chloride. The resulting suspension was kept at room temperature for 12 h. Filtration and concentration left a syrup which crystallized on scratching. The solid was suspended in water, filtered, and recrystallized from acetone/hexane giving colorless crystals.

The ***N*-benzoyl-*N'*-oxamoylureas 12c, 12d and 12f** were prepared following procedures similar to the one presented above employing dichloromethane or chloroform as solvents. Melting points and yields are given in Table I.

D. 1-Aryl-3-(ω-benzamidoalkyl)imidazolidine-2,4,5-triones (13b–d) from 12b–d (General Procedure). Suspensions of 1-benzoyl-3-oxamoylureas **12b–d** in methanol (ca. 1.0 g per 20–50 mL of solvent) were heated to reflux. The starting materials dissolved slowly and progress of the rearrangement was followed by TLC or IR. As soon as the reactions were complete (10 min to 2.5 h), part of the solvent was removed and water was added to precipitate the products, which were collected and purified for analysis by recrystallization from methanol/water. Extended heating of the methanolic solutions after completed rearrangement can cause further degradation of the parabanates and thus result in lower yields.

No rearrangement to **13a** was observed on prolonged heating of **12a** in methanol (18 h; the odor of methyl benzoate indicated partial cleavage in a different manner) or briefly in DMF or DMF/water.

1-Phenyl-3-(2-benzamidoethyl)imidazolidine-2,4,5-trione (13a) via Cyclization. *N*-Phenyl-*N'*-(2-benzamidoethyl)urea[14] (2.83 g, 0.01 mol) and oxalyl chloride (1.26 g, 0.01 mol) were heated to reflux for 1 h in 50 mL of dichloromethane. The resulting reaction solution was evaporated leaving an oily residue which was dissolved in acetone. Gradual addition of water to beginning turbidity and scratching caused separation of 2.48 g of **13a;** the crude material was recrystallized from methanol/water (colorless crystals); yield and mp are given in Table I.

In a similar manner, **1-phenyl-3-(5-benzamidopentyl)imidazolidine-2,4,5-trione (13d)** was obtained from *N*-phenyl-*N'*-(5-benzamidopentyl)urea[15] and oxalyl chloride in refluxing chloroform (45% yield).

Hydrolytic cleavage of **13d** in aqueous potassium hydroxide–methanol (1:3) at room temperature yielded the corresponding *N*-phenyl-*N'* (5-benzamidopentyl)urea in 90% yield.

Registry No.—**1a**, 96-31-1; **1b**, 120-93-4; **1c**, 1852-17-1; **1d**, 19055-93-7; **8**, 67488-36-2; **10**, 67488-37-3; *N*-phenyl-*N'*-(β-benzamidoethyl)urea, 67488-38-4; oxalyl chloride, 79-37-8; *N*-phenyl-*N'*-(5-benzamidopentyl)urea, 67488-39-5; benzoyl chloride, 98-88-4; benzenesulfonyl chloride, 98-09-9; *p*-toluenesulfonyl chloride 98-59-9; aniline, 62-53-3; 1,3-dimethylimidazolidine-2,4,5-trione, 5176-82-9; 1,5-diaminopentane, 462-94-2; *N*-(5-aminopentyl)-*N'*-phenylurea, 67488-40-8.

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(15) This urea, mp 118–120 °C (Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.25; H, 7.13; N, 12.89) was prepared in quantitative yield in analogy to literature procedures[14] from 1,5-diaminopentane via *N*-(5-aminopentyl)-*N'*-phenylurea, mp 124–125 °C (4% yield; Anal. Calcd for $C_{12}H_{19}N_3O$: C, 65.12; H, 8.65; N, 18.99. Found: C, 65.15; H, 8.81; N, 18.87).

Pteridines. 45. Synthesis and Properties of Some Isothiazolo[4,5-*b*]pyrazines and Isothiazolo[4,5-*g*]pteridines[1,2]

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Several isothiazolo[4,5-*b*]pyrazines and isothiazolo[4,5-*g*]pteridines were prepared utilizing 3-methyl- and 3-methylmercapto-4-nitroso-5-acetamidoisothiazole (**5a,b**) as key starting materials. All attempts to desulfurize these fused isothiazoles were uniformly unsuccessful. Reaction of 3-methylmercapto-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine (**6b**) with diethyl malonate in the presence of base unexpectedly resulted in the formation of the pyrido[2,3-*b*]isothiazolo[4,5-*e*]pyrazine **14** rather than cleavage of the isothiazole ring.

The classical synthetic route to pteridines involves condensation of a preformed 4,5-diaminopyrimidine with an appropriately functionalized two-carbon unit (e.g., an α-keto, α-hydroxy, or α-bromocarbonyl compound).[3] This so-called Isay route to pteridines, despite its attractive simplicity, suffers from the serious disadvantage that a mixture of structural isomers is formed when the two-carbon reaction component is itself unsymmetrical.[4] In addition, however, the requisite pyrimidine intermediates are often extremely insoluble and difficult to manipulate, and there are obvious structural limitations in the other reaction component which provides carbons 6 and 7 of the pteridine ring along with their associated substituents. Furthermore, pteridines are notoriously insoluble and chemically recalcitrant compounds whose chemical manipulation by the usual methods of synthetic organic chemistry poses severe problems. We have developed and exploited over the past few years an alternative synthetic pathway to pteridines which involves the prior synthesis of pyrazine (as opposed to pyrimidine) intermediates, followed by final annelation of the fused pyrimidine ring. This procedure possesses many chemical and manipulative advantages which have been summarized elsewhere.[5] However, since certain types of pteridine derivatives have thus far not been directly accessible by this latter pathway (e.g., acyl derivatives), we have a continuing interest in exploring new synthetic methodologies. The present paper describes a projected strategy for the preparation of 6-acyl derivatives via isothiazolo[4,5-*b*]pyrazines and isothiazolo[4,5-*g*]pteridines, both

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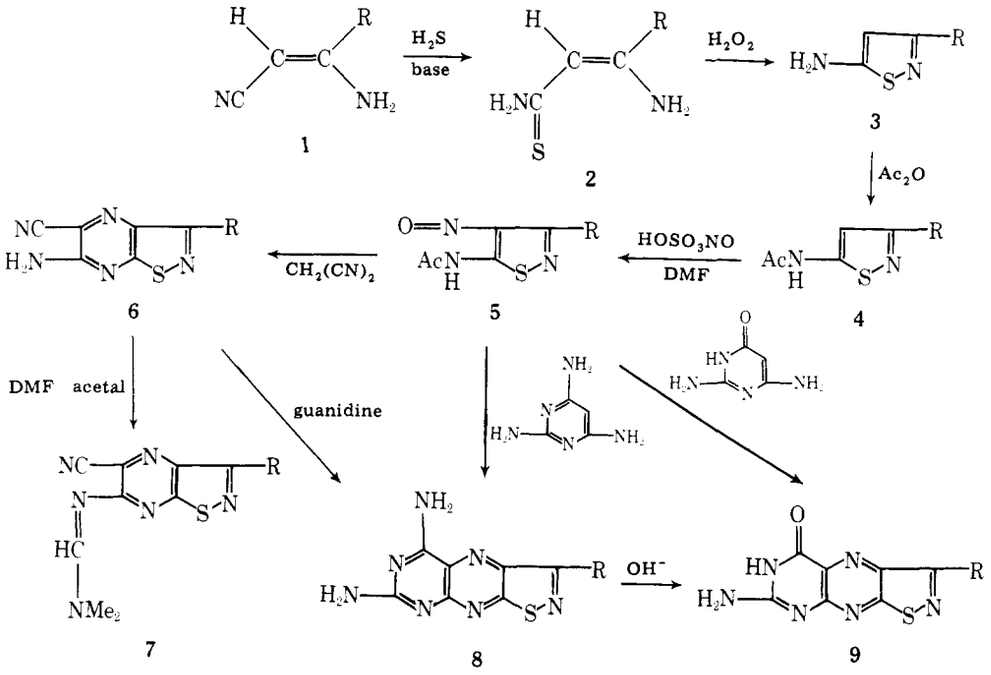
Scheme I



a, R = CH_3
b, R = SCH_3

of which possess potential carbonyl groups in the C=N unit of the isothiazole ring. Fused isothiazoles can be considered as latent amines, alkyl, or acyl groups, since they can be carried through a long synthetic sequence unscathed, to be destroyed in a final step by reductive desulfurization with release of the desired functionality (see, for example, Woodward's elegant colchicine synthesis,[6] and the recently described preparation of 6-amino-5-methylpyrimidines from isothiazolo[3,4-*d*]-pyrimidines).[7]

We have prepared several isothiazolo[4,5-*g*]pteridines as outlined in Scheme I. 5-Amino-3-methylisothiazole (**3**) was synthesized by the general method of Slack[8] and Goerdeler[9] by hydrogen peroxide oxidation of the thioamide **2a,** which is readily prepared by base-catalyzed addition of hydrogen sulfide to acetonitrile dimer (**1a**).[10] We found it best not to isolate **3a,** but to convert it directly with acetic anhydride to 3-methyl-5-acetamidoisothiazole (**4a**). The latter is a known compound,[9] but various modifications in the above synthetic sequence have resulted in a much improved preparation. The key intermediate in our projected synthesis of isothiazolo[4,5-*g*]pteridines was 3-methyl-4-nitroso-5-acetamidoisothiazole (**5a**), but its preparation from **4a** was not straightforward. Classical nitrosation procedures in acetic acid either with isoamyl nitrite or with sodium nitrite under many attempted reaction conditions were unsuccessful; in one attempt utilizing isoamyl nitrite a transient deep green color was observed, indicative of the formation of the desired **5a,** but this color shortly faded and the reaction mixture turned dark brown. Successful nitrosation of **4a** was finally achieved, however, utilizing nitrosyl hydrogen sulfate in dimethylformamide at room temperature.

Condensation of **5a** with malononitrile provided the isothiazolopyrazine **6a** in low (25–30%) yield.[11] Many variations in reaction conditions with aprotic and protic solvents, the use of varying amounts of different bases such as triethylamine, sodium methoxide, and pyridine, and inverse addition of reactants were explored, but in every case the reaction mixtures turned dark brown and contained large amounts of tarry material. We attribute this decomposition or polymerization to base-catalyzed reactions involving the acidic 3-methyl group[10] of the isothiazole component **5a,** since analogous cyclizations involving the corresponding 3-methylmercapto derivative (**5b,** vide infra) proceeded without complication in quantitative yield.

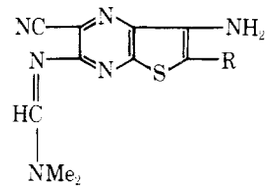
Condensation of the isothiazolopyrazine **6a** with guanidine gave 3-methyl-5,7-diaminoisothiazolo[4,5-*g*]pteridine (**8a**), which could alternatively be prepared in a single step by condensation of **5a** with 2,4,6-triaminopyrimidine. Similarly, condensation of **5a** with 2,4-diamino-6(1*H*)-pyrimidone gave the isothiazolo[4,5-*g*]pterin **9a,** which was also prepared by alkaline hydrolysis of the 5-amino group of **8a.**

We then explored the possible desulfurization of these fused isothiazole derivatives in an attempt to generate 2-amino-3-cyano-5-acetylpyrazine (from **6a**) and the corresponding 6-acetyl derivatives of 2,4-diaminopteridine (from **8a**) and of pterin itself (from **9a**). Raney nickel desulfurization is a well-established synthetic procedure in organic chemistry;[12] deactivation of the nickel by boiling in acetone for a short period is known to allow retention of desulfurization capabilities but to inhibit the reduction of carbonyl and other functional groups sensitive to hydrogenation.[13,14] Furthermore, the pyrazine ring should be stable to Raney nickel desulfurization conditions, since 3-hydroxypyrazolo[*b*]pyrazines are readily converted under these conditions to 2-amino-3-carboxamidopyrazines in moderate to good yield.[15]

All attempts to effect desulfurization of these isothiazole intermediates, however, proved fruitless. Neither **6a** nor its dimethylaminomethyleneamino derivative **7a** (prepared from **6a** and dimethylformamide dimethyl acetal) gave any identifiable product. Many different types of freshly prepared Raney nickel, such as W7,[16] W4,[17] and the modification described by Fieser and Fieser,[14] under many different types of conditions in which solvents, temperature, amounts of reagents, and time of reaction were all varied, were explored with **6a,** but similar discouraging results were obtained from every experiment. Reaction mixtures were all monitored by TLC until starting material had disappeared, but separation of the nickel and evaporation of solvent led only to small amounts of tarry residues which were completely absorbed on charcoal

in attempted purifications. Control experiments showed that pyrazines and pteridines closely related to the anticipated products could be treated with charcoal under similar conditions without any loss by absorption, and we conclude that complete destruction of the substrates took place under the above reaction conditions.

Similar discouraging results were obtained upon attempted Raney nickel desulfurization of thieno[2,3-*b*]pyrazines **10** (which should lead to 5-(1-aminoalkyl)pyrazines) and the 6-methylmercaptopyrazine **11**;[18] only small amounts of oily



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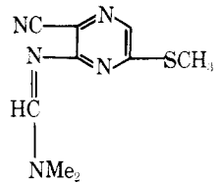

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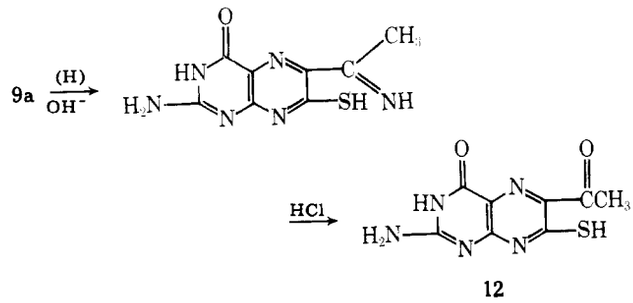
polymeric tars were formed, regardless of variations in the reaction conditions. It appears that pyrazinyl radicals, which are presumably formed upon homolytic cleavage of the C–S bond,[12] are inherently unstable and that, as a consequence, reductive desulfurization of sulfur-substituted pyrazines, regardless of the nature of the sulfur substituent, will probably be unsuccessful. This conclusion is unfortunately reinforced by our attempts to desulfurize the isothiazolopteridines **8a** and **9a**. Thus, attempted desulfurization of **9a** in 1% sodium hydroxide solution resulted again in the formation of a polymeric tar. Since 3-methyl-5,7-diaminoisothiazolo[4,5-*g*]pteridine (**8a**) was only soluble in acid, reductive desulfurization was attempted with Raney nickel (once prewashed with concentrated formic acid) in concentrated formic acid as solvent,[19] but a complex mixture of dark solids was obtained from which no identifiable single compound could be isolated.[20]

Chemical reduction of **9a** was also explored. Addition of sodium hydrosulfite to an alkaline solution of **9a** resulted in the immediate precipitation of the trihydrate of the sodium salt of **9a** (see Experimental Section). Addition of concentrated hydrochloric acid to this reaction mixture, followed by several hours of stirring at room temperature, gave an orange solid whose physical and spectral properties were consistent with structure **12**, the product of S–N hydrogenolysis followed



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by acid hydrolysis of the resulting imine. Once again, however, reductive desulfurization had not been achieved, despite the successful introduction of the desired acetyl grouping into the pteridine nucleus.

By a sequence of reactions analogous to those described in Scheme I for the preparation of **6a**, we prepared the corresponding 3-methylmercaptoisothiazolo[4,5-*b*]pyrazine **6b**. Thus, methylation of malonic acid dithioamide with methyl iodide gave 3-amino-3-methylmercaptoacrylthioamide (**2b**), which was oxidized with hydrogen peroxide to 3-methylmercapto-5-aminoisothiazole (**3b**); in contrast to the very labile **3a**, **3b** proved to be a stable crystalline solid. Acetylation of **3b** with acetic anhydride followed by nitrosation with nitrosyl hydrogen sulfate in dimethylformamide solution gave **5b**, which was condensed with malononitrile to **6b** in quantitative yield.

In view of the difficulties experienced above in attempted desulfurization of **6a**, **8a**, and **9a**, we did not explore reductive desulfurization of **6b**. Instead, we envisioned **6b** as a potentially versatile intermediate for the introduction of functionality at position 3 by nucleophilic displacement either of the methylthio grouping or the corresponding methylsulfone, thus providing (assuming an eventually successful reductive cleavage) a route to a variety of 6-acylpteridine derivatives.

We report here on the reaction of **6b** with the sodium salt of diethyl malonate. It is known that 3-chloro-1,2-benzoisothiazole may react with nucleophiles either at C-3, with displacement of chloride ion, or at the ring sulfur atom with concomitant ring opening, elimination of chloride ion, and generation of an ortho-substituted nitrile.[21] When C–H acidic methylene compounds such as diethyl malonate are employed as the nucleophile, the ring-opened *o*-cyano substituted intermediate subsequently cyclizes to a benzo[*b*]thiophene derivative.[22] We thus anticipated, based on this close analogy, that reaction of **6b** with the sodium salt of diethyl malonate would probably follow path a indicated in Scheme II to give the thieno[*b*]pyrazine **13**. An analogous isothiazole to thiophene rearrangement has been reported with some isothiazolo[5,4-*b*]pyridines.[23] In fact, this ring transformation might be expected to proceed even more readily in the present case because of the better leaving-group capabilities of the methylthio grouping compared with chloride ion. However, under the same reaction conditions employed by Clarke et al. for the conversion of 3-chloro-1,2-benzoisothiazole to benzo[*b*]thiophenes, **6b** and diethyl malonate gave the pyrido[2,3-*b*]isothiazolo[4,5-*e*]pyrazine **14**. No displacement either on carbon or on sulfur takes place; instead, acylation of the amino group in the pyrazine ring by diethyl malonate (path b) is followed by intramolecular cyclization across the ortho-situated nitrile grouping to generate the 5-amino fused pyridine derivative **14**.

In an attempt to avoid initial reaction of diethyl malonate with the 6-amino function in **6b**, the latter was converted to its 6-dimethylaminomethyleneamino derivative **7b** with dimethylformamide dimethyl acetal. However, **7b** failed to react with diethyl malonate in the presence of sodium ethoxide at room temperature, even after 6 days. When the reaction mixture was heated, starting material disappeared completely within a few hours, but TLC indicated the simultaneous formation of at least ten compounds.

Experimental Section

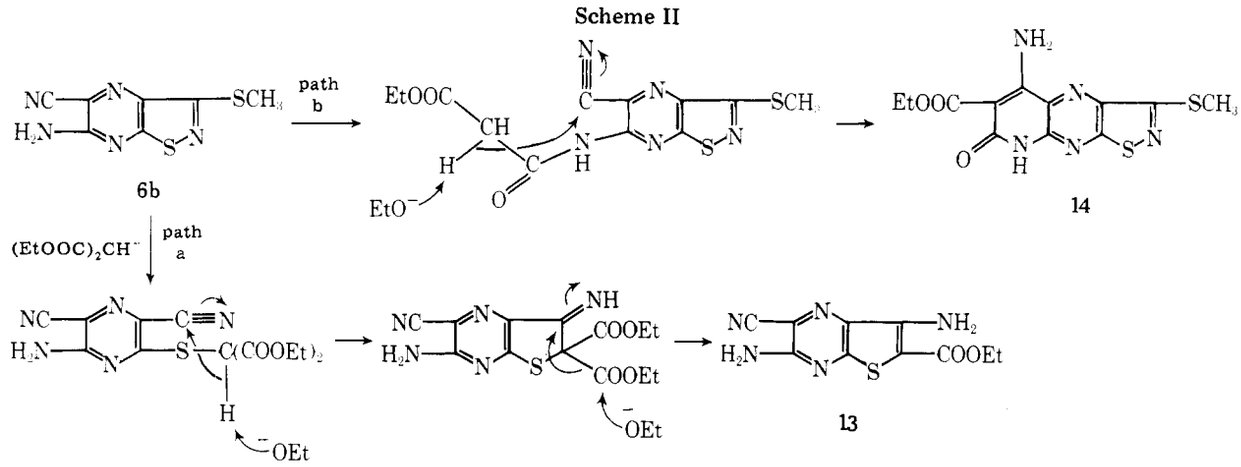
3-Methyl-5-acetamidoisothiazole (4a). To a chilled (0 °C) solution of 11.4 g (0.1 mol) of β-iminothiobutyramide in 200 mL of methanol was added dropwise 11.5 g (0.1 mol) of 30% hydrogen peroxide. After 15 min of stirring, the methanol was removed by evaporation under reduced pressure, the residual solid was dissolved in ether, and the resulting solution was dried over anhydrous $MgSO_4$. The dried ether solution was then reduced to a small volume by evaporation under reduced pressure and 40 mL of acetic anhydride was added. The reaction was exothermic, and a white precipitate separated. After 3 h of stirring, the solid was removed by filtration and recrystallized from water (Norite) to give 12.6 g (81%) of **4a** as white needles, mp 173–174 °C (lit.[8] mp 180–181 °C).

3-Methyl-4-nitroso-5-acetamidoisothiazole (5a). To a solution of 7.8 g (50 mmol) of 3-methyl-5-acetamidoisothiazole in 48 mL of dry dimethylformamide, chilled to 0 °C, was added in small portions 6.35 g (50 mmol) of nitrosyl hydrogen sulfate. After 2 h of stirring, the green solution was poured into water and the light green solid collected by filtration and recrystallized from ether to give 5.0 g (57%) of **5a** as a bright green crystalline solid, mp 166–167 °C.

Anal. Calcd for $C_6H_7N_3O_2S$: C, 38.91; H, 3.81; N, 22.69; S, 17.31. Found: C, 38.86; H, 3.70; N, 22.76; S, 17.11.

3-Methyl-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine (6a). To a slurry of 3.7 g (20 mmol) of 3-methyl-4-nitroso-5-acetami-

Scheme II



doisothiazole in 80 mL of ethanol, chilled to 0 °C, was added a solution of 4.0 g (40 mmol) of triethylamine and 1.6 g (24 mmol) of malononitrile in 20 mL of ethanol. After addition was complete, the reaction mixture was stirred to 0 °C for 8 h and the separated solid then was removed by filtration and recrystallized from ethanol (Norite) to give 2.0 g (26%) of **6a** as bright yellow needles, mp 203–205 °C (followed by resolidification).

Anal. Calcd for $C_7H_5N_5S$: C, 43.96; H, 2.64; N, 36.63; S, 16.77. Found: C, 44.03; H, 2.50; N, 36.39; S, 16.78.

3-Methyl-5,7-diaminoisothiazolo[4,5-*g*]pteridine (8a). Method A. A mixture of 4.65 g (25 mmol) of 3-methyl-4-nitroso-5-acetamidoisothiazole and 3.17 g (25 mmol) of 2,4,6-triaminopyrimidine in 50 mL of acetic acid was heated with stirring to 100 °C. A clear solution was thus obtained, which was then stirred at room temperature. After 2 h, a yellow solid started to separate and after 5 h of stirring, the reaction mixture was filtered and the collected yellow solid was washed with acetic acid followed by ether and then dried in vacuo. The crude product was stirred vigorously for 1 h in hot acetone, removed by filtration, rinsed with acetone, and then dried under reduced pressure at 140 °C: yield, 5.72 g (98%); mp >310 °C.

Anal. Calcd for $C_8H_7N_7S$: C, 41.20; H, 3.02; N, 42.04; S, 13.75. Found: C. 41.13, H, 2.84; N, 42.16; S, 14.23.

Method B. A solution of 86 mg (0.5 mmol) of 3-methyl-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine in 8 mL of methanol was treated with 1 equiv of guanidine in methanol (prepared by dissolving equivalent amounts of guanidine hydrochloride and sodium methoxide in methanol, and filtering off the precipitated sodium chloride), and the reaction mixture was heated under reflux for 5 h. The precipitated yellow solid was removed by filtration, washed well with methanol followed by ether, and dried [140 °C (0.01 Torr)], yield 90 mg (77%). It was analytically pure without further purification and was identical in all respects with the material prepared by method A.

3-Methylisothiazolo[4,5-*g*]pterin (9a). Method A. A mixture of 2.82 g (15 mmol) of 3-methyl-4-nitroso-5-acetamidoisothiazole and 2.16 g (15 mmol) of 2,4-diamino-6(1*H*)-pyrimidinone in 75 mL of acetic acid was heated on a steam bath for 1.5 h, at which point no residual isothiazole could be detected by TLC (benzene/acetone (9:1) on silica gel). The hot reaction slurry was then filtered and the collected solid was washed with acetic acid followed by ethanol and ether. The crude product was further purified by dissolution in 50 mL of 0.1 N NaOH, acidification with concentrated HCl, and dilution with 50 mL of water; filtration then gave 1.85 g (79%) of **9a** as a light green-yellow solid, mp >360 °C.

Anal. Calcd for $C_8H_6N_6OS$: C, 41.02; H, 2.58; N, 35.87; S, 13.69. Found: C, 41.08; H, 2.31; N, 35.63; S, 13.90.

Method B. A slurry of 100 mg of 3-methyl-5,7-diaminoisothiazolo[4,5-*g*]pteridine in 5 mL of 1 N NaOH was heated under reflux with stirring until complete solution was achieved (30 min). Cooling of the reaction mixture resulted in the separation of yellow crystals of the hydrated sodium salt of **9a.** The mixture was cooled overnight at 2–5 °C and filtered, and the collected solid was triturated with dilute hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and dried [140 °C (0.01 Torr)] to give 65 mg (65%) of analytically pure **9a,** identical in all respects with the material prepared by method A.

6-Acetyl-7-mercaptopterin (12). To a solution of 250 mg of 3-methylisothiazolo[4,5-*g*]pterin in 25 mL of 0.1 N NaOH was added in two portions 370 mg of sodium hydrosulfite. The clear solution rapidly turned turbid with the separation of 3-methylisothiazolo[4,5-*g*]pterin sodium salt trihydrate as a yellow solid, mp >360 °C. (Anal. Calcd for $C_8H_5N_6OSNa{\cdot}3H_2O$: C, 30.97; H, 3.57; N, 27.09. Found: C, 31.28; H, 3.59; N, 27.13.) After 15 min at room temperature, the slurry was treated with 1 mL of concentrated HCl and then stirred overnight. The resulting bright yellow-orange solid was collected by filtration, suspended in water, and then dissolved by the careful addition of 0.1 N NaOH. The resulting orange solution was treated with Norite and filteraid and filtered, and the filtrate was acidified with concentrated HCl to give 230 mg of **12** as an orange-yellow solid, mp >300 °C dec.

Anal. Calcd for $C_8H_7N_5O_2S{\cdot}1.5H_2O$: C, 39.00; H, 3.28; N, 28.46; S, 13.05. Found: C, 39.53; H, 3.03; N, 28.52; S, 12.58.

3-Methyl-5-cyano-6-(dimethylaminomethyleneamino)isothiazolo[4,5-*b*]pyrazine (7a). To a mixture of 5 mL of tetrahydrofuran and 5 mL of dimethylformamide dimethyl acetal was added 1.0 g of 3-methyl-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine. Immediate solution was achieved, but after a few minutes the product started to precipitate. It was removed by filtration (a small amount of additional product could be obtained by concentration of the filtrate) and recrystallized from ether to give 1.05 g (81%) of **7a** as a colorless solid, mp 152–153.5 °C.

Anal. Calcd for $C_{10}H_{10}N_6S$: C, 48.76; H, 4.09; N, 34.12; S, 13.02. Found: C, 48.93; H, 4.06; N, 34.05; S, 12.96.

3-Amino-3-methylmercaptoacrylthioamide (2b). To a slurry of 26.8 g (0.20 mol) of malonic acid dithioamide in 80 mL of dimethylformamide at room temperature was added dropwise 32.0 g (0.23 mol) of methyl iodide at such a rate that the temperature of the reaction mixture did not rise above 37 °C. The reaction mixture was then stirred for 2 h after addition was complete, by which time all of the remaining malonic acid dithioamide had dissolved. The reaction mixture was then chilled to 0 °C and poured slowly into a chilled solution of 19.0 g (0.23 mol) of sodium bicarbonate in 500 mL of water. Filtration then gave 19.3 g of crude product which still contained a small amount of unreacted malonic acid dithioamide. The crude product was extracted with ether, utilizing a Soxhlet extractor, from which pure **2b** crystallized upon concentration: yield, 16.0 g (54%); mp 104.5–105.5 °C. The product may be obtained in the form of colorless crystals upon recrystallization from methanol or ether.

Anal. Calcd for $C_4H_8N_2S_2$: C, 32.41; H, 5.44; N, 18.90; S, 43.26. Found: C, 32.65; H, 5.22; N, 19.14; S, 43.18.

3-Methylmercapto-5-aminoisothiazole (3b). To a solution of 1.48 g (10 mmol) of 3-amino-3-methylmercaptoacrylthioamide in 20 mL of methanol, chilled to 0 °C, was added dropwise 1.15 g (10 mmol) of 30% hydrogen peroxide. After addition was complete, the reaction mixture was stirred for 1 h at room temperature and then evaporated to dryness. The residue was dissolved in 40 mL of ether, the ether solution was dried over anhydrous $MgSO_4$, and the reaction mixture was concentrated by evaporation to induce crystallization: yield, 1.1 g (75%); mp 116.5–118 °C. The product was obtained in the form of colorless crystals by recrystallization from ether (Norite).

Anal. Calcd for $C_4H_6N_2S_2$: C, 32.85; H, 4.14; N, 19.16; S. 43.85. Found: C, 33.09; H, 3.89; N, 19.25; S, 43.78.

3-Methylmercapto-5-acetamidoisothiazole (4b). A solution of 2.19 g of 3-methylmercapto-5-aminoisothiazole in 6 mL of acetic anhydride and 10 mL of tetrahydrofuran was stirred at room temperature for 3 h. The reaction mixture became warm after a few minutes of stirring, and after 1 h the product started to separate. The reaction slurry was cooled to 0 °C and filtered, and the product was crystallized from methanol (Norite) to give 2.6 g (92%) of **4b** as colorless crystals, mp 196–197 °C.

Anal. Calcd for $C_6H_8N_2OS_2$: C, 38.28; H, 4.27; N, 14.88; S, 34.06. Found: C, 38.49; H, 4.45; N, 14.67; S, 34.14.

3-Methylmercapto-4-nitroso-5-acetamidoisothiazole (5b). To a solution of 0.94 g (5 mmol) of 3-methylmercapto-5-acetamidoisothiazole in 4 mL of dry dimethylformamide was added in small portions 0.72 g (5.5 mmol) of nitrosyl hydrogen sulfate. The reaction mixture was stirred for 1 h, diluted with 20 mL of water, and filtered to give a dark green solid which was collected by filtration, washed with water, and recrystallized from ethanol: yield, 0.95 g (79%); mp 230 °C dec.

Anal. Calcd for $C_6H_7N_3O_2S_2$: C, 33.17; H, 3.25; N, 19.35; S, 29.52. Found: C, 33.45; H, 3.14; N, 19.66; S, 29.37.

3-Methylmercapto-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine (6b). A mixture of 2.42 g (11.1 mmol) of 3-methylmercapto-4-nitroso-5-acetamidoisothiazole, 1.0 g (15 mmol) of malononitrile, and 1.2 g (12 mmol) of triethylamine in 20 mL of ethanol was refluxed for 1 h and the resulting greenish yellow precipitate was collected by filtration and washed with ethanol followed by ether. Recrystallization from ethanol (Norite) gave 2.23 g (94%) of **6b** as yellow crystals, mp >270 °C dec (with decomposition starting with 210 °C).

Anal. Calcd for $C_7H_5N_5S_2$: C, 37.65; H, 2.26; N, 31.37; S, 28.72. Found: C, 37.47; H, 2.29; N, 31.18; S, 28.75.

3-Methylmercapto-5-cyano-6-(dimethylaminomethyleneamino)isothiazolo[4,5-*b*]pyrazine (7b). A slurry of 1.0 g of 3-methylmercapto-5-cyano-6-aminoisothiazolo[4,5-*b*]pyrazine in 15 mL of dimethylformamide dimethyl acetal was stirred at room temperature for 24 h, by which time TLC indicated complete disappearance of starting material. The reaction mixture was evaporated to dryness, the residue was triturated with ether and filtered, and the product was recrystallized from ethanol (Norite) to give 1.24 g (quantitative) of **7b** as a greenish yellow solid, mp 211–213 °C.

Anal. Calcd for $C_{10}H_{10}N_6S_2$: C, 43.15; H, 3.62; N, 30.19; S, 23.04. Found: C, 42.87; H, 3.62; N, 30.09; S, 23.15.

3-Methylmercapto-5-amino-6-carboethoxypyrido[2,3-*b*]isothiazolo[4,5-*e*]pyrazin-7(8H)-one (14). A slurry of 0.565 g (2.5 mmol) of 3-methylmercapto-5-cyano-6-aminoisothiazolo[4,5-*b*]-pyrazine, 400 mg (2.5 mmol) of diethyl malonate, and 20 mL of ethanol containing 120 mg (5 mmol) of sodium was stirred at room temperature for 4 days, by which time TLC indicated that no starting material remained. The reaction mixture was concentrated under reduced pressure and filtered to give 0.8 g (98%) of the orange-yellow sodium salt of **14.** Dissolution of this salt in dimethylformamide followed by addition of a small amount of acetic acid resulted in the separation of analytically pure bright yellow **14,** mp 305–310 °C dec.

Anal. Calcd for $C_{12}H_{11}N_5O_3S_2$: C, 42.72; H, 3.29; N, 20.76; S, 19.01. Found: C, 42.66; H, 3.30; N, 20.81; S, 18.96.

Registry No.—**2b,** 67209-06-7; **3b,** 67209-07-8; **4a,** 67209-08-9; **4b,** 67209-09-0; **5a,** 67209-10-3; **5b,** 67209-11-4; **6a,** 67209-12-5; **6b,** 67209-13-6; **7a,** 67209-14-7; **7b,** 67209-15-8; **8a,** 67209-16-9; **9a,** 67209-17-0; **9a** Na salt, 67209-18-1; **12,** 67209-19-2; **14,** 67209-20-5; **14** Na salt, 67209-21-6; β-iminothiobutyramide, 32081-55-3; nitrosyl hydrogen sulfate, 7782-78-7; malononitrile, 109-77-3; 2,4,6-triaminopyrimidine, 1004-38-2; guanidine, 113-00-8; 2,6-diamino-4(3*H*)-pyrimidinone, 56-06-4; dimethylformamide dimethyl acetal, 4637-24-5; malonic acid dithioamide, 6944-34-9; diethyl malonate, 510-20-3.

References and Notes

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(2) We are indebted for the support of this work to the National Cancer Institute, National Institutes of Health (Grant No. CA 12876), Eli Lilly & Co., Lonza AG, and Hoffmann-La Roche & Co., Ltd.
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