthiazoline-2-thiones[2]

Isoo Ito, Taisei Ueda, Yoshio Kuroyanagi, and Kenji Suzuki

Faculty of Pharmaceutical Sciences, Nagoya City University[3]

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Syntheses of some pyridoxine derivatives having a thiazoline ring or a thiazolium ring at the 5-position are described. 3-(3-Hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)-methyl-4-methylthiazoline-2-thione(IX) was synthesized from α^4, 3-O-isopropylideneiso-pyridoxamine(VII), carbon disulfide, ammonium hydroxide, and chloropropanone. Similarly X, XI, and XII were obtained by employing appropriate alkyl chloride instead of chloropropanone. Treatment of IX, X, XI, and XII with 30% hydrogen peroxide and 35% hydrochloric acid gave 3-(3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methyl-4-methyl-5-substitutedthiazoliumchloride hydrochlorides (XIII, XIV, XV, XVI).

Keywords——pyridoxines; thiazoline-2-thiones; thiazolium chlorides; α^4, 3-O-isopropylideneisopyridoxamine; α^4,3-O-isopropylidenepyridoxal

Among the sulfur-containing pyridoxine derivatives some compounds are known to be pharmacologically effective such as pyridoxine-5-disulfide,[4] pyridoxal-5-disulfide,[5] and pyridoxamine-5-disulfide.[6] The compounds appearing in the title were synthesized expecting pharmacologically effective properties.

α^4,3-O-Isopropylideneisopyridoxamine[7] (VII), a material for the synthesis of thiazoline-thiones (IX, X, XI, XII), was prepared from pyridoxine[8] (I) as outlined in Chart 1. In order to obtain α^4,3-O-isopropylidenepyridoxal[9] (II), dry hydrogen chloride was passed into the suspension of I in acetone according to Korytnk's method.[9] Korytnyk, *et al.*[9] obtained only the compound (II), while we could isolate α^4,α^5-O-isopropylidenepyridoxol[10] (III) besides II in a ratio of 2: 3. Oxidation of II with manganese dioxide[11] followed by the reaction with hydroxylamine afforded α^4,3-O-isopropylideneisopyridoxal oxime[7] (VI). Brooks, *et al.*[7] obtained VII in 32% yield by the reduction of VI with lithium aluminum hydride. However, we could obtain VII in 83% yield by the reduction of VI with zinc-acetic acid. Catalytic reduction of VI with palladium on charcoal gave VII in 42% yield, which was also prepared from α^4,3-O-isopropylidene-5-chloromethyl-2-methylpyridine[12] (IV) and ammonium hydroxide in 38% yield.

Treatment of VII with 25% ammonium hydroxide, carbon disulfide, and chloropropanone followed by hydrolysis with 10% hydrochloric acid gave 3-(3-hydroxy-4-hydroxymethyl-2-

1) Part I: I. Ito, Y. Kuroyanagi, and K. Suzuki, *Yakugaku Zasshi*, **95**, 944 (1975).
2) A part of this paper was presented at the 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April 1969.
3) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
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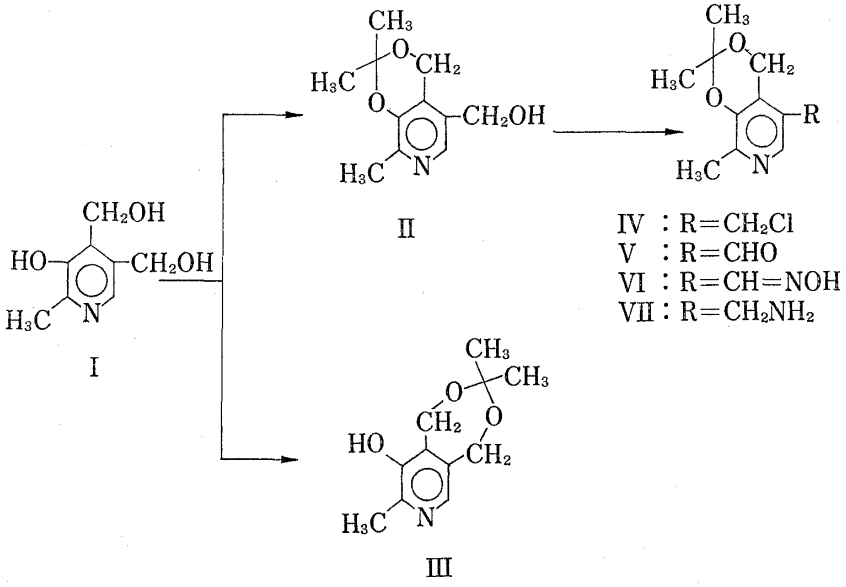

Chart 1

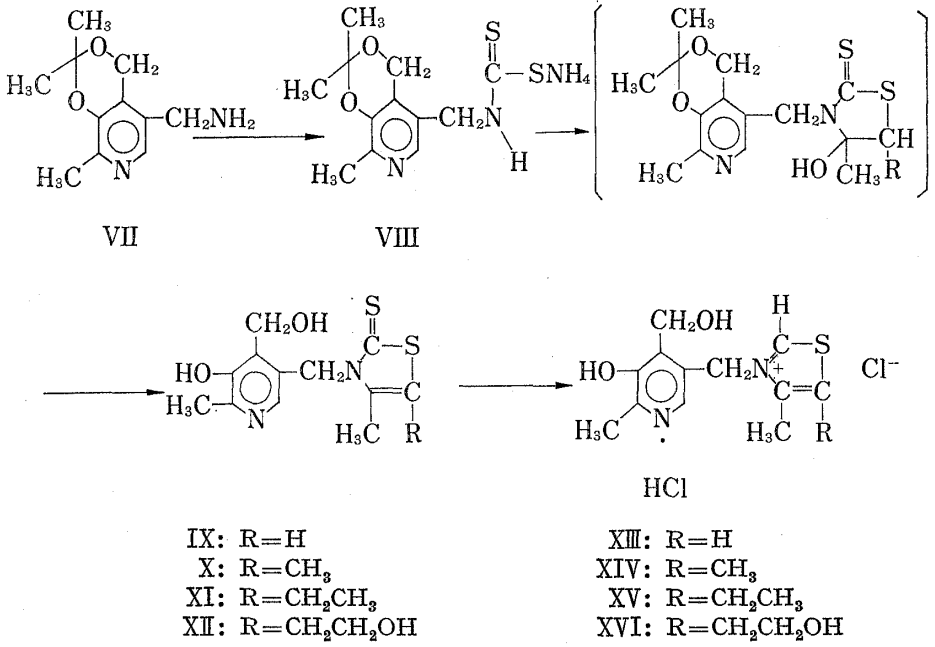

Chart 2

methyl-5-pyridyl)methyl-4-methylthiazoline-2-thione (IX) in 65% yield. The intermediate, ammonium N-(α^4,3-O-isopropylideneisopyridoxyl) dithiocarbamate (VIII) was prepared by the reaction of VII with 25% ammonium hydroxide and carbon disulfide in 50% yield. VIII was unstable in the air and decomposed gradually evolving hydrogen sulfide. IX was obtained by the reaction of VIII with chloropropanone followed by hydrolysis with 10% hydrochloric acid in 18% yield. IX showed positive reaction for the Gibbs's[13] and Grotes's[14] reagents. This facts supported the existence of –OH and >C=S groups in the compound (IX). In the ultraviolet (UV) spectrum of IX, the maximum absorption was observed at 321 nm (log ε=4.10), which is a typical absorption of thiazoline-2-thiones.[15] Its nuclear magnetic reso-

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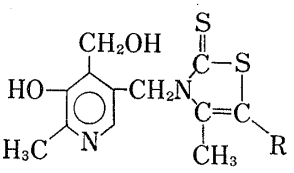
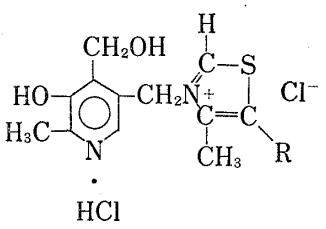
Table I. 3-(3-Hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methyl-4-methyl-5-substitutedthiazoline-2-thiones



Compound No.	R	mp (°C) (decomp.)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
IX	H	215—216	65	$C_{12}H_{14}O_2N_2S_2$	51.04 (51.31)	5.00 (4.93)	9.92 (9.97)
X	CH_3	232—233	34	$C_{13}H_{16}O_2N_2S_2$	52.68 (53.07)	5.44 (5.30)	9.45 (9.56)
XI	CH_2CH_3	185—185.5	36	$C_{14}H_{18}O_2N_2S_2$	54.14 (54.13)	5.85 (5.60)	9.02 (8.96)
XII	CH_2CH_2OH	199—199.5	53	$C_{14}H_{18}O_3N_2S_2$	51.51 (51.72)	5.51 (5.63)	8.58 (8.61)

Table II. 3-(3-Hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methyl-4-methyl-5-substitutedthiazolium Hydrochloride



Compound No.	R	mp (°C) (decomp.)	Yield (%)	Formula	Analysis Calcd. (Found) C	H	N
XIII	H	218—219	63	$C_{12}H_{16}O_2N_2SCl_2$	44.59 (44.64)	4.99 (5.02)	8.67 (8.69)
XIV	CH_3	142—142.5	70	$C_{13}H_{18}O_2N_2SCl_2$	46.30 (46.45)	5.38 (5.23)	8.31 (8.19)
XV	CH_2CH_3	137—138	53	$C_{14}H_{20}O_2N_2SCl_2$	47.87 (47.85)	5.74 (6.10)	7.98 (7.73)
XVI	CH_2CH_2OH	185—185.5	71	$C_{14}H_{20}O_3N_2SCl_2$	45.78 (45.64)	5.49 (5.48)	7.63 (7.52)

nance (NMR) spectrum disclosed two methyl groups at τ 7.87 and 7.66, N-methylene at τ 4.46, and O-methylene at τ 5.19. An aromatic proton on pyridine ring (6-position) was observed at τ 2.89, and the proton of thiazoline ring (5-position) at τ 3.20, whose signal was easily discriminable by the comparison of the NMR spectra of other 5-substituted thiazoline-2-thiones.

The reaction of VII with 25% ammonium hydroxide, carbon disulfide, and α-haloketones gave corresponding 5-substituted thiazoline-2-thiones (X, XI, XII) (Table I). In order to obtain thiazolium chloride (XIII), IX was treated with 35% hydrochloric acid and 30% hydrogen peroxide to give 3-(3-hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methyl-4-methylthiazoliumchloride hydrochloride (XIII), whose elementary analysis well agreed with the assigned structure. XIII was negative for the Gibbs's reagent suggesting the disappearance of >C=S group. Similary to the preparation of XIII, XIV, XV, and XVI were prepared from X, XI, and XII.

Experimental[16]

α^4,3-O-Isopropylidenepyridoxol[9] (II)——Pyridoxine hydrochloride[8] (I) (12 g) was suspended in dry, freshly distilled acetone (250 ml), and cooled with ice. Dry hydrogen chloride was passed into the suspension for 1 hr, and the mixture was cooled at −10° for 2 hr. The crystals were collected by filtration. The crystals were dissolved in 100 ml of H_2O, and the solution was made alkaline with 10% aq. NaOH solution. The resulting crystals were collected by filtration, washed with water, and recrystallized from H_2O to give colorless needles of mp 110—110.5° (lit.[9] 111—112°). Yield 3 g (25%).

α^4,α^5-O-Isopropylidenepyridoxol[10] (III) was obtained from the alkaline filtrate in the above procedure as follows: The alkaline filtrate was neutralized with 10%HCl to give colorless needles of mp 180—183° (from EtOH) (lit.[10] 184—185°). Yield 2 g (16%).

α^4,3-O-Isopropylideneisopyridoxamine[7] (VII)——(a): Zinc powder (2 g) was added into a solution of α^4,3-O-isopropylideneisopyridoxal oxime[7] (VI) (10 g) in 150 ml of AcOH under stirring for 3 hr. The mixture was filtered and the filtrate was condensed to about 30 ml, and made alkaline with 25% ammonium hydroxide. The resulting crystals were collected by filtration, and recrystallized from cyclohexane to give colorless needles of mp 88—90° (lit.[7] mp 89—90°). Yield 7.5 g (83%).

(b): A solution of VI (1 g) in 50 ml of MeOH was agitated under atomospheric pressure of hydrogen in the presence of 1 g of 5% palladium on charcoal for 6 hr. The catalyst was filtered off, and the filtrate was evaporated to give crystals which were recrystallized from cyclohexane, colorless needles of mp 88.5—90°, yield 400 mg (42%).

(c): Ammonium gas was saturated in the cooled solution of α^4,3-O-isopropylidene-5-chloromethyl-2-methylpyridine[12] (IV) (1 g) in 40 ml of EtOH. The mixture was heated at 85° for 5 hr in an autoclave. EtOH was distilled and the residue was dissolved in H_2O (15 ml). The solution was made alkaline with 25% ammonium hydroxide to obtain colorless needles of mp 88—90° (from cyclohexane), yield 300 mg (38%).

Ammonium N-(α^4,3-O-Isopropylideneisopropyridoxyl)dithiocarbamate (VIII)——A mixture of 2.1 g of VII, 40 ml of EtOH, 1.5 ml of 25% NH_4OH, and 0.8 g of CS_2 was allowed to stand overnight to obtain colorless needles of mp 152—153° (decomp.). Yield 1.5 g (50%). *Anal.* Calcd. for $C_{12}H_{19}O_2N_3S_2$: C, 47.82; H, 6.35; N, 13.94. Found: C, 47.58; H, 6.62; N, 13.75. UV λ_{max}^{EtOH} nm (log ε): 291 (4.37), 257 (4.19). NMR (DMSO-d_6) τ: 2.05—3.15 (4H, broad singlet, NH_4), 8.52 (6H, singlet, $>C<^{CH_3}_{CH_3}$), 7.74 (3H, singlet, 2-CH_3), 5.40 (2H, broad singlet, 5-CH_2–NH–), 5.06 (2H, singlet, 4-CH_2-O-), 1.40 (1H, broad singlet, –NH–).

3-(3-Hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methyl-4-methylthiazoline-2-thione (IX)——(a): A mixture of VII (4 g), EtOH (60 ml), KI (3 g), chloropropanone (2 g), 25% NH_4OH (2.8 ml), and CS_2(2 g) was allowed to stand overnight at room temperature. Solvent was distilled and the residue was dissolved in 10% HCl (30 ml) and filtered. The filtrate was neutralized with 10% aq. NaOH to give crystals, which were recrystallized from EtOH to give colorless needles of mp 216° (decomp.). Yield 3.5 g (65%). IR ν_{max}^{KBr} cm^{-1}: 1180 (C=S). UV λ_{max}^{EtOH} nm (log ε): 321 (4.10), 293 (3.89). NMR (DMSO-d_6) τ: 3.20 (1H, quartet, J=1.2 Hz, =CH–S–), 4.46 (2H, singlet, –CH_2–N), 5.19 (2H, singlet, 4-CH_2–O–), 7.87 (3H, doublet, J=1.2 Hz, 4-CH_3), 7.66 (3H, singlet, 2-CH_3), 2.89 (1H, singlet, an aromatic proton on pyridine ring (6-position)).

X, XI, and XII were similarly prepared using 3-chloro-2-butanone, 3-chloro-2-pentanone, or 3-chloro-4-oxo-pentyl acetate instead of chloropropanone (Table I).

(b): A mixture of VIII (300 mg), EtOH (10 ml), KI (150 ml) and chloropropanone (100 mg) was heated on a water-bath for 1 hr. EtOH was distilled and the residue was dissolved in 10% HCl (5 ml) and filtered. The filtrate was neutralized with 10% aq. NaOH to give crystals, which were recrystallized from EtOH to give colorless needles of mp 214—215.5° (decomp.), yield 50 mg (18%).

General Procedure for the Synthesis of 3-(3-Hydroxy-4-hydroxymethyl-2-methyl-5-pyridyl)methyl-4-methyl-5-substituted Thiazoliumchloride Hydrochloride (XIII, XIV, XV, XVI) (Table II)——Thiazoline-2-thiones (0.002 mole) was dissolved in 35% HCl (15 ml) and 30% H_2O_2 (500 mg) was added to this solution with stirring for 10 min. Saturated $BaCl_2$ solution was added and the resulting $BaSO_4$ was filtered off. The filtrate was evaporated and the residue was extracted with EtOH. Ether (5 ml) was added and cooled. The resulting crystals were recrystallized from EtOH–ether to give colorless needles. Negative Grote's test.

Acknowledgement The authors express their deep gratitude to the members of the Microanalytical Center of this Faculty for elemental analyses and measurement of NMR spectra.

16) All the melting points were determined on a Yanagimoto Micro Melting Point apparatus and were not corrected. The IR spectra were measured with a Nihon Bunko Spectroscopic Co. Ltd. Model IR-S. The NMR spectra were measured with a Japan Electron Optics Laboratory Co. JNM-MH-60 spectrometer using tetramethylsilane as internal standard. The UV absorption spectra were recorded with a Hitachi Recording Spectrometer EPS-3T.