BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 3218—3220 (1972)

# Studies of Dithiobiurets. I. Some New Cyclization Reactions of 1,1-Dimethyl-2,4-dithiobiuret

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(Received March 2, 1972)

Several cyclization reactions of dithiobiurets have been known hitherto. For instance, alkyl or aryldithiobiurets (**1**) react with aldehydes or ketones in the presence of hydrogen chloride to give hexahydrotriazine derivative (**2**).[1] Another example is their oxidation. They are easily oxidized with bromine or iodine to yield 1,2,4-dithiazole derivatives (**3**), which are known as thiurets.[2] Dixit obtained the same compounds by the oxidative debenzylation of the *S*-benzylisodithiobiurets, (**4**) and (**5**).[3] He also obtained benzothiazole and 1,2,4-thiadiazole derivatives, (**6**) and (**7**),[3] which were formed as by-products when a large quantity of nonpolar solvents were used at the time of the oxidation.

We wish to report here some cyclization reactions of 1,1-dimethyldithiobiuret (**8**). Like thiourea, it reacted with α,β-dichloroethyl acetate to form a thiazole derivative (**9**) in a 27% yield. Fromm and Philippe[4] reacted phenyldithiobiuret with monochloroacetone and obtained a product which melted at 163°C. They considered that the structure was **10** or **11**. Compound **10** can easily be obtained by the reaction of 4-methylthiazole and phenylisothiocyanate (mp 174—175°C)[5] or 4-methyl-2-thiazolylisothiocyanate and aniline (mp 168—169°C).[6] We tried Fromm's method and confirmed that the product had not an **11** but a **10** structure; the structure was identified by the undepressed mixed melting points and by comparing the infrared spectrum with that of an authentic sample. Choubey and Singh[7] obtained 2-arylimino-3-arylthiazolidin-4-ones when arylthioureas were

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[1] E. Fromm, *Ann.*, **275**, 20 (1893); A. E. S. Fairfull and D. A. Peak, *J. Chem. Soc.*, **1955**, 803.

[2] E. Fromm, *Ber.*, **28**, 1096 (1895); S. N. Dixit, *J. Indian Chem. Soc.*, **38**, 44 (1961).

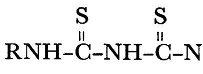
[3] S. N. Dixit, *ibid.*, **38**, 988 (1961); **39**, 407 (1962); **40**, 153 (1963).

[4] E. Fromm and E. Philippe, *Ber.*, **32**, 835 (1899).

[5] F. Fromm and R. Kapeller-Alder, *Ann.*, **467**, 259 (1928); T. Uno and S. Akihama, *Yakugaku Zasshi*, **80**, 1015 (1960); A. Silberg, D. Tefas, and D. Bedeleanu, *Acad. rep. populare Romane*, **3**, 70 (1952), *Chem. Abstr.*, **50**, 12043f (1956).

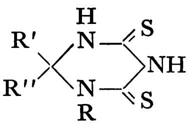
[6] O. E. Schultz and K. K. Gauri, *Arch. Pharm.*, **295**, 146 (1962).

[7] V. N. Choubey and H. Singh, This Bulletin, **43**, 2233 (1970).

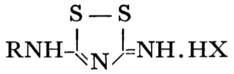


$\mathrm{RNH{-}\overset{\overset{S}{\|}}{C}{-}NH{-}\overset{\overset{S}{\|}}{C}{-}NH_2}$

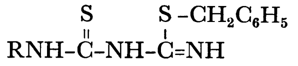
(**1**)



(**2**)

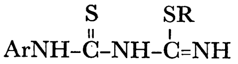


(**3**)



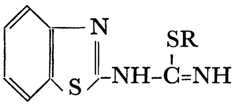
$\mathrm{RNH{-}\overset{\overset{S}{\|}}{C}{-}NH{-}\overset{\overset{S{-}CH_2C_6H_5}{|}}{C}{=}NH}$

(**4**)

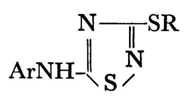


$\mathrm{ArNH{-}\overset{\overset{S}{\|}}{C}{-}NH{-}\overset{\overset{SR}{|}}{C}{=}NH}$

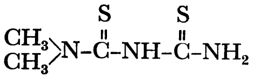
(**5**)



(**6**)

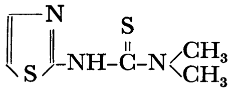


(**7**)

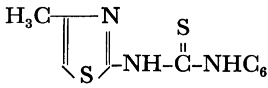


$\mathrm{{CH_3 \atop CH_3}{>}N{-}\overset{\overset{S}{\|}}{C}{-}NH{-}\overset{\overset{S}{\|}}{C}{-}NH_2}$

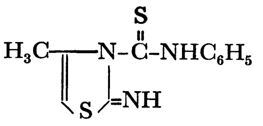
(**8**)



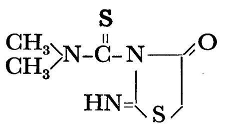
(**9**)



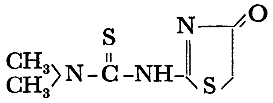
(**10**)



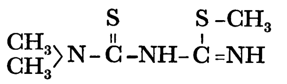
(**11**)



(**12**)

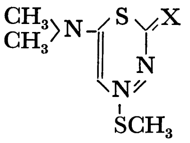


(**13**)



$\mathrm{{CH_3 \atop CH_3}{>}N{-}\overset{\overset{S}{\|}}{C}{-}NH{-}\overset{\overset{S{-}CH_3}{|}}{C}{=}NH}$

(**14**)



(**15**) X=O
(**16**) X=S
(**17**) $X=NSO_2C_6H_5$-*p*-CH
(**18**) $X=NSO_2CH_3$

treated with monochloroacetyl chloride in the presence of sodium acetate. Compound **8** also reacted with the chloride to give a thiazolin-4-one derivative (**13**). When an equimolar pyridine was used instead of sodium acetate, monochloroacetylation occurred at the 3-position and **12** was obtained as a by-product. It was converted to the thiazoline derivative **13** by acid treatment. 1,1-Dimethyl-4-*S*-methylisodithiobiuret (**14**) reacted with phosgene and thiophosgene to yield 1,3,5-thiadiazine derivatives, (**15**) and (**16**). Imidoyl dichlorides also reacted with **14** to give 2-substituted imino-1,3,5-thiadiazine derivatives, (**17**) and (**18**).

## Experimental

*2-(3,3-Dimethylthioureido)thiazole (**9**).* A suspended solution of 1,1-dimethyldithiobiuret **8** (16.3 g) in 100 m*l* of water was heated at 70°C, and then 19 g of *α,β*-dichloroethyl acetate were added with stirring. The solution gradually become homogeneous. The reaction mixture was then stirred for 1 hr and cooled at 0°C. The crystals thus precipitated were filtered and recrystallized from methanol; 6 g of white plates (hydrochloride) were thus obtained. Mp 175—176°C with decomposition.

Found: C, 32.43; H, 4.57; N, 18.85; S, 28.30; Cl, 16.05%. Required for $C_6H_{10}ClN_3S_2$: C, 32.14; H, 4.47; N, 18.75; S, 28.57; Cl, 16.07%. This was converted to the free base by treatment with aqueous sodium hydroxide. Mp 122—123°C.

Found: C, 38.55; H, 4.82; N, 22.25; S, 34.30%.

Required for $C_6H_9N_3S_2$: C, 38.50; H, 4.81; N, 22.46; S, 34.22%.

*4-Methyl-2-(3-phenylthioureido)thiazole (**10**).* A mixture of phenyldithiobiuret (3 g) and monochloroacetone (2.7 g) was heated at 85°C for 10 min, and then 50 m*l* of acetone were added. The precipitate was filtered and recrystallized from ethanol. Then 2.8 g of the hydrochloride, melting at 162—163°C (Ref. 4: mp 163°C), were obtained. The hydrochloride (2.8 g) was dissolved in 15 m*l*) of pyridine, a 50-m*l* portion of ice water was added, and then the precipitate was collected. Recrystallization from ethanol gave 2.2 g of white prisms; mp 173—174°C. No depression of the melting points was observed when this substance was mixed with an authentic sample, obtained from 2-amino-4-methylthiazole and phenylisothiocyanate.

*2-(3,3-Dimethylthioureido)thiazolin-4-one (**13**).* A mixture of 1,1-dimethyldithiobiuret **8** (5 g), anhydrous sodium acetate (2.5 g), and monochloroacetyl chloride (3.4 g) in 50 m*l* of absolute ethanol was refluxed for 1.5 hr. After the sodium chloride had been filtered off, the solvent was evaporated *in vacuo*. The residue was washed with 30 m*l* of 1 N-hydrochloric acid and recrystallized from ethanol as yellow scalies (3.5 g); mp 208—209°C with decomposition. IR: 1700 cm$^{-1}$ (C=O), 1580, 1550, NMR: $\delta$ 3.27 ppm (s, 6H, $NMe_2$), 4.50 (s, 2H, $CH_2$). UV: $\lambda_{max}$ (in alc) 224 m$\mu$ (log $\varepsilon$ 4.26), 241 (4.23), 287 (4.15). Found: C, 35.21; H, 4.43; N, 20.50; S, 31.74%. Required for $C_6H_9N_3OS_2$: C, 35.47; H, 4.43; N, 20.69; S, 31.53%.

*3-(N,N-Dimethylthiocarbamoyl)-2-iminothiazolin-4-one (**12**).* Into a solution of 1,1-dimethyldithiobiuret **8** (2 g) and pyridine (1 g) in 10 m*l* of acetone, monochloroacetyl chloride (1.5 g) was added at 0°C, after which the mixture was allowed to stand for 10 hr at room temperature. The precipitated plates were filtered and dissolved in 50 m*l* of water. After the solution had then been neutralized with sodium carbonate, the yellow powder was separated and recrystallized from ethanol to give 0.3 g of yellow prisms; mp 138—139°C with decomposition.

IR: 3400 cm$^{-1}$ (NH), 1720 (C=O), 1605, 1530. UV: $\lambda_{max}$ (in alc) 283 m$\mu$ (log $\varepsilon$ 4.48). NMR: $\delta$ 3.45 ppm (s, 2H, $CH_2$), 3.30 and 3.18 (s, $NMe_2$). Found: C, 35.58; H, 4.58; N, 20.63; S, 31.74%. Required for $C_6H_9N_3OS_2$: C, 35.47; H, 4.43; N, 20.69; S, 31.53%.

From the reaction mixture, 1.3 g of **13** were obtained.

*Isomerization of 3-(*N,N*-dimethylthiocarbamoyl)-2-iminothiazolidin-4-one (**12**).* The sample (0.1 g) was dissolved in 10 m*l* of 1N-hydrochloric acid, and the mixture was allowed to stand overnight. The precipitated yellow scalies were collected. This substance was identified with **13** by means of IR, tlc, and a mixed mp determination.

*6-Dimethylamino-4-methylthio-2*H*-1,3,5-thiadiazin-2-one (**15**).* 1,1-Dimethyl-4-*S*-methylisodithiobiuret **14** (2.5 g) was dissolved in 50 m*l* of tetrahydrofuran, and then phosgene (5 g) in 20 m*l* of tetrahydrofuran was added at 0°C. An insoluble white powder was filtered off and dried. Recrystallization from ethanol afforded 2 g of white crystals (hydrochloride); mp 170—172°C with decomposition. Found: C, 29.89; H, 4.17; N, 17.28; S, 26.47; Cl, 14.78%. Required for $C_6H_{10}ClN_3OS_2$: C, 30.06; H, 4.18; N, 17.54; S, 26.72; Cl, 14.82%. IR: 1690 cm$^{-1}$(C=O), 1600, 1530. The neutralization of this hydrochloride with potassium carbonate gave the base **15**; it was then recrystallized from ethanol as white plates. Mp 157—158°C. IR: 1650 cm$^{-1}$ (C=O), 1560. UV: $\lambda_{max}$ (in alc) 224 m$\mu$ (log $\varepsilon$ 3.66), 283 (4.08), 302$^{sh}$ (4.01). Found: C, 35.23; H, 4.33; N, 20.52; S, 31.65%. Required for $C_6H_9N_3OS_2$: C, 35.47; H, 4.43; N, 20.69; S, 31.53%.

*6-Dimethylamino-4-methylthio-2*H*-1,3,5-thiadiazin-2-thione(**16**).* The isodithiobiuret **14** (1 g) was dissolved in 50 m*l* of tetrahydrofuran, and then thiophosgene (0.7 g) in 5 m*l* of the same solvent was added at 0°C. After the reaction mixture had been stirred for 1 hr, a yellow precipitate was filtered off. The solid (0.8 g) was recrystallized from ethanol as yellow crystals. Mp 192—193°C. UV: $\lambda_{max}$ (in alc) 238 m$\mu$ (log $\varepsilon$ 4.18), 297 (4.36), 379 (4.14). Found: C, 32.93; H, 4.15; N, 19.01; S, 43.78%. Required for $C_6H_9N_3S_3$: C, 32.88; H, 4.11; N, 19.18; S, 43.84%.

*6-Dimethylamino-4-methylthio-2-tosylimino-2*H*-1,3,5-thiadiazine (**17**).* To a mixture of the isodithiobiuret (3.2 g) and tosylcarbonimidoyl dichloride (5 g) in 50 m*l* of dry benzene, triethylamine (2 g) was added. The solution was warmed at 50°C for 1 hr and then poured into ice water. The benzene layer was washed with 1N-hydrochloric acid and dried over sodium sulfate. After the solvent had been evaporated, the residue was washed with methanol and recrystallized from acetone. White scalies (1.5 g) were thus obtained. Mp 159—160°C. UV: $\lambda_{max}$ (in alc) 228 m$\mu$ (log $\varepsilon$ 4.39), 301 (4.35), 333 (4.28). NMR: (in $CDCl_3$) $\delta$ 2.41 ppm (s, 3H, Me), 2.50 (s, 3H, SMe), 3.18, 3.35 (s, s, $NMe_2$), 7.28 (d, 2H, arom), 7.95 (d, 2H, arom). Found: C, 43.71; H, 4.63; N, 15.72; S, 26.84%. Required for $C_{13}H_{16}N_4O_2S_3$: C, 43.82; H, 4.50; N, 15.73; S, 26.96%.

*6-Dimethylamino-4-methylthio-2-methylsulfonylimino-2*H*-1,3,5-thiadiazine (**18**).* This was prepared by the same method from 3.2 g of the isodithiobiuret, 3.5 g of methylsulfonylcarbonimidoyl dichloride, and 2 g of triethylamine. The yield was 2 g. It was recrystallized from acetone as white scalies. Mp 174—175°C. UV: $\lambda_{max}$ (in alc) 226 m$\mu$ (log $\varepsilon$ 4.33), 298 (4.40), 327 (4.29). NMR: (in $CDCl_3$) $\delta$ 2.58 ppm (s, 3H, SMe), 3.13 (s, 3H, $SO_2Me$), 3.22 and 3.39 (s, s, 6H, $NMe_2$). Found: C, 29.84; H, 4.33; N, 19.95; S, 34.37%. Required for $C_7H_{12}N_4O_2S_3$: C, 30.00; H, 4.29; N, 20.00; S, 34.29%.