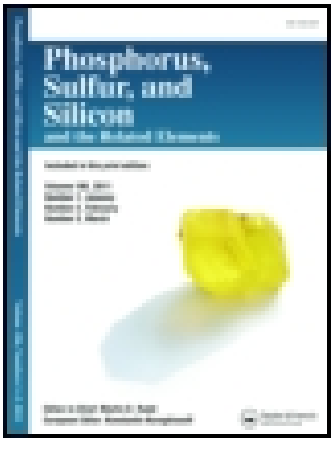

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REACTIONS OF 2-MERCAPTO-8H-CYCLOHEPTA[d]THIAZOL-8-ONE WITH ALKYL HALIDES AND ACETYLENIC COMPOUNDS

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REACTIONS OF 2-MERCAPTO-8*H*-CYCLOHEPTA[*d*]THIAZOL-8-ONE WITH ALKYL HALIDES AND ACETYLENIC COMPOUNDS

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The reactions of 2-mercapto-8*H*-cyclohepta[*d*]thiazol-8-one (**1**) with alkyl halides and relared halogeno-compounds gave 2-*S*-substituted 8*H*-cyclohepta[*d*]thiazol-8-ones **3a–g** in good yields. In the presence of sodium hydride, 3-*N*-substituted compounds **4a,e** were also isolated as minor products, besides the products **3a,e**. The reactions with acetylenic compounds gave 2-*S*-ethenyl-substituted products **6a–c**.

Key words: 2-mercapto-8*H*-cyclohepta[*d*]thiazol-8-one, alkyl halide, reactive acetylene, substitution reaction.

INTRODUCTION

Three decades ago, it was proposed[1] that 2-mercapto-8*H*-cyclohepta[*d*]thiazol-8-one (**1**) exists in tautomeric thiazoline form **1′**. This was deduced by comparison of its UV spectrum with that of 2-methylthio-8*H*-cyclohepta[*d*]thiazol-8-one. Recently, we confirmed this phenomenon by preparation of another isomer, 3-methyl-8-oxo-3,8-dihydrocyclohepta[*d*]thiazoline-2-thione, and by spectroscopic measurements.[2] Thus, it was found that compound **1** has two reactive centers for electrophilic species. In this paper, the reactions of compound **1** with a variety of organic halo-substituted and acetylenic compounds are described.

RESULTS AND DISCUSSION

Reactions with Alkyl Halides and Related Compounds

When a solution of 2-mercapto-8*H*-cyclohepta[*d*]thiazol-8-one (**1**) and methyl iodide (**2a**) in *N,N*-dimethylformamide was stirred for 2 h at room temperature in the presence of potassium carbonate, a *S*-methylated compound, 2-methylthio-8*H*-cyclohepta[*d*]thiazol-8-one (**3a**)[1] was obtained in excellent yield (87%). In a similar manner, the reactions with ethyl iodide (**2b**), isopropyl iodide (**2c**), allyl bromide (**2d**), benzyl bromide (**2e**), 2-bromo-4′-methylacetophenone (**2f**), and 2-chloromethylbenzimidazole (**2g**) gave the corresponding *S*-substituted products **3b–g** in good yields. These results might be attributed to high reactivity of the sulfur atom.

On the other hand, the reaction with **2a,e** were carried out at elevated temperature

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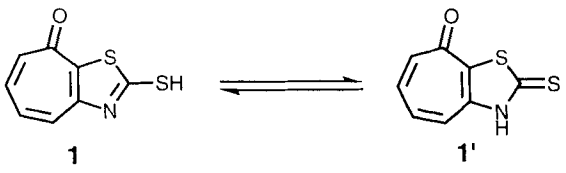
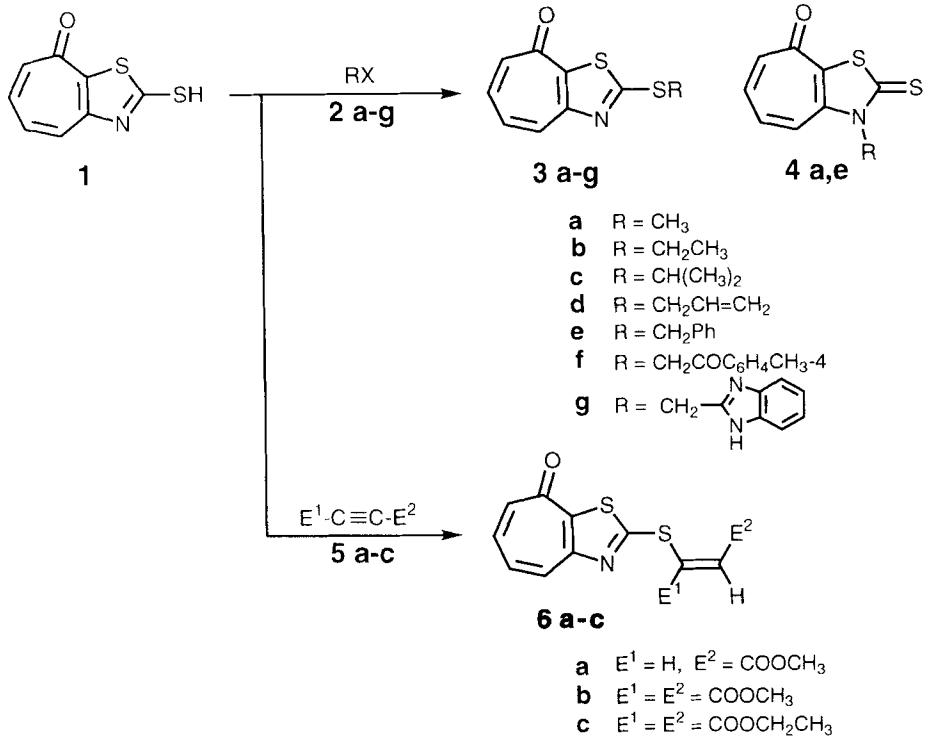


SCHEME I



SCHEME II

in the presence of sodium hydride to afford two types of products i.e. *S*-alkylated compounds **3a,e** as major products and *N*-alkylated compounds, 3-methyl- and 3-benzyl-8-oxo-3,8-dihydrocyclohepta[*d*]thiazoline-2-thione **4a,e**, as minor products. It is thought that compound **1** formed the corresponding anion by sodium hydride and the anionic center was delocalized onto the nitrogen atom at the 3-position and the sulfur atom in the mercapto group.

Reactions with Alkynes

A solution of compound **1** and a large excess of methyl propiolate (**5a**) in benzene was refluxed for 24 h to afford 2-[{(*Z*)-2-methoxycarbonylethenyl}thio]-8*H*-cyclohepta[*d*]thiazol-8-one (**6a**) as colorless needles in 23% yield. Compound **1** was also recovered in 56% yield. The structure of **6a** was established on the basis of elemental analysis and spectral data. In the IR spectrum, two carbonyl absorption bands were

observed at 1720 and 1630 cm^{-1} and assigned to the ester and tropone carbonyl group, respectively. The ^1H NMR spectrum exhibited signals at δ 3.87 (OCH_3), 6.86–7.67 (5-, 6-, 7-H), 6.24 (=CH—CO—), 7.85 (4-H), and 8.35 (—S—CH=). The coupling constant between the two olefinic protons is J = 10 Hz. This means that their configuration is *cis*. The MS data also gave satisfactory results.

Although this reaction was tried in a polar solvent, acetonitrile, the yield of **6a** was not improved (35%) and the unchanged **1** was recovered (51%). Then, the reaction was carried out in refluxing xylene to give **6a** in an excellent yield (91%). It was found that the reaction temperature is a more important factor than the polarity of the medium.

In a similar manner, the reactions of **1** with dimethyl acetylenedicarboxylate (**5b**) were carried out in refluxing benzene (10 h) and xylene (7 h) to give 2-[{(*Z*)-1,2-bis(methoxycarbonyl)ethenyl}thio]-8*H*-cyclohepta[*d*]thiazol-8-one (**6b**) as colorless needles in 81 and 89% yield, respectively. The structure was confirmed by elemental analysis and spectral data. In the ^1H NMR spectrum, the olefinic proton was observed at δ 7.13. The corresponding calculated values of the olefinic proton for *Z*- and *E*-form on the basis of Pascual's method[3] are δ 7.23 and 6.44, respectively. Thus, the configuration of the compounds **6b** was assigned to the *Z*-form.

Compound **1** was treated with diethyl acetylenedicarboxylate (**5c**) in refluxing benzene (7 h) and xylene (7 h) to afford 2-[{(*Z*)-1,2-bis(ethoxycarbonyl)ethenyl}-thio]-8*H*-cyclohepta[*d*]thiazol-8-one (**6c**) as an oily material in 56 and 73% yield, respectively. The structure of compound **6c** was also confirmed spectroscopically.

EXPERIMENTAL

The melting points were determined with a Yanagimoto MP-S2 apparatus and are uncorrected. The IR spectra were taken on a JASCO A-102 spectrophotometer. The ^1H NMR spectra were recorded with a JEOL JNM-PMX60SI spectrometer (60 MHz). The mass spectra were obtained with a JEOL JMS-DX300 spectrometer.

2-Methylthio-8H-cyclohepta[d]thiazol-8-one (**3a**)

a) A solution of 2-mercapto-8*H*-cyclohepta[*d*]thiazol-8-one (**1**) (100 mg) and methyl iodide (**2a**) (0.1 ml) in *N*,*N*-dimethylformamide (10 ml) was stirred for 2 h in the presence of potassium carbonate (100 mg) at room temperature. The reaction mixture was poured into an ice-water medium and extracted with ethyl acetate. After drying over sodium sulfate, the extract was concentrated and chromatographed on a Wakogel B-10 plate (30 × 30 cm) with chloroform to give **3a**. Yield 93 mg (87%); mp 113–114°C (lit,[1] 112–113°C).

b) A mixture of **1** (100 mg) and 60% sodium hydride (60 mg) in *N*,*N*-dimethylformamide (10 ml) was stirred for 30 min at room temperature. After adding methyl iodide (1 ml), the mixture was heated for 10 h at 60°C (bath temperature), worked up, as described above, and chromatographed to give compound **3a** and 3-methyl-8-oxo-3,8-dihydrocyclohepta[*d*]thiazoline-2-thione (**4a**).[2] **3a**: Yield 73 mg (69%). **4a**: Yield 29 mg (27%); mp 260–261°C (lit,[2] 260–261°C).

2-Ethylthio-8H-cyclohepta[d]thiazol-8-one (**3b**)

A solution of **1** (100 mg) and ethyl iodide (**2b**) (0.1 ml) in *N*,*N*-dimethylformamide (10 ml) was stirred for 2 h in the presence of potassium carbonate (100 mg) at room temperature. The reaction mixture was worked up, as described above, to give **3b**. Yield 96 mg (84%); yellow needles (from chloroform); mp 84–85°C; IR ($CHCl_3$): ν_{max} 1629 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.50 (3H, t, J = 7 Hz, CH_3), 3.35 (2H, q, J = 7 Hz, CH_2), 6.87–7.60 (3H, m), 7.79 (1H, dd, J = 10, 2 Hz, 4-H); MS: m/z (%) 223 (M^+, 100), 208 (9), 195 (18), 190 (26), 180 (10), 167 (36), 162 (37), 108 (24). Found: C, 53.72; H, 3.97; N, 6.03; M^+, 223.0139. Calcd for $C_{10}H_9NOS_2$: C, 53.78; H, 4.06; N, 6.27; M, 223.0125.

2-Isopropylthio-8H-cyclohepta[d]thiazol-8-one (**2c**)

A solution of **1** (100 mg) and isopropyl iodide (**2c**) (0.1 ml) in *N,N*-dimethylformamide (10 ml) was stirred for 90 min in the presence of potassium carbonate (100 mg) at room temperature. The reaction mixture was worked up, as described above, to give **3c**. Yield 111 mg (90%); yellow oil; IR ($CHCl_3$): ν_{max} 1629 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.50 (6H, d, J = 7 Hz, 2 × CH_3), 4.20 (1H, sept, J = 7 Hz, —CH<), 6.77–7.53 (3H, m), 7.75 (1H, dd, J = 10, 2 Hz, 4-H); MS: m/z (%) 237 (M^+, 68), 222 (9), 204 (54), 195 (63), 167 (100), 108 (21). Found: M^+, 237.0262. Calcd for $C_{11}H_{11}NOS_2$: M, 237.0282.

2-Allylthio-8H-cyclohepta[d]thiazol-8-one (**3d**)

A solution of **1** (100 mg) and allyl bromide (**2d**) (0.1 ml) in *N,N*-dimethylformamide (10 ml) was stirred for 20 min in the presence of potassium carbonate (100 mg) at room temperature. The reaction mixture was worked up, as described above, to give **3d**. Yield 109 mg (90%); yellow oil; IR ($CHCl_3$): ν_{max} 1630 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 3.96–4.07 (3H, m, —CH_2CH=), 4.20 (2H, d, J = 6 Hz, =CH_2), 6.83–7.57 (3H, m), 7.82 (1H, dd, J = 10, 2 Hz, 4-H); MS: m/z (%) 235 (M^+, 53), 220 (100), 202 (26), 192 (15), 149 (20), 122 (16), 108 (33). Found: M^+, 235.0120. Calcd for $C_{11}H_9NOS_2$: M, 235.0125.

2-Benzylthio-8H-cyclohepta[d]thiazol-8-one (**3e**)

a) A solution of **1** (100 mg) and benzyl bromide (**2e**) (0.1 ml) in *N,N*-dimethylformamide (10 ml) was stirred for 2 h in the presence of potassium carbonate (100 mg) at room temperature. The reaction mixture was worked up, as described above, to give **3e**. Yield 129 mg (88%); colorless needles (from chloroform); mp 136–137°C (lit,[1] 138–140°C); IR ($CHCl_3$): ν_{max} 1630 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.56 (2H, s, CH_2), 6.83–7.77 (8H, m), 8.33 (1H, dd, J = 10, 2 Hz, 4-H); MS: m/z (%) 285 (M^+, 41), 252 (14), 91 (100). Found: M^+, 285.0279. Calcd for $C_{15}H_{11}NOS_2$: M, 285.0282.

b) A mixture of **1** (100 mg) and 60% sodium hydride (60 mg) in *N,N*-dimethylformamide (10 ml) was stirred for 30 min at room temperature. After adding benzyl bromide (174 mg), the mixture was heated for 10 h at 60°C (bath temperature), worked up as described above, and chromatographed to give compound **3e** [yield 60 mg (41%)] and 3-benzyl-8-oxo-3,8-dihydrocyclohepta[*d*]thiazoline-2-thione (**4e**). Yield 10 mg (7%); pale yellow crystals (from chloroform); mp 84–85°C; IR ($CHCl_3$): ν_{max} 1625 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.50 (2H, s, CH_2), 7.13–7.67 (9H, m); MS: m/z (%) 285 (M^+, 41), 252 (14), 91 (100). Found: M^+, 285.0276. Calcd for $C_{15}H_{11}NOS_2$: M, 285.0282.

2-[(4-Methylbenzoyl)methyl]thio-8H-cyclohepta[d]thiazol-8-one (**3f**)

A solution of **1** (100 mg) and 2-bromo-4′-methylacetophenone (**2f**) (330 mg) in *N,N*-dimethylformamide (10 ml) was refluxed for 24 h in the presence of potassium carbonate (100 mg). The reaction mixture was worked up as described above, to give **3f**. Yield 127 mg (76%); yellow crystals (from chloroform); mp 105–107°C; IR ($CHCl_3$): ν_{max} 1680 (C=O), 1628 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.43 (3H, s, CH_3), 4.90 (2H, s, CH_2), 6.80–8.17 (8H, m). Found: C, 62.06; H, 4.17; N, 4.23. Calcd for $C_{17}H_{13}NO_2S_2$: C, 62.36; H, 4.00; N, 4.28.

2-(2-Benzimidazolylmethyl)thio-8H-cyclohepta[d]thiazol-8-one (**3g**)

A solution of **1** (100 mg) and 2-chloromethylbenzimidazole (**2g**) (170 mg) in *N,N*-dimethylformamide (10 ml) was stirred for 2 h in the presence of potassium carbonate (100 mg) at room temperature. The reaction mixture was worked up as described above, to give **3g**. Yield 153 mg (91%); colorless crystals (from chloroform); mp 224–226°C; IR ($CHCl_3$): ν_{max} 1629 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 4.87 (2H, s, CH_2), 6.87–8.00 (9H, m); MS: m/z (%) 325 (M^+, 56), 292 (5), 264 (4), 195 (12), 163 (10), 131 (100). Found: C, 58.78; H, 3.36; N, 12.83; M^+, 325.0334. Calcd for $C_{16}H_{11}N_3OS_2$: C, 59.06; H, 3.41; N, 12.91; M, 325.0343.

2-[[(Z)-2-Methoxycarbonylethenyl]thio]-8H-cyclohepta[d]thiazol-8-one (**6a**)

a) A solution of **1** (100 mg) and methyl propiolate (**5a**) (300 mg) in benzene (10 ml) was refluxed for 24 h, worked up as described above, and chromatographed on a Wakogel B-10 plate (30 × 30 cm) with chloroform to give **6a** [yield 33 mg (23%)] and **1** [yield 56 mg (56%)]. **6a**: Colorless needles (from chloroform); mp 176–178°C; IR ($CHCl_3$): ν_{max} 1720 (C=O), 1630 (C=O), 1270 cm^{-1} (C—O); ^1H NMR ($CDCl_3$): δ 3.87 (3H, s, OCH_3), 6.24 (1H, d, J = 10 Hz, 2′-CH=), 6.86–7.67 (3H, m), 7.85 (1H, dd, J = 10, 2 Hz, 4-H), 8.35 (1H, d, J = 10 Hz, —S—CH=); MS: m/z (%) 279 (M^+, 10), 248 (2), 220 (100), 192 (12). Found: C, 51.36; H, 3.08; N, 5.31; M^+, 279.0015. Calcd for $C_{12}H_9NO_3S_2$: C, 51.60; H, 3.25; N, 5.01; M, 279.0024.

b) A solution of **1** (100 mg) and methyl propiolate (**5a**) (300 mg) in acetonitrile (10 ml) was refluxed for 10 h, worked up as described above, to give **6a** [yield 50 mg (35%)] and **1** [yield 51 mg (51%)].

c) A solution of **1** (100 mg) and methyl propiolate (**5a**) (300 mg) in xylene (10 ml) was refluxed for 10 h, worked up as described above, to give **6a**. Yield 130 mg (91%).

2-[[(Z)-1,2-(Dimethoxycarbonyl)ethenyl]thio]-8H-cyclohepta[d]thiazol-8-one (**6b**)

a) A solution of **1** (100 mg) and dimethyl acetylenedicarboxylate (**5b**) (300 mg) in benzene (10 ml) was refluxed for 10 h and worked up as described above to give **6b**. Yield 140 mg (81%); colorless needles (from chloroform); mp 162–164°C; IR ($CHCl_3$): ν_{max} 1730 (C=O), 1630 (C=O), 1256 cm^{-1} (C—O); ^1H NMR ($CDCl_3$): δ 3.73 (3H, s, 2'-$COOCH_3$), 3.87 (3H, s, 1'-$COOCH_3$), 6.80–7.63 (3H, m), 7.13 (1H, s, =CH—), 7.84 (1H, dd, J = 10, 2 Hz, 4-H); MS: m/z (%) 337 (M^+, 1), 306 (3), 278 (100), 250 (15), 108 (10). Found: C, 49.58; H, 3.26; N, 4.07; M^+, 337.0070. Calcd for $C_{14}H_{11}NO_5S_2$: C, 49.84; H, 3.29; N, 4.15; M, 337.0078.

b) A solution of **1** (100 mg) and dimethyl acetylenedicarboxylate (**5b**) (300 mg) in acetonitrile (10 ml) was refluxed for 7 h, worked up as described above, to give **6b**. Yield 154 mg (89%).

2-[[(Z)-1,2-(Diethoxycarbonyl)ethenyl]thio]-8H-cyclohepta[d]thiazol-8-one (**6c**)

a) A solution of **1** (100 mg) and diethyl acetylenedicarboxylate (**5c**) (300 mg) in benzene (10 ml) was refluxed for 7 h and worked up as described above to give **6c**. Yield 105 mg (56%); yellow oil; IR ($CHCl_3$): ν_{max} 1724 (C=O), 1630 (C=O), 1247 cm^{-1} (C—O); ^1H NMR ($CDCl_3$): δ 1.13 (3H, t, J = 7 Hz, 2'-CH_3), 1.17 (3H, t, J = 7 Hz, 1'-CH_3), 4.20 (2H, q, J = 7 Hz, 2'-CH_2), 4.45 (2H, q, J = 7 Hz, 1'-CH_2), 6.80–7.67 (3H, m), 7.13 (1H, s, =CH—), 7.81 (1H, dd, J = 10, 2 Hz, 4-H); MS: m/z (%) 365 (M^+, 1), 320 (4), 292 (100), 264 (36), 108 (9). Found: M^+, 365.0387. Calcd for $C_{16}H_{15}NO_5S_2$: M, 365.0391.

b) A solution of **1** (100 mg) and dimethyl acetylenedicarboxylate (**5c**) (300 mg) in xylene (10 ml) was refluxed for 7 h, worked up as described above, to give **6c**. Yield 137 mg (73%).

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