83. Pteridines

Part XLII[1])

Synthesis and Properties of 8-Substituted 2,4-Dithiolumazines

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Condensation reactions of the 5-amino-6-(subst. amino)-2,4-dithiouracils **12** and **13** with diacetyl or benzil led to the 6,7,8-trisubstituted 2,4-dithiolumazines **14–16**. Methylation of these compounds affected both thio functions forming various types of 2,4-bis(methylthio)lumazine derivatives depending on the nature of the substituents at C(7) and N(8). The 6,7,8-trimethyl-2,4-dithiolumazine (**14**) was converted into 7,8-dihydro-6,8-dimethyl-7-methyl-idene-2,4-bis(methylthio)pteridine (**17**), whereas the 8-methyl-6,7-diphenyl-(**15**) and the 8-(2-hydroxyethyl)-6,7-di-phenyl-2,4-dithiolumazine (**16**) yielded the corresponding covalent inter- or intramolecular 7,8-adducts **18–21**. The unusual structures were proven by spectroscopic means and those of the alcohol adducts **20** and **21**, furthermore, confirmed by X-ray analysis.

1. Introduction. – The 8-substituted lumazines [2–4] show interesting chemical and physical properties due to the special quinonoid-type π-electron distribution in such molecules. Gradual substitution of the O-atoms by S-atoms led to the formation of 8-substituted 2-thio- [5] and 4-thiolumazines [1] and will now be extended to the 8-substituted 2,4-dithiolumazine series. This type of compounds can be regarded as model substances for the anticipated synthesis of 6,7-dimethyl-8-(D-ribityl)-2,4-dithiolumazine, a potential antagonist of the naturally occurring precursor [6] [7] in riboflavin biosynthesis. So far, 8-substituted 2,4-dithiolumazines have not been synthesized and described in the literature.

2. Syntheses. – Difficulties encountered on the direct thiation reaction of 8-substituted lumazines and 2-thiolumazines prompted us to look for another synthetic approach leading to the 8-substituted 2,4-dithio analogs. Starting the synthesis from 6-(subst. amino)-2-thiouracils [5] had also little success since only the 6-[(2-hydroxyethyl)amino]-2-thiouracil could be converted into the 2,4-dithio derivative **11** by P_4S_{10} in a low 8% yield. Attempts to transform 2-thiobarbituric acid (**1**) into 4-chloro-2-thiouracil by $POCl_3$ in presence of various tertiary amines under a broad variety of reaction conditions were also unsuccessful. However, we noticed that **1** reacted with a 2:1 mixture of $POCl_3$ and N,N-diethylaniline under reflux to a single product in almost quantitative yield which turned out to be bis(4,6-dichloropyrimidin-2-yl) disulfide (**2**). This reaction was unex-

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pected and without any precedence in literature, since we have to assume that POCl$_3$ functions in this case also as an oxidizing agent. *Brown* [8] mentioned a similar reaction, however, without reporting experimental details, *i.e.* the transformation of 2-thiouracil with POCl$_3$/PCl$_5$ to bis(4-chloropyrimidin-2-yl) disulfide. Since PCl$_5$ possesses oxidative properties, a mechanistic explanation of this reaction is more obvious.

The easy availability of **2** allowed then a selective buildup of monomeric uracil derivatives. Simple acid- and base-catalyzed hydrolyses as well as reductive hydrolyses, however, did not lead to any definite reaction product. Treatment with NaHS always yielded trithiobarbituric acid (**5**), but a more selective monosubstitution of one Cl-atom

Scheme 1
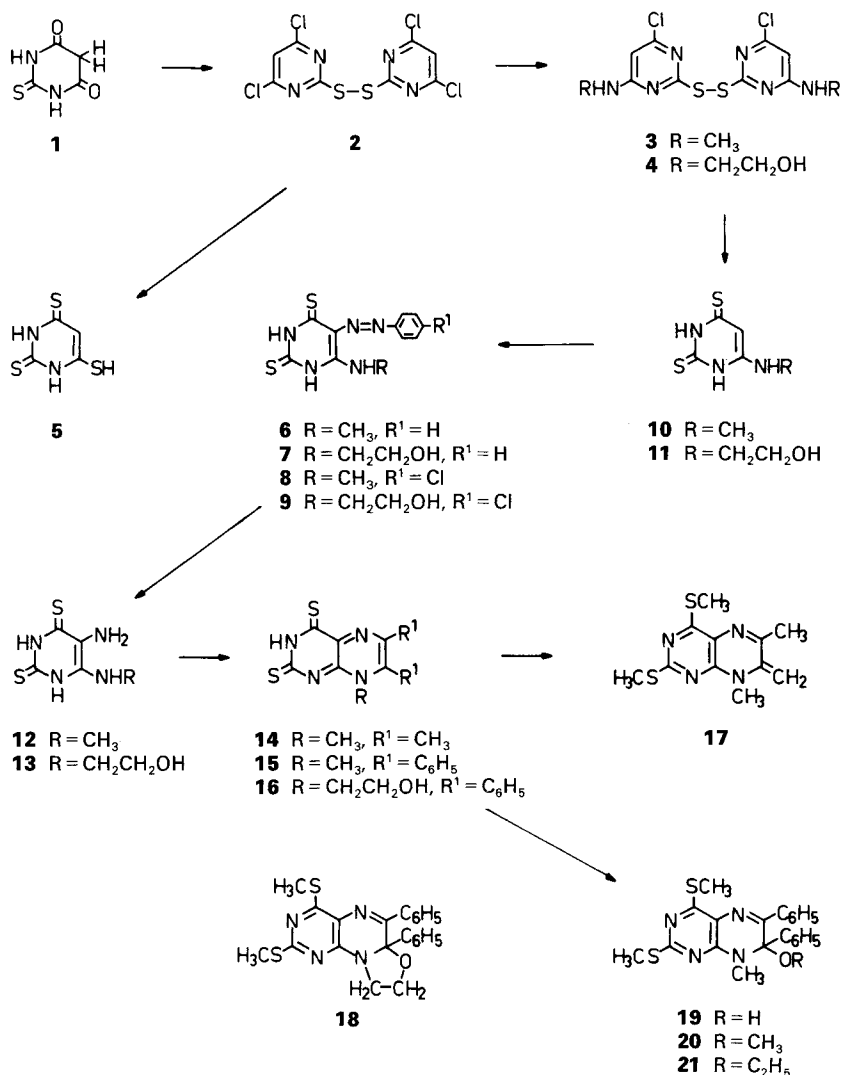
or the simple reductive cleavage of the disulfide bond could not be achieved. Also the mild reductive scission of the disulfide bond by triphenylphosphane [9] was unsuccessful yielding a large number of products.

Fortunately, a more controlled reaction of 2 took place with primary amines which preferentially induced a displacement of one Cl-atom in either pyrimidine moiety. Thus, with MeNH$_3$AcO/MeNH$_2$ at room temperature, bis[4-chloro-6-(methylamino)-pyrimidin-2-yl] disulfide (3) was obtained in 89% yield. Treatment of 3 with NaHS led then to 6-(methylamino)-2,4-dithiouracil (10). The latter could also be obtained in a one-pot reaction from 2 in a subsequent stepwise manner with the same reagents. By this procedure, 6-[(2-hydroxyethyl)amino]-2,4-dithiouracil (11) was prepared in an overall yield of 70%. Both 10 and 11 coupled in excellent yields with the phenyldiazonium or 4-chlorophenyldiazonium cation to the corresponding 5-arylazo derivatives 6–9. Reduction of the azo function was then best performed by (NH$_4$)$_2$S but was also achieved with sodium dithionite, giving the unexpectedly stable 5-amino-6-(methylamino)- (12) and 5-amino-6-[(2-hydroxyethyl)amino]-2,4-dithiouracil (13), respectively, which could be recrystallized from H$_2$O as free base or from dilute HCl solution as hydrochloride salt.

Condensation reactions of 12 and 13 with diacetyl or benzil were not so straightforward as in other analogous cases due to difficulties in purification of the products 14–16. The 8-substituted 2,4-dithiolumazines are light-sensitive and show also some lability on acid treatment, thus explaining the moderate yields of the acid-catalyzed condensations.

Furthermore, we were interested in the methylation of the 8-substituted 2,4-dithiolumazines, allowing for additional characterization of this type of compounds. Treatment of 14 with dimethyl sulfate in alkaline medium resulted in methylation at each S-atom, yielding 7,8-dihydro-6,8-dimethyl-7-methylidene-2,4-bis(methylthio)pteridine (17) in which the 7-methylidene group is due to a relatively high C–H acidity of the 7-CH$_3$ group. The structure of this compound was deduced from its ^{1}H-NMR spectrum (AB pattern for CH$_2$=C(7)). Analogous structures have formerly been found in the lumazine [3] [10] and pterin [11] [12] series.

Methylation of 15 led to additional pseudo-base formation in neutral medium by nucleophilic addition of OH$^-$ to the C(7) position (→19). In good yields, the OH group of 7,8-dihydro-7-hydroxy-8-methyl-2,4-bis(methylthio)-6,7-diphenylpteridine (19) could be displaced by alkoxy groups using alcohols in an acid-catalyzed acetalization (→20 and 21). The structures of the alkoxy derivatives 20 and 21 were unambiguously proven by X-ray analyses (see below).

When the methylation was applied to 8-(2-hydroxyethyl)-6,7-diphenyl-2,4-dithiolumazine (16), a more sophisticated structure arose from intramolecular addition of the 2-hydroxyethyl group to C(7), giving 8,9-dihydro-2,4-bis(methylthio)-6,6a-diphenyl-6aH-oxazolo[2,3-h]pteridine (18). Since in the monoanion species of 16, the oxazolidine moiety is already present, alkylation in alkaline medium took place in the usual manner at the S-atoms giving rise to 18. The structure of 18 was proven by ^{1}H-NMR spectroscopy (see Chapt. 3).

3. Structures and Physical Data. – The structural characterization of the newly synthesized compounds were performed in the usual manner by elemental analyses, pK_a determination, and UV and ^{1}H-NMR spectroscopy as well as X-ray analysis in the case of 20 and 21.

A comparison of the physical data of the 2,4-dithiouracils with those of the 2-thio [13] and 4-thio analogs [1] indicate that the presence of a second thioamide group lowers expectedly the basic properties of the molecules and enhances logically the acid strength of the corresponding functions *(Table 1)*. The UV spectra of the 2,4-dithiouracils are shifted most bathochromically as compared to the 2-thio and 4-thio series and show analogous blue shifts of the characteristic long-wavelength band when going from the neutral species either to the cation or the anion forms. Deprotonation of a thioamide function of the 2,4-dithiouracils is always associated with a hypsochromic shift, whereas normally anion formation of hydroxy N-heterocycles show a red shift due to stronger resonance of the functional group with the ring system. The spectroscopic and acid-base properties of the new compounds **10** and **11** are in good agreement with the structurally closely related, known 6-amino-2,4-dithiouracil [16] of which the physical data have been redetermined more accurately (see *Table 1*).

Similar molecular features control the physical properties of the 6,7,8-trisubstituted 2,4-dithiolumazines **14–16**. They are less basic and stronger acids in comparison to their 2- [1] and 4-thio counterparts [13] and exhibit a red-shifted UV/VIS absorption. The shifts of *ca.* 50 nm to lower wavelengths on cation formation is in agreement with the protonation site at N(1), indicating a partial localisation of π-electrons in the quinonoid-type merocyanine resonance system. On the other hand, the even stronger blue shift on anion formation in **14** is best explained by deprotonation from the 7-CH_3 group, whereas the analogous shift in **15** is due to nucleophilic addition of OH^- to the C(7) center and not to deprotonation at N(3). The accumulation of three more or less bulky substituents on the three adjacent C- and N-atoms of **15** causes a substantial internal strain which is best released by transferring the sp^2-hybridized C(7) center into a sp^3 configuration.

A special case is revealed by **16** which shows as a neutral species in aqueous medium (pH 2) and in CH_3CN a relatively low extinction of the long-wavelength band, but a quite intensive shoulder at 353 and 398 nm, respectively. This spectral anomaly is due to the fact that **16** exists in solution in equilibrium with its cyclic covalent adduct **22** *(Scheme 2)*.

Scheme 2

16   **22**   **23**
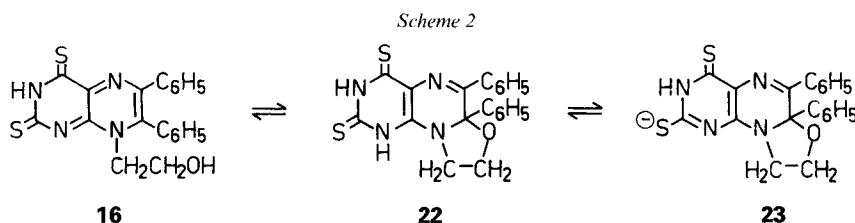
The monoanion of **16** obviously consists exclusively of the cyclic adduct form **23** since the absorption at 518 nm has completely disappeared on account of the band at 396 nm.

Similar considerations of the physical data of the 2,4-bis(methylthio) derivatives **17–21** confirm the proposed structural assignments. Since the UV spectra of the neutral species are very much alike, they all possess a 7,8-dihydro structure. Protonation of **17** (pK_a 3.28) takes place at the exocyclic methylidene function yielding a resonance-stabilized cation in a cross-conjugated π-electron system which absorbs at longer wavelengths. On the other hand, the basic 'pK_a values' of **18–21** are not true equilibrium constants of a

Table 1. *Physical Data of Pyrimidine Derivatives*

	pK_a in H_2O	UV spectra[a] λ_{max} [nm]	lg ε	pH	Molecular form[b]	^{1}H-NMR spectra (D_6)DMSO; δ [ppm]
5	-0.76	285 357	4.40 4.18	-2.7	O	12.3 (br. *s*, ring NH);
	9.16	283 373	4.57 4.59	4.0	—	12.0 (br. *s*, ring NH);
	13.26	258 296 356	4.23 4.38 4.39	11.0	— —	6.9 (br. *s*, NH_2); 5.85 (*s*, H–C(5))
		268 328	4.57 4.16	2N KOH	— — —	
6-Amino-2,4-dithiouracil	-1.24	233 280 [312]	4.16 4.38 [3.92]	-3.0	+	
	5.44	213 282 328	4.30 4.47 4.44	2.0	O	
		219 247 317	4.29 4.39 4.38	8.0	—	
10	-1.15	238 277 319	4.24 4.42 3.97	-3.0	+	12.3 (br. *s*, 1 H);
	5.32	220 282 332	4.19 4.44 4.45	2.0	O	12.1 (br. *s*, ring NH);
	13.49	219 256 318	4.20 4.52 4.30	10.0	—	6.6 (br. *s*, NH); 5.8 (*s*, H–C(5));
		265 306	4.48 4.02	3N KOH	— —	2.75 (*d*, CH_3N)
11	-1.31	239 279 321	4.24 4.45 3.96	-3.0	+	12.3 (br. *s*, 1 H);
	4.94	221 283 333	4.20 4.43 4.47	1.0	O	11.9 (br. *s*, ring NH); 6.8 (br. *s*, NH);
	13.31	219 256 319	4.19 4.52 4.30	8.0	—	5.9 (*s*, H–C(5)); 4.4 (br. *s*, OH);
		264 306	4.48 4.04	2N KOH	— —	3.5 (*t*, CH_2); 3.2 (*t*, CH_2)
12	1.95	286 331	4.45 4.38	-1.0	+	
	4.82	275 [340] 358	4.27 [4.16] 4.20	3.4	O	
	13.32	250 [288] 340	4.41 [3.97] 4.17	9.0	—	
		[252] [280] 319	[4.17] [4.00] 3.97	2N KOH	— —	
13	1.80	223 286 334	4.08 4.45 4.39	-1.0	+	
	4.52	276 [332] 361	4.27 [4.09] 4.21	3.0	O	
	13.15	250 [286] 343	4.40 [3.98] 4.19	7.0	—	
		248 [285] 322	4.29 [3.96] 4.00	2N KOH	— —	

[a]) Values in brackets refer to shoulders.
[b]) + = cation, O = neutral form, — = monoanion, — — = dianion, — — — = trianion.

Table 2. *Physical Data of 8-Substituted 2,4-Dithiolumazine Derivatives*

	pK_a in H_2O	λmax [nm]					lg ε					pH	Molecular form[b]
14	−0.76	222	274	308	[398]	421	3.85	4.28	4.06	[3.74]	4.17	−3.0	+
		252	283	339		472	4.16	4.07	4.34		4.07	2.0	○
	5.65	214	284	367		[409]	4.23	4.46	4.36		[3.76]	8.0	−
15		253	277	325	[422]	455	4.23	4.32	4.23	[3.79]	4.28	−2.0	+
			289	350		506		3.96	4.39		4.21	1.0	○
		246	282	347	390		4.33	4.43	4.34	4.27		13.0	−
		251	290	357	[438]	516	4.28	3.97	4.49	[3.91]	4.24	CH_3CN	○
16		[224]	284	331		458	[4.20]	4.41	4.29		3.75	−3.0	+
		[254]	281	336	[353]	506	4.25	4.34	4.24	[4.18]	3.47	2.0	○
		247	285	352	396		4.31	4.30	4.16	4.18		13.0	−
		249	[285]	362	[398]	518	4.24	[4.16]	4.34	[4.03]	3.75	CH_3CN	○
17	3.28	241	268	298	[375]	428	4.20	4.11	4.17	[3.93]	4.15	0.0 + MeOH	+
		[232]	256	[269]	[290]	[301]	[4.09]	4.42	[4.28]	[4.07]	[4.05]		
		329	338	377	[389]	[415]	4.01	4.01	3.97	[3.93]	[3.60]	6.0 + MeOH	○
19	1.79	241	[264]	312	[396]	468	4.34	[4.13]	4.32	[3.91]	4.27	0.0 + MeOH	+
		233	280	373	[380]	[401]	4.35	4.42	4.22	[4.20]	[4.03]	4.0 + MeOH	○
20	1.81	241	[265]	312	[400]	467	4.34	[4.13]	4.33	[3.93]	4.28	0.0 + MeOH	+
		233	280	373	[378]	[400]	4.36	4.43	4.23	[4.22]	[4.03]	4.0 + MeOH	○
21	1.77	241	[264]	311	[400]	467	4.35	[4.14]	4.34	[3.94]	4.27	0.0 + MeOH	+
		233	280	[373]	378	[402]	4.36	4.42	[4.20]	4.22	[4.00]	4.0 + MeOH	○
18	1.20	243	[265]	311	[385]	469	4.32	[4.10]	4.27	[3.97]	4.19	−0.5 + MeOH	+
		237	281	[372]	379	[399]	4.33	4.40	[4.23]	4.24	[4.09]	4.0 + MeOH	○

a) Values in brackets refer to shoulders.
b) + = cation, ○ = neutral form, − = monoanion.

Brönsted base with its corresponding cation but have to be explained as the relation of a pseudo-base with its cation form. Protonation will proceed at the 7-O function followed by an elimination of H_2O or alcohol *(Scheme 3)*.

Scheme 3
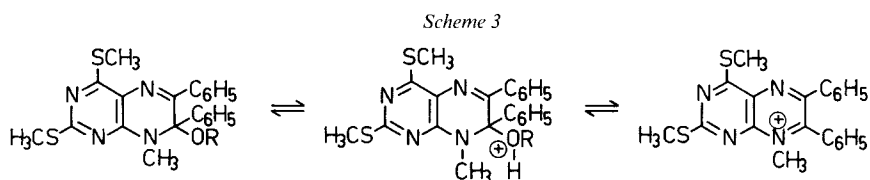
From the NMR spectra of **18–21**, it can be derived that some of the aromatic protons are located at lower field than expected which accounts for a coplanar conformation of the 6-phenyl substituent with the pteridine nucleus. A structural proof of the oxazolopteridine **18** is also deduced from its NMR spectrum which reveals a characteristic pattern of signals for the ethano moiety *(Fig. 1)*. The protons possess similar chemical shifts and are diastereotopic because of the adjacent chiral C(6a) center. The complex coupling pattern of the *ABCD* system was simulated with the empirically derived coupling constants and revealed perfect agreement with the observed spectrum after only one iteration.
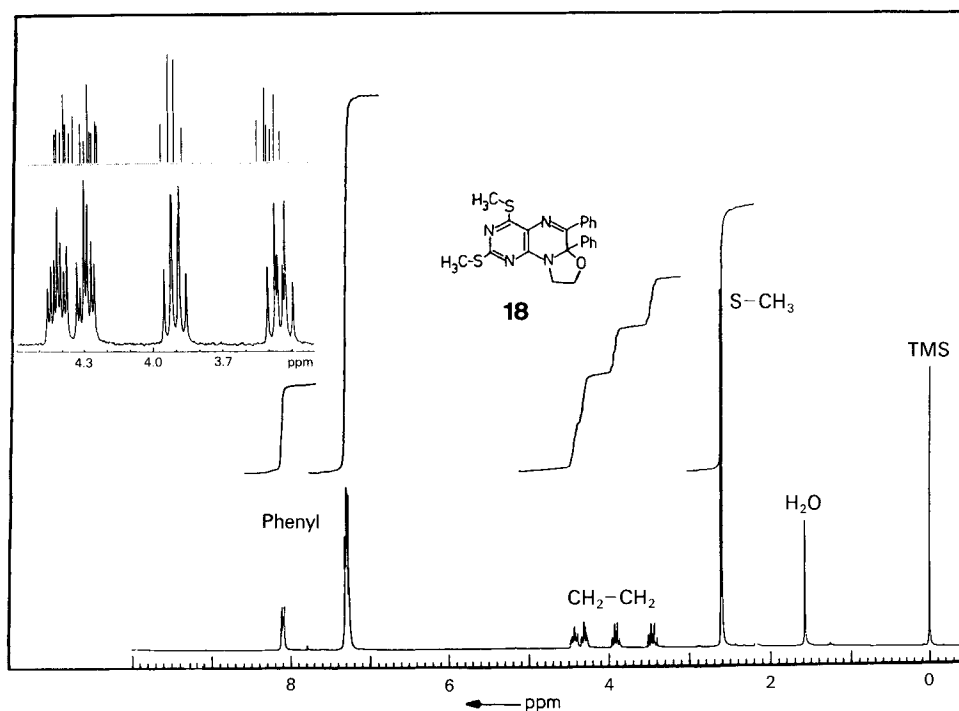

Fig. 1. *¹H-NMR spectrum* (CDCl₃) *of* **18**

Finally, unambiguous proof for the structures of the alkoxy-adducts **20** and **21** is based upon X-ray structure determinations. The crystallographic data are given in *Table 3* and the structures in *Figs. 2* and *3*.

Table 3. *Crystallographic Data of 7,8-Dihydro-7-methoxy-8-methyl-2,4-bis(methylthio)-6,7-diphenylpteridine* (**20**) *and 7-Ethoxy-7,8-dihydro-8-methyl-2,4-bis(methylthio)-6,7-diphenylpteridine* (**21**)

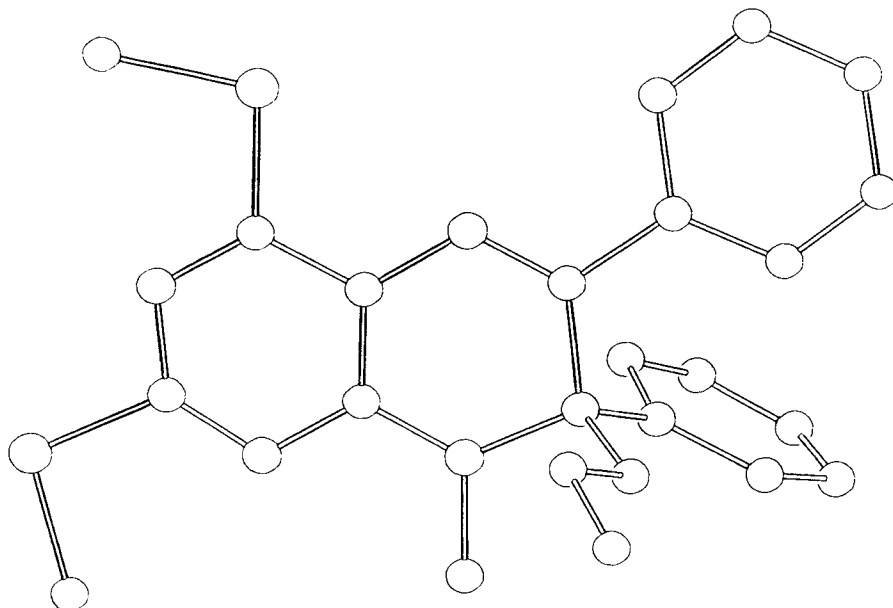| Compound	**20**	**21**
	$1°$	$1°$
	$2.2° \leqslant \omega \leqslant 29.3° \min^{-1}$	$1.8° \leqslant \omega \leqslant 29.3° \min^{-1}$
	$2° \leqslant 2\theta \leqslant 42°$	$2° \leqslant \theta \leqslant 40°$
Empirical formula	$C_{22}H_{22}N_4OS_2$	$C_{23}H_{24}N_4OS_2$
Mol. wt.	422.6	436.6
Space group	$P2_1/c$	$P2_1/c$
a [pm]	991.2 (5)	1697 (3)
b [pm]	1756.0 (7)	1852 (2)
c [pm]	1447 (1)	1485 (2)
β	135.66 (2)	102.5 (1)
V [pm^3]	$2125 \cdot 10^6$	$4456 \cdot 10^6$
Z	4	8
$d_{calc.}$ [g·cm^{-3}]	1.32	1.27
μ-MoK [cm^{-1}]	2.7	2.5
T [K]	233	308
Reflections used	2544	4257
Independent reflections	1599 ($I > 2\sigma$)	3135 ($I > 4\sigma$)
R_1	0.067	0.105
R_2	0.067	0.111

Fig. 2. *Crystal structure of* **20**
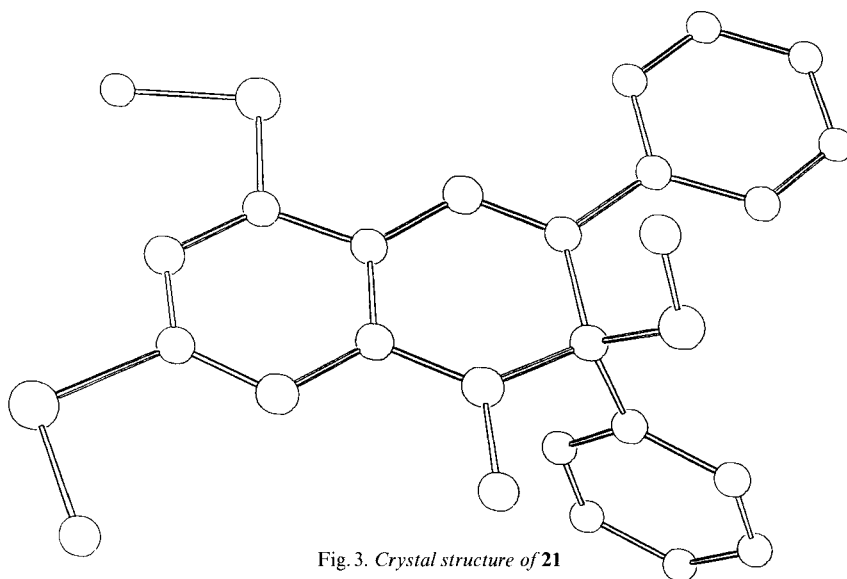
Fig. 3. *Crystal structure of* **21**

Crystals were obtained from acetone/MeOH/H₂O and CHCl₃/EtOH, respectively, and the intensities were collected on a *Syntex-P3* diffractometer in the ω-scan mode using MoKₐ radiation. The structures were solved with the program system SHELXTL [14]. The H-atoms were located in difference *Fourier* maps after anisotropic refinement of the other atoms and were refined with individual isotropic temperature factors. No attempt was made to determine the absolute structure in the crystals. All crystallographic data are deposited at the *Cambridge Crystallographic Data Center*.

Experimental Part

General. See [1]. ¹H-NMR: *Jeol JNM-MH 100* and *Bruker WM-250*. X-Ray: *Synthex-P3* diffractometer, MoKₐ 71.069 ppm, graphite monochromator, ω-scan.

1. *Bis(4,6-dichloropyrimidin-2-yl) Disulfide* (**2**). A mixture of POCl₃ (200 ml), *N,N*-diethylaniline (90 ml), and 2-thiobarbituric acid (**1**; 35 g, 0.24 mol) is refluxed for 1.5 h, then evaporated to a sirup, and treated with ice (800 g) by stirring for several h. The precipitate is collected and dried over KOH in the vacuum desiccator: yellowish powder, 39.0 g (89%). The material is pure enough for further reactions. An anal. pure sample is obtained by silica-gel chromatography with hexane/CHCl₃ 2:1→1:1 and recrystallization from CHCl₃/MeOH. Colourless crystals. M.p. 152°. UV (MeOH): 248 (4.35), 275 (sh, 4.02). ¹H-NMR (CDCl₃): 7.2 (*s*, H–C(5)). Anal. calc. for C₈H₂Cl₄N₄S₂ (360.1): C 26.69, H 0.56, Cl 39.38, N 15.56, S 17.81; found: C 26.72, H 0.56, Cl 39.44, N 15.43, S 17.44.

2. *Bis[4-chloro-6-(methylamino)pyrimidin-2-yl] Disulfide* (**3**). To a soln. of 4.0 g (11.1 mmol) of **2** in dioxane (40 ml), MeOH (10 ml) is added, followed by MeNH₃OAc (20 g) within 2.5 h with stirring. Finally, 25 ml of a 6.7M MeNH₂ soln. in MeOH are added dropwise within 1.5 h, and the mixture is stirred for 2 h (TLC control). Then it is diluted with H₂O (40 ml) and evaporated to half of its volume. The precipitate is collected, washed with H₂O and dried in a desiccator: yellowish powder, 3.45 g (89%). The product is pure enough for further reactions. A pure sample is obtained by chromatography on silica gel with CHCl₃/MeOH 20:1. Recrystallization from CHCl₃/MeOH 1:1 gives colourless crystals. M.p. 209–210°. UV (MeOH): 234 (4.50), 288 (4.02). ¹H-NMR ((D₆)DMSO): 8.0 (br. *m*, 2 NH); 6.4 (*s*, 2 H, H–C(5,5′)); 2.8 (*d*, 2 CH₃N). Anal. calc. for C₁₀H₁₀Cl₂N₆S₂ (349.3): C 34.39, H 2.89, N 24.06; found: C 34.64, H 2.78, N 23.65.

3. *2,4,6-Trithiobarbituric acid* (5) [16]. A mixture of a 20% (NH$_4$)$_2$S soln. (5 ml) and dioxane (5 ml) is heated to 100°. Then, 0.365 g (1 mmol) of 2 in dioxane (10 ml) are added and refluxed for 15 min. After evaporation, the residue is dissolved in hot dilute NaOH, treated with charcoal, filtered, and the soln. acidified with 2N HCl. The precipitate is filtered after cooling and dried: orange-yellow crystals, 0.21 g (59%). M.p. > 330°. Anal. calc. for C$_4$H$_4$N$_2$S$_3$ (176.3): C 27.25, H 2.29, N 15.90; found: C 27.45, H 2.28, N 15.81.

4. *6-(Methylamino)-5-(phenylazo)pyrimidine-2,4(1H,3H)-dithione* (6). In H$_2$O (60 ml) and 5N NaOH (6 ml), 10 (0.865 g, 5 mmol) is dissolved and the pH adjusted to 10 by addition of 5N AcOH. The soln. is cooled to 5° and then a 1M soln. of benzenediazonium chloride (7 ml) added dropwise with stirring. The pH is kept between 9 and 10 by simultaneous addition of dil. NaOH soln. The mixture is then warmed to 70°, acidified to pH 3–4, and the red precipitate collected by suction. The product is washed with H$_2$O, little MeOH, and Et$_2$O and dried: red powder, 1.07 g (77%). M.p. 213–215° (dec.). The product can be used for further reactions. An anal. pure sample is obtained by chromatography on a silica-gel column with CHCl$_3$ and then CHCl$_3$/MeOH 20:1. The main fraction is evaporated to a small volume and the precipitate dried: red crystal powder. M.p. 239° (dec.). UV (MeOH): 236 (4.38), 253 (4.43), 260 (sh, 4.38), 291 (4.07), 464 (4.58). Anal. calc. for C$_{11}$H$_{11}$N$_5$S$_2$ (277.4): C 47.63, H 4.00, N 25.25; found: C 47.59, H 3.97, N 25.18.

5. *6-[(2-Hydroxyethyl)amino]-5-(phenylazo)pyrimidine-2,4(1H,3H)-dithione* (7). A soln. of NaOH (24 g, 0.6 mol) and 11 (20.3 g, 0.1 mol) in H$_2$O (700 ml) is adjusted to pH 9–10 with AcOH and cooled to 5°. Then, a soln. of benzenediazonium chloride (prepared from 11.6 g of aniline) is added dropwise with stirring. The pH is kept between 9 and 10 by simultaneous addition of dil. NaOH soln. Finally, the soln. is warmed to 70°, acidified to pH 3–4, and the red precipitate collected. After washing and drying, a red powder is obtained: 30.7 g (100%). M.p. 200–202° (dec.). UV (pH 10, +30% MeOH): 243 (4.33), 260 (sh, 4.30), 308 (4.35), 416 (4.33).

6. *5-(4-Chlorophenylazo)-6-(methylamino)pyrimidine-2,4(1H,3H)-dithione* (8). Analogous to the preceding procedure, with 10 (17.3 g, 0.1 mol) in H$_2$O (600 ml), NaOH (24 g, 0.6 mol), and a soln. of 4-chloro-benzenediazonium chloride (prepared from 15.95 g of 4-chloroaniline). On workup, a red solid is obtained: 28.94 g (93%). M.p. 190–193° (dec.). UV (pH 10, +30% MeOH): 244 (4.22), 264 (sh, 4.06), 310 (4.19), 320 (sh, 4.17), 423 (4.21).

7. *5-(4-Chlorophenylazo)-6-[(2-hydroxyethyl)amino]pyrimidine-2,4(1H,3H)-dithione* (9). Analogous to the preceding procedure, with 11 (5.07 g, 25 mmol) in H$_2$O (300 ml), 5N NaOH (30 ml), 5N AcOH (20 ml), and 1M 4-chlorobenzenediazonium chloride: red crystal powder, 8.47 g (99%). M.p. 203–205° (dec.). The crude material is pure enough for further reactions. UV (pH 10, +30% MeOH): 246 (4.29), 266 (sh, 4.12), 312 (4.31), 322 (sh, 4.29), 425 (4.32).

8. *6-(Methylamino)pyrimidine-2,4(1H,3H)-dithione* (10). a) To a soln. of 2.21 g (6.33 mmol) of 3 in dioxane (25 ml), a soln. of 70% NaHS (3 g) in H$_2$O (20 ml) is added and heated to reflux till a clear soln. is obtained. The mixture is then stirred for another 4 h at r.t., evaporated to half of the volume, H$_2$O (30 ml) is added, the mixture treated with charcoal and filtered hot. The filtrate is acidified with 5N HCl (10 ml) and, after cooling, the precipitate is washed and dried: 1.97 g (90%). The crude product contains a small amount of sulfur but is pure enough for further reactions. An anal. pure sample is obtained by recrystallization of 1.1 g from H$_2$O (700 ml) and treatment with charcoal: 0.7 g. M.p. 291–293° (dec.). Anal. calc. for C$_5$H$_7$N$_3$S$_2$ (173.3): C 34.66, H 4.07, N 24.25, S 37.01; found: C 34.75, H 4.31, N 24.04, S 36.76.

b) In a mixture of dioxane (50 ml), MeOH (10 ml), and AcOH (1 ml), 4.1 g (11.4 mmol) of 2 are dissolved by gentle warming. After cooling to r.t., 6.7N MeNH$_2$ in MeOH (25 ml) is added dropwise with stirring (TLC control). The reaction is stopped by addition of 70% NaHS (4 g) in H$_2$O (30 ml), when the educt has almost disappeared. The mixture is then heated a few min under reflux, treated with charcoal, diluted with H$_2$O (250 ml), and acidified by 1N HCl (30 ml). The insoluble sulfur is filtered from the hot soln., the filtrate concentrated to ca. 50 ml, and the precipitate collected (2.87 g). The material is reprecipitated from dil. NaOH soln./1N HCl with charcoal: yellowish powder, 2.12 g (56%).

9. *6-[(2-Hydroxyethyl)amino]pyrimidine-2,4(1H,3H)-dithione* (11). a) For 2 h, 6-[(2-hydroxyethyl)amino]-2-thiouracil [13] and P$_4$S$_{10}$ (25 g) in dry pyridine (300 ml) are heated under reflux. The dark-red soln. is evaporated to a sirup, the residue heated in H$_2$O (200 ml) for 2.5 h and then kept at r.t. for 1 day. The precipitate (4.7 g) is collected and the filtrate acidified with HCl to pH 2 to give a second crop (3.7 g). On evaporation to half of the volume, another precipitate is obtained which is recrystallized from H$_2$O (100 ml) with charcoal: yellowish crystals, 1.17 g (8%). M.p. 239–240° (dec.). From the first two precipitates are obtained another 1.41 g on recrystallization from H$_2$O. Anal. calc. for C$_6$H$_9$N$_3$OS$_2$ (203.3): C 35.45, H 4.46, N 20.67; found: C 35.33, H 4.54, N 20.39.

b) To a soln. of 36 g (0.1 mol) of **2** in dioxane (150 ml), 30.5 g (0.5 mol) of 2-aminoethanol in EtOH (50 ml) are added slowly dropwise with stirring. After 1 h, H_2O (20 ml) is added to get a clear soln. again. Then, another 12 g of 2-aminoethanol in H_2O (15 ml) is added slowly and the soln. stirred for 1 h and evaporated to half of the volume. $NaHS \cdot H_2O$ (37 g, 0.5 mol) in H_2O (100 ml) is added and the mixture heated to reflux for a few min. It is treated with charcoal, filtered, and the filtrate acidified by 6N HCl to pH 1. After cooling over night, the orange precipitate is washed with H_2O, MeOH, and Et_2O and dried at 100°. Evaporation of the filtrate to a smaller volume gives a second crop. The crude material containing some sulfur is recrystallized from H_2O (2.2 l) and 1N HCl (25 ml): brownish-yellow needles, 28.34 g (70%).

10. *5-Amino-6-(methylamino)pyrimidine-2,4(1H,3H)-dithione* (**12**). For 1.5 h, 15.58 g (50 mmol) of **6** in dioxane (50 ml) and 20% $(NH_4)_2S$ soln. (100 ml) are heated under reflux. The mixture is evaporated and then the whole procedure repeated with the residue under the same conditions. After evaporation, the residue is heated to boiling in 1N HCl (150 ml), treated with charcoal, filtered, and then the pH of the filtrate adjusted to 3–3.5 by addition of NH_3. On cooling, a yellowish precipitate is obtained: 5.98 g (64%). M.p. > 320°. An anal. pure sample is obtained by recrystallization from dil. AcOH with charcoal. Anal. calc. for $C_5H_8N_4S_2$ (188.3): C 31.90, H 4.28, N 29.76; found: C 31.87, H 4.28, N 29.21.

11. *5-Amino-6-[(2-hydroxyethyl)amino]pyrimidine-2,4(1H,3H)-dithione* (**13**). Analogous to the preceding procedure, with 6.1 g of **9** in dioxane (25 ml) and 20% $(NH_4)_2S$ soln. (50 ml). After evaporation, the residue is dissolved in 100 ml of hot H_2O, the pH adjusted to 3 and then treated with charcoal and filtered. On cooling, a yellowish precipitate is obtained: 2.52 g (65%). M.p. 229° (dec.). Anal. calc. for $C_6H_{10}N_4OS_2$ (218.3): C 33.01, H 4.62, N 25.67; found: C 33.16, H 4.51, N 25.09.

Recrystallization of the material from 1N HCl yielded **13** · HCl as yellowish needles. M.p. 202–204° (dec.). Anal. calc. for $C_6H_{10}N_4OS_2 \cdot HCl$ (254.8): C 28.29, H 4.35, N 21.99; found: C 28.19, H 4.26, N 21.49.

12. *6,7,8-Trimethylpteridine-2,4(3H,8H)-dithione* (**14**). *a)* To a mixture of 1N HCl (20 ml), AcOH (3 ml), and 0.1 g (0.53 mmol) of **12** at 80°, 0.5 ml of diacetyl in EtOH (10 ml) are added dropwise and then kept at 80° for 1 h. After cooling, a red precipitate is collected: 0.051 g (40%). M.p. 225–226° (dec.). ¹H-NMR ((D_6)DMSO): 13.4 (br. *s*, NH); 4.00 (*s*, CH_3N); 2.67 (*s*, CH_3–C(7)); 2.58 (*s*, CH_3–C(6)).

b) For 45 min, 0.2 g (1.06 mmol) of **12** and 0.3 ml of diacetyl in DMF (15 ml) are heated to 80°. The mixture is acidified by 1N HCl (5 ml), cooled, and the precipitate collected: 0.157 g (63%). M.p. 220–221° (dec.). Anal. calc. for $C_9H_{10}N_4S_2$ (238.3): C 45.36, H 4.23, N 23.51; found: C 44.76, H 4.18, N 23.26.

13. *8-Methyl-6,7-diphenylpteridine-2,4(3H,8H)-dithione* (**15**). To a hot soln. of benzil (0.55 g, 2.62 mmol) in EtOH (20 ml) are added dropwise 0.25 g (1.33 mmol) of **13** in AcOH (10 ml) and 1N HCl (20 ml). The soln. is then heated for 1 h under reflux and the brown-red precipitate collected after cooling: 0.225 g (47%). M.p. 267° (dec.). ¹H-NMR ((D_6)DMSO): 12.3 (br. *s*, NH); 7.5 (*m*, C_6H_5–C(7)); 7.2 (*m*, C_6H_5–C(6)); 3.65 (*s*, CH_3N). Anal. calc. for $C_{19}H_{14}N_4S_2$ (362.5): C 62.96, H 3.89, N 15.46, S 17.69; found: C 63.14, H 3.99, N 15.23, S 17.85.

14. *8-[(2-Hydroxyethyl)amino]-6,7-diphenylpteridine-2,4(3H,8H)-dithione* (**16**). To the hot soln. of 0.4 g (1.9 mmol) of benzil in EtOH (15 ml), 0.215 g (1 mmol) of **13** in 0.1N HCl (10 ml) and EtOH (5 ml) are added. The mixture is refluxed for 3 min and then cooled over night. The precipitate is washed with H_2O and little MeOH: brownish-red crystals, 0.246 g (63%). M.p. > 155° (dec.). ¹H-NMR ((D_6)DMSO): 12.8 (br. *s*, NH); 7.3–7.9 (*m*, 10 arom. H); 4.3 (*m*, CH_2); 3.7 (*m*, CH_2). Anal. calc. for $C_{20}H_{16}N_4OS_2 \cdot 0.5 H_2O$ (401.5): C 59.83, H 4.27, N 13.95; found: C 59.14, H 4.09, N 13.70.

15. *7,8-Dihydro-6,8-dimethyl-7-methylidene-2,4-bis(methylthio)pteridine* (**17**). To a mixture of acetone (6 ml), H_2O (10 ml), 1N NaOH (6 ml), and 0.31 g (1.3 mmol) of **14**, 0.4 ml of Me_2SO_4 are added dropwise within 30 min. After stirring for another 30 min, the soln. is evaporated to a small volume and the orange precipitate collected (0.27 g). The crude material in $CHCl_3$ is chromatographed on a silica-gel column with $CHCl_3$. The main fraction is evaporated and the residue recrystallized from acetone (35 ml)/H_2O (7 ml) with charcoal: yellow needles, 0.155 g (45%). M.p. 149–150°. ¹H-NMR ($CDCl_3$): 4.45 (*d*, H–C(7)); 4.25 (*d*, H–C(7)); 3.25 (*s*, CH_3N); 2.50 (*s*, CH_3S); 2.48 (*s*, CH_3S); 2.25 (*s*, CH_3–C(6)). Anal. calc. for $C_{11}H_{14}N_4S$ (166.4): C 49.60, H 5.30, N 21.03; found: C 49.50, H 5.18, N 20.85.

16. *8,9-Dihydro-2,4-bis(methylthio)-6,6a-diphenyl-6aH-oxazolo[2,3-h]pteridine* (**18**). To a mixture of dioxane (18 ml), 0.5N NaOH (12 ml) and 0.6 g (1.5 mmol) of **16**, Me_2SO_4 (0.6 ml) in dioxane (1 ml) is added slowly and dropwise at r.t. A yellow precipitate separates out first and dissolves again after some time. After stirring for 30 min, the soln. is acidified with 5N AcOH and then the dioxane distilled off *in vacuo*, whereby a precipitate is obtained. The material is purified by silica-gel chromatography using toluene. The main fraction is evaporated and

the residue recrystallized from acetone/H_2O 4:1: yellowish crystals, 0.12 g (19%). M.p. 202–203°. ^{1}H-NMR (CDCl$_3$): 8.1 (*m*, 2 arom. H); 7.3 (*m*, 8 arom. H); 4.45 (*m*, 1 H, NCH$_2$CH$_2$O); 4.3 (*m*, 1 H, NCH$_2$CH$_2$O); 3.9 (*m*, 1 H, NCH$_2$CH$_2$O); 3.45 (*m*, 1 H, NCH$_2$CH$_2$O); 2.60 (*s*, CH$_3$S); 2.59 (*s*, CH$_3$S). Anal. calc. for C$_{22}$H$_{20}$N$_4$OS$_2$ (420.6): C 62.83, H 4.79, N 13.32; found: C 62.52, H 4.97, N 13.13.

17. *7,8-Dihydro-7-hydroxy-8-methyl-2,4-bis(methylthio)-6,7-diphenylpteridine* (**19**). To a mixture of acetone (10 ml), 1N NaOH (8 ml), and 0.725 g (2 mmol) of **15**, Me$_2$SO$_4$ (0.5 ml) is added dropwise with stirring. A precipitate is formed which is collected after 1 h. The material is reprecipitated from half conc. HCl soln./acetone by addition of 5N NaOH till pH 14. The precipitate (0.75 g) is dissolved in dioxane, the soln. mixed with 8 g of silica gel and evaporated, and this material put on a silica-gel column (3 × 10 cm) for chromatography, first with toluene (200 ml), then toluene/AcOEt 20:1 (300 ml), and finally toluene/AcOEt 10:1 (300 ml). The main fraction is evaporated: yellow crystal powder, 0.72 g (88%). A sample is recrystallized from acetone/H_2O 5:1 or from MeCN: yellowish crystals. M.p. 205–206° (dec.). ^{1}H-NMR (CDCl$_3$): 7.25–7.7 (*m*, 10 arom. H); 2.90 (*s*, CH$_3$N); 2.57 (*s*, CH$_3$S); 2.54 (*s*, CH$_3$S). Anal. calc. for C$_{21}$H$_{20}$N$_4$OS$_2$ (408.6): C 61.74, H 4.93, N 13.71; found: C 61.79, H 5.04, N 13.90.

18. *7,8-Dihydro-7-methoxy-8-methyl-2,4-bis(methylthio)-6,7-diphenylpteridine* (**20**). *a*) By gentle warming 0.28 g (0.68 mmol) of **19** are dissolved in acetone (10 ml), MeOH (5 ml), and 1N HCl/MeOH (2 ml). The soln. is neutralized by 5N NaOMe (colour change from red to yellow), then evaporated, and the residue treated with H_2O. The insoluble precipitate yields, on crystallization from acetone (25 ml), MeOH (5 ml), and little H_2O on slow partial evaporation in a desiccator, yellow crystals: 0.2 g (69%). M.p. 143–144°. These crystals are used for the determination of the X-ray structure.

b) To a mixture of dioxane (7.5 ml), 1N NaOH (7.5 ml), and 0.543 g (1.5 mmol) of **15**, Me$_2$SO$_4$ (0.71 ml) is added dropwise with stirring. After 30 min, the soln. is acidified by AcOH to pH 4 and then the dioxane distilled off in vacuum. The yellow precipitate (0.63 g) is recrystallized from CHCl$_3$/MeOH 1:1 to give yellow crystals: 0.355 g (56%). M.p. 143°. ^{1}H-NMR (CDCl$_3$): 7.4–8.1 (*m*, 10 arom. H); 3.3 (*s*, CH$_3$O); 2.90 (*s*, CH$_3$N); 2.60 (*s*, 2 CH$_3$S). Anal. calc. for C$_{22}$H$_{22}$N$_4$OS$_2$ (422.6): C 62.53, H 5.25, N 13.26; found: C 62.48, H 5.30, N 13.22.

19. *7-Ethoxy-7,8-dihydro-8-methyl-2,4-bis(methylthio)-6,7-diphenylpteridine* (**21**). From CHCl$_3$/EtOH 2:1 and one drop of 5N HCl, 0.085 g of **20** are recrystallized. On slow concentration of the soln. in a desiccator, nice yellow crystals are obtained: 0.054 g (61%). M.p. 152–154°. ^{1}H-NMR (CDCl$_3$): 7.2–8.0 (*m*, 10 arom. H); 3.4 (*q*, CH$_3$CH$_2$O); 2.84 (*s*, CH$_3$N); 2.59 (*s*, CH$_3$S); 2.58 (*s*, CH$_3$S); 1.25 (*t*, CH$_3$CH$_2$O). Anal. calc. for C$_{23}$H$_{24}$N$_4$OS$_2$ (436.6): C 63.29, H 5.54, N 12.87; found: C 63.25, H 5.56, N 12.79.

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