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Aminomethylation of Thiamine Disulfides and Formation of Cyclobismethylenethiamine from N-Aminomethylated Thiamine Disulfide

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Aminomethylation of O-benzoylthiamine disulfide (VI) with chloromethyldialkylamine (VIII), methylenebisdialkylamine (IX) and ethyl piperidinomethyl ether (Xb) was carried out to afford the corresponding N-aminomethylated compounds (XI).

The reaction of thiamine disulfide (VII) with VIII or Mannich reaction of VII by the use of 37% formalin and piperidine gave N-aminomethylated compound (XIIb) without formation of the N,O-substituted compound which was reacted with both NH_2 and OH groups.

Cyclobismethylenethiamine (II) was obtained by the treatment of XIIb with mercaptoethanol. The results supported that II would be formed through N-aminomethylthiamine (V).

We have found previously the formation of cyclobismethylenethiamine (II)[2] by the reaction of thiamine (I) with formalin in the presence of secondary amines. Most recently we have described[3] the validities of S-aminomethylthiamine (III) and N-hydroxymethyl-

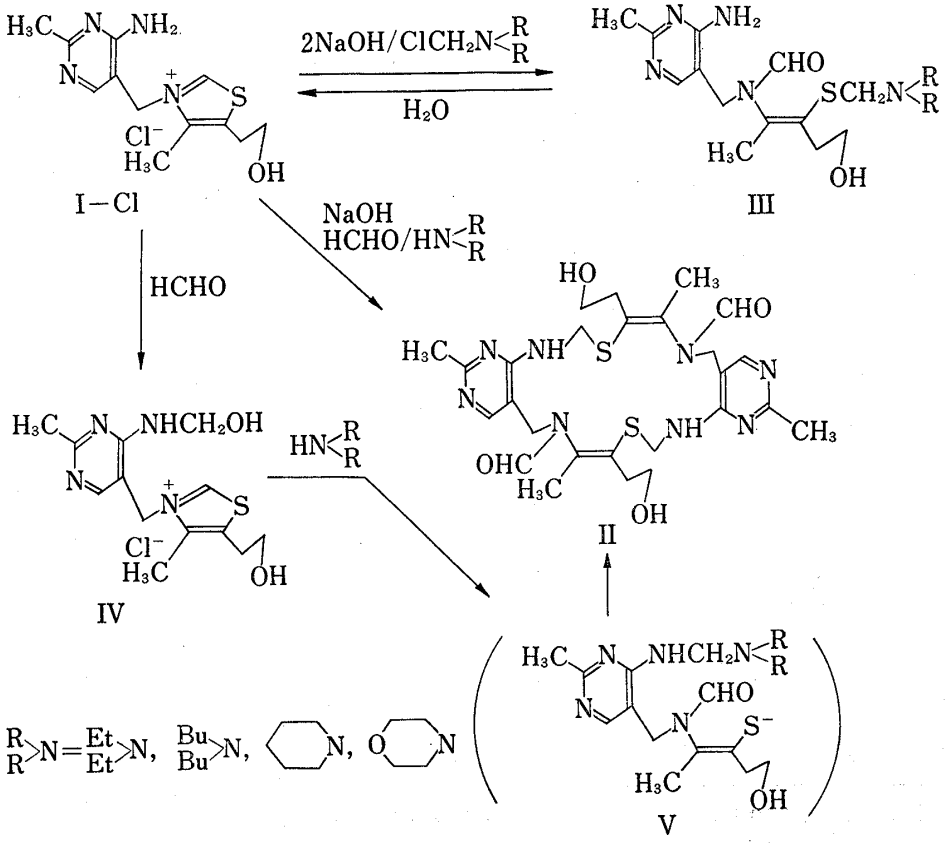

Chart 1

1) Location: *16–89 Kashima-3-chome, Yodogawa-ku, Osaka, 532, Japan.*
2) N. Yoneda, K. Hagio, H. Yasuo, and Y. Matsuoka, *Vitamin*, **44**, 258 (1971).
3) H. Yasuo, *Chem. Pharm. Bull.* (Tokyo), **24**, 845 (1976).

thiamine (IV) as a possible intermediate in the process to II. From the reactions and properties of III and IV, we presumed that II would be formed through N-aminomethylthiamine (V), though we did not succeed to isolate V because of its unstability.

In this paper, we describe the synthesis of N-aminomethylthiamine disulfides by aminomethylation of thiamine disulfides and an attempt to the formation of II using the corresponding N-aminomethylated compound. We firstly examined the N-aminomethylation of O-benzoylthiamine disulfide (VI) containing only NH_2 group as a reactive function. Aminomethylation[4] of VI with chloromethyldialkylamine (VIII), methylenebisdialkylamine (IX)[5] and ethyl piperidinomethyl ether (Xb)[6] was carried out in organic solvent, because VI was insoluble in water. When a chloroform solution of VI was allowed to react with freshly prepared chloromethylpiperidine (VIIIb)[7] in the presence of triethylamine at room temperature, N-piperidinomethyl-O-benzoylthiamine disulfide (XIb) was obtained as colourless prisms, mp 143—145° (decomp.), in 76.0% yield. The infrared (IR) spectrum of XIb showed the presence of O-benzoyl group at 1720 cm^{-1}. The ultraviolet (UV) spectrum of XIb showed maxima at 233 and 280 nm in ethanol. The nuclear magnetic resonance (NMR) spectrum of XIb revealed a doublet at 4.50 ppm and a broad triplet at 7.0 ppm which were due to the methylene protons and NH proton of $-NHCH_2N<$group, respectively. On treatment with deuterium oxide, the signal of NH disappeared and the doublet at 4.50 ppm changed to singlet. Similarly the reaction of VI with chloromethylmorpholine (VIIIc) afforded N-morpholinomethyl-O-benzoylthiamine disulfide (XIc) in 72.5% yield. However, the reaction of VI with chloromethyldimethylamine (VIIIa) did not give the expected N-dimethylaminomethyl compound (XIa), but gave a small amount of unstable product, which was presumed to be half N-aminomethylated compound (XIII) on the basis of the NMR spectrum. XIII would be produced by the partial hydrolysis of XIa during treatment of the reaction mixture

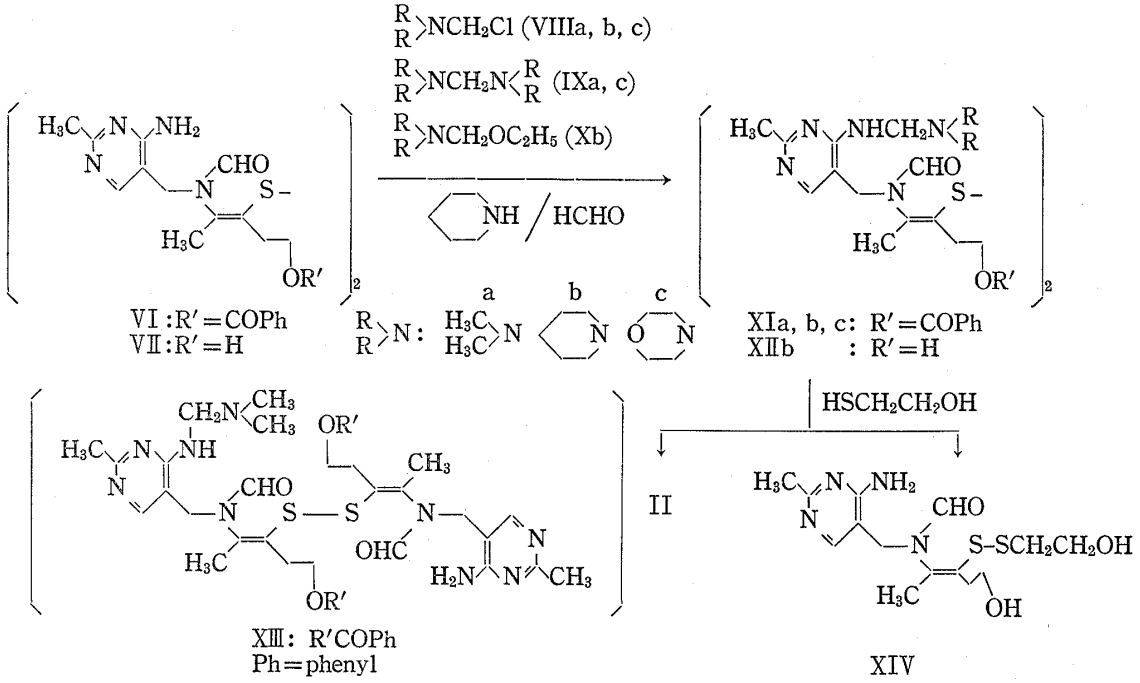

Chart 2

4) *a*) H. Böhme, E. Mundlos, W. Lehners, and Otto-Erich, *Chem. Ber.*, **90**, 2008 (1957); *b*) H. Böhme and K. Harkte, *ibid.*, **96**, 604 (1963); *c*) H. Böhme and D. Eichler, *ibid.*, **100**, 2131 (1967).
5) *a*) J.R. Feldman and E.C. Wagner, *J. Org. Chem.*, **7**, 31 (1942); *b*) S.V. Lieberman and E.C. Wagner, *ibid.*, **14**, 1001 (1949); *c*) N.A. Dzbanovskii, S.V. Marochko, and A.N. Kost, *Sbornik Statei Obshchei Khim., Akad. Nauk S.S.S.R.*, **1**, 607 (1953) [*Chem. Abstr.*, **49**, 985 *e* (1955)].
6) J.E. Fernandez, C. Powell, and J.S. Fowler, *J. Chem. Eng. Data*, **8**, 600 (1963).
7) H. Böhme and K. Harkte, *Chem. Ber.*, **93**, 1305 (1960).

with water to remove triethylamine hydrochloride. Since the use of VIIIa did not give desirable compound (XIa), methylenebisdimethylamine (IXa) was used instead of VIIIa. On heating VI and IXa up to 80°, XIa was obtained as a colourless powder in 41.2% yield, mp 149—151° (decomp.), without treatment with water. However, the reaction hardly proceeded at room temperature. The structure of XIa was confirmed by the spectral data and elemental analysis. Although XIb and XIc were rather stable in the presence of water, XIa thus obtained was decomposed to both VI and XIII in a tetrahydrofuran (THF)–water solution. This decomposition was observed on thin-layer chromatography (TLC) [alumina, $CHCl_3$–EtOH (10: 1), *Rf*: XIa 0.55; XIII 0.53; VI 0.51]. Similarly XIc was yielded in 58.5% from VI and methylenebismorpholine (IXc). XIb was also obtained in 78.6% yield by the reaction of VI with Xb in chloroform under reflux.

Thiamine disulfide (VII) bearing both NH_2 and OH groups in the molecule was then used and the reaction of VII with VIIIb was achieved. When VII was allowed to react with 2.2 molar ratio of VIIIb in dimethylformamide (DMF) in the presence of triethylamine, colourless prisms, mp 136—138° (decomp.), were obtained. The product was confirmed to be N-piperidinomethylthiamine disulfide (XIIb) by the following spectral data and elemental analysis. The UV spectrum of XIIb showed maxima at 244 and 282 nm in ethanol and its IR spectrum exhibited bands at 3300 and 1065 cm^{-1} (OH). The NMR spectrum of XIIb showed a broad triplet at 7.10 ppm and a doublet at 4.35 ppm attributable to the NH proton and the methylene protons of $-NHCH_2N<$ group, respectively. By irradiation of 7.10 ppm, the signal of 4.35 ppm changed to singlet. The reaction of VII with 5.5 molar ratio of VIIIb afforded XIIb exculsively in 65.0% yield without formation of the other N,O-substituted compound[8] coupled with both NH_2 and OH groups. When the hydrochloride of VII was allowed to react with VIIIb in DMF, the starting material was recovered quantitatively.

Although Mannich reaction of 4-aminopyrimidine compounds had been reported by Hirano, *et al.*,[9] in this study the reaction of VII with 2.2 molar ratio of formalin and piperidine was carried out to investigate the reactivity of the two functional groups (hydroxy and amino group) of VII. In this reaction, only XIIb was isolated in 80.0% yield, which was identified with authentic sample obtained by the reaction of VII and VIIIb. Even when 6.0 molar ratio of formalin and piperidine were treated with VII, XIIb was exculsively obtained in 76.5% yield without formation of the other N,O-substituted compound.

As mentioned above, it was found that the NH_2 group on the pyrimidine ring reacted rather easily with VIII, IX and X to afford N-aminomethylated compounds.

It is well known that the S-S bond of thiamine disulfide is cleaved by treatment with mercaptan.[10] Accordingly, it is expected that the treatment of XIIb with mercaptan would form II by the nucleophilic attack of RS anion to the methylene of the $-NHCH_2N<$ group, as presumed in the preceding paper.[3] A suspended solution of XIIb in water was treated with 2.0 molar ratio of mercaptoethanol at room temperature. The reaction mixture became gradually clear and then was extracted with chloroform. From the chloroform-extract which showed several spots on TLC, an oily residue was obtained and the residue was purified by column chromatography on silica gel. Compound II was isolated from the first eluent of chloroform–ethanol (4: 1) in 14.7% yield and identified with an authentic specimen by TLC and IR spectrum. From the second fraction, thiamine β-hydroxyethyl disulfide (XIV) was obtained in 18.6% yield and identified with an authentic specimen prepared by Yurugi's method.[11] Other by-products could not be characterized successfully.

8) Böhme, *et al.* reported the synthesis of methyl piperidino methyl ether by the reaction of methanol with VIIIb in the presence of triethylamine in ether (See reference 4 *b*). Although β-phenethyl alcohol allowed to react with VIIIb in the presence of triethylamine in DMF, an expected ether compound was not obtained but the starting materials were recovered quantitatively.

9) H. Hirano and H. Yonemoto, *Yakugaku Zasshi*, **76**, 234 (1956).

10) S. Yurugi, H. Kawasaki, and S. Noguchi, *Yakugaku Zasshi*, **75**, 498 (1955).

11) S. Yurugi, *Yakugaku Zasshi*, **74**, 1157 (1954).

The results are briefly summarized as follows.

(1) The NH_2 group of O-benzoylthiamine disulfide (VI) reacted easily with chloromethyldialkylamine (VIII), methylenebisdialkylamine (IX) and ethyl piperidinomethyl ether (Xb) to afford the corresponding N-aminomethylated compounds (XI).

(2) The reaction of thiamine disulfide (VII) with chloromethylpiperidine (VIIIb) afforded only N-aminomethylated compound (XIIb), and N,O-substituted compound was not obtained even by the treatment with excess of VIIIb.

(3) Compound XIIb was also obtained by the reaction of VII with formalin and piperidine in a good yield.

(4) Cyclobismethylenethiamine (II) was isolated by the treatment of XIIb with mercaptoethanol. Thiamine β-hydroxyethyl disulfide (XIV) was also obtained.

(5) The results of the above (3) and (4) support that II would be formed through N-aminomethylthiamine (V).

Experimental[12)]

Reaction of O-Benzoylthiamine Disulfide (VI) with Chloromethyldialkylamine (VIII): a) N-Piperidinomethyl-O-benzoylthiamine Disulfide (XIb)——A solution of 1.15 g (0.0015 mole) of VI and 0.30 g (0.003 mole) of Et_3N in $CHCl_3$ (25 ml) was added to a suspension of chloromethylpiperidine (VIIIb) which was freshly prepared from 1.10 g (0.006 mole) of methylenebispiperidine (IXb) and 0.47 g (0.006 mole) of CH_3COCl in THF (20 ml) according to the Böhme's method.[3,7)] After stirring for 3.5 hr at room temperature (23—25°), the reaction mixture was evaporated *in vacuo* and the resulting oil was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 5% $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and then evaporated. The residual oil was crystallized with ether to afford 1.10 g (76.0%) of XIb as a colourless powder. Recrystallization from acetone–ether gave colourless prisms, mp 143—145° (decomp.). *Anal.* Calcd. for $C_{50}H_{64}O_6N_{10}S_2$; mol. wt., 965.27: C, 62.21; H, 6.68; N, 14.51; S, 6.64. Found; mol. wt., 958.30: C, 62.26; H, 6.76; N, 14.30; S, 6.81. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1720, 1645, 1110, 710. NMR ($CDCl_3$) δ: 1.40—1.70 (12 H, m, piperidine-$CH_2CH_2CH_2\times2$), 1.98 (6H, s, $\underset{\underline{CH_3}}{\overset{N\quad S}{\rangle{=}\langle}}\times2$), 2.47 (6H, s, Pm-$C_2$-$CH_3\times2$), 2.50—2.80 (12 H, m, piperidine-$\underline{CH_2}NCH_2\times2$, $\underline{CH_2}CH_2OCO\times2$), 4.20—4.55 (12H, m, $CH_2\underline{CH_2}OCO\times2$, Pm-$C_5$-$\underline{CH_2}\times2$, $NHCH_2N\times2$), 6.90—7.15 (2H, b, t, $NH\times2$), 7.69 (2H, s, Pm-C_6-$H\times2$), 7.82 (2H, s, $NCHO\times2$).

b) N-Morpholinomethyl-O-benzoylthiamine Disulfide (XIc)——A solution of 1.15 g (0.0015 mole) of VI and 0.30 g (0.003 mole) of Et_3N in $CHCl_3$ (25 ml) was added to a suspension of chloromethylmorpholine (VIIIc) which was freshly prepared from 1.12 g (0.006 mole) of methylenebismorpholine (IXc) and 0.47 g (0.006 mole) of CH_3COCl in THF (20 ml), and the reaction mixture was stirred for 3.5 hr at 23—25°. The reaction mixture was worked up in a similar manner as above to give 1.05 g (72.5%) of XIc. Recrystallization from acetone–ether gave colourless prisms, mp 134—136° (decomp.). *Anal.* Calcd. for $C_{48}H_{60}O_8N_{10}S_2$; mol. wt., 969.22: C, 59.48; H, 6.24; N, 14.45; S, 6.61. Found; mol. wt., 953.30: C, 59.46; H, 6.20; N, 14.42; S, 6.65. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1720, 1645, 1115, 710. NMR ($CDCl_3$) δ: 2.0 (6H, s, $\underset{\underline{CH_3}}{\overset{N\quad S}{\rangle{=}\langle}}\times2$), 2.50 (6H, s, Pm-$C_2$-$CH_3\times2$), 2.55—2.80 (12 H, m, morpholine-$CH_2NCH_2\times2$, $\underline{CH_2}CH_2OCO\times2$), 3.63—3.80 (8H, m, morpholine-$CH_2OCH_2\times2$), 4.20—4.60 (12 H, m, $CH_2\underline{CH_2}OCO\times2$, $NHCH_2N\times2$, Pm-C_5-$CH_2\times2$), 7.0—7.40 (2H, b, t, $NH\times2$), 7.72 (2 H, s, Pm-C_6-$H\times2$), 7.85 (2 H, s, $NCHO\times2$).

Reaction of VI with Methylenebisdialkylamine (IX): a) N-Dimethylaminomethyl-O-benzoylthiamine Disulfide (XIa)——A mixture of 1.15 g (0.0015 mole) of VI and 10.0 g (0.10 mole) of methylenebisdimethylamine (IXa) was heated at 80° for 1.5 hr with stirring. After cooling, a precipitated colourless powder was filtered, washed with *n*-hexane and ether and then dried. Reprecipitation from acetone–ether gave 0.55 g (41.2%) of XIa as a colourless powder, mp 149—151° (decomp.). *Anal.* Calcd. for $C_{44}H_{56}O_6N_{10}S_2$: C, 59.70; H, 6.37; N, 15.82; S, 7.24. Found: C, 59.67; H, 6.33; N, 15.37; S, 7.28. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1720, 1640, 1115, 710. NMR ($CDCl_3$) δ: 2.0 (6H, s, $\underset{\underline{CH_3}}{\overset{N\quad S}{\rangle{=}\langle}}\times2$), 2.43 [12H, s, $N(CH_3)_2\times2$], 2.49 (6H, s, Pm-C_2-$CH_3\times2$),

12) All melting points are uncorrected. NMR spectra were taken on a Hitachi Perkin-Elmer R-20 A in $CDCl_3$ solution with tetramethylsilane as an internal standard. Chemical shifts are given in δ (ppm) values. Abbreviations used are s=singlet, d=doublet, t=triplet, m=multiplet, and b=broad. IR spectra were taken in nujol mull on a Shimadzu IR-27 G spectrometer. Molecular weights were measured on a Hitachi Perkin-Elmer 115 Apparatus in $CHCl_3$.

2.70 (4H, t, $\underline{CH_2}CH_2OCO\times2$), 4.20—4.50 (12 H, m, $CH_2\underline{CH_2}OCO\times2$, $NHCH_2N\times2$, Pm-C_5-$CH_2\times2$), 7.72 (2 H, s, Pm-C_6-$H\times2$), 7.86 (2 H, s, $NCHO\times2$).

b) **XIc**——A solution of 1.15 g (0.0015 mole) of VI and 1.70 g (0.009 mole) of IXc in $CHCl_3$ (20 ml) was heated for 10 hr under reflux. After concentration *in vacuo*, the residual oil was washed with *n*-hexane and ether to obtain 0.85 g (58.5%) of XIc as a colourless powder. Recrystallization from acetone–ether gave colourless prisms, mp 134—136° (decomp.) and this compound was identified with the product obtained by the reaction of VI with VIIIc.

Reaction of VI with Ethyl Piperidinomethyl Ether (Xb): XIb——A solution of 3.86 g (0.005 mole) of VI and 1.86 g (0.013 mole) of Xb in $CHCl_3$ (40 ml) was heated under reflux for 9 hr. After concentration *in vacuo*, the residual oil was washed with *n*-hexane to obtain 3.80 g (78.6%) of XIb as a colourless powder. Recrystallization from acetone–ether gave colourless prisms, mp 143—145° (decomp.). This compound was identified with the product obtained by the reaction of VI with VIIIb.

Reaction of Thiamine Disulfide (VII) with VIIIb: N-Piperidinomethylthiamine Disulfide (XIIb)——A mixture of 2.20 g (0.004 mole) of VII and 0.89 g (0.0088 mole) of Et_3N in DMF (60 ml) was added to a suspension of VIIIb which was prepared from 1.60 g (0.0088 mole) of IXb and 0.69 g (0.0088 mole) of CH_3COCl in ether (30 ml) in the usual way. After stirring for 30 min at 23—25°, the reaction mixture became to a clear solution and stirring was continued further 30 min at the same temperature. The reaction mixture was concentrated *in vacuo* to yield a viscous residue, which was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to leave an oily residue. On treatment with H_2O (20 ml) this oil solidified as a colourless powder of XIIb (2.0 g, 68.2%). Recrystallization from acetone–ether gave colourless prisms, mp 136—138° (decomp.). *Anal.* Calcd. for $C_{36}H_{56}O_4N_{10}S_2$; mol. wt., 757.06: C, 57.11; H, 7.45; N, 18.50; S, 8.47. Found; mol. wt., 751.56: C, 56.94; H, 7.47; N, 18.78; S, 8.42. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3175, 1655, 1120, 1065. NMR ($CDCl_3$) δ: 1.40—1.70 (12 H, m, piperidine-CH_2-$CH_2CH_2\times2$), 2.0 (6H, s, $\underset{\underset{CH_3}{|}}{N}=\underset{|}{S}\times2$), 2.46 (6H, s, Pm-$C_2$-$CH_3\times2$), 2.50—2.80 (12 H, m, piperidine-CH_2-$NCH_2\times2$, $\underline{CH_2}CH_2OH\times2$), 3.45 (4H , b, t, $CH_2\underline{CH_2}OH\times2$), 3.90—4.10 (2 H, b, $OH\times2$), 4.35 (8H, b, d, $NH\underline{CH_2}N\times2$, Pm-$C_5$-$CH_2\times2$), 6.90—7.20 (2 H, b, t, $NH\times2$), 7.71 (2 H, s, Pm-C_6-$H\times2$), 7.90 (2 H, s, $NCHO\times2$).

When 5.5 molar ratio of VIIIb was used in this reaction, XIIb was obtained in 65.0% yield.

Reaction of VII with Formalin and Piperidine: XIIb——To a solution of 1.40 g (0.0025 mole) of VII in a diluted HCl [10% HCl (1.80 g, 0.005 mole)–H_2O (10 ml)] was added 0.80 g (0.0075 mole) of Et_3N with stirring under ice cooling. To the above solution was added successively 0.45 g (0.0055 mole) of 37% formalin and 0.47 g (0.0055 mole) of piperidine at 23—25°. After stirring overnight, the colourless precipitates were collected, washed with H_2O and dried to obtain 1.50 g (80.0%) of XIIb. Recrystallization from acetone–ether gave colourless prisms, mp 136—138° (decomp.). This compound was identified with the product obtained by the reaction of VII with VIIIb.

When 6.0 molar ratio of 37% formalin and piperidine were used in this reaction, XIIb was obtained in 76.5% yield.

The Reaction of Xb with Mercaptoethanol——To a suspension of 1.0 g (0.00132 mole) of XIIb in H_2O (10 ml) was added 0.21 g (0.00264 mole) of $HSCH_2CH_2OH$ with stirring at 23—25°. The reaction mixture became gradually to a clear solution and the pH of the solution indicated 9.4. After stirring over night, the reaction mixture was saturated with NaCl and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel (Kieselgel 60, 30 g). From the first eluent of $CHCl_3$–EtOH (4:1), II (0.06 g, 14.9%), mp 284—289° (decomp.), was obtained and XIII[11] (0.09 g, 18.6%), mp 148—149° (decomp.), was isolated from the second eluent of the same solvent.

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