Studies on the Imidazo[4,5-*d*]pyridazine Ring System. Course of Alkylation of Imidazo[4,5-*d*]pyridazine-4-thione[1]

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Received August 4, 1980

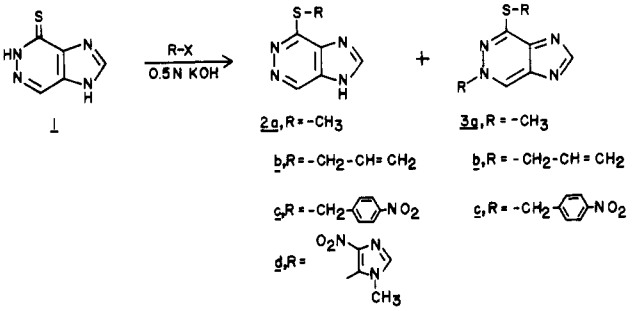
The syntheses of certain 4-(alkylthio)-, 4-[(arylalkyl)thio]-, and 4-(arylthio)imidazo[4,5-*d*]pyridazines from imidazo[4,5-*d*]pyridazine-4-thione (1, 4-SIP) are described. When 1 equiv of alkylating agent is used, alkylation occurs, as expected, on sulfur; however, when an excess of alkylating agent is employed, dialkylated products are formed. A rigorous spectroscopic study and an unequivocal synthesis of 6-methyl-4-(methylthio)imidazo-[4,5-*d*]pyridazine (**3a**) has shown the second site of alkylation to be N6 of the imidazo[4,5-*d*]pyridazine ring.

6-Mercaptopurine (6-MP), an antimetabolite of hypoxanthine, has exhibited significant activity against human leukemia.[3] Analogues of this drug have also demonstrated chemotherapeutic activity, even immunosuppressive properties. For example, azathioprine [6-(1-methyl-4-nitroimidazol-5-yl)thiopurine] has been used in patients as an immunosuppressive agent following organ transplantation.[4] In a quest for structurally similar antimetabolites which might possess potential chemotherapeutic or biological activities, we explored the imidazo[4,5-*d*]-pyridazine ring system.[5] Early reports[6] indicated that certain analogues of this ring system possess some biological activity. Recently, preliminary investigations from our laboratories[7] showed that certain 4-substituted imidazo[4,5-*d*]pyridazines, e.g., imidazo[4,5-*d*]pyridazine-4-thione (1, 4-SIP), function as substrates for the purine salvage pathway enzymes. Thus, in view of these data, we initiated an investigation aimed at synthesizing selected 4-(alkylthio)-, 4-[(arylalkyl)thio]-, and 4-(arylthio)-imidazo[4,5-*d*]pyridazines.

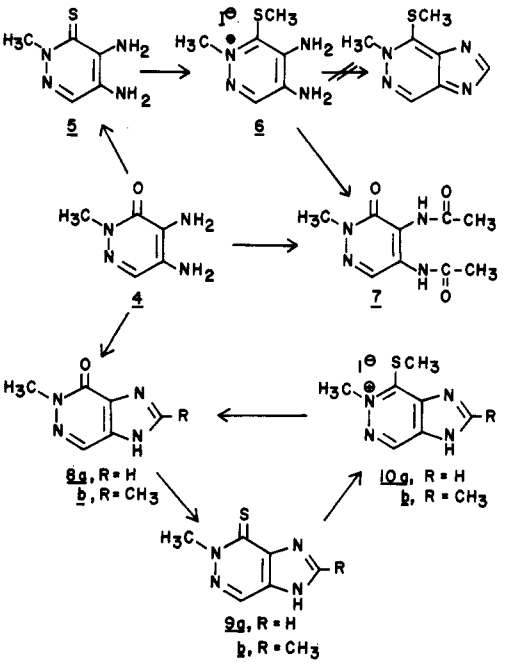
The synthesis of such analogues from 4-SIP (1)[8] was not as straightforward as anticipated. It was expected that treatment of 1 with the appropriate alkylating agent in basic media (0.5 N potassium hydroxide) would provide only the desired S-alkylated derivatives (Scheme I). A common practice in heterocyclic chemistry is to use a slight excess of alkylating agent, especially with the more volatile ones. Adoption of this practice, in our case, led to the formation of two products, the desired S-alkylated heterocycle and a S,N-dialkylated product; the latter was confirmed by elemental analysis and ^{1}H NMR spectroscopy.

The occurrence of a dialkylated heterocycle was first detected during the preparation of 4-(allylthio)imidazo-[4,5-*d*]pyridazine (**2b**). The presence of the dialkylated derivative **3b** was more noticeable in smaller runs where

Scheme I



Scheme II



the precise measurement of allyl bromide was difficult to control. We soon found that if exactly 1 equiv of allyl bromide was employed, only the S-alkylated product was formed. Treatment of **2b** with an additional amount of allyl bromide afforded the S,N-dialkylated derivative **3b**. Alternately, when 1 reacted with a twofold excess of allyl bromide, the sole product was **3b**; from TLC it was apparent that **2b** formed initially and then was converted to **3b**.

We now concentrated on the structures of **3b** and the other S,N-dialkylated heterocycles (**3a** and **3c**). The course alkylation of 6-(methylthio)purine has been rigorously established;[9] however, there is no similar study published

(1) Presented in part at the 4th Annual NERMCIAP Meeting, Storrs, CT, Apr 29, 1978; Abstract No. 9.

(2) The recipient of a University of Rhode Island Graduate Fellowship, 1979–1980.

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(4) G. B. Elion and G. H. Hitchings in "Antineoplastic and Immunosuppressive Agents", A. C. Sartorelli and D. G. Jones, Eds., Springer-Verlag, New York, Heidelberg, West Berlin, 1975, Part II, pp 404–425.

(5) For a recent review on the imidazo[4,5-*d*]pyridazine ring system see M. Tišler, and B. Stanovnik, *Chem. Heterocycl. Compds.*, **27**, 801–850 (1972).

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Table I. Ultraviolet Spectral Data for Certain Imidazo[4,5-*d*]pyridazines[a]

compd	pH	λ_{max}, nm	$10^{-3}\epsilon$	λ_{min}, nm	$10^{-3}\epsilon$	compd	pH	λ_{max}, nm	$10^{-3}\epsilon$	λ_{min}, nm	$10^{-3}\epsilon$
2a	1	300.0 sh[b]	4.92	256.5	3.82			276.5	5.35	263.0	4.75
		277.0	7.56	220.0	7.15			246.0	11.87	234.0	8.70
		237.5	11.57					219.0	16.38		
	c	272.5	8.16	243.5	3.84		11	307.0	3.33	291.0	2.99
		223.0	13.05					273.0	5.22	263.0	4.88
	11	289.5	5.07	255.5	4.90			246.0	12.14	233.5	8.34
		277.0	7.43					224.0	11.98		
		230.5	15.17			**3b**	1	314.5 sh	3.69	263.5	5.86
2b	1	303.5 sh	4.71	259.0	4.50			280.0	8.77	226.5	9.46
		278.0	8.00	222.5	8.42			244.5	14.08		
		240.0	12.30				*c*	307.5	4.92	294.0	4.57
	c	275.0	8.00	245.0	3.88			275.0	7.64	265.5	7.32
		224.5 sh	13.55	216.0	12.55			246.5	16.06	238.0	14.31
	11	278.5	7.11	256.0	4.81			221.5	25.39		
		226.5	17.49				11	310.0	4.15	293.5	3.30
2c	1	306.0 sh	11.95	256.0	10.72			273.0	6.51	266.0	6.23
		279.5	17.12	220.0	8.22			247.5	14.54	238.0	12.39
		241.5	15.65					226.0	18.93		
	c	277.5	16.13	243.0	7.40	**3c**	1	307.5 sh	11.38	255.0	20.91
		225.0 sh	17.78					272.5	23.66	229.0	15.09
	11	279.5	15.02	250.0	9.19			248.5	21.21		
		226.0	20.05				*c*	318.5 sh	9.05	258.0	20.26
2d	1	290.0	8.60	279.0	8.43			270.5	21.20	236.0	18.10
		269.0	8.62	256.5	8.04			248.5	22.16		
		234.5	15.53	226.0	8.18		11	318.5 sh	9.27	259.0	19.83
	c	315.0 sh	4.99	245.5	8.18			273.5	21.98	237.0	17.67
		264.0	9.70					250.0	21.77		
		222.0 sh	21.35					225.5	24.48		
	11	272.0	7.49	257.0	6.93	**10a**	1	300.5	10.16	258.0	2.90
		228.0	23.60					232.5	22.18		
3a	1	316.5 sh	2.29	261.0	3.46		*c*	300.5	9.95	262.5	2.90
		279.0	6.27	223.5	4.97			229.5	26.06		
		242.5	10.47				11	301.5	10.62	266.5	3.05
	c	307.0	3.28	292.5	3.04			230.5	27.31		

[a] Each compound was dissolved in water (10 mg/100 mL), and from this stock solution the final dilution was made with the appropriate solvent. [b] sh = shoulder. Full UV data for compounds **4-9**, **10b**, and **14-21** are available as supplementary material. [c] H_2O.

for 4-(methylthio)imidazo[4,5-*d*]pyridazine (**2a**) or for that matter on any imidazo[4,5-*d*]pyridazine. Like purine, this ring system has four sites available for N-alkylation and could lead to one of four possible isomers, i.e., either the S,N1-, S,N3-, S,N5-, or S,N6-dialkylated imidazo[4,5-*d*]-pyridazine.

A simple method used to determine the site of N-alkylation of aromatic heterocycles is to compare the ultraviolet spectra of the compound in question with those of a model methyl derivative which has been prepared by an umambiguous route. We chose to synthesize 5-methyl-4-(methylthio)imidazo[4,5-*d*]pyridazine as our first model derivative and followed the pathway illustrated at the top of Scheme II. 4,5-Diamino-2-methylpyridazin-3-one[10] (**4**) was required as starting material and was prepared via a four-step synthesis starting with methylhydrazine and mucochloric acid.[11] Thiation of **4** with P_2S_5 in β-picoline afforded 4,5-diamino-2-methylpyridazine-3-thione (**5**). Subsequent methylation of **5** with methyl iodide provided 4,5-diamino-2-methyl-3-(methylthio)-pyridazinium iodide (**6**), an essential precursor to the proposed 5-methyl-4-(methylthio)imidazo[4,5-*d*]pyridazine. Attempted ring closure of **6** by using either diethoxymethyl acetate,[14] *N*,*N*-dimethylformamide–phosphorus oxychloride,[15] or triethyl orthoformate–acetic anhydride failed to give the desired product. Therefore, we abandoned this route and approached the synthesis of 5-methyl-4-(methylthio)imidazo[4,5-*d*]pyridazine in another manner.

Treatment of **4** with triethyl orthoformate–acetic anhydride effected ring closure and provided a good yield of **8a**. Subsequent thiation, followed by methylation, afforded 5-methyl-4-(methylthio)imidazo[4,5-*d*]pyridazinium iodide (**10a**). We proved methylation occurred on sulfur rather than on nitrogen by warming **10a** in 0.5 N potassium hydroxide which cleanly converted it back to **8a**.[16] Replacing triethyl orthoformate with triethyl orthoacetate furnished the 2-methyl analogue **8b** and ultimately **9b** and **10b**. These derivatives played an important role in our ^{1}H NMR studies. To our surprise when **6** was treated with triethyl

(10) F. Reicheneder and K. Dury, Belgium Patent 660637; *Chem. Abstr.*, **64**, 5108*g* (1966).

(11) Reaction of mucochloric acid with methylhydrazine affords 4,5-dichloro-2-methylpyridazin-3-one (**21**). The synthesis of this heterocycle has been described by the aforementioned method[12] or by methylation of **11**.[13] The exact experimental details for use of methylhydrazine, to our knowledge, are not available in the literature, and, therefore, we have included our procedure in the Experimental Section.

(12) (a) F. Reicheneder and K. Dury, German Patent 1086238; *Chem. Abstr.*, **56**, 5982*i* (1962); (b) K. Dury, *Angew. Chem., Int. Ed. Engl.*, **4**, 292 (1965); (c) R. Schoenbecke and K. Kloimstein, *Monatsh. Chem.*, **99**, 15 (1968).

(13) (a) R. F. Homer, H. Gregory, and L. F. Wiggins, *J. Chem. Soc.*, 2191 (1948); (b) J. Bourdais, *Bull. Soc. Chim. Fr.*, 2124 (1964); (c) K. Hattori, H. Azuma, and T. Terai, Japanese Patent 9592; *Chem. Abstr.*, **68**, 59599 (1968); (d) M. Iizuka, N. Igari, and S. Ito, U.S. Patent 3496160; *Chem. Abstr.*, **73**, 16258, 1970; (e) M. Takaya, M. Sato, K. Tarashima, H. Tanizawa, and Y. Maki, *J. Med. Chem.*, **22**, 53 (1979).

(14) J. A. Montgomery and W. E. Fitzgibbon, Jr., in "Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods, And Techniques", L. B. Townsend and R. S. Tipson, Eds., Wiley-Interscience, New York, 1978, Part 2, p 995.

(15) G. L. Anderson, B. H. Rizkalla, and A. D. Broom, *J. Org. Chem.*, **39**, 937 (1974).

(16) Fifteen milligrams of **10a** was gently warmed (60 °C) in 0.5 N KOH (2 mL). Immediately the reminiscent odor of methanethiol was apparent. Within 15 min the reaction was complete. The reaction mixture was lyophilized and dissolved in Me_2SO-d_6, and a ^{1}H NMR spectrum was obtained. It was identical with that of **8a** originally prepared from **4**.

Table II. Effects on Certain Proton Chemical Shifts of Imidazo[4,5-*d*]pyridazine-4-thione (1) Caused by S-Alkylation and N-Alkylation[a]

compd	shift, δ						
	H2[b]	H7[b]	Δδ(H7 − H2)	SCH_3	NCH_3	C2 CH_3	other
1[c]	8.76	9.05					
2a	8.82	9.63	0.81	2.87			13.09 (br s, 1, NH)
2b	8.80	9.63	0.83				4.28 (d, 2, *S*-CH_2, J = 6 Hz), 5.13–5.70 (m, 2), 5.80–6.67 (m, 1)
2c	8.75	9.57	0.82				7.90 and 8.30 (AB q, 2, J = 8.5 Hz, $SCH_2C_6H_4NO_2$), 4.97 (s, 2, *S*-CH_2)
2d	8.86	9.66	0.80				3.83 (s, 3, NCH_3[d]), 8.43 (s, 1, H2[d])
17		9.34		2.77		2.62	
10b		9.47		3.33	4.43	2.73	
18		9.47		2.65	4.40	2.57	
3a	8.48	9.90	1.42	2.68	4.42		
3b	8.50	9.78	1.28				4.02 (d, 2, *S*-CH_2, J = 6 Hz), 5.00–6.00 (m, 8)
3c	8.70	10.16	1.46				4.73 (s, 2, *S*-CH_2), 6.07 (s, 2, *N*-CH_2), 7.58–8.33 (m, 8)

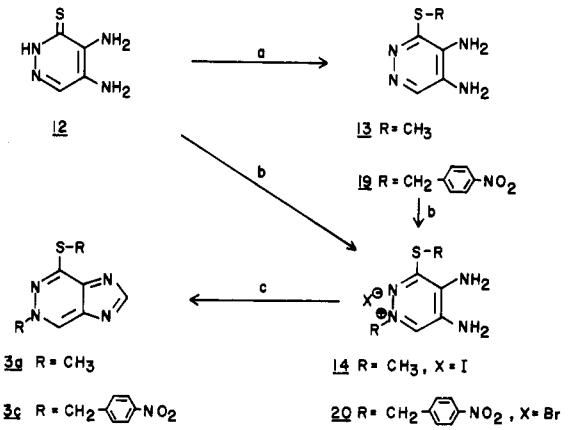
[a] All samples were dissolved in Me_2SO-d_6 containing 1% Me_4Si. Chemical shifts are in parts per million with respect to Me_4Si. Unless indicated all signals are singlets. [b] Assigned according to Martin and Castle.[8] [c] Reference 17. [d] Signals of the imidazole ring.

orthoacetate–acetic anhydride, a desulfurized, ring-opened intermediate (7) was isolated instead of the expected **10b**. It is worth mentioning that a small amount of **7** was also isolated from the annulation reaction of **4** with triethyl orthoacetate–acetic anhydride. A comparison of the ultraviolet spectra of **10a** with those of **3a** (see Table I) immediately showed that these heterocycles were different and indicated that alkylation had not occurred on the nitrogen atom (N5) adjacent to the methylthio group.

During the course of this investigation we were engaged in another study which involved the synthesis of certain 4-substituted *v*-triazolo[4,5-*d*]pyridazines. This investigation required 4,5-diamino-3-(methylthio)pyridazine (**13**, Scheme III) as one of the intermediates. Attempting to synthesize **13** from 4,5-diaminopyridazine-3-thione (**12**)[17] with the suggested amount[18] of methyl iodide produced a single, dimethylated heterocycle, the structure of which, determined by an X-ray crystallographic analysis,[19] was shown to be 4,5-diamino-1-methyl-3-(methylthio)-pyridazinium iodide (**14**). The amount of methyl iodide was indeed a critical factor in the preparation of **14**: if precisely 1 equiv of methyl iodide was used, **13** was the sole product, whereas if an excess was employed, only **14** was isolated. As with the alkylation experiments leading to **3b**, **13** could be converted to **14** in the presence of additional methyl iodide.

The structure of **14** turned out to be extremely valuable in explaining the course of alkylation of 4-SIP (**1**); furthermore, this heterocycle provided for the first time concrete evidence for the course of alkylation of 3-substituted pyridazines.[20] It had been postulated that groups which activate the adjacent nitrogen (N2), e.g., methyl (+I), gave rise to N2-alkylated derivatives whereas those substituents which deactivate this position, e.g., methylthio (−I), favored alkylation on N1. The structures of the *N*-alkyl, 3-substituted pyridazines so formed had never been confirmed by an unambiguous synthesis and were based solely on physical evidence (mainly UV spectra).[21]

Scheme III[a]



[a] (a) CH_3I or *p*-nitrobenzyl bromide (1 equiv), 0.5 N KOH; (b) CH_3I or *p*-nitrobenzyl bromide (excess), 0.5 N KOH; (c) triethyl orthoformate/acetic anhydride (**3a**), diethoxymethyl acetate (**3c**).

Indirectly, the structure of **14** also established the structural assignment of **6** as well as the direction of ring closure of mucochloric acid with methylhydrazine. Ring closures with methylhydrazine have been known[22] to produce the unexpected product, and this coupled with the wide range of melting points reported for 4,5-dichloro-2-methylpyridazin-3-one (**21**)[11] led us to believe that this might have happened in the preparation of **21**. The structure of **14** removed this doubt.

Treatment of **14** with triethyl orthoformate–acetic anhydride effected ring closure to provide 6-methyl-4-(methylthio)imidazo[4,5-*d*]pyridazine (**3a**), which was identical, in all respects, with **3a** obtained from the alkylation of **1** or **2a** with methyl iodide. Thus, we established the site of N-alkylation on **3a** as N6. An inspection of the UV spectral data for **3b** (Table I) showed them to be nearly identical with those recorded for **3a** and estab-

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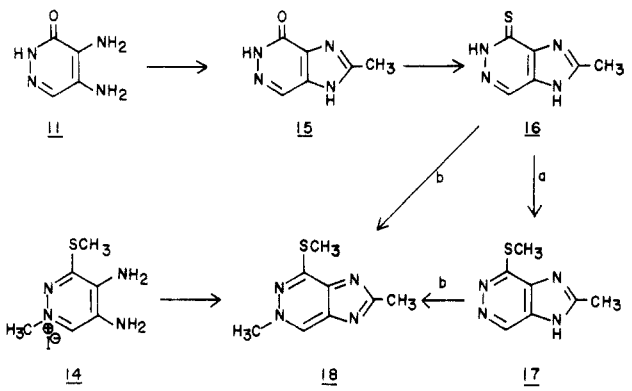
(21) G. B. Barlin and A. C. Young, *J. Chem. Soc. B*, 1261 (1971).
(22) (a) C. L. Dickenson, J. K. Williams, and B. C. McKusick, *J. Org. Chem.*, **29**, 1915 (1964); (b) S. M. Hecht and D. Werner, *J. Chem. Soc., Perkin Trans. 1*, 1903 (1973); (c) R. A. Earl, R. J. Pugmire, G. R. Revankar, and L. B. Townsend, *J. Org. Chem.*, **40**, 1822 (1975).

Scheme IV[a]



[a] (a) Methyl iodide (1 equiv), 0.5 N KOH; (b) methyl iodide (excess), 0.5 N KOH.

lished the structure of **3b** as 6-allyl-4-(allylthio)imidazo-[4,5-*d*]pyridazine; however, a similar conclusion could not be made for **3c**, since the UV spectra of **3c** did not closely resemble those of **3a**.

We felt an alternate solution to this problem might be possible by means of ^{1}H NMR spectroscopy. An earlier ^{1}H NMR study,[23] which examined the effect of quaternization on the chemical shifts of 3-methylpyridazine, tentatively assigned the structures of the N1 and N2 methiodides (which existed as a 8:2 mixture, respectively) by chemical shift arguments. The H6 signal of the N1 isomer was found to resonate at a lower field than the H6 signal of the N2 isomer. We examined the spectra of the 2-methylated analogues **10b**, **17**, and **18** (Scheme IV) for a similar trend (Table II). These three analogues allow us to concentrate entirely on the H7 signal (which corresponds to the H6 position of the pyridazine ring) and measure the effect of N-alkylation on its chemical shift. The H7 proton chemical shifts of the N5- (**10b**) and N6-(**18**) methylated analogues were deshielded as compared to the H7 chemical shift of **17**; however, in each case the magnitude was the same. The only observed influence on proton chemical shifts caused by N-methylation was on the *S*-methyl resonance of **10b**. We became convinced that these rather disappointing results were due to the absence of quaternization in **18**. Our suspicions were confirmed when the H6 chemical shift data of **6** and **14** were compared with that of **13**. It became apparent that quaternization was an extremely important factor and that a structural assignment of these two heterocycles based on the 3-methylpyridazine chemical shift arguments would have provided the correct answer. An attempt to correlate the site of N-alkylation with the chemical shift of the H7 proton for the bicyclic heterocycles was unsuccessful, but the data did reveal two interesting trends: when alkylation occurred exclusively on sulfur, the H7 signal experienced a downfield shift as compared to its chemical shift in **1**; in addition, the observed difference between the H7 and H2 ($\delta_{H7} - \delta_{H2}$) chemical shifts was found to be constant regardless of the alkyl or aryl group attached to sulfur. This difference was enhanced when the N6 position was alkylated. The heterocycle **3c** obeyed this second trend; however, a structural assignment based solely on this spectral feature would be equivocal.

Thus, we synthesized **3c** via an unambiguous pathway (Scheme III). 4,5-Diaminopyridazine-3-thione (**12**) was treated with an equimolar quantity of *p*-nitrobenzyl bromide in the presence of 0.5 N potassium hydroxide to furnish 4,5-diamino-3-[(*p*-nitrobenzyl)thio]pyridazine (**19**). N1-Alkylation with an additional amount of *p*-nitrobenzyl bromide afforded 4,5-diamino-1-(*p*-nitrobenzyl)-3-[(*p*-nitrobenzyl)thio]pyridazinium bromide (**20**). Likewise, if **12** was treated with an excess of *p*-nitrobenzyl bromide the S,N1-dialkylated species (**20**) was formed exclusively. Cyclization of **20** with diethoxymethyl acetate provided 6-(*p*-nitrobenzyl)-4-[(*p*-nitrobenzyl)thio]imidazo[4,5-*d*]-pyridazine which was identical with **3c** obtained from the alkylation of **1**. Therefore, **3c** is 6-(*p*-nitrobenzyl)-4-[(*p*-nitrobenzyl)thio]imidazo[4,5-*d*]pyridazine.

In conclusion, this study establishes the course of alkylation of 4-SIP (**1**). Alkylation occurs first on sulfur and then at position N6. Our data also support the earlier hypothesis[20] that electronic effects govern the course of N-alkylation of pyridazines. The site of N-alkylation is strongly influenced by the type of substituent (either +I or −I) residing on position C3. The addition of a second ring does not seem to alter this mode of alkylation. For example, ribosylation of 4-[(trimethylsilyl)oxy]imidazo-[4,5-*d*]pyridazine[24] leads predominantly to the N6 riboside. In view of these data, we suggest that an earlier structural assignment of 7-amino-1-(β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazine[25] should be changed to 4-amino-6-(β-D-ribofuranosyl]imidazo[4,5-*d*]pyridazine, an alternate structure considered at the time of publication.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The infrared spectra were determined in pressed potassium bromide disks with a Beckman IR-8 spectrophotometer. The ^{1}H NMR spectra were determined on a Varian A-60 or Varian EM-360A 60 MHz spectrometer. ^{13}C NMR spectra were obtained on a Varian CFT-20 at ambient temperature. A flip angle (α) of 42.5° was employed. Chemical shifts are expressed in parts per million with respect to Me_4Si. The ultraviolet absorption spectra were recorded on a Beckman DB-GT grating spectrophotometer. Thin-layer chromatography was run on precoated (0.25 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave ultraviolet light (254 nm) was used to detect the UV absorbing spots. EM silica gel 60 PF-254 was used for thick-layer and short-column chromatography. EM silica gel 60 (70–230 mesh ASTM) was employed for routine column chromatography. All solvent proportions were by volume. Evaporations were performed with a Büchi Rotovapor at 40 °C unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories.

General Procedure for the Alkylation of Imidazo[4,5-*d*]pyridazine-4-thione (1, 4-SIP). To a solution of **1** in 0.5 N KOH was added the desired alkylating agent. The reaction mixture was stirred at room temperature and monitored by TLC. When the reaction was complete, the precipitate which formed was collected by filtration, washed with cold water (ca. 2 × 10 mL), dried, and crystallized from ethanol–water. If no precipitate formed, the excess solvent was removed in vacuo, and the crude residue was crystallized from ethanol–water. When an excess of alkylating agent was used, the two products formed were separated either by fractional crystallization or by silica gel column chromatography. Chromatographic fractions containing the individual heterocycles were pooled and evaporated to dryness, and the pure solids were recrystallized from ethanol–water (see Table III).

6-Methyl-4-(methylthio)imidazo[4,5-*d*]pyridazine (3a). From Ring Closure of 14. A mixture of **14** (1.36 g, 4.6 mmol), triethyl orthoformate (5.8 mL), and acetic anhydride (5.8 mL) was heated at reflux for 5 h. The solvent was removed in vacuo, and the residue was partially purified on a short column (3 × 3

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Table III. Alkylating of Imidazo[4,5-*d*]pyridazine-4-thione (1, 4-SIP) at Room Temperature

alkylating agent (mmol)	amt of 4-SIP, mmol	amt of 0.5 N KOH, mL	reaction time, h	product[a] (% yield)	purification procedure	crystallizing solv	mp, °C
methyl iodide (88.3)	85.0	170	18	**2a** (63)	fractional cryst	95% EtOH	242[b]
				3a (1)	fractional cryst	95% EtOH	229-230
allyl bromide (11.2)	9.21	20	2[c]	**2b** (63)	column chromatog[d]	50% EtOH	158-159
				3b (8.5)	column chromatog	none	87-88
(2.0)	2.0	4	2	**2b**[e] (65)	crystallization	50% EtOH	
(10.0)	4.0	20	24	**3b**[e,f] (68.5)	column chromatog[g]	none	
p-nitrobenzyl bromide (3.96)	3.3	6.6	11[c]	**2c** (11)	column chromatog[h]	95% EtOH	237-238
				3c (9)	column chromatog	95% EtOH	244-245
(9.2)	9.2	22	3	**2c**[i] (96)	crystallization	95% EtOH	
(1.25)	0.5	2.5	20	**3c**[i] (71)	crystallization	95% EtOH	
5-chloro-4-nitro-1-methylimidizole[j] (7.2)	6.6	15	18[k]	**2d** (66)	crystallization	90% EtOH	267-268

[a] Satisfactory analyses (C, H, N, S; ±0.4%) were obtained for **2b-d** and **3a-c**. [b] Lit.[8] 234-235 °C. [c] Allowed to stand 12 h at 4 °C. [d] Eluent, chloroform-ethanol (99.6:0.4); **2b** was the second compound off of the column. [e] The UV, IR, and ^{1}H NMR spectra of **2b** and **3b**, as well as their respective mixture melting points, showed them to be identical with their aforementioned counterparts. [f] TLC indicated **2b** was formed in 2 h and then was gradually converted to **3b**. [g] Eluent, chloroform-methanol (99:1). [h] Eluent, chloroform-ethanol (95:5); **2c** was the first compound off of the column. [i] The UV, IR, and ^{1}H NMR spectra of **2c** and **3c**, as well as their respective mixture melting points, showed them to be identical with their counterparts isolated by column chromatography. [j] Reference 26. [k] Allowed to stand an additional 4 h at 4 °C.

cm) by using chloroform–methanol (9:1) as eluent. The fractions containing **3a** were pooled and evaporated to dryness under diminished pressure. The residue was applied to a thick-layer plate (2 mm) and developed with chloroform–methanol (8:2). This material was crystallized from 95% ethanol to provide 300 mg or pure **3a** (36.5%) as light yellow needles, mp 229–230.5 °C. This material was identical (mixture melting point, UV, IR, and ^{1}H NMR) with **3a** isolated from the alkylation of **1**.

6-Allyl-4-(allylthio)imidazo[4,5*d*]pyridazine (3b). From 2b with Excess Allyl Bromide. 4-(Allylthio)imidazo[4,5-*d*]-pyridazine (**2b**; 192 mg, 1.0 mmol) was dissolved in 5.0 mL of 0.5 N KOH, and to this solution was added an excess of allyl bromide (0.13 mL, 1.5 mmol). The reaction mixture was stirred at room temperature for 24 h and then worked up as described in Table III to furnish 150 mg of pure **3b** (65%). This heterocycle was identical (UV, IR, ^{1}H NMR, and mixture melting point) with **3b** isolated from the alkylation **1**.

6-(*p*-Nitrobenzyl)-4-[(*p*-nitrobenzyl)thio]imidazo[4,5-*d*]pyridazine (3c). From Ring Closure of 20. 4,5-Diamino-1-(*p*-nitrobenzyl)-3-[(*p*-nitrobenzyl)thio]pyridazinium bromide (**20**; 269 mg, 0.55 mmol) was stirred in diethoxymethyl acetate,[14] and the mixture heated at 100 °C for 2 h. The reaction was allowed to cool to room temperature, and the excess solvent was removed under diminished pressure. The residue was crystallized from 95% ethanol to afford 168 mg (72.4%) of **3c** as yellow needles; UV, IR, ^{1}H NMR, and mixture melting point indicated that this heterocycle was identical with **3c** isolated from the alkylation of **1**.

4,5-Diamino-2-methylpyridazine-3-thione (5). Phosphorus pentasulfide (Alfa; 4.75 g, 21.4 mmol) was added to a stirred suspension of 4,5-diamino-2-methylpyridazin-3-one[10] (**4**; 2 g, 14.3 mmol) in β-picoline (120 mL). The mixture was heated at reflux for 5 h. After this period, the reaction was allowed to cool to room temperature, and the β-picoline was removed in vacuo. Ice-cold water (ca. 100 mL) was added to the syrupy residue and the mixture allowed to reach room temperature. The mixture was then heated on a steam bath for 2 h, and a 10% aqueous sodium hydroxide solution was added dropwise until all of the suspended solid dissolved. The hot solution was treated with Norit and filtered through a Celite pad. The filtrate was carefully acidified to pH 1 with concentrated HCl. A yellow precipitate formed during the acidification procedure. The mixture was allowed to stand at 4 °C for 18 h. The solid material was collected by filtration, washed with cold, distilled water (2 × 20 mL), and air-dried to provide 1.33 g of **5** (59.7%). An analytical sample was recrystallized from 95% ethanol to furnish **5** as golden needles: mp 229–231 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 4.08 (s, 3, NCH_3), 5.83 (br s, 2, NH_2), 5.97 (br s, 2, NH_2), 7.83 (s, 1, H6).

Anal. Calcd for $C_5H_8N_4S$: C, 38.45; H, 5.16; N, 35.87; S, 20.53. Found: C, 38.54; H, 5.15; N, 36.01; S, 20.57.

4,5-Diamino-2-methyl-3-(methylthio)pyridazinium Iodide (6). 4,5-Diamino-2-methylpyridazine-3-thione (**5**; 2.1 g, 13.4 mmol) and methyl iodide (30 mL) were heated under gentle reflux for 24 h. After the mixture cooled to room temperature, the precipitate was collected by filtration and crystallized from 95% ethanol to provide a quantitative yield of **6** (4.0 g). An analytical sample was obtained by recrystallization from 95% ethanol: mp 199–203 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.53 (s, 3, SCH_3), 4.41 (s, 3, NCH_3), 6.91 (br s, 2, NH_2), 7.78 (br s, 2, NH_2), 8.32 (s, 1, H6); ^{13}C NMR[27] (Me_2SO-d_6) 16.2 (SCH_3), 49.7 (NCH_3), 132.5 (C6), 134.9 (C3), 137.1, 137.5 ppm.

Anal. Calcd for $C_6H_{11}N_4SI$: C, 24.17; H, 3.72; N, 18.79. Found: C, 24.33; H, 3.56; N, 19.11.

4,5-Diacetamido-2-methylpyridazin-3-one (7). 4,5-Diamino-2-methyl-3-(methylthio)pyridazinium iodide (**6**; 1.44 g, 4.83 mmol), triethyl orothoacetate (23 mL) and acetic anhydride (23 mL) were heated at reflux for 3 h and then allowed to cool to room temperature. The excess solvent was removed in vacuo. The solid residue was triturated with ethanol, filtered, and then crystallized from 95% ethanol to furnish **7**: 360 mg (38.3%); mp 195–196 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (s, 3, $COCH_3$), 2.17 (s, 3, $COCH_3$), 3.70 (s, 3, NCH_3), 8.47 (s, 1, H6), 9.35 (br s, 1, NH), 9.65 (br s, 1, NH).

Anal. Calcd for $C_9H_{12}N_4O_3$: C, 48.04; H, 5.73; N, 24.90. Found: C, 48.31; H, 5.65; N, 25.19.

5-Methylimidazo[4,5-*d*]pyridazin-4-one (8a). 4,5-Diamino-2-methylpyridazin-3-one[10] (**4**; 4 g, 28.5 mmol) was added to a solution of triethyl orthoformate (24 mL) and acetic anhydride (24 mL), and the mixture was heated at reflux for 3.5 h. After the reaction mixture was allowed to cool to room temperature, the precipitate which had formed was collected by filtration, washed with cold, absolute ethanol (2 × 10 mL), and air-dried. The crystalline solid was recrystallized from 95% ethanol to provide 4.07 g (95%) of **8a**. An analytical sample was recrystallized from 95% ethanol to afford **8a** as white needles: mp 225–227 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.82 (s, 3, NCH_3), 8.50 (br s, 2, H2 and H7).

Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.00; H, 3.90; N, 37.52.

2,5-Dimethylimidazo[4,5-*d*]pyridazin-4-one (8b), and 4,5-Diacetamido-2-methylpyridazin-3-one (7). A mixture of **4**[10] (5 g, 35.7 mmol), triethyl orthoacetate (30 mL), and acetic anhydride (30 mL) was stirred and heated at reflux for 4.5 h. The reaction was allowed to cool, and then the solvent was removed in vacuo until precipitation occurred. The solid was collected by filtration, washed with cold, absolute ethanol, and crystallized

(27) Off-resonance decoupling experiments verified the assignment of C6.

from 95% ethanol to furnish crystalline **8b**: 1.5 g (25.6%); mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.43 (s, 3, C2 CH_3), 3.68 (s, 3, NCH_3), 8.22 (s, 1, H7).

Anal. Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.12. Found: C, 51.17; H, 4.90; N, 34.44.

The original filtrate and wash were combined and evaporated in vacuo to dryness. This residue was applied to a silica gel column (150 g, 4.5 × 23.5 cm), and the column was eluted with chloroform–methanol (99:1) to give 310 mg (3.9%) of **7**. This heterocycle was identical (chromatographic mobility, IR, UV, and ^{1}H NMR) with **7** prepared from the attempted cyclization of **6**.

5-Methylimidazo[4,5-*d*]pyridazine-4-thione (9a). To a stirred mixture of **8a** (3.72 g, 26.7 mmol) in 180 mL of β-picoline was added P_2S_5 (8.9 g, 40 mmol). The mixture was heated at reflux for 6.5 h and then worked up in a manner similar to that described for **5**. Crystallization from 95% ethanol afforded **9a** (800 mg, 18%) as plates: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 4.25 (s, 3, NCH_6), 8.63 (s, 1, H2), 8.96 (s, 1, H7).

Anal. Calcd for $C_6H_6N_4S$: C, 43.36; H, 3.64; N, 33.71. Found: C, 43.26; H, 3.51; N, 33.74.

2,5-Dimethylimidazo[4,5-*d*]pyridazine-4-thione (9b). 2,5-Dimethylimidazo[4,5-*d*]pyridazin-4-one (**8b**; 1.0 g, 6.1 mmol), P_2S_5 (2.03 g, 9.1 mmol), and β-picoline (50 mL) were reacted in a manner similar to that described for **9a**. After the workup, the crude solid was purified on a silica gel column (50 g, 3.5 × 14.0 cm) with chloroform–methanol (99:1) as the eluent to give 300 mg (27.3%) of **9b**. An analytical sample was obtained by recrystallization from 95% ethanol to furnish **9b** as light, yellow needles: mp 261.5–262 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.53 (s, 3, C2 CH_3), 4.17 (s, 3, NCH_3), 8.70 (s, 1, H7).

Anal. Calcd for $C_7H_8N_4S$: C, 46.65; H, 4.47; N, 31.09; S, 17.79. Found: C, 46.59; H, 4.55; N, 31.21; S, 17.59.

5-Methyl-4-(methylthio)imidazo[4,5-*d*]pyridazinium Iodide (10a). A mixture of 5-methylimidazo[4,5-*d*]pyridazine-4-thione (**9a**; 400 mg, 2.4 mmol) and methyl iodide (6 mL) was heated under gentle reflux for 48 h and cooled to room temperature. The crystalline precipitate was removed by filtration and recrystallized from absolute ethanol to give **10a** (0.33 g, 76%) as crystals: mp 268–271 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.38 (s, 3, SCH_3), 4.43 (s, 3, NCH_3), 9.07 (s, 1, H2), 9.53 (s, 1, H7).

Anal. Calcd for $C_7H_9N_4SI$: C, 27.28; H, 2.94; N, 18.18; S, 10.40. Found: C, 27.39; H, 2.84; N, 17.98; S, 10.15.

2,5-Dimethyl-4-(methylthio)imidazo[4,5-*d*]pyridazinium Iodide (10b). 2,5-Dimethylimidazo[4,5-*d*]pyridazine-4-thione (**9b**; 100 mg, 0.55 mmol) was suspended in 5 mL of methyl iodide, and the mixture was heated at gentle reflux for 2 h. After the mixture cooled to room temperature, the precipitate was collected by filtration, washed with absolute ethanol (5 mL), and recrystallized from absolute ethanol to furnish 102 mg (57.6%) of **10b**, mp 158.5–160.5 °C.

Anal. Calcd for $C_8H_{11}N_4SI$: C, 29.83; H, 3.44; N, 17.39; S, 9.95. Found: C, 29.95; H, 2.87; N, 17.33; S. 10.15.

4,5-Diamino-1-methyl-3-(methylthio)pyridazinium Iodide (14). Method A. To a solution of **12**[17] (2.67 g, 18.8 mmol) in 54 mL of 0.5 N KOH was added methyl iodide (9 mL, 143 mmol), and the reaction mixture was stirred at room temperature in a tightly stoppered flask for 17 h. The precipitate which formed was removed by filtration, and a small quantity was examined by TLC (chloroform–methanol, 8:2). This solid was shown to be contaminated with trace amounts of **13** and therefore was resuspended in 54 mL of 0.5 N KOH containing 9 mL of methyl iodide. After the mixture was stirred an additional 24 h at room temperature, the solid material was collected by filtration and crystallized from 95% ethanol to afford 1.96 g (61%) of **14** as yellow needles: mp 261–262 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.63 (s, 3, SCH_3), 4.23 (s, 3, NCH_3), 6.69 (br s, 2, NH_2), 7.27 (br s, 2, NH_2), 8.50 (s, 1, H6); ^{13}C NMR[27] (Me_2SO-d_6) 13.3 (SCH_3), 49.6 (NCH_3), 128.8 (C6), 132.1, 133.2, 143.8 (C3) ppm.

Anal. Calcd for $C_6H_{11}N_4SI$: C, 24.17; H, 3.72; N, 18.79. Found: C, 24.31; H, 3.56; N, 19.06.

Method B. 4,5-Diamino-3-(methylthio)pyridazine (**13**; 1.56 g, 10 mmol) was dissolved in 25 mL of 0.5 N KOH containing methyl iodide (0.78 mL, 12.5 mmol). The reaction mixture was stirred at room temperature for 24 h, and the precipitate which formed was collected by filtration. Examination of the solid by TLC indicated that the reaction was incomplete. The solid was resuspended in 0.5 N KOH (16 mL) and methyl iodide (1 mL, 16 mmol) and stirred for an additional 40 h at room temperature. The solid material was removed by filtration and crystallized from 95% ethanol to furnish **14** (0.65 g, 22%). UV, IR, ^{1}H NMR, and a mixture melting point indicated that this heterocycle was identical with **14** prepared by method A.

2-Methylimidazo[4,5-*d*]pyridazin-4-one (15). A mixture of **11**[10] (5 g, 39.6 mmol), triethyl orthoacetate (30 mL), and acetic anhydride (30 mL) was heated at reflux for 4 h and then allowed to cool to room temperature. The precipitate was collected by filtration, washed with ethanol (2 × 10 mL), and crystallized from ethanol–water (8:2) to provide **15** (4.94 g, 83%) as fine needles: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.52 (s, 3, C2 CH_3), 8.30 (s, 1, H7), 11.34 (br s, 1, NH), 12.40 (br s, 1, NH).

Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.37; H, 4.08; N, 37.54.

2-Methylimidazo[4,5-*d*]pyridazine-4-thione (16). To a stirred suspension of **15** (4.53 g, 30 mmol) in dry pyridine (160 mL) was added P_2S_5 (14.56 g, 66 mmol). The mixture was heated at reflux for 5 h and then worked up according to the procedure described for **5**, with one exception, that the crystallization solvent was water–ethanol (6:4). This procedure provided 3.60 g (72%) of **16**. An analytical sample was prepared by recrystallization from the same mixed solvent to give **16** as white needles: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.59 (s, 3, C2 CH_3), 8.79 (s, 1, H7), 13.65 (br s, 1, NH), 14.35 (br s, 1, NH).

Anal. Calcd for $C_6H_6N_4S$: C, 43.36; H, 3.64; N, 33.71; S, 19.29. Found: C, 43.16; H, 3.54; N, 33.16; S, 19.29.

2-Methyl-4-(methylthio)imidazo[4,5-*d*]pyridazine (17). To a solution of **16** (2.06 g, 12.4 mmol) in 26 mL of 0.5 N KOH was added methyl iodide (0.73 mL, 12.4 mmol). The reaction mixture was stirred at room temperature for 9 h, and the solid which precipitated was collected by filtration. This solid was washed with absolute ethanol (2 × 10 mL) and then crystallized from ethanol–water (8:2) to provide 1.34 g (60%) of **17** as small, yellow granules. Recrystallization of **17** from ethanol–water (8:2) furnished an analytical sample, mp 270–272 °C.

Anal. Calcd for $C_7H_8N_4S$: C, 46.65; H, 4.47; N, 31.09. Found: C, 46.98; H, 4.91; N, 31.30.

2,6-Dimethyl-4-(methylthio)imidazo[4,5-*d*]pyridazine (18). Method A. 2-Methylimidazo[4,5-*d*]pyridazine-4-thione (**16**; 330 mg, 2 mmol) was dissolved in 10 mL of 0.5 N KOH, and to this solution was added methyl iodide (0.31 mL, 5 mmol). The reaction mixture was stirred at room temperature for 24 h. The resulting precipitate was collected by filtration, washed with cold, absolute ethanol (2 × 5 mL), and then crystallized from absolute ethanol to give 270 mg (71%) of **18** as white needles, mp 241–242 °C.

Anal. Calcd for $C_8H_{10}N_4S$: C, 49.46; H, 5.19; N, 28.84; S, 16.51. Found: C, 49.48; H, 5.05; N, 29.04; S, 16.29.

Method B. 2-Methyl-4-(methylthio)imidazo[4,5-*d*]pyridazine (**17**; 180 mg, 1 mmol), methyl iodide (0.1 mL, 1.5 mmol), and 0.5 N KOH (3 mL) were reacted in a manner similar to that described in method A to furnish 130 mg (68%) of **18**. UV, IR, chromatographic mobilities, and a mixture melting point indicated **18** was identical with an authentic sample prepared by method A.

Method C. A mixture of **14** (200 mg, 0.67 mmol), triethyl orthoacetate (3 mL), and acetic anhydride (3 mL) was heated at reflux for 3 h and then cooled to room temperature. The excess solvent was removed in vacuo, and the residue was purified on a short column by using chloroform–methanol (10:1) as eluent to provide 60 mg (46%) of **18**. This heterocycle was identical, in all respects, with an authentic sample prepared by method A.

4,5-Diamino-3-[(*p*-nitrobenzyl)thio]pyridazine (19). To a solution of **12** (284 mg, 2 mmol) in 4 mL of 0.5 N KOH was added *p*-nitrobenzyl bromide (432 mg, 2 mmol). The reaction mixture was stirred at room temperature for 3 h. The precipitate which formed was collected by filtration, washed with ethanol (2 × 5 mL), and crystallized from 95% ethanol. Recrystallization of this solid from 95% ethanol afforded **19** (343 mg, 62%) as clusters of orange crystals: mp 206–207 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 4.67 (s, 2, $SCH_2C_6H_4NO_2$), 5.27 (br s, 2, NH_2), 5.65 (br s, 2, NH_2), 7.74 and 8.24 (AB q, 4, $SCH_2C_6H_4NO_2$, J = 9.5 Hz), 8.25 (s, 1, H6).

Anal. Calcd for $C_{11}H_{11}N_5O_2S$: C, 47.64; H, 4.00; N, 25.25; S, 11.56. Found: C, 47.68; H, 4.07; N, 25.21; S, 11.40.

4,5-Diamino-1-(*p*-nitrobenzyl)-3-[(*p*-nitrobenzyl)thio]-pyridazinium Bromide (20). Method A. 4,5-Diaminopyridazine-3-thione (12; 284 mg, 2 mmol) was dissolved in 10 mL of 0.5 N KOH, and to this solution was added *p*-nitrobenzyl bromide (1.08 g, 5 mmol). The reaction mixture was stirred at room temperature for 20 h. The resulting precipitate was collected by filtration, washed with ethanol (2 × 5 mL), and crystallized from 95% ethanol to provide 500 mg (50%) of **20** as yellow needles: mp 255–256 °C dec; ^{1}H NMR[28] (Me_2SO-d_6) δ 4.73 (s, 2, $SCH_2C_6H_4NO_2$), 5.97 (s, 2, $NCH_2C_6H_4NO_2$), 7.00 (br s, 2, NH_2).

Anal. Calcd for $C_{18}H_{17}N_6O_4SBr$: C, 43.82; H, 3.47; N, 17.03. Found: C, 44.04; H, 3.43; N, 16.89.

Method B. *p*-Nitrobenzyl bromide (32.4 mg, 0.15 mmol) was added to a solution of **19** (27.7 mg, 0.1 mmol) in 0.3 mL of 0.5 N KOH, and the mixture was stirred at room temperature for 20 h. The precipitated solid was removed by filtration, washed with absolute ethanol (5 mL), and crystallized from 95% ethanol to give 32 mg (65%) of **20** as needles. This heterocycle was identical (chromatographic mobility, UV, IR, and mixture melting point) with **20** prepared by method A.

4,5-Dichloro-2-methylpyridazin-3-one (21). To a three-necked, round-bottomed flask (500 mL), fitted with a condenser and dropping funnel, were added mucochloric acid (50 g, 300 mmol; Aldrich) and absolute ethanol (255 mL). The resulting solution was mechanically stirred and cooled to 5 °C. To this cooled solution was added methylhydrazine (21 mL, 300 mmol) dropwise, while the temperature was carefully maintained at 5 °C. After the addition of the methylhydrazine was complete, the reaction mixture was allowed to stir at 5 °C for 1 h and come to room temperature, and it was then heated at reflux for 4 h. After cooling to room temperature, the solution was concentrated under diminished pressure to ca. 150 mL. When the mixture was allowed to stand, pale yellow crystals formed. The crystalline material was collected by filtration and recrystallized from ethanol–water (9:1) to furnish 39 g (72.4%) of pure **21**: mp 88–89 °C (lit. mp 78–79 °C,[12a] 134–144 °C,[12b] 89–90 °C[13e]); ^{1}H NMR (Me_2SO-d_6) δ 3.75 (s, 3, NCH_3), 8.20 (2, 1, H6).

(28) The signal of the other amino group was buried among the signals of the aromatic protons. This was confirmed by D_2O exchange. We were unable to assign the chemical shifts of the *p*-nitrobenzyl moiety protons. The low-field (δ 7.62, 8.43) doublets of both sets were visible (J = 9.5 Hz); however, the high-field signals of each quartet were merged together.

Acknowledgment. The authors thank Professor Elie Abushanab for running the ^{13}C NMR spectra and for many helpful discussions. We also thank Professor George Osborne and Ms. Sylvia Stoner for technical assistance.

Registry No. **1**, 22121-15-9; **2a**, 22121-14-8; **2b**, 76756-49-5; **2c**, 76756-50-8; **2d**, 76756-51-9; **3a**, 76756-52-0; **3b**, 76756-53-1; **3c**, 76756-54-2; **4**, 4725-76-2; **5**, 76756-55-3; **6**, 76756-56-4; **7**, 76756-57-5; **8a**, 76756-58-6; **8b**, 76756-59-7; **9a**, 76756-60-0; **9b**, 76756-61-1; **10a**, 76756-62-2; **10b**, 76756-63-3; **11**, 28682-73-7; **12**, 28682-74-8; **13**, 28682-75-9; **14**, 76756-64-4; **15**, 76756-65-5; **16**, 76756-66-6; **17**, 76756-67-7; **18**, 76756-68-8; **19**, 76756-69-9; **20**, 76756-70-2; **21**, 933-76-6; methyl iodide, 74-88-4; allyl bromide, 106-95-6; *p*-nitrobenzyl bromide, 100-11-8; 5-chloro-4-nitro-1-methylimidazole, 4897-25-0; mucochloric acid, 87-56-9; methylhydrazine, 60-34-4.

Supplementary Material Available: Ultraviolet spectral data of compounds 4–10 and 14–21 (4 pages). Ordering information is given on any current masthead page.

A General Approach to 4-Substitution of 2-Alkylfurans

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Received February 11, 1981

Treatment of 2-alkylfurans with butyllithium followed by diphenyl disulfide yields 2-(phenylthio)-5-alkylfurans. When the 2-(phenylthio)-3-bromo-5-alkylfurans arising by bromination of the latter are treated with *tert*-butyllithium, the corresponding 3-lithio derivative is produced and it can be trapped by electrophiles such as alkyl iodides, aldehydes, trimethylsilyl chloride, and carbon dioxide. Raney nickel desulfurization of the product of such trapping produces 4-substituted-2-alkylfurans.

The substitution behavior of 2-alkylfurans has been known for many years.[1] Electrophilic substitution gives the product of attack at the 5-position as the major product, if problems of polysubstitution and destruction of the furan nucleus can be overcome.[1,2] Alternatively 2,5-disubstituted furans can be prepared by removal of the acidic 5-furyl hydrogen by an alkyllithium reagent followed by quenching of the resulting carbanion with a suitable electrophile.[3]

In cases where a different substitution pattern has been sought, recourse is usually made to synthesis of the furan ring from acyclic precursors[4a] or lactones[4b] in which the desired groups (or suitable equivalents) are already present. It was our desire to develop a convenient method of

Scheme I

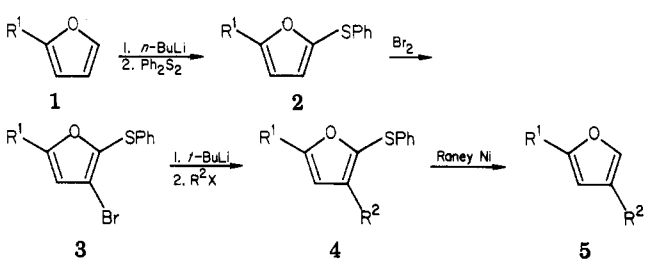

Table I. Phenylsulfenylation of Furans (1 → 2)

R^1	% yield	R^1	% yield
n-C_6H_{17}	95	$CH(OC_2H_5)_2$	71
CH_3	85	H	42
n-C_4H_9	61	SPh	0

(1) Dunlop, A. P.; Peters, F. N. "The Furans"; Reinhold: New York, 1953; p 29. (b) Paquette, L. A. "Modern Heterocyclic Chemistry"; Benjamin: Reading, MA, 1968; pp 102–149.

(2) Friedel–Crafts alkylation, for instance, is generally unsuccessful as the furan ring is destroyed by the harsh conditions.[1]

(3) (a) Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216. (b) Buchi, G.; Wuest, H. *Ibid.* **1966**, *31*, 977. (c) Lie Ken Jie, M. S. F.; Lam, C. H. *Chem. Phys. Lipids* **1978**, *21*, 275.

0022-3263/81/1946-2473$01.25/0 © 1981 American Chemical Society