2-Acetylpyridine Thiosemicarbazones. 8. Derivatives of 1-Acetylisoquinoline as Potential Antimalarial Agents[1,2]

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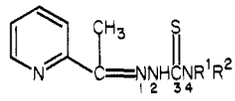
A series of 1-acetylisoquinoline thiosemicarbazones was prepared in order to evaluate their antimalarial properties. This was achieved by the reaction of 1-acetylisoquinoline with methyl hydrazinecarbodithioate to give methyl 3-[1-(1-isoquinolinyl)ethylidene]hydrazinecarbodithioate (II). Displacement of the *S*-methyl group from this intermediate by various primary and secondary amines afforded the desired 1-acetylisoquinoline thiosemicarbazones (III). Thiosemicarbazides in which the azomethine moiety of the latter was reduced could be prepared by the reaction of II with $NaBH_4$ to give methyl 3-[1-(1-isoquinolinyl)ethyl]hydrazinecarbodithioate (VIII). Reaction of VIII with the appropriate amine gave 1-[1-(1-isoquinolinyl)ethyl]thiosemicarbazides (IX). Evaluation of the antimalarial activity of series III and IX in mice infected with *Plasmodium berghei* indicated that cures were attainable at dose levels of 40–160 mg/kg.

The emergence of clinically significant multidrug-resistant falciparum malaria in various parts of the world (e.g., Southeast Asia, Africa, and South America[3]) has prompted the search for novel antimalarial agents whose mode of action is unlike those currently in use. 2-Acetylpyridine thiosemicarbazones (I) constitute a new



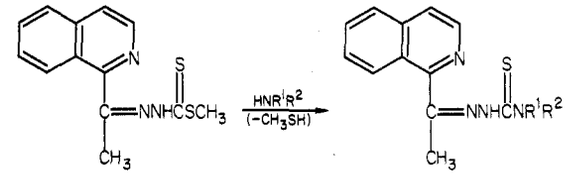
I

class of potential antimalarial agents[4,5] whose mode of action is, at present, under investigation. These compounds, in addition, possess a wide variety of other chemotherapeutic properties.[6]

We have investigated the effects of molecular modification upon antimalarial activity in an expanding series of compounds analogous to I and have described our observations in an earlier publication.[7] Furthermore, we have found that N^4,N^4-disubstitution in the thiosemicarbazone moiety enhances antimalarial activity and that incorporation of the N^4 nitrogen atom into various medium-sized rings is even more effective in increasing antimalarial activity.[5] Also, the reduction of the ethylidene moiety to afford an ethyl linkage results in retention of activity.[7] Replacement of the 2-pyridinyl ring by a 2-quinolinyl moiety gives less effective, but less toxic, analogues.[2]

In light of the favorable structure–activity relationship achieved by going from the antileukemic 2-formylpyridine thiosemicarbazones to the 1-formylisoquinoline thiosemicarbazones,[8–10] we synthesized a representative series of 1-acetylisoquinoline thiosemicarbazones for evaluation in our system. In the present series, the alkylidene group is maintained in an α position relative to the heterocyclic N atom. Because thiosemicarbazides derived from antimalarial thiosemicarbazones also show antimalarial activity,[2,7] 1-[1-(1-isoquinolinyl)ethyl]thiosemicarbazides were also prepared and evaluated. In general, R^1 and R^2 groups of III and IX were chosen that had been observed in our earlier studies to contribute to the antimalarial properties of 2-acylpyridine thiosemicarbazones.

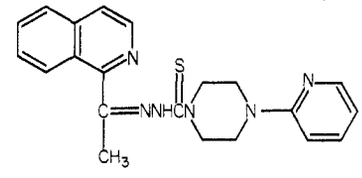
Chemistry. Methods for the formation of N^4-substituted thiosemicarbazones have been reported by us in previous papers of this series.[2,4] Reaction of 1-acetylisoquinoline[11] with methyl hydrazinecarbodithioate afforded methyl 3-[1-(1-isoquinolinyl)ethylidene]hydrazinecarbodithioate (II). The *S*-methyl group of this intermediate



II III

dithio ester is readily displaced by primary and secondary amines, yielding the desired 1-acetylisoquinoline thiosemicarbazones, III (cf. Table I).

A thiosemicarbazone that was deemed worth screening, based on 2-acetylpyridine data, is 4-(2-pyridinyl)-1-piperazinecarbothioic acid [1-(1-isoquinolinyl)-ethylidene]hydrazide (IV). Although the corresponding



IV

thiosemicarbazide (**19**) could be prepared in routine fashion, IV could not be isolated. Extended heating (i.e., for 48 h rather than the typical 8–10 h) of an ethanol solution of the two reactants, II and 1-(2-pyridinyl)-

(1) This is contribution no. 1671 to The Army Research Program on Drug Development.
(2) For paper 7 in this series, see Klayman, D. L.; Scovill, J. P.; Bartosevich, J. P.; Bruce, J.; Massie, S. P.; Grant, S. D.; Gonzalez, A. *Eur. J. Med. Chem.*, in press.
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(7) Klayman, D. L.; Scovill, J. P.; Bartosevich, J. F.; Bruce, J. *J. Med. Chem.* **1983**, *26*, 35.
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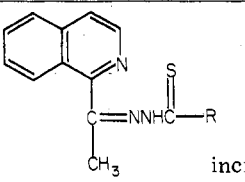
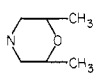
(11) Crowne, F. R.; Breckenridge, J. G. *Can. J. Chem.* **1954**, *32*, 641.

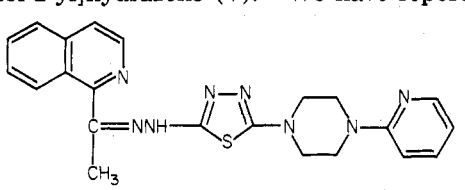
Table I. Antimalarial Activity of 1-Acetylisoquinoline Thiosemicarbazones against *Plasmodium berghei* in Mice



no.	R	mp, °C	yield, %	formula	recrystn solvent	increase in mean survival time, days, and no. of cures at the following dosage, mg/kg[a] 40	80	160	320	640
1	$NHCH_2C_6H_5$	114-115	36	$C_{19}H_{18}N_4S$	MeOH	0.1		0.9		0.5
2	$N(CH_3)_2$	108-110	45	$C_{14}H_{16}N_4S$	MeOH	7.3A	C(1/5)	9.2A	T(5/5)	T(5/5)
3	$N(CH_3)$-c-C_6H_{11}	99-101	46	$C_{19}H_{24}N_4S$	MeOH	9.5A	7.9A	C(3/5), T(1/5)	C(3/5)	T(5/5)
4	c-NC_4H_8	179-181	91	$C_{16}H_{18}N_4S$	MeCN	3.5	C(2/5)	C(2/5)	C(2/5)	T(5/5)
5	c-NC_6H_{12}	107-108	77	$C_{18}H_{22}N_4S$	MeOH	7.8A	6.9A	C(1/5)	C(2/5)	C(1/5), T(4/5)
6	c-NC_5H_9-4-CH_3	113-114	63	$C_{18}H_{22}N_4S$	EtOH	C(1/5)	C(1/5)	C(2/5), T(1/5)	T(5/5)	T(5/5)
7		138-139	76	$C_{20}H_{24}N_4S$	MeOH	C(2/5)	C(3/5)	C(5/5)	C(5/5)	C(5/5)
8		128-130	51	$C_{18}H_{22}N_4OS$	EtOH	3.5	8.6A	C(3/5)	C(3/5), T(1/5)	C(1/5), T(2/5)
9	c-NC_5H_9-4-C_6H_5	148-149	84	$C_{23}H_{24}N_4S$	EtOH	2.7	5.7	C(1/5)	C(1/5)	C(4/5)

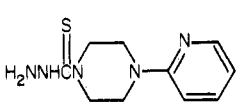
[a] A = active; C = cure; T = toxic. These terms are defined in ref 4 and 14.

piperazine, caused evolution of H_2S in addition to methyl mercaptan and led to the formation of methyl 1-isoquinolinyl ketone [5-[4-(2-pyridinyl)-1-piperazinyl]-1,3,4-thiadiazol-2-yl]hydrazone (V). We have reported in a

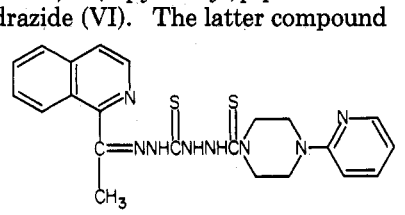


V

preliminary communication[12] on such a transformation and believe that the formation of V occurs via the initial formation of IV, which then hydrolyzes to 1-acetylquinoline and the thiosemicarbazide, 1-(2-pyridinyl)piperazine-4-thiocarboxylic acid hydrazide (VI). The latter compound



VI



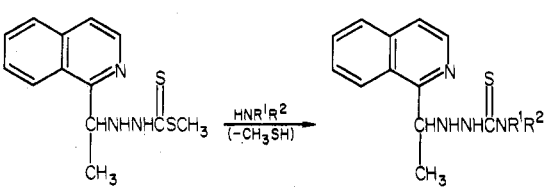
VII

may react with either II or IV to form the thiadiazole, V. Presumably, V results via an attack of the NH_2 group of VI upon the thiocarbonyl moiety of either II or IV to give the likely intermediate, a 1-amino-2,5-dithiobiurea (VII). This is followed by attack of one of the thiocarbonyl sulfur atoms upon the carbon atom of the second thiocarbonyl group, effecting ring closure and elimination of H_2S to afford V. This proposed mechanism is supported by our observation that thiosemicarbazide VI reacts with either II or 1-acetylquinoline to form V. Whereas VII was not isolated in this example, 1-amino-2,5-dithiobiureas have been obtained in related reactions.[12]

(12) Scovill, J. P.; Klayman, D. L. "Abstracts of Papers", 28th Congress of Pure and Applied Chemistry, Vancouver, BC, Aug 16-22, 1981, Abstr OR238.

The preparation of VI by the reaction of 1-(2-pyridinyl)piperazine with 4-methyl-4-phenyl-3-thiosemicarbazide utilizes the observation made by us of the ease of displacement by aliphatic amines of certain substituents (e.g., *N*-alkylanilino and *N*-arylanilino) when they are located at position 4 of a thiosemicarbazide.[12]

The reduction of dithio ester (II) with $NaBH_4$ afforded methyl 3-[1-(1-isoquinolinyl)ethyl]hydrazinecarbodithioate, VIII. The *S*-methyl group of this compound could be



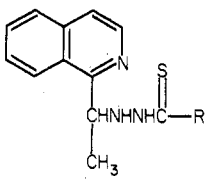
VIII IX

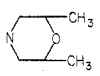
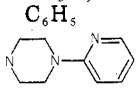
displaced by primary and secondary amines to give the desired 1-[1-(1-isoquinolinyl)ethyl]thiosemicarbazides, IX (cf. Table II).

Results and Discussion

Except for the sole N^4-monosubstituted derivative, compound **1**, all of the thiosemicarbazones derived from 1-acetylisoiquinoline displayed curative activity against *Plasmodium berghei* at at least one dosage level up to 640 mg/kg (cf. Table I). The N^4,N^4-dimethyl derivative, **2**, showed a low level of curative effect, curing one out of five animals at a dose level of 80 mg/kg. Higher doses resulted in animal deaths. Only thiosemicarbazone **7** proved capable of curing 100% of the test animals and this occurred at a dose of 160 mg/kg. It is interesting to note that toxic effects were not exhibited by this compound until a dose level of 640 mg/kg was administered. The analogous 2-acetylpyridine thiosemicarbazone (cf. ref 5) was one of the most active in its series, curing five out of five animals at a dose of 160 mg/kg. This 2-acetylpyridine thiosemicarbazone produced toxicity at 320 mg/kg. Thiosemicarbazones of 1-acetylisoquinoline that cured a majority of the test animals were compounds **3**, **8**, and **9** at doses of 160, 160, and 640 mg/kg, respectively.

Table II. Antimalarial Activity of 1-[2-(1-Isoquinolinyl)ethyl]thiosemicarbazides against *Plasmodium berghei* in Mice



no.	R	mp, °C	yield, %	formula	recrystn solvent	increase in mean survival time, days, and no. of cures at the following dosage, mg/kg[a] 40	80	160	320	640
10	$NHCH_2C_6H_5$	151-152	69	$C_{19}H_{20}N_4S$	EtOH	0.3		0.9		0.1
11	$N(CH_3)_2$	149-150	52	$C_{14}H_{18}N_4S$	EtOH	6.2		C(2/5), T(1/5)		T(5/5)
12	$N(CH_3)$-c-C_6H_{11}	154-155	67	$C_{19}H_{26}N_4S$	EtOH	C(2/5)	C(3/5)	C(2/5), T(2/5)	C(1/5), T(3/5)	C(1/5), T(3/5)
13	c-NC_4H_8	142	61	$C_{16}H_{20}N_4S$	MeCN	5.1	7.1A	C(3/5)	C(3/5), T(2/5)	C(1/5), T(4/5)
14	c-NC_6H_{12}	162-164	72	$C_{18}H_{24}N_4S$	MeCN	5.1	7.1A	C(3/5)	C(3/5), T(2/5)	C(2/5), T(2/5)
15	c-NC_5H_9-4-CH_3	128-130	43	$C_{18}H_{24}N_4S$	EtOH	7.6A	8.9A	C(3/5)	T(5/5)	T(5/5)
16		149-150	72	$C_{20}H_{26}N_4S$	MeCN	9.7A	C(1/5)	C(5/5)	C(4/5)	C(3/5)
17		140-142	16	$C_{18}H_{24}N_4OS$	MeCN	5.9	5.7	C(2/5)	C(3/5), T(1/5)	C(2/5), T(1/5)
18	c-NC_5H_9-4-C_6H_5	169	60	$C_{25}H_{26}N_4S$	MeCN	1.6	1.0	C(2/5)	C(1/5)	C(4/5)
19		166-167	78	$C_{21}H_{24}N_6S$	EtOH	1.6	2.7	6.6A	7.7A, T(2/5)	C(3/5), T(1/5)

[a] A = active; C = cure; T = toxic. These terms are defined in ref 4 and 14.

1-[1-(1-Isoquinolinyl)ethyl]thiosemicarbazides present a similar pattern of structure and activity (cf. Table II). The N^4-monosubstituted analogue, **10**, was devoid of antimalarial activity. The N^4,N^4-dimethyl derivative, **11**, shows a low level of curative activity at 160 mg/kg, with toxicity evident at higher doses. N^4-cyclohexyl-N^4-methylthiosemicarbazide **12** is more active than the corresponding thiosemicarbazone **3**; however, among the remaining members of this series, the reverse is seen. Only one thiosemicarbazide, **16**, proved capable of curing 100% of the test animals, and this occurred at a dose of 160 mg/kg. The latter compound and compound **7** are derivatives in which the N^4 nitrogen atom is incorporated into the 3 position of the bicyclo[3.2.2]nonane ring system. Compounds that proved capable of curing a majority of the test animals at at least one dose level included **12–15**, and **17–19**.

The 1,3,4-thiadiazole hydrazone, IV, although it shares a number of structural similarities with **19**, proved to be inactive, further stressing the importance of the thiocarbonyl moiety for activity.

Conclusion

As a series, the 1-acetylisoquinoline thiosemicarbazones are less potent antimalarials than the corresponding pyridine analogues. Nevertheless, it can be seen that employment of the structural relationships that we regard as essential for biological activity has led to the design of novel thiosemicarbazones possessing antimalarial properties.

Experimental Section

Melting points were taken on Thomas-Hoover apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as KBr disks. NMR spectra were run on either a JEOL FX90Q or Varian T-60A spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. Satisfactory elemental analyses (±0.3% of calculated values) were obtained for all compounds.

Methyl 3-[1-(1-Isoquinolinyl)ethylidene]hydrazinecarbodithioate (II). A solution of 24.4 g (0.2 mol) of methyl hydrazinecarbodithioate[4] in 75 mL of EtOH was treated with 34.2 g (0.2 mol) of 1-acetylisoquinoline,[11] and the reaction mixture was heated under reflux for 25 min. The product that separated was collected and washed with MeOH to afford 53.5 g (97%) of pale yellow crystals of methyl 3-[1-(1-isoquinolinyl)ethylidene]-hydrazinecarbodithioate (II), mp 170–172 °C. An analytical sample was prepared by two recrystallizations from MeCN and afforded pale yellow plates of II: mp 172–174 °C; IR 1593, 1497, 1300, 1069, 830, 753, 745, 682, 664 cm^{-1}. Anal. ($C_{13}H_{13}N_3S_2$) C, H, N, S.

3-Azabicyclo[3.2.2]nonane-3-thiocarboxylic Acid 2-[1-(1-Isoquinolinyl)ethylidene]hydrazide (7). The preparation of this compound by the reaction of dithio ester II with an amine exemplifies the preparation of N^4-substituted and N^4,N^4-disubstituted thiosemicarbazones of 1-acetylisoquinoline. A solution of 3.0 g (10.9 mmol) of II in 100 mL of EtOH was heated with 1.36 g (10.9 mmol) of 3-azabicyclo[3.2.2]nonane for 8–10 h. The solvent was removed under reduced pressure, and the residual oil slowly crystallized upon standing. The crystals of **7** were washed with EtOH and collected. An analytical sample was prepared by recrystallization three times from MeOH: IR 2930, 2860, 1595, 1500, 1417, 1340, 1193, 878, 825, 787, 750 cm^{-1}. Anal. ($C_{20}H_{24}N_4S$) C, H, N, S.

Methyl 1-Isoquinolinyl Ketone [5-[4-(2-Pyridinyl)-1-piperazinyl]-1,3,4-thiadiazol-2-yl]hydrazone (V). Method A. A suspension of 2.75 g (10 mmol) of II in 10 mL of EtOH was treated with 2.0 g (12.5 mmol) of 1-(2-pyridinyl)piperazine, and the mixture was heated at reflux for 48 h. The crystals that had separated were collected and washed with MeOH, affording 2.0 g (93%) of pale yellow needles of methyl 1-isoquinolinyl ketone [5-[4-(2-pyridinyl)-1-piperazinyl]-1,3,4-thiadiazol-2-yl]hydrazone: mp 237–239 °C dec; IR 3050, 2850, 1595, 1515, 1467, 1435, 1237, 943, 820, 773, 735 cm^{-1}. Anal. ($C_{22}H_{22}N_8S$) C, H, N, S.

Method B. A solution of 474 mg (2 mmol) of thiosemicarbazide VI and 342 mg (2 mmol) of 1-acetylquinoline in 60 mL of EtOH was heated at reflux for 8 h. The reaction mixture was chilled, and the crystals that separated were collected to give 245 mg

(57%) of pale yellow crystals of V, mp 234–236 °C dec, which was identical with that obtained by method A.

Method C. A solution of 197 mg (0.72 mmol) of carbodithioate II and 170 mg (0.72 mmol) of thiosemicarbazide VI in 30 mL of MeCN was heated at reflux for 8 h. The reaction mixture was chilled, and the crystals that separated were collected to give 188 mg (62%) of pale yellow crystals of V, mp 235–237 °C dec, which was identical with that obtained by method A.

1-(2-Pyridinyl)piperazine-4-thiocarboxylic Acid Hydrazide (VI). A solution of 181 mg (1 mmol) of 4-methyl-4-phenyl-3-thiosemicarbazide[13] and 163 mg (1 mmol) of 1-(2-pyridinyl)piperazine in 5 mL of MeOH was heated at reflux for 3 h. The solution was chilled, and the crystals that separated were collected to give 115 mg (48%) of colorless needles of VI: mp 184–185 °C (from MeOH); IR 3270, 3220, 3010, 2880, 1600, 1550, 1488, 1445, 1231, 1210, 982, 946, 768, 728 cm^{-1}. Anal. ($C_{10}H_{15}N_5S$) C, H, N, S.

Methyl 3-[1-(1-Isoquinolinyl)ethyl]hydrazinecarbodithioate (VIII). A suspension of 10 g (36.3 mmol) of carbodithioate II in 100 mL of EtOH was treated portionwise with 2.5 g (66 mmol) of $NaBH_4$, and the mixture was stirred for 2 h. An additional 2.5 g (66 mmol) of $NaBH_4$ was added, and stirring was continued for 2 h. The solution was poured into 100 mL of H_2O and treated cautiously with 6 mL of glacial HOAc. The gum that separated was extracted into 100 mL of $CHCl_3$, the extract was washed with three 100-mL portions of H_2O, and the dried $CHCl_3$ solution was evaporated under reduced pressure. The residual oil was rubbed under 25 mL of cold EtOH, and the crystals that formed were collected. This afforded 7.5 g (75%) of colorless rosettes, mp 107–109°C. An analytical sample of VIII was prepared by crystallization from MeCN: mp 109–110 °C; IR 3230 (NH), 3140, 2978, 1622, 1590, 1535, 1449, 1305, 1101, 1045, 1005, 818, 743 cm^{-1}. Anal. ($C_{13}H_{15}N_3S_2$) C, H, N, S.

3-Azabicyclo[3.2.2]nonane-3-thiocarboxylic Acid 2-[1-(1-Isoquinolinyl)ethyl]hydrazide (16). The preparation of 1-[1-(1-isoquinolinyl)ethyl]thiosemicarbazides from carbodithioate VIII is exemplified by the following reaction. A solution of 4.85 g (17.3 mmol) of VIII in 15 mL of EtOH was treated with 2.35 g (18.8 mmol) of 3-azabicyclo[3.2.2]nonane, and the mixture was heated under reflux for 8 h. The solution was chilled, and the product that separated was collected, affording 4.3 g (72%) of colorless cubes of **16**. An analytical sample was prepared by two crystallizations from MeCN: IR 3220 (NH), 3170 (NH), 2930, 1619, 1583, 1559, 1480, 1345, 1282, 825, 749 cm^{-1}. Anal. ($C_{20}H_{26}N_4S$) C, H, N, S.

Biological Method. The compounds described herein were tested at the Leo Rane Laboratory, University of Miami, Miami, FL, against a drug-sensitive strain of *Plasmodium berghei* (strain KBG 173) in mice. Details of the test procedure are given in the first paper in this series[4] and by Osdene, Russell, and Rane.[14]

Registry No. **1**, 87555-46-2; **2**, 87555-47-3; **3**, 87555-48-4; **4**, 85748-57-8; **5**, 75013-89-7; **6**, 87555-49-5; **7**, 87555-50-8; **8**, 87555-51-9; **9**, 87555-52-0; **10**, 87555-53-1; **11**, 87555-54-2; **12**, 87555-55-3; **13**, 87555-56-4; **14**, 87555-57-5; **15**, 87555-58-6; **16**, 87555-59-7; **17**, 87555-60-0; **18**, 87555-61-1; **19**, 87555-62-2; II, 85748-38-5; IV, 87555-63-3; V, 87555-64-4; VI, 87555-65-5; VIII, 87555-66-6; 1-acetylisoquinoline, 58022-21-2; 4-methyl-4-phenyl-3-thiosemicarbazide, 21076-05-1; methyl hydrazinecarbodithioate, 5397-03-5.

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2-Acetylpyridine Thiosemicarbazones. 9. Derivatives of 2-Acetylpyridine 1-Oxide as Potential Antimalarial Agents[1,2]

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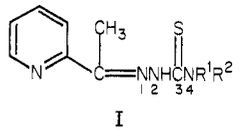
In view of the antimalarial activity in mice of 2-acetylpyridine thiosemicarbazones, a series of analogous 1-oxides was prepared for evaluation. Their synthesis was achieved by the reaction of 2-acetylpyridine 1-oxide with methyl hydrazinecarbodithioate to give methyl 3-[1-(2-pyridinyl 1-oxide)ethylidene]hydrazinecarbodithioate (II). Reaction of the latter intermediate with secondary amines afforded the desired 2-acetylpyridine 1-oxide thiosemicarbazones (III). Reduction of the azomethine linkage of II with $NaBH_4$ gave methyl 3-[1-(2-pyridinyl 1-oxide)ethyl]-hydrazinecarbodithioate (IV) whose *S*-methyl group was then displaced by amines to give a 1-[1-(2-pyridinyl 1-oxide)ethyl]thiosemicarbazide, V. Antimalarial activity of III was evaluated against both *Plasmodium berghei* in the mouse and *Plasmodium falciparum* in an automated in vitro test system. In both cases, 2-acetylpyridine 1-oxide thiosemicarbazones were found to be less active than the corresponding de-1-oxide analogues. When compounds V were evaluated against *Plasmodium berghei* in the mouse, a diminution of activity was similarly seen in comparison to the analogues not bearing the 1-oxide moiety.

Various 2-acetylpyridine thiosemicarbazones (I) possess



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antitrypanosomal,[3] antibacterial,[4-7] antiviral,[8] and antileukemic[9,10] properties. Inasmuch as our attention has centered upon the antimalarial effects of these compounds,[11,12] their analogues,[2,13-16] and their derivatives,[9] a program of molecular modification has been undertaken

(1) This is contribution no. 1684 to the Army Research Program on Drug Development.

(2) For paper no. 8 in this series, see: Klayman, D. L.; Scovill, J. P.; Bruce, J.; Bartosevich, J. F. *J. Med. Chem.*, preceding paper in this issue.

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