7.02 (1 H, d, J = 6 Hz, 5-H), 7.66 (1 H, d, J = 6 Hz, 6-H), 9.67 (1 H, s, 1-H); IR ν_{max} 3410, 3245, 3170, 3100 ($NHCOCH_3$, NH) 1697 (C=O) cm^{-1}. Anal. ($C_9H_{11}N_3O$) C, H, N.

4-(Acetylamino)-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (13). An intimate mixture of 12 (0.9 g, 5 mmol), 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (3.2 g, 10 mmol), and *p*-toluenesulfonic acid (50 mg) was heated at 135 °C with stirring in vacuo (25 mm) for 40 min. The resulting solid was neutralized with saturated K_2CO_3 solution and extracted with chloroform (150 mL × 3). The residue of the chloroform layer concentration was chromatographed on a silica gel column eluting with EtOAc–MeOH (95:5) to give 0.6 g (28%) of 13 (R_f 0.58) and 0.55 g (50%) of 10 (R_f 0.38): ^1H NMR ($CDCl_3$) δ 2.06, 2.08, 2.1, and 2.17 (12 H, 4 s, four CH_3), 2.93 (2 H, m, 3-H), 3.7 (2 H, m, 2-H), 4.22 (3 H, s, 4′-H and 5′-CH_2), 5.2–5.5 (2 H, m, 3′-H and 2′-H), 6.15 (1 H, d, J = 7 Hz, 1′-H), 7.24 (2 H, m, 5-H and 4-NH), 7.91 (1 H, d, J = 6 Hz, 6-H). Anal. ($C_{20}H_{25}N_3O_8$) C, H, N.

4-(Acetylamino)-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-pyrrolo[2,3-*b*]pyridine (14). A mixture of 0.7 g (1.6 mmol) of 13, dissolved in 35 mL of dry xylene, and 0.36 g (1.6 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was heated under reflux for 1.5 h and then cooled to room temperature. The solid was removed and washed three times with EtOAc, and the filtrate was concentrated. The residue was chromatographed on a silica gel column eluting with EtOAc to give 250 mg (35%) of 14 (R_f 0.54): ^1H NMR ($CDCl_3$) δ 2.00, 2.07, 2.1, and 2.21 (12 H, 4 s, 4 CH_3), 4.35 (3 H, s, 4′-H and 5′-CH_2), 5.57 (1 H, m, 3′-H), 5.78 (1 H, m, 2′-H), 6.58 (2 H, m, 1′-H and 3-H), 7.25 (1 H, d, J = 3 Hz, 2-H), 7.92 (1 H, d, J = 5 Hz, 5-H), 8.23 (1 H, d, J = 5 Hz, 6-H), 8.39 (1 H, s, 4-NH). Anal. ($C_{20}H_{23}N_3O_8$) C, H, N.

4-Amino-1-β-D-ribofuranosyl-1*H*-pyrrolo[2,3-*b*]pyridine (15). A mixture of 140 mg (0.323 mmol) of 15, 10 mL of methanol, and 3 mL of 1 N methanolic sodium methoxide solution was refluxed for 2 h. The solution was cooled and neutralized with IRC 50 (H^+ form). The resin was removed by filtration, and the filtrate was concentrated to dryness to give a residue, which was chromatographed on a silica gel column. Elution with EtOAc–MeOH (7:3) yielded 15 as an oil, which crystallized from absolute ethanol to give 55 mg (0.207 mmol, 64%): mp 252–253 °C dec; ^1H NMR (Me_2SO) δ 3.58 (2 H, m, 5′-CH_2), 3.92 (1 H, m, 4′-H), 4.1 (1 H, m, 3′-H), 4.58 (1 H, m, 2′-H), 4.8–5.3 (3 H, large s, 2′,3′,5′-OH), 5.96 (1 H, d, J = 6 Hz, 1′-H), 6.33 (3 H, m, 5-H and 4-NH_2), 6.58 (1 H, d, J = 3 Hz, 3-H), 7.28 (1 H, d, J = 3 Hz, 2-H), 7.72 (1 H, d, J = 5 Hz, 6-H); UV (C_2H_5OH) λ_{max} 229 nm (log ε 4.41), 273 (3.92), 293 (4.02), 301 (3.97). Anal. ($C_{12}H_{15}N_3O_4$) C, H, N.

4-Amino-1-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrrolo[2,3-*b*]pyridine (16). A suspension of 15 (50 mg, 0.188 mmol) in dry acetone (10 mL) was mixed with *p*-toluenesulfonic acid monohydrate (71 mg, 0.37 mmol) and stirred at room temperature for 1 h. Then solid sodium hydrogen carbonate (580 mg) was added, and stirring was continued for 24 h. The solid was filtered off, and the filtrate was evaporated to dryness. The residue was chromatographed on a silica gel column eluting with EtOAc to give 40 mg (0.133 mmol, 70%) of 16: ^1H NMR (Me_2SO) δ 1.31 and 1.54 [each 3 H, s, $C(CH_3)_2$], 3.55 (2 H, m, 5′-CH_2), 4.11 (1 H, m, 4′-H), 4.93 (1 H, m, 3′-H), 5.16 (2 H, m, 2′-H and 5′-OH), 6.17 (2 H, m, 5-H and 1′-H), 6.27 (2 H, s, 4-NH_2), 6.6 (1 H, d, J = 3 Hz, 3-H), 7.3 (1 H, d, J = 3 Hz, 2-H), 7.73 (1 H, d, J = 5 Hz, 6-H). Anal. ($C_{15}H_{19}N_3O_4$) C, H, N.

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2-Acetylpyridine Thiosemicarbazones. 4. Complexes with Transition Metals as Antimalarial and Antileukemic Agents[1,2]

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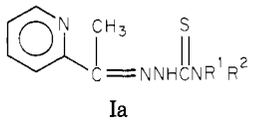
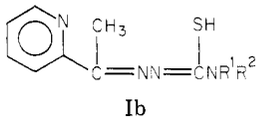
Reaction of the 2-acetylpyridine thiosemicarbazones, 3-azabicyclo[3.2.2]nonane-3-thiocarboxylic acid 2-[1-(2-pyridyl)ethylidene]hydrazide (IIIa), its selenium analogue (IIIb), 1*H*-hexahydroazepine-1-thiocarboxylic acid 2-[1-(2-pyridyl)ethylidene]hydrazide (IV), and 1*H*-octahydroazocine-1-thiocarboxylic acid 2-[1-(2-pyridyl)-ethylidene]hydrazide (V) with Cu(II), Ni(II), Fe(III), and Mn(II) salts gave crystalline complexes. Relative to the free ligands, these complexes show reduced antimalarial activity in mice infected with *Plasmodium berghei*; however, antileukemic properties are enhanced by coordination with the above-mentioned metals.

We have recently reported on a series of 2-acetylpyridine thiosemicarbazones (Ia) that possess significant antimalarial activity.[3,4] The molecular features that have been shown to be essential for antimalarial activity are the presence of a 2-pyridylalkylidene moiety[4] and a thiocarbonyl[4] or selenocarbonyl[1] group (in contrast to a carbonyl group). These features would also be expected to promote effective transtion-metal chelating properties.[5] In addition, we have observed that the presence of certain bulky groups at position N^4 of the thiosemicarbazone moiety greatly enhances antimalarial activity.[4] The formation of complexes with transition metals has been implicated in the mechanism of action of the structurally related 2-formylpyridine thiosemicarbazones.[6,7]



Ia

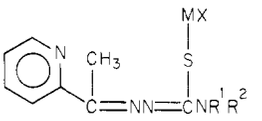


Ib

Saryan et al.[8] have shown that the iron complexes of some α-N-heterocyclic thiosemicarbazones are three- to

(1) For paper 3 in this series, see Klayman, D. L.; Scovill, J. P.; Bartosevich, J. F.; Mason, C. J. *Eur. J. Med. Chem.* **1981**, *16*, 317.
(2) This is contribution no. 1640 to the Army Research Program on Malaria.
(3) Klayman, D. L.; Bartosevich, J. F.; Griffin, T. S.; Mason, C. J.; Scovill, J. P. *J. Med. Chem.* **1979**, *22*, 855.
(4) Klayman, D. L.; Scovill, J. P.; Bartosevich, J. F.; Mason, C. J. *J. Med. Chem.* **1979**, *22*, 1367.
(5) (a) Mathew, M.; Palenik, G. J. *J. Am. Chem. Soc.* **1969**, *91*, 6310. (b) Ablov, A. V.; Belichuk, N. I. *Russ. J. Inorg. Chem.* **1969**, *14*, 93.
(6) French, F. A.; Blanz, E. J.; DoAmaral, J. R.; French, D. A. *J. Med. Chem.* **1970**, *13*, 1117.
(7) Agrawal, K. C.; Sartorelli, A. C. *Prog. Med. Chem.* **1978**, *15*, 349.
(8) Saryan, L. A.; Ankel, E.; Krishnamurti, C.; Petering, D. H.; Elford, H. *J. Med. Chem.* **1979**, *22*, 1218.

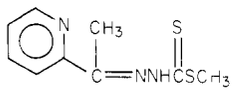
Table I. Transition Metal Complexes of 2-Acetylpyridine Thiosemicarbazones



no.	ligand	M	X	mp, °C dec	formula	yield, %	recrystn solvent	color and cryst form
1	IV	Cu(II)	Cl^-	261-262	$C_{14}H_{19}ClCuS$	79	DMF	dark green needles
2	IV	Ni(II)	Cl^-	278-279	$C_{14}H_{19}ClN_4NiS$	88	DMF	reddish brown needles
3	IV	Fe(III)	$2Cl^-$	217-218	$C_{14}H_{19}Cl_2FeN_4S$	80	MeCN	black prisms
4	IV	Mn(II)	*a*	298-300	$(C_{14}H_{19}N_4S)_2Mn$	69	DMF-H_2O	pale yellow needles
5	IV	Cu(II)	NCS^-	217-218	$C_{15}H_{19}CuN_5S_2$	62	PrCN	dark green prisms
6	IV	Ni(II)	NCS^-	234-236	$C_{15}H_{19}N_5NiS_2$	59	MeCN	reddish brown needles
7	IIIa	Cu(II)	Cl^-	260-261	$C_{16}H_{21}ClCuN_4S$	93	DMF	dark green needles
8	IIIb	Cu(II)	Cl^-	273-274	$C_{16}H_{21}ClCuN_4Se$	90	DMF	dark green needles
9	IIIa	Ni(II)	Cl^-	300-302	$C_{16}H_{21}ClN_4NiS$	85	DMF	reddish brown needles
10	IIIa	Fe(III)	$2Cl^-$	271-272	$C_{16}H_{21}Cl_2FeN_4S$	93	MeCN	black hexagonal plates
11	IIIa	Cu(II)	NCS^-	227-229	$C_{17}H_{21}CuN_5S_2$	87	MeCN	dark green prisms
12	IIIa	Ni(II)	NCS^-	277-278	$C_{17}H_{21}N_5NiS_2$	71	MeCN	orange square plates
13	V	Cu(II)	Cl^-	234-235	$C_{15}H_{21}ClCuN_4S$	96	DMF	bronze needles
14	V	Fe(III)	$2Cl^-$	216-218	$C_{15}H_{21}Cl_2FeN_4S$	86	MeOH	black cubes

[a] Bisligand complex which crystallizes without a gegenion.

sixfold more active as inhibitors of ribonucleotide reductase than the free ligands. They also noted an intensification of antitumor activity upon complexation. The antitumor properties of a number of transition-metal complexes of methyl 3-[1-(2-pyridyl)ethylidene]carbodithioate (II) have

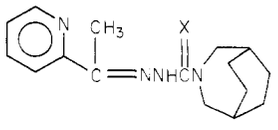


II

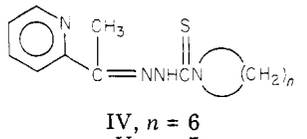
been reported by Das and Livingstone.[9] Of the derivatives of II, the chloro–Ni(II) complex was the most active against P388 leukemia in mice, having a T/C of 153% at a dose of 6.2 mg/kg. The chloro–Cu(II) complex was less active, having a T/C of 115% at a dose 0.8 mg/kg.

In view of these considerations, we decided to prepare transition metal complexes of several selected 2-acetylpyridine thiosemicarbazones and selenosemicarbazones in order to investigate their antimalarial and their antitumor properties.

Chemistry. The preparation of the requisite thiosemicarbazones[4] and selenosemicarbazones[1] was described in previous papers of this series. In solution, thiosemicarbazones probably form an equilibrium mixture of the thione (Ia) and thiol (Ib) tautomers. Loss of the thiol proton from the form Ib affords a singly charged tridentate ligand. The ligands investigated in this paper, IIIa, IIIb, IV, and V, have high affinities for first row transition metal



IIIa, X = S
b, X = Se

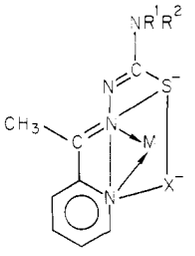


IV, *n* = 6
V, *n* = 7

ions. When equimolar ethanolic solutions of the thio- or selenosemicarbazones were combined with a metal chloride, the chloro complexes separated from the hot solution. Thiocyanato–Cu(II) complex 11 could be formed by refluxing a solution of the thiosemicarbazone IIIa with $Cu(SCN)_2(NH_3)_4$.[10]

Alternatively, chloro–Cu(II) complex 7 could be converted to thiocyanato complex 11 by refluxing a solution of 7 in propionitrile containing 1 equiv of potassium thiocyanate (Table I). Similarly, chloro–Ni(II) complex 9 was converted to thiocyanato–Ni(II) complex 12.

The products that were obtained from Cu(II) and Ni(II) are monoligand complexes that have been assigned the square planar structures represented by VI. This con-



VI

clusion is in accord with the microanalytical data, which require a 1:1:1 ratio of ligand, metal ion, and gegenion (i.e., Cl^- or NCS^-). The square planar structure of thiocyanato–Ni(II) complex 12 was established by a single-crystal X-ray study.[11] The thiocyanate ion is bonded to nickel through the N atom. The ν (C≡N) infrared absorption which appears as a single band at ~2080 cm^{-1} in the spectra of both 11 and 12 is indicative of a unidentate N-bonded thiocyanate.[12] These considerations rule out an octahedral complex, such as that reported by Mathew and Palenik[5a] for bis(isoquinoline-1-carboxaldehyde thiosemicarbazonato)nickel(II), which they obtained by the reaction of isoquinoline-1-carboxaldehyde thiosemicarbazone and $NiCl_2$. Reaction of $MnCl_2$ with thiosemicarbazone IV give a bisligand complex (4) which probably possesses an octahedral structure similar to that described by Mathew and Palenik.

Microanalytical data for the products obtained from the reaction of thiosemicarbazone ligands with $FeCl_3$ indicate

(9) Das, M.; Livingstone, S. E. *Br. J. Cancer* **1978**, *37*, 466.

(10) Jacobsen, C. A. "Encyclopedia of Chemical Reactions"; Reinhold: New York, 1953; Vol. V. p 21.

(11) Performed by Drs. J. V. Silverton and A. Bavoso, National Institutes of Health, Bethesda, MD. Details of this work will be published elsewhere.

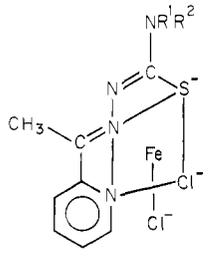
(12) Ali, M. A.; Livingstone, S. E.; Phillips, D. J. *Inorg. Chim. Acta* **1972**, *6*, 555.

Table II. Antimalarial Activity of Transition Metal Complexes of 2-Acetylpyridine Thiosemicarbazones against *Plasmodium berghei* in ICR/HA Swiss Mice

	increase in mean survival time (days) and no. of cures at dosage, mg/kg[a]				
no.	40	80	160	320	640
1	3.9		9.1A		0.1
2	0.2		0.6, T(1/5)		1.8, T(4/5)
3	4.3		C(2/5)		T(4/5)
4	−0.4	3.2	4.6	7.1A	C(5/5)
5	C(1/5)		6.5A		T(4/5)
6			−0.1		0.7
7	0.6	C(2/5)	C(5/5)	C(1/5), T(4/5)	C(1/5), T(4/5)
8	3.4	2.6	5.0	5.8	8.7A
9	0.4, T(2/5)		0.1, T(1/5)		−0.4, T(4/5)
10	1.1		5.3		C(4/5)
11	C(1/5)	7.1A	C(2/5)	7.8A	T(5/5)
12	0.1		0.7		−0.1
13	C(1/5)	C(1/5)	C(1/5), T(3/5)	C(2/5), T(1/5)	C(2/5), T(3/5)
14	0.1	3.5	7.3A	13.0A	C(2/5)

[a] T = toxic; A = active; C = cure. See Experimental Section for definitions.

a 1:1:2 ratio of ligand, metal ion, and gegenion. A study of the magnetic and spectroscopic (UV and Mössbauer) properties of dichloro-iron(III) complex **10** is currently underway in order to elucidate its stereochemistry and electronic structure. Preliminary results suggest that this compound possesses a square pyramid structure, VII.[13]



VII

Results and Discussion

Antimalarial Activity. The ability to cure mice infected with *Plasmodium berghei* was investigated in a series of complexes of Fe(III), Cu(II), and Ni(II) with three N^4,N^4-disubstituted thiosemicarbazones of 2-acetylpyridine (Table II). The free ligands showed curative activity (3/5 infected animals) at dosage levels from 40 to 160 mg/kg. Only one of the metal complexes approached this level of activity, namely, Cu(II) complex **7**, which cured 5/5 infected animals at a dosage of 160 mg/kg. Complexes of Ni(II) were inactive, whereas complexes of Fe(III) were of lower activity than the corresponding Cu(II) complexes.

It is interesting to note that whereas antimalarial activity was retained in this series of thiosemicarbazones upon complexation with transition metals, these complexes appear to offer no therapeutic advantage over the free ligands.

Antitumor Activity. Nine thiosemicarbazone metal complexes were evaluated for antitumor activity against the leukemia P388 cell line in mice (Table III). The free ligands possess intrinsic antitumor activity, exemplified by 3-azabicyclo[3.2.2]nonane-3-thiocarboxylic acid 2-[1-(2-pyridyl)ethylidene]hydrazide, IIIa, which has a T/C value of 126% at a dose level of 6.5 mg/kg. Selenium analogue, IIIb, shows comparable activity with a T/C of 129% at the same dose level. Ligand IV was inactive, having a T/C value of 117% at a dose of 6.25 mg/kg.

Table III. Antitumor Activity of Transition Metal Complexes of 2-Acetylpyridine Thiosemicarbazones against Leukemia P388 in the Mouse

no.	treatment schedule	dose, mg/kg	wt difference (T − C), %	T/C, %
1	A[a]	25	−3.6	121
		12.5	−3.4	126
3	B[b]	6.25	−2.1	160
		3.13	−0.4	134
		1.56	0.0	126
4	A	200	−1.6	99
		100	−1.8	113
5	B	25	−2.9	178
		12.5	−2.2	178
		6.25	−1.5	164
6	B	50	−1.4	136
		25	−1.4	103
		12.5	−1.6	99
7	A	200	−1.1	115
		100	−0.4	101
9	B	6.25	−2.0	153
12	B	200	−1.8	139
		100	−1.2	125
		50	−1.3	109
13	A	12.5	−2.1	129
		6.25	−0.9	127
		3.13	−0.2	101

[a] Experimental animals were treated 4 times daily with the indicated dose, beginning on day 1 and ending on day 3. [b] Experimental animals were treated 1 time daily with the indicated dose, beginning on day 1 and ending on day 5.

Most of the metal complexes that were investigated showed significant (T/C ≥ 125%) antitumor activity. As was the case in the antimalarial series, the highest level of activity was exhibited by a Cu(II) complex, i.e., compound **5**. The Fe(III) complex **3** had only slightly lower activity. In contrast to the antimalarial findings, where Ni(II) complexes were inactive, Ni(II) complexes **6**, **9**, and **12** had significant antitumor activity. Whereas metal ion complexation lowers antimalarial activity, antitumor activity is enhanced by coordination.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus. Infrared spectra were run as KBr disks on a Perkin-Elmer Model 283 spectrophotometer. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. Satisfactory elemental analyses (±0.3%) were obtained for all compounds.

Chloro[*N*,*N*-3-azabicyclo[3.2.2]nonane-3-thiocarbohydrazonato][1-(2-pyridyl)ethylidene]copper(II) (7). The method for the preparation of the metal complexes of 2-acetylpyridine thiosemicarbazones is exemplifed in the following procedure. A solution of 8.20 g (27 mmol) of 3-azabicyclo[3.2.2]nonane-3-thiocarboxylic acid 2-[1-(2-pyridyl)ethylidene]hydrazide[4] in 400 mL of hot EtOH was treated with a solution of 4.60 g (27 mmol) of $CuCl_2 \cdot 2H_2O$ in 50 mL of hot EtOH. The product, **7**, that separated was collected, washed with EtOH, and dried. An analytical sample was prepared by two recrystallizations from DMF: IR 2935, 2863, 1595, 1492, 1467, 1445, 1435, 1295, 1205, 874, 767, 330 cm^{-1}.

Thiocyanato[*N*,*N*-3-azabicyclo[3.2.2]nonane-3-thiocarbohydrazonato][1-(2-pyridyl)ethylidene]copper(II) (11). Method A. A solution of 200 mg (0.66 mmol) of 3-azabicyclo[3.2.2]nonane-3-thiocarboxylic acid 2-[1-(2-pyridyl)ethyldene]-hydrazide[4] in 10 mL of EtOH was treated with a solution of 164 mg (0.66 mmol) of $Cu(SCN)_2 \cdot 4(CH_3)$[10] in ethanolic ammonium hydroxide (5 mL of EtOH + 2 mL of concentrated NH_4OH). The

(13) Results provided by Dr. Y. K. Bhoon, University of Delhi, India. A paper describing his findings has been submitted for publication.

solution was heated to boiling and filtered, and the filtrate was chilled. The crystals that separated were collected and washed with MeOH. An analytical sample was prepared by recrystallization from MeCN: IR 2940, 2910, 2870, 2084 (SCN^-), 1601, 1495, 1460, 1437, 1300, 1274, 1202, 877, 778, 771 cm^{-1}.

Method B. A solution of 500 mg (1.25 mmol) of **7** in 75 mL of refluxing propionitrile was treated with a solution of 122 mg (1.25 mmol) of KSCN in 20 mL of propionitrile. The solution was heated under reflux for 15 min and chilled, and the crystals that separated were collected. Recrystallization was effected from MeCN to give 235 mg (44%) of **11**. Infrared spectra of the products obtained by methods A and B were identical.

Thiocyanato[*N*,*N*-3-azabicyclo[3.2.2]nonane-3-thiocarbohydrazonato][1-(2-pyridyl)ethylidene]nickel(II) (12). A suspension of 800 mg (2.02 mmol) of chloro[3-azabicyclo-[3.2.2]nonane-3-thiocarboxylic acid 2-[1-(2-pyridyl)ethylidene]-hydrazinato]nickel(II) (**9**) in 70 mL of acetonitrile was treated with 250 mg (2.57 mmol) of KCNS and heated at reflux for 5 min. The reaction mixture was chilled, and the product was collected by filtration and washed well with H_2O to remove KCl. An analytical sample was prepared by recrystallization from MeCN: IR 2935, 2910, 2860, 2090, 1600, 1500, 1465, 1448, 1437, 1305, 1195, 777 cm^{-1}.

Biological Methods. The compounds described in this paper were tested for antimalarial activity at the Dr. Leo Rane Laboratory, University of Miami, Miami, FL, against a drug-sensitive strain of *Plasmodium berghei* (strain KBG 173) in ICR/HA Swiss 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 they die before the 6th day, "inactive" if they die between the 6th and 12th day, "active" if the mean survival time is at least doubled, and "curative" if the mice survive at least 60 days postinfection. Compounds that 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 of this series and by Osdene, Russell, and Rane.[14]

The antitumor activity of the thiosemicarbazones and their metal complexes was determined at the National Cancer Institute (NIH), Bethesda, MD, by the standard screening procedure (cf. Instruction 14) in the P388 lymphocytic leukemic test system. The tumor inoculum of 10^6 ascites cells was implanted on day 0 ip in CD_2F_2 (CDF_1) mice. The drugs were administered daily ip in accordance with the treatment schedule indicated in Table III. A compound is considered active when T/C (test/control) survival times produce a percentage >125.

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

Synthesis and Pharmacology of Metabolically Stable *tert*-Butyl Ethers of Morphine and Levorphanol

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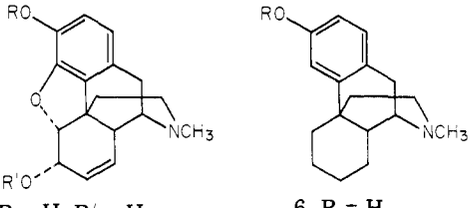
3-*O*-*tert*-Butylmorphine (**5**) was prepared from 6-*O*-acetylmorphine (**3**) via alkylation with *N*,*N*-dimethylformamide di-*tert*-butyl acetal, followed by hydrolytic removal of the 3-(dimethylamino)-2-propenoate group. The same process was used to prepare the *tert*-butyl ether of levorphanol (**6**), (-)-3-*tert*-butoxy-*N*-methylmorphinan (**8**). Both **5** and **8** exhibited in vitro affinity for the opiate receptor comparable to codeine and had analgesic properties in the writhing test. Only **5** exhibited activity in the tail-flick procedure and neither compound showed significant antitussive activity.

Our interest in *tert*-butyl analogues of codeine (**2**) and levomethorphan (**7**) was prompted by the expectation that replacement of the methyl group on the phenolic oxygen by a *tert*-butyl group would prevent the in vivo metabolic conversions to morphine (**1**) and levorphanol (**6**), respectively, with their attendant undesirable side effects. Disregarding the controversial hypothesis[1] that the analgesic activity of codeine (**2**) in man may be due to its metabolic conversion to morphine,[2] we envisaged the possibility that compounds **5** and **8** would retain the analgesic properties of the corresponding methyl ethers. We also speculated that (-)-3-*tert*-butoxy-*N*-methylmorphinan (**8**), the *tert*-butyl ether of levorphanol (**6**), might exhibit enhanced analgesic potency in comparison to **5**, since **6** is analgetically more potent than morphine (**1**).[3]

Chemistry. Conventional methods[4] for the preparation of *tert*-butyl ethers require strong acid catalysis and were precluded for the synthesis of **5**, since such conditions readily rearrange morphine (**1**).[5] However, based on the observation that *N*,*N*-dimethylformamide acetals[6] alkylate phenols, treatment of certain phenols with excess *N*,*N*-dimethylformamide di-*tert*-butyl acetal[7,8] at elevated temperature furnished the corresponding *tert*-butyl ethers.[9]

Chart I



1, R = H; R′ = H
2, R = CH_3; R′ = H
3, R = H; R′ = $C(=O)CH_3$
4, R = $C(CH_3)_3$; R′ = $C(=O)CH=CH_2N(CH_3)_2$
5, R = $C(CH_3)_3$; R′ = H

6, R = H
7, R = CH_3
8, R = $C(CH_3)_3$

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‡ Pharmacology Department.

(1) (a) G. Sanfilippo, *Bull. Soc. Ital. Biol. Sper.*, **24**, 723 (1958); (b) T. Johannesson and L. A. Woods, *Acta Pharmacol. Toxicol.*, **21**, 381 (1964).
(2) (a) T. Johannesson and J. Schou, *Acta Pharmacol. Toxicol.*, **20**, 165 (1963); (b) T. K. Alder, *J. Pharmacol. Exp. Ther.*, **140**, 155 (1963); (c) E. L. Way and T. K. Alder, *Pharmacol. Rev.*, **12**, 383 (1960).
(3) N. B. Eddy, H. Halbach, and O. J. Branden, *Bull. W.H.O.*, **17**, 569 (1957).

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