[Chem. Pharm. Bull. 31(6)2094—2102(1983)]

# Thiazole Analogs of Benzomorphans. III.[1] Syntheses of 4,5,6,7,8,9-Hexahydro-4,8-methano-5-methylthiazolo[4,5-*c*]azocine and 4,5,6,7,8,9-Hexahydro-4,8-methano-5-methylthiazolo[5,4-*c*]azocine

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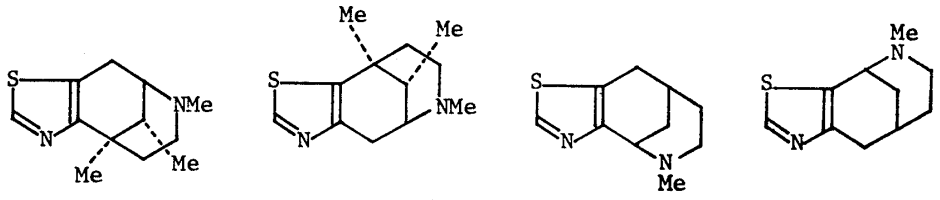
(Received January 13, 1983)

Syntheses of 4,5,6,7,8,9-hexahydro-4,8-methano-5-methylthiazolo[4,5-*c*]azocine (III) and 4,5,6,7,8,9-hexahydro-4,8-methano-5-methylthiazolo[5,4-*c*]azocine (IV) are described. Thiazolization of 2-azabicyclo[3.3.1]nonan-8-one (V) gave the 2-aminothiazole (VII), which was converted into III by deamination, hydrolysis of the benzoyl group and Eschweiler–Clarke *N*-methylation. The 2-hydroxyl derivative (XIII) was also synthesized.

On the other hand, compound (IV) was synthesized by cyclization of the olefinic urethane (XXI) with phenylselenenyl chloride, as a key step. Deselenation of XXII with triphenyltin hydride followed by $LiAlH_4$ reduction gave IV. The urethane (XXI) was prepared from the 2-aminothiazole (XVIIa), which was obtained by condensation of the bromodiketone (XVI) and thiourea.

**Keywords**——analgesic activity; 2-aminothiazole; thiazolomorphan; phenylselenenyl chloride; 4,5,6,7,8,9-hexahydro-4,8-methano-5-methylthiazolo[4,5-*c*]azocine; 4,5,6,7,8,9-hexahydro-4,8-methano-5-methylthiazolo[5,4-*c*]azocine

In previous papers, we have reported syntheses of thiazolo[4,5-*f*]morphan (I)[2] and thiazolo[5,4-*f*]morphan (II),[1] in which the benzene ring of 6,7-benzomorphan has been replaced by a thiazole ring. The analgesic activity of I is comparable to that of morphine, and the variation in the fusing mode of the thiazole ring between I and II caused a considerable difference in potency. These findings prompted us to investigate other thiazolomorphans. In this paper, we describe syntheses of 4,5,6,7,8,9-hexahydro-4,8-methano-5-methylthiazolo[4,5-*c*]azocine (2-methylthiazolo[5,4-*g*]morphan) (III) and 4,5,6,7,8,9-hexahydro-4,8-methano-5-methylthiazolo[5,4-*c*]azocine (2-methylthiazolo[4,5-*g*]morphan) (IV).




I II III IV

Chart 1

## 4,5,6,7,8,9-Hexahydro-4,8-methano-5-methylthiazolo[4,5-*c*]azocine (III)

The thiazolomorphan (III) was synthesized starting from 2-aza-2-benzoylbicyclo[3.3.1]-nonan-8-one (V) as outlined in Chart 2. Preparation of the starting material (V) has already been reported by two different groups, *i.e.*, those of Dolby[3] and Adachi.[4] We obtained V according to Dolby except for the final step, oxidation of 2-aza-2-benzoylbicyclo[3.3.1]nonan-8-ol with chromic acid. The yield of V in this step was remarkably improved by the use of pyridinium chlorochromate.

Treatment of V with pyridinium hydrobromide perbromide afforded the bromoketone (VI) as a sole product. A double doublet ($J$=7 and 10 Hz) at $\delta$ 5.07 in the proton nuclear magnetic

resonance ($^1$H-NMR) spectrum of VI was assigned to the axial proton at the $C_7$-position adjacent to the bromo substituent. Condensation of VI with thiourea gave 2-amino-5-benzoyl-4,5,6,7,8,9-hexahydro-4,8-methanothiazolo[4,5-*c*]azocine (VII). On diazotization and subsequent treatment with calcium hypophosphite, VII was deaminated to VIII in 63% yield. On the other hand, Sandmeyer reaction of VII gave a mixture of VIII and the chloride (IX) in 16 and 57% yields, respectively. Hydrogenolysis of IX gave also VIII in good yield. The $^1$H-NMR spectrum of VIII showed a new singlet at $\delta$ 8.60 due to the $C_2$-proton in the thiazole ring. Acid hydrolysis of VIII followed by *N*-methylation with formalin and formic acid afforded the desired thiazolomorphan (III) in 70% yield as an oil, which was crystallized as an oxalate.

It is well known that a phenolic hydroxyl group at the 2′-position in 6,7-benzomorphan enhances the analgesic effect.[5] Thus, we synthesized the 2-hydroxyl derivative of III. The

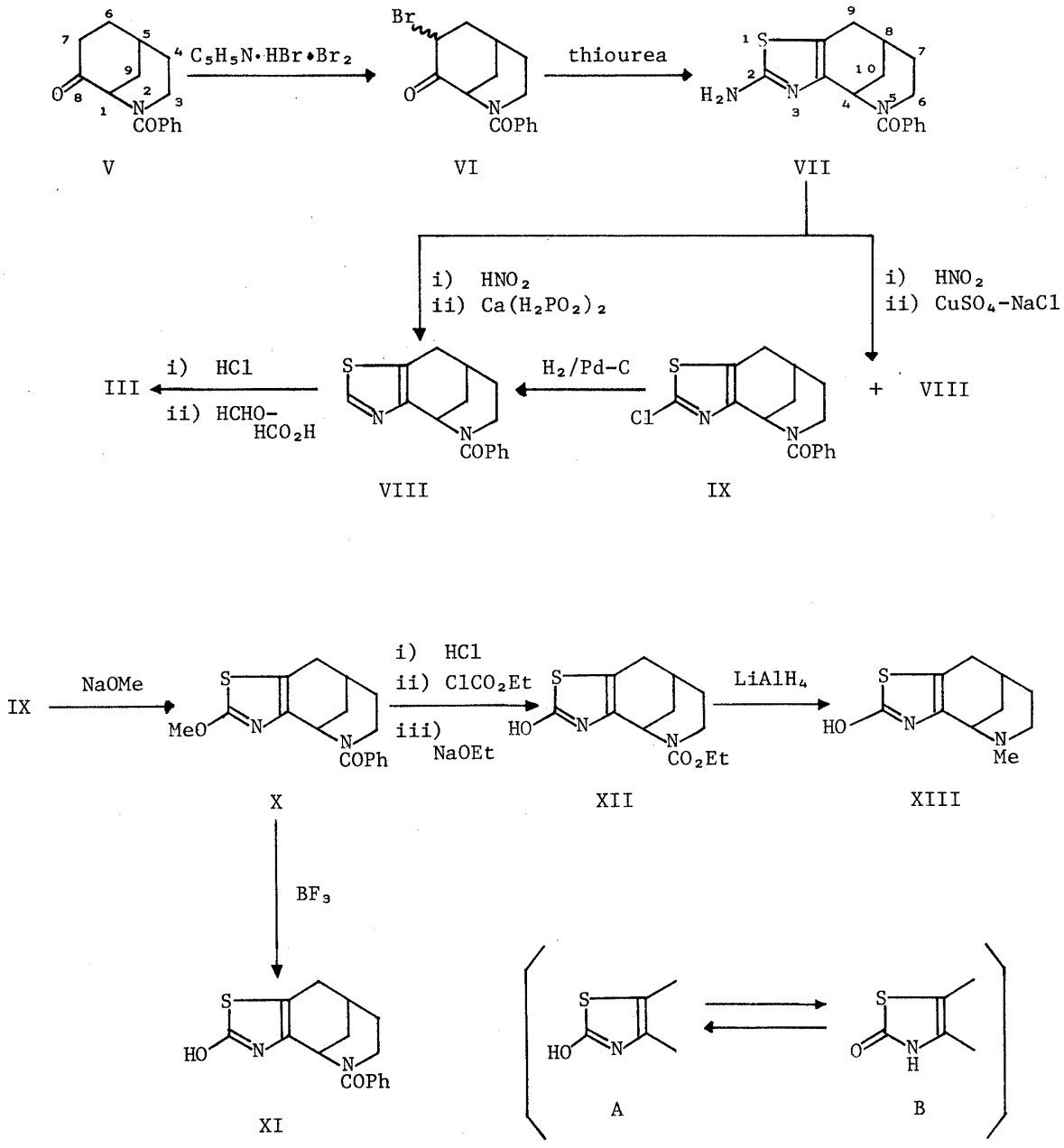



Chart 2

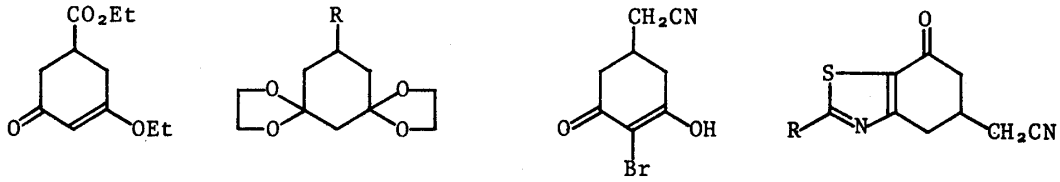
chloride (IX) was converted to the 2-methoxythiazole (X) by treatment with sodium methoxide in methanol. Treatment of X with boron trifluoride gave the partially hydrolyzed product (XI), in which the amido function at the 5-position still remained. Hence X was hydrolyzed with 6 N hydrochloric acid in order to remove the benzoyl group, then the crude product was treated with ethyl chloroformate. Gas chromatographic–mass spectrometric (GC–MS) analysis of this reaction mixture indicated that the main product was the bis-ethoxycarbonyl substituted compound (*m/e* 340, $M^+$). Therefore, solvolysis of the mixture with sodium ethoxide in ethanol was carried out and the urethane (XII) was obtained in 35% yield from X. Lithium aluminum hydride ($LiAlH_4$) reduction of XII gave 4,5,6,7,8,9-hexahydro-2-hydroxy-4,8-methano-5-methylthiazolo[4,5-*c*]azocine (XIII) as colorless needles in 61% yield.

The $^1$H-NMR spectra of VII—X are complicated and indicate that the compounds consist of mixtures of corresponding rotamors involving the amido function. The $^1$H-NMR spectrum of the thiazolomorphan (III) showed a singlet due to the *N*-methyl group at $\delta$ 2.25, a triplet ($J$=3 Hz) due to the $C_4$-proton at $\delta$ 4.03 and a singlet due to the $C_2$-proton at $\delta$ 8.58. On the other hand, the spectrum of the 2-hydroxyl derivative (XIII) exhibited a singlet due to the *N*-methyl group at $\delta$ 2.43 and a deuterium oxide-exchangeable signal at $\delta$ 9.71, and the signal of the $C_4$-proton overlapped with the other aliphatic signals.

In general, compounds (XI—XIII) are capable of existing in two tautomeric forms, 2-hydroxythiazole (A) and 4-thiazolin-2-one (B).[6] The infrared (IR) spectra of all compounds (XI—XIII) have bands at 1680 $cm^{-1}$ (Nujol), and these indicate that form (B) is predominant in the solid state.

**4,5,6,7,8,9-Hexahydro-4,8-methano-5-methylthiazolo[5,4-*c*]azocine (IV)**

5-Cyanomethyl-4,5,6,7-tetrahydro-7-oxobenzothiazole (XVIIc), a key intermediate for the synthesis of IV, was obtained by thiazolization of 2-bromo-5-cyanomethyl-1,3-cyclohexanedione (XVI) followed by deamination of the resulting 2-aminothiazole derivative (XVIIa). The diketone (XVI) was prepared in the following manner (Chart 3).




XIV

XVa: R=$CO_2Et$
XVb: R=$CH_2OH$
XVc: R=$CH_2OTs$
XVd: R=$CH_2CN$

XVI

XVIIa: R=$NH_2$
XVIIb: R=Cl
XVIIc: R=H

Chart 3

The ester (XVa), which was obtained by ketalization of 3-ethoxy-5-ethoxycarbonyl-2-cyclohexen-1-one (XIV),[7] was reduced with $LiAlH_4$. The resulting alcohol (XVb) was converted to the crystalline tosylate (XVc) without further purification. Treatment of XVc with sodium cyanide in refluxing methyl cellosolve gave the nitrile (XVd). Although the absorption band due to the cyano group was absent in the IR spectrum of XVd, its structure was deduced on the basis of the mass spectrum (MS) and the elemental analysis. The protecting groups of XVd were removed with 50% acetic acid, then the crude product was treated with one equivalent of bromine to give the bromodiketone (XVI). Its IR spectrum has bands at 2220, 1660 and 1595 $cm^{-1}$, and these indicate the presence of the cyano and the conjugated $\beta$-diketone functions. Condensation of XVI with thiourea in pyridine afforded the 2-aminothiazole (XVIIa), which was deaminated to the key intermediate (XVIIc) by Sandmeyer reaction and subsequent hydrogenolysis of the resulting chloride (XVIIb) over

palladium-carbon. In contrast with the case of VII, Sandmeyer reaction of XVIIa gave XVIIb exclusively in 81% yield and no replacement by hydrogen was observed. In the case of XVIIa, the $C_7$-carbonyl group may promote the replacement of the corresponding diazonium group by chloride ion. The $^1$H-NMR spectrum of XVIIc showed a new singlet characteristic of the $C_2$-proton in the thiazole ring at $\delta$ 9.04.

Transformation of XVIIc into the thiazolomorphan (IV) is illustrated in Chart 4. Reduction of XVIIc with sodium borohydride gave the alcohol (XVIII) as a sole product. Although the $^1$H-NMR spectrum of XVIII showed a double doublet ($\delta$ 4.99, $J$=6 and 9 Hz) due to the $C_7$-proton adjacent to the hydroxyl group, the stereochemistry was not confirmed. Azeotropic dehydration of XVIII with *p*-toluenesulfonic acid in refluxing toluene gave XIX. Its $^1$H-NMR spectrum showed a double multiplet ($J$=9.5 Hz) due to the $C_6$-proton at $\delta$ 5.90 and a doublet ($J$=9.5 Hz) due to the $C_7$-proton at $\delta$ 6.62. Reduction of XIX with $LiAlH_4$ gave the amine (XX), from which the crystalline urethane (XXI) was derived on treatment with *p*-methoxybenzyl *S*-(4,6-dimethylpyrimidin-2-yl) thiolcarbonate.[8] The $^1$H-NMR spectrum of XXI showed two signals due to the olefinic protons at $\delta$ 5.84 (dd, $J$=3.5 and 10 Hz, $C_6$–H) and $\delta$ 6.47 (dd, $J$=1.5 and 10 Hz, $C_7$–H). Its IR spectrum exhibited bands due to the secondary urethane at 3460 and 1715 cm$^{-1}$.

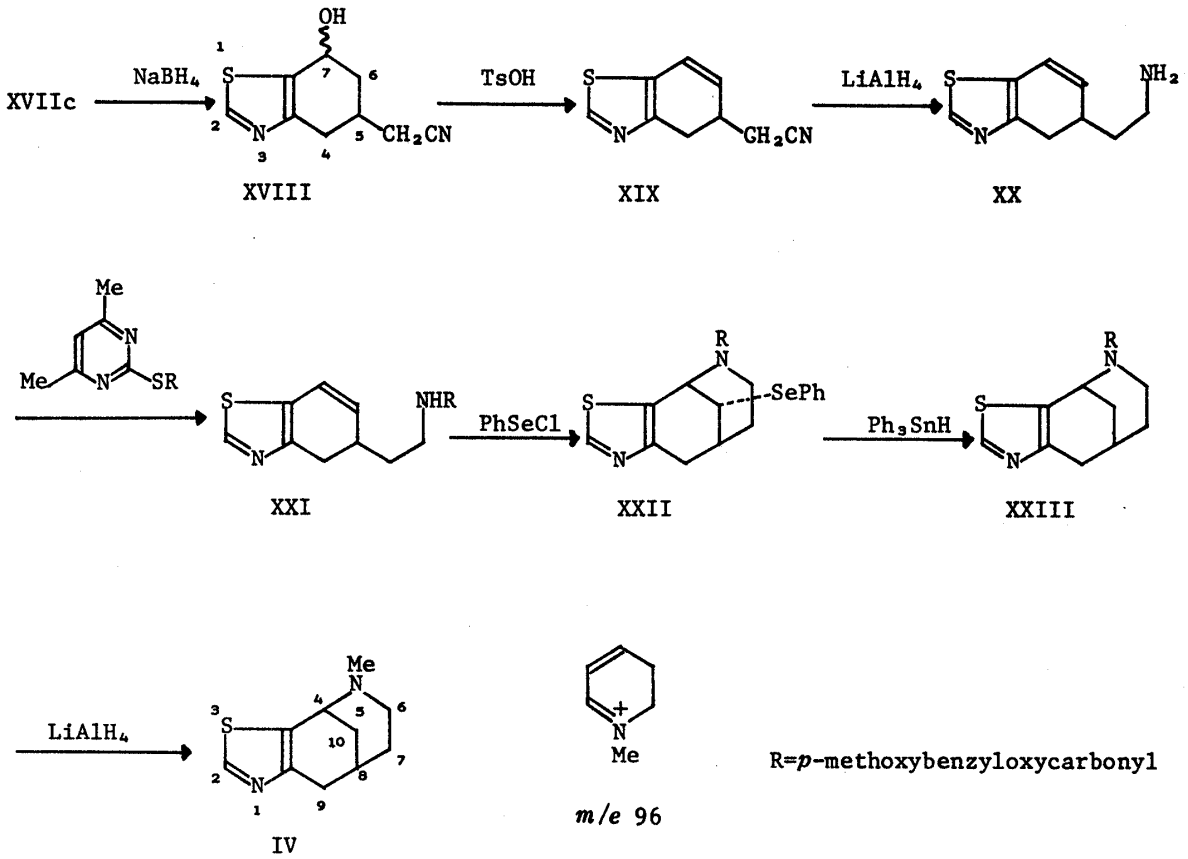



Chart 4

The final process in the synthesis is the cyclization of the olefinic urethane (XXI). Treatment of XXI with phenylselenenyl chloride and silver trifluoroacetate[9] in dichloromethane[10] gave the selenide (XXII) exclusively in 91% yield. The IR spectrum of XXII has a carbonyl band at 1685 cm$^{-1}$ and no band of the NH group, and suggests the cyclized structure for XXII. Deselenation of XXII with triphenyltin hydride[11] gave XXIII quantitatively. The $^1$H-NMR spectrum of XXII is complicated and shows temperature-dependent effects. In its spectrum at 50°C, a triplet ($\delta$ 3.69 $J$=3 Hz) due to the $C_{10}$-proton adjacent to the phenylselenenyl

group[12] and a broad signal ($\delta$ 5.71, $W_H$=8.6 Hz) due to the $C_4$-proton were observed. Irradiation of the signal at $\delta$ 5.71 changed the triplet at $\delta$ 3.69 to a doublet ($J$=3 Hz), and irradiation at $\delta$ 3.69 sharpened the broad signal at $\delta$ 5.71. The $^1$H-NMR spectrum of XXIII showed a broad signal ($\delta$ 5.48, $W_H$=9.5 Hz) due to the $C_4$-proton. These results suggest the occurrence of regioselectivity in the cyclization of XXI to XXII.

Finally, reduction of XXIII with $LiAlH_4$ gave the thiazolomorphan (IV) in 84% yield as an oil, which was crystallized as a dihydrochloride. The structure of IV was defined by comparison of the $^1$H-NMR spectrum and the MS with those of III. The $^1$H-NMR spectrum of IV was very similar to that of III, and showed a singlet due to the *N*-methyl group at $\delta$ 2.22, a triplet ($J$=3 Hz) due to the $C_4$-proton at $\delta$ 3.97 and a singlet due to the $C_2$-proton at $\delta$ 8.67. Similar fragmentation patterns were observed in the MS of III and IV. Furthermore, the MS of III, IV and XIII had a common fragment ion peak at *m/e* 96 characteristic of this type of morphan skeleton.[13] These data defined the structure of IV, and hence the regioselective cyclization of XXI to XXII was proved unambiguously.

## Biological Activity

The thiazolomorphans prepared in this study were evaluated for analgesic activity by the acetic acid-induced writhing method in mice (subcutaneous injection). The $ED_{50}$'s for the oxalate of III and the free base (XIII) were approximately 40 and 100 mg/kg. On the other hand, the dihydrochloride of IV was very toxic; its minimum lethal dose was 20 mg/kg, and serious convulsions were observed at 10 mg/kg.

## Experimental

Melting points were measured on a Yanaco PM-S3 apparatus (a hot stage type) and are uncorrected. IR spectra were determined on a JASCO IRA-1 spectrometer. MS were recorded on a Shimadzu LKB-9000 or a JEOL 01SG spectrometer. $^1$H-NMR spectra were taken on a JEOL PMX-60 or a JEOL PS-100 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard unless otherwise stated. All organic extracts were dried over anhydrous magnesium sulfate. Concentration of all solutions was carried out by evaporation under reduced pressure. Column chromatography was performed with Kieselgel 60 (Merck, 230—400 mesh) or Aluminiumoxid 90 (Merck, activity II—III).

**2-Aza-2-benzoylbicyclo[3.3.1]nonan-8-one (V)**——2-Aza-2-benzoylbicyclo[3.3.1]nonan-8-ol[3] (32.6 g, 0.13 mol) was added all at once to a stirred suspension of pyridinium chlorochromate (43.2 g, 0.20 mol) in dry $CH_2Cl_2$ (1300 ml). After being stirred for 1 d at room temperature, the reaction mixture was decanted and the residue was washed with $CH_2Cl_2$. The supernatant and the washings were combined, and the solution was passed through an alumina column. The eluate was washed successively with dil. HCl and water, dried, and concentrated to give 26.8 g (83%) of V as a pale yellow syrup, which solidified on standing. Recrystallization from benzene–hexane gave colorless needles, mp 78—79°C (lit.[4] mp 72—77°C).

**2-Aza-2-benzoyl-7-bromobicyclo[3.3.1]nonan-8-one (VI)**——Pyridinium hydrobromide perbromide (4.53 g, 14.2 mmol) was added to an ice-cooled solution of V (3.29 g, 13.5 mmol) in AcOH (25 ml) with stirring. After being stirred overnight at room temperature, the reaction mixture was treated with water and extracted with AcOEt. The extract was washed successively with aq. $NaHCO_3$ solution and water, dried, and concentrated to give 4.24 g (97%) of VI as a yellow oil. Crystallization from EtOH gave colorless prisms, mp 119—121°C. *Anal.* Calcd for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01; N, 4.35. Found: C, 56.00; H, 4.88; N, 4.48. IR (Nujol): 1740, 1610 cm$^{-1}$. $^1$H-NMR $\delta$: 1.80—2.80 (7H, m), 3.40—4.00 (2H, m), 4.71 (1H, t, $J$=2.5 Hz, 1-H), 5.07 (1H, dd, $J$=7 and 10 Hz, 7-H), 7.34 (5H, s, aromatic H). MS *m/e*: 321, 323 ($M^+$).

**2-Amino-5-benzoyl-4,5,6,7,8,9-hexahydro-4,8-methanothiazolo[4,5-*c*]azocine (VII)**——A mixture of VI (3.70 g, 11.0 mmol) and thiourea (0.91 g, 12.0 mmol) in tetrahydrofuran (THF) (70 ml) was refluxed for 4 h. After removal of the solvent, the residue was dissolved in dil. HCl. The solution was washed with ether, made basic with aq. NaOH solution, and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give 1.20 g (79%) of VII as a colorless foam. IR ($CHCl_3$): 3380, 1605 cm$^{-1}$. MS *m/e*: 299 ($M^+$).

The perchlorate of VII was recrystallized from MeOH to give colorless prisms, mp 237—238.5°C. *Anal.* Calcd for $C_{16}H_{18}ClN_3O_5S$: C, 48.06; H, 4.54; N, 10.51. Found: C, 48.06; H, 4.53; N, 10.38.

**5-Benzoyl-4,5,6,7,8,9-hexahydro-4,8-methanothiazolo[4,5-*c*]azocine (VIII)**——A solution of $NaNO_2$ (1.48 g, 21.5 mmol) in water (6 ml) was added dropwise to a stirred solution of VII (3.59 g, 12.0 mmol) in 40% $H_2SO_4$ (30 ml) at −7°C. After being stirred for 30 min, the diazotized solution was added to a stirred suspen-

sion of $Ca(H_2PO_2)_2$ (20 g) in water (50 ml) at the same temperature. The mixture was stirred for 1 h at 0°C, then filtered and washed well with $CHCl_3$. The filtrates and the washings were combined and the organic layer was separated, washed with water, and dried. The solution was passed through an alumina column and the eluate was concentrated. The residue was crystallized from AcOEt to give 2.14 g (63%) of VIII as pale yellow needles, mp 152—153.5°C. *Anal.* Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.46; H, 5.74; N, 9.80. IR ($CHCl_3$): 1615 $cm^{-1}$. $^1$H-NMR $\delta$: 1.60—4.75 (9H, m), 5.21 (2/3H, m), 6.19 (1/3H, m), 7.30—7.80 (5H, m, aromatic H), 8.60 (1H, s, 2-H). MS *m/e*: 284 ($M^+$).

**5-Benzoyl-2-chloro-4,5,6,7,8,9-hexahydro-4,8-methanothiazolo[4,5-*c*]azocine (IX)**——A solution of $NaNO_2$ (5.53 g, 80.2 mmol) in water (15 ml) was added dropwise to a stirred solution of VII (20.0 g, 66.9 mmol) in 40% $H_2SO_4$ (100 ml) at −12°C. After being stirred for 2 h at the same temperature, the diazotized solution was added to an ice-cooled solution of $CuSO_4 \cdot 5H_2O$ (50 g) and NaCl (50 g) in water (100 ml) with vigorous stirring. Stirring was continued for 2 h at room temperature, then the reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. The residue was chromatographed on a silica gel column. Elution with benzene–AcOEt (9 : 1) gave 12.2 g (57%) of IX as a yellow oil. Crystallization from AcOEt–hexane gave pale yellow needles, mp 110—112°C. *Anal.* Calcd for $C_{16}H_{15}ClN_2OS$: C, 60.28; H, 4.74; N, 8.79. Found: C, 60.27; H, 4.80; N, 8.83. IR ($CHCl_3$): 1615 $cm^{-1}$. $^1$H-NMR $\delta$: 1.50—3.40 (8H, m), 4.20—4.70 (1H, m), 5.07 (2/3H, m), 6.00 (1/3H, m), 7.46 (5H, m, aromatic H). MS *m/e*: 318, 320 ($M^+$).

Elution with benzene–AcOEt (7 : 3) gave 3.06 g (16%) of VIII as a yellow oil. Crystallization from AcOEt gave yellow needles, mp 151—153°C, which were shown to be identical with an authentic sample by comparison of the IR spectra and by mixed melting point determination.

**Hydrogenolysis of IX**——A mixture of IX (318 mg, 1.0 mmol), triethylamine (120 mg, 1.2 mmol) and 10% Pd-C (90 mg) in EtOH (25 ml) was shaken with $H_2$ under atmospheric pressure. After removal of the catalyst and the solvent, the residue was dissolved in $CHCl_3$. The solution was washed with water, dried, and concentrated to give 255 mg (90%) of a colorless oil, which was shown to be identical with VIII by comparison of the IR spectra.

**4,5,6,7,8,9-Hexahydro-4,8-methano-5-methylthiazolo[4,5-*c*]azocine (III)**——A mixture of VIII (4.57 g, 16.1 mmol) and 6 N HCl (40 ml) in EtOH (40 ml) was refluxed for 16 h. The reaction mixture was concentrated to remove EtOH. The aqueous solution was washed with ether, made basic with aq. $NaHCO_3$ solution, and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. The residue was refluxed with 35% formalin (10 ml) and formic acid (40 ml) for 3 h. The reaction mixture was concentrated and the residue was dissolved in water. The solution was made basic with aq. $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give 2.19 g (70%) of III as a pale yellow oil. $^1$H-NMR $\delta$: 1.40—3.50 (9H, m), 2.25 (3H, s, N–Me), 4.03 (1H, t, $J$=3 Hz, 4-H), 8.58 (1H, s, 2-H). MS *m/e*: 194 (33%, $M^+$), 150 (28%), 136 (100%), 96 (54%), 94 (29%).

The oxalate of III was recrystallized from EtOH–ether to give colorless needles, mp 187—191°C. *Anal.* Calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85. Found: C, 50.52; H, 5.61; N, 9.69.

**5-Benzoyl-4,5,6,7,8,9-hexahydro-4,8-methano-2-methoxythiazolo[4,5-*c*]azocine (X)**——A mixture of IX (17.3 g, 54.3 mmol) and NaOMe (3.0 g of Na in 200 ml of abs. MeOH) was refluxed for 17 h under argon. After removal of the solvent, the reaction mixture was treated with water and extracted with ether. The extract was washed with water, dried, and concentrated to give 14.6 g (86%) of X as a yellow oil. Crystallization from ether–hexane gave colorless prisms, mp 99—100°C. *Anal.* Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 64.79; H, 5.76; N, 8.99. IR ($CHCl_3$): 1610 $cm^{-1}$. $^1$H-NMR $\delta$: 1.40—3.50 (8H, m), 4.02 (3H, s, O–Me), 4.20—4.70 (1H, m), 4.84 (2/3H, m), 5.83 (1/3H, m), 7.40—7.60 (5H, m, aromatic H). MS *m/e*: 314 ($M^+$).

**5-Benzoyl-4,5,6,7,8,9-hexahydro-2-hydroxy-4,8-methanothiazolo[4,5-*c*]azocine (XI)**——A solution of X (1.93 g, 6.15 mmol) and $BF_3$–etherate (10 ml) in abs. MeOH (50 ml) was allowed to stand for 1 d at room temperature. The solution was poured into ice-water and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. Crystallization of the residue from MeOH gave 0.92 g (50%) of XI as colorless needles, mp 244—246°C. *Anal.* Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 64.02; H, 5.31; N, 9.25. IR (Nujol): 3140, 3060, 1680, 1605 $cm^{-1}$. $^1$H-NMR $\delta$: 1.50—3.60 (9H, m), 5.35 (1H, m, $W_H$=9 Hz, 4-H), 7.34 (5H, s, aromatic H), 10.06 (1H, br s, exchangeable with $D_2O$). MS *m/e*: 300 ($M^+$).

**5-Ethoxycarbonyl-4,5,6,7,8,9-hexahydro-2-hydroxy-4,8-methanothiazolo[4,5-*c*]azocine (XII)**——A mixture of X (7.01 g, 22.3 mmol), 6 N HCl (100 ml) and MeOH (40 ml) was refluxed for 20 h. The reaction mixture was concentrated to remove MeOH. The aqueous solution was washed with ether, then concentrated to dryness. A solution of $ClCO_2Et$ (10 ml) in $CHCl_3$ (30 ml) was added dropwise to an ice-cooled mixture of the residue and $Na_2CO_3$ (10 g) in water (50 ml) with stirring. After being stirred for 2 h at room temperature, the reaction mixture was made acidic with dil. HCl and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. A mixture of the residual oil and NaOEt (5.5 g of Na in 200 ml of abs. EtOH) was allowed to stand overnight under argon. After removal of the solvent, the reaction mixture was treated with ice-water, made acidic with dil. HCl, and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. Crystallization of the residue from acetone gave 2.07 g (35%) of

XII as pale yellow needles, mp 214—219°C. *Anal.* Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.97; H, 6.16; N, 10.18. IR (Nujol): 3250, 3120, 1680, 1640 $cm^{-1}$. $^1$H-NMR ($CDCl_3$: $d_4$-MeOH =20 : 1) $\delta$: 1.32 (3H, t, $J$=7 Hz, $OCH_2\underline{CH_3}$), 1.60—3.60 (9H, m), 4.18 (2H, q, $J$=7 Hz, $O\underline{CH_2}CH_3$), 4.67 (1H, dd, $J$=7 and 2 Hz, 4-H). MS *m/e*: 268 ($M^+$).

**4,5,6,7,8,9-Hexahydro-2-hydroxy-4,8-methano-5-methylthiazolo[4,5-*c*]azocine (XIII)**——$LiAlH_4$ (1.00 g, 26.3 mmol) was added portionwise to a stirred solution of XII (2.04 g, 7.6 mmol) in dry THF (250 ml) and the mixture was refluxed for 3 h. After treatment with water, the reaction mixture was filtered and the residue was washed with THF. The filtrates and the washings were combined, and the mixture was dried and concentrated. The product was chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH (9 : 1) gave 0.97 g (61%) of XIII as a colorless solid. Recrystallization from AcOEt gave colorless needles, mp 181—184°C. *Anal.* Calcd for $C_{10}H_{14}N_2OS$: C, 57.11; H, 6.71; N, 13.32. Found: C, 56.97; H, 6.67; N, 13.42. IR (Nujol): 3150, 3050, 2770, 2640, 1680, 1655 $cm^{-1}$. $^1$H-NMR $\delta$: 2.43 (3H, s, N–Me), 9.71 (1H, br s, exchangeable with $D_2O$). MS *m/e*: 210 (27%, $M^+$), 209 (44%, $M^+$–H), 122 (39%), 96 (80%), 59 (100%).

**13-Ethoxycarbonyl-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane (XVa)**——A mixture of XIV (10.5 g, 49 mmol), ethylene glycol (7.3 g, 118 mmol) and TsOH (0.5 g) in benzene (180 ml) was refluxed for 18 h with azeotropic removal of water. After cooling, the reaction mixture was washed successively with aq. $NaHCO_3$ solution and water, dried, and concentrated. Recrystallization of the residual solid from ether–hexane gave 12.8 g (96%) of XVa as a colorless powder, mp 73—75°C. *Anal.* Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.32; H, 7.27. IR ($CHCl_3$): 1750 $cm^{-1}$. $^1$H-NMR $\delta$: 1.25 (3H, t, $J$=7 Hz, $OCH_2\underline{CH_3}$), 1.50—3.10 (7H, m), 3.90—4.40 (10H, m). MS *m/e*: 272 ($M^+$).

**13-Tosyloxymethyl-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane (XVc)**——A solution of XVa (20.0 g, 74 mmol) in dry ether (100 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (4.3 g, 114 mmol) in dry ether (520 ml). After being refluxed for 1 h, the reaction mixture was treated with aq. Rochelle salt solution. The precipitates were filtered off and washed with $CHCl_3$. The filtrate and the washings were combined and the mixture was concentrated to give 16.8 g of XVb as a colorless syrup. IR ($CHCl_3$): 3480 $cm^{-1}$. $^1$H-NMR $\delta$: 1.00—2.20 (7H, m), 1.79 (1H, s, exchangeable with $D_2O$, –OH), 3.53 (2H, d, $J$=6 Hz, $-\underline{CH_2}OH$), 3.95 (8H, m). MS *m/e*: 230 ($M^+$).

A solution of XVb (16.8 g) in dry pyridine (40 ml) was added dropwise with stirring to an ice-cooled solution of TsCl (18.6 g, 98 mmol) in dry pyridine (40 ml). After standing overnight at room temperature, the reaction mixture was concentrated and the residue was treated with ice-water, made acidic (pH 3.8) with dil. HCl, and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. Recrystallization of the residual solid from benzene–hexane gave 23.3 g (83%) of XVc as colorless plates, mp 108—109.5°C. *Anal.* Calcd for $C_{18}H_{24}O_7S$: C, 56.24; H, 6.29. Found: C, 55.97; H, 6.20. IR ($CHCl_3$): 1370, 1180 $cm^{-1}$. $^1$H-NMR $\delta$: 1.05—2.20 (7H, m), 2.47 (3H, s, aromatic Me), 3.80—4.10 (10H, m), 7.38 and 7.83 (each 2H, d, $J$=8.5 Hz, aromatic H).

**13-Cyanomethyl-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane (XVd)**——A mixture of XVc (150 g, 0.39 mol), NaCN (30 g, 0.61 mol) and methyl cellosolve (700 ml) was refluxed for 3 h under argon. After removal of the solvent, the residual oil was dissolved in $CHCl_3$. The solution was washed with water, dried, and passed through a silica gel column. Elution with $CHCl_3$ gave a colorless syrup, which was crystallized from benzene–hexane to give 82.3 g (88%) of XVd as colorless plates, mp 123—124°C. *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.36; H, 7.21; N, 5.88. $^1$H-NMR $\delta$: 1.20—2.60 (9H, m), 3.94 (8H, m). MS *m/e*: 239 ($M^+$).

**2-Bromo-5-cyanomethyl-1,3-cyclohexanedione (XVI)**——A solution of XVd (75.0 g, 0.31 mol) in 50% AcOH (400 ml) was heated at 60°C for 18 h. The reaction mixture was cooled in an ice-bath and a solution of $Br_2$ (50.2 g, 0.31 mol) in AcOH (50 ml) was added dropwise with stirring to the cooled mixture. After being stirred for 15 min at 0°C, the reaction mixture was concentrated. The residue was triturated with water and filtered off. Recrystallization of the pasty cake from MeOH–water gave 61.0 g (85%) of XVI as colorless fine prisms, mp 177—178.5°C. *Anal.* Calcd for $C_8H_8BrNO_2$: C, 41.77; H, 3.51; N, 6.09. Found: C, 41.76; H, 3.22; N, 5.91. IR (Nujol): 2220, 1660, 1595 $cm^{-1}$. MS *m/e*: 229, 231 ($M^+$).

**2-Amino-5-cyanomethyl-4,5,6,7-tetrahydro-7-oxobenzothiazole (XVIIa)**——A mixture of XVI (40.4 g, 0.18 mol), thiourea (14.7 g, 0.19 mol) in pyridine (400 ml) was stirred for 16 h at room temperature, then refluxed for 1 h under argon. The hot mixture was diluted with hot water (400 ml). After cooling, the mixture was filtered to give 17.4 g of XVIIa as amber needles, mp 253—255°C. The filtrate was concentrated, and the residue was triturated with water and filtered off. The brown powder was dissolved in dil. HCl and the solution was filtered to remove insoluble material. Basification of the filtrate with aq. NaOH solution followed by collection of the precipitates gave an additional 14.0 g of XVIIa as a yellow powder, mp 252—254°C, and the total yield of XVIIa was raised to 31.4 g (86%). Recrystallization from MeOH gave pale yellow needles, mp 253—255°C. *Anal.* Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.28. Found: C, 52.19; H, 4.22; N, 20.46. IR (Nujol): 3380, 3270, 2220, 1630 $cm^{-1}$. $^1$H-NMR ($d_6$-DMSO) $\delta$: 2.40—3.00 (7H, m), 8.20 (2H, s, exchangeable with $D_2O$, $-NH_2$). MS *m/e*: 207 ($M^+$).

**2-Chloro-5-cyanomethyl-4,5,6,7-tetrahydro-7-oxobenzothiazole (XVIIb)**——A solution of $NaNO_2$ (3.67 g, 53.2 mmol) in water (10 ml) was added dropwise at −12°C to a stirred solution of XVIIa (10.0 g, 48.4 mmol) in 50% $H_2SO_4$ (50 ml) and 35% HCl (50 ml). After being stirred for 1 h at the same temperature,

the diazotized solution was added to an ice-cooled solution of $CuSO_4 \cdot 5H_2O$ (30 g) and NaCl (30 g) in water (80 ml) with vigorous stirring. Stirring was continued for 1 h at room temperature, then the reaction mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give 8.83 g (81%) of XVIIb as a pale yellow solid. Recrystallization from EtOH gave colorless needles, mp 92—93°C. *Anal.* Calcd for $C_9H_7ClN_2OS$: C, 47.69; H, 3.11; N, 12.36. Found: C, 47.76; H, 3.10; N, 12.25. IR (Nujol): 2220, 1660 $cm^{-1}$. $^1H$-NMR $\delta$: 2.50—3.60 (7H, m). MS *m/e*: 226, 228 ($M^+$).

**5-Cyanomethyl-4,5,6,7-tetrahydro-7-oxobenzothiazole (XVIIc)**——A mixture of XVIIb (2.87 g, 12.7 mmol), triethylamine (2.0 ml, 14.5 mmol) and 10% Pd-C (280 mg) in EtOH (50 ml) was shaken with $H_2$ under atmospheric pressure at 70°C. After removal of the catalyst and the solvent, the residue was dissolved in $CHCl_3$. The solution was washed with water and dried, then passed through a silica gel column. The eluate was concentrated and the product was crystallized from MeOH to give 2.13 g (88%) of XVIIc as colorless plates, mp 144—145°C. *Anal.* Calcd for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.44; H, 4.20; N, 14.55. IR ($CHCl_3$): 2225, 1675 $cm^{-1}$. $^1H$-NMR $\delta$: 2.50—3.60 (7H, m), 9.04 (1H, s, 2-H). MS *m/e*: 192 ($M^+$).

**5-Cyanomethyl-4,5-dihydrobenzothiazole (XIX)**——A mixture of XVIIc (9.36 g, 48.8 mmol) and $NaBH_4$ (1.52 g, 39.9 mmol) in EtOH (70 ml) was stirred for 20 h at room temperature. The reaction mixture was diluted with water and the excess reagent was decomposed with dil. HCl. The mixture was made basic with aq. $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated to give 9.46 g (quantitative yield) of XVIII as a pale yellow syrup. IR ($CHCl_3$): 3600, 3350, 2225 $cm^{-1}$. $^1H$-NMR $\delta$: 1.10—3.20 (7H, m), 4.99 (1H, dd, $J$=6 and 9 Hz, 7-H), 5.05 (1H, br s, exchangeable with $D_2O$, –OH), 8.67 (1H, s, 2-H). MS *m/e*: 194 ($M^+$).

A mixture of XVIII (9.46 g) and TsOH (0.70 g) in toluene (350 ml) was refluxed for 2 d with azeotropic removal of water. After cooling, the reaction mixture was washed successively with aq. $NaHCO_3$ solution and brine, dried, and concentrated to give 7.47 g (87%) of XIX as a pale yellow syrup. High-resolution MS *m/e* Calcd for $C_9H_8N_2S$: 176.0408 ($M^+$). Found: 176.0405 ($M^+$). IR ($CHCl_3$): 2225 $cm^{-1}$. $^1H$-NMR $\delta$: 2.40—3.50 (5H, m), 5.90 (1H, m, 6-H), 6.62 (1H, d, $J$=9.5 Hz, 7-H), 8.57 (1H, s, 2-H).

**2-(4,5-Dihydro-5-benzothiazolyl)-*N*-(*p*-methoxybenzyloxycarbonyl)ethylamine (XXI)**——A solution of XIX (9.78 g, 55.6 mmol) in dry THF (50 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (4.00 g, 105 mmol) in dry ether (400 ml) under argon. After being stirred for 4 h at room temperature, the reaction mixture was treated with aq. Rochelle salt solution and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated to give 6.54 g (65%) of XX as a red oil. $^1H$-NMR $\delta$: 1.39 (2H, br s, exchangeable with $D_2O$, $-NH_2$), 1.55—1.90 (2H, m), 2.70—3.00 (5H, m), 5.85 (1H, dd, $J$=3 and 10 Hz, 6-H), 6.47 (1H, dd, $J$=1.5 and 10 Hz, 7-H), 8.54 (1H, s, 2-H).

A mixture of XX (6.54 g, 36.3 mmol) and *p*-methoxybenzyl *S*-(4,6-dimethylpyrimidin-2-yl)thiolcarbonate (11.0 g, 36.2 mmol) in $CHCl_3$ (200 ml) was stirred for 4 h at room temperature. The reaction mixture was washed successively with aq. $NaHCO_3$ solution and water, dried, and concentrated. The residue was chromatographed on a silica gel column. Elution with AcOEt–hexane (4 : 6) afforded a colorless syrup, which was crystallized from ether–hexane to give 8.95 g (72%) of XXI as colorless needles, mp 74—75°C. *Anal.* Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.63; H, 5.85; N, 8.05. IR ($CHCl_3$): 3460, 1715 $cm^{-1}$. $^1H$-NMR $\delta$: 1.69 (2H, m), 2.70—3.40 (5H, m), 3.80 (3H, s, O–Me), 4.75 (1H, br s, exchangeable with $D_2O$, –NH), 5.03 (2H, s, O–$\underline{CH_2}$Ph), 5.84 (1H, dd, $J$=3.5 and 10 Hz, 6-H), 6.47 (1H, dd, $J$=1.5 and 10 Hz, 7-H), 6.85 and 7.27 (each 2H, d, $J$=9 Hz, aromatic H), 8.54 (1H, s, 2-H). MS *m/e*: 344 ($M^+$).

**Cyclization of XXI with Phenylselenenyl Chloride and Silver Trifluoroacetate**——A solution of phenylselenenyl chloride (0.63 g, 3.2 mmol) in dry $CH_2Cl_2$[10] (10 ml) was added dropwise to an ice-cooled solution of XXI (1.01 g, 2.9 mmol) and silver trifluoroacetate (0.78 g, 3.5 mmol) in dry $CH_2Cl_2$ (15 ml) with stirring. After being stirred for 15 h at room temperature, the reaction mixture was washed successively with aq. $NaHCO_3$ solution and water, dried, and concentrated. The residue was chromatographed on a silica gel column. Elution with AcOEt–hexane (1 : 1) gave 1.33 g (91%) of XXII as a colorless syrup. IR ($CHCl_3$): 1685 $cm^{-1}$. $^1H$-NMR (at 50°C) $\delta$: 1.70—2.00 (2H, m), 2.40—2.96 (3H, m), 3.45 (1H, dd, $J$=6.5 and 18 Hz), 3.69 (1H, t, $J$=3 Hz, 10-H), 3.81 (3H, s, PhO–Me), 3.81—4.00 (1H, m), 5.06 (2H, s, O–$\underline{CH_2}$Ph), 5.71 (1H, br s, $W_H$=8.6 Hz, 4-H), 6.80—7.60 (9H, m, aromatic H), 8.70 (1H, s, 2-H). MS *m/e*: 500 ($M^+$).

**Deselenation of XXII with Triphenyltin Hydride**——A mixture of XXII (4.58 g, 9.2 mmol) and triphenyltin hydride (12.8 g, 36.5 mmol) in dry toluene (30 ml) was refluxed for 4 h under argon. The reaction mixture was chromatographed on a silica gel column. Elution with AcOEt–hexane (1 : 1) gave a colorless syrup, and it was further passed through an alumina column with $CHCl_3$ as the eluting solvent to give 3.13 g (99%) of XXIII as a colorless syrup. High-resolution MS *m/e* Calcd for $C_{18}H_{20}N_2O_3S$: 344.1193 ($M^+$). Found: 344.1167 ($M^+$). IR ($CHCl_3$): 1680 $cm^{-1}$. $^1H$-NMR $\delta$: 1.30—4.10 (9H, m), 3.73 (3H, s, PhO–Me), 5.05 (2H, s, O–$\underline{CH_2}$Ph), 5.48 (1H, br s, $W_H$=9.5 Hz, 4-H), 6.83 and 7.24 (each 2H, d, $J$=8.5 Hz, aromatic H), 8.56 (1H, s, 2-H).

**4,5,6,7,8,9-Hexahydro-4,8-methano-5-methylthiazolo[5,4-*c*]azocine (IV)**——A solution of XXIII (3.13 g, 9.1 mmol) in dry THF (40 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.95 g, 25.0 mmol) in dry THF (80 ml). After being refluxed for 3 h under argon, the reaction mixture was treated with aq. Rochelle salt solution and extracted with $CHCl_3$. The extract was washed with water and concentrated.

The residue was dissolved in dil. HCl and the solution was washed with $CHCl_3$, made basic with aq. NaOH solution, and extracted with $CHCl_3$. This extract was washed with water, dried, and concentrated to give 1.48 g (84%) of IV as a reddish oil. $^1$H-NMR $\delta$: 1.40—3.30 (9H, m), 2.22 (3H, s, N–Me), 3.97 (1H, t, $J$= 3 Hz, 4-H), 8.67 (1H, s, 2-H). MS *m/e*: 194 (81%, $M^+$), 165 (24%), 150 (41%), 136 (100%), 96 (49%).

The dihydrochloride of IV was recrystallized from EtOH to give a pale yellow powder, mp 245—246°C (dec.). *Anal.* Calcd for $C_{10}H_{16}Cl_2N_2S$: C, 44.95; H, 6.04; N, 10.48. Found: C, 44.91; H, 5.94; N, 10.28.

**Acknowledgement** The authors are grateful to Profs. S. Sakai and N. Aimi of Chiba University and Prof. A. Tanaka of this university for their helpful advice and encouragement. They are also grateful to Dr. N. Muto of this university and Dr. T. Mizuhashi of Nihon Iyakuhin Kogyo Co., Ltd. for their advice and cooperation in the pharmacological testing.

## References and Notes

1) Part II: K. Katsuura, K. Yamaguchi, S. Sakai and K. Mitsuhashi, *Chem. Pharm. Bull.*, **31**, 1518 (1983).
2) K. Katsuura, M. Ohta and K. Mitsuhashi, *Chem. Pharm. Bull.*, **29**, 1780 (1981); *idem*, *ibid.*, **30**, 4378 (1982).
3) L.J. Dolby and S.J. Nelson, *J. Org. Chem.*, **38**, 2882 (1973).
4) J. Adachi, K. Nomura, K. Shiraki and K. Mitsuhashi, *Chem. Pharm. Bull.*, **22**, 658 (1974).
5) O.J. Braenden, N.B. Eddy and H. Halbach, *Bull. World Health Organ.*, **13**, 937 (1955); P.S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965).
6) C. Roussel, M. Chanon and R. Barone in "Thiazole and Its Derivatives," ed. by J.V. Metzger, John Wiley and Sons, Inc., New York, N.Y., 1979, Chapter VII.
7) E.E. van Tamelen and G.T. Hildahl, *J. Am. Chem. Soc.*, **78**, 4405 (1956).
8) T. Nagasawa, K. Kuroiwa, K. Narita and Y. Isowa, *Bull. Chem. Soc. Jpn.*, **46**, 1269 (1973).
9) D.L.J. Clive, C.K. Wong, W.A. Kiel and S.M. Menchen, *J. Chem. Soc., Chem. Commun.*, 379 (1978).
10) The dichloromethane used in this reaction was washed with conc. sulfuric acid and distilled over anhydrous potassium carbonate, in order to remove methanol contained as a stabilizer.
11) D.L.J. Clive, G. Chittattu and C.K. Wong, *J. Chem. Soc., Chem. Commun.*, 41 (1978).
12) Although the spectral data for XXII do not provide rigorous proof for the orientation of the phenylselenenyl group, it is assigned as *trans* to the urethane function by assuming the $S_N2$ mode of ring closure.
13) J. Adachi, K. Nomura and K. Mitsuhashi, *Chem. Pharm. Bull.*, **24**, 85 (1976).