Synthesis and Properties of Thiazolo[5,4-*d*]pyrimidine 1-Oxides

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Synthesis and properties of hitherto unknown thiazolo[5,4-*d*]pyrimidine 1-oxides are described. For example, the reaction of 6-chloro-1,3-dimethyl-5-nitrouracil (I) with methyl thioglycolate in the presence of excess triethylamine afforded 2-methoxycarbonyl-4,6-dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione 1-oxide (IIIa), which is a versatile intermediate for the preparation of various thiazolo[5,4-*d*]pyrimidine derivatives.

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Thiazolo[5,4-*d*]pyrimidine ring system would be of medicinal interest since it can be considered at first glance as a thia analogue of purine by virtue of the five membered ring to the pyrimidine nucleus. Although the chemistry of thiazolo[5,4-*d*]pyrimidines has been relatively studied, the synthesis and properties of their *N*-oxides have scarcely been understood. Namely, of the three possible structural types of thiazolo[5,4-*d*]pyrimidine *N*-oxides, the only *N*-oxide reported in the literature is that of 6-oxide (1). As part of a continuing study on the chemistry of this attractive heterocycle (2), we now wish to report the synthesis and properties of hitherto unknown thiazolo-[5,4-*d*]pyrimidine 1-oxides.

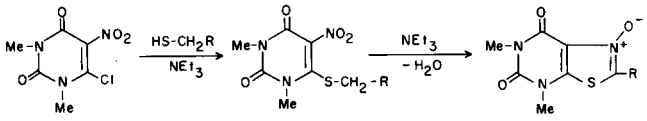
In order to prepare the desired *N*-oxides, we first examined the applicability of the method for the synthesis of benzothiazole *N*-oxides by the cyclization reaction which consists in the reaction of *o*-nitrochlorobenzenes with thioglycolic esters in the presence of base (3). Thus, the addition of excess triethylamine to a mixture of 6-chloro-1,3-dimethyl-5-nitrouracil (I) (4) and methyl or ethyl thioglycolate in ethanol at $-5°$ for 1 hour caused the separation of the corresponding 2-alkoxycarbonyl-4,6-dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione 1-oxides (IIIa and IIIb) in 50 and 47% yield, respectively. Similarly, the reaction of I with *p*-nitrobenzylmercaptan gave the 2-(4-nitrophenyl)thiazolopyrimidine 1-oxide (IIIc) albeit in low yield (21%).

The structures of IIIa-c were readily confirmed by the satisfactory elemental analyses and spectral data. In particular, the mass spectra of these compounds revealed, respectively, a strong parent ion and a remarkable M^+-16 ion due to the presence of *N*-oxide.

The reaction of I with mercaptans leading to III apparently involves the initial formation of the intermediacy of 6-substituted methylenethio-1,3-dimethyl-5-nitrouracils (IIa-c) and subsequent base catalyzed dehydrative cyclization. In fact, *eg*, the reaction of Ib with ethyl thioglycolate in the presence of an equimolar amount of triethylamine afforded IIb in 43% yield, and subsequent treatment with the base provided IIIb in 95% yield.

In contrast with the above results, treatment of I with ethyl or benzylmercaptan in the presence of excess triethylamine yielded the corresponding 6-substituted methylenethio-5-nitrouracils (IId and IIe) in 50 and 33% yield, respectively, and the expected thiazolopyrimidine 1-oxides could not be isolated. The preferential formation of IId and IIe is probably due to the unactivated nature of their methylene groups (Scheme I).

Scheme I

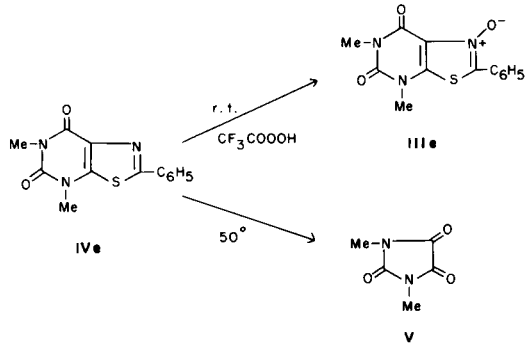


I IIa-e IIIa-c

a: R = COOMe
b: R = COOEt
c: R = 4-NO_2-C_6H_4
d: R = Me
e: R = C_6H_5

Besides the successful synthesis of thiazolopyrimidine 1-oxides by the cyclization reaction described above, we next investigated the direct *N*-oxidation of 4,6-dimethyl-2-phenylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione (IVe) (2) as a model compound. Thus, treatment of (IVe) with trifluoroperacetic acid at room temperature for 72 hours gave the desired 2-phenylthiazolopyrimidine 1-oxide (IIIe) in 57% yield. The characterization of IIIe as 1-oxide and not as 3-oxide was base on the absence of sulfoxide absorption bands in the ir spectrum. It is interesting to note that the formation of IIIe is greatly depending on the reaction conditions, *ie*, when this reaction was carried out at the

Scheme II

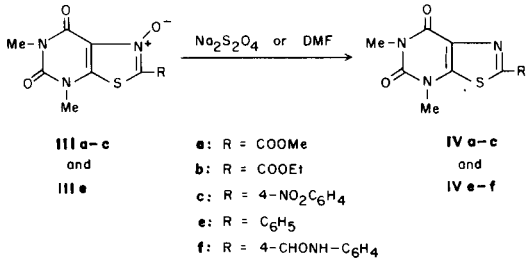


IVe IIIe V

elevated temperature (50°), the product obtained in 56% yield was found to be the unexpected 1,3-dimethylparabanic acid (V). Although the mechanism for the conversion of IVe to V is not clear at present, a similar type of reaction has been reported for caffeine and theophylline (5,6) (Scheme II).

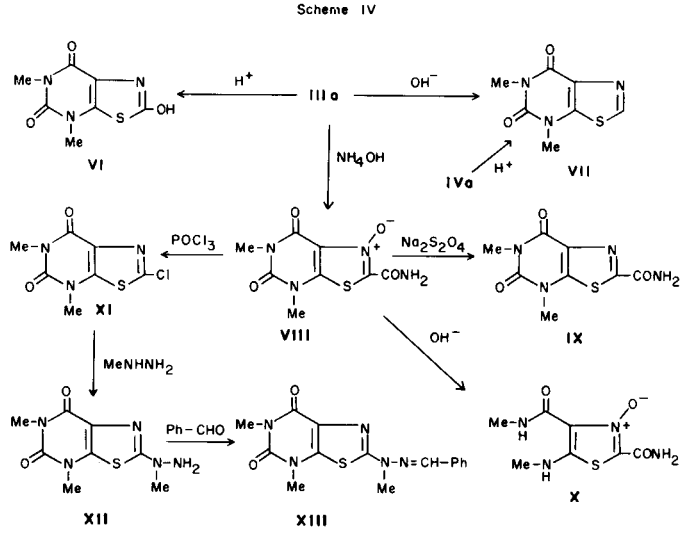
The thiazolopyrimidine 1-oxides (IIIa-c and IIIe) underwent ready reductive or oxidative deoxygenation to yield the parent thiazolopyrimidines. Namely, treatment of the appropriate oxides with sodium dithionite in water at room temperature for 3 hours (reductive deoxygenation) or with dimethylformamide at reflux for 3 hours (oxidative deoxygenation) gave the corresponding thiazolopyrimidines (IVa-c and IVe) in high yields, respectively. When the reaction of IIIc with sodium dithionite was carried out in formic acid, the product isolated in 84% yield was found to be the 2-(4-formylaminophenyl)thiazolopyrimidine (IVf) (Scheme III).

Scheme III



The reaction of IIIa with 10% hydrochloric acid at 95° for 15 minutes resulted in the formation of 2-hydroxythiazolopyrimidine (VI) in 64% yield. This reaction presumably involves the initial hydrolytic decarboxylation of the methoxycarbonyl group and subsequent acid catalyzed rearrangement of the *N*-oxide. In contrast to the acid, treatment of IIIa with 1% sodium hydroxide in refluxing ethanol for 1 hour caused the hydrolytic decarboxylation of the methoxycarbonyl group and the deoxygenation of the *N*-oxide to give the 2-unsubstituted thiazolopyrimidine (VII) in 15% yield. The compound VII was alternately obtained in 78% yield by the reaction of IVa with 5% hydrochloric acid. Reaction of IIIa with methanolic ammonia at room temperature for 1 hour gave the 2-carbamoylthiazolopyrimidine 1-oxide (VIII) in 83% yield, while the treatment of IIIa with methanolic ammonia under reflux for 5 hours resulted in the formation of (VII) in 62% yield. As expected, oxidative deoxygenation by refluxing of VIII with dimethylformamide gave the 2-carbamoylthiazolopyrimidine (IX) in 60% yield. In contrast with the behavior of IIIa towards alkali, the reaction of VIII with 1% sodium hydroxide in refluxing methanol for 3 hours resulted in the cleavage of the uracil nucleus to give 2-carbamoyl-5-methylamino-4-*N*-methylcarbamoylthiazole 3-oxide (X) in 68% yield. Refluxing of VIII with phosphorus oxychloride for 3 hours afforded the 2-chlorothiazolopyrimidine (XI) in 75% yield. The compound XI is reactive enough toward nucleophiles and serves as a starting material for further derivatives of thiazolopyrimidine. For example, the reaction of XI with methylhydrazine smoothly gave the 2-(1′-methylhydrazino)thiazolopyrimidine (XII) and whose structure was confirmed by its conversion into 2-(1′-methylbenzylidenehydrazino)thiazolopyrimidine (XIII) with benzaldehyde (Scheme IV).

Scheme IV



EXPERIMENTAL

Melting points were taken on a YANACO micro-hot-stage melting point apparatus and are uncorrected. Nmr spectra were determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as the internal standard. Identity of the compounds was confirmed by comparison of the ir spectra determined in Nujol on a JASCO IR-E spectrophotometer. The molecular weight for all compounds were correctly analyzed by mass spectroscopy with a JEOL D-300 spectrometer by a direct-inlet system at 70 eV.

6-Substituted Methylenethio-1,3-dimethyl-5-nitrouracils (IIa-b and d-e).

To a suspension of 6-chloro-1,3-dimethyl-5-nitrouracil (I) (4) (0.22 g, 0.001 mole) and the appropriate mercaptans (0.001 mole) in ethanol (5 ml), triethylamine (0.1 g, 0.001 mole) was added at −5° with stirring. After stirring at the same temperature for 1 hour, the precipitates were filtered off, washed with chilled methanol, and recrystallized from ethanol to give the corresponding IIa-b and d-e.

Compound IIa.

This compound had mp 102-103° (0.07 g, 24%).

Anal. Calcd. for $C_9H_{11}N_3O_6S$: C, 37.36; H, 3.84; N, 14.53. Found: C, 37.18; H, 4.04; N, 14.65.

Compound IIb.

This compound had mp 77-78° (0.13 g, 43%).

Anal. Calcd. for $C_{10}H_{13}N_3O_6S$: C, 39.59; H, 4.33; N, 13.86. Found: C, 39.45; H, 4.23; N, 14.14.

Compound IId.

This compound had mp 110-111° (0.12 g, 49%).

Anal. Calcd. for $C_8H_{11}N_3O_4S$: C, 39.17; H, 4.53; N, 17.13. Found: C, 39.40; H, 4.55; N, 17.30.

Compound IIe.

This compound had mp 132-133° (0.1 g, 33%).

Anal. Calcd. for $C_{13}H_{13}N_3O_4S$: C, 50.80; H, 4.27; N, 13.67. Found: C, 50.60; H, 4.18; N, 13.73.

2-Alkoxycarbonyl-4,6-dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione 1-Oxides (IIIa-b).

Method A.

To a mixture of I (11 g, 0.05 mole) and the appropriate thioglycolate (0.05 mole) in ethanol (30 ml), triethylamine (10 g, 0.1 mole) was added dropwise over a period of 1 hour at −5° with stirring. The precipitates were filtered off, washed with ethanol, dried, and recrystallized from ethanol gave the corresponding IIIa-b.

Compound IIIa.

This compound had mp 147-148° (6.78 g, 50%); nmr (DMSO-d_6): δ 3.26 (3H, s, N-Me), 3.50 (3H, s, N-Me), 3.89 (3H, s, OMe).

Anal. Calcd. for $C_9H_9N_3O_5S$: C, 39.84; H, 3.35; N, 15.49. Found: C, 39.62; H, 3.32; N, 15.54.

Compound IIIb.

This compound had mp 138-139° (6.71 g, 47%); nmr (DMSO-d_6): δ 1.40 (3H, t, J = 7 cps, -CH_3), 3.30 (3H, s, N-Me), 3.57 (3H, s, N-Me), 4.40 (2H, q, J = 7 cps, -CH_2-).

Anal. Calcd. for $C_{10}H_{11}N_3O_5S$: C, 42.09; H, 3.89; N, 14.73. Found: C, 42.31; H, 3.71; N, 14.94.

Method B.

To a stirring suspension of IIb (0.3 g, 0.001 mole) in ethanol (3 ml), triethylamine (0.2 g, 0.002 mole) was added at −5°. After stirring for 1 hour, the precipitates were filtered off, washed with chilled methanol, and dried to give IIIb (0.27 g, 95%), which is identical with the compound obtained by the Method A.

4,6-Dimethyl-2-(4-nitrophenyl)thiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione 1-Oxide (IIIc).

To a mixture of I (1.1 g, 0.005 mole) and *p*-nitrobenzylmercaptan (0.85 g, 0.005 mole) in methanol (10 ml), triethylamine (2.53 g, 0.025 mole) was added dropwise at 0° with stirring. After stirring for 5 hours, the precipitates were filtered off and recrystallized from ethanol to give IIIc (0.35 g, 21%), mp 206-207°.

Anal. Calcd. for $C_{13}H_{10}N_4O_5S$: C, 46.70; H, 3.02; N, 16.76. Found: C, 46.84; H, 3.03; N, 16.89.

The filtrate which removed crude IIIc was evaporated *in vacuo* and the residue was extracted with chloroform. Evaporation of the chloroform extracts *in vacuo* gave the unreacted I (0.65 g, 59%).

4,6-Dimethyl-2-phenylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione 1-Oxide (IIIe).

A mixture of 4,6-dimethyl-2-phenylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione (IVe) (2) (0.55 g, 0.002 mole), trifluoroacetic acid (10 ml), and 30% hydrogen peroxide (3 ml) was stirred at room temperature for 72 hours. The reaction mixture was poured onto crushed ice (30 g) and the resulting solution was concentrated to the half volume *in vacuo*. The precipitates were filtered off, dried, and recrystallized from a mixture of dimethylformamide and ethanol to give IIIe (0.33 g, 57%), mp 182-183°C.

Anal. Calcd. for $C_{13}H_{11}N_3O_3S$: C, 53.96; H, 3.84; N, 14.53. Found: C, 53.80; H, 3.82; N, 14.53.

2-Substituted 4,6-Dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)diones (IVa-c and e-f).

Method A.

A mixture of the appropriate IIIa-c and e (0.001 mole) and sodium dithionite (0.52 g, 0.003 mole) in water (5 ml) was stirred at room temperature for 3 hours. The precipitates were filtered off, washed well with water, dried, and recrystallized from ethanol to give the corresponding IVa-c and e.

Compound IVa.

This compound had mp 214-216° (0.24 g, 96%); nmr (DMSO-d_6): δ 3.33 (3H, s, N-Me), 3.58 (3H, s, N-Me), 4.00 (3H, s, OMe).

Anal. Calcd. for $C_9H_9N_3O_4S$: C, 42.34; H, 3.56; N, 16.46. Found: C, 42.12; H, 3.59; N, 16.39.

Compound IVb.

This compound had mp 208-209° (0.26 g, 95%); nmr (DMSO-d_6): δ 1.38 (3H, t, J = 7 cps, -CH_3), 3.32 (3H, s, N-Me), 3.57 (3H, s, N-Me), 4.43 (2H, q, J = 7 cps, -CH_2-).

Anal. Calcd. for $C_{10}H_{11}N_3O_4S$: C, 44.60; H, 4.13; N, 15.61. Found: C, 44.52; H, 4.07; N, 15.80.

Compound IVc.

This compound had mp 295-298° (0.28 g, 89%).

Anal. Calcd. for $C_{13}H_{10}N_4O_4S$: C, 49.05; H, 3.17; N, 17.60. Found: C, 48.93; H, 3.22; N, 17.47.

Compound IVe.

This compound had mp 221-224° (0.25 g, 90%), and it is identical with the authentic sample (2).

Method B.

A mixture of the appropriate IIIa-c and e (0.0005 mole) and dimethylformamide (3 ml) was refluxed for 3 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with chilled ethanol. The insoluble material was filtered off and recrystallized from ethanol to give the corresponding IVa-c and e, which are identical with the compounds obtained in the Method A, in 85-93% yields.

Method C.

A mixture of IIIc (0.05 g, 0.00015 mole) and sodium dithionite (0.1 g, 0.0006 mole) in formic acid (2 ml) was refluxed for 2 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with water. The insoluble material was filtered off, dried, and recrystallized from ethanol to give 2-(4-formylaminophenyl)-4,6-dimethylthiazolo[5,4-*d*]-pyrimidine-5,7-(4*H*,6*H*)dione (IVf) (0.04 g, 84%), mp >300°.

Anal. Calcd. for $C_{14}H_{12}N_4O_3S$: C, 53.15; H, 3.83; N, 17.71. Found: C, 53.17; H, 3.92; N, 17.75.

1,3-Dimethylparabanic Acid (V).

A mixture of IVe (0.27 g, 0.001 mole), trifluoroacetic acid (5 ml), and 30% hydrogen peroxide (2.5 ml) was stirred at 50° for 72 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with water. The insoluble material was filtered off, washed well with water, dried, and recrystallized from ethanol to give V (0.08 g, 56%), mp 150-155° (Lit mp 145-155.5° (5)); nmr (DMSO-d_6): δ 3.00 (6H, s, two N-Me).

Anal. Calcd. for $C_5H_6N_2O_3$: C, 42.25; H, 4.26; N, 19.71. Found: C, 42.08; H, 4.17; N, 19.52.

2-Hydroxy-4,6-dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione (VI).

A mixture of IIIa (0.27 g, 0.001 mole) and 10% hydrochloric acid (1 ml) was heated at 95° for 15 minutes. After cooling, the precipitates were filtered off, washed well with water, dried, and recrystallized from ethanol to give VI (0.14 g, 64%), mp. 264-268°.

Anal. Calcd. for $C_7H_7N_3O_3S$: C, 39.43; H, 3.32; N, 19.71. Found: C, 39.16; H, 3.19; N, 19.44.

4,6-Dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione (VII).

Method A.

A suspension of IIIa (0.27 g, 0.001 mole) in ethanol (10 ml) containing 1% sodium hydroxide (1 ml) was refluxed for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was covered with ethanol. The insoluble material was filtered off and recrystallized from ethanol to give VII (0.03 g, 15%), mp 272-274°.

Anal. Calcd. for $C_7H_7N_3O_2S$: C, 42.62; H, 3.58; N, 21.31. Found: C, 42.62; H, 3.62; N, 20.91.

Method B.

A suspension of IVa (1.28 g, 0.005 mole) in 5% hydrochloric acid (30 ml) was heated at 95° for 3 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with ethanol. The insoluble material was filtered off and recrystallized from ethanol to give VII (0.77 g, 78%), which is identical with the compound obtained by the Method A.

Method C.

A suspension of IIIa (0.27 g, 0.001 mole) in methanol (5 ml) containing 2% ammonia (2 ml) was refluxed for 5 hours. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized from ethanol to give VII (0.12 g, 62%), which is identical with the compound obtained by the Method A.

2-Carbamoyl-4,6-dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione 1-Oxide (VIII).

A suspension of IIIa (0.27 g, 0.001 mole) in methanol (5 ml) containing 1% ammonia (2 ml) was stirred at room temperature for 1 hour. The precipitates were filtered off and recrystallized from dimethylformamide to give VIII (0.21 g, 83%), mp 241-242°; nmr (deuteriotrifluoroacetic acid): δ 3.60 (3H, s, N-Me), 3.80 (3H, s, N-Me), 7.66 (1H, br, NH), 9.53 (1H, br, NH).

Anal. Calcd. for $C_8H_8N_4O_4S$: C, 37.49; H, 3.15; N, 21.87. Found: C, 37.56; H, 3.28; N, 21.68.

2-Carbamoyl-4,6-dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione (IX).

A mixture of VIII (0.26 g, 0.001 mole) and dimethylformamide (3 ml) was refluxed for 3 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with ethanol. The insoluble material was filtered off and recrystallized from a mixture of dimethylformamide and ethanol to give IX (0.15 g, 60%), mp >300°.

Anal. Calcd. for $C_8H_8N_4O_3S$: C, 39.99; H, 3.36; N, 23.32. Found: C, 40.18; H, 3.56; N, 23.07.

2-Carbamoyl-5-methylamino-4-*N*-methylcarbamoylthiazole 3-Oxide (X).

A suspension of VIII (0.26 g, 0.001 mole) in methanol (5 ml) containing 1% sodium hydroxide (1 ml) was refluxed for 3 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with water. The insoluble material was filtered off and recrystallized from ethanol to give X (0.16 g, 68%), mp 266-267°.

Anal. Calcd. for $C_7H_{10}N_4O_3S$: C, 36.51; H, 4.39; N, 24.34. Found: C, 36.46; H, 4.26; N, 24.13.

2-Chloro-4,6-dimethylthiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione (XI).

A mixture of VIII (0.26 g, 0.001 mole) and phosphorus oxychloride (2 ml) was refluxed for 3 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with ice-water. The precipitates were filtered off, washed well with water, dried and recrystallized from ethanol to give XI (0.17 g, 75%), mp 228-229°.

Anal. Calcd. for $C_7H_6ClN_3O_2S$: C, 36.29; H, 2.62; N, 18.14. Found: C, 36.51; H, 2.87; N, 18.00.

4,6-Dimethyl-2-(1′-methylhydrazino)thiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione (XII).

A mixture of XI (0.23 g, 0.001 mole) and methylhydrazine (0.14 g, 0.003 mole) in methanol (5 ml) was refluxed for 1 hour. After cooling, the precipitates were filtered off and recrystallized from dimethylformamide to give XII (0.22 g, 92%), mp 287-288°.

Anal. Calcd. for $C_8H_{11}N_5O_2S$: C, 39.82; H, 4.60; N, 29.03. Found: C, 39.98; H, 4.33; N, 28.86.

4,6-Dimethyl-2-(1′-methylbenzylidenehydrazino)thiazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione (XIII).

A mixture of XII (0.24 g, 0.001 mole) and benzaldehyde (0.11 g, 0.001 mole) in ethanol (10 ml) was refluxed for 1 hour. After cooling, the precipitates were filtered off and recrystallized from ethanol to give XIII (0.25 g, 75%), mp >300°.

Anal. Calcd. for $C_{15}H_{15}N_5O_2S$: C, 54.69; H, 4.60; N, 21.26. Found: C, 54.42; H, 4.55; N, 21.23.

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REFERENCES AND NOTES

(1) G. B. Brown, G. Levin, S. Murphy, A. Sele, H. C. Reilly, G. S. Tarnowski, F. A. Schmid, M. N. Teller, and C. C. Stock, *J. Med. Chem.*, **8**, 190 (1965).

(2) K. Senga, J. Sato, and S. Nishigaki, *Chem. Pharm. Bull.*, **26**, 765 (1978).

(3) K. Wagner, H. Hietzer, and L. Oehlmann, *Chem. Ber.*, **106**, 640 (1973).

(4) T. K. Liao and C. C. Cheng, *J. Heterocyclic Chem.*, **1**, 212 (1964).

(5) T. J. Delia and G. B. Brown, *J. Org. Chem.*, **31**, 178 (1966) and references cited therein.

(6) The reaction of 4,6-dimethyl-2-phenyloxazolo[5,4-*d*]pyrimidine-5,7-(4*H*,6*H*)dione with trifluoroperacetic acid under the same conditions also gave V; K. Senga, M. Ichiba, K. Matsuyama, and S. Nishigaki: unpublished result.