to form a clear orange solution was injected. In small (~100 mg) portions an additional amount of phosphonium salt was added to the solution until a trace remained undissolved within 20 min. The mixture was then cooled to −60 °C. An equivalent solution of 6-methoxy-8-nitroquinoline-4-carboxaldehyde (**5**) in dry THF (1 g/100 mL) was saturated with argon at −60 °C and added to the ylide solution. Stirring was continued for about 2 h. For the preparation of the trans isomers, the light gray-brown mixture was decomposed with an excess of ethanolic HCl. After basifying the yellow-brown solution with excess ammonia, the solvents were removed in vacuo. The residue was extracted with methylene chloride, 10 volumes of ether were added, and the decanted or filtered solution was evaporated to dryness. The residue crystallized upon addition of methanol. The product **6** was removed by filtration and the mother liquor chromatographed on Florisil with chloroform as the eluent to give additional amounts of **6**. In a modified workup, the solution which resulted after 2 h of stirring at room temperature was not acidified with HCl but immediately evaporated to a syrup. Methylene chloride–ether fractionation as above gave an olefin which crystallized upon addition of methanol but contained about 60% of the cis isomer instead. The cis and trans isomers could be separated by chromatography on Florisil. Individual examples are described in Table III.

General Procedure for 4-(β-Alkylvinyl)-8-amino-6-methoxyquinolines 8. To a mixture of 10 g of $SnCl_2 \cdot 2H_2O$ in 20 mL of ethanol, 40 mL of concentrated hydrochloric acid, and 330 mg of granular tin, 10 mmol of the 8-nitroquinoline derivative **6** was added in small portions with stirring while the temperature was kept at 0 °C. After 45 min, the external cooling was removed so the suspension could warm to room temperature. After warming the mixture at 30 °C for about 2 h, it was diluted with 40 mL of water, basified with 5 N sodium hydroxide, and extracted repeatedly with methylene chloride. The extract after drying with sodium sulfate was evaporated to give the 8-aminoquinoline derivative **8** in 80–90% yield. These products were used in the next step without further purification.

General Procedure for 4-Alkyl-8-amino-6-methoxyquinolines 7. A methanol solution (150 mL) of 2 g of 4-(β-alkylvinyl)-6-methoxy-8-nitroquinoline (**6**) was shaken with 3 g of wet Raney nickel under 45 lb/in.^{2} of hydrogen pressure while a temperature of 50 °C was maintained. The hydrogen pressure remained constant after 7 h. The cooled mixture was filtered, the solvent was evaporated, and the residue was vacuum dried. The amino compound (obtained in ~95% yield) was used for subsequent alkylation without further purification.

4-(Alkylvinyl)- and 4-Alkyl-8-[(4′-amino-1′-methylbutyl)amino]-6-methoxyquinolines (2 and 3). The amino compound **7** or **8** (~2 g) was heated with stirring at 105–110 °C under argon while a solution of 2 equiv of 4-iodo-1-phthalimidopentane in 2 g of triethylamine was added very slowly over a period of about 24 h. The pasty mixture was extracted with 30 mL of benzene, cooled, filtered, and concentrated under vacuum. The remaining yellow-brown syrup was purified by passing through a column of 200 g of silica gel 60 (Merck) using chloroform as the eluent. The pure alkylated amine recovered as a yellow syrup was refluxed with 4 equiv of hydrazine in 50 mL of ethanol. After 2–3 h, the cooled mixture was filtered and the filtrate concentrated under vacuum. The residue was treated with methylene chloride and filtered, and the filtrate was concentrated under vacuum. If needed, the methylene chloride treatment was repeated. Individual examples are described in Table IV.

Acknowledgment. The authors express their gratitude to Drs. E. A. Steck and R. E. Strube for many helpful suggestions and discussions during the course of this work. This work was supported by the U.S. Army Medical Research and Development Command under Research Contract DADA-17-74-C-4107. This is contribution no. 1539 to the Army Research Program on Malaria.

References and Notes

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(3) E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, **89**, 2758 (1967).
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(6) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(7) Test data were supplied by Dr. E. A. Steck, Walter Reed Army Institute of Research.
(8) Compounds **2c** and **2f** were not tested for antimalarial activity. However, these compounds, as well as all the other primaquine analogues reported in this paper, were evaluated for antileishmanial activity against *Leishmania donovani* in hamsters. Tests were carried out by Dr. W. L. Hanson, University of Georgia, Athens, Ga. [see W. L. Hanson, W. L. Chapman, Jr., and K. E. Kinnoman, *Int. J. Parasitol.*, **7**, 443 (1977), and references cited therein for a description of the test]. None of the compounds showed significant activity in this screen [see K. E. Kinnamon, E. A. Steck, P. S. Loizeaux, W. L. Hanson, W. L. Chapman, Jr., and V. B. Waits, *Am. J. Trop. Med. Hyg.*, **27**, 75 (1978)].
(9) A. Maercker, *Org. React.*, **14**, 270 (1965).

2-Acetylpyridine Thiosemicarbazones. 2. N^4,N^4-Disubstituted Derivatives as Potential Antimalarial Agents[1,2]

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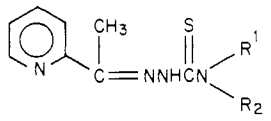
The most effective antimalarial agents among the N^4-monosubstituted 2-acetylpyridine thiosemicarbazones recently described by us have a cyclohexyl or a phenyl substituent and produce cures in *Plasmodium berghei* infected mice at a dose of 160 and 320 mg/kg, respectively. We report here on a related series of N^4,N^4-disubstituted 2-acetylpyridine thiosemicarbazones. Several members of this group bearing alkyl or cycloalkyl substituents at N^4 show activity superior to the most active monosubstituted 2-acetylpyridine thiosemicarbazones. However, the greatest improvement in potency was seen when the N^4-nitrogen atom was incorporated into a six- or seven-membered ring, such as the piperidine, piperazine, or azabicyclo[3.2.2]nonane systems, to give compounds with curative properties at a dose level as low as 20 mg/kg.

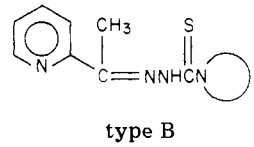
Recently, we reported[1] on a series of thiosemicarbazones obtained from 2-acetylpyridine which we found to be among the first such derivatives to possess antimalarial activity. It was shown that the molecular features essential for activity are a 2-pyridylethylidene moiety, the presence of the thiocarbonyl group (in contrast to a carbonyl group),

and certain bulky or cyclic structures at N^4. The highest level of activity was achieved when the N^4 monosubstitution was phenyl and cyclohexyl, cures being obtained against *Plasmodium berghei* in mice at a dose of 320 and 160 mg/kg, respectively. In that paper, we described compounds which are exclusively monosubstituted at N^4 of the thiosemicarbazone moiety.

In this article, we report on the synthesis and antimalarial activity of a series of 2-acetylpyridine thiosemicarbazones which are disubstituted at N^4. The compounds described fall into two classes, namely, those which have two groups at N^4 (type A) and those in which



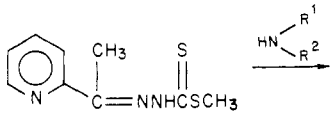
type A



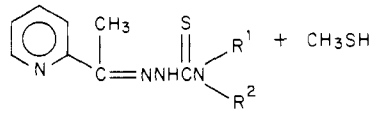
type B

N^4 is part of a ring system (type B).

Chemistry. Of the three general methods utilized by us to synthesize N^4-monosubstituted thiosemicarbazones of 2-acetylpyridine,[1] only one lent itself to the production of the N^4,N^4-disubstituted variety. That method entailed the displacement of the *S*-methyl group of methyl 3-[1-(2-pyridyl)ethylidene]hydrazinecarbodithioate (I) by a

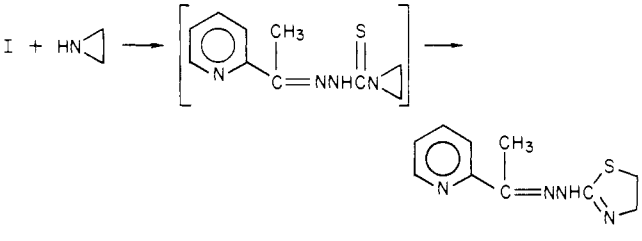


I



secondary amine. Type A and type B thiosemicarbazones formed with equal ease.

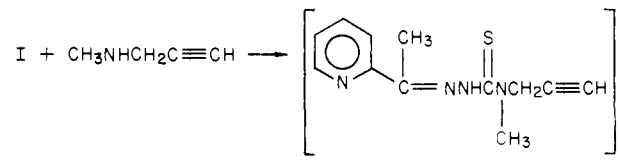
The general thiosemicarbazone synthesis, described above, failed to provide the desired product when either ethylenimine or *N*-methylpropargylamine was used as the nucleophile. In the former case, the presumed intermediate thiocarbamoylaziridine underwent a facile ring expansion to give 2-acetylpyridine 2-(2-thiazolinyl)hydrazone (II). The related isomerization has been studied by



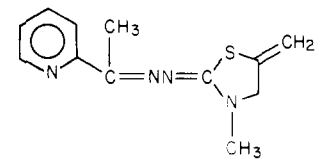
II

Deutsch and Fanta,[3] who converted 1-(*N*-phenylthiocarbamoyl)aziridine to 2-anilino-2-thiazoline by catalysis with hot concentrated hydrochloric acid. Heine[4] has reviewed isomerizations of aziridine derivatives caused by nucleophilic reagents and by thermolysis.

In the case of the displacement reaction of *N*-methylpropargylamine on I, the expected 2-acetylpyridine 4-methyl-4-propargyl-3-thiosemicarbazone (III) was not obtained but rather a compound identified as 3-methyl-5-methylene-2-thiazolidinone 1-(2-pyridylethylidene)hydrazone (IV). This structural assignment is based on the following considerations: elemental analysis and mass spectrometry revealed that the product was isomeric with the proposed intermediate III, whereas the lack of absorbance near 3300 cm^{-1} in the infrared, seen in the related compound 2-acetylpyridine 4-propargyl-3-thiosemicarbazone, indicated the absence of the terminal acetylenic moiety.[5] These data suggested the possibility that an intramolecular cyclization involving the thiocarbonyl group and the carbon–carbon triple bond had occurred. Additional confirmation for structure IV was found in the NMR spectrum of the product, which showed multiplets δ 4.55 and 5.43 corresponding to the endocyclic and exocyclic methylene protons.

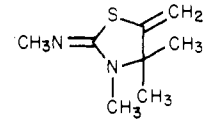


III

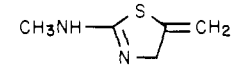


IV

Precedence for structure IV may be found in the work of Easton et al.,[6] who noted that it was very difficult to isolate a noncyclic product when an N-substituted propargylamine was treated with an isothiocyanate. They prepared 3,4,4-trimethyl-5-methylene-2-(methylimino)-thiazolidine (V) by reaction of 3-(methylamino)-3-methyl-1-butyne with methyl isothiocyanate. Eloy and Deryckere[7] observed 2-(methylamino)-5-methylene-2-thiazoline (VI) as the major product when propargylamine reacted with methyl isothiocyanate.

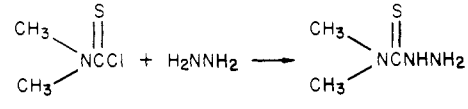


V

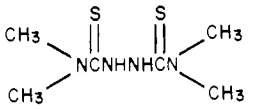


VI

The compound, 2-acetylpyridine 4,4-dimethyl-3-thiosemicarbazone (1) was made not only by the above-mentioned general method but also from the requisite thiosemicarbazide (VII). Without giving experimental details, Jensen[8] reported to have made 4,4-dialkyl-3-thiosemicarbazides in low yield by the action of hydrazine hydrate on dialkylthiocarbamoyl chlorides. Better yields were achieved, however, using dialkylthiocarbamoylthioglycolic acids as precursors. Inasmuch as dimethylthiocarbamoyl chloride is now commercially available, it was of interest to reexamine its utility as a starting material for VII. We observed that when the reaction was run in hydroxylic solvents only a yellow-orange solid was obtained, which was presumably tetramethylthiuram monosulfide.[9] Acetonitrile as a reaction medium allowed the formation of some VII and a mixture of byproducts, predominant among which was 1,1,6,6-tetramethyl-2,5-dithiobiurea (VIII).[10] The use of carbon tetrachloride as the reaction medium, however, gave VII, which separated in good purity from the biphasic reaction mixture in 87%



VII



VIII

yield. The use of diethyl ether afforded an 84% yield of VII and chloroform, a 65% yield of VII. The thiosemicarbazide is distinguishable from VIII in that it reacts with ammoniacal silver nitrate solution to give a black precipitate of silver sulfide, whereas the latter gives a yellow gelatinous precipitate.

Results and Discussion

The group of compounds of type A, where R^1 and R^2 are both alkyl (1–5), appear to be rather toxic and, except for the N^4,N^4-diethyl compound 2, shows no antimalarial activity. Compound 2 shows both toxic deaths and cures at moderate doses. It is of interest that the N^4,N^4-dimethyl compound 1 is one of the most potent antibacterial compounds in vitro in the entire series of 2-acetylpyridine thiosemicarbazones.[11]

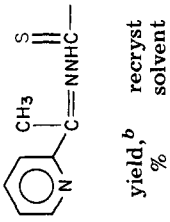
N^4-Substitution by both a methyl and a cycloalkyl group as in compounds 6–8 gave cures in the 80–320 mg/kg range and exhibited toxicities at the higher dosage levels. The thiosemicarbazone derived from *N*-methylglucosamine (9) was inactive. N^4-Methyl and -benzyl substitution gave compound 10, which exhibited both cures and toxicity in the range 80–640 mg/kg. Extension of the benzyl side chain to phenethyl in compound 11 eliminated toxicity but gave a compound which was curative only at 640 mg/kg. A related compound, N^4-methyl-N^4-2-(2-pyridylethyl) (12), was toxic at the lowest levels tested and inactive. The N^4,N^4-dibenzyl compound 13 also was inactive.

The type B compounds which were tested had the N^4-nitrogen atom incorporated into 4–9-membered and 13-membered rings. In general, optimum activity was found to reside in the six-membered cycles, simple alkyl substitution about the ring having a profound influence on the extent of antimalarial properties exhibited. The first member of the subseries, the azetidine compound 14, was inactive; the pyrrolidine 15 was slightly active and more toxic; however, placement of methyl groups at both the 2 and 5 positions of the pyrrolidine ring gave compound 16 showing moderate curative activity and decreased toxicity. Whereas the parent compound of the piperidine group 17 was inactive, activity could similarly be imparted by placement of methyl groups about the ring. Thus, high curative activity at 40 mg/kg was exhibited by the 2- and 4-methylpiperidinyl compounds 18 and 20, respectively. The presence of two methyl groups (as in compounds 21 and 22) or a 2-ethyl (23), 4-phenyl (25), or 4-benzyl (26) group on the piperidine ring resulted in compounds which were still curative, albeit at higher doses. The presence of a 4-hydroxy (24) or an acetal function (27) led to inactive piperidino derivatives.

The tetrahydropyridino compound 28 was essentially inactive, as was piperidine 17, but placement of a phenyl ring in the 4 position of the former compound (29) led to improvement in antimalarial activity, as was seen in 26. The morpholino compound 30 was highly toxic at the lowest dosage level, but situating methyl groups at both the 3 and 5 positions (31) gave a compound which, despite its toxicity, also gave cures at 20 mg/kg.

In the balance of the series, where rings were 7, 8, 9, and 13 membered (compounds 32–35, respectively), cures were seen in the first two compounds in the dosage of 80–640 mg/kg with some deaths due to compound toxicity occurring only with the seven-membered compound. The latter two compounds of this group were not toxic, only

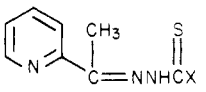
Table I. Antimalarial Activity of Type A 2-Acetylpyridine N^4,N^4-Disubstituted Thiosemicarbazones against *Plasmodium berghei* in Mice



no.	R^1	R^2	mp, °C	formula	yield,[b] %	recryst solvent	increase in mean surv time (days) and no. of cures at dosage, mg/kg[a] 40	80	160	320	640
1	CH_3	CH_3	155–156[d]	$C_{10}H_{14}N_4S$	87, 73[c]	MeOH	0.5, T(3/5)		0.0, T(5/5)		0.0, T(5/5)
2	C_2H_5	C_2H_5	115–116	$C_{12}H_{18}N_4S$	40	C_6H_6–C_6H_{12}	7.2A	C(1/5), T(1/5)	C(1/5), T(2/5)		0.0, T(5/5)
3	n-C_3H_7	n-C_3H_7	82–83	$C_{14}H_{22}N_4S$	30	pet. ether	0.0, T(5/5)		0.0, T(5/5)		3.0
4	i-C_4H_9	i-C_4H_9	105–106	$C_{16}H_{26}N_4S$	18	pet. ether	–0.2		0.8, T(2/5)		0.5, T(2/5)
5	CH_3	n-C_4H_9	76–77	$C_{13}H_{20}N_4S$	44	pet. ether	5.9	8.1A	6.9A, T(3/5)	0.0, T(5/5)	0.0, T(5/5)
6	CH_3	c-C_5H_9	113–114	$C_{14}H_{20}N_4S$	72	C_6H_{12}	1.5	C(1/5)	C(4/5)	6.0, T(5/5)	0.0, T(5/5)
7	CH_3	c-C_6H_{11}	96	$C_{15}H_{22}N_4S$	30	C_6H_6	3.7		C(1/5), T(3/5)		–0.3 T(3/5)
8	CH_3	c-C_8H_{15}	102–103	$C_{17}H_{26}N_4S$	83	C_6H_{12}	3.2	9.6A	C(2/5)	C(4/5)	12.1A, T(1/5)
9	CH_3	$-CH_2C(OHH)C(OHH)CCH_2OH$ (H OHH H)	145–147	$C_{15}H_{24}N_4O_5S$	15	EtOH	0.2		1.4		0.3, T(3/5)
10	CH_3	$-CH_2C_6H_5$	106–107	$C_{16}H_{18}N_4S$	60	MeOH	4.0	C(1/5), T(1/5)	C(1/5), T(2/5)	C(1/5), T(2/5)	C(1/5), T(3/5)
11	CH_3	$-CH_2CH_2C_6H_5$	122–123	$C_{17}H_{20}N_4S$	82	MeOH	0.4		7.2A		C(2/5)
12	CH_3	$-CH_2CH_2$-2-pyridyl	104–105	$C_{16}H_{19}N_5S$	62	C_6H_6–C_6H_{12}	1.7, T(1/5)	3.3	0.0, T(5/5)	6.7A, T(4/5)	0.0, T(5/5)
13	$-CH_2C_6H_5$	$-CH_2C_6H_5$	156	$C_{22}H_{22}N_4S$	33	EtOH	–0.1		1.6, T(1/5)		–0.2, T(3/5)

[a] T = toxic; A = active; C = cure. See Experimental Section for definitions. [b] Yields have not been optimized. [c] Prepared from 4,4-dimethyl-3-thiosemicarbazide. See Experimental Section. [d] Decomposition.

Table II. Antimalarial Activity of Type B 2-Acetylpyridine N⁴-Azacyclic Thiosemicarbazones against *Plasmodium berghei* in Mice



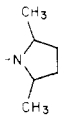
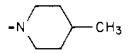
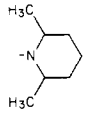
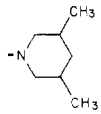
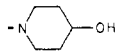
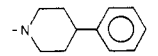
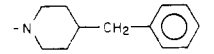
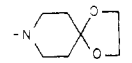
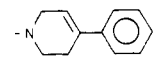
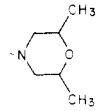
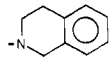
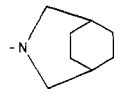
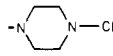
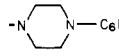
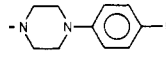
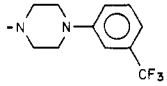
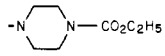
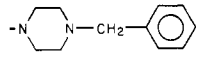
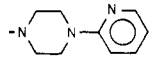
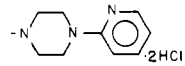
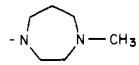
no.	X	mp, °C	formula	yield,[b] %	recrystn solvent	increase in mean surv time (days) and no. of cures at dosage, mg/kg[a]				
						40	80	160	320	640
14		175-176	$C_{11}H_{14}N_4S$	47	CH_3CN	1.7		0.0, T(5/5)		0.0, T(5/5)
15		147-148	$C_{12}H_{16}N_4S$	59	MeOH	8.9A, T(3/5)		0.0, T(5/5)		0.0, T(5/5)
16		117	$C_{14}H_{20}N_4S$	30	MeOH	4.7	C(1/5)	C(3/5), T(1/5)	0.0, T(5/5)	0.0, T(5/5)
17		152-153	$C_{13}H_{18}N_4S$	73	EtOH	−0.4		−0.4		0.0
18		108–109	$C_{14}H_{20}N_4S$	79	MeOH	C(3/5)		0.0, T(5/5)		0.0, T(5/5)
19		155-156	$C_{14}H_{20}N_4S$	78	EtOH	4.1		C(1/5), T(2/5)		0.0, T(5/5)
20		119-120	$C_{14}H_{20}N_4S$	87	MeOH	C(3/5)		0.0, T(5/5)		0.0, T(5/5)
21		135-141[g]	$C_{15}H_{22}N_4S$	44	MeOH	0.5	1.6	6.3	C(3/5)	C(3/5), T(1/5)
22		137-140	$C_{15}H_{22}N_4S$	19	MeOH	5.6	C(4/5)	C(4/5)	0.0, T(5/5)	−0.4, T(4/5)
23		103	$C_{15}H_{22}N_4S$	40	C_6H_{12}	5.6		C(3/5)		−0.2, T(2/5)
24		143-144	$C_{13}H_{18}N_4OS$	78	MeOH	−0.1, T(1/5)		0.0, T(5/5)		0.6, T(4/5)
25		174-175	$C_{19}H_{22}N_4S$	86	EtOH	0.4	C(1/5)	C(3/5)	C(5/5)	C(5/5)
26		135.5[g]	$C_{20}H_{24}N_4S$	79	EtOH	0.4	2.8	C(2/5)	C(4/5)	C(5/5)
27		150–152	$C_{15}H_{20}N_4O_2$	50	CH_3CN	0.0, T(5/5)		0.0, T(5/5)		0.0, T(5/5)
28		145-146	$C_{13}H_{16}N_4S$	71	MeOH	4.0		1.4, T(4/5)		7.4A, T(4/5)
29		188-189[g]	$C_{19}H_{20}N_4S$	80	$CHCl_3$	0.8	2.0	C(1/5)	C(3/5)	C(4/5)
30		182-185	$C_{12}H_{16}N_4OS$	58	MeOH	0.0, T(5/5)		0.0, T(5/5)		0.0, T(5/5)
31		153-155	$C_{14}H_{20}N_4OS$	56	EtOH	C(2/5), T(2/5)[c]		0.0, T(5/5)		0.0, T(5/5)
32		161-162	$C_{14}H_{20}N_4S$	51	MeOH	6.2A	C(4/5)	C(3/5), T(1/5)	C(2/5), T(2/5)	C(2/5), T(3/5)
33		166	$C_{15}H_{22}N_4S$	91	MeOH	0.6	C(1/5)	C(3/5)	C(5/5)	C(4/5)

Table II (*Continued*)

no.	X	mp, °C	formula	yield,[b] %	recrystn solvent	increase in mean surv time (days) and no. of cures at dosage, mg/kg[a] 40	80	160	320	640
34		166	$C_{16}H_{24}N_4S$	82	MeOH	−0.3		1.7		9.0A
35		134–135	$C_{20}H_{32}N_4S$	86	MeOH	0.0		0.1		2.9
36		185[d]	$C_{16}H_{16}N_4S$	79	THF	0.5		0.3, T(3/5)		0.3, T(4/5)
37		146	$C_{17}H_{18}N_4S$	87	MeOH	3.5		7.7A		C(4/5)
38		156	$C_{16}H_{22}N_4S$	46	MeOH	C(3/5)[e]	C(3/5)	C(5/5)	0.2	0.4, T(4/5)
			4-substituted piperazino compounds							
39		154–155	$C_{13}H_{19}N_5S$	54	C_6H_{12}	0.0, T(5/5)		0.0, T(5/5)		0.0, T(5/5)
40		180–182[g]	$C_{18}H_{21}N_5S$	48	MeOH	7.0A	11.7A	C(4/5)	−0.1, T(1/5)	−0.4, T(5/5)
41		185–186[g]	$C_{18}H_{20}FN_5S$	14	EtOH	C(1/5)		C(5/5)		9.0A
42		171–172	$C_{19}H_{20}F_3N_5S$	51	CH_3CN	0.1	2.4	C(2/5)	C(1/5), T(3/5)	C(3/5), T(2/5)
43		171[g]	$C_{15}H_{21}N_5O_2S$	46	MeOH	C(2/5), T(2/5)		0.0, T(5/5)		0.0, T(5/5)
44		171–172	$C_{19}H_{23}N_5S$	43	MeOH	1.6	4.4	5.6	C(5/5)	C(2/5)
45		181–182[g]	$C_{17}H_{20}N_6S$	57	CH_3CN	C(4/5)[f]	C(5/5)	C(2/5)	0.7, T(2/5)	0.0, T(5/5)
46		156–162[g]	$C_{17}H_{22}Cl_2N_6S$	60	washed with CH_3CN	3.2	C(2/5)	C(3/5)	C(3/5)	0.0, T(5/5)
47		146–147	$C_{14}H_{21}N_5S$	36	CH_3CN	0.8, T(1/5)		0.8, T(4/5)		0.0, T(5/5)

[a] T = toxic; A = active; C = cure. See Experimental Section for definitions. [b] Yields have not been optimized. [c] At a dose of 20 mg/kg, C(3/5); 10 mg/kg, A 6.8. [d] S: calcd, 10.82; found, 11.47. [e] At a dose of 20 mg/kg, C(1/5). [f] At a dose of 20 mg/kg, C(3/5). [g] Decomposition.

34 showing a trace of activity at 640 mg/kg.

Of the related indolino (**36**) and tetrahydroisoquinolyl (**37**) compounds, only the latter showed cures at the highest dose tested. The compound 3-azabicyclo[3.2.2]nonane-3-thiocarboxylic acid 2-[1-(2-pyridyl)ethylidene]hydrazide (**38**), one of the most active in the series, was curative in the dosage range of 20–160 mg/kg, whereas at higher doses toxicity became apparent.

Like the piperidino compounds, the activity of the 4-substituted piperazino derivatives was strongly dependent on the nature of the substituents. The most active compounds were those which are 4-substituted with 4-fluorophenyl (**41**), carboethoxy (**43**), and 2-pyridyl (**45**). The latter, exhibiting curative action at 20 mg/kg, is considered to be the most active 2-acetylpyridine thiosemicarbazone we have developed to date. Toxicity did not appear until the 320 mg/kg level. Most 2-acetylpyridine thiosemicarbazones, while soluble in dilute hydrochloric acid, are insufficiently strong bases to form isolable hydrochloride salts. A dihydrochloride salt of **45**, compound **46**, could be prepared because of the additional basic moieties present in the molecule. It was of interest to evaluate the effect of aqueous solubility on the biological properties of the otherwise highly water-insoluble thiosemicarbazones. It was then demonstrated that compound **46** was a less active antimalarial than the free base. This diminution of activity cannot be accounted for by the reduced quantity of the active constituent due to the presence of the 2 equiv of hydrogen chloride. The 4-phenyl (**40**), 4-[3-(trifluoromethyl)phenyl] (**42**), and 4-benzyl (**44**) derivatives had moderate activity, whereas the 4-methyl (**39**) derivative was totally inactive. Similar to **39**, the 4-methylhomopiperazine compound **47** was toxic and inactive.

Conclusion

Whereas the most active antimalarial of the N^4-monosubstituted 2-acetylpyridine thiosemicarbazones exhibits curative action at a dose level of 160 mg/kg, many of the type A N^4,N^4-disubstituted variants give evidence of cures at the 80 mg/kg drug level. Even more substantial improvement was achieved with the type B thiosemi-

carbazones, several of which (i.e., **31**, **38**, and **45**) demonstrated curative action at 20 mg/kg. This is a 16-fold improvement in potency over the lead compound, 2-acetylpyridine 4-phenyl-3-thiosemicarbazone.

The nature of the molecular configuration about N^4 strongly governs the antimalarial properties of the compounds of this series. The incorporation of N^4 into a medium-sized (i.e., six- or seven-membered) monocyclic or bicyclic system seems to be important for the optimization of activity.

Experimental Section

Melting points were taken on a Fisher-Johns hot stage interfaced with a Bailey Instruments BAT-8 digital thermometer. Infrared spectra of solid samples were run as KBr pellets on a Perkin-Elmer Model 283 spectrometer. NMR spectra were run on a Varian T60-A spectrometer using Me_4Si as an internal standard. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. Satisfactory elemental analyses (±0.4% of calculated values) were obtained for all compounds except where noted otherwise. Mass spectra were determined on a Finnigan 3100D spectrometer operated in the CI mode using CH_4 as the reagent gas.

2-Acetylpyridine N^4,N^4-Disubstituted 3-Thiosemicarbazones. General Procedure. To 2.4 g (0.02 mol) of methyl 3-[1-(2-pyridyl)ethylidene]hydrazinecarbodithioate (I)[1] in 50 mL of MeOH was added 0.02 mol of an appropriate secondary amine. The solution was heated at reflux until the evolution of MeSH essentially ceased. The volatile thiol was detected by the yellow color it imparts to filter paper moistened with $Pb(OAc)_2$ solution which was placed at the exit of the reflux condenser. Reaction times ranged from 3 to 10 h.

In the case of displacement by dimethylamine, 2 equiv, contained in a 40% aqueous solution, rather than 1, was used to compensate for loss of the reactant due to its volatility. A satisfactory yield was obtained.

It is of interest that, whereas N^4-monosubstituted 2-acetylpyridine-3-thiosemicarbazones are generally white or pale yellow, the N^4,N^4-disubstituted tend to be brilliant yellow in color.

2-Acetylpyridine 2-(2-Thiazolinyl)hydrazone (II). Method A. A suspension of 2.25 g (0.01 mol) of I in 5 mL of CH_3CN was treated with 0.83 g (1 mL, 0.02 mol) of ethylenimine. A vigorous, exothermic reaction ensued with the rapid evolution of MeSH. The solution was heated to reflux for 4 h and cooled. The crystals which separated were collected and recrystallized from CH_3CN to give 1.1 g (47%) of white prisms of 2-acetylpyridine 2-(2-thiazolinyl)hydrazone (II): mp 146–147 °C; NMR ($CDCl_3$) δ 2.48 (s, 3 H), 3.18 (t, 2 H), 3.73 (t, 2 H). Anal. ($C_{10}H_{12}N_4S$) C, H, N, S.

Method B. A solution of 500 mg (4.13 mmol) of 2-acetylpyridine in 10 mL of MeOH was treated with 500 mg (3.25 mmol) of 2-hydrazino-2-thiazoline hydrochloride,[12] followed by 5 mL of triethylamine and 5 mL of H_2O. The solution was warmed gently for a few minutes and then cooled. The crystals which separated were collected and recrystallized from CH_3CN, affording 230 mg (24%) of white prisms of 2-acetylpyridine 2-(2-thiazolinyl)-hydrazone, mp 146–147 °C. The IR spectra of the compounds prepared by methods A and B were identical.

3-Methyl-5-methylene-2-thiazolidinone 1-(2-Pyridylethylidene)hydrazone (IV). A solution of 9.8 g (43.4 mmol) of I and 3.0 g (43.4 mmol) of *N*-methylpropargylamine in 30 mL of MeOH was heated at reflux until evolution of MeSH ceased (ca. 48 h). The solution was cooled to give 6.97 g (66%) of pale-yellow needles, mp 110–111 °C (from MeOH), consisting of 3-methyl-5-methylene-2-thiazolidinone 1-(2-pyridylethylidene)hydrazone (IV): NMR ($CDCl_3$) δ 2.72 (s, 3 H, C-CH_3), 3.37 (s, 3 H, N-CH_3), 4.55 (t, 2 H), 5.43 (t, 2 H), 7.42 (m, 1 H), 7.87 (t of d, 1 H), 8.42 (br d), 8.78 (br d); MS *m/e* (relative intensity) 247 (M + 1, 100), 246 (70), 133 (35), 132 (30), 78 (42). Anal. ($C_{12}H_{14}N_4S$) C, H, N, S.

Propargyl Isothiocyanate. A solution of 11.5 g (0.1 mol) of thiophosgene in 30 mL of CH_2Cl_2 was combined with a solution of 10.5 g (0.1 mol) of Na_2CO_3 in 100 mL of H_2O and the biphasic mixture was cooled to ca. 8 °C. Then 5.5 g (0.1 mol) of propargylamine in 10 mL of H_2O was added with rapid stirring over 1 h, followed by stirring for an additional 2 h. The two layers were separated, the CH_2Cl_2 solution was dried, and the product, after removal of the solvent at atmospheric pressure, was distilled at 43 °C (15 mmHg) to afford 6.71 g (69%) of propargyl isothiocyanate: IR (neat) 3310 (HC≡), 2940, 2100 (br, –NCS), 1437, 1340, 1098, 937 cm^{-1}; NMR ($CDCl_3$) δ 2.53 (t, 1 H, J = 2 Hz), 4.32 (d, 2 H, J = 2 Hz). Anal. (C_4H_3NS) C, H, N, S.

2-Acetylpyridine 4-Propargyl-3-thiosemicarbazone. A solution of 4.17 g (31 mmol) of 2-acetylpyridine hydrazone[13] in 5 mL of MeOH was treated with 3.0 g (31 mmol) of propargyl isothiocyanate, causing an exothermic reaction. The mixture was allowed to stand at room temperature overnight and cooled, and the crystals which separated were collected, affording 6.0 g (83%) of pale-yellow needles of 2-acetylpyridine 4-propargyl-3-thiosemicarbazone: mp 161 °C (from MeOH); IR 3332 (N-H), 3317 (≡CH), 3223 (N-H); NMR δ 2.35 (t, 1 H, ≡CH), 2.45 (s, 3 H, CH_3), 4.60 (pair of doublets, 2 H, CH_2C≡). As a monosubstituted thiosemicarbazone, it reacts positively to give a black precipitate of silver sulfide with ammoniacal silver nitrate solution. Anal. ($C_{11}H_{12}N_4S$) C, H, N, S.

4,4-Dimethyl-3-thiosemicarbazide (VII). To a vigorously stirring ice-cooled mixture of 12 mL of 85% hydrazine hydrate and 7 mL of CCl_4 was added dropwise over 30 min 4.92 g (0.04 mol) of dimethylthiocarbamoyl chloride in 10 mL of CCl_4. The reaction mixture was stirred an additional 1.5 h. The precipitate which formed was then collected, washed with a small volume of cold CCl_4, and dried to give 4.18 g (87%) of 4,4-dimethyl-3-thiosemicarbazide, mp 154–155 °C. The CCl_4 filtrate, containing a mixture of the desired product and 1,1,6,6-tetramethyl-2,5-thiobiurea (VIII),[10] was not worked up. An analytical sample of VII was prepared by recrystallization from EtOH: mp 158–159 °C (lit.[8,9] mp 156–157 °C); IR 3310, 3250, 2940, 1615, 1530, 1390, 1360, 980, 670 cm^{-1}; NMR ($CDCl_3$) δ 3.25 (s, N-CH_3). Anal. ($C_3H_9N_3S$) C, H, N, S.

When the above-described reaction was run identically in Et_2O (except that 24 mL of solvent was required to dissolve the dimethylthiocarbamoyl chloride), an 84% yield of VII was obtained, mp 147–149 °C, which on recrystallization from $CHCl_3$ gave IV melting at 156.5 °C: IR same as given above. Anal. ($C_3H_9N_3S$) C, H, N, S.

2-Acetylpyridine 4,4-Dimethyl-3-thiosemicarbazone (1). A 10-mL MeOH solution containing 1.2 g (0.01 mol) of VII and 1.45 g (0.012 mol) of 2-acetylpyridine was heated under reflux on a steam bath for 4 h. The solution was cooled and the product which separated was collected and recrystallized two times from MeOH to give 1.6 g (73%) of 2-acetylpyridine 4,4-dimethyl-3-thiosemicarbazone (1), mp 154–155 °C. Its IR spectrum was identical with that of 1 made by the displacement reaction.

Biological Method. The compounds described herein were tested at the Dr. Leo Rane Laboratory, University of Miami, Miami, FL, against a drug-sensitive strain of *Plasmodium berghei* (strain KBG 173) in mice. Five mice per dose level are infected by the intraperitoneal administration of parasitized erythrocytes. Untreated infected animals, which serve as controls, die, on the average, after 6.2 days. A candidate drug is given 72 h after the mice are infected and is judged to be "toxic" if the infected mice die before the 6th day, "inactive" if they die between the 6th and 12th days, "active" if the mean survival time of 6.2 days is at least doubled, and "curative" if the mice survive 60 days postinfection. Compounds which are "active" or "curative" at a dose of 40 mg/kg are retested at several lower dose levels, but results are not reported unless extension of mouse survival time is observed. Details of the test procedure were given in the first paper in this series and by Osdene, Russell, and Rane.[14]

Acknowledgment. We acknowledge with thanks the continued interest and encouragement of Drs. Craig J. Canfield and Thomas R. Sweeney.

References and Notes

(1) For paper 1 in this series, see D. L. Klayman, J. F. Bartosevich, T. S. Griffin, C. J. Mason, and J. P. Scovill, *J. Med. Chem.*, **22**, 855 (1979).
(2) This is contribution no. 1541 to the Army Research Program on Malaria.
(3) A. S. Deutsch and P. E. Fanta, *J. Org. Chem.*, **21**, 892 (1956).

(4) W. H. Heine, *Angew. Chem., Int. Ed. Engl.*, 1, 528 (1962).
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Substituted 3-Amino-1,1-diaryl-2-propanols as Potential Antidepressant Agents

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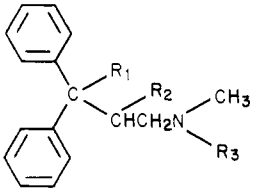
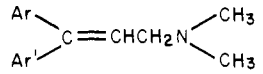
Following the discovery that 3-(dimethylamino)-1,1-diphenyl-2-propanol hydrobromide (1) possesses potent reserpine-prevention activity in mice, a series of analogues of 1 was synthesized and evaluated as potential antidepressant agents. Several routes to analogues of 1 were evaluated, the most generally applicable of which was the regiospecific ring opening of a suitably functionalized 1,1-diaryl-2,3-epoxypropane (obtained in three stages from the corresponding benzophenone) with the appropriate amine. The more interesting compounds of the series were evaluated for their propensity to cause undesirable peripheral anticholinergic effects, all compounds tested being markedly less active than imipramine on this parameter. On the basis of its good activity in biochemical and pharmacological animal models of depression, together with its relative lack of anticholinergic side effects, 1-(3-chlorophenyl)-3-(dimethylamino)-1-phenyl-2-propanol hydrochloride (**20**, BRL 14342) was chosen for further evaluation.

The discovery of a novel antidepressant free of monoamine oxidase inhibiting properties and without the untoward cardiovascular and anticholinergic effects of the tricyclic antidepressants remains a key target of medicinal research. During the reinvestigation of a series of diarylpropanamines, originally reported[1] to be devoid of significant pharmacological activity, several compounds, including 1, were found to possess antireserpine activity in mice. Such activity is considered to be indicative of those antidepressants which are thought to exert their desired effects primarily by potentiating the actions of neuronal catecholamines (particularly noradrenaline). Antidepressant activity has been claimed for other diarylpropanamines (**2**,[2] **3**,[3] **4**,[4] and **5**[5]) and diarylpropenamines (**6**[2] and **7**[6]), although it should be noted that **7**, which is thought to act primarily by inhibiting neuronal 5-hydroxytryptamine uptake, possesses only a weak antireserpine effect.[7] This paper is concerned with the synthesis of novel analogues of 1 and their evaluation as potential antidepressants.



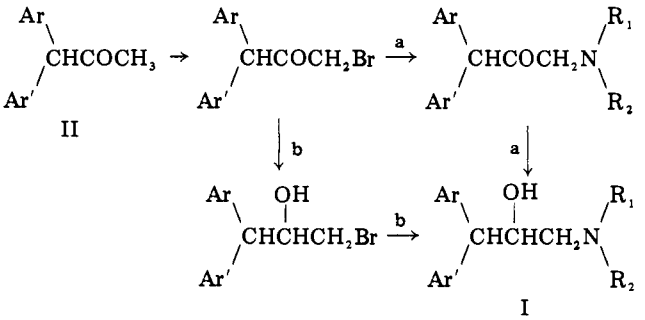
1, R_1 = H; R_2 = OH; R_3 = CH_3·HBr
2, R_1 = R_2 = H; R_3 = H, CH_3
3, R_1 + R_2 = CH_2; R_3 = H, CH_3
4, R_1 = OH; R_2 = H; R_3 = CH_3
5, R_1 = R_2 = H; R_3 = $CH_2CH_2CH_2OH$



6, Ar = Ar' = C_6H_5
7, Ar = 4-BrC_6H_4; Ar' = 3-pyridyl

Chemistry. Attention was first directed toward the synthesis of analogues (**8**–**33**) of 1 containing substituents in one or both of the phenyl groups and with a variety of substituted amino groups; the results are summarized in Table I.

Scheme I



Initially, the required substituted 1,1-diaryl-3-amino-2-propanols I were prepared from the corresponding 1,1-diaryl-2-propanones II by the original (Scheme I, path a) or modified (Scheme I, path b) literature[1] procedure. Difficulties in the synthesis and nonregiospecific bromination of II prompted a search for alternative routes to I.

In one approach (Scheme II, path a) the appropriately substituted benzophenone III, which was either commercially available or readily synthesized, was reacted with methoxymethylenetriphenylphosphorane to give the vinyl ether IV, which on acid hydrolysis yielded the aldehyde V. Low yields in the Wittig reaction and difficulties in the purification of both IV and V necessitated an alternative synthesis of V (Scheme II, path b). Reaction of III with dimethylsulfoxonium methylide[8] gave the epoxide VI, which underwent smooth rearrangement with boron trifluoride etherate to give V. Further reaction of V with dimethylsulfoxonium methylide gave the epoxide VIII, which on treatment with the appropriate amine yielded I. No purification of intermediates V, VI, or VII was carried out.

The limiting stage in the above synthesis is the conversion of V to VII. With 2,2-diphenylethanal, a 90% yield

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