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Potential Antitumor Agents. 14. 4-Substituted 2-Formylpyridine Thiosemicarbazones[1]

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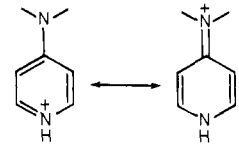
A series of 4-substituted 2-formylpyridine thiosemicarbazones has been synthesized which contain a tertiary N at the 4 position. These materials were obtained by reacting 4-nitro-2-picoline *N*-oxide, either directly or after conversion to the corresponding 4-chloro derivative, with a variety of secondary amines. Rearrangement of the 4-substituted 2-picoline *N*-oxides with Ac_2O yielded respective methyl acetates, which upon acid hydrolysis, MnO_2 oxidation, and reaction with thiosemicarbazide resulted in the desired compounds. An alternate procedure which consisted of reacting 4-chloro-2-formylpyridine ethylene acetal with various amines, followed by hydrolysis and reaction with thiosemicarbazide, was also employed. Introduction of an alkyl group at the 3 position of the pyridine ring of 4-morpholino-2-formylpyridine thiosemicarbazone was achieved by utilizing 2,3-dimethyl-4-nitropyridine *N*-oxide; this material was converted to the corresponding 4-chloro derivative which was then subjected to nucleophilic substitution. 4-Morpholino-2-formylpyridine thiosemicarbazone was the most active antineoplastic agent of this series in mice bearing Sarcoma 180 ascites cells and was significantly superior to 5-hydroxy-2-formylpyridine thiosemicarbazone in this test system.

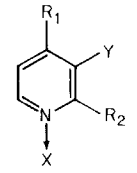
α-(N)-Heterocyclic carboxaldehyde thiosemicarbazones have significant antineoplastic activity in a variety of experimental tumor systems.[2-10] The reductive conversion of ribonucleotides to deoxyribonucleotides, catalyzed by the enzyme ribonucleotide reductase, appears to be the major site of action of these agents; blockade of this enzyme results in inhibition of DNA synthesis.[11-15] Since these agents are extremely water insoluble, hydroxylated derivatives were synthesized to (a) solubilize these compounds as sodium salts[16] and (b) enhance therapeutic efficacy.[3,4] The potent antineoplastic activity of the most promising of the hydroxylated derivatives, 5-hydroxy-2-formylpyridine thiosemicarbazone (5-HP), in animal systems was not attained in man[17-19] for two reasons: (a) 5-HP has relatively low inhibitory potency for ribonucleotide reductase[14] and (b) rapid metabolism to an *O*-glucuronide and elimination of 5-HP occurred in man.[18] Amino-substituted derivatives were therefore synthesized to eliminate the problem of *O*-glucuronide formation and allow water solubility as acid salts. As a result, 5-amino-1-formylisoquinoline and 2-formyl-4-(*m*-amino)-phenylpyridine thiosemicarbazones have been synthesized;[20,21] these agents possessed broad-spectrum antineoplastic activity in murine neoplasms. Since these agents were designed to take advantage of a hypothetical hydrophobic zone of interaction between the inhibitor and ribonucleotide reductase, they had high affinity for the target enzyme.[20,21] The amino group of these compounds, however, is readily susceptible to certain metabolic transformations by N-substitution (e.g., acetylation, methylation, and glucuronidation) which may result in inactivation. Confirming this possibility was the finding that acetylation of 5-amino-1-formylisoquinoline resulted in a compound devoid of antineoplastic activity.[4] For this reason, 4-methyl-5-amino-1-formylisoquinoline thiosemicarbazone was synthesized with the methyl group placed adjacent to the 5-amino function to provide steric protection from metabolic substitution and potential inactivation.[22]

We now report the synthesis of a series of 4-substituted 2-formylpyridine thiosemicarbazones, in which a tertiary nitrogen, as part of different ring systems, was inserted to achieve the assets of NH_2-substituted derivatives while (a) minimizing conjugation of the N atom employed for solubilization and (b) utilizing the postulated hydrophobic bonding zone present in or adjacent to the inhibitor binding site on the enzyme by varying the size of the substituted ring. The latter feature was also enhanced by insertion of an additional CH_3 group at the 3 position of the pyridine nucleus in one of the most active members of this series; such substitution has been shown to increase the affinity of 2-formylpyridine thiosemicarbazone toward the target enzyme.[23] Introduction of an alkyl group at the 3 position would also result in steric hinderance which would be expected to decrease the base-strengthening effect of 4-substituted amines on the ring nitrogen; this would tend to reduce the cationic forms shown below.



Formation of these cations would be undesirable since N*N*S* tridentate chelate formation with transition

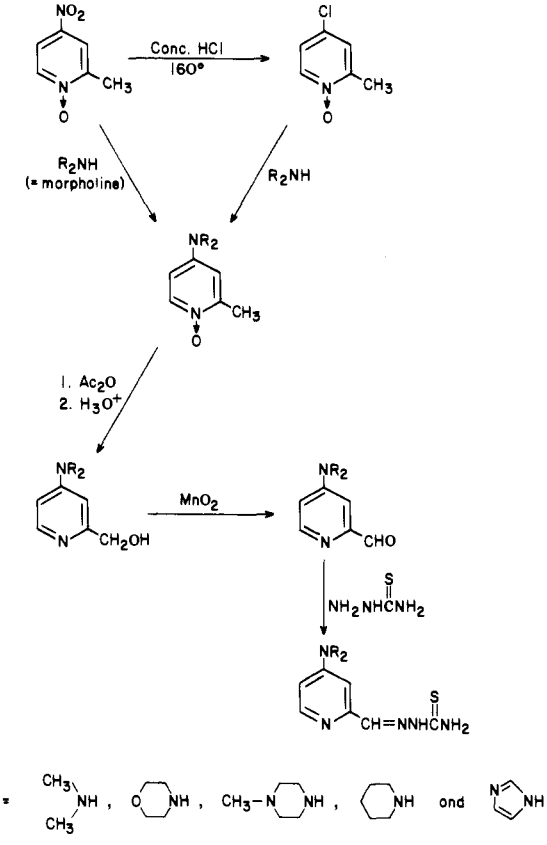
Table I



Compd	R_1	R_2	X	Y	Crystn solvent	Mp or bp (mm), °C	Yield, %	Formula	Analyses
1	$N(CH_3)_2$	CH_3	O	H		Semisolid	95	$C_8H_{12}N_2O$	
2	$N(CH_3)_2$	CH_2OAc		H	Me_2CO-hexanes	58-59	94	$C_{10}H_{14}N_2O_2$	
3	$N(CH_3)_2$	CH_2OH		H	Me_2CO	108-110	46	$C_8H_{12}N_2O$	C, H, N
4	$N(CH_3)_2$	CHO		H		Oil	92	$C_8H_{10}N_2O$	
5	$N(CH_3)_2$	$CHNNHCSNH_2$		H	EtOH-H_2O	227-228 dec	85	$C_5H_{13}N_5S$	C, H, N
6	c-$N(CH_2CH_2)_2O$	CH_3	O	H	Me_2CO	175-177	92	$C_{10}H_{14}N_2O_2$	C, H, N
7	c-$N(CH_2CH_2)_2O$	CH_2OAc		H	Et_2O	85-86	67	$C_{12}H_{16}N_2O_3$	
8	c-$N(CH_2CH_2)_2O$	CH_2OH		H	C_6H_6-hexanes	82-84	74	$C_{10}H_{14}N_2O_2$	C, H, N
9	c-$N(CH_2CH_2)_2O$	CHO		H	Et_2O	97	61	$C_{10}H_{12}N_2O_2$	
10	c-$N(CH_2CH_2)_2O$	$CHNNHCSNH_2$		H	DMF-EtOH	239-240	91	$C_{11}H_{15}N_5OS$	C, H, N
11	c-$N(CH_2CH_2)_2N$-CH_3	CH_3	O	H	Me_2CO	58-59	68	$C_{11}H_{13}N_3O$	C, H, N
12	c-$N(CH_2CH_2)_2N$-CH_3	CH_2OAc		H		Oil	64	$C_{13}H_{19}N_3O_2$	
13	c-$N(CH_2CH_2)_2N$-CH_3	CH_2OH		H		Oil	52	$C_{11}H_{17}N_3O$	
14	c-$N(CH_2CH_2)_2N$-CH_3	CHO		H	Et_2O-petr ether	77-79	54	$C_{11}H_{15}N_3O$	
15	c-$N(CH_2CH_2)_2N$-CH_3	$CHNNHCSNH_2$		H	EtOH	223-225	72	$C_{12}H_{18}N_6S\cdot0.5H_2O$	C, H, N
16	c-NC_5H_{10}	CH_3	O	H		Oil	92	$C_{11}H_{16}N_2O$	
17	c-NC_5H_{10}	CH_2OAc		H		155-165 (0.1)	51	$C_{13}H_{18}N_2O_2$	
18	c-NC_5H_{10}	CH_2OH		H		Oil	82	$C_{11}H_{16}N_2O$	
19	c-NC_5H_{10}	CHO		H		Oil	67	$C_{11}H_{14}N_2O$	
20	c-NC_5H_{10}	$CHNNHCSNH_2$		H	DMF-EtOH	235-236 dec	54	$C_{12}H_{17}N_5S$	C, H, N
21		CH_3	O	H	Me_2CO	193-194	43	$C_9H_9N_3O$	C, H, N
22		CH_2OAc		H	Et_2O	74-76	60	$C_{11}H_{11}N_3O_2$	
23		CH_2OH		H	$CHCl_3$	146-147	82	$C_9H_9N_3O$	C, H, N
24		CHO		H	Et_2O	141-142	80	$C_9H_7N_3O$	
25		$CHNNHCSNH_2$		H		225-227	85	$C_{10}H_{10}N_6S\cdot0.5H_2O$	C, H, N
26	Cl			H		93-95 (0.2)	77	$C_8H_8ClNO_2$	C, H, N
27	c-C_4H_8			H	Et_2O-petr ether	79-80	53	$C_{12}H_{16}N_2O_2$	C, H, N

28	c-NC_4H_8	$CHNNHCSNH_2$	H	EtOH	227–228 dec	66	$C_{11}H_{15}N_5S$	C, H, N
29	$N(CH_2CH_2OH)_2$		H	Me_2CO	128–129	38	$C_{12}H_{18}N_2O_4$	C, H, N
30	$N(CH_2CH_2OH)_2$	$CHNNHCSNH_2$	H	EtOH (90%)	219–220 dec	78	$C_{11}H_{17}N_5O_2S$	C, H, N
31	Cl	CH_3 O	CH_3	Et_2O–petr ether	52–53 (hygroscopic) 104–105 (dry)	83	C_7H_8ClNO	
32	Cl	CH_2OAc	CH_3		Oil	91	$C_9H_{10}ClNO_2$	C, H, N
33	Cl	CH_2OH	CH_3	petr ether	46–47	75	C_7H_8ClNO	
34	Cl	CHO	CH_3		Oil	78	C_7H_6ClNO	
35	Cl		CH_3		Oil	68	$C_9H_{10}ClNO_2$	
36	c-$N(CH_2CH_2)_2O$		CH_3	Et_2O	136	58	$C_{13}H_{18}N_2O_3$	C, H, N
37	c-$N(CH_2CH_2)_2O$	$CHNNHCSNH_2$	CH_3	EtOH	215–217	82	$C_{12}H_{17}N_5OS$	C, H, N

Scheme I



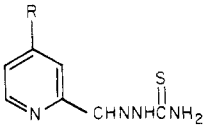
metals would be decreased and such potential is necessary for inhibition of both ribonucleotide reductase and tumor growth.[24]

Chemistry. Synthesis of these compounds was carried out by utilizing 2-picoline *N*-oxide as the starting material. Nitration of 2-picoline *N*-oxide yielded the 4-nitro derivative which on treatment with concentrated HCl according to published procedure[25] produced 4-chloro-2-picoline *N*-oxide. This latter material reacted with various secondary amines to produce 4-substituted derivatives (Scheme I). The amines utilized in this reaction were dimethylamine, morpholine, *N*-methylpiperazine, piperidine, and imidazole. Selection of these amines was based on their basicities in an effort to cover a relatively wide range of pK_a values. Direct nucleophilic substitution of 4-nitro-2-picoline *N*-oxide was also successful when employed with one of the amines (i.e., morpholine). However, the yields with this latter methodology were much smaller.

Oxidation of the 2-CH_3 group to the aldehyde was carried out by treatment of 4-substituted 2-picoline *N*-oxides with excess Ac_2O to yield corresponding acetoxymethyl derivatives, which upon either acid or base hydrolysis produced 2-carbinols. These materials were oxidized further with MnO_2 to yield the corresponding 2-carboxaldehydes, which upon reaction with thiosemicarbazide resulted in the desired thiosemicarbazones.

Introduction of the pyrrolidino group onto the pyridine ring employing the reaction sequence shown in Scheme I with pyrrolidine (pK_a 11.27) resulted in a considerable amount of polymerization and very low yields. Therefore, an alternate procedure shown in Scheme II was designed. 4-Chloro-2-picoline *N*-oxide was initially converted to 4-chloro-2-carboxaldehyde by a published procedure;[25] the aldehyde was then protected by forming an ethylene ketal which upon nucleophilic substitution with pyrrolidine produced the corresponding pyrrolidino ketal in 53% yield. Reaction of this material with thiosemicarbazide in the

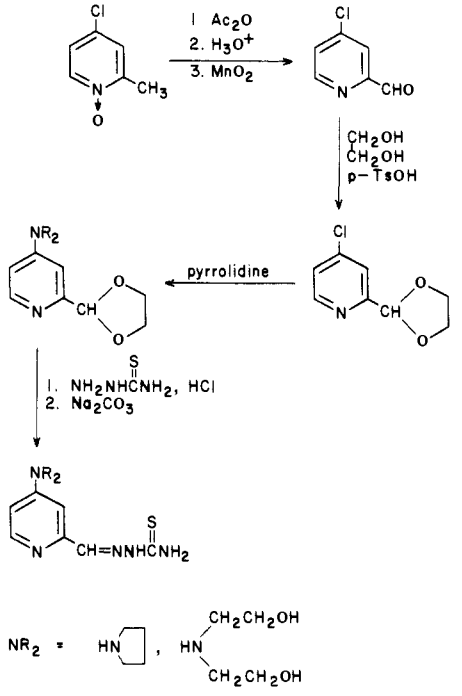
Table II. Effect of 4-Substituted 2-Formylpyridine Thiosemicarbazones on the Survival Time of Mice Bearing Sarcoma 180 Ascites Cells



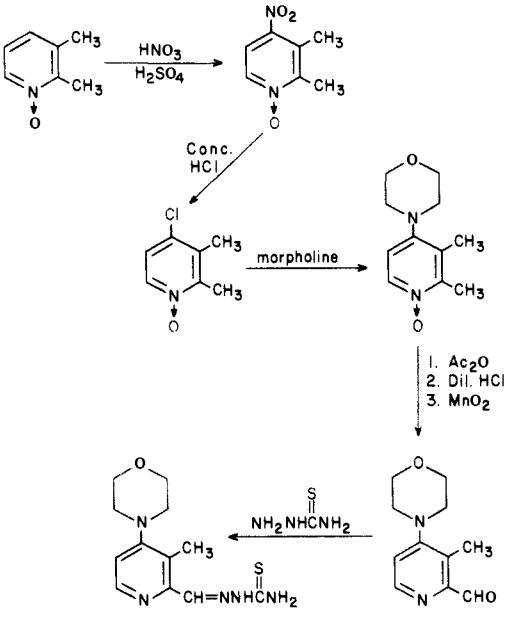
Compd	R	Max effective daily dose, mg/kg[a]	Av Δ wt, %[b]	Av survival time, days ± SE	50-Day survivors[c]	% T/C[d]
Control			+24.4	13.6 ± 0.4	0/25	
5	$N(CH_3)_2$	40	+3.3	20.7 ± 3.4	0/10	152
10	$c\text{-}N(CH_2CH_2)_2O$	60	−7.2	38.0 ± 3.7	4/10	279
15	$c\text{-}N(CH_2CH_2)_2N\text{-}CH_3$	30	+12.4	15.0 ± 1.0	0/5	110
20	$c\text{-}NC_5H_{10}$	40	+2.2	22.3 ± 3.2	0/10	164
25		40	+18.9	13.6 ± 1.1	0/5	100
28	$c\text{-}NC_4H_8$	40	+6.4	18.2 ± 0.2	0/5	134
30	$N(CH_2CH_2OH)_2$	40	+5.5	20.8 ± 2.2	0/5	153
37	$c\text{-}N(CH_2CH_2)_2O$, 3-CH_3	40	+0.6	19.8 ± 0.8	0/5	146

[a] Administered once daily for six consecutive days beginning 24 h after tumor implantation; dose levels were administered in a range of 10–80 mg/kg for each compound. [b] Average weight change from onset to termination of drug treatment. [c] The number of tumor-bearing animals that survived at least 50 days; these mice were calculated as 50-day survivors in the determination of average survival time. [d] % T/C = (treated/control) × 100.

Scheme II



Scheme III



presence of hydrochloric acid produced the desired 4-pyrrolidino-2-formylpyridine thiosemicarbazone. A similar procedure was also utilized for introducing a diethanolamino group.

Insertion of a 3-CH_3 group onto one of the most active compounds of this series, i.e., 4-morpholino-2-formylpyridine thiosemicarbazone, was carried out (a) to determine the steric influence of this substituent on the properties of the 4-morpholino derivative and (b) to enhance interaction of the inhibitor with the hydrophobic bonding zone of the target enzyme, ribonucleotide reductase. Synthesis was achieved by utilizing the sequence of reactions shown in Scheme III. 2,3-Dimethylpyridine *N*-oxide was converted to the 4-chloro derivative via formation of a 4-nitro analogue[26] utilizing a procedure similar to that employed for the formation of 4-chloro-2-picoline *N*-oxide.[25] The 4-chloro derivative was then transformed through a series of reactions to the 2-carboxaldehyde, followed by ketal formation and nucleophilic substitution. Relevant data for compounds synthesized are listed in Table I.

Biological Results and Discussion. The antitumor activity of the newly synthesized compounds was determined by measuring their abilities to prolong the survival time of mice bearing Sarcoma 180 ascites cells; the results of these tests are shown in Table II. The 4-morpholino derivative **10** was the most potent α-(N)-heterocyclic carboxaldehyde thiosemicarbazone of this series; this agent caused an increase in the average survival time of tumor-bearing mice from 13.6 days for control nondrug-treated animals to 38 days at the maximum effective daily dosage level (60 mg/kg) of **10**. The other members of this series were considerably less active as anticancer agents in this test system.

Table III. Comparative Effects of the Thiosemicarbazones of 4-Morpholino-2-formylpyridine (10) and 5-Hydroxy-2-formylpyridine (5-HP) on the Survival Time of Mice Bearing Sarcoma 180 Ascites Cells

Compd	Daily dosage, mg/kg[a]	Av Δ wt, %[b]	Av survival time, days ± SE	% 50-day survivors[c]
None		+24.4	13.6 ± 0.4	0
5-HP	20	+1.4	25.3 ± 2.9	10
	40	-0.5	30.5 ± 2.6	13
	60	-3.3	31.4 ± 2.0	20
	80	-16.2	16.8 ± 5.0	0
10	20	-1.2	24.8 ± 1.4	0
	40	-2.0	34.8 ± 3.5	33
	60	-7.0	38.0 ± 3.7	40
	80	-5.9	38.2 ± 3.5	20

[a] Administered once daily for six consecutive days beginning 24 h after tumor implantation. [b] Average weight change from onset to termination of drug treatment. [c] The percent of tumor-bearing animals that survived at least 50 days; these mice were calculated as 50-day survivors in the determination of average survival time.

Although attempts were not made to determine the pK_a values of the newly synthesized derivatives, no correlation between the pK_a values of the substituted amines employed and the biological potencies of the product drugs could be ascertained. Thus, for example, substitution of morpholine (pK_a 8.33, compound **10**) and diethanolamine (pK_a 8.88, compound **30**) resulted in the most active tumor-inhibitory member of this series and an inactive agent, respectively. Introduction of a 3-CH_3 group onto **10** produced compound **37** which was markedly less active against Sarcoma 180 than the parent compound. This finding was unexpected since earlier results have demonstrated that insertion of the hydrophobic CH_3 group onto the 3 position of the pyridine ring system increased the affinity of the inhibitor for the target enzyme, ribonucleoside diphosphate reductase.[23] A possible explanation for the lowering of the anticancer activity of **10** when a CH_3 group was introduced onto position 3 of the pyridine ring is that the 3-CH_3 group of **37** forces the 4-morpholino substituent and the pyridine ring out of coplanarity; this explanation requires the necessity of a coplanar molecule for the biological activity of this class of compounds.

Table III presents a comparison of the dose–response data for compound **10** and 5-hydroxy-2-formylpyridine thiosemicarbazone (5-HP), the clinically tested agent of the α-(N)-heterocyclic carboxaldehyde thiosemicarbazone class, against Sarcoma 180 ascites cells. The results demonstrate that **10** was comparatively more active than 5-HP in increasing the life span of animals bearing this neoplasm. Thus, at its maximum effective daily dosage range of 60–80 mg/kg, compound **10** increased the average survival time of tumor-bearing mice from 13.6 to 38 days, while in comparison 5-HP at its optimum dosage range of 40–60 mg/kg per day prolonged life to about 31 days and was mirrored by a higher percentage of mice surviving for at least 50 days following treatment with compound **10**. At the highest dose level tested (80 mg/kg per day), mice treated with 5-HP showed significant toxicity as manifested by 16.2% loss in body weight and a reduction in the average survival time to 16.8 days; whereas, in contrast, compound **10** did not produce this degree of toxicity when employed over a similar dosage range. These results suggest that compound **10** possesses therapeutic advantage over 5-HP. In addition, since the tertiary nitrogen at position 4 of **10** would be expected to be minimally or not susceptible to metabolic transformation and yet may be readily formulated for clinical use as a water-soluble acid salt, it may have significant advantage over other amino-substituted derivatives [i.e., 4-(*m*-amino)phenyl-2-formylpyridine thiosemicarbazone[20] and 5-amino-1-formylisoquinoline thiosemicarbazone[4]] recommended for clinical trial as a second generation agent of this class.

Experimental Section

Melting points, determined in capillary tubes using a Thomas-Hoover stirred-liquid apparatus, are corrected. Infrared spectra of compounds were obtained with a Perkin-Elmer Model 257 spectrophotometer, with thin films of liquids and KBr pellets of solids, and uv spectra using a Perkin-Elmer Model 402 ultraviolet-visible spectrophotometer with agents dissolved in absolute ethanol. NMR spectra were determined with a Varian T-60A spectrometer with Me_4Si as an internal standard. Elemental analyses were performed by the Baron Consulting Company, Orange, Conn. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical values.

Antitumor Activity. Experiments were performed on CD-1 mice. Transplantation of Sarcoma 180 ascites cells was carried out as previously described[4] using a donor mouse bearing a 7-day tumor growth. Mice were weighed during the course of the experiments, and the percentage change in body weight from onset to termination of therapy was used as an indication of drug toxicity. Determination of the sensitivity of ascitic neoplasms to these agents was based on the prolongation of survival time of animals afforded by the drug treatments.

Reaction of 4-Chloro-2-picoline *N*-Oxide with Secondary Amines. 4-Chloro-2-picoline *N*-oxide[25] (4.29 g, 0.03 mol) was treated with 0.09 mol of an appropriate amine. In the case of morpholine and imidazole the mixture was refluxed at 140° for 16 h. Reaction with *N*-methylpiperazine was complete in 4 h at 140°. Piperidine was heated with the *N*-oxide in a bomb at 140° for 5 h. Dimethylamine was also allowed to react in a bomb at 140°; in this instance heating was maintained for 16 h. After completion of the reactions, the mixtures were dissolved in 50 ml of water, treated with activated charcoal, and filtered. Sodium carbonate (20 g) was added to each of the filtrates, which were then evaporated under vacuum to dryness. The residues were extracted with $CHCl_3$ and dried ($MgSO_4$), and the solvent was removed under vacuum to yield the various 4-substituted derivatives of 2-picoline *N*-oxide. These materials were recrystallized from an appropriate solvent which is listed in Table I.

Conversion of 4-Substituted 2-Picoline *N*-Oxides to 2-Pyridylcarbinols. 4-Substituted 2-picoline *N*-oxides (0.02 mol) were each mixed with 40 ml of Ac_2O and heated at 110° for 2.5 h. The excess Ac_2O was removed under vacuum and the residual esters were extracted with Et_2O. The solvent was removed to leave the crude esters which were directly hydrolyzed in most cases by heating with 1.5 molar equiv of NaOH in 90% ethanol for 1.5 h. The formation of the esters was confirmed in each case by both ir and NMR data. After alkaline hydrolysis of the various esters, the solvent was removed under vacuum, the residues were extracted with $CHCl_3$ and dried ($MgSO_4$), and the solvent was removed. The resulting residual 2-pyridylcarbinols were recrystallized from an appropriate solvent.

Oxidation of 4-Substituted 2-Pyridylcarbinols. The 4-substituted 2-pyridylcarbinols (0.01 mol) were dissolved in 100 ml of $CHCl_3$ and treated with 8.0 g of activated MnO_2 (Winthrop Laboratories). The mixtures were each heated under reflux for 20 min (*N*-methylpiperazine), 30 min (piperidine), 45 min (morpholine), and 2 h (dimethylamine and imidazole), following which they were filtered through Celite and the $CHCl_3$ was removed under vacuum to leave the various aldehydes.

Thiosemicarbazones. The crude aldehydes were used directly to form thiosemicarbazones by reaction with molar equivalent quantities of thiosemicarbazide in the presence of 2 ml of dilute AcOH. After 5–10 min of heating, the solutions were made alkaline with NaOH. The thiosemicarbazones which formed were filtered, dried, and recrystallized from an appropriate solvent.

4-Chloro-2-formylpyridine Ethylene Acetal (26). To 1.41 g (0.01 mol) of 4-chloro-2-pyridinecarboxaldehyde in 200 ml of benzene was added 0.15 g of *p*-toluenesulfonic acid and 2 ml of

ethylene glycol. The mixture was refluxed for 24 h using a Dean-Stark trap to remove the water which formed during condensation. The mixture was then extracted with 5 ml of 10% $NaHCO_3$. The benzene layer was separated, washed with 5 ml of water, dried ($MgSO_4$), and removed under vacuum to leave the desired compound.

4-Pyrrolidino-2-formylpyridine Ethylene Acetal (27). To 0.93 g (0.005 mol) of **26** was added 3 ml of pyrrolidine and the solution was refluxed for 2 h. Excess pyrrolidine was removed under vacuum, the residue was extracted with Et_2O, the solvent removed, and the residue was crystallized from Et_2O and petroleum ether.

4-Bis(hydroxyethyl)amino-2-formylpyridine Ethylene Acetal (29). To 0.93 g (0.005 mol) of **26** was added 3 g of diethanolamine. This mixture was heated at 140° for 8 h, extracted with 100 ml of $CHCl_3$, treated with activated charcoal, and filtered, and the solvent was removed under vacuum. The residue was crystallized from acetone.

4-Morpholino-3-methyl-2-formylpyridine Ethylene Acetal (36). This compound was synthesized by a procedure similar to that described for **27** except that heating of **35** with morpholine was carried out at 140° for 40 h.

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References and Notes

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Synthesis and Antilipidemic Properties of *cis*-7-Chloro-3a,8b-dihydro-3a-methylfuro[3,4-*b*]benzofuran-3(1*H*)-one, a Tricyclic Clofibrate Related Lactone Having a Structural Resemblance to Mevalonolactone[1]

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The synthesis for the title lactone **2**, designed to be an antagonist of the enzyme HMG-CoA reductase (E.C. 1.1.1.34), is described. Lactone **2**, its synthetic tricyclic hemiacetal precursor **4**, and clofibrate were investigated for their antilipidemic activity in 7-day treated normal and in Triton WR-1339 induced hyperlipidemic male Sprague–Dawley rats. After 7-day drug administration to normal rats, lactone **2** was less effective than clofibrate in lowering HMG-CoA reductase activity and serum cholesterol; however, unlike clofibrate, lactone **2** did not increase liver weight or liver–body weight ratio or lower serum triglycerides. Since hemiacetal **4** selectively influenced triglycerides in normal animals, lactone **2** and hemiacetal **4** appear to have differential hypolipidemic effects. In the Triton hyperlipidemic model **2** and **4** lowered elevated triglycerides; only **4** significantly reduced elevated cholesterol levels; but neither **2** nor **4** was as effective as clofibrate. Differences in the observed antilipidemic properties for clofibrate, **2**, and **4** in the two animal models are discussed. On the basis of preliminary biological data described in this article it is concluded that tricyclic analogues **2** and **4** represent reasonable leads for the development of new antilipidemic agents.

A major action of clofibrate (**1**) involves its hypotriglyceridemic activity, and for these reasons this drug is mainly effective in the treatment of patients with hyperlipoproteinemia types III, IV, and V.[2] However, clofibrate also inhibits 3-hydroxy-3-methylglutaryl-CoA reductase activity (HMG-CoA reductase, E.C. 1.1.1.34) in vivo[3] and its hypocholesterolemic activity, in part, may be related to its ability to block cholesterol biosynthesis. For purposes of developing new compounds which might retain the hypotriglyceridemic properties of clofibrate, but exhibit