27649-96-3; **3u**, 27649-95-2; anthracene, 120-12-7; fumaric acid, 110-17-8; (*E*)-dibenzoylethene, 959-28-4; fumarodinitrile, 764-42-1; cinnamic acid, 621-82-9; acrylic acid, 79-10-7; maleic anhydride, 108-31-6; vinylene carbonate, 872-36-6; dimethyl acetylenedicarboxylate, 762-42-5; ethyl acetylenecarboxylate, 623-47-2.

**Supplementary Material Available:** Specification of the selective inclusion properties of **2n** (Table III), complete list of crystallographic information (Table IV), lists of positional parameters and equivalent isotropic/isotropic temperature factors of the non-hydrogen atoms and of the hydrogen atoms (Table VI), bond lengths (Table VII) and bond angles (Table VIII) involving non-hydrogen atoms, fractional atomic coordinates of the calculated hydrogen positions (Table IX), and anisotropic thermal parameters of the non-hydrogen atoms (Table X) (23 pages). Ordering information is given on any current masthead page. Listings of observed and calculated structure factors are available directly from the author.

# Studies on the Molybdenum Cofactor: Model Synthetic Routes Directed at Form B

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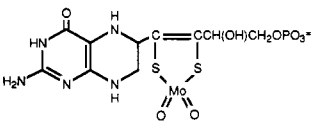
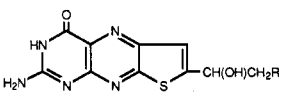
A general method for the conversion of available pyrazine intermediates to 6,7-dihydrothieno[2,3-*b*]pyrazines, and then to 6,7-dihydrothieno[3,2-*g*]pterins, has been developed as a model synthetic strategy for an approach to Form B of the molybdenum cofactor.

Molybdenum is present in trace amounts in the tissues of a broad range of biological species, including algae, fungi, bacteria, plants, animals, and humans, and has recently been recognized as an essential trace element for human health.[1] Molybdenum functions as a prosthetic metal in a number of enzymes that catalyze redox reactions; these enzymes also require a common organic cofactor for their activity, which was once thought to be a protein[2] but has recently been shown to be a novel pterin derivative with a sulfur-containing 6-alkenyl side chain.[3,4] This organic cofactor has been termed molybdopterin. The complex of molybdenum with molybdopterin, referred to as the molybdenum cofactor, has been found to be a universal cofactor for all molybdenum-containing enzymes studied with the single exception of nitrogenase, which has its own unique iron–molybdenum cofactor.[5–7] Structure **1** has been proposed for the molybdenum cofactor.

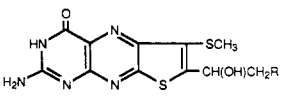
Molybdopterin differs from other organic enzyme cofactors such as FAD, biotin, pyridoxal phosphate, etc. in being extraordinarily unstable in the free form; when released from the enzyme, it is rapidly degraded to inactive products. As a consequence, its structure has been probed indirectly by EXAFS examination of the molybdenum enzyme active sites,[8,9] by chemical degradation, and by spectroscopic studies of its stable (but inactive) oxidation products.[3,10–13] One of these oxidation products is a thieno[3,2-*g*]pterin, termed Form B, for which structure **2** has been suggested. The only sulfur-containing pterin natural product previously known is the thieno[3,2-*g*]pterin derivative urothione, which was first isolated from human urine in 1940[14] and synthesized 27 years later in 0.3% yield from pteridine intermediates.[15–19] Structure **3**, which was ultimately assigned to urothione, received strong support through comparison with deoxyurothione (**4**), which we synthesized several years ago by an unambigous route,[20] and has recently been rigorously confirmed by direct comparison with (±)-urothione prepared by a new and unequivocal total synthesis.[21] The discovery that children suffering from biochemical abnormalities due to combined deficiencies of sulfite oxidase and xanthine dehydrogenase lacked the active molybdenum cofactor, and that their urine samples were devoid of urothione, confirmed that this latter compound was the urinary metabolite of the molybdenum cofactor.[3,22]



**1**



**2**, R = $OPO_3H^-$
**5**, R = OH



**3**, R = OH
**4**, R = H

† Present address: Wyeth-Ayerst Research, CN 8000, Princeton, NJ 08543-8000.

(1) For excellent reviews, see: (a) *Molybdenum and Molybdenum-Containing Enzymes*; Coughlan, M. P., Ed.; Pergamon: New York, 1980. (b) *Molybdenum Enzymes*; Spiro, T. G., Ed.; Wiley-Interscience: New York, 1985. (c) Burgmayer, S. J. N.; Stiefel, E. I. *J. Chem. Ed.* **1985**, *62*, 443.

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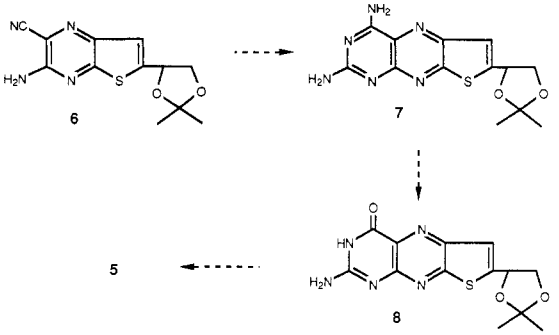
(11) Rajagopalan, K. V.; Johnson, J. L.; Hainline, B. E. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1982**, *41*, 2608.

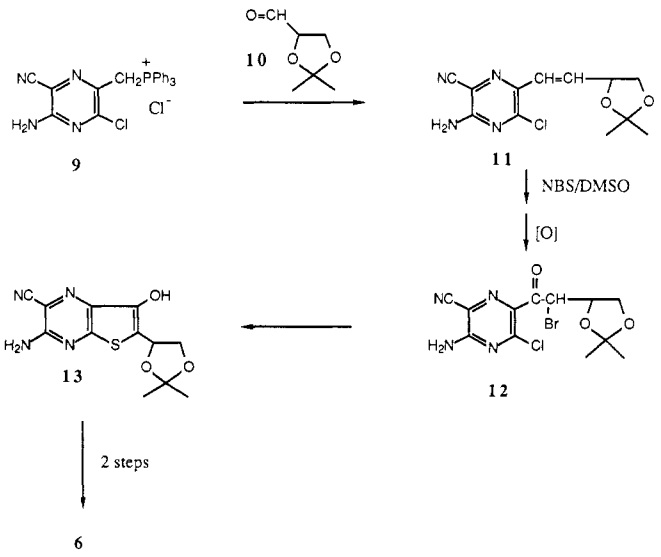
(12) Johnson, J. L.; Hainline, B. E.; Rajagopalan, K. V.; Arison, B. H. *J. Biol. Chem.* **1984**, *259*, 5414.

0022-3263/88/1953-5839$01.50/0 

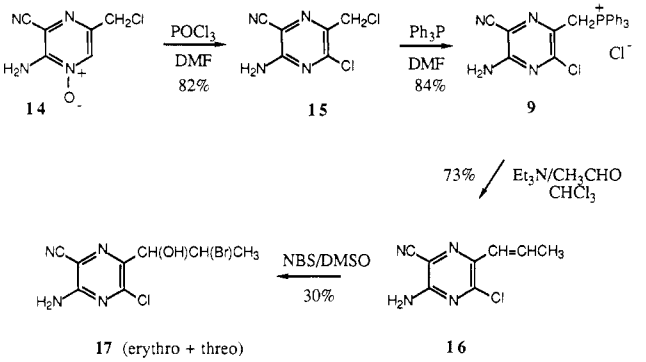
**Scheme I**



**Scheme II**



**Scheme III**



In 1984, structure **2** was proposed for Form B based upon proton NMR and mass spectral analyses.[12] Since this material is available only in nanogram quantities by oxidative degradation of molybdopterin, further direct structural studies are extremely difficult, and for this reason we have undertaken a synthetic program aimed at the unequivocal preparation of all of the above-mentioned degradation products of molybdopterin, as well as molybdopterin itself.[23] We describe in this paper a model study aimed at the preparation of 6,7-dihydrothieno[2,3-*b*]pyrazines and 6,7-dihydrothieno[3,2-*g*]pteridine intermediates. A procedure for the oxidation of the latter dihydro system to the fully aromatic thieno[3,2-*g*]pteridine ring system has already been described.[12]

Our initial strategy was to prepare the highly functionalized thieno[2,3-*b*]pyrazine **6**, which was then to be cyclized with guanidine to the thieno[3,2-*g*]pteridine **7** and subsequently hydrolyzed to the pterin derivative **8**.[20] Deprotection of the diol functionality would then give the dephospho derivative of Form B (**5**) (Scheme I). Our projected route to **6** involved a Wittig condensation of the ylide derived from phosphonium salt **9** with D-glyceraldehyde acetonide (**10**). Treatment of the resulting olefin **11** with *N*-bromosuccinimide in aqueous DMSO[24] was expected to give a bromohydrin possessing the desired regiochemistry based on previous studies on similar systems in our laboratory.[25] Oxidation of the bromohydrin to the bromo ketone **12**, followed by cyclization with sodium sulfide, would then give **13**, which was then to be converted to **6** by reduction followed by dehydration (Scheme II).

The viability of this proposed strategy was examined (see Scheme III) by utilization of acetaldehyde rather than the very sensitive acetonide of D-glyceraldehyde. Phosphonium salt **9** was obtained in two steps from 2-amino-5-(chloromethyl)-3-cyanopyrazine 1-oxide (**14**).[26] Thus, treatment of **14** with phosphorus oxychloride in DMF followed by aqueous workup gave 2-amino-6-chloro-5-(chloromethyl)-3-cyanopyrazine (**15**)[27] in 82% yield, which was converted in 84% yield to the phosphonium salt **9** with triphenylphosphine in DMF. Wittig condensation of **9** with acetaldehyde gave the 6-chloro-5-propenylpyrazine **16** in 73% yield. It was not possible to determine by proton NMR (250 MHz) whether a single isomer or a mixture of isomers had been formed, since the chemical shifts of the vinylic protons overlapped and no long-range coupling to the methyl group could be discerned. However, reaction of **16** with *N*-bromosuccinimide in aqueous DMSO gave the bromohydrin **17** as a 95:5 mixture of erythro–threo isomers (albeit in low yield). The major isomer was determined to be erythro on the basis of precedent established by Sun,[25] who had observed in a study of 1,2-disubstituted 1-arylpropanes that the chemical shifts of the methyl protons of erythro isomers of this type are shifted to higher field in comparison to the threo isomers, possibly due to anisotropic effects caused by ring currents (phenyl, pyrazine, or pteridine). The disappointing yield of bromohydrin **17** is believed to be due to side reactions in-

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(17) Goto, M.; Sakurai, A.; Ohta, K.; Yamakami, H. *J. Biochem. (Tokyo)* **1969**, *65*, 611.
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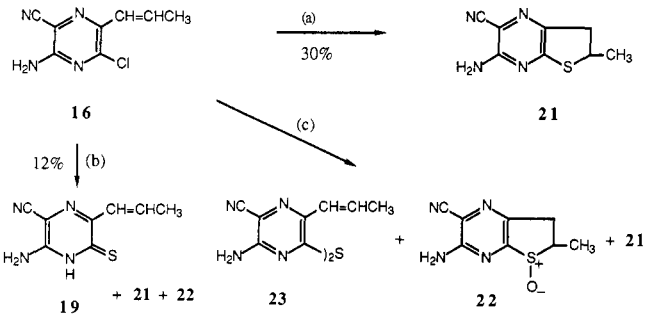
(22) Johnson, J. L.; Waud, W. R.; Rajagopalan, K. V.; Duran, M.; Beemer, F. A.; Wadman, S. K. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3715.
(23) During the course of this work, a brief report on a synthesis of racemic (dephospho) Form B from 7-acetylthieno[3,2-*g*]pterin appeared (Ushio, K.; Ishizuka, M.; Kogushi, M.; Fukui, S.; Toraya, T. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 256).
(24) Dalton, D. R.; Dutta, V. P.; Jones, D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5498.
(25) Sun, J.-H., Ph.D. Thesis, Princeton University, 1983.
(26) Compound **14** was prepared by reaction of β-chloropyruvaldoxime (Taylor, E. C.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 806, with some modification) and aminomalononitrile tosylate according to the procedure of Jacobi, P. A., Ph.D. Thesis, Princeton University, 1973, p 157. It is also commercially available from Aldrich Chemical Co.
(27) This reaction was capricious at first giving mixtures of **15** and its [(*N*,*N*-dimethylamino)methylene]amino derivative. Treatment of the mixtures with 6 N HCl with vigorous stirring overnight gave uncontaminated **15**. Later it was found that mixtures could be avoided by using a minimum of ice during workup.

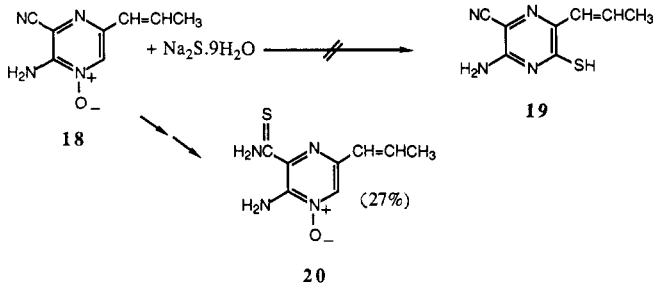
**Scheme IV**[a]



[a] (a) $Na_2S·9H_2O$, DMF, 25 °C, $H^+$, $CHCl_3$, Δ; (b) $Na_2S·9H_2O$, DMF, $H^+$, $CH_3CN$, 25 °C; (c) $Na_2S$.

volving the 6-chloro substituent, since chloropyrazines are known to react readily with nucleophiles when the chloro substituent is para to an electron-withdrawing group.

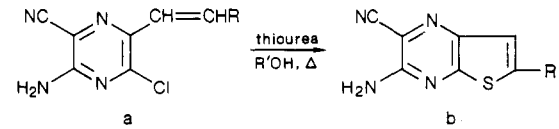
We then examined the possible conversion of 2-amino-3-cyano-5-propenylpyrazine 1-oxide (**18**)[28] to its 6-mercapto derivative **19** by reaction with 1 equiv of sodium sulfide nonahydrate. However, the only product isolated (in 27% yield) was the thioamide **20**; no addition whatsoever to C-6

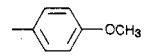


apparently occurred under these conditions. We therefore approached the possible preparation of **19** by reaction of the chloropropenylpyrazine **16** with sodium sulfide nonahydrate in DMF at room temperature. Workup by acidification and hot extraction gave, to our surprise, the fully cyclized dihydrothieno[2,3-*b*]pyrazine **21** in 30% yield. Indeed, there is precedent for such a cyclization; treatment of 2-mercapto-3-vinylquinolines (themselves prepared from the corresponding 2-chloroquinolines by reaction with thiourea in refluxing ethanol followed by hydrolysis of the resulting isothiouronium salts)[29] with a 10-fold excess of sodium acetate in boiling acetic acid for 6 h yields modest to low yields of 2,3-dihydrothieno[2,3-*b*]quinolines.[30] However, efforts to develop the above synthesis of **21** into a general approach to dihydrothienopyrazines proved capricious. Varying amounts of the mercapto compound **19** and the *S*-oxide **22** always accompanied the formation of **21**. The use of anhydrous sodium sulfide in place of its nonahydrate gave the dipyrazyl sulfide **23** as the major reaction product, along with minor amounts of **21** and its *S*-oxide **22** (Scheme IV).

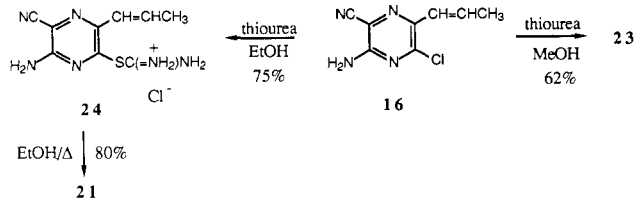
Discouraged by these results, we turned to the isothiouronium salt procedure[29] for the preparation of the mercapto intermediate **19**. Treatment of **16** with thiourea in refluxing methanol gave the dipyrazyl sulfide **23** in excellent yield. Replacement of methanol by ethanol yielded the isothiouronium salt **24** in 75% yield; however, attempts to convert this intermediate to the mercapto compound

**Table I. A General Synthesis of 6-Substituted 6,7-Dihydrothieno[2,3-*b*]pyrazines**

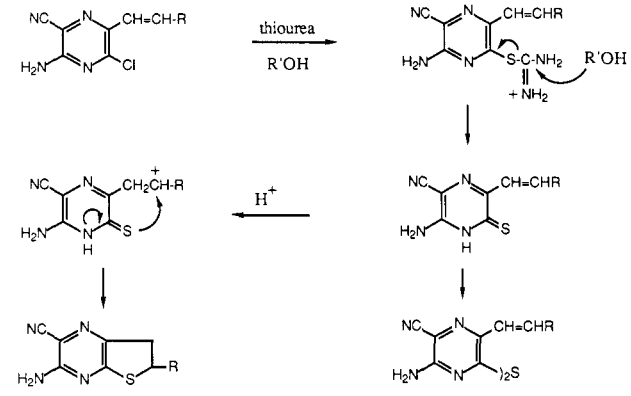


| no. | R | R'OH | time, h | yield, % |
|---|---|---|---|---|
| **21** | $CH_3$ | ethanol | 84 | 50 |
| **25** | $CH(CH_3)_2$ | ethanol | 74 | 64 |
| *trans*-**26** | CH=CHPh | 1-propanol | 67 | 41 |
| **27** |  | 1-propanol | 59 | 73 |
| *trans*-**28** |  | 1-propanol | 72 | 78 |
| *trans*-**29** |  | 1-propanol | 69 | 80 |

**Scheme V**



**Scheme VI**



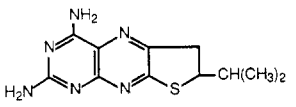
**19** with aqueous base gave a mixture of unidentified products, none of which contained a nitrile group. Since examination (proton NMR) of the filtrate residue from the ethanol reaction revealed the presence of a very small amount of the dihydrothienopyrazine **21**, we heated the isothiouronium salt **24** in a large volume of ethanol and followed the course of the reaction by TLC. After 21 h an 80:20 mixture of **21** and the dipyrazyl sulfide **23** was obtained. It was then found that this overall transformation of **16** to **21** could be carried out in one step by heating **16** with thiourea in refluxing ethanol for an extended period of time (4.5 days). This facile and efficient thiourea-mediated conversion of **16** to **21** proved to be general (Scheme V). Table I summarizes our results with a variety of 6-chloro-5-alkenylpyrazines.

A mechanism for this thiourea-mediated dihydrothienopyrazine synthesis is suggested in Scheme VI in view of the effects of substituents indicated in Table I. The overall reaction is presumably acid-catalyzed, since our initial work with sodium sulfide nonahydrate led only as far as the sodium mercaptide intermediate, which cyclized only upon acidification. The success of the reactions described in Table I appears to be related to the generation of a β-carbocation by protonation. Since the use of methanol as solvent led to the dipyrazyl sulfide **23** as the

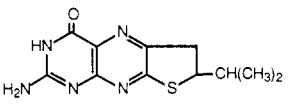
(28) Taylor, E. C.; Kobayashi, T. *J. Org. Chem.* **1973**, *38*, 806.
(29) Shanmugam, P.; Kanakarajan, K.; Soundararajan, N.; Gnanasekaran, A. *Synthesis* **1976**, *4*, 253.
(30) Shanmugam, P.; Kanakarajan, K.; Soundararajan, N. *Synthesis* **1976**, *9*, 595.

major reaction product, whereas the use of ethanol with the same substrate gave the dihydrothienopyrazine, it appears that higher temperatures favor intramolecular cyclization over an intermolecular pathway involving what we presume to be nucleophilic attack by the mercaptopyrazine intermediate either on the chloropyrazine starting material or on the intermediate isothiouronium salt (there is no evidence of $H_2S$ evolution in this reaction). The mercapto intermediate **19** isolated in the $Na_2S \cdot 9H_2O$ reaction and suggested as an intermediate in the thiourea-mediated cyclization was characterized by spectral comparison with **19** prepared by reaction of chlorovinylpyrazine **16** with commercially available $NaSH \cdot XH_2O$.

This model study of possible routes to Form B (dephospho) was then completed with the 6-isopropyldihydrothieno[2,3-*b*]pyrazine **25b**, which was chosen because of similarity of the branched secondary alkyl substituent with the Form B side chain. Guanidine cyclization of **25b** in refluxing methanol gave the diaminopteridine **30** in 92% yield as a bright yellow solid, which exhibited blue fluorescence under both short- and long-wavelength UV light. This fluorescence is a characteristic of all the dihydrothienopyrazines in Table I. Although alkaline hydrolysis of **30** led only to extensive decomposition, acidic hydrolysis gave the dihydrothienopterin **31** in modest yield.




30




31

The final product is sensitive to prolonged exposure to acid, as could be readily confirmed by examination of its NMR spectrum over a period of time in deuteriated trifluoroacetic acid containing a few drops of DMSO-$d_6$. When the above strategy is eventually applied to the synthesis of Form B, therefore, care will have to be taken to avoid acidic degradation.

We have thus successfully demonstrated that the 6,7-dihydrothieno[3,2-*g*]pterin ring system can be formed from 6,7-dihydrothieno[2,3-*b*]pyrazines, which in turn have been prepared by a thiourea-mediated ring closure of available pyrazine intermediates. Attempts are currently under way to apply this methodology to the preparation of Form B of the molybdenum cofactor.

## Experimental Section

**2-Amino-6-chloro-5-(chloromethyl)-3-cyanopyrazine (15).** A 500-mL, three-necked flask was equipped with an overhead mechanical stirrer, an addition funnel, and a thermometer. A solution of 2-amino-5-(chloromethyl)-3-cyanopyrazine 1-oxide (**14**)[26] (12.0 g, 64 mmol) in DMF (120 mL) was cooled to −5 °C ($CO_2/CCl_4$ bath), stirred vigorously, and freshly distilled phosphorus oxychloride (24 mL, 40.2 g, 260 mmol) was added dropwise over 40 min to the vigorously stirred solution at −5 to −10 °C (a thick yellow precipitate separated initially). When the exothermic reaction was over (15–30 min), the cooling bath was removed, and the dark solution was allowed to warm to room temperature and stir overnight. A 1-L Erlenmeyer flask was half-filled with crushed ice, and the solution was poured over it. The precipitate that formed was suspended in the aqueous phase with vigorous mechanical stirring for 17–24 h, isolated by filtration, washed with water, and dried in vacuo at 45 °C to give 10.7 g (82%) of product as a cream-colored solid, mp 190–190.5 °C with decomposition, 172 °C (sintering);[31] IR (Nujol) 3350, 3310, 3210, 3190 ($NH_2$), 2225 (CN), 1648 (vs, C=N), 1555, 1200 (s), 1033 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 7.96 (br s, 2 H, $NH_2$), 4.74 (s, 2 H, $CH_2Cl$); TLC (silica gel, 5% acetonitrile in chloroform) $R_f$ 0.43 blue fluorescence short wavelength UV.

**[(2-Amino-6-chloro-3-cyanopyrazin-5-yl)methyl]triphenylphosphonium Chloride (9).** A magnetically stirred solution of 2-amino-6-chloro-5-(chloromethyl)-3-cyanopyrazine (**15**) (9.90 g, 0.049 mol) and triphenylphosphine (11.61 g, 0.050 mol) in DMF (75 mL) was heated for 24 h in an oil bath maintained at 80–90 °C. After cooling to room temperature, the precipitate was isolated by filtration, washed with DMF, rinsed with ether, and air-dried to give 19.18 g (84%) of product as an off-white powder, mp 300 °C (charring). The analytical sample was obtained as pale yellow crystals, mp 340 °C (300 °C charring), by recrystallization from a minimum amount of methanol: IR (Nujol) 3442 (m, $NH_2$), 2220 (w, CN), 1599, 1250, 1110 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 5.41 (d, 2 H, $J$ = 14.8 Hz, $CH_2P$), 7.70–8.01 (m, 17 H, phenyl and $NH_2$). Anal. Calcd for $C_{24}H_{19}N_4Cl_2P$: C, 61.95; H, 4.12; N, 12.04; Cl, 15.24; P, 6.66. Found: C, 61.83; H, 4.10; N, 11.92; Cl, 15.43; P, 6.61.

**2-Amino-6-chloro-3-cyano-5-(1-propenyl)pyrazine (16).** Triethylamine (2.1 mL, 1.5 g, 15 mmol) was added to a suspension of [(2-amino-6-chloro-3-cyanopyrazin-5-yl)methyl]triphenylphosphonium chloride (**9**) (3.51 g, 7.5 mmol) in chloroform (300 mL). The mixture became rose-colored. Freshly distilled acetaldehyde (5.0 mL, 3.9 g, 88.5 mmol) was added, and the slurry was stirred at room temperature for 16.5 h. The amber solution was washed with water (50 mL), dried over sodium sulfate, and rotary evaporated under reduced pressure to give a mustard-colored solid. Recrystallization from ethanol (75 mL) gave 0.77 g (53%) of **16** as mustard-colored crystals, mp 238.5 °C dec. A second crop, 0.29 g (20%), mp 235 °C dec, was recovered from the filtrate on standing. The analytical sample was obtained by chromatography of 286 mg of product on silica gel (10 g), eluting with chloroform. The sample was collected as a blue-violet fluorescent band. Rotary evporation of the solvent in vacuo gave 181 mg of yellow solid, which was recrystallized from benzene to give yellow crystals (105 mg). A second chromatography on silica gel, eluting with 20% ether in petroleum ether (bp 30–60 °C), gave 84 mg of product as a deep yellow solid: mp 242.5–243 °C dec; TLC (silica gel, 5% acetonitrile in chloroform) $R_f$ 0.33; IR (Nujol) 3395, 3315, 3220 ($NH_2$), 2230 (CN), 1640 (vs br, pyrazine and CH=CH), 1205 (vs, aminopyrazine); $^1H$ NMR (DMSO-$d_6$) δ 7.64 (br s, $NH_2$), 6.66–6.49 (m, CH=CH), 1.89 (d, 3 H, $J$ = 4.8 Hz, $CH_3$), irradiation at 6.6 collapsed the doublet at 1.89 to a singlet; $^{13}C$ NMR (DMSO-$d_6$) δ 154.67, 147.09, 136.58, 131.22, 122.87, 115.24, 109.66, 18.05; mass spectrum, $m/z$ (relative intensity) 194 ($M^+$, 100), 159 ($M^+$ − Cl, 96), 132 (10), 105 (14). Anal. Calcd for $C_8H_7N_4Cl$: C, 49.37; H, 3.63; N, 28.79; Cl, 18.22. Found: C, 49.27; H, 3.73; N, 28.32; Cl, 18.33.

**2-Amino-3-cyano-6-chloro-5-(2-bromo-1-hydroxypropyl)-pyrazine (17).** 2-Amino-3-cyano-6-chloro-5-(1-propenyl)pyrazine (**16**) (500 mg, 2.5 mmol) was dissolved in 12.5 mL of dimethyl sulfoxide containing 1.0 mL of water, cooled to 10 °C, and treated with *N*-bromosuccinimide (885 mg, 5.0 mmol, recrystallized from water). The cooling bath was removed, and the amber solution was allowed to stir for 1.5 h. It was then poured into water (125 mL) to precipitate a yellow solid. Solid sodium chloride was added, and the mixture was stirred for 1 h. The product was extracted into 1:1 ether–tetrahydrofuran (75 mL), and the phases were separated. The aqueous phase was extracted with additional 1:1 ether–tetrahydrofuran (2 × 75 mL), and the combined organic layers were dried over sodium sulfate and rotary evaporated to give a solid contaminated by an orange oil. The crude mixture was treated with anhydrous ether and decanted from an orange oily residue. Removal of solvent under reduced pressure gave a viscous yellow oil, which was triturated with carbon tetrachloride and allowed to stand in a freezer (−20 °C) overnight. A pale yellow solid was collected by vacuum filtration and recrystallized from carbon tetrachloride to give a white crystalline solid contaminated by traces of yellow oil. A second recrystallization from toluene with the addition of Celite gave 140 mg (19%) of a microcrystalline yellow solid, mp 171–172 °C dec. Concentration of the filtrate yielded an additional 80 mg (11%), mp 168–170 °C dec.

A 100-mg sample was recrystallized from 18 mL of 2:1 carbon tetrachloride–chloroform to give 70 mg of pale yellow crystals, mp 174–175 °C dec. TLC analysis (silica gel, 20% acetonitrile

(31) Jacobi, P. A., Ph.D. Thesis, Princeton University, 1973, p 157, reported mp 190–191 °C for the analytical sample recrystallized from benzene–cyclohexane.

in chloroform) revealed a major blue-violet fluorescent spot at $R_f$ 0.44 and a minor blue-violet fluorescent spot at $R_f$ 0.52. These compounds were separated by chromatography of a 50-mg sample on silica gel (3 g), eluting with chloroform to give 2.3 mg of the threo isomer of **17** as a white crystalline solid, mp 183–184 °C, and 38.6 mg of the erythro isomer of **17**, mp 172.5–173 °C: erythro IR ($CHCl_3$) 3580, 3510, 3405 ($NH_2$ and OH), 2230 (w, CN), 1615 (vs, aminopyrazine) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.42 (br s, 2 H, $NH_2$), 5.13 (dd, 1 H, $J$ = 8.8 Hz, $H_a$), 4.5–4.1 (m, 1 H, $H_b$), 2.96 (d, 1 H, $J$ = 8.8 Hz, OH), 1.78 (d, 3 H, $CH_3$); threo IR ($CHCl_3$) 3580, 3510, 3405 ($NH_2$ and OH), 2230 (w, CN), 1615 (vs, aminopyrazine) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.40 (br s, 2 H, $NH_2$), 4.89 (dd, 1 H, $J$ = 8.8 Hz, $H_a$), 4.7–4.4 (m, 1 H, $H_b$), 3.56 (d, 1 H, $J$ = 8.8 Hz, OH), 1.86 (d, 3 H, $CH_3$); mass spectrum, $m/z$ (relative intensity) 292 ($M^+$ + 2, 15), 290 ($M^+$, 14), 210 ($M^+$ – Br, 19), 193 ($M^+ - H_2O$ – Br, 34), 185 (75), 183 (74), 92 (100), 91 (98); HRMS calcd for $C_8H_8N_4O^{79}Br^{37}Cl$ or $C_8H_8N_4O^{81}BrCl$ 291.9550, found 291.9545; calcd for $C_8H_8N_4O^{79}Br^{35}Cl$ 289.9570, found 289.9579.

**2-Amino-5-(1-propenyl)-3-thioamidopyrazine 1-Oxide (20).** Sodium sulfide nonahydrate (750 mg, 3.11 mmol) was added to a stirred solution of 2-amino-3-cyano-5-(1-propenyl)pyrazine 1-oxide (18)[32] (500 mg, 2.83 mmol) in DMF (10 mL) under nitrogen. The yellow reaction mixture turned deep orange instantly and then deep red. After being stirred for 27 h at room temperature, the solvent was removed under reduced pressure on a rotary evaporator at 60–70 °C to give a deep red residue, which was dissolved in water (50–75 mL) and filtered to isolate a yellow orange solid. Amberlyst 15 resin (2 g) was added to the filtrate, and a yellow solid began to precipitate. After the mixture was stirred for 3 days, chloroform (75 mL) was added and the two-phase system was vigorously stirred for 1 h. The layers were separated, and the aqueous phase was extracted two times with chloroform. The chloroform extracts were combined, dried over magnesium sulfate, and evaporated under reduced pressure to give a yellow orange solid. This was combined with the yellow orange solid isolated by filtration, and the crude product was purified by flash chromatography on silica gel, eluting with mixtures of acetonitrile in methylene chloride. The product was eluted by 10% acetonitrile in methylene chloride to give, after evaporation of the solvent, 160 mg (27%) of **20** as deep yellow crystals: mp 191–192 °C; IR (Nujol) 3360, 3325, 3223, 3180, 3120, 1620 (s), 1605 (vs), 1535, 1225 (vs), 1145 (vs) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 8.67 (br s, $NH_2$), 8.58 (s, 1 H, pyrazine H), 6.87 (m, 1 H, C=C*H*$CH_3$), 6.31 (dd, 1 H, $J$ = 15.8 Hz, $^4J$ = 1.53 Hz, C*H*=$CHCH_3$), 1.86 (dd, 3 H, $J$ = 6.57 Hz, $^4J$ = 1.53 Hz, $CH_3$) irradiation at 1.86 collapsed 6.31 and 6.87 to two doublets ($J$ = 15.8 Hz); mass spectrum, $m/z$ (relative intensity) 210 ($M^+$, 56), 194 ($M^+$ – 0, 100), 193 ($M^+$ – OH, 63), 176 ($M^+ - H_2S$, 68). Anal. Calcd for $C_8H_{10}N_4OS$: C, 45.70; H, 4.79; N, 26.65; S, 15.25. Found: C, 45.93; H, 4.77; H, 26.42; S, 15.34. Starting material (103 mg, 21% recovery) was eluted from the column by 20% acetonitrile in methylene chloride.

**3-Amino-2-cyano-6-methyl-6,7-dihydrothieno[2,3-*b*]pyrazine (21). Sodium Sulfide Nonahydrate as Reagent. Method A.** Sodium sulfide nonahydrate (256 mg, 1.07 mmol) was added to a stirred solution of 2-amino-6-chloro-3-cyano-5-(1-propenyl)pyrazine (**16**) (186 mg, 0.96 mmol) in DMF (10 mL) under nitrogen. Within 1–2 min the reaction mixture changed from golden to deep red. After the mixture was stirred for 5.5 h at room temperature, the solvent was removed from the cloudy dark mixture by rotary evaporation on a Büchi cold finger apparatus at 25–30 °C (1 mmHg). The remaining red oil was dissolved in water (75 mL) and filtered through a pad of Celite to separate a small amount of orange solid. The pale orange filtrate was combined with 500 mg (4.9 mequiv/g) of Amberlyst 15 resin and allowed to stir overnight. A yellow-orange precipitate and resin was recovered by vacuum filtration. On prolonged standing yellow crystals precipitated in the filtrate. These were isolated by filtration and dried to give 23 mg (13%) of **21**. Additional product was obtained by extracting the mixture of solid and resin several times with boiling chloroform and decanting from the insolubles. The extracts were combined, allowed to cool to room temperature, dried over sodium sulfate, and rotary evaporated under reduced pressure to give a red-orange residue. Column chromatography of the residue on silica gel (3.5 g), eluting with 10% acetonitrile in chloroform, gave 55 mg (30%) of dihydrothienopyrazine **21** as a yellow-orange solid, mp 246–248 °C dec (at 240 °C yellow needles sublimed, with charring at 162 °C). Vacuum sublimation of a 2-mg sample gave 1 mg of yellow crystals, mp 245–246 °C dec; IR (KBr) 3382, 3315, 3205 ($NH_2$), 2218 (CN), 1640 (vs), 1553 (vs), 1532 (s), 1465, 1378, 1335 (s), 1260 (s), 1190 (vs), 1090 (br), 1039 (br) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.12 (br s, 2 H, exchangeable with $D_2O$, $NH_2$), 4.08–3.91 (m, 1 H, CH), 3.34 and 2.80 (2 dd, partly obscured by water peak, $CH_aH_b$) 1.44 (d, 3 H, $J$ = 6.4 Hz, $CH_3$); $^1H$ NMR (2.5:1 v/v $CDCl_3$–DMSO-$d_6$) $\delta$ 6.36 (br s, 2 H, $NH_2$), 4.17–3.81 (m, collapsed to a distorted triplet by irradiation at 1.43, CH), 3.34 (dd, C*H*$_a$H$_b$), 2.73 (dd, CH$_a$*H*$_b$), 1.43 (d, collapsed to a singlet by irradiation at 4.07, $J$ = 6.4 Hz, 3 H, $CH_3$); $^1H$ NMR (pyridine-$d_5$, 300 MHz) $\delta$ 4.92 (br s, 2 H, $NH_2$), 3.90 (m, 1 H, CH), 3.24 (dd, 1 H, $J_1$ = 8.09 Hz, $J_2$ = 16.18 Hz, C*H*$_a$H$_b$), 2.76 (apparent dd, 1 H, CH$_a$*H*$_b$), 1.31 (d, 3 H, $J$ = 6.67 Hz, $CH_3$); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 165.24, 156.13, 144.00, 118.97, 116.97, 41.39, 22.49, 16.53; mass spectrum, $m/z$ (relative intensity) 192 ($M^+$, 100), 177 ($M^+ - CH_3$, 77), 159 ($M^+$ – SH, 10), 150 ($M^+ - C_3H_7$, 11); HRMS calcd for $C_8H_8N_4S$ 192.0469, found 192.0466 ± 0.002.

**Method B.** Sodium sulfide nonahydrate (679 mg, 2.83 mmol) was added to a stirred solution of 2-amino-6-chloro-3-cyano-5-(1-propenyl)pyrazine (**16**) in DMF (25 mL) under nitrogen, and the reaction mixture was stirred at room temperature for 24 h. Within 20 min the golden solution turned red. After 24 h a pale orange opaque mixture resulted. The solvent was removed on a rotary evaporator under water aspirator vacuum at 60–70 °C to give a dark red oil, which was dissolved in water (50 mL) and combined with 1.25 g of Amberlyst 15 resin. A red-orange solid precipitated slowly. The mixture was slurried for a few minutes and then allowed to stand under nitrogen for 2 days. The solids were collected by filtration, stirred with acetonitrile to dissolve the product, and filtered. Evaporation of the filtrate under reduced pressure gave a red-orange residue, which was purified by column chromatography on silica gel, eluting with chloroform to give 179 mg of a mixture of dihydrothienopyrazine **21** and the 6-thione **19**, TLC (silica gel, 20% acetonitrile in chloroform) $R_f$ 0.46 blue fluorescence short wavelength UV for the dihydrothienopyrazine; $R_f$ 0.55 yellow visible, absorbs short wavelength UV for the 6-thione. Also isolated by elution with 1–5% acetonitrile in chloroform was 15 mg (3%) of **22**, the *S*-oxide of the dihydrothienopyrazine, $R_f$ 0.21 blue fluorescence under short wavelength UV. Vacuum sublimation of the mixture of **21** and **19** at 180–200 °C (1 mmHg) gave 80.6 mg (16%) of the dihydrothienopyrazine **21** as yellow needles, mp 242–244 °C. This material can also be recrystallized from benzene without change in the melting point. It was identical by IR, NMR, and TLC analyses with the material prepared by method A.

**3-Amino-2-cyano-6-methyl-6,7-dihydrothieno[2,3-*b*]pyrazine *S*-Oxide (22):** see procedure above; IR (Nujol) 3380, 3310, 3205 ($NH_2$), 2215 (CN), 1640, 1545, 1530, 1188 $cm^{-1}$; $^1$NMR (DMSO-$d_6$) $\delta$ 7.30 (br s, 2 H, $NH_2$) 4.7–4.5 (m, 1 H, CH), 3.7–3.5 (m), 1.42 (d, 3 H, $J$ = 6.4 Hz, $CH_3$); mass spectrum, $m/z$ (relative intensity) 208 ($M^+$, 100), 191 ($M^+$ – OH, 32) 190 ($M^+ - H_2O$, 24); HRMS calcd for $C_8H_8N_4SO$ 208.0419, found 208.0399 ± 0.0021.

**2-Amino-3-cyano-6-mercapto-5-(1-propenyl)pyrazine (19).** To a stirred solution of 2-amino-3-cyano-6-chloro-5-(1-propenyl)pyrazine (**16**) (195 mg, 1.02 mmol) in DMF (5 mL) was added $NaSH \cdot XH_2O$ [85 mg, 41.2% sulfur (Aldrich), 1.1 equiv of sulfur] under nitrogen. An immediate color change from gold to yellow-brown was observed. Within 30 min at room temperature the reaction mixture was bright orange and cloudy. After the mixture was stirred overnight, the solvent was removed on a rotary evaporator at 60–70 °C and water aspirator vacuum to give a gummy yellow-brown residue. The residue was dissolved in THF and filtered through Celite to remove dark brown insoluble material. The filtrate was chromatographed on basic alumina (25 g, Baker reagent), eluting with mixtures (10–50%) of ether in petroleum ether (bp 30–60 °C). The product was eluted by 50% ether–petroleum ether. Evaporation of the solvent in vacuo gave 23 mg (12%) of **19** as a rust-colored solid, mp 211 °C (with charring at 176 °C and darkening at 145 °C). This material was dissolved in 100 mL of boiling benzene and filtered hot, and the

(32) Taylor, E. C.; Kobayashi, T. *J. Org. Chem.* **1978**, *38*, 2817.

filtrate was concentrated to ca. 10 mL on a rotary evaporator. Dilution with an equal volume of petroleum ether and standing led to the separation of 2.2 mg of **19** as golden yellow crystals, mp 217 °C: IR (Nujol) 3435, 3330, 3215, 2215 (CN), 1650 (br sh), 1620 (vs), 1530, 1195 (vs) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.26 (br s, 2–3 H), 6.62–6.57 (m, 2 H, CH=CH), 1.93 (d, 3 H, $J$ = 4 Hz, $CH_3$) irradiation at 6.6 collapsed the doublet at 1.93 to a singlet; mass spectrum, $m/z$ (relative intensity) 192 ($M^+$, 30) 190 ($M^+$ – 2, 55),[33] 177 ($M^+ - CH_3$, 38), 139 (49), 126 (100). This compound is unstable; by the time an attempt was made to obtain a precise mass measurement it no longer gave the molecular ion.

**6-Bis[2-amino-3-cyano-5-(1-propenyl)pyrazyl] Sulfide (23).** A suspension of 2-amino-6-chloro-3-cyano-5-(1-propenyl)pyrazine (**16**) (195 mg, 1 mmol) and thiourea (81 mg, 1.1 mmol) in methanol (2.0 mL) was heated under reflux for 93 h. A yellow precipitate was isolated by hot filtration of the reaction mixture and washed with hot methanol to give 82.2 mg (47%) of product as a bright yellow solid, mp 232 °C dec. A second crop precipitated from the filtrate upon cooling to room temperature. This was isolated by filtration and dried to give an additional 27 mg (15%) of product, mp 215 °C dec. The analytical sample was prepared by recrystallization of 60 mg from 6 mL of 1:1 ethanol–benzene to give 50 mg of yellow crystals: mp 234 °C dec; IR (Nujol) 3440 (sharp), 3350, 3330, 3290 (sh), 3225, 3165 2235 (w, CN), 1625 (s), 1535 (s), 1190–1202 (vs) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.30 (br s, 4 H, $NH_2$), 6.56–6.51 (m, 4 H, 2 CH=CH), 1.85 (dd, 6 H, $J$ = 5.6 Hz, $^4J$ = 1.6 Hz, 2 $CH_3$); mass spectrum, $m/z$ (relative intensity) 350 ($M^+$, 64), 335 (65), 309 (17), 283 (9), 191 (100), 177 (21), 159 (26). Anal. Calcd for $C_{16}H_{14}N_8S$: C, 54.85; H, 4.03; N, 31.98; S, 9.15. Found: C, 54.90; H, 4.22; N, 31.82; S, 9.28.

**Preparation of 23 from 16 and Anhydrous Sodium Sulfide.** Anhydrous sodium sulfide (88 mg, 1.13 mmol) was added to a solution of 2-amino-6-chloro-3-cyano-5-(1-propenyl)pyrazine (**16**) (195 mg, 1 mmol) in dry DMF (10 mL) under a nitrogen atmosphere, and the yellow-brown solution was stirred at room temperature for 5.5 h. The solvent was evaporated on a Büchi cold finger apparatus (25 °C, 1 mmHg) to give a brown oil. Addition of water (10 mL) caused a mustard-colored solid to precipitate. The solid was collected by filtration and dried (25 °C, 1 mmHg) to give 75.2 mg (43%) of **23**, which was identical by NMR and IR spectroscopy with **23** prepared from **16** and thiourea as described above. The yellow-orange aqueous filtrate was diluted with water (20 mL), and Amberlyst 15 resin (500 mg) was added. A yellow-orange solid began to precipitate immediately. After stirring under $N_2$ overnight, the solids were collected by filtration and extracted with boiling chloroform (40 mL). After hot filtration to remove the resin, the filtrate was cooled to room temperature, dried ($Na_2SO_4$), and evaporated under reduced pressure to give 10.6 mg of a mustard-colored solid, which was a 2:1 mixture of dihydrothienopyrazine **21** and its $S$-oxide **22** by comparison of its NMR spectrum with spectra of authentic material.

**2-Amino-3-cyano-6-isothioureido-5-(1-propenyl)pyrazine Hydrochloride (24).** A suspension of 2-amino-6-chloro-3-cyano-5-(1-propenyl)pyrazine (**16**) (195 mg, 1 mmol) and thiourea (130 mg, 1.7 mmol) in ethanol (2.0 mL) was heated under reflux for 4 h under nitrogen. After 3 h a deep red solution containing a trace of solid was observed. After 4 h under reflux, TLC analysis (silica gel, 20% ethyl acetate in hexanes) revealed no starting material and a yellow spot at the origin. After cooling to room temperature 157.7 mg (75%) of isothiouronium salt **24** was obtained as a bright yellow solid: mp 205 °C dec; IR (Nujol) 3430 (sharp), 3300–3000, 2210 (CN), 1660, 1620, 1540, 1195 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 9.69 (br s, 4 H, exchangeable with $D_2O$, $H_2NCNH_2^+$), 7.74 (br s, 2 H, exchangeable with $D_2O$, $NH_2$), 6.59–6.54 (m, 2 H, CH=CH), 1.90 (d, 3 H, $J$ = 4.8 Hz, $CH_3$); mass spectrum, $m/z$ (relative intensity)[34] 290 (100), 235 ($M^+$, 25), 234 ($M^+$ – 1, 88), 219 (15), 192 (63), 191 (55), 190 (63), 177 (45), 159 (80). This compound is an intermediate in the cyclization of chlorovinylpyrazine **16** to the dihydrothieno[2,3-*b*]pyrazine **21**. Because it is a salt, it was difficult to obtain analytically pure. It could not be heated because of its propensity to cyclize. Reprecipitation from DMF solution by ether failed to give an analytically pure sample. A precise mass could not be obtained because the high probe temperature needed to vaporize the compound caused extensive decomposition.

**Conversion of Isothiouronium Chloride 24 to 3-Amino-2-cyano-6-methyl-6,7-dihydrothieno[2,3-*b*]pyrazine (21).** Isothiouronium chloride **24** (71 mg, 0.26 mmol) was dissolved in ethanol (20 mL) and heated under reflux in a nitrogen atmosphere for 21 h. Rotary evaporation of the solvent under reduced pressure gave a mustard-colored residue, which was washed well with water, collected by filtration, and dried to give 50 mg (100%) of crude **21**. The solid was shown by NMR to be an 80:20 mixture of dihydrothieno[2,3-*b*]pyrazine **21** and dipyrazyl sulfide **23**.

**Conversion of 6-Chlorovinylpyrazine 16 to 3-Amino-2-cyano-6-methyl-6,7-dihydrothieno[2,3-*b*]pyrazine (21).** A suspension of 2-amino-3-cyano-5-(1-propenyl)-6-chloropyrazine (**16**) (132 mg, 0.68 mmol) and thiourea (87.4 mg, 1.15 mmol) in ethanol (3.0 mL) was heated under reflux and under nitrogen for 24 h. Additional ethanol was then added (10.0 mL), and heating was continued for 3.5 days. The hot reaction mixture was filtered to give 8.3 mg of product as a mustard-colored solid, mp 245–247 °C. The filtrate was reduced to 5 mL by boiling, allowed to cool slowly to room temperature, and kept in a freezer (–20 °C) overnight. Rust-colored crystals were isolated by filtration and were washed with a minimum amount of cold ethanol, and dried at 50 °C (1 mmHg) to give 57.3 mg (total yield 50%) of product, mp 245–247 °C. The compound was identical by TLC, IR, and NMR analyses with the material prepared above by the sodium sulfide nonahydrate method.

**2-Amino-6-chloro-3-cyano-5-(3-methyl-1-butenyl)pyrazine (25a).** [(2-Amino-6-chloro-3-cyanopyrazin-5-yl)methyl]triphenylphosphonium chloride (**9**) (4.00 g, 8.6 mmol) was suspended in chloroform (200 mL). Triethylamine (2.0 mL, 1.46 g, 14.4 mmol) was added, resulting in a color change from off-white to deep rose. Isobutyraldehyde (8.0 mL, 10.08 g, 140 mmol) was added, and the reaction mixture was heated under reflux and under nitrogen for 21 h. The rose color gradually faded, and a clear dark solution was obtained. After being cooled to room temperature, the solution was washed with water (3 × 150 mL) and saturated sodium chloride solution (150 mL). The aqueous layers were combined and extracted with chloroform (100 mL). The chloroform layers were combined, dried over magnesium sulfate, and evaporated on a rotary evaporator under reduced pressure to give a mustard-colored slush, which was suspended in benzene (10 mL) with vigorous stirring for 10–20 min. A mustard-colored solid was collected by filtration, washed well with benzene, and dried in vacuo at 50 °C to give 1.16 g (60%) of product, mp 177–178 °C. Recrystallization from 1:1 benzene–cyclohexane gave the analytical sample as yellow, needlelike crystals, mp 177–177.5 °C: TLC (silica gel, 40% ethyl acetate in hexanes) $R_f$ 0.51 yellow visible, absorbs short wavelength UV light, yellow fluorescence long wavelength UV; IR (KBr) 3390, 3320, 3220 ($NH_2$), 2230 (CN), 1635 (vs), 1550, 1470, 1373, 1200 (vs), 1035, 978 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 6.98–6.49 (m, 2 H, CH=CH), 5.23 (br s, 2 H, $NH_2$), 2.75–2.23 (m, 1 H, $CH(CH_3)_2$), 1.12 (d, 6 H, $J$ = 6.59 Hz, $CH(CH_3)_2$) irradiation at 2.53 collapsed the doublet at 1.12 to a singlet and collapsed the multiplet at 6.98–6.49 to overlapping doublets, $J$ = 15 Hz; mass spectrum, $m/z$ (relative intensity) 224 ($M^+$ + 2, 20) 222 ($M^+$, 57), 207 ($M^+ - CH_3$, 100) 187 ($M^+$ – Cl, 88), 167 (46). Anal. Calcd for $C_{10}H_{11}N_4Cl$: C, 53.94; H, 4.98; N, 25.16; Cl, 15.92. Found: C, 54.13; H, 5.00; N, 25.31; Cl, 16.07.

**Conversion of 25a to 3-Amino-2-cyano-6-isopropyl-6,7-dihydrothieno[2,3-*b*]pyrazine (25b).** A suspension of 2-amino-6-chloro-3-cyano-5-(3-methyl-1-butenyl)pyrazine (**25a**) (1.00 g, 4.5 mmol) and thiourea (580 mg, 7.6 mmol) in ethanol (10 mL) was warmed to reflux under nitrogen. The resultant solution was heated for 74 h. Upon cooling to room temperature, a solid crystallized from the dark solution. After chilling in an ice bath for 1.5 h, the crystals were collected by filtration, washed with ethanol, and air-dried to give 634 mg (64%) of product as a mustard-colored solid, mp 190–191 °C, which appeared to be ca. 95% pure by NMR. The analytical sample was obtained by

(33) Since there was no evidence of dihydrothienopyrazine ($M^+$ = 190) in the NMR spectrum, it is proposed that the peak at 190 is due to thermal cyclization and aromatization in the probe (probe temperature 250 °C).

(34) A probe temperature of 280 °C was required to vaporize this compound, which decomposes at 205 °C. Consequently, the peak at 290 (100) reflects this decomposition. The fragments at 192, 191, 190, 177, and 159 are also found in the mass spectrum of 2-amino-3-cyano-6-mercapto-5-(1-propenyl)pyrazine (**19**).

recrystallization of 100 mg of material from 3 mL of 1-propanol. After slow cooling to room temperature and standing overnight, 49.0 mg of pure **25b** was isolated, mp 194–194.5 °C: TLC (silica gel, 40% ethyl acetate in hexanes) $R_f$ 0.47 blue-violet fluorescence under short wavelength and long wavelength UV; IR (KBr) 3405, 3310 ($NH_2$), 2215 (s, CN), 1625, 1540 (br), 1455, 1365, 1328, 1180 (vs, br), 1100–1000 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 80 MHz) $\delta$ 7.08 (br s, $NH_2$), 4.20–3.65 (m, SC*H*), 3.45–2.74 (m partly obscured by water peak, $CH_aH_b$), 2.20–1.67 (m, C*H*$(CH_3)_2$), 0.92 (br d, 6 H, 2 $CH_3$); $^1H$ NMR (pyridine-$d_5$, 300 MHz) $\delta$ 4.96 (br s, $NH_2$), 3.80–3.73 (m, 1 H, SC*H*), 3.23 (apparent dd, 1 H, C$H_aH_b$), 2.93 (apparent dd, 1 H, $CH_aH_b$), 1.85–1.74 (m, 1 H, C*H*$(CH_3)_2$), 0.85 (overlapping doublets, 6 H, $J_1$ = 6.83 Hz, $J_2$ = 6.89 Hz, CH$(CH_3)_2$); UV (0.1 N HCl) $\lambda_{max}$ nm ($10^{-3}$ $\epsilon$) 220 (17.14), 267 (9.42), 382 (16.68); mass spectrum, $m/z$ (relative intensity) 220 ($M^+$, 56), 203 ($M^+$ – $NH_3$, 57), 177 ($M^+$ – $CH(CH_3)_2$, 100), 150 ($M^+$ – $C_4H_9$, 14), 133 (11). Anal. Calcd for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43; S, 14.55. Found: C, 54.78; H, 5.57; N, 25.16; S, 14.80.

**2-Amino-6-chloro-3-cyano-5-(4-phenyl-1,3-butadienyl)-pyrazine (26a).** Triethylamine (0.5 mL, 364 mg, 3.6 mmol) was added to a stirred suspension of [(2-amino-6-chloro-3-cyano-pyrazin-5-yl)methyl]triphenylphosphonium chloride (**9**) (1.00 g, 2.15 mmol) in chloroform (50 mL). Freshly distilled *trans*-cinnamaldehyde (1.0 mL, 1.05 g, 7.93 mmol) was added to the rose-colored mixture, and the system was placed under nitrogen and heated under reflux for 22 h. The reaction mixture was filtered to collect a bright yellow precipitate, which was suspended in benzene, collected by filtration, and dried at 45 °C (1 mmHg) to give 396 mg (65%) of **26a**, mp 259–261 °C. Recrystallization (58 mg) from 1-propanol (15 mL) gave the analytical sample (35 mg) as a deep yellow crystalline solid, mp 260–261 °C: TLC (silica gel, 40% ethyl acetate in hexanes) $R_f$ 0.53 yellow visible, absorbs short wavelength UV, yellow fluorescence long wavelength UV; IR (KBr) 3401, 3310 3210 ($NH_2$), 2225 (CN), 1630 (vs, br), 1550, 1475, 1370, 1300, 1196 (vs), 1038, 996, 745, 685 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.82 (br s, 2 H, $NH_2$), 7.54 (d, 2 H, $J$ = 9 Hz, CH=CH), 7.39–7.17 (m, 5 H, phenyl), 6.93 (d, 2 H, $J$ = 15 Hz, CH=CH); mass spectrum, $m/z$ (relative intensity) 282 ($M^+$, 41), 247 ($M^+$ – Cl, 10), 205 ($M^+$ – $C_6H_5$, 100), 128 (27), 115 (27); HRMS calcd for $C_{15}H_{11}N_4Cl$ 282.0672, found 282.0672.

**3-Amino-2-cyano-6-*trans*-styryl-6,7-dihydrothieno[2,3-*b*]pyrazine (26b).** A suspension of 2-amino-6-chloro-3-cyano-5-(4-phenyl-1,3-butadienyl)pyrazine (**26a**) (283 mg, 1.0 mmol) and thiourea (130 mg, 1.70 mmol) in 1-propanol (4.0 mL) was heated under reflux in a nitrogen atmosphere for 67 h. After 24 h, a color change from yellow to orange was observed. TLC (silica gel, 40% ethyl acetate in hexanes) of the reaction mixture vs starting material **26a** ($R_f$ 0.53, absorbs short wavelength, yellow fluorescence long wavelength UV) revealed the major component to be at the origin (orange visible, isothiouronium salt). More 1-propanol (8.0 mL) was added, and heating was continued for an additional 43 h. After cooling to room temperature, the reaction mixture was filtered to separate 6-bis[2-amino-3-cyano-5-(4-phenyl-1,3-butadienyl)pyrazyl] sulfide (57 mg); IR (KBr) 3440 (w), 3345 (br), 3190, 2225 (CN), 1616 (vs br), 1535, 1445, 1372, 1195 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.54–7.51 (m, 8 H), 7.37–7.16 (m, 10 H), 6.92–6.84 (dd, 4 H, $J_1$ = 9 Hz, $J_2$ = 15 Hz). Rotary evaporation of the filtrate under reduced pressure gave a mustard-colored residue, which was suspended in 15–20 mL of water for 10 min, filtered, and dried over Drierite at 45 °C and 1 mmHg to give 114 mg (41%) of the product as a deep gold crystalline solid, mp 212–213 °C. Recrystallization from methanol–water gave the analytical sample, mp 212–213 °C: TLC (silica gel, 40% ethyl acetate in hexanes) $R_f$ 0.47, blue-violet fluorescence short and long wavelength UV; IR (KBr) 3350 (sh), 3380, 3310, 3205 ($NH_2$), 2215 (CN) 1645–1610 (s), 1550–1520 (vs), 1460, 1370, 1330 (s), 1190 (vs), 1030, 960, 745, 685 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.54–7.20 (m, 7 H, $C_6H_5$ and $NH_2$), 6.69 (d, 1 H, $J$ = 15 Hz, C=C*H*Ph), 6.52 (dd, 1 H, $J_1$ = 9 Hz, $J_2$ = 15 Hz, C*H*=C), 4.92 (q, 1 H, $J$ = 9 Hz, SC*H*), 3.44 (apparent dd, 1 H, C$H_aH_b$), 3.15 (apparent dd, 1 H, $CH_aH_b$); mass spectrum, $m/z$ (relative intensity) 280 ($M^+$, 86), 247 ($M^+$ – SH, 11), 203 ($M^+$ – $C_6H_5$, 100), 189 ($M^+$ – $C_7H_7$, 14), 176 ($M^+$ – $C_8H_8$, 19), 165 (12), 115 (40), 91 (17), 77 (17). Anal. Calcd for $C_{15}H_{12}N_4S$: C, 64.27; H, 4.31; N, 19.98; S, 11.44. Found: C, 64.40; H, 4.21; N, 19.86; S, 11.62.

**2-Amino-6-chloro-3-cyano-5-styrylpyrazine (27a).** Triethylamine (2.1 mL, 1.5 g, 15 mmol) was added to a suspension of [(2-amino-6-chloro-3-cyanopyrazin-5-yl)methyl]triphenylphosphonium chloride (**9**) (3.51 g, 7.5 mmol) in chloroform (300 mL). Benzaldehyde (2.5 mL, 2.38 g, 22.5 mmol) was then added to the rose-colored mixture, which was stirred at room temperature for 20 h and under reflux for 15 min to give a yellow solution. TLC analysis (silica gel, 40% ethyl acetate–hexanes) indicated no remaining phosphonium salt, $R_f$ 0, blue fluorescence. Rotary evaporation of the solvent in vacuo gave a yellow-orange solid, which was suspended in benzene. After 5 min the yellow crystals were isolated by filtration and dissolved in chloroform. The chloroform solution was washed with water (3 × 500 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give 1.35 g (70%) of product: mp 236–238 °C. The analytical sample was obtained as shiny yellow crystals by recrystallization from a large volume of absolute ethanol: mp 240–241 °C; IR (KBr) 3375, 3315, 3210, 3190 ($NH_2$), 2228 (CN), 1640, 1550, 1470, 1375, 1200, 1040 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.83 (br s, 2 H, $NH_2$), 7.75–7.56 (m, 2 H, CH=CH), 7.50–7.26 (m, 5 H, phenyl); mass spectrum, $m/z$ (relative intensity), 258 ($M^+$ + 2, 33) 256 ($M^+$, 100), 221 ($M^+$ – Cl, 41), 194 ($M^+$ – Cl – HCN, 14), 140 (30), 128 (17), 115 (24), 102 (18). Anal. Calcd for $C_{13}H_9N_4Cl$: C, 60.83; H, 3.53; N, 21.83; Cl, 13.81. Found: C, 60.67; H, 3.58; N, 21.82; Cl, 14.18.

**3-Amino-2-cyano-6-phenyl-6,7-dihydrothieno[2,3-*b*]-pyrazine (27b).** A suspension of 2-amino-6-chloro-3-cyano-5-styrylpyrazine (**27a**) (200 mg, 0.78 mmol) and thiourea (101 mg, 1.33 mmol) in 1-propanol (3.0 mL) was heated under reflux in a nitrogen atmosphere for 59 h. The reaction mixture was filtered hot to remove insolubles. The filtrate was chilled in an ice bath and filtered. Rotary evaporation of the solvent under reduced pressure gave a mustard-colored residue, which was suspended in water for 20 min, filtered, and dried (50 °C and 1 mmHg) to give 145 mg (73%) of product as a gold solid, mp 173–176 °C dec. Recrystallization from 1:1 toluene–cyclohexane with addition of Darco and Celite gave the analytical sample as a gold microcrystalline solid: mp 178–179 °C dec; IR (KBr) 3390, 3315, 3210 ($NH_2$), 2218 (s, CN), 1635, 1548 (br, s), 1463, 1372, 1330, 1258, 1190, 1085 (br, s), 1030 (br, s), 798 (s); $^1H$ NMR ($CDCl_3$ plus DMSO-$d_6$, 250 MHz) $\delta$ 7.41–7.34 (m, 5 H, $C_6H_5$) 5.17–5.11 (m, 3 H, $NH_2$ and SC*H*), 3.65 (dd, 1 H, $J_1$ = 17 Hz, $J_2$ = 9 Hz, C$H_aH_b$), 3.41 (dd, 1 H, $J_1$ = 17 Hz, $J_2$ = 8 Hz), irradiation at 5.1 simplified the doublet of doublets at 3.65 and 3.41 to doublets; mass spectrum, $m/z$ (relative intensity) 254 ($M^+$, 100), 221 ($M^+$ – SH, 19), 177 ($M^+$ – $C_6H_5$, 26); HRMS calcd for $C_{13}H_{10}N_4S$ 254.0626, found 254.0623; calcd for $C_7H_5N_4S$ ($M^+$ – $C_6H_5$) 177.0235, found 177.0238.

**2-Amino-6-chloro-3-cyano-5-(*p*-methoxystyryl)pyrazine (28a).** Triethylamine (0.5 mL, 364 mg, 3.6 mmol) was added to a suspension of [(2-amino-6-chloro-3-cyanopyrazin-5-yl)-methyl]triphenylphosphonium chloride (**9**) (1.00 g, 2.15 mmol) in chloroform (50 mL). *p*-Anisaldehyde [1.2 mL of 98% aldehyde (Aldrich), 1.3 g, 10 mmol] was added to the rose-colored mixture, and the system was placed under nitrogen and warmed to reflux. After 24 h the hot reaction mixture was filtered to give a deep yellow solid. The solid was suspended in benzene (15 mL) for 15 min, collected by filtration, washed thoroughly with benzene, and dried at 25 °C (1 mmHg) to give 546 mg (89%) of **28a**, mp 234–235 °C. Recrystallization (90 mg) from 1-propanol (10 mL) gave the analytical sample (52.0 mg) as lustrous golden crystals: mp 234–235 °C; TLC (silica gel, ether) $R_f$ 0.61, yellow visible, absorbs short wavelength UV, yellow fluorescence long wavelength UV; IR (KBr) 3380, 3320, 3215 ($NH_2$), 2225 (w, CN), 1643 (s), 1605, 1553, 1512, 1245, 1203, 1172, 1030, 963 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.72 (br s, 2 H, $NH_2$), 7.56 (d, 2 H, $J$ = 8.5 Hz, aromatic H), 7.35 (d, 1 H, $J$ = 15.9 Hz, C*H*=C), 7.12 (d, 1 H, $J$ = 15.9 Hz, C=C*H*), 6.90 (d, 2 H, $J$ = 8.5 Hz, aromatic H); mass spectrum, $m/z$ (relative intensity) 286 ($M^+$, 100), 271 ($M^+$ – $CH_3$, 7), 251 ($M^+$ – Cl, 12), 243 (18), 208 (6); HRMS calcd for $C_{14}H_{11}N_4OCl$ 286.0621, found 286.0626.

**3-Amino-2-cyano-6-(*p*-methoxyphenyl)-6,7-dihydrothieno[2,3-*b*]pyrazine (28b).** A suspension of 2-amino-6-chloro-3-cyano-5-(*p*-methoxystyryl)pyrazine (**28a**) (150 mg, 0.52 mmol) and thiourea (68 mg, 0.89 mmol) in 1-propanol (3.0 mL) was heated under reflux under nitrogen for 48 h. Additional 1-propanol (5.0 mL) was added, and heating was continued for an additional 24 h. The cloudy red-brown reaction mixture was

filtered while hot to remove a brown solid. Rotary evaporation of the filtrate under reduced pressure gave a yellow-orange residue, which was suspended in water (15–20 mL) for 2.5 h, filtered, and dried (55 °C and 1 mmHg) to give 115 mg (78%) of product as a deep yellow crystalline solid, mp 194–196 °C. Recrystallization of **28b** (41 mg) from xylenes (5 mL) gave the analytical sample as deep yellow crystals (23 mg), mp 200–201 °C: TLC (silica gel, ether) $R_f$ 0.63, yellow visible, blue-violet fluorescence short and long wavelength UV; IR (KBr) 3380, 3320, 3210 ($NH_2$), 2222 (CN), 1640, 1545, 1508, 1463, 1248 (vs), 1228 (sh), 1188 (vs), 1175 (sh), 1030 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.11 (AB q, 4 H, $J$ = 9 Hz, aromatic H), 5.12 (t, 1 H, $J$ = 9 Hz, SC*H*), 5.07 (br s, 2 H, $NH_2$), 3.81 (s, 3 H, $OCH_3$), 3.61 (dd, 1 H, $J_1$ = 9 Hz, $J_2$ = 18 Hz, $CH_aH_b$), 3.39 (dd, 1 H, $J_1$ = 9 Hz, $J_2$ = 18 Hz, $CH_aH_b$); mass spectrum, $m/z$ (relative intensity) 284 ($M^+$, 100), 269 ($M^+ - CH_3$, 7), 251 ($M^+ - CH_3 - H_2O$, 7), 177 (7), 126 (25); HRMS calcd for $C_{14}H_{12}N_4O^{32}S$ 284.0732, found 284.0711; calcd for $C_{14}H_{12}N_4O^{34}S$ 286.0690, found 286.0690.

**2-Amino-6-chloro-3-cyano-5-[β-(2′-thienyl)vinyl]pyrazine (29a).** Triethylamine (0.5 mL, 364 mg, 3.6 mmol) was added to a suspension of [(2-amino-6-chloro-3-cyanopyrazin-5-yl)-methyl]triphenylphosphonium chloride (**9**) (1.00 g, 2.15 mmol) in chloroform (50 mL). A color change from off-white to pink occurred. After stirring for 30 min, 2-thiophenecarboxaldehyde (1.0 mL, 1.2 g, 11.7 mmol) was added. The system was flushed with nitrogen and maintained under a positive nitrogen pressure while the reaction mixture was warmed to reflux. As soon as the aldehyde was added, the pink reaction mixture began to turn yellow. After 1.5 h under reflux a clear orange solution was observed. Upon cooling to room temperature and stirring overnight, a precipitate formed, which was collected by filtration, washed with chloroform, and air-dried to give 390 mg (69%) of product as an orange microcrystalline solid, mp 238–239 °C dec. Removal of solvent from the filtrate by rotary evaporation under reduced pressure gave an orange residue, which was suspended in benzene for 20 min, filtered and air-dried, and then suspended in water (25 mL) for 30 min, filtered, and dried at 50 °C (1 mmHg) to give 24 mg (4%) of additional **29a**, mp 235–236 °C dec. Recrystallization (52 mg) from 1-propanol (5 mL) gave the analytical sample (37 mg) as lustrous orange crystals: mp 238–239 °C dec; TLC (silica gel, 40% ethyl acetate in hexanes) $R_f$ 0.52 yellow visible, absorbs short wavelength UV, yellow fluorescence long wavelength UV; IR (KBr) 3419, 3330, 3219 ($NH_2$), 2225 (CN), 1635 (vs), 1615 (sh), 1550, 1475, 1220 (sh), 1200 (vs), 1180 (sh) $cm^{-1}$; $^1H$ NMR (acetone-$d_6$ + DMSO-$d_6$, 300 MHz) $\delta$ 7.70 (d, 1 H, $J$ = 15 Hz, C*H*=C) 7.51–7.48 (br m, 3 H), 7.38 (d, 1 H, $J$ = 3 Hz), 7.16–7.09 (m, 2 H); mass spectrum, $m/z$ (relative intensity) 262 ($M^+$, 100), 227 ($M^+ - Cl$, 36), 200 (8), 173 (8), 146 (12), 135 (10); HRMS calcd for $C_{11}H_7N_4ClS$ 262.0080, found 262.0078.

**3-Amino-2-cyano-6-(2′-thienyl)-6,7-dihydrothieno[2,3-*b*]-pyrazine (29b).** A suspension of 2-amino-6-chloro-3-cyano-5-[β-(2′-thienyl)vinyl]pyrazine (**29a**) (200 mg, 0.76 mmol) and thiourea (100 mg, 1.32 mmol) in 1-propanol (3.0 mL) was heated under reflux in a nitrogen atmosphere for 69 h. TLC analysis (silica gel, 30% tetrahydrofuran in hexanes) revealed no remaining starting material ($R_f$ 0.24, absorbs short wavelength UV yellow fluorescence long wavelength, and a blue-violet fluorescent spot at $R_f$ 0.20 for product, plus trace impurities). The reaction mixture was cooled to room temperature and filtered to separate insolubles. The filtrate was rotary evaporated to give a red-brown residue, which was suspended in water (15 mL) with vigorous stirring for 30 min, filtered, and dried (50 °C and 1 mmHg) to give 159 mg (80%) of product as a rust-colored solid, mp 177–179 °C dec. The analytical sample was prepared by recrystallization of 50 mg of **29b** from water–methanol (7 mL, 2:5 v/v) with the addition of Darco and Celite. After being slowly cooled to room temperature and then allowed to stand in a refrigerator (5 °C) overnight, 23 mg of pure product was collected as rust-colored crystals, mp 180–182 °C dec; IR (KBr) 3390, 3310, 3215 ($NH_2$), 2219 (CN), 1640 (s, br), 1545 (s, br), 1195 (vs) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.28 (d, 1 H, $J$ = 5 Hz, thiophene H), 7.07 (d, 1 H, $J$ = 4 Hz, thiophene H), 6.96 (dd, 1 H, $J_1$ = 4 Hz, $J_2$ = 5 Hz, thiophene H), 5.41 (apparent t, 1 H, SC*H*), 5.11 (br s, 2 H, $NH_2$), 3.69 (apparent dd, 1 H, $CH_aH_b$), 3.47 (apparent dd, 1 H, $CH_aH_b$); mass spectrum, $m/z$ (relative intensity) 260 ($M^+$, 100), 227 ($M^+ - SH$, 21), 215 ($M^+ - HCS$, 7), 176 (7). Anal. Calcd for $C_{11}H_8N_4S_2$: C, 50.75; H, 3.10; N, 21.52; S, 24.63. Found: C, 50.98; H, 3.16; N, 21.44; S, 24.36.

**2,4-Diamino-7-isopropyl-6,7-dihydrothieno[3,2-*g*]pteridine (30).** Sodium (27 mg, 1.17 mmol) was dissolved in dry methanol (5.0 mL, distilled from $CaH_2$) under nitrogen. Guanidine hydrochloride (99 mg, 1.04 mmol) was added with stirring, and after a few minutes the cloudy solution was filtered directly into a round-bottom flask containing 3-amino-2-cyano-6-isopropyl-6,7-dihydrothieno[2,3-*b*]pyrazine (**25b**) (100 mg, 0.45 mmol) and a magnetic stirring bar. The funnel was rinsed with 1–2 mL of dry methanol. The reaction mixture was placed under nitrogen and heated under reflux for 24 h. The pyrazine soon dissolved, giving an amber solution from which the pteridine gradually precipitated. The reaction was followed by TLC (silica gel, 40% ethyl acetate in hexanes) for the disappearance of pyrazine **25b** ($R_f$ 0.48, blue fluorescence). After the mixture was cooled to room temperature and refrigerated (5 °C) overnight (18 h), the precipitate was isolated by filtration, washed sequentially with methanol, water, and ether and air-dried to give 109 mg (92%) of the product as a bright yellow solid, mp 330–330.5 °C dec: TLC (Analtech RSP-F 3:1:1 2-propanol–methanol–ammonia) $R_f$ 0.80 blue fluorescence short and long wavelength UV; IR (KBr) 3450, 3335, 3300 (sh), 3125 (br) ($NH_2$), 2960 (CH), 1665 (w), 1605 (br, s), 1578 (br, s), 1295 (vs), 1208, 1025 (vs) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz), $\delta$ 7.32 (br s, 2 H, $NH_2$) 6.43 (br s, 2 H, $NH_2$), 4.02–3.97 (m, 1 H, SCH), 3.46–3.23 (m, partly obscured by water peak), 3.09 (dd, 1 H, $J_1$ = 6.97 Hz, $J_2$ = 17.1 Hz, $CH_aH_b$), 1.95 (m, 1 H, $CH(CH_3)_2$), 0.96 (overlapping doublets, $J_1$ = 6.85 Hz, $J_2$ = 6.98 Hz, 6 H, $CH(CH_3)_2$); UV (0.1 N HCl) $\lambda_{max}$ nm ($10^{-3}$ $\epsilon$) 205 (19.8), 224 (19.6), 267 (8.34), 374 (18.5); mass spectrum, $m/z$ (relative intensity) 262 ($M^+$, 45), 219 ($M^+ - CH(CH_3)_2$, 50), 199 (28), 155 (18), 91 (100); HRMS calcd for $C_{11}H_{14}N_6S$ 262.1001, found 262.1007; calcd for $C_8H_7N_6S$ ($M^+ - C_3H_7$) 219.0453, found 219.0452; calcd for $C_8H_4N_5S$ ($M^+ - C_3H_7 - NH_3$) 202.0187, found 202.0183.

**2-Amino-7-isopropyl-6,7-dihydrothieno[3,2-*g*]pteridin-4-(3*H*)-one (31).** A suspension of 2,4-diamino-7-isopropyl-6,7-dihydrothieno[3,2-*g*]pteridine (**30**) (100 mg, 0.38 mmol) in 1 N HCl (20 mL) was heated under reflux in a nitrogen atmosphere for 9 h and then cooled to room temperature and allowed to stir overnight (14 h). The deep yellow-orange reaction mixture was filtered through a glass frit to remove a small amount of undissolved material, which was washed with 1 N HCl (20 mL). The combined filtrates were treated with 3 N NaOH (50 mL) introduced through a clean frit, and then diluted with water (200 mL) and warmed to 70 °C. The stirred solution was acidified with glacial acetic acid (10 mL) to precipitate a yellow solid. The mixture was allowed to cool slowly to room temperature and stand in a refrigerator (5 °C) for 24 h. The product was collected by centrifugation, washed with water and then with ethanol, and collected on a filter paper in a Hirsch funnel. After being rinsed with ethanol and ether and dried at 100 °C (1 mmHg) for 1 h, 43 mg (43%) of product was obtained as a yellow powder, mp 384 °C dec: TLC (Analtech RSP-F, 3:1:1 2-propanol–methanol–ammonia) $R_f$ 0.57 blue-violet fluorescence short and long wavelength UV; IR (KBr) 3500–3000, 2942 (w), 2860 (vw), 2800–2700, 1710–1610 (vs), 1534, 1505, 1312, 1140, 1020, 850 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) $\delta$ 6.90 (br s, 2 H, $NH_2$), 4.05–3.97 (m, 1 H, SC*H*), 3.50–3.40 (m, partly hidden by water peak, $CH_aH_b$), 3.12 (dd, 1 H, $J_1$ = 6.94 Hz, $J_2$ = 17.26 Hz, $CH_aH_b$), 2.02–1.95 (m, 1 H, $CH(CH_3)_2$), 0.97 (overlapping doublets, 6 H, $J_1$ = 6.85 Hz, $J_2$ = 7.11 Hz, $CH(CH_3)_2$); $^1H$ NMR (TFA-*d* plus a few drops of DMSO-$d_6$, 300 MHz), $\delta$ 4.15–4.05 (m, 1 H, SC*H*), 3.58 (dd, 1 H, $CH_aH_b$), 3.35–3.20 (m, 1 H, $CH_aH_b$), 2.20–2.00 (m, 1 H, $CH(CH_3)_2$), 1.05 (overlapping doublets, 6 H, $CH(CH_3)_2$); UV (0.1 N HCl) $\lambda_{max}$ nm ($10^{-3}$ $\epsilon$) 225 (47.4), 272 (10.4), 289 (9.36), 366 (37.7); HRMS (FAB) calcd for $C_{11}H_{14}NOS$ (M + 1) 264.0919, found 264.0916.

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**25b**, 116749-39-4; **26a**, 116749-56-5; **26b**, 116749-40-7; **27a**, 116749-57-6; **27b**, 116749-41-8; **28a**, 116749-58-7; **28b**, 116749-42-9; **29a**, 116749-59-8; **29b**, 116749-43-0; **30**, 116749-60-1; **31**, 116749-61-2; isobutyraldehyde, 78-84-2; *trans*-cinnamaldehyde, 14371-10-9; 6-bis[2-amino-3-cyano-5-(4-phenyl-1,3-butadienyl)pyrazyl] sulfide, 116784-48-6; benzaldehyde, 100-52-7; *p*-anisaldehyde, 123-11-5; 2-thiophenecarboxaldehyde, 98-03-3; guanidine hydrochloride, 50-01-1; molybdenum cofactor, 73508-07-3.

# An Anomalous Dipyrrole Product from Attempted Synthesis of a Tetraarylporphyrin

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Heating of *o*-acetoxybenzaldehyde with pyrrole in hot acetic acid under Adler/Rothemund conditions yields a bright red ($\gamma_{max}$ 515 nm) dipyrrolic compound and only minor quantities of the expected tetraarylporphyrin. Using NMR, mass spectrometry, and X-ray crystallography, we show the red material to be the dibenzofuranylpyrromethene **3**. A mechanism for the formation of this material is presented.

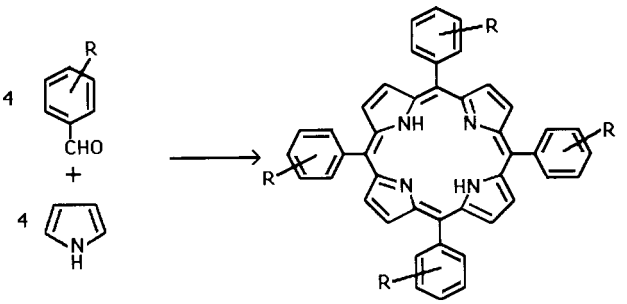
## Introduction

Recently there has been considerable interest in the mechanism of the ubiquitous formation of tetraarylporphyrins from pyrrole and aryl aldehydes (Scheme I). These porphyrins have been used extensively in physicochemical studies of biomimetic transformations, as well as being models in a host of biologically related problems.

Badger et al.[3] were the first to exploit the so-called Rothemund reaction[4] and to consider the mechanism and the problem of chlorin formation during the cyclization.[5] In 1970 Dolphin[6] showed that a porphyrinogen was the first isolable true intermediate in the condensation reaction; the mechanism of the subsequent oxidation of porphyrinogen to porphyrin and chlorin (dihydroporphyrin) was discussed, using sterically hindered systems (octamethyltetraphenylporphyrin[6] and octaethyltetraphenylporphyrin[7]). More recently, Gonsalves and Pereira[8] and Lindsey et al.[9] have used the facile formation of porphyrinogens as a means to obtain higher yields of porphyrin in a two-stage process.

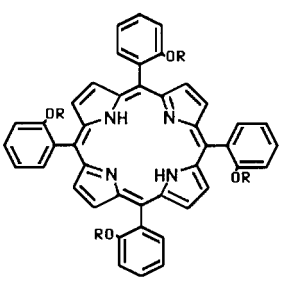
Badger's early work[3] on the Rothemund reaction resulted in isolation of the zinc(II) complex of a pyrromethene when the cyclization was carried out in the presence of zinc(II) acetate and pyridine in a sealed tube; this compound was not a true intermediate in the synthesis because it could not be efficiently converted, under the normal reaction conditions, into porphyrin. A similar zinc(II) pyrromethene was isolated in about 40% yield and fully characterized by Hill and Williamson[10] during the attempted synthesis of tetrakis(2,6-dichlorophenyl)-

**Scheme I. Synthesis of Tetraarylporphyrins from Pyrrole and Aryl Aldehydes**

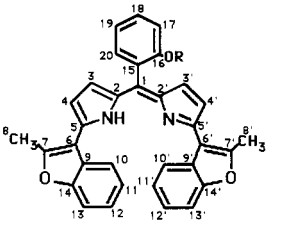


porphyrin from pyrrole and 2,6-dichlorobenzaldehyde in refluxing collidine in the presence of zinc(II) acetate. More recently still, Marchon et al.[11] obtained low yields of zinc(II) pyrromethenes from attempted syntheses of tetramesitylporphyrin under similar conditions.

We have found that the presence of zinc(II) is not always essential for isolation of pure pyrromethenes from Rothemund-type cyclizations. When *o*-hydroxybenzaldehyde or *o*-methoxybenzaldehyde was heated with pyrrole in acetic acid, the expected porphyrins (**1** and **2**, respectively) were isolated. However, when *o*-acetoxybenzaldehyde was



**1** R = H
**2** R = Me



**3** R = COCH$_3$
**4** R = H

used with pyrrole, only a minor amount of material bearing a Soret absorption band in its optical spectrum was isolated. Instead, a bright red crystalline product was ob-

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