[Chem. Pharm. Bull. 21(6)1300—1304(1973)]

UDC 547.789'781.04 : 546.171.1.04

An Unusual Heterocyclic Transformation in Liquid Ammonia[1]

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(Received November 17, 1972)

By the action of liquid ammonia, the cycloadducts of isothiocyanates with 3,4-dimethyl-5-(2-hydroxy)ethylthiazolium ylides (Ia—b) are converted into spiro[3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4'-(5'-iminoimidazolidine)] derivatives (IIa—b), while the reactions of liquid ammonia with N-benzyl analogues (Ic—e) afford 3-aryl-6,8-dimethyl-2,9-dithia-4,6,8-triazatricyclo[3,3,0,$1^{1,5}$]oct-3-enes (IIIa—c) involving an unusual base-catalyzed cleavage reaction of the fused spiro thiazolidine ring. A possible mechanism of the novel transformation reaction is suggested.

Cycloadditions of isothiocyanates with N-substituted 4-methyl-5-(2-hydroxy)ethylthiazolium ylides were previously reported to give spiro[perhydrofuro[2,3-*d*]thiazole-2,4'-imidazolidine] derivatives (I).[3] Mass spectra of these cycloadducts exhibited fragment ion corresponding to (M^+-2S) species, which was suggested to be generated by the mechanism shown below (Chart 1). If the suggested mechanism is correct, mass spectrum of a derivative of I in which 5'-thiocarbonyl group is replaced by other functional group should lack the (M^+-2S) ion. To ascertain this, it is necessary to prepare the derivative lacking sulfur atom at 5'-position of I. This paper is concerned with the preparation of some 5'-imino derivatives of the cycloadducts and an unusual base-induced decomposition reaction of the fused thiazolidine ring system of I leading to bridged episulfide derivatives.

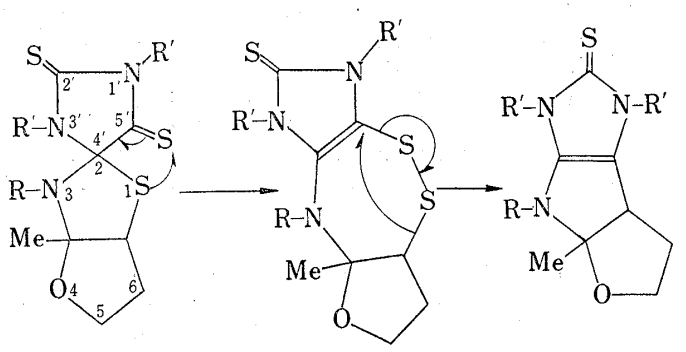


Chart 1

When the cycloadduct of methyl isothiocyanate with 3,4-dimethyl-5-(2-hydroxy)ethylthiazolium ylide (Ia)[3] was treated with liquid ammonia in a sealed tube for 20 hr at room temperature, spiro[3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4'-(1',3'-dimethyl-5'-iminoimidazolidine-2'-thione)] (IIa), mp 118—120°, was obtained in a low yield (5%). Structural assignment for IIa was based on the facts as follows. Elemental analysis of IIa was agreeable with the formula $C_{11}H_{18}ON_4S_2$ indicating that one sulfur atom in Ia was replaced by NH. Infrared (IR) spectrum of IIa shows absorption bands at 3245 cm^{-1} (NH), 1669 cm^{-1} (C=N) and 1280 cm^{-1} (C=S). IIa exhibits no ultraviolet (UV) absorption maximum due to imidazolidine-2,4-dithione chromophore,[3] while a maximum is observed at 271 mμ (log ε=4.02), which indicates that one of the two thiocarbonyl groups of Ia is eliminated. Nuclear magnetic resonance (NMR) spectrum of IIa shows, in addition to three N-CH_3 signals at τ 6.42[s], 6.75[s]

1) A preliminary report was presented in A. Takamizawa and S. Matsumoto, *Tetrahedron Letters*, **1969**, 2875. This paper constitutes the Part LXXIX of the series on Studies on Pyrimidine Derivatives and Related Compounds. Part LXXVIII, A. Takamizawa, I. Makino and S. Yonozawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 785 (1973).

2) Location: *Fukushima-ku, Osaka, 553, Japan.*

3) A. Takamizawa, K. Hirai, S. Matsumoto, S. Sakai, and Y. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 910 (1969).

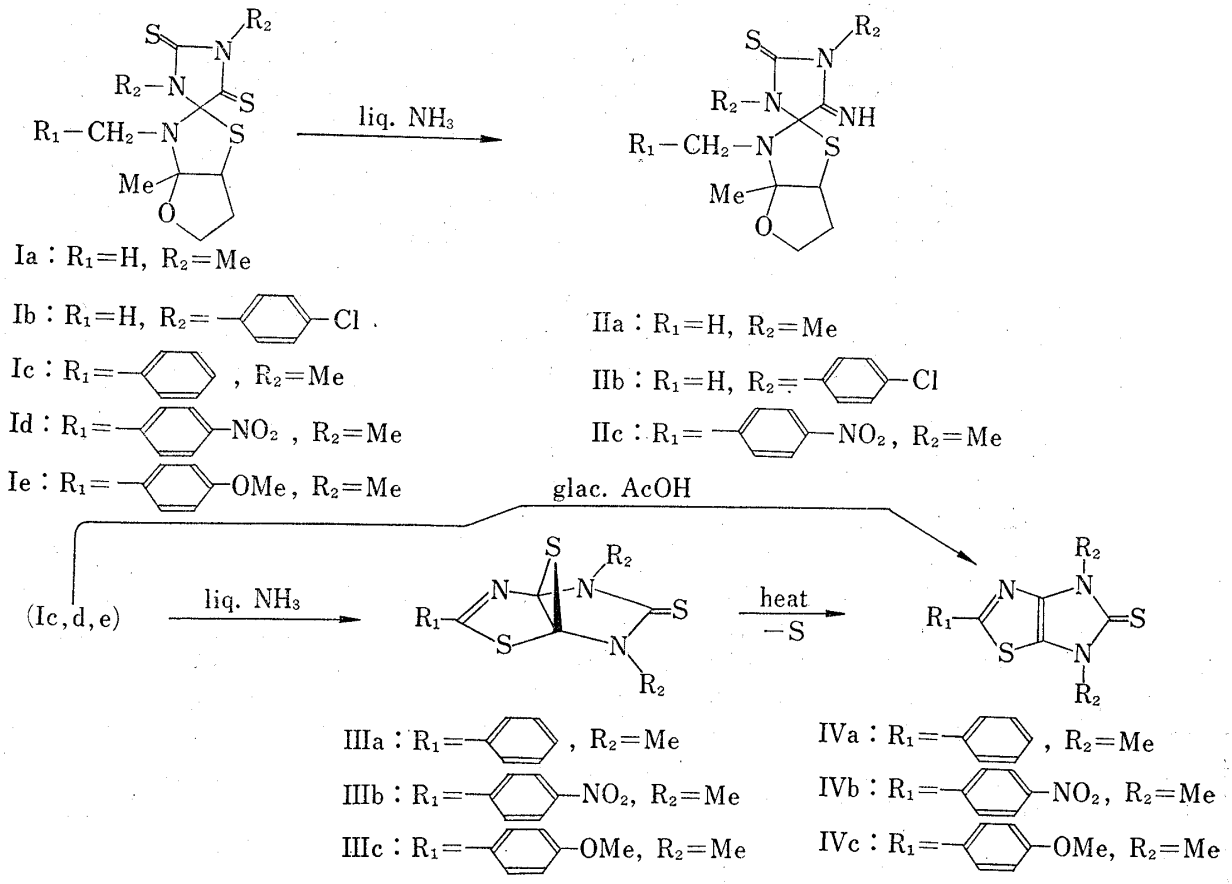


Chart 2

and 7.83^{s}, a C-CH_3 signal at τ 8.34^{s} besides a complex multiplet in the τ 5.5—8.0 region, being in close analogy with that of the starting material. The cycloadduct of *p*-chlorophenyl isothiocyanate with 3,4-dimethyl-5-(2-hydroxy)ethylthiazolium ylide (Ib) also gave a corresponding 5′-imino derivative IIb, mp 120—123°, in a better yield (56%) on treatment with liquid ammonia under the same condition employed for Ia. Spectroscopic data of IIb are also in good agreement with the structure (see Experimental). The fact that IIb gives N,N′-di-*p*-chlorophenyl thiourea on treatment with aq. HCl provides an additional support for the assigned structure. As expected, the mass spectra of both IIa and IIb exhibit no ion corresponding to (M^+-2S) species confirming that one of the two extruded sulfur atoms is placed in the 5′-thiocarbonyl group of I and the suggested fragmentation mechanism is thus supported.[4]

In the case of the reaction of ammonia upon the cycloadduct bearing a benzyl substituent at the fused thiazolidine nitrogen atom, it was found that a different type of product is formed involving a facile cleavage of the thiazolidine ring. Thus, treatment of the cycloadduct Ic,[3] which was obtained by the reaction of methyl isothiocyanate with 3-benzyl-4-methyl-5-(2-hydroxy)ethylthiazolium ylide, with liquid ammonia in a seeled tube for 20 hr at room temperature gave no corresponding 5′-imino derivative, while a product IIIa, $C_{12}H_{11}N_3S_3$, mp 118—121°, being obtained in 83% yield. IR spectrum of IIIa shows strong bands at 1674 cm^{-1} (C=N) and 1290 cm^{-1} (C=S), whereas no band due to NH is observed. IIIa gives a simple NMR spectrum only exhibiting five aromatic protons in the τ 2.4—2.9 region and two N-CH_3 groups at τ 6.15^{s} and 6.23^{s}. On heating of IIIa in toluene at 100° for 30 min, sulfur was readily extruded to give a quantitative yield of 2-phenyl-4,6-dimethyldihydro-

4) Y. Nakagawa, S. Matsumoto, and A. Takamizawa, *Mass Spectrometry* (Japan), **18**, 1044 (1970).

imidazo[4,5-*d*]thiazole-5-thione (IVa) which has been obtained directly from Ic by heating in glac. AcOH or by treating with NaOEt.[3] UV spectrum of IIIa exhibits an absorption maximum at 274 mμ (log ε=3.99), whereas IVa has maxima at 249 mμ (log ε=4.07), 280 mμ (log ε=4.15) and 375 mμ (log ε=4.32), indicating that the sulfur extrusion from IIIa results a marked increase of conjugation. It is reasonable to consider that IIIa has an episulfide group which is placed between two five membered rings and that the sulfur is bridged between two carbons highly substituted by hetero atoms, since certain episulfides are known to undergo readily thermal desulfurization to give carbon-carbon double bond when the generated double bond is situated in a highly conjugated system.[5] The structure of IIIa is thus assigned as 3-phenyl-6,8-dimethyl-2,9-dithia-4,6,8-triazatricyclo[3,3,0,$1^{1,5}$]oct-3-ene. Sectroscopic data cited above are in good agreement with the assigned structure. Reaction of *p*-nitrobenzyl derivative Id[3] with liquid ammonia proceeded more rapidly to give a corresponding bridged episulfide IIIb, mp *ca.* 120° (decomp.), within 3 hr at room temperature, although the isolated yield of the product varied from 15—30% because of considerable instability of the product. In this case, 5′-imino derivative IIc, mp 171—174°, was also isolated. Thermal desulfurization of the episulfide IIIb proceeded rapidly at 100° in toluene to give 2-*p*-nitrophenyl-4,6-dimethyldihydroimidazo[4,5-*d*]thiazole-5-thione (IVb)[3] quantitatively, and the desulfurization gradually proceeded even at room temperature. In the case of the reaction of liquid ammonia with *p*-methoxybenzyl derivative Ie which was prepared by reacting methyl isothiocyanate with 3-*p*-methoxybenzyl-4-methyl-5-(2-hydroxy)ethylthiazolium chloride according to the method described previously,[3] the corresponding episulfide IIIc was obtained only in a trace quantity under the same condition employed for Ic, although it could not be isolated in a pure state. On heating at 100° in toluene, the crude product IIIc gave 2-*p*-methoxyphenyl-4,6-dimethyldihydroimidazo[4,5-*d*]thiazole-5-thione (IVc) which was also derivable directly from Ie in 20% yield by heating in glac. AcOH.

For the mechanism of this unique decomposition reaction, there is a possibility that the reaction can proceed thermally without liquid ammonia. This possibility however, was eliminated by the fact that Ic was found to be quite stable in refluxing toluene. The observed influence of the nature of the substituent attached to the fused thiazolidine nitrogen atom upon the ease of formation of the bridged episulfide indicates that the reaction proceeds by an ionic mechanism involving a carbanion α to the thiazolidine nitrogen. A plausible explana-

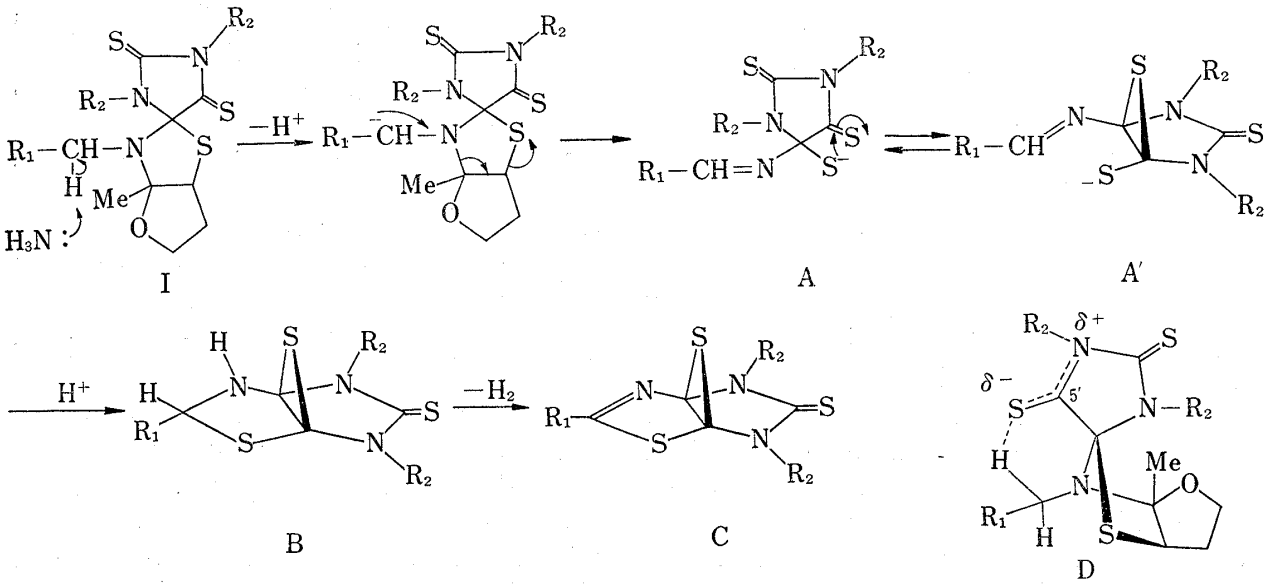


Chart 3

5) For example, see R.H. Schlessinger and A.G. Schultz, *J. Am. Chem. Soc.*, **90**, 1676 (1968).

tion of the formation of episulfide derivative is, as shown in Chart 3, that the reaction possibly proceeds by elimination of the α-hydrogen followed by decomposition of the thiazolidine ring to give sulfide anion A and A′, then intramolecular addition of the sulfide A′ to C=N double bond will give B and auto-oxidation of B will lead to the final product C. It is also possible that the elimination of α-hydrogen and the decomposition of the thiazolidine ring occur concertedly. Base-catalyzed carbanion reactions of some benzyl amine derivatives in liquid ammonia usually require a strong base such as metal amide as the proton acceptor.[6] The fact that the present reaction proceeds without such a strong base suggest that the hydrogens of the α-carbon are considerably activated. A part of the enhanced reactivity of the α-hydrogen is probably attributed to the presence of 5′-thiocarbonyl group (D) because a 5′-imino derivative IIc was recovered unchanged essentially in a quantitative yield when treated with liquid ammonia for 3 hr at room temperature, while, in the same condition, Id was partly converted into the episulfide IIIb as cited before. In addition to the participation of 5′-thiocarbonyl group, the fragmentation reaction may be facilitated by the strain of the fused spiro ring system.

Experimental

All melting points were determined in capillaries and uncorrected. NMR spectra were taken on a Varian Associates A-60 spectrometer in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard. UV spectra were taken on a Hitachi EPS-3 spectrophotometer in 99% EtOH. IR spectra were taken in nujol mull on a Japan Spectroscopic Company IR-S spectrophotometer using a NaCl prism. Column chromatographies were carried out by using SiO_2 (Davision, Grade 950) unless otherwise indicated.

Spiro[3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dimethyl-5′-iminoimidazolidine-2′-thione)] (IIa)——500 mg of spiro[3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dimethylimindazolidine-2′,5′-dithione)] (Ia)[3] was suspended in 20 ml of liq. NH_3 in a sealed tube ($\phi=2$ cm, $l=30$ cm), and the suspension was allowed to stand for 20 hr at room temperature. After evaporation of ammonia, water was added to the residue and extracted with $CHCl_3$. The $CHCl_3$ extract, after washing with water and drying over anhyd. Na_2SO_4, was concentrated *in vacuo* to leave a brown oily residue which was chromatographed with AcOEt. The AcOEt eluate afforded a crystalline product which was recrystallized from acetone to give IIa as pale yellow prisms, mp 118—120°. Yield 20 mg (5%). *Anal.* Calcd. for $C_{11}H_{18}ON_4S_2$: C, 46.11; H, 6.33; N, 19.55; S, 22.38. Found: C, 45.95; H, 6.48; N, 19.63; S, 22.39. IR ν_{max} cm^{-1}: 3245 (NH), 1669 (C=N), 1280 (C=S). UV λ_{max} mμ (log ε): 271 (4.02). NMR τ: 6.42, 6.75, 7.83 (each 3H, s, 3×N-CH_3), 8.34 (3H, s, C_{3a}-CH_3), 5.5—8.0 (5H, m, -$\dot{C}HCH_2CH_2O$).

Spiro[3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-di-*p*-chlorophenyl-5′-iminoimidazolidine-2′-thione)] (IIb)——500 mg of spiro[3,3a-dimethylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-di-*p*-chlorophenyl-imidazolidine-2′,5′-dithione)] (Ib)[3] was suspended in 20 ml of liq. NH_3 in a sealed tube with the same volume as employed for Ia, and the suspension was allowed to stand for 20 hr at room temperature. After evaporation of ammonia, the resulting residue was washed with water and extracted with $CHCl_3$. The $CHCl_3$ extract, after drying over anhyd. Na_2SO_4, was concentrated *in vacuo* to leave a crystalline residue which was recrystallized from acetone to give IIb as pale yellow prisms, mp 120—123°. Yield 270 mg (56%). *Anal.* Calcd. for $C_{21}H_{20}ON_4S_2Cl_2$: C, 52.59; H, 4.20; N, 11.68; S, 13.38; Cl, 14.79. Found: C, 52.31; H, 4.25; N, 11.45; S, 13.43; Cl, 14.50. IR ν_{max} cm^{-1}: 3240 (NH), 1670 (C=N), 1283 (C=S). UV λ_{max} mμ (log ε): 273 (4.12). NMR τ: 2.2—2.8 (8H, m, 2×  -Cl), 6.2—8.1 (5H, m, -$\dot{C}HCH_2CH_2O$), 7.47 (3H, s, N-CH_3), 8.40 (3H, s, C_{3a}-CH_3).

Acid Hydrolysis of IIb——200 mg of IIb was dissolved in the mixture of 15% aq. HCl (3 ml) and EtOH (3 ml), and the solution was allowed to stand overnight at room temperature. After the reaction mixture being made neutral by addition of Na_2CO_3, EtOH was removed by evaporation *in vacuo*, and the aq. residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over anhyd. Na_2SO_4 and concentrated to give N,N′-di-*p*-chlorophenyl thiourea (92 mg, 67%) which was identified with the authentic specimen by IR comparison.

3-Phenyl-6,8-dimethyl-2,9-dithia-4,6,8-triazatricyclo[3,3,0,$1^{1,5}$]oct-3-ene (IIIa)——500 mg of spiro-[3-benzyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dimethylimidazolidine-2′,5′-dithione)] (Ic)[3] was suspended in 20 ml of liq. NH_3 in a sealed tube ($\phi=2.5$ cm, $l=40$ cm), and the suspension was allowed to stand for 20 hr at room temperature. Considerable amounts of orange crystals were precipitated in the tube.

6) For example, see S.W. Kantor and C.R. Hauser, *J. Am. Chem. Soc.*, 73, 4122 (1951).

After evaporation of ammonia, the resulting crystalline residue was washed adequately with cold MeOH, then collected by suction and washed with MeOH and acetone and finally with ether to give essentially pure IIIa as orange prisms, mp 118—211° (decomp.). Yield 320 mg (83%). *Anal.* Calcd. for $C_{12}H_{11}N_3S_3$: C, 49.10; H, 3.78; N, 14.32; S, 32.77. Found: C, 49.26; H, 3.77; N, 14.58; S, 32.92. IR ν_{max} cm^{-1}: 1674 (C=N), 1274 1290 (C=S). UV λ_{max} mμ (log ε): 274 (3.99). NMR τ: 2.4—2.9 (5H, m, ), 6.15, 6.23 (each 3H, s, 2×N-CH_3).

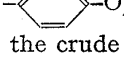
Thermal Desulfurization of IIIa——150 mg of IIIa was heated in 10 ml of toluene for 30 min at 100°. The color of the reaction mixture gradually changed from brown to yellow, and finally a pale yellow solution was obtained. Then the reaction mixture was cooled in an ice bath, and the precipitated sulfur was removed by filtration. Concentration of the filtrate *in vacuo* gave 2-phenyl-4,6-dimethyldihydroimidazo-[4,5-*d*]thiazole-5-thione (IVa)[3] as essentially pure crystals (125 mg, 93%) which were identified with the authentic specimen by IR comparison.

3-*p*-Nitrophenyl-6,8-dimethyl-2,9-dithia-4,6,8-triazatricuclo[3,3,0,$1^{1,5}$]oct-3-ene (IIIb) and Spiro[3-*p*-nitrobenzyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dimethyl-5′-iminoimidazolidine-2′-thione)] (IIc)——600 mg of spiro[3-*p*-nitrobenzyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dimethylimidazolidine-2′,5′-dithione)] (Id)[3] was suspended in 25 ml of liq. NH_3 in a sealed tube (ϕ=2.5 cm, l=40 cm). The suspension rapidly turned out to a dark red solution. After standing 3 hr at room temperature, ammonia was removed by evaporation, then the resulting residue was washed with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to leave a brown oily residue which was chromatographed with AcOEt. The first eluate gave IIIb as an unstable brown solid, mp *ca.* 120° (decomp.). Yield 70—140 mg (15—30%). IR ν_{max} cm^{-1}: 1673 (C=N), 1289 (C=S). UV λ_{max} mμ (log ε): 281.5 (4.12). IIIb could not be obtained in an analytically pure state because of its considerable instability. The second eluate gave IIc which was recrystallized from MeOH to give yellow prisms, mp 171—174°. Yield *ca.* 130 mg (23%). *Anal.* Calcd. for $C_{17}H_{21}O_3N_5S_2$: C, 50.10; H, 5.19; O, 11.78; N, 17.19; S, 15.74. Found: C, 50.05; H, 5.16; O, 11.88; N, 17.05; S, 15.72. IR ν_{max} cm^{-1}: 3240 (broad, NH), 1673 (C=N), 1280 (C=S). UV λ_{max} mμ (log ε): 271 (4.01). NMR τ: 6.90, 6.93 (each 3H, s, 2X N-CH_3), 8.32 (3H, s, C_{3a}-CH_3).

Thermal Desulfurization of IIIb——20 mg of IIIb was heated in 5 ml of toluene at 100° for 30 min. After evaporation of toluene *in vacuo*, the resulting crystalline residue was washed with cold MeOH and recrystallized from MeOH to give 2-*p*-nitrophenyl-4,6-dimethyldihydroimidazo[4,5-*d*]thiazole-5-thione (IVb)[3] (17 mg, 95%) which was identified with the authentic specimen by IR comparison. In the UV spectrum of IIIb in EtOH, a new maximum was gradually appeared at 442 mμ at room temperature, which indicates that a part of IIIb decomposes to IVb spontaneously at room temperature.

Spiro[3-*p*-methoxybenzyl-3a-methylperhydrofuro[2,3-*d*]thiazole-2,4′-(1′,3′-dimethylimidazolidine-2′,5′-dithione)] (Ie)——4.3 g of 3-*p*-methoxybenzyl-4-methyl-5-(2-hydroxy)ethylthiazolium chloride (this compound was prepared by reacting *p*-methoxybenzyl chloride with 4-methyl-5-(2-hydroxy)ethylthiazole) was dissolved in 30 ml of abs. DMF. To the solution 5 g of NEt_3 and 5 g of MeNCS were added and the mixture was stirred at 40—45° for 6 hr. After evaporation of DMF *in vacuo*, the residue was washed with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over anhyd. Na_2SO_4 and concentrated to leave a brown oil which was chromatographed over Al_2O_3 (Merck, neutral) column with $CHCl_3$. From the first eluate Ie was obtained as a pale yellow oil. Yield 2.1 g (34%). UV λ_{max} mμ: 325. Ie was used for the next run without further purification.

Reaction of Ie with Liquid Ammonia——1.1 g of Ie was dissolved in 20 ml of liq. NH_3 in a sealed tube (ϕ=2.5 cm, l=40 cm), and the solution was allowed to stand for 20 hr at room temperature. After evaporation of ammonia, the residue was washed with water and extracted with $CHCl_3$. The $CHCl_3$ extract was then washed with water, dried over anhyd. Na_2SO_4 and concentrated to leave a brown oily residue which was chromatographed with AcOEt. The first eluate gave an unidentified product as dark red crystals (mp 129—130°), and the second eluate gave 3-*p*-methoxyphenyl-6,8-dimethyl-2,9-dithia-4,6,8-triazatricyclo-[3,3,0,$1^{1,5}$]oct-3-ene (IIIc) as a crude pale yellow powder (Yield 7.5 mg). IR ν_{max} cm^{-1}: 1680 (C=N), 1286 (C=S). UV λ_{max} mμ: 276. IIIc was not further purified because of the insufficient quantity.

2-*p*-Methoxyphenyl-4,6-dimethyldihydroimidazo[4,5-*d*]thiazole-5-thione (IVc)——a) 1 g of Ie was dissolved in 15 ml of glac. AcOH, and the solution was heated at 90—100° for 6 hr. After standing overnight at room temperature, the reaction mixture was concentrated *in vacuo* to leave a crystalline residue which was washed with acetone and recrystallized from MeOH to give IVc as yellow prisms, mp 240—243°. Yield 140 mg (20%). *Anal.* Calcd. for $C_{13}H_{13}ON_3S_2$: C, 53.61; H, 4.50; N, 14.43; S, 21.98. Found: C, 53.33; H, 4.46; N, 14.40; S, 22.56. UV λ_{max} mμ (log ε): 281 (4.12), 374 (4.32). NMR τ: 2.23, 3.06 (each 2H, d, J=9 Hz, ), 6.13 (3H, s, OCH_3), 6.15, 6.23 (each 3H, s, 2×N-CH_3).

b) 5 mg of the crude IIIc was heated in *ca.* 1 ml of toluene at 100° for 30 min, then toluene was removed by evaporation *in vacuo*. The resulting crystalline residue was washed with water then with ether to give IVc (3.5 mg) which was identified with the authentic specimen obtained by the method a) by comparing IR spectra.