2-Acetylpyridine Thiosemicarbazones. 5. 1-[1-(2-Pyridyl)ethyl]-3-thiosemicarbazides as Potential Antimalarial Agents[1,2]

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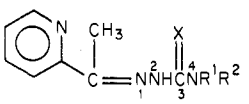
Reduction of the azomethine bond of 2-acetylpyridine thio- and selenosemicarbazones with sodium borohydride readily afforded the corresponding thio- or selenosemicarbazides when they were N^4,N^4-disubstituted. This conversion failed, however, when the thio- or selenosemicarbazones were N^4-substituted or unsubstituted. A more general route to the desired thio- or selenosemicarbazides consisted of reduction with sodium borohydride of methyl 3-[1-(2-pyridyl)ethylidene]hydrazinecarbodithioate to give the 2-pyridylethyl derivative. Displacement of methyl mercaptan from the thio ester moiety of the latter by amines produced 1-[1-(2-pyridyl)ethyl]-3-thiosemicarbazides. These compounds were somewhat more active as antimalarial agents in *Plasmodium berghei* infected mice than the corresponding thiosemicarbazones; however, the enhancement of activity was accompanied by an increase in toxicity. Compound 7, 3-azabicyclo[3.2.2]nonane-3-carbothioic acid 2-[1-(2-pyridyl)ethyl]hydrazide, is the most potent derivative of 2-acetylpyridine we have evaluated to date.

A thiosemicarbazone possessing antitumor activity against L1210 leukemia in mice was first reported by Brockman et al.[3] The compound, 2-formylpyridine thiosemicarbazone, was later used as the model for further study by other workers[4] who synthesized and evaluated numerous α-N-heterocyclic carboxaldehyde thiosemicarbazones as antineoplastic agents. But for a few exceptions, these compounds were unsubstituted at N^4. A clue to their mechanism of action is the finding that the α-N-heterocyclic thiosemicarbazones are potent inhibitors of ribonucleoside diphosphate reductase.[5]

Our research group has investigated thiosemicarbazones derived from 2-acetylpyridine (Ia), a class of compounds

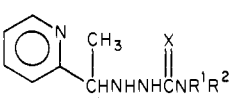


Ia, X = S
Ib, X = Se

that has shown a broad spectrum of chemotherapeutic properties, including antimalarial[6,7] and antitumor[1] activity in vivo, as well as antibacterial,[8] antitrypanosomal,[9] and antiviral[10] activity in vitro. Selenosemicarbazones of 2-acetylpyridine (Ib) also have antimalarial activity.[11] A wide variety of N^4 substituents has been investigated by us.

Previous papers in this series have explored the influence of structural modifications upon biological activity. In particular, it has been observed that (1) exchange of the sulfur atom of the thiocarbonyl group for oxygen results in elimination of activity, whereas selenium, in general, retains activity; (2) the point of attachment of the ethylidene moiety to the pyridine ring must be at the 2-position and that attachment at the 3- and 4-positions eliminates activity; (3) the pyridine ring, when replaced by phenyl, results in loss of activity; (4) transition-metal complexes of Ia and Ib, i.e., utilizing the latter as univalent, tridentate ligands, with Cu(II), Ni(II), and Fe(III) leads to active antimalarials, albeit with reduced activity.

In this article we report the synthesis and antimalarial properties of thio- and selenosemicarbazides of types IIa and IIb, respectively, where the pyridylethylidene moiety of Ia and Ib has been replaced by pyridylethyl.



IIa, X = S
IIb, X = Se

Chemistry. The thiosemicarbazides, IIa, required for this investigation could be prepared by either of two methods. Method A entailed the direct conversion of a thiosemicarbazone to the corresponding thiosemicarbazide by reduction with sodium borohydride in ethanol. Surprisingly, the effectiveness of this method was limited to N^4,N^4-disubstituted thiosemicarbazones (Ia, R^1, $R^2 \neq H$). Attempts to reduce thiosemicarbazones where $R^1 = R^2 =$ H or R^1 or R^2 = H resulted in the recovery of starting material. In seeking an explanation for the resistance of the N^4-substituted and unsubstituted thiosemicarbazones to reduction by borohydride one can consider the tautomeric thiosemicarbazone system, III ↔ IV. Loss of an N^4 proton from tautomer IV gives the resonance-stabilized anions V and VI. Form VI would be expected to be a major contributor, as there is stabilization of an alkyl anion α to a 2-pyridyl position due to the electron-attracting inductive and resonance effects of the ring nitrogen atom.[12]

(1) For paper no. 4 in this series, see Scovill, J. P.; Klayman, D. L.; Franchino, C. F. *J. Med. Chem.* **1982**, *25*, 1261.
(2) This is contribution no. 1648 to the Army Research Program on Malaria.
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(4) For several representative papers, see Agrawal, K. C.; Sartorelli, A. C. *Handb. Exp. Pharmacol.* **1975**, *38*(part 2) 793. Antholine, W. E.; Knight, J. M; Petering, D. H *J. Med. Chem.* **1976**, *19*, 339. Antonini, I.; Claudi, F.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *Eur. J. Med. Chem.* **1979**, *14*, 89. French, F. A.; Blanz, Jr., E. J.; Shaddix, S. C.; Brockman, R. W. *J. Med. Chem.* **1974**, *17*, 172. Lemke, T. L.; Shek, T. W.; Cates, L. A.; Smith, L. K.; Cosby, L. A.; Sartorelli, A. C. *Ibid.* **1977**, *20*, 1351. Lin, A. J.; Agrawal, K. C.; Sartorelli, A. C. *Ibid.* **1972**, *15*, 615. Sartorelli, A. C.; Agrawal, K. C.; Booth, B. A.; Pittman, J.; Bartholomew, D. G.; Broom, A. D. *Ibid.* **1976**, *19*, 830.
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(8) Dobek, A. S.; Klayman, D. L.; Dickson, E. J., Jr.; Scovill, J. P. Tramont, E. C. *Antimicrob. Agents Chemother.* **1980**, *18*, 27.
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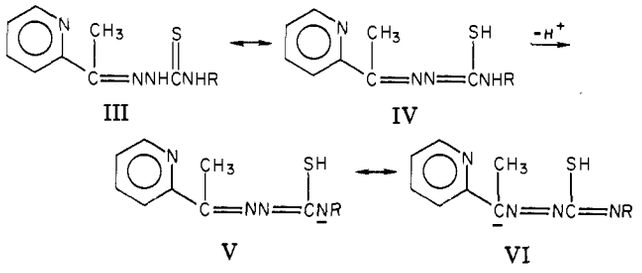
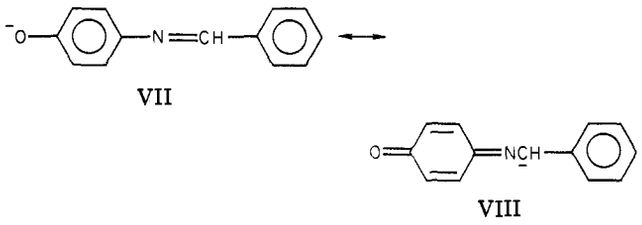


III IV V VI

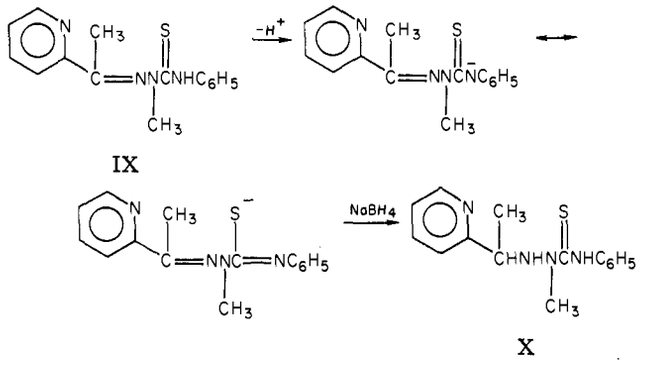
Attack by hydride ion at this anionic carbon would be unfavorable. An N^4,N^4-disubstituted thiosemicarbazone is unable to enter into this type of resonance.

In a related example, *N*-benzylidene-*p*-aminophenol could not be reduced to the corresponding secondary amine with borohydride,[13] whereas many other Schiff bases are reduced by this reagent.[14] The failure of the reaction to proceed may similarly be due to the presence of a tautomeric anionic extended resonance system (VII ↔ VIII) that inhibits the addition of hydride ion to the azomethine carbon atom.



VII VIII

Substitution of N^2 with an alkyl group in 2-acetylpyridine thiosemicarbazone (IX) interrupts the resonance

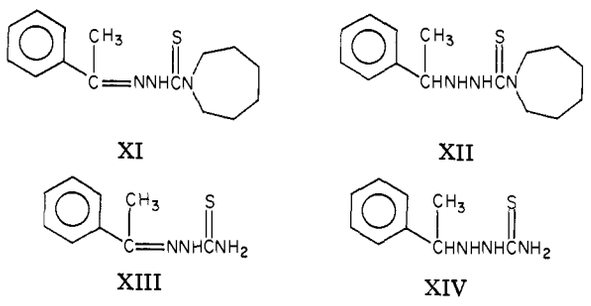


IX X

system and should allow reduction of the azomethine moiety as an isolated double bond. Experimentally, it is observed that IX is, indeed, rapidly reduced to the corresponding thiosemicarbazide, X.

In addition to 2-acetylpyridine thiosemicarbazone, the related 3- or 4- acetylpyridine thiosemicarbazones are also highly resistant to borohydride reduction. This phenomenon may similarly be related to the acidity of the α position observed in alkylpyridines. Whereas the resonance effect can play a role only in the 2- and 4-alkylpyridines, there is, nevertheless, a sufficiently appreciable electron-attracting inductive effect in the 3-alkylpyridines to allow for stable carbanion formation.[12]

To ascertain the influence of the pyridine ring vs. a phenyl ring, acetophenone thiosemicarbazones were subjected to borohydride reduction. An N^4,N^4–disubstituted thiosemicarbazone of acetophenone (XI) was readily reduced to the corresponding thiosemicarbazide XII by $NaBH_4$ in ethanol.

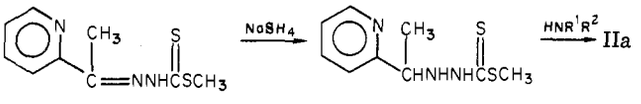


XI XII

XIII XIV

An intermediate case is presented by acetophenone thiosemicarbazone (XIII). This compound is reduced slowly by a large excess of borohydride to the corresponding thiosemicarbazide (XIV). The reduction of XIII to XIV by sodium amalgam has been reported by Hoggarth and Young.[15] The preparation of some thiosemicarbazides by the borohydride reduction of thiosemicarbazones was performed by Jensen et al.[16] Although they were successful in preparing a variety of thiosemicarbazides in this manner, they did not make any general observations concerning the scope or limitations of the reaction, other than to observe that: "This method could not be used directly to prepare thiosemicarbazides substituted both in 1- and 2-positions." Successful reductions by Jensen et al. included the preparation of 1-benzyl-3-thiosemicarbazide from benzaldehyde thiosemicarbazone and 1-benzyl-4,4-dimethyl-3-thiosemicarbazide from benzaldehyde 4,4-dimethyl-3-thiosemicarbazone. The attempted reduction of benzophenone thiosemicarbazone was not successful.

Method B for the synthesis of thiosemicarbazides gave desired products regardless of N^4 substitution. Methyl 3-[1-(2-pyridyl)ethylidene]hydrazine carbodithioate, XV,



XV XVI

was readily reduced to methyl 3-[1-(2-pyridyl)ethyl]-hydrazinecarbodithioate, XVI, by sodium borohydride in ethanol. The SCH_3 group of XVI was readily displaced by amines to give the requisite 1-[1-(2-pyridyl)ethyl]-3-thiosemicarbazides, IIa (cf. Table I). The ease of the reducibility of XV, in contrast to the marked resistance of N^4-substituted or unsubstituted 2-acetylpyridine thiosemicarbazones to borohydride, is explicable by the lack of an exchangeable proton in structure XV necessary for the establishment of an extended system of conjugation.

Selenosemicarbazones, Ib, were easily reduced to the corresponding N^4,N^4-disubstituted selenosemicarbazides by sodium borohydride. It is interesting to note that whereas the N^4,N^4-disubstituted thiosemicarbazones are colored yellow and the N^4,N^4-disubstituted selenosemicarbazones are orange, the corresponding thio- and selenosemicarbazides are colorless.

Results and Discussion

Two considerations governed the selection of compounds to be prepared as thiosemicarbazone analogues for this study. It was considered desirable to have representatives of the three classes of thiosemicarbazones that have proven

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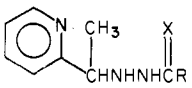
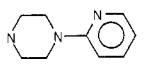
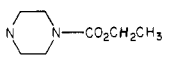
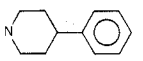
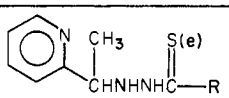
Table I. 1-[1-(2-Pyridyl)ethyl]-3-thio- and -selenosemicarbazides

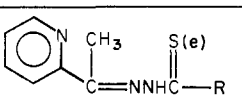


no.	R	X	mp, °C	synth method[a]	yield, %	formula	recrystn solvent
1	$NHCH_2C_6H_5$	S	89-90	B	21	$C_{15}H_{18}N_4S$	Et_2O
2	$N(CH_3)_2$	S	142-143	B	73	$C_{10}H_{16}N_4S$	EtOH
3	c-NC_4H_8	S	169-170	B	68	$C_{12}H_{18}N_4S$	MeOH
4	c-NC_5H_9-4-CH_3	S	131-132	B	58	$C_{14}H_{22}N_4S$	EtOH
5	c-NC_6H_{12}	S	129-130 128-129	A, B	49, 60	$C_{14}H_{22}N_4S$	MeCN
6	c-NC_6H_{12}	Se	129-130 dec	A	41	$C_{14}H_{22}N_4Se$	MeOH
7		S	145-146	A, B	58, 39	$C_{16}H_{24}N_4S$	MeCN
8		Se	145-146 dec	A	81	$C_{16}H_{24}N_4Se$	MeCN
9		S	168-170	B	58	$C_{17}H_{22}N_6S$	MeCN
10		S	154-155	B	39	$C_{15}H_{23}N_5O_2S$	EtOH
11		S	168-170	B	60	$C_{19}H_{24}N_4S$	EtOH
12	$N(CH_3)$-c-C_6H_{11}	S	134-135	B	43	$C_{15}H_{24}N_4S$	EtOH
13	SCH_3	S	105-106	B	58	$C_9H_{13}N_3S_2$	MeCN

[a] See Chemistry section for a description of methods A and B.

Table II. Comparison of Antimalarial Properties of 2-Acetylpyridine Thiosemicarbazides and Related Thiosemicarbazones





	increase in mean survival time, days, and no. of cures at dosage, mg/kg							increase in mean survival time, days, and no. of cures at dosage, mg/kg					
no.[a]	20	40	80	160	320	640	no.[a]	20	40	80	160	320	640
1		−0.1		0.7		2.4 T(3/5)	1a		0.5		3.7		10.6A T(2/5)
2	2.0	3.2 T(1/5)		T(5/5)		T(5/5)	2a		0.5, T(3/5)		T(5/5)		T(5/5)
3	1.3	5.2		C(1/5) T(3/5)		T(5/5)	3a		8.9A, T(3/5)		T(5/5)		T(5/5)
4		C(1/5)		C(1/5) T(3/5)		T(5/5)	4a		C(3/5)		T(5/5)		T(5/5)
5		2.4		T(5/5)		T(5/5)	5a		6.2A	C(4/5)	C(3/5), T(1/5)	C(2/5), T(2/5)	C(2/5), T(3/5)
6[c]	0.3	5.9	6.1	C(1/5)	C(3/5) T(2/5)	C(2/5) T(2/5)	6a[c]		1.7	4.6	7.3	C(2/5)	C(2/5)
7	C(4/5),[d] T(1/5)	T(5/5)		C(1/5) T(3/5)		T(5/5)	7a	C(1/5)	C(3/5)	C(3/5)	C(5/5)	0.2	0.4, T(4/5)
8[c]	−0.3	0.5	5.5	C(2/5)	C(4/5) T(1/5)	−0.3 T(4/5)	8a[c]	−0.1	0.8	5.9	C(1/5)	C(2/5)	C(3/5)
9	0.4	C(1/5)	C(3/5)	C(5/5)	C(2/5) T(1/5)	T(5/5)	9a	C(3/5)	C(4/5)	C(5/5)	C(2/5)	0.7, T(2/5)	T(5/5)
10	5.9	7.2A T(3/5)		T(5/5)	T(5/5)	T(5/5)	10a		C(2/5), T(2/5)		T(5/5)		T(5/5)
11		C(1/5)		C(4/5)		T(5/5)	11a		0.4	C(1/5)	C(3/5)	C(5/5)	C(5/5)
12	2.9 T(1/5)	3.7	7.1A T(1/5)	C(3/5) T(1/5)	C(2/5) T(3/5)		12a		3.7	9.6A	C(2/5)	C(4/5)	12.1A, T(1/5)

[a] R groups are identical for thiosemicarbazones and thiosemicarbazides on the same line. [b] T = toxic; A = active; c = cure. See Experimental Section for details. [c] Selenosemicarbazone and selenosemicarbazide. [d] At a dose of 10 mg/kg, C(2/5); 5 mg/kg, 7.9A.

to have significant antimalarial properties. These include (1) N^4-substituted derivatives, represented by compound 1; (2) N^4,N^4-dialkyl derivatives, represented by compounds 2 and 12; and (3) compounds where N^4 is contained in a medium ring, which includes all remaining examples. The majority of choices were made to correspond to thiosemicarbazones that displayed a high level of antimalarial activity. Thiosemicarbazones **4a**, **7a**, and **9a** cured a majority of the test animals at dose levels of 40 mg/kg or lower. The only thiosemicarbazide which approached this level of activity was compound **7**, which cured two of five test animals at a dose of 10 mg/kg (cf. Table II). The latter compound, 3-azabicyclo[3.2.2]nonane-3-carbothioic acid 2-[1-(2-pyridyl)ethyl]hydrazide, is actually the most potent 2-acetylpyridine derivative we have tested to date. Six other thiosemicarbazides (**3**, **6**–**8**, **11**, and **12**) either

produced a greater percentage of cures at the lowest curative level or produced cures at a lower dosage level than the corresponding thiosemicarbazones.

As a group, the thiosemicarbazides may be considered to be more toxic than the corresponding thiosemicarbazones. Thus, four thiosemicarbazides (**7**, **8**, **11**, and **12**) produced toxic deaths at a lower dose than the corresponding thiosemicarbazones, whereas in two cases (**3a** and **6a**) the thiosemicarbazone was the more toxic of the pair. In the remaining cases, toxic deaths became evident at identical dose levels. The occurrence of a high level of antimalarial activity in the thiosemicarbazides series causes us to somewhat modify our previous contention that the 2-pyridylethylidene moiety is an essential molecular feature for obtaining antimalarial activity.[6,7,11] The retention and, in some cases, enhancement of antimalarial activity in the thiosemicarbazide series may be explicable on the basis that substitution of a 2-pyridylethyl moiety for that of a 2-pyridylethylidene, while increasing the flexibility of the resultant molecule and preventing electronic delocalization over the pyridine ring into the conjugated thiosemicarbazone moiety, does not greatly effect essential intramolecular distances.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra of solid samples were run as KBr disks on a Perkin-Elmer Model 283 spectrophotometer. NMR spectra were run on a Varian T60-A spectrometer with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Satisfactory analyses (±0.3% of calculated values) were obtained for all compounds.

Hexahydro-1*H*-azepine-1-carbothioic Acid 2-[1-(2-Pyridyl)ethyl]hydrazide (5). The method for the preparation of thio- or selenosemicarbazides by the reduction of 2-acetylpyridine thio- or selenosemicarbazones is exemplified in the following procedure. A suspension of 5.0 g (18.1 mmol) of hexahydro-1*H*-azepine-1-carbothioic acid 2-[1-(2-pyridyl)-ethylidene]hydrazide in 30 mL of EtOH was treated portionwise with 1.2 g (31 mmol) of sodium borohydride over the course of 2 h. The resulting colorless solution was treated with 100 mL of water and then cautiously neutralized with ca. 3 mL of glacial HOAc. The crystals that separated were collected and washed with water. The crude material was crystallized twice: IR 3270, 3200, 2980, 2940, 2865, 1590, 1503, 1490, 1335, 1272, 1198, 1002, 787, 755 cm^{-1}.

Methyl 3-[1-(2-Pyridyl)ethyl]hydrazinecarbodithioate (XVI). A suspension of 12.5 g (55.5 mmol) of methyl 3-[1-(2-pyridyl)ethylidene]hydrazinecarbodithioate[6] in 50 mL of EtOH was treated portionwise with 2.0 g of sodium borohydride (53 mmol) over the course of 0.5 h. At this time, an additional 0.50 g (13.2 mmol) of sodium borohydride was added, and the solution stirred for another hour. The reaction mixture was diluted with 50 mL of water and cautiously neutralized with 5 mL of glacial HOAc. The gum that separated soon crystallized upon rubbing. The crystals were collected and washed with water. Crystallization from MeCN (25 mL) afforded 7.6 g of colorless prisms: mp 105–106 °C; IR 3200, 2910, 1595, 1535, 1435, 1042, 1008, 785, 755, 631, 609 cm^{-1}; NMR δ 1.47 (d, 3 H, J = 8 Hz), 2.60 (s, 3 H), 4.27 (q, 1 H, J = 8 Hz). Anal. ($C_9H_{13}N_3S$) C, H, N, S.

3-Azabicyclo[3.2.2]nonane-3-carbothioic Acid 2-[1-(2-Pyridyl)ethyl]hydrazide (7). The method for the preparation of thiosemicarbazides by displacement of the *S*-methyl group of a carbodithioate by a primary or secondary amine is exemplified in the following procedure. A solution consisting of 2.27 g (10 mmol) of methyl 3-[1-(2-pyridyl)ethyl]hydrazinecarbodithioate (XVI) and 1.25 g (10 mmol) of 3-azabicyclo[3.2.2]nonane in 5 mL of EtOH was heated at reflux for 6 h. The solution was chilled and scratched, and the crystals that separated were collected. Crystallization afforded white, cottony needles: IR 3217, 2935, 2900, 2860, 1595, 1560, 1505, 1195, 1002, 775, 751, 627, 537 cm^{-1}.

Hexahydro-1*H*-azepine-1-carbothioic Acid 2-(1-Phenylethylidene)hydrazide (XI). A solution of 1.12 g (10 mmol) of methyl 3-(1-phenylethylidene)thiocarbohydrazide[16] and 1.0 g (10 mmol) of hexamethylenimine in 5 mL of MeOH was heated at reflux for 8 h. The solution was chilled, and the crystals that separated were collected. This afforded 1.09 g (58%) of XI as yellow needles, mp 101–104 °C. An analytical sample was prepared by crystallization from CH_3CN, mp 104 °C. Anal. ($C_{15}H_{21}N_3S$) C, H, N, S.

1-Methyl-*N*-phenyl-2-[1-(2-pyridyl)ethylidene]-hydrazinecarbothioamide (IX). A solution of 4.0 g (33 mmol) of 2-acetylpyridine in 15 mL of CH_3CN and 1.52 g (33 mmol) of methylhydrazine was heated at reflux for 30 min. The solution was then treated with 4.46 g (33 mmol) of phenyl isothiocyanate, and heating continued for 4 h. The mixture was cooled overnight and the crystals that separated were washed with MeOH. This afforded 5.48 g (58%) of colorless cubes of IX, mp 134–136 °C. An analytical sample was prepared by crystallization from CH_3CN, mp 136–137 °C: NMR δ 1.93 (s, 3 H, C-CH_3), 3.53 (s, 3 H, N-CH_3), 6.57 (s, 1 H, N-H), 6.67–7.33, (m, 7 H), 7.50 (t of d, 1 H), 867 (br d, 1 H). Anal. ($C_{15}H_{16}N_4S$) C, H, N, S.

1-Methyl-*N*-phenyl-2-[1-(2-pyridyl)ethyl]hydrazine-carbothioamide (X). The preparation of this compound by the reduction of 1-methyl-*N*-phenyl-2-[1-(2-pyridyl)ethylidene]-hydrazinecarbothioamide (IX) is representative of the methods employed for the reduction of variously substituted thiosemicarbazones by sodium borohydride in ethanol. A solution of 1.0 g (3.5 mmol) of IX in 25 mL of warm (50 °C) ethanol was treated with 500 mg (13.2 mmol) of $NaBH_4$. The solution was then allowed to stir overnight. The reaction mixture was then treated with 50 mL of H_2O, and 2 mL of glacial acetic acid was added cautiously. Ethanol was removed under reduced pressure and a yellow gum separated. The mixture was rubbed and chilled, and soon crystallized. The crystals were collected and crystallized twice from methanol. This afforded 400 mg (40%) of colorless needles of 1-methyl-*N*-phenyl-2-[1-(2-pyridyl)ethyl]hydrazine-carbothioamide: mp 112–114 °C; NMR δ 1.42 (d, 3 H, J = 7 Hz), 3.55 (s, 3 H, N-CH_3). Anal. ($C_{15}H_{19}N_4S$) C, H, N, S

Reduction of acetophenone thiosemicarbazone by the procedure above afforded a 35% yield of 2-(1-phenylethyl)hydrazine-carbothioamide (XIV), mp 157–158 °C (lit.[15,16] mp 156 °C). Anal. ($C_9H_{13}N_3S$) C, H, N, S.

Reduction of yellow hexahydro-1*H*-azepine-1-carbothioic acid 2-(1-phenylethylidene)hydrazide (XI) by the procedure above afforded an 85% yield of colorless hexahydro-1*H*-azepine-1-carbothioic acid 2-(1-phenylethyl)hydrazide (XII): mp 97–103 °C; NMR δ 1.38 (d, 3 H, J = 7 Hz), 4.23 (q, 1 H, J = 7 Hz), 7.37 (s, 5 H). Anal. ($C_{15}H_{23}N_3S$) C, H, N, S.

Reduction of 2-acetylpyridine thiosemicarbazone, 3-acetylpyridine thiosemicarbazone, or 4-acetylpyridine thiosemicarbazone could not be effected by employing the above procedure. In each case, a nearly quantitative return of starting material was obtained.

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. Young ICR/HA Swiss mice, ranging in weight from 18 to 22 g, are administered intraperitoneally a standard inoculum of heparinized heart's blood containing 4×10^7 cells, a minimum of 90% of which are parasitized. The cells are drawn from donor mice that had been infected 1 week earlier with *Plasmodium berghei*. All the untreated infected animals, which serve as controls, die after 6–8 days, with a mean survival time of 6.2 days. Every compound is tested at several dose levels. At each level, the candidate drug is given subcutaneously in a single dose as a peanut oil suspension to mice 72 h after they are infected. The compounds are judged to be "toxic" if the infected treated mice die before the 6th day, i.e., before the time when the untreated mice begin to die; "active" if the mean survival time of the mice is at least doubled; and "curative" if the mice survive 60 days postinfection. Details of the test procedure were given in Osdene, Russel, and Rane.[18]

Registry No. 1, 83476-76-0; **1a**, 70618-35-8; **2**, 83476-77-1; **2a**, 71555-14-1; **3**, 83476-78-2; **3a**, 71555-26-5; **4**, 83476-79-3; **4a**, 71555-61-8; **5**, 83476-80-6; **5a**, 71555-41-4; **6**, 83476-81-7; **6a**,

(18) Osdene, T. S.; Russel, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.

79514-45-7; **7**, 83476-82-8; **7a**, 71555-47-0; **8**, 83476-83-9; **8a**, 79514-43-5; **9**, 83476-84-0; **9a**, 71555-54-9; **10**, 83476-85-1; **10a**, 71555-52-7; **11**, 83476-86-2; **11a**, 71555-34-5; **12**, 83476-87-3; **12a**, 71555-19-6; IX, 83476-90-8; X, 83476-91-9; XI, 75488-62-9; XII, 83476-92-0; XIII, 2302-93-4; XIV, 21198-20-9; XV, 26151-76-8; XVI, 83476-88-4; hexahydro-1*H*-azepine, 111-49-9; 3-azabicyclo-[3.2.2]nonane, 283-24-9; 1-(2-pyridinyl)piperazine, 34803-66-2; methyl 3-(1-phenylethylidene)thiocarbohydrazide, 83476-89-5; 2-acetylpyridine, 1122-62-9; methylhydrazine, 60-34-4; phenyl isothiocyanate, 103-72-0.

Bicyclic Lactones Derived from Kainic Acid as Novel Selective Antagonists of Neuroexcitatory Amino Acids[1]

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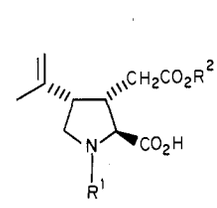
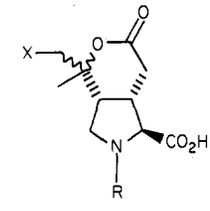
The bicyclic [2*S*-(2α,3β,4β)]-2-carboxy-4-(1-hydroxy-1-methylethyl)-3-pyrrolidineacetic acid δ-lactone (**4**), as well as its 4-[1-hydroxy-1-(iodomethyl)ethyl], 4-[1-hydroxy-1-(hydroxymethyl)ethyl], and 4-[1-hydroxy-1-[(phenylthio)methyl]ethyl] analogues, **6**, **7**, and **9**, respectively, were designed and synthesized as potential selective antagonists of neuroexcitatory amino acids. When applied to rat brain slices, these lactones, which are chemically derived from kainic acid, inhibit the stimulation of Na^+ fluxes induced by the neuroexcitants kainic acid and *N*-methyl-D-aspartic acid. Lactone **4** and the hydroxy lactone **7** block preferentially the response to *N*-methyl-D-aspartic acid, while the iodo lactone **6** and the phenylthio lactone **9** are mainly kainic acid antagonists. Total inhibitions can be obtained, half of the maximal effect being observed at lactone concentrations in the range of 0.2–3 mM.

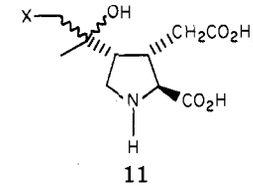
Glutamic and aspartic acids are powerful excitants of neuronal cells in the mammalian central nervous system, where they have been suggested to function as natural excitatory neurotransmitters.[2-4] They are also suspected of being involved in the etiology of neurological disorders like the epilepsies and Huntington's chorea.[5,6] Studies of the effects of glutamic acid and other acidic amino acids on neuronal excitability have led to the recognition of different classes of excitatory amino acid receptor sites.[7,8] The pharmacological characterization of these receptors involved the use of compounds such as 2-amino-5-phosphonovaleric acid,[9] D-α-aminoadipic acid,[10] D-α-aminosuberic acid,[10] γ-D-glutamylglycine,[11] and diethyl glutamate,[12] which are capable of inhibiting the effects of some excitatory amino acids. However, the scarcity of available antagonists, as well as their relatively poor selectivity and receptor affinity, call for the elaboration of a larger variety of specific antagonists. In addition to their utility in research, such compounds may provide a basis for the development of drugs for the therapy of brain disorders resulting from excessive excitation. As part of an effort toward this aim, chemical modifications of the well-known neuroexcitant kainic acid (**1**)[13] have been



1, $R^1 = R^2 = H$
2, $R^1 = H$; $R^2 = Me$
3, $R^1 = CO_2Bu^t$; $R^2 = H$



4, X = R = H
5, X = I; R = CO_2Bu^t
6, X = I; R = H
7, X = OH; R = H
8, X = SPh; R = CO_2Bu^t
9, X = SPh; R = H
10, X = OH; R = CO_2Bu^t



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carried out. This unsaturated dicarboxylic amino acid was converted into the bicyclic lactones **4**, **6**, **7**, and **9** by cyclization of the γ-carboxy function onto the double bond of the isopropenyl group. The design and synthesis of these compounds as potential antagonists were prompted by the knowledge that esterification of an excitatory amino acid may lead to a product which, while devoid of agonist properties, displays antagonist activity. This is true for

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