Table III[a] (Continued)

Drug	Dose, mg/kg per day	Survivors	Weight change, g	Average days of survival: Treated	Average days of survival: Control	T/C, %	50-day survivors
43	75	6	−4.8	15.4	9.8	157	1
	50	6	−2.5	21.3	10.3	207	2
	33	6	−2.1	19.1	10.3	197	
	22	6	+1.0	16.3	10.2	159	
	15	6	+1.7	12.1	9.6	126	
44	53	6	−1.5	17.2	9.6	179	1
	37	6	−2.1	19.1	10.3	197	2
	24	6	−0.9	18.9	10.3	195	
	16	6	−0.4	17.0	9.8	173	
	11	6	+1.8	15.1	9.8	154	
	7	6	+1.3	13.6	10.2	133	

[a] Only those results providing significant T/C values have been given. Doses *ca.* 0.2 log higher than the greatest dose quoted were toxic; those 0.2 log lower than lowest quoted gave T/C's $\leq$ 125%.

vigorous stirring, clarifying, and repptg with acid. Most of the examples examined crystd well from EtOH–H_2O.

The amide intermediates necessary for 26–35 were prepd by phosphorazo coupling[10] of acid and amine component. Nitro functions were reduced to the amines with Fe as previously described.[10]

Compounds previously not reported are shown in Table II.

9-(2-Methylthio)ethylaminoacridine. Equimolar proportions of 1-methylthioethylamine and 9-chloracridine were heated together in 2 vol of anhyd PhOH at 120° for 40 min. After addn of excess cold 4 *N* NaOH, product was removed in PhH. The solvent layer, after thorough washing with 4 *N* NaOH and H_2O, was shaken with successive small vol of 4 *N* HCl, the cryst hydrochloride resulting being removed progressively. Crystn from MeOH–H_2O–NaCl afforded yellow needles (68%), mp 268–269°. *Anal.* ($C_{16}H_{16}N_2S \cdot HCl$) C, H, N, S

9-[2-(Morpholin-1-yl)ethylamino]acridine. Essentially the same experimental conditions as above produced the desired product as the dihydrochloride, yellow needles from small vol of 3 *N* HCl (54% yield), mp 282–283°. *Anal.* ($C_{19}H_{21}N_3O \cdot 2HCl$) C, H, N, Cl.

Biological Testing. The routine test consists of ip inoculation of 10^5 L1210 cells into 18.5–22.5 g C_3H/DBA_2F_1 hybrids on day 1; drug treatment was initiated 24 hr later and contd for 5 days. Dosage was in 0.2 ml vol, H_2O being used as the suspending medium. Groups of 6 animals per dose level were used with one control group for every 5 tests. The wt change column in Table III records the difference between initial wt and that at day 8 for survivors. The number of animals surviving as long or longer than controls is listed under survivors. Doses have been rounded off to 2 significant figures. Details of testing of inactive comps have not been given.

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Potential Antitumor Agents. 8. Derivatives of 3- and 5-Benzyloxy-2-formylpyridine Thiosemicarbazone

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A series of derivatives of 3- and 5-benzyloxy-2-formylpyridine thiosemicarbazone was synthesized and their antineoplastic activity was measured against sarcoma 180 ascites tumor cells. 3-(*m*-Aminobenzyloxy)-2-formylpyridine thiosemicarbazone was a potent antitumor agent, increasing the life-span of tumor-bearing mice over untreated animals by a factor of 2.4 at the optimal daily dose level of 80 mg/kg with no demonstrable signs of toxicity to the host. 5-(*m*-Hydroxybenzyloxy)-2-formylpyridine thiosemicarbazone and 5-(*m*-acetaminobenzyloxy)-2-formylpyridine thiosemicarbazone were marginally active.

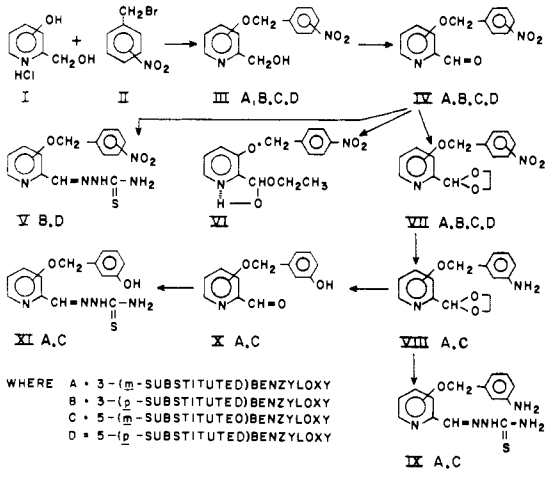
The antineoplastic effect of a variety of thiosemicarbazones of α-(N-heterocyclic) carboxaldehydes has been actively investigated during the past few years.[1-11] The pyridine and isoquinoline rings have been found to be the most biologically active systems investigated.[2] Intensive studies on structure-activity relationships based on the modification of these two ring systems have indicated that no simple parametric rationale explains the effect of various substituents on activity against neoplastic cells. These findings may in part be due to the poor water solubility of this type of compound which limits their cellular uptake *in vivo*. The relative insolubility also imposes a limitation on the practi-

cal application of otherwise very potent compounds in patients with disseminated tumors. That 5-hydroxy-2-formylpyridine thiosemicarbazone (5-HP) was chosen as the first compound of this class for clinical test is the result of the water solubility of its sodium salt, as well as its relatively great therapeutic index against transplanted experimental tumors.[5,8,10,12] However, due to its (a) extensive gastrointestinal toxicity,[13,14] (b) relatively short-lived activity,[13] and (c) low potency for the target enzyme,[15] a water-soluble (in salt form or otherwise) compound of this class with greater affinity for the target enzyme or with a longer biological half-life or both is necessary.

An understanding of the biochemical basis for the carcinostatic activity of this class of compounds has made the rational design of a clinically more effective agent a feasible approach. 1-Formylisoquinoline thiosemicarbazone (IQ-1), one of the most potent tumor inhibitors of this class, and several other related analogs have been shown[15,16] to inhibit the synthesis of DNA by inhibiting ribonucleoside diphosphate reductase, an iron-dependent enzyme which catalyzes the conversion of ribonucleotides to deoxyribonucleotides. Comparison of the enzymatic inhibitory activity of 2-formylpyridine thiosemicarbazone (PT) and its derivatives indicated that introduction of a Me group at either the 3, 4, or 5 position of PT enhances inhibitory activity.[17] IQ-1, which can be visualized as PT with a benzene ring fused across the 3 and 4 positions of the pyridine ring, is approximately 2.5-fold more inhibitory to ribonucleoside diphosphate reductase than PT.[16,17] In contrast, however, the presence of an OH group at either the 3 (3-hydroxy-2-formylpyridine thiosemicarbazone, 3-HP) or 5 (5-HP) positions decreases inhibitory potency at least 10-fold.[15] These findings suggest the possible existence of a hydrophobic bonding zone adjacent to the inhibitor binding site of the enzyme. Exploration and utilization of this hypothetical binding zone could lead to the fabrication of a better inhibitor of this class. To this end, the present investigation reports the synthesis of a series of meta- and para-substituted benzyloxy derivatives of PT and the antineoplastic potency and host toxicity of these compounds in mice bearing sarcoma 180 ascites cells.

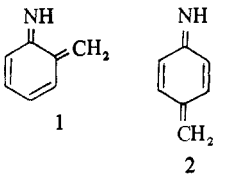
Chemistry. The synthetic steps employed are shown in Scheme I and are described in the Experimental Section.

SCHEME I



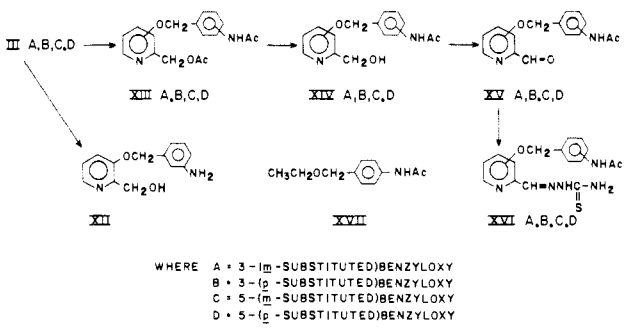
Formation of stable hemiacetals VIA and VIB occurred when IVA and IVB, respectively, were recrystallized from ethanol. The hemiacetal OH group formed a strong intramolecular H bond (3180 cm^{-1}, KBr). Interestingly, the corresponding 5 isomers, IVC and IVD, failed to form stable hemiacetals with ethanol under similar conditions. Although stable cyclic hemiacetals are rather common among carbohydrates and steroids,[18] there are relatively few examples of stable noncyclic hemiacetals.[19] The nmr spectrum in $CDCl_3$ indicated that an equilibrium between free aldehyde and hemiacetal existed in an approximately 1:1 ratio.

Although catalytic hydrogenation of *m*-nitrobenzyloxypyridine VIIA and VIIC, using 5% Rh/carbon[20] as catalyst under 10 psi pressure, gave a good yield of the corresponding amine VIIIA and VIIIC, the para isomers VIIB and VIID failed to give the desired amines under the same conditions. The difference in the behavior of *p*- or *o*-methoxymethylaniline and the meta isomer toward the Grignard reagent has been documented.[21] Thus, *o*- or *p*-methoxymethylaniline reacted with PhMgBr to give *o*- or *p*-quinomonomethanimine (**1** or **2**), a key intermediate which formed



with excess Grignard reagent and *o*- or *p*-benzylaniline. The meta isomer failed to react with the Grignard reagent and the original amine was recovered. Since the pyridinoxy group of compound VIIB is a much better leaving group than the methoxy group, the ethereal linkage of compound VIIB or VIID was presumably cleaved when the nitro group was reduced to an amino function to form *p*-quinomonomethanimine (**2**) which then polymerized. Similar results were obtained with the attempted reduction of the nitro intermediates IIIA,B,C,D to the corresponding amines (Scheme II) using Fe powder in a glacial AcOH;[20] the *m*-

SCHEME II



nitro isomers (IIIA and IIIC) were readily reduced to the corresponding amines with this reagent, whereas attempts to reduce the *p*-nitro isomer IIIB with the same reagent were unsuccessful. However, treatment of IIIA,B,C, or IIID with Fe powder and AcOH in the presence of Ac_2O at 60° gave diacetylated derivatives XIIIA,B,C,D in high yield.[22] The different results observed with IIIB when it was subjected to reduction by Fe powder in AcOH in both the presence and absence of Ac_2O provided further evidence of the direct participation of the *p*-NH_2 group in the cleavage of the benzylic ether linkage. The formation of NHAc decreased the availability of the free electon pair on the N atom and therefore increased the stability of the ether bond. Selective hydrolysis of the ester group in all cases was best obtained by refluxing XIII in 0.25 *N* ethanolic KOH solution. However, when 1 *N* ethanolic KOH solution was

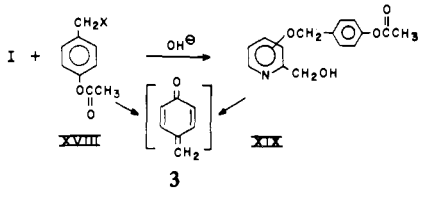
Table I

No.	Method	Recrystn solvent	Yield, %	Mp, °C
IIIA	A	EtOH	70	123–124
IIIC	A	C_6H_6 + petr ether	60	81–83
IIID	A	C_6H_6	38	121–123
IVA	B	EtOAc	70	151–152
IVC	B	EtOH	60	106–108
IVD	B	EtOAc	62	140–141
VB	Ref 3	EtOH	78	216–217 dec
VD	Ref 3	DMSO + EtOH	68	236–237 dec
VIIB	C	EtOAc	78	115–117
VIIC	C	EtOAc	78	103–104
IXC	D	EtOH	40	200 dec
XIC	E	EtOH + H_2O	30	180–182 dec
XIIIB	F	EtOAc	83	161–162
XIIIC	F	C_6H_6 + hexanes	70	104–105
XIIID	E	C_6H_6	66	116–118
XIVB	G	Acetone	50	173–175
XIVC	G	EtOAc + hexanes	46	135–136
XIVD	G	EtOAc	58	182–184
XVA	B	EtOAc + hexanes	60	78–80
XVB	B	EtOAc + hexanes	80	156–158
XVC	B	EtOAc + hexanes	68	113–114
XVD	B	EtOAc + hexanes	60	138–139
XVIA	Ref 3	DMSO + H_2O	79	230–231 dec
XVIB	Ref 3	EtOH	45	152–153 dec
XVIC	Ref 3	EtOH	79	186–189 dec
XVID	Ref 3	EtOH	79	220–221 dec

used, a new ether was formed which was identified by nmr and ir spectroscopy as XVII. The alcohol XIV was oxidized to the aldehyde XV with an excess of MnO_2, and the thiosemicarbazone XVI was prepared according to the standard procedure.

An alternate approach for the synthesis of the para isomer of XIA or XIC involved treatment of I (Scheme III)

SCHEME III



3

with *p*-acetoxybenzyl halide (Cl or Br) (XVIII) in the presence of base at room temperature; this procedure failed to give the desired ether intermediate XIX. Instead, an unknown high-melting product precipitated from the reaction mixture within 30 min. This unknown product showed no carbonyl peak in ir and was insoluble in all solvents except base. It is conceivable that the ester groups of compounds XVIII and XIX were readily hydrolyzed under the reaction conditions and an active intermediate, *p*-quinone methide (3),[23] was formed which then underwent polymerization.

Physical constants and the method of preparation of compounds are given in Table I.

Biological Evaluation. The magnitude of the antineoplastic potency against sarcoma 180 ascites cells of the active compounds of this series are shown in Table II. The results indicate that IXA was the most effective carcinostatic agent in this series prolonging the life-span of tumor-bearing mice to 32.3 days at the optimal daily dose level with no demonstrable signs of toxicity to the host. Compounds with borderline inhibitory activity against sarcoma 180 were XVIC and XIC; at the optimal dose and sequence levels these compounds produced survival times of 17.8 and 16.4 days, respectively. With only one exception (XVIC) the compounds with an NO_2 or NHAc group at the meta or para positions of the benzene ring of this series were inactive against this tumor. Although only the 3 isomer IXA of the amino analogs was biologically active, only the 5 isomer proved to be an effective antineoplastic agent in the OH-substituted series. The potent antitumor activity exhibited by IXA suggests that it is feasible to introduce a hydrophobic bridge between the biologically active ring system and a polar group required for water solubility.

Table II. Effect of Derivatives of 3- and 5-Benzyloxy-2-formylpyridine Thiosemicarbazone on the Survival Time of Mice Bearing Sarcoma 180 Ascites Cells

Compound	Maximal effective dose, mg/kg	No. of daily doses[a]	Av Δ wt, %[b]	Av survival days ± S.E.
None			+22.5	13.4 ± 1.8
IXA	40	2	+2.9	32.3 ± 7.7
XIC	30	2	+3.9	16.4 ± 1.0
XVIC	40	1	+13.2	17.8 ± 2.1

[a] Administered once or twice daily at 12-hr intervals for 6 consecutive days beginning 24 hr after tumor implantation. [b] Average weight change from onset to termination of drug treatment.

Experimental Section

Biological Methods. Compounds were tested for antineoplastic activity in mice bearing sarcoma 180 ascites cells. Complete details of the biological methods have been described earlier.[3]

Chemical Methods. All melting points were measured on a calibrated Thomas-Hoover capillary melting point apparatus. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by the Baron Consulting Co., Orange, Conn. Spectral data were obtained using a Perkin-Elmer 257 grating ir spectrophotometer, and Varian A-60 and A-60A spectrometers. The latter instrument used Me_4Si as an internal standard. Nmr and ir spectra were as expected. Where analyses are indicated only by symbols of elements, analytical results obtained for those elements are within 0.4% of the theoretical values.

3-(*p*-Nitrobenzyloxy)-2-hydroxymethylpyridine (IIB) (Method A). Commercial grade (85% pure) 3-hydroxy-2-hydroxymethylpyridine·HCl (8.0 g, 0.05 mole) was suspended in 150 ml of 95% EtOH. To the suspension KOH (85% pure pellet form, 6.5 g, 0.1 mole) in 100 ml of 95% EtOH and *p*-nitrobenzyl bromide (10.8 g, 0.05 mole) were added subsequently. The mixt was stirred at room

temp for 48 hr. The yellow ppt was collected, washed with water, and recrystd from 95% EtOH to give 4 g (30%) of yellow needles: mp 140–141°. *Anal.* ($C_{13}H_{12}N_2O_4$) C, H, N.

3-(*p*-Nitrobenzyloxy)pyridine-2-carboxaldehyde (IVB) (Method B). Compd IIIB (1 g, 3.8 moles) was dissolved in 50 ml of $CHCl_3$. A commercial grade of activated MnO_2 (Winthrop Labs) (1.5 g) was added and the mixt was refluxed overnight with stirring. The soln was filtered (with Celite filter-aid), and the filtrate evapd to dryness under reduced pressure to give a yellow residue. Recrystn from EtOAc and hexanes gave yellow crystals (0.9 g, 90%): mp 149–150°. *Anal.* ($C_{13}H_{10}N_2O_4$) C, H, N.

When the sample was recrystd from EtOH, stable hemiacetal crystals (yellow needles) formed. Upon heating, EtOH was lost at about 110° and then the residue melted at 145–146°: ir (KBr) 3180 cm^{-1} (broad); nmr ($CDCl_3$) 1.24 (two overlapping triplets, 3 H), 2.24 (S, 1 H), 3.72 (two overlapping quartets, 2 H), 5.34 (two overlapping singlets, 2 H), 5.86 (m, 0.5), 7.50 (m, 4 H), 8.24 (m, 3 H), 10.28 (S, 0.5 H). *Anal.* ($C_{15}H_{16}N_2O_6$) C, H, N.

3-(*m*-Nitrobenzyloxy)-2-formylpyridine Ethylene Acetal (VIIA) (Method C). Aldehyde (IVA) (1.8 g, 7 mmoles), ethylene glycol (2.5 ml), and a catalytic amount of *p*-toluenesulfonic acid were refluxed in C_6H_6 (100 ml) overnight using a Dean–Stark trap to remove the H_2O formed. The soln was cooled to room temp, washed (aqueous $NaHCO_3$), dried (Na_2SO_4), and evapd to dryness under reduced pressure. The residue was recrystd from EtOAc and hexanes to give white needles (1.5 g, 71.4%): mp 106–108°. *Anal.* ($C_{15}H_{14}N_2O_5$) C, H, N.

3-(*m*-Aminobenzyloxy)-2-formylpyridine Ethylene Acetal (VIIIA). Compd VIIA (3 g, 10 mmoles) in 150 ml of 95% EtOH and 5% Rh/C (1 g) was hydrogenated in a Parr-Shaker at room temp and 10 psi pressure for 30 min. The catalyst was removed by filtration and the filtrate was evapd to dryness under reduced pressure to give pale yellow crystals (1.5 g, 60%): mp 96–98°. *Anal.* ($C_{15}H_{16}N_2O_3$) C, H, N.

3-(*m*-Aminobenzyloxy)-2-formylpyridine Thiosemicarbazone (IXA) (Method D). Amine (VIIIA) (1.5 g, 6 mmoles), thiosemicarbazide (0.7 g, 7.7 mmoles), and concd HCl (1.5 ml) were added to 50% EtOH (70 ml) and heated on a steam bath for 30 min. EtOH was removed under reduced pressure. The crude product was dissolved in 150 ml of H_2O, filtered, and then neutralized with $NaHCO_3$. The yellow ppt was collected and recrystd from EtOH to give yellow crystals (0.5 g, 33.3%): mp 116–119° (shrink at 88–90°). *Anal.* ($C_{14}H_{15}N_5OS \cdot 0.5C_2H_5OH$) C, H; N: calcd, 21.60; found, 22.78.

3-(*m*-Hydroxybenzyloxy)pyridine-2-carboxaldehyde Thiosemicarbazone (XIA) (Method E). Crude amine (VIIIA) (0.3 g, 1.2 mmoles) was dissolved in 4 ml of aqueous H_2SO_4 which contains 0.25 ml of concd H_2SO_4. The soln was cooled to below 5° with an ice bath. A cold $NaNO_2$ aqueous soln (0.18 g in 1 ml of H_2O) was slowly added with rapid stirring to an end point with KI–starch paper. The soln was allowed to stand at room temp for 15 min and then heated at 50° for 15 min. The solvent was evapd to dryness under reduced pressure. The red gummy residue was dissolved in 10 ml of 95% EtOH, and thiosemicarbazide (0.15 g in 5 ml of H_2O) and a drop of glacial AcOH were added and heated on a steam bath for 10 min. The soln was evapd to dryness under reduced pressure. The orange powder was dissolved in 10 ml of dil NaOH soln, filtered, and acidified with AcOH to give an orange powder (0.2 g, 60%): mp 118–120°. *Anal.* ($C_{14}H_{14}N_4O_2S$) C, H, N, S.

3-(*m*-Aminobenzyloxy)-2-hydroxymethylpyridine (XII). (1) Compd IIIA (1 g, 3.8 mmoles) and Fe powder (5 g) were added to glacial AcOH (25 ml). The mixt was stirred and heated to 60°; an exothermic reaction took place. The highly viscous reaction mixt was then stirred at 85° for 20 min and filtered. The ppt was washed several times with 25 ml of AcOH. The filtrate and the washings were combined and lyophilized. The residue was dissolved in $CHCl_3$, washed with aqueous $NaHCO_3$ soln, H_2O, dried (Na_2SO_4), and evapd to dryness to give an oil which crystd from C_6H_6 and hexanes to give needles (0.2 g, 23%): mp 119–121°. *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N.

(2) Compd IIIA (1 g, 3.8 mmoles), and 5% Rh/C (0.25 g) were hydrogenated in 200 ml of 95% EtOH at room temp and 10 psi pressure for 30 min. Catalyst was removed by filtration and the filtrate was evapd to dryness under reduced pressure. The residue was crystd from C_6H_6 and hexanes to give light brown crystals (0.45 g, 50%): mp 119–120°.

3-(*m*-Acetaminobenzyloxy)-2-acetoxymethylpyridine (XIIIA) (Method F). Compd IIIA (1 g, 3.8 mmoles), Ac_2O (5 ml), Fe powder (5 g), and AcOH (25 ml) were stirred and heated to 60° when an exothermic reaction ensued. The reaction mixt was then heated at 80° for 20 min and filtered, and the ppt was washed with 20 ml of Ac_2O. The filtrate and washings were combined and lyophilized. The residue was dissolved in $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and evapd to yield an oil which crystd on standing. Recrystn from EtOAc and hexanes gave white crystals (0.52 g, 42%): mp 119–121°. *Anal.* ($C_{17}H_{18}N_2O_4$) C, H, N.

3-(*m*-Acetaminobenzyloxy)-2-hydroxymethylpyridine (XIVA) (Method G). Ester (XIIIA) (1.25 g, 4 mmoles) and NaOH (0.33 g, 8.75 mmoles) were refluxed in 40 ml of 50% EtOH for 2 hr. The solvent was evapd to dryness under reduced pressure. The solid residue was washed with H_2O, dried, and crystd from EtOAc to give 0.4 g (40%) of white crystals: mp 142–143.5°. *Anal.* ($C_{15}H_{16}N_2O_3$) C, H, N.

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