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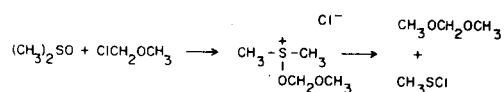
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5-Alkyl- or arylthio-2,4-pyrimidinediones, **1-8**, were prepared from uracil and alkane- or arenesulfonyl chlorides. Indole reacted similarly to give the 2,3-di- and 3-substituted derivatives, **15-19**.

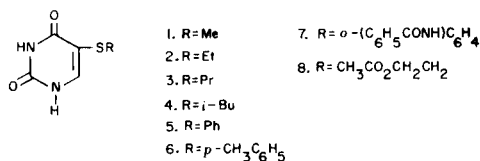
J. Heterocyclic Chem., **16**, 567 (1979).

It was reported (1) that uracil was converted to 5-alkylthio-2,4-pyrimidinedione (**1**) in a mixture of dimethylsulfoxide and chloromethyl methyl ether. The active species was considered to be methanesulfonyl chloride, generated as shown in the following scheme.



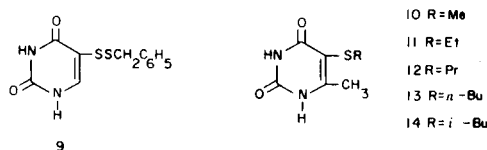
In fact uracil was found to react with methanesulfonyl chloride to give **1**. Though addition of sulfonyl chlorides to double bonds is well known (2), neither one-step addition-elimination reactions nor substitute reactions on double bonds have been widely studied.

Thus, uracil was treated with methane-, ethane-, propane-, 2-methylpropane-, benzene-, *p*-toluene-, *o*-benzamidobenzene-, or 2-methoxycarbonylthanesulfonyl chlorides to give the corresponding uracil thioethers, **1-8**.

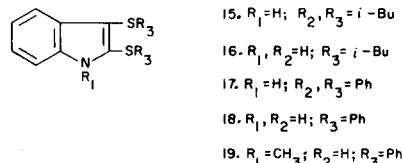


The more stable sulfonyl chlorides, *i.e.*, trichloromethanesulfonyl chloride and *o*-nitrobenzenesulfonyl chloride, did not react with uracil. In some of these experiments, sulfonyl chlorides were generated from the corresponding disulfides and sulfur chloride and were used *in situ* (see Experimental). In the same way, dibenzyl disulfide was treated with sulfur chloride expecting the formation of phenylmethanesulfonyl chloride. When uracil was treated with this reaction mixture, the product which was obtained in a low yield (5%) was the disulfid, **9**.

6-Methyl-2,4-pyrimidinedione reacted similarly to give the thioethers, **10-14**. However, 2',3',5'-tri-*O*-benzoyluridine was unaltered under the same conditions.



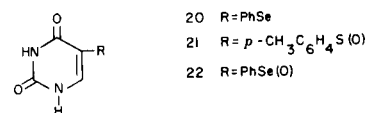
After many unsuccessful attempts to prepare alkyl- or arylthio derivatives of aromatic compounds through similar procedures, it was found that indole reacted with sulfonyl chlorides. Thus, indole reacted with 2-methylpropanesulfonyl and benzenesulfonyl chlorides to give the corresponding 2,3-di-substituted and 3-substituted derivatives, **15-18** depending upon the amount of reagents used. Intramolecular thiation of the indole moiety of a tryptophan cyclopeptide, phallion, *via* a sulphenyl chloride intermediate was recently reported (3).



The reason why 1-methylindole was easily converted to **19** with benzenesulfonyl chloride, while 2',3',5'-tri-benzoyluridine was stable toward the same reagent, is not clear.

The position of substitution in **16** was shown by nmr: *i.e.*, the C₃-H signal at δ 6.67 was no longer observed in **16** and the broad C-3 signal at δ 106.3 was revealed to couple with the -SCH₂- protons (*t*, *J* = 5 Hz) by irradiating all of the aromatic protons.

Benzeneselenenyl chloride also reacted with uracil to give the selenoether, **20**. 2',3',5'-Tri-*O*-benzoyluridine was unaffected by this reagent. Peracid oxidation of **6** and **20** afforded the sulfoxide, **21**, and the selenoxide, **22**.



In summary, the usefulness of sulfonyl chlorides as alkyl- or arylthiation reagents in limited cases was clarified. This work may also support the proposed pathway through which uracil was converted to 5-methylthio-2,4-pyrimidinedione by a mixture of dimethylsulfoxide and chloromethyl methyl ether (1).

EXPERIMENTAL

General Procedure for Alkyl- or Arythiation Using Sulfonyl Chlorides. Method A.

An excess of an alkane- or arenesulfonyl chloride was added dropwise to a stirred solution of the starting material in dimethylformamide cooled in an ice-water bath. The solution was further stirred at room temperature overnight in a well-ventilated hood. The solution was then evaporated to dryness through a trap cooled with a dry ice-acetone bath and the residue was washed with water to obtain a crude product, which was purified by crystallization from proper solvents or by silica gel chromatography.

Method B.

To a solution of an alkyl or aryl disulfide in 1,1,2,2-tetrachloroethane cooled at -15° , was added dropwise an equivalent amount of sulfonyl chloride. Stirring was continued for one hour at room temperature. The solution of a sulfonyl chloride, thus obtained, was added dropwise to a solution of the starting material in dimethylformamide cooled at 0° . After the solution was further stirred overnight at room temperature, it was evaporated to dryness and the residue was washed with water to obtain a crude product.

2-Methylpropanesulfonyl Chloride.

Dry chlorine (14.4 g., 0.20 mole) was added to diisobutyl disulfide (31.6 g., 0.18 mole) cooled at -15° , and after the mixture was left overnight it was distilled, b.p. $31^{\circ}/21$ mm, yield 26.2 g. (74%).

Anal. Calcd. for C_4H_8ClS (124.63): C, 38.55; H, 7.28; S, 25.73; Cl, 28.44. Found: C, 38.65; H, 7.20; S, 26.07; Cl, 28.60.

5-Methylthio-2,4-pyrimidinedione (1).

The yield from 560 mg. (5 mmoles) of uracil and 1 g. (12 mmoles) of methanesulfonyl chloride (4) (Method A) was 560 mg. (71%), m.p. $>300^{\circ}$ (dimethyl sulfoxide-ethanol); ms: M^+ 158. The ir and uv spectra were the same as those of the sample which was prepared by treatment of uracil with a mixture of dimethyl sulfoxide and chloromethyl methyl ether (1).

Anal. Calcd. for $C_5H_8N_2O_2S$ (158.19): C, 37.96; H, 3.82; N, 17.71; S, 20.27. Found: C, 37.70; H, 3.75; N, 17.46; S, 20.04.

5-Ethylthio-2,4-pyrimidinedione (2).

The yield from 560 mg. (5 mmoles) of uracil and 1 g. (10 mmoles) of ethanesulfonyl chloride (5) (Method A) was 600 mg. (70%), m.p. 255° (dimethylformamide-water); ms: M^+ 172.

Anal. Calcd. for $C_6H_{10}N_2O_2S$ (172.21): C, 41.84; H, 4.68; N, 16.27; S, 18.62. Found: C, 41.42; H, 4.51; N, 16.41; S, 18.46.

5-Propylthio-2,4-pyrimidinedione (3).

The yield from 560 mg. (5 mmoles) of uracil and 1 g. (9 mmoles) of propanesulfonyl chloride (6) (Method A) was 670 mg. (72%), m.p. 261° (dimethylformamide-benzene); ms: m/e 186 (M^+), 144 ($M^+ - CH_2CH=CH_2$).

Anal. Calcd. for $C_7H_{10}N_2O_2S$ (186.24): C, 45.14; H, 5.41; N, 15.05; S, 17.22. Found: C, 45.08; H, 5.33; N, 15.08; S, 17.07.

5-(2-Methylpropylthio)-2,4-pyrimidinedione (4).

The yield from 560 mg. (5 mmoles) of uracil and 1.2 g. (9.6 mmoles) of 2-methylpropanesulfonyl chloride (Method A) was 940 mg. (90%), m.p. $267-268^{\circ}$ (dimethylformamide-butyl acetate); ms: m/e 200 (M^+), 144 ($M^+ - (CH_3)_2C=CH_2$).

Anal. Calcd. for $C_9H_{12}N_2O_2S$ (200.28): C, 47.98; H, 6.04; N, 13.99; S, 16.01. Found: C, 47.81; H, 5.97; N, 14.04; S, 15.95.

5-Phenylthio-2,4-pyrimidinedione (5).

A crude product prepared from 560 mg. (5 mmoles) of uracil, 700 mg. (3.2 mmoles) of diphenyl disulfide and 410 mg. (3 mmoles) of sulfonyl chloride (Method B) was washed with hot propanol and was crystallized

from dimethylformamide and propanol and then from dimethylformamide and water, yield 800 mg. (73%), m.p. $271-272^{\circ}$; uv (methanol): λ max nm (ϵ) 300 sh (5,500), 246 (20,200).

Anal. Calcd. for $C_{10}H_8N_2O_2S$ (220.25): C, 54.53; H, 3.66; N, 12.72; S, 14.56. Found: C, 54.36; H, 3.64; N, 12.66; S, 14.39.

5-*p*-Tolylthio-2,4-pyrimidinedione (6).

A crude product prepared from 1.3 g. (11.6 mmoles) of uracil, 2.96 g. (12 mmoles) of di-*p*-tolyl disulfide and 1.6 g. (11.8 mmoles) of sulfonyl chloride (Method B) was washed with ethyl acetate and crystallized from dimethylformamide and water, yield 1.74 g. (74%), m.p. $293-295^{\circ}$; uv (methanol): λ max nm (ϵ) 245 (11,500), 275 (6,400), 300 (3,500).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$ (234.28): C, 56.39; H, 4.30; N, 11.96; S, 13.69. Found: C, 55.98; H, 4.22; N, 11.94; S, 13.54.

5-*o*-Benzamidophenyl-2,4-pyrimidinedione (7).

A crude product prepared from 560 mg. (5 mmoles) of uracil, 1.39 g. (3.05 mmoles) of *o,o'*-dibenzamidodiphenyl disulfide and 450 mg. (3.3 ml.) of sulfonyl chloride (Method B) was washed with chloroform, and crystallized from dimethylformamide and water, yield 1.18 g. (70%), m.p. $>300^{\circ}$; ms: M^+ 339; uv (methanol): λ max 237 nm (ϵ : 16,300).

Anal. Calcd. for $C_{17}H_{13}N_3O_2S$ (339.37): C, 60.16; H, 3.86; N, 12.38; S, 9.45. Found: C, 60.00; H, 3.94; N, 12.39; S, 9.43.

5-(2-Methoxycarbonylethylthio)-2,4-pyrimidinedione (8).

A crude product prepared from 560 mg. (5 mmoles) of uracil, 750 mg. (3.15 mmoles) of 3,3'-dithiodipropionic acid methyl ester and 450 mg. (3.33 mmoles) of sulfonyl chloride was washed with chloroform and crystallized from dimethylformamide and water, yield 810 mg. (57%), m.p. $215-217^{\circ}$; ms: m/e 230 (M^+), 199 ($M^+ - CH_3O$), 170 ($M^+ - HCOOCH_3$); uv (methanol): λ max 274 nm (ϵ 5,900).

Anal. Calcd. for $C_8H_{10}N_2O_4$ (216.22): C, 41.73; H, 4.38; N, 12.17; S, 13.93. Found: C, 41.74; H, 4.38; N, 12.09; S, 13.73.

5-Benzylthio-2,4-pyrimidinedione (9).

Uracil (560 mg., 5 mmoles) was treated with a mixture of dibenzyl disulfide (1.5 g., 6.1 mmoles) and sulfonyl chloride (800 mg., 6 mmoles) following the general procedure for alkylthiation (Method B). The reaction mixture was evaporated to dryness and the product was extracted with hot ethyl acetate. A large quantity of unextractable material was found to be uracil. On standing the ethyl acetate solution in a refrigerator, 60 mg. (5%) of **9** was crystallized. Recrystallization from butyl acetate afforded an analytically pure sample, which softened at $210-214^{\circ}$ and did not melt at 300° ; ms: m/e 266 (M^+), 234 ($M^+ - S$), 144 ($M^+ - PhCH=S$); uv (methanol): λ max 265 nm (ϵ 9,200).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S_2$ (266.35): C, 49.60; H, 3.78; N, 10.52; S, 24.08. Found: C, 49.44; H, 3.78; N, 10.57; S, 23.81.

6-Methyl-5-methylthio-2,4-pyrimidinedione (10).

The yield from 630 mg. (5 mmoles) of 6-methyl-2,4-pyrimidinedione, 470 mg. (5 mmoles) of dimethyl disulfide and 680 mg. (5 mmoles) of sulfonyl chloride (Method B) was 450 mg. (52%), m.p. $298-305^{\circ}$ dec. (propanol); ms: M^+ 172; uv (methanol): λ max nm (ϵ) 276 (8,400), 253 (7,800), 235 (7,400).

Anal. Calcd. for $C_6H_8N_2O_2S$ (172.21): C, 41.84; H, 4.68; N, 16.27; S, 18.62. Found: C, 41.81; H, 4.70; N, 16.28; S, 18.52.

5-Ethylthio-6-methyl-2,4-pyrimidinedione (11).

The yield from 630 mg. (5 mmoles) of 6-methyl-2,4-pyrimidinedione and 1 g. (10 mmoles) of ethanesulfonyl chloride (Method A) was 400 mg. (43%), m.p. $253-256^{\circ}$ dec. (butyl acetate); ms: m/e 186 (M^+), 158 ($M^+ - C_2H_4$).

Anal. Calcd. for $C_7H_{10}N_2O_2S$ (186.24): C, 45.14; H, 5.41; N, 15.05; S, 17.22. Found: C, 44.91; H, 5.33; N, 14.89; S, 17.02.

6-Methyl-5-propylthio-2,4-pyrimidinedione (12).

The yield from 630 mg. (5 mmoles) of 6-methyl-2,4-pyrimidinedione and 1.2 g. (11 mmoles) of propanesulfonyl chloride (Method A) was 870

mg. (87%), m.p. 229-231° (dimethylformamide-benzene); ms: m/e 200 (M⁺), 158 (M⁺-CH₃-CH=CH₂).

Anal. Calcd. for C₈H₁₂N₂O₂S (200.27): C, 47.98; H, 6.04; N, 13.99; S, 16.01. Found: C, 47.69; H, 5.95; N, 14.07; S, 15.93.

5-Butylthio-6-methyl-2,4-pyrimidinedione (13).

The yield from 630 mg. (5 mmoles) of 6-methyl-2,4-pyrimidinedione and 1.4 g. (11 mmoles) of butanesulfonyl chloride (6) (Method A) was 980 mg. (92%), m.p. 199-200° (dimethylformamide-benzene); ms: m/e 214 (M⁺), 158 (M⁺-CH₂CH₂CH=CH₂).

Anal. Calcd. for C₈H₁₄N₂O₂S (214.29): C, 50.44; H, 6.58; N, 13.08; S, 14.97. Found: C, 50.19; H, 6.52; N, 13.07; S, 14.97.

6-Methyl-5-(2-methylpropylthio)-2,4-pyrimidinedione (14).

The yield from 630 mg. (5 mmoles) of 6-methyl-2,4-pyrimidinedione and 1.4 g. (11 mmoles) of 2-methylpropanesulfonyl chloride (Method A) was 1.02 g. (95%), m.p. 226-227° (propanol); ms: m/e 214 (M⁺), 158 (M⁺-C(CH₃)₂C=CH₂).

Anal. Calcd. for C₉H₁₄N₂O₂S (214.29): C, 50.44; H, 6.58; N, 13.08; S, 14.97. Found: C, 50.10; H, 6.55; N, 13.00; S, 14.88.

2,3-Bis(2-methylpropylthio)indole (15) and 3-(2-Methylpropylthio)indole (16).

Tlc showed that a crude product prepared from indole (585 mg., 5 mmoles) and 2-methylpropanesulfonyl chloride (1 g., 8 mmoles) (Method A) consisted of two uv absorbing compounds, which were separated by silica gel chromatography. The less polar compound, **15**, was eluted with a mixture of hexane and benzene (1:1), yield 420 mg. (29%), syrup; ms: m/e 293 (M⁺), 237 (M⁺-CH₂=C(CH₃)₂), 181 (M⁺-2CH₂=C(CH₃)₂), 149 (M⁺-CH₂=C(CH₃)₂-SCH₂=C(CH₃)₂); ¹H nmr (deuteriochloroform): δ 0.98 and 1.00 (two d, 12, 4 CH₃).

Anal. Calcd. for C₁₆H₂₀NS₂ (293.49): C, 65.47; H, 7.90; N, 4.77; S, 21.85. Found: C, 65.20; H, 7.75; N, 4.80; S, 21.62.

The more polar compound, **16**, was eluted with benzene, yield 670 mg. (65%), syrup; ms: m/e 205 (M⁺), 149 (M⁺-CH₂=C(CH₃)₂); ¹H nmr (deuteriochloroform): δ 0.98 (d, 6, 2 CH₃).

Anal. Calcd. for C₁₂H₁₅NS (205.32): C, 70.19; H, 7.36; N, 6.82; S, 15.62. Found: C, 70.27; H, 7.35; N, 6.81; S, 15.59.

In another run, the amount of 2-methylpropanesulfonyl chloride was increased to 1.5 g. (12 mmoles), keeping other conditions unchanged. The yields of **15** and **16** were 770 mg. (53%) and 190 mg. (19%), respectively.

2,3-Diphenylthioindole (17) and 3-Phenylthioindole (18).

Tlc showed that a crude product prepared from indole (1.4 g., 12 mmoles), diphenyl disulfide (1.3 g., 6 mmoles) and sulfuryl chloride (800 mg., 5.9 mmoles) (Method B) consisted of two uv absorbing compounds, which were separated by silica gel chromatography. The less polar compound, **17**, was eluted with a mixture of hexane and benzene (1:1), yield 610 mg. (15%), m.p. 98-99° (benzene-hexane); uv (methanol): λ max 292 nm (ε 16,000).

Anal. Calcd. for C₂₀H₁₅NS₂ (333.47): C, 72.03; H, 4.53; N, 4.20; S, 19.23. Found: C, 72.17; H, 4.56; N, 4.20; S, 19.01.

The more polar compound, **18**, was eluted with benzene, yield 2.27 g. (84%), m.p. 152-153° (benzene-hexane).

Anal. Calcd. for C₁₄H₁₁NS (225.31): C, 47.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 47.61; H, 4.95; N, 6.19; S, 14.16.

In another run, the amount of indole was decreased to 585 mg. (5 ml.), keeping other conditions unchanged. Only **17** was obtained, yield, 1.6 g. (96%).

1-Methyl-3-phenylthioindole (19).

A crude product prepared from *N*-methylindole (870 mg., 6.64 mmoles), diphenyl disulfide (730 mg., 3.35 mmoles) and sulfuryl chloride (500 mg., 3.7 mmoles) (Method B) was applied to silica gel chromatography, eluting with a mixture of hexane and benzene (2:1), to give 1.39 g. (88%) of **19**, m.p. 90° (benzene).

Anal. Calcd. for C₁₅H₁₃NS (239.33): C, 75.27; H, 5.47; N, 5.85; S, 13.40. Found: C, 75.23; H, 5.49; N, 5.85; S, 13.18.

5-Phenylseleno-2,4-pyrimidinedione (20).

To a solution of diphenyl diselenide (800 mg., 2.56 mmoles) in tetrachloroethane (10 ml.) cooled at 0°, was added sulfuryl chloride (340 mg., 2.52 mmoles) to obtain a solution of benzeneselenenyl chloride, which was added dropwise to a solution of uracil (560 mg., 5 mmoles) in dimethylformamide (40 mmoles) cooled at 0°. Stirring was continued at room temperature for 1 hour. After evaporation of the solvent, the residue was washed with propanol and dissolved in a small amount of dimethylformamide without heating. Undissolved material was found to be uracil. Addition of water afforded 1.02 g. (76%) of **20**, m.p. 256-258°; ms: M⁺ 267; uv (methanol): λ max nm (ε) 243 (10,400), 263 sh (8,800), 300 (2,600).

Anal. Calcd. for C₁₀H₈N₂O₂Se (267.14): C, 44.94; H, 3.02; N, 10.49. Found: C, 44.93; H, 3.06; N, 10.60.

5-*p*-Toluenesulfinyl-2,4-pyrimidinedione (21).

To a solution of **6** (2.34 g., 10 mmoles) in trifluoroacetic acid (50 ml.) cooled at -15°, was added portionwise *m*-chloroperbenzoic acid (1.72 g., 10 mmoles), and the solution was left overnight at room temperature. After the solvent was removed by evaporation, the residue was washed with acetone and crystallized from dimethylformamide and water, yield 186 mg. (74%); m.p. 245-246°.

Anal. Calcd. for C₁₁H₁₀N₂O₂S (250.28): C, 52.78; H, 4.03; N, 11.20; S, 12.81. Found: C, 52.30; H, 4.12; N, 11.19; S, 12.56.

5-Benzeneseleninyl-2,4-pyrimidinedione (22).

Oxidation of **20** (267 mg., 1 mmole) to **22** with *m*-chloroperbenzoic acid (172 mg., 1 mmole) was carried out under similar conditions as described in the preceding section, yield 175 mg. (66%), double m.p. 170° and 205-215° dec. (dimethylsulfoxide-water).

Anal. Calcd. for C₁₀H₈N₂O₂Se (283.14): C, 42.42; H, 2.85; N, 9.90. Found: C, 42.49; H, 2.87; N, 9.93.

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