Reactions of 4*H*-Pyran-4-thiones with Ammonia, Hydrazine, and Guanidine

Hiromichi Besso,* Kimiaki Imafuku,† and Hisashi Matsumura
Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami, Kumamoto 860

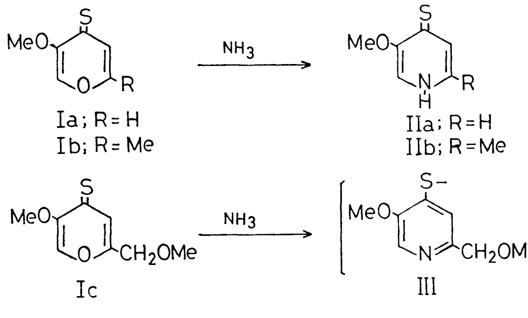
(Received March 22, 1977)

The reaction of 4*H*-pyran-4-thiones with ammonia gave 4(1*H*)-pyridinethiones or bis(4-pyridyl) disulfide, while that of 3-methoxy-2-methyl-4*H*-pyran-4-thione with guanidine gave the 1,3-thiazine derivative. 4*H*-Pyran-4-thiones reacted with hydrazine to afford pyridazines, pyrazoles, and 1-amino-4(1*H*)-pyridinethiones. 4*H*-Pyran-4-thiones having the hydroxyl group in the β-position gave the pyridazine derivatives.

Elkaschef and Nosseir[1] obtained 4(1*H*)-pyridinethiones by the reaction of 4*H*-pyran-4-thiones with ammonia. Ainsworth and Jones[2] reported that the reaction of 4-pyrones with hydrazine gives the pyrazole derivatives. Kotani and Tatsumi[3] obtained the 1,4-dihydropyridazine derivative and the pyrazole derivatives by the reaction of kojic acid with hydrazine. However, little is known about the reaction of 4*H*-pyran-4-thiones with hydrazine.[4] We wish to report the reactions of several 4*H*-pyran-4-thiones with ammonia, hydrazine, and guanidine.

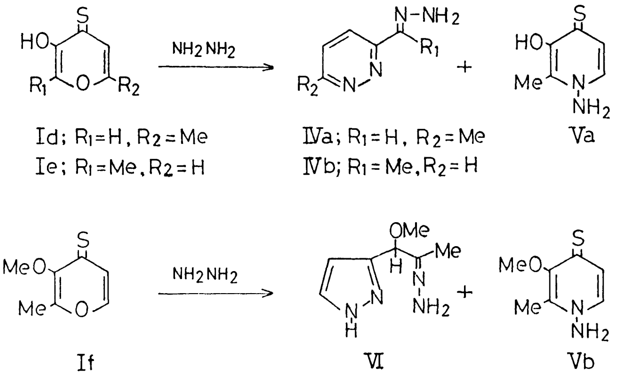
Results and Discussion

*Reaction of 4*H*-Pyran-4-thiones with Ammonia.* The reaction of 3-methoxy-4*H*-pyran-4-thione (Ia) and 5-methoxy-2-methyl-4*H*-pyran-4-thione (Ib) with ammonia gave respectively 3-methoxy-4(1*H*)-pyridinethione (IIa) and 5-methoxy-2-methyl-4(1*H*)-pyridinethione (IIb), while that of 5-methoxy-2-methoxymethyl-4*H*-pyran-4-thione (Ic) with ammonia gave bis(5-methoxy-2-methoxymethyl-4-pyridyl) disulfide (III) but no 4(1*H*)-pyridinethione. It is thought that the disulfide is produced by further oxidation of 5-methoxy-2-methoxymethyl-4(1*H*)-pyridinethione which might be obtained by the mechanism proposed by Elkaschef and Nosseir.[1] The presence of sulfur in the three products (IIa, IIb, and III) was confirmed by Sugiyama's method.[5]



Scheme 1.

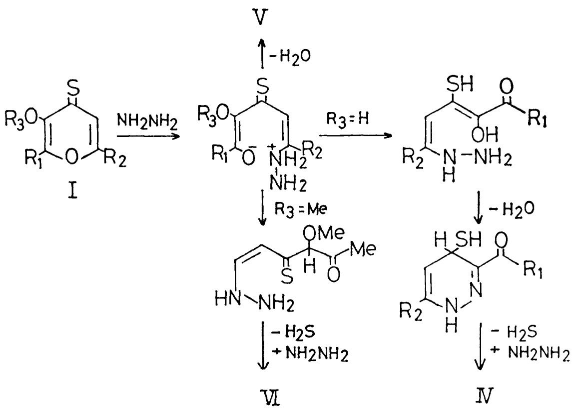
*Reaction of 4*H*-Pyran-4-thiones with Hydrazine.* The reaction of 5-hydroxy-2-methyl-4*H*-pyran-4-thione (Id) with hydrazine hydrate gave 6-methyl-3-pyridazinecarbaldehyde hydrazone (IVa), and that of 3-hydroxy-2-methyl-4*H*-pyran-4-thione (Ie) with hydrazine hydrate gave 3-acetylpyridazine hydrazone (IVb) and 1-amino-3-hydroxy-2-methyl-4(1*H*)-pyridinethione (Va), respectively.



Scheme 2.

Ichimoto[6,7] reported that the attack of hydrazine occurs on the 2- and 6-positions of 3-hydroxy-2-methyl 4-pyrone. It seems that hydrazine attacks on the 6-position of 3-hydroxy-2-methyl-4*H*-pyran-4-thione (Ie) and the 2-position of 5-hydroxy-2-methyl-4*H*-pyran-4-thione (Id), the adducts formed giving the pyridazine derivatives (IVa) and (IVb) according to Scheme 3. The elimination of hydrogen sulfide was confirmed by its conversion into copper(II) sulfide.

The reaction of 3-methoxy-2-methyl-4*H*-pyran-4-thione (If) with hydrazine hydrate is of some interest because of lack of hydroxyl group in the β-position. Actually, the reaction gave the pyrazole derivative but no pyridazine derivative. The products were α-(3-pyrazolyl)-α-methoxyacetone hydrazone (Vb) and 1-amino-3-methoxy-2-methyl-4(1*H*)-pyridinethione (Vb). It was impossible to obtain the 6-membered ring as pyridazines because of the methoxyl group in the β-position, as shown in Scheme 3.



Scheme 3.

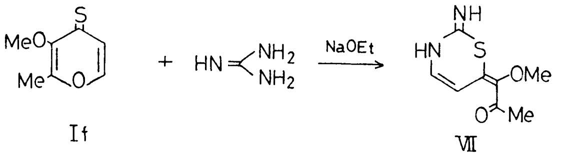
---

* Present address: Wakunage Pharmaceutical Co., Ltd., Koda-machi, Takata-gun, Hiroshima 729-64.

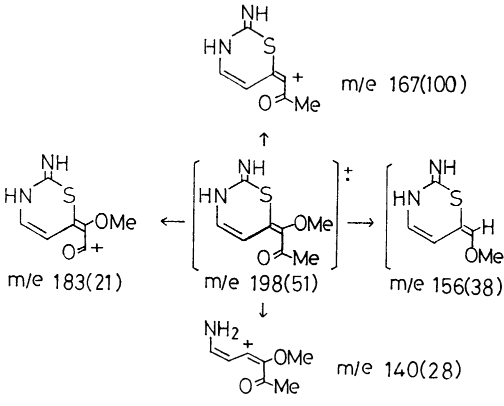
† To whom correspondence should be addressed.

It was found that hydrazine attacks on the 2-position of 5-hydroxy-2-methyl-4*H*-pyran-4-thione (Id) and on the 6-position of 3-hydroxy-2-methyl-4*H*-pyran-4-thione (Ie), and pyridazine (IVa) and (IVb), respectively, are produced by the elimination of water and hydrogen sulfide. However, 4*H*-pyran-4-thiones having no hydroxyl group in the β-position gave the pyrazole derivatives by the elimination of hydrogen sulfide.[4]

Reaction of 3-Methoxy-2-methyl-4H-pyran-4-thione (If) with Guanidine. When 3-methoxy-2-methyl-4*H*-pyran-4-thione (If) was treated with guanidine, the 1,3-thiazine derivative (VII) was obtained in 8.2% yield. The structure was confirmed by the spectral and analytical data. The NMR spectrum in CF_3COOH shows peaks at 2.41 for C–CH_3, 3.84 for O–CH_3, 8.8—8.3 for NH, and 7.01 and 9.65 for –CH=CH–. The IR spectrum shows bands at 3200, 1690, and 1610 cm^{-1}. The mass spectrum shows peak at *m/e* 198 for parent. The fragmentation of VII is shown in Scheme 5. The presence of sulfur was also confirmed as mentioned above.

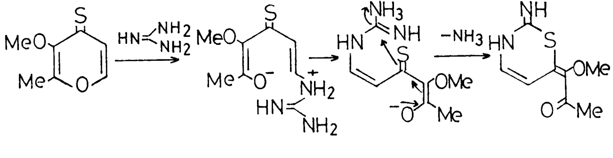


Scheme 4.



Scheme 5.

We postulate a mechanism in which the amino group of guanidine attacks on the 6-position of 3-methoxy-2-methyl-4*H*-pyran-4-thione (If), and the 1,3-thiazine derivative is formed by the elimination of ammonia from the adduct yielded (Scheme 6).



Scheme 6.

Experimental

The melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. All the ^1H NMR spectra were recorded with a Hitachi-Perkin-Elmer R-24 spectrometer (60 MHz), with tetramethylsilane as an internal reference. The IR spectra were taken on a JASCO IRA-1 spectrophotometer, and the UV spectra on a Hitachi EPS-3T spectrophotometer. The mass spectra were taken on a JMS-01 SG-2 mass spectrometer.

Materials. All the 4*H*-pyran-4-thiones were prepared by the reaction of the corresponding 4-pyrones with phosphorus pentasulfide in dry benzene: 5-hydroxy-2-methyl-4*H*-pyran-4-thione (Id); mp 99.5—100.5 °C (lit,[6]) 100—101 °C). 3-Hydroxy-2-methyl-4*H*-pyran-4-thione (Ie): mp 78—79 °C (lit,[8]) 81—82 °C). 3-Methoxy-4*H*-pyran-4-thione (Ia); mp 110—114 °C (from carbon tetrachloride); Yield, 36%; IR(KBr) 1604 cm^{-1}; NMR($CDCl_3$) δ: 7.45(d, 1H, *J*=4.7 Hz), 7.45(s, 1H), 7.26(d, 1H, *J*=4.7 Hz), 3.83(s, 3H). Found: C, 50.49; H, 4.26%. Calcd for $C_6H_6O_2S$: C, 50.71; H, 4.26%. 5-Methoxy-2-methyl-4*H*-pyran-4-thione (Ib); mp 98.5—100 °C (from carbon tetrachloride); Yield, 40%; IR(KBr) 1615 cm^{-1}; NMR($CDCl_3$) δ: 7.43(s, 1H), 7.22(s, 1H), 3.82(s, 3H), 2.24(s, 3H). Found: C, 53.55; H, 5.06%. Calcd for $C_7H_8O_2S$: C, 53.84; H, 5.16%. 5-Methoxy-2-methoxymethyl-4*H*-pyran-4-thione (Ic); mp 56—56.5 °C (from benzene-petroleum ether); Yield, 37%; IR(KBr) 1635 cm^{-1}; NMR($CDCl_3$) δ: 7.47(s, 1H), 7.36(s, 1H), 4.24(s, 2H), 3.86(s, 3H), 3.46(s, 3H). Found: C, 51.48; H, 5.33%. Calcd for $C_8H_{10}O_3S$: C, 51.59; H, 5.42%. 3-Methoxy-2-methyl-4*H*-pyran-4-thione (If); mp 61—63 °C (from petroleum ether); Yield, 47%; IR(KBr) 1625 cm^{-1}; NMR ($CDCl_3$) δ: 7.39 (d, 1H, *J*=5.0 Hz), 7.16(d, 1H, *J*=5.0 Hz), 3.85(s, 3H), 2.36(s, 3H). Found: C, 53.58; H, 5.14%. Calcd for $C_7H_8O_2S$: C, 53.84; H, 5.16%.

Reaction of 4H-Pyran-4-thiones with Ammonia. *a) 3-Methoxy-4(1H)-pyridinethione (IIa)*: A mixture of 3-methoxy-4*H*-pyran-4-thione (Ia) (104 mg) and 28% aqueous ammonia solution (0.8 ml) was heated in a sealed tube at 60 °C for 5 min. Ammomia and water were evaporated off, and the residue was recrystallized from methanol to afford IIa, yellow-ochre prisms. Yield 46 mg (44%); mp 149—152 °C; IR (KBr) 3160, 2800, 1602 cm^{-1}; NMR(CF_3COOH) δ: 8.3—7.7(m, 3H), 4.20(s, 3H). Found: C, 50.80; H, 5.02; N, 9.94%. Calcd for C_6H_7NOS: C, 51.06; H, 5.02; N, 9.95%.

b) 5-Methoxy-2-methyl-4(1H)-pyridinethione (IIb): A mixture of 5-methoxy-2-methyl-4*H*-pyran-4-thione (Ib) (187 mg) and 28% aqueous ammonia solution (1.5 ml) was heated in a sealed tube at 60 °C for 10 min. Ammonia and water were evaporated off, and the residue was recrystallized from ethyl acetate to afford IIb, yellow micro-crystals. Yield 123 mg (66%); mp 156—158 °C; IR(KBr) 3245, 2800, 1615 cm^{-1}; NMR(CF_3COOH) δ: 7.9—7.5(m, 2H), 4.15(s, 3H), 2.69(s, 3H). Found: C, 54.04; H, 5.78; N, 8.90%. Calcd for C_7H_9NOS: C, 54.19; H, 5.81; N, 9.03%.

c) Bis(5-methoxy-2-methoxymethyl-4-pyridyl) Disulfide (III): A mixture of 5-methoxy-2-methoxymethyl-4*H*-pyran-4-thione (Ic) (164 mg) and 28% aqueous ammonia solution (0.4 ml) was heated in a sealed tube at 60 °C for 10 min. Ammonia and water were evaporated off, and the residue was recrystallized from methanol to afford III, pale yellow needles. Yield, 46 mg (28%); mp 123—123.5 °C; IR (KBr) 1565 cm^{-1}; NMR($CDCl_3$) δ: 8.07(s, 1H), 7.45(s, 1H), 4.44 (s, 2H), 4.00(s, 3H), 3.29(s, 3H); *m/e* 368 (parent). Found: C, 52.03; H, 5.47; N, 7.64%. Calcd for $C_{10}H_{20}N_2O_4S_2$: C, 52.13; H, 5.47; N, 7.60%.

Reaction of 5-Hydroxy-2-methyl-4H-pyran-4-thione (Id) with Hydrazine Hydrate: A mixture of 5-hydroxy-2-methyl-4*H*-pyran-4-thione (Id) (203 mg, 1.4 mmol) and 80% hydrazine hydrate (280 mg, 3 mmol) in methanol (10 ml) was refluxed for 30 min. After methanol had been evaporated off, the residue was recrystallized from benzene to give 6-methyl-3-

pyridazinecarbaldehyde hydrazone (IVa), yellow plates. Yield, 85 mg (44%); mp 180—182 °C; IR(KBr) 3350, 3200, 1635, 1585 cm^{-1}; NMR(CDCl$_3$) δ: 9.03(dd, 1H, J=4.5 and 1.5 Hz), 8.06(s, 1H), 7.95(dd, 1H, J=1.5 and 8.0 Hz), 7.41 (dd, 1H, J=4.5 and 8.0 Hz), 6.5—5.5(br, 2H), 2.67(s, 3H); UV λ_{max}(MeOH) nm(log ε) 230(3.74), 291(4.28). Found: C, 52.85; H, 5.91; N, 41.28%. Calcd for $C_6H_8H_4$: C, 52.92; H, 5.92; N, 41.15%.

*Reaction of 3-Hydroxy-2-methyl-4*H*-pyran-4-thione (Ie) with Hydrazine Hydrate.* A mixture of 3-hydroxy-2-methyl-4*H*-pyran-4-thione (Ie) (434 mg, 3 mmol) and 80% hydrazine hydrate (550 mg, 6 mmol) in methanol (10 ml) was refluxed for 1.5 h. After methanol had been evaporated off, the residue was filtered and recrystallized from methanol to give 1-amino-3-hydroxy-2-methyl-4(1*H*)-pyridinethione (Va), yellow needles. Yield, 91 mg (19%); mp 165 °C (dec); IR(KBr) 3250, 1615 cm^{-1}; NMR(CF$_3$COOH) δ: 8.09(d, 1H, J=8.0 Hz), 7.50(d, 1H, J=8.0 Hz), 2.81(s, 3H); UV λ_{max}(MeOH) nm(log ε) 254(3.98), 275(3.36), 348(4.27). Found: C, 45.36; H, 5.03; N, 17.71%. Calcd for $C_6H_8N_2OS$: C, 46.15; H, 5.16; N, 17.94%. The filtrate was evaporated off to dryness, and the residue was recrystallized from carbon tetrachloride to give 3-acetylpyridazine hydrazone (IVb), yellow micro-crystals. Yield, 145 mg (35%); mp 67—69 °C; IR(KBr) 3350, 3210, 1645, 1570 cm^{-1}; NMR(CDCl$_3$) δ: 9.03(dd, 1H, J=1.5 and 4.5 Hz), 8.06(dd, 1H, J=1.5 and 8.0 Hz), 7.34(dd, 1H, J=4.5 and 8.0 Hz), 6.2—5.4(br, 2H), 2.37(s, 3H); UV λ_{max}(MeOH) nm(log ε) 224(3.69), 288 (4.06); *m/e* 136 (parent). Found: C, 52.72; H, 5.89; N, 41.18%. Calcd for $C_6H_8N_4$: C, 52.92; H, 5.92; N, 41.15%.

*Reaction of 3-Methoxy-2-methyl-4*H*-pyran-4-thione (If) with Hydrazine Hydrate.* A mixture of 3-methoxy-2-methyl-4*H*-pyran-4-thione (If) (404 mg, 2.5 mmol) and 80% hydrazine hydrate (510 mg, 5.5 mmol) in methanol (10 ml) was allowed to stand at roon temperature for 1 h. After methanol had been evaporated off, the residue was filtered and recrystallized from methanol to afford 1-amino-3-methoxy-2-methyl-4(1*H*)-pyridinethione (Vb), yellow plates. Yield, 116 mg (27%); mp 150—152 °C(dec); IR(KBr) 3200, 3150, 1620, 1590 cm^{-1}; NMR(CF$_3$COOH): 8.25(d, 1H, J=7.9 Hz), 7.64(d, 1H, J=7.9 Hz), 4.00(s, 3H), 2.85(s, 3H); UV λ_{max}(MeOH) nm(log ε) 252(3.89), 285(3.21), 349(4.33). Found: C, 49.29; H, 5.86; N, 16.40%. Calcd for $C_7H_{10}N_2OS$: C, 49.40; H, 5.92; N, 16.46%. The solvent was evaporated off from the filtrate, and the residue was extracted with chloroform. After chloroform had been evaporated off, an oily product was obtained and confirmed to be α-(3-pyrazolyl)-α-methoxyacetone hydrazone (VI). Yield, 255 mg (58%); IR(CHCl$_3$) 3200, 1620 cm^{-1}; NMR(CDCl$_3$) δ: 7.53(d, 1H. J=2.2 Hz), 6.24(d, 1H, J=2.2 Hz), 4.94(s, 1H), 3.35(s, 3H), 1.72(s, 3H). This hydrazone decomposed within one day, not forming picrate.

*Reaction of 3-Methoxy-2-methyl-4*H*-pyran-4-thione (If) with Guanidine.* To a sodium ethoxide solution, prepared from sodium (180 mg, 8 mmol) and absolute ethanol (8 ml), were added guanidine hydrochloride (700 mg, 8 mmol) and 3-methoxy-2-methyl-4*H*-pyran-4-thione (If) (244 mg, 1.5 mmol) and the mixture was stirred at room temperature for 5 min. The reaction mixture was poured into water and extracted with chloroform. Chloroform was evaporated off, and the residue was recrystallized from ethyl acetate to give 1,3-thiazine derivative (VII), yellow plates. Yield, 25 mg (8.2%); mp 212 °C (dec); IR (KBr) 3200, 1690, 1610 cm^{-1}; NMR(CF$_3$COOH) δ: 9.65(d, 1H, J=2.0 Hz), 8.8—8.3(br, 2H), 7.01(d, 1H, J=2.0 Hz), 3.84(s, 3H), 2.41(s, 3H); *m/e* 198(parent). Found: C, 48.43; H, 5.14; N, 14.04%. Calcd for $C_8H_{10}N_2O_2S$: C, 48.48; H, 5.09; N, 14.14%.

The authors wish to thank Dr. Kazu Kurosawa of Kumamoto University for valuable discussions and Mr. Shuichi Ueda of Taiho Pharmaceutical Co., Ltd. for the measurement of mass spectra.

References

1) M. A.-F. Elkaschef and M. H. Nosseir, *J. Am. Chem. Soc.*, **82**, 4344 (1960).

2) C. Ainsworth and R. G. Jones, *J. Am. Chem. Soc.*, **76**, 3172 (1954).

3) R. Kotani and C. Tatsumi, *Bull. Univ. Osaka Pref.*, *B*, **10**, 33 (1960).

4) I. E.-S. El-Kholy, F. K. Refra, and G. Soliman, *J. Chem. Soc.*, **1962**, 1857.

5) N. Sugiyama, "Yuki-kagobutsu no Biryo Kakunin-ho," Baifukan, Tokyo (1957), p. 135.

6) I. Ichimoto, *Bull. Univ. Osaka Pref.*, *B*, **22**, 209 (1970).

7) I. Ichimoto, Y. Kitaoka, and C. Tatsumi, *Tetrahedron*, **22**, 841 (1966).

8) K. Blazevic, K. Jakopcic, and V. Hahn, *Bull. Sci. Cons. Acad. Sci. Arts RSF Yougoslavie*, *A*, **14**, 1 (1969); *Chem. Abstr.*, **71**, 61124f (1969).