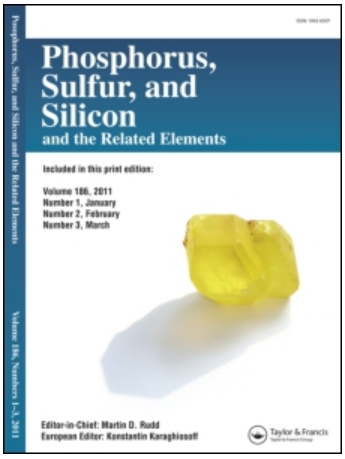

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1,1-DISUBSTITUTED-6-[1-(ARYLETHYLIDENE) AMINO]-2,5-DITHIOBIUREAS

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1,1-DISUBSTITUTED-6-[1-(ARYLETHYLIDENE) AMINO]-2,5-DITHIOBIUREAS

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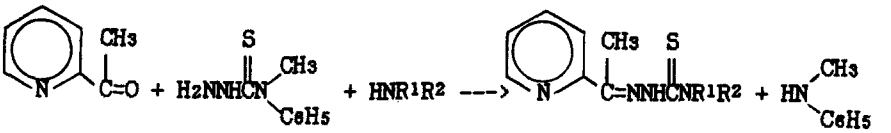
Reaction of 2-acetylpyridine with 4-methyl-4-phenyl-3-thiosemicarbazide afforded 1-methyl-1-phenyl-6-[1-(2-pyridinylethylidene)amino]-2,5-dithiobiurea (**2a**) rather than the expected thiosemicarbazone, 2-acetylpyridine 4-methyl-4-phenyl-3-thiosemicarbazone, **1**. The N-methylaniline moiety of **1** is particularly susceptible to nucleophilic attack. Biurea **2a** is formed by the displacement of the N-methylanilino moiety of in by the hydrazino amino group at 4-methyl-4-phenyl-3-thiosemicarbazide. The formation of biureas was shown to be a general feature of the reaction of N^4-aryl-N^4-alkyl-3-thiosemicarbazides with ketones.

Key words: 6-amino-2,5-dithiobiureas; antimalarial agents; thiocarbonyl activated transamination reaction; *Plasmodium berghei*.

The facile synthesis of N^4-substituted thiosemicarbazides and thiosemicarbazones by a thiocarbonyl activated transamination reaction was recently described in this journal.[1] Thus, condensation of 2-acetylpyridine and 4-methyl-4-phenyl-3-thiosemicarbazide with the desired amine produced N^4-substituted thiosemicarbazones of 2-acetylpyridine, **1**. (Scheme 1).



1

SCHEME 1

When the weakly nucleophilic aromatic amine aniline was employed, the reaction took a different course, and 1-methyl-1-phenyl-6-[1-(2-pyridinyl-ethylidene)-amino]-2,5-dithiobiurea, **2**, was obtained. Evidently, the terminal amino group in the hydrazino moiety of 4-methyl-4-phenyl-3-thiosemicarbazide is a better nucleophile than the amino group of aniline. When aniline was omitted from the reaction

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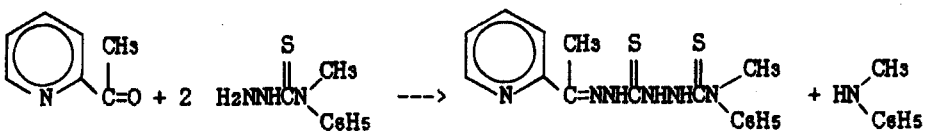
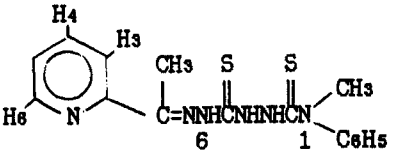
mixture, and the mole ratio adjusted to two equivalents of thiosemicarbazide per mole of 2-acetylpyridine, an 89% yield of biurea **2** could be obtained (Scheme 2).



2

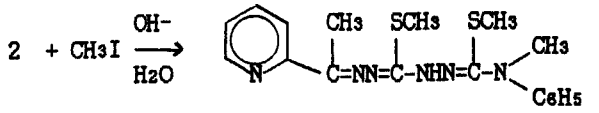
SCHEME 2

The assignment of structure **2** to the product of the reaction is supported by spectroscopic and chemical observations. The nmr spectrum showed N-methyl and C-methyl groups as sharp singlets at 3.69 and 2.39 ppm, respectively. Absorbances at 8.57, 8.19, and 7.72 could be assigned to the pyridine ring protons H_6, H_3, and H_4 (cf. structure A). Two of the three exchangeable N-H protons could be observed as singlets at 8.86 and 8.64 ppm, respectively. The absence of an exchangeable proton in the region of 12–14 ppm shows that the hydrazone proton at N^6 is not hydrogen bonded to the pyridine ring N-atom, suggesting that the conformation about the azomethine bond must be *E*.[2] The signal for the H_5 proton of the pyridine ring and the remaining exchangeable protons overlap with the unresolved signals of the phenyl ring.



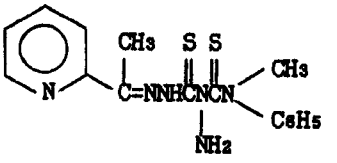
A

Reaction of **2** with iodomethane in aqueous base gave the di-S-methyl derivative, **3**, as the free base. This confirmed that the carbon-nitrogen skeleton of **2** was arrayed as a 6-amino-2,5-dithiobiurea, rather than the isomeric 1,3-diamino-2,4-dithiobiuret



3

moiety, as depicted in structure **4**.



4

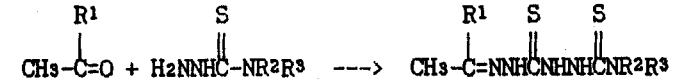
The unusual condensation depicted in Scheme 2 appears to be a general feature of the reaction of N^4-aryl-N^4-alkyl-3-thiosemicarbazides with ketones. Thus, reaction of 4-methyl-4-phenyl-3-thiosemicarbazide, 4-ethyl-4-phenyl-3-thiosemicarbazide (**5a**) or 1H-1,2,3,4-tetrahydroquinoline-1-thiocarboxylic acid hydrazide (**5b**) with a variety of aromatic or heteroaromatic methyl ketones afforded disubstituted-6-[1-(arylethylidene)amino]-2,5-dithiobiureas (cf. Table I).

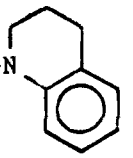
5b

The formation at the aminobiureas is rationalized by the following mechanism. Condensation of the ketone and thiosemicarbazide produces the intermediate thiosemicarbazone, **B**. Nucleophilic attack by the amino group of the thiosemicarbazide upon the activated thiocarbonyl group of **B** affords the tetrahedral intermediate **C**, loss of the arylalkylamine moiety from intermediate **C** affords the 6-amino-2,5-dithiobiurea, **D** (cf. Scheme 3).

TABLE I

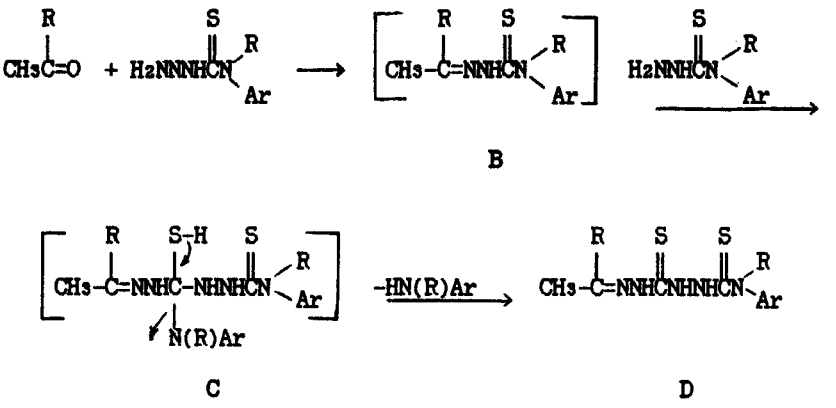
1,1-Disubstituted-6-[1-(aryl)ethylidene]amino-2,5-dithiobiureas



Cmpd. No.	R^1	NR^2R^3	formula[a]	mp, °C	yield, %
2a	2-pyridyl	$-N(CH_3)(C_6H_5)$	$C_{16}H_{18}N_6S_2$	154-155	89
2b	2-pyridyl	$-N(C_2H_5)(C_6H_5)$	$C_{17}H_{20}N_6S_2$	134-135	85
2c	2-pyridyl	$-N(C_6H_5)_2$[b]	$C_{21}H_{20}N_6S_2$	171-176	79
2d	2-pyridyl		$C_{18}H_{20}N_6S_2$	152-153	48
2e	C_6H_5	$-N(CH_3)(C_6H_5)$	$C_{17}H_{19}N_5S_2$	218-219	57
2f	2-pyrazinyl	" "	$C_{15}H_{17}N_7S_2$	141 dec	32
2g	2-thiazolyl	" "	$C_{14}H_{18}N_6S_3$	150-151	36
2h	2-quinolyl	" "	$C_{20}H_{20}N_6S_2$	160-161	83
2i	1-isoquinolyl	" "	$C_{20}H_{20}N_6S_2$	163 dec	59
2j	3-isoquinolyl	" "	$C_{20}H_{20}N_6S_2$	161-162	62

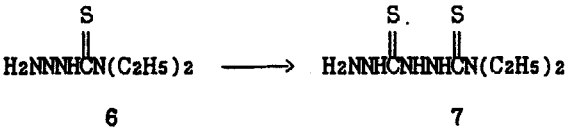
[a] All products recrystallized from EtOH except **2a** (MeCN).

[b] The requisite thiosemicarbazide, 4,4-diphenyl-3-thiosemicarbazide was prepared by K. A. Jansen, *et al.*, Acta Chem. Scand. 22, 38 (1968).



SCHEME 3

A number of investigators have observed that the dialkylamino group of N^4, N^4-disubstituted thiosemicarbazones and thiosemicarbazides may be subject to nucleophilic displacement. Larsen and Binderup reported that thermolysis of N^4,N^4-diethyl-3-thiosemicarbazide (**6**) gave 1-amino-6,6-diethyl-2,5-dithiobiurea, **7**.[3] Klayman and Lin described a facile synthesis



of thiosemicarbazones by the thiocarbonyl activated transamination of the corresponding N^4,N^4-dimethyl thiosemicarbazones.[4] In an analogous reaction, it has been shown that the N^4-methyl-N^4-phenyl moiety of 2-acetylpyridine 4-methyl-4-phenyl-3-thiosemicarbazone was particularly prone to displacement by amine nucleophiles.[1] The ready formation of 1,1-disubstituted-6-[1-(arylethylidene)amino]-2,5-dithiobiureas may be regarded as a novel example of the aforementioned reactions which is brought about by the unusual liability of the N^4-alkyl-N^4-aryl moiety to displacement. This reaction provides an entree into a class of compounds which has hitherto received little attention. It is interesting to note that 1-methyl-1-phenyl-6-[1-(2-pyridinyl)ethylidene amino]-2,5-dithiobiura (**2a**) shows substantial antimalarial activity. At a dose of 40 mg/Kg, **2a** cured 9 of 15 mice infected with *Plasmodium berghei,* while at a dose of 20 mg/Kg, 1 of 5 mice were cured. Significant antimalarial activity was observed for doses as low as 2.5 mg/Kg, where the mean survival time for treated animals was more than twice that of untreated controls (14.4 days versus 6.1 days). Surprisingly, none of the other dithiobiureas in this series showed comparable biological activity.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a Perkin Elmer Mdl 283 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian HR 220 spectrometer in $CDCl_3$ solution with tetramethylsilane as

the internal standard. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Satisfactory microanalyses (± 0.3%) were obtained for each compound.

1H-1,2,3,4-Tetrahydroquinoline-1-thiocarboxylic acid hydrazide (**5b**). The preparation of the aromatic thiosemicarbazides **5a** and **5b** is exemplified by the following procedure: A suspension of 13.3 g (0.1 mole) of 1H-1,2,3,4-tetrahydroquinoline in 100 mL of H_2O was treated with 7.60 g (0.1 mole) of carbon disulfide and a solution of 11.6 g (0.11 mole) of KOH in 100 mL of H_2O. The reaction mixture was stirred at room temperature for 18h. The aqueous solution was separated from unreacted amine and treated with 11.6 g (0.1 mole) of sodium chloroacetate. This solution was allowed to stand at room temperature for 5h and was then acidified with 10 mL of conc. HCl. The intermediate thiglycolic acid ester separated as an oil which soon solidified. It was collected by filtration and washed well with H_2O. This afforded 13 g of the crude ester, which was used immediately without further purification. A solution of this ester in 25 mL of 85% hydrazine hydrate was heated upon the steam bath for 10 min. An oil separated which soon crystallized. The product was recrystallized from EtOH, affording 5.95 g (64%) of colorless needles of **5b**, mp 90–92°C (with resolidification); ir 3260, 3160, 2950, 2930, 1640, 1480, 1370, 1078, 1035, 995, 925, 860, 845 cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}N_3S$: C, H, N, S.
N^4-Ethyl-N^4-phenyl-3-thiosemicarbazide (**5a**) was prepared similarly (20%) and had mp 113–114°C (with resolidification).

Anal. Calcd. for $C_9H_{13}N_3S$: C, H, N, S.

1-Methyl-1-phenyl-6-[1-(2-pyridinyl)ethylidene amino]-2,5-dithiobiurea (**2a**). The preparation of 1-(arylethylidene)amino 2,5-dithiobiureas (**2**) is exemplified in the following procedure: A solution of 1.83 g (10 mmole) of 4-methyl-4-phenyl-3-thiosemicarbazide[1] and 660 mg (5 mmole) of 2-acetylpyridine in 6 mL of MeCN was heated at 60°C for 45 min. The solution was chilled overnight and the crystals which separated were collected, washed with cold MeCN, and recrystallized from MeCN. This afforded 1.62 g (89%) of pale yellow needles of **2a**, mp 154–155°C: ir 3260, 3210, 1595, 1588, 1562, 1485, 1436, 1412, 1343, 1272, 1215, 1105, 884, 700 cm^{-1}; nmr δ 8.86 (s, 1H, NH), 8.64 (s, 1H, NH), 8.57 ("d", 1H, J = 4.5 Hz, H_6), 8.18 ("d", 1H, J = 8 H_z, H_2), 7.72 ("t of ds", 1H, J = 8 hz, J = 2 Hz, H_4), 7.45 (m, 6H), 3.69 (s, 3H, N—CH_3), 2.39 (s, 3H, C—CH_3).

Anal. Calcd. for $C_{16}H_{18}N_6S_2$: C, H, N, S.

3-Methyl-5-[N-methylanilino(methylthio)methylene]-1-[1-(2-pyridinyl)ethylidene]-3-thioisocarbohydrazide (**3**). A suspension of 500 mg (1.39) mmole of **2a** in a solution consisting of 5 mL of 50% aqueous NaOH and 5 mL of EtOH was treated with 2 mL of CH_3I. An oil separated after a few minutes of stirring and was extracted into 50 mL of Et_2O. The organic solution was washed with H_2O (3 × 50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was recrystallized from MeOH to afford 425 mg (79%) of yellow rods of **3**, mp 102–104°C: ir 3330 (NH), 3060, 2924, 1567, 1529, 1252, 1155, 832, 777, 701 cm^{-1}. nmr δ 9.43 (s, 1H, NH), 8.54 ("d", 1H, J = 5.5 Hz, H_6), 8.14 ("d", 1H, J = 7.5 Hz, H_3), 7.68 ("t of ds", 1H, J = 7 hz, J = 1.5 Hz, H_4), 7.18 (m, 6H), 3.40 (s, 3H, N-CH_3), 2.51 (S, 3H, S-CH_3), 2.30 (s, 3H, S-CH_3), 2.23 (s, 3H, C-CH_3).

Anal. $C_{18}H_{22}N_6S_2$: C, H, N, S.

Antimalarial Studies

The compounds described herein were tested against a drug-sensitive strain of *P. berghei* (strain KGB 173) in mice. Five mice per dose level were infected by the intraperitoneal administration of parasitized erythrocytes. Untreated infected animals, which served as controls, died (on the average) after 6.2 d. A candidate drug was given 72 h after the mice were infected and was judged to be toxic if the infected mice died before day 6, inactive if they died between day 6 and day 12, active if the mean survival time of 6.2 d was at least doubled, and curative if the mice survived 60 d postinfection. Compounds which were active or curative at a dose of 40 mg/kg were retested at several lower dose levels, but results are not

reported unless extension of mouse survival time was observed. Details of the test procedure were given by Osdene et al.[5]

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