Table VI. 4-(*N*-Alkyl-*N*-methylamino)-4-(*m*-hydroxyphenyl)cyclohexan-1-one Ethylene Ketals

no.	chromat solv	mp, °C	yield, %	recrystn solv	formula
24d	MeOH-CH_2Cl_2(7.5:1)	*b*	72		$C_{20}H_{32}ClNO_3 \cdot 0.5H_2O$
24b	MeOH-$CHCl_3$[a](7.5:1)	203-204	31	$CHCl_3$-CH_3CN	$C_{19}H_{30}ClNO_3$
24e	MeOH-$CHCl_3$[a](3.5:1)	*b,c*	10		$C_{23}H_{30}ClNO_3$
24c	MeOH:$CHCl_3$[b](5:1)	214-215	50	CH_2Cl_2-CH_3CN	$C_{19}H_{28}ClNO_3$
24a		204-207	49	$CHCl_3$-EtOAc	$C_{18}H_{28}ClNO_3$

[a] Chromatographed on high-performance LC column. [b] Amorphous. [c] No satisfactory analysis could be obtained: M_r calcd 367; MS, *m/e* 367 (M^+).

under H_2 for 24 h. The catalyst was then collected on a filter and washed exhaustively with $CHCl_3$. The filtrate was taken to dryness. If crystalline, the residue was recrystallized. Alternately this was converted to the free base and chromatographed. The appropriate fractions were then combined, reconverted to the HCl salt, and recrystallized.

4-(*N*-Butyl-*N*-methylamino)-4-(*m*-hydroxyphenyl)cyclohexan-1-one Ethylene Ketal (15b). Using the above three-step procedure and $CH_3(CH_2)_2COCl$ as the acid chloride, there was obtained **15b** (51%), mp 209–211 °C, identical in all respects (IR, NMR, and TLC) with a sample prepared by the aminonitrile method. Anal. ($C_{19}H_{30}ClNO_3$) C, H, N.

Biology. Methods. The biological testing consisted of a battery of standard assays.[6] Briefly, CF-1 female mice were dosed subcutaneously with a suspension (or solution) of the test compound in 0.25% aqueous methylcellulose and 15 min later subjected to a series of procedures to detect analgesia, sedation, and narcotic antagonism. The tail-flick, tail-pinch and HCl writhing procedures were used to detect analgesia, whereas the inclined screen test was used to measure sedation. After the completion of the tests (about 45 min postinjection), 6.3 mg/kg morphine sulfate was given subcutaneously and 15 min later the mice were retested on the tail-flick procedure to determine if the compound might have narcotic antagonist properties. Blockade of morphine-induced elevation of tail-flick latency was scored as antagonism. Six mice were tested at each dose in this battery of assays. When multiple doses were examined, the ED_{50} values were calculated by the method of Spearman and Karber.[8]

Acknowledgment. The authors acknowledge the technical assistance of R. A. Lewis.

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Notes

Cognition-Activating Properties of 3-(Aryloxy)pyridines

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A series of 3-(aryloxy)pyridines was found to possess activity in enhancing retention for passive avoidance learning in mice. This test was used to select compounds with potential therapeutic properties for the treatment of cognitive disorders. Reference drugs that gave positive results in this procedure included *d*-amphetamine, magnesium pemoline, methyl phenidate, picrotoxin, phenytoin, and ethosuximide. All active compounds gave inverted U-shaped dose–response curves. The most active compounds of the 3-(aryloxy)pyridines included 3-phenoxypyridine (1), 3-(2-fluorophenoxy)pyridine (2), 3-(4-fluorophenoxy)pyridine (4), 3,3′-oxybis(pyridine) (23), and 3,3′-oxybis(pyridine) 1-oxide (24). 3-Phenoxypyridine (1) was clearly superior to all of the analogues tested in terms of the level of retention, grammometric potency, and the breadth of its inverted U-shaped dose–response curve. It was given the designation of CI-844 and after a detailed study of its pharmacological profile was submitted for preclinical toxicology.

Cognitive dysfunctions occur in persons of all ages as a result of many conditions including diseases, accidents and injuries, developmental defects, and normal aging. An agent that would act favorably on learning/memory mechanisms would have vast sociopolitical, cultural, and economic implications.[1]

One major area where such an agent would be most beneficial is the treatment of the estimated 5–10% of school-age children who suffer from some type of learning disability such as minimal brain dysfunction (or attentional deficit disorder).[2,3] A second important area of application for a cognition-enhancing drug is at the other end of the developmental continuum: the cognitive disorders and intellectual impairments that regularly occur in the elderly. This area is partly the result of the remarkable progress that has been made in health care in the 20th century, resulting in the large increase in the number of people who live to old age. Age-related cognitive impairments are found both in normal senesence and in patients with senile organic brain syndrome.[4,5]

Treatments for learning disabilities in the young have mainly employed amphetamine-like stimulants to produce a calming effect and increase attention.[6-8] Drugs which

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(4) M. E. Jarvik, E. R. Gritz, and N. G. Schneider, *Behav. Biol.*, **7**, 643 (1972).
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Table I. Retention Results on Reference Agents

agent	test doses,[a] mg/kg ip (free base)									
	0.15	0.32	0.63	1.25	2.5	5.0	10	20	40	80
d-amphetamine	45	80	100	60	65	28				
l-amphetamine				70	75	90	35			
pemoline magnesium						30	70	83	83	77
caffeine			70	87	37	37	3		3	0
methyl phenidate				50	50	90	65	87		
imipramine						65	80	77	72	L[b]
pentylenetetrazol						80	65	80	80	L[b]
nicotine		70	75	53	27	L[b]				
strychnine		70	75							
picrotoxin		65	80	90	80	70				
physostigmine	45	35	L							
phenytoin sodium				85	75	90	43	55	50	15
ethosuximide							63	90	70	95[c]
pentobarbital sodium			23	40	7					
scopolamine	65	65	30	35						
LiCl			60	84	70	0	31		23	38
tranylcypromine						75	80	55	L[b]	
diazepam				53	40	41				
tetrabenazine				59	63	33				
pimozide	43	40	27							
chlorpromazine				70	70	20				

[a] Where values are not given, the compound was not tested at this dose. Numbers are the percent retention. [b] L indicates the test compound was lethal at this dose. [c] This compound was tested at 160 and 320 mg/kg with retention results of 50 and 60%, respectively.

are presently employed to treat the cognitive impairments of the elderly have shown only limited benefits and are not widely accepted.[9,10] At one time cognitive impairment in the elderly was ascribed to atherosclerotic interruptions in blood flow. Recent evidence indicates that, at most, 10% of senility may be associated with circulatory disruption.[11,12] Useful reviews covering drug effects upon cognition and suspected neurotransmitters in this area have been written by Weissman,[13] Gylys and Tilson,[14] Scott,[15] and Cole.[16]

The methodological and conceptual problems encountered in searching for "learning/memory, performance-enhancing, cognition-activating, or psychostimulant" drugs are imposing. Most animal models that have been reported are either time consuming or unreliable.[17] It is also apparent from past experience that showing activity in animals is far easier than finding efficacy in human disorders, suggesting that many animal models lack validity. Thus, the selection of animal test models which are at once practical and predictive is critical to the success of a drug discovery program in this area.

This report describes the results from a drug discovery program looking for novel compounds for the treatment of cognitive disorders. Described below are the pharmacological test method, study of reference compounds, and SAR from a series of compounds, leading to the identification of a new potential therapeutic entity for the treatment of cognitive disorders.

Pharmacology. We have chosen to assume that an agent which favorably influences learning or memory in young, normal animals will do the same in cognitively impaired patients. The primary test employed to identify cognition-enhancing properties was facilitation of single trial passive avoidance response in mice. The method was a modification of the procedure developed by Essman and Alpern.[18] A number of known pharmacological agents, some reported to possess useful learning and memory effects,[13,14] were evaluated by this method (Table I).

Of the reference drugs tested, some produced positive effects according to the rating system used. These included *d*-amphetamine, magnesium pemoline, methyl phenidate, picrotoxin, phenytoin, and ethosuximide. The assumption that an agent that will favorably influence learning or memory in young normal animals will do the same in cognitively impaired patients is supported by the activity of the stimulants in this test as well as in young humans[6-8] and, possibly, by the activity shown by the two anticonvulsant examples. Depressant agents, such as chlorpromazine, pimozide, diazepam, and pentobarbital sodium, produced either no effect or disruptive effects. We have consistently observed an inverted U-shaped dose–effect curve in this type of test as has been reported by others.[19,20] This may result from inadequate drug levels at low doses and the invoking of disruptive side effects at supratherapeutic doses. This may also explain part of the difficulties in demonstrating clinical efficacy that have plagued this area of research.

Chemistry and Structure–Activity Relationships. A group of 100 compounds was selected for testing from a file containing approximately 82 000. Compounds were selected on the basis of their chemical structures being unlike any known central nervous system active agents available at that time. One of these compounds was 3-phenoxypyridine (1), a known compound[21] that had been filed as an intermediate and reported earlier to have gastric antisecretory activity.[22] This compound demonstrated

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(15) F. L. Scott, *Aging*, **8**, 151–184 (1979).
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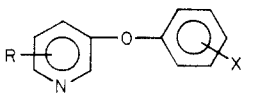
(18) W. B. Essman and H. Alpern, *Psychol. Rep.*, **14**, 731 (1964).
(19) J. Krivanek and J. L. McGaugh, *Agents Actions*, **1**, 36 (1969).
(20) J. L. McGaugh and J. Krivanek, *Physiol. Behav.*, **5**, 1437 (1970).
(21) R. R. Renshaw and R. C. Conn, *J. Am. Chem. Soc.*, **59**, 197 (1937).

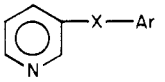
Table II. 3-(Aryloxy)pyridines



no.	X	R	retention test test doses,[a] mg/kg sc (free base) 0.63	1.25	2.5	5.0	20	80	ref & expl[b] method	bp (mmHg) or mp, °C	yield, %	formula[c]
1[d]	H	H	65	90	90	100	70	35	*e*, A	147-149 (12)	68	$C_{11}H_9NO$
2	2-F	H	60	65	80	90	85	50	*f*, A	124-125 (10)	20[g]	$C_{11}H_8FNO$
3	3-F	H	65	75	75	90	55	55	*h*, A	124-125 (9)	46	$C_{11}H_8FNO$
4	4-F	H	35	60	85	95	80	50	*i*, A	125-127 (9)	65	$C_{11}H_8FNO$
5	2-Cl	H	60	45	40	95	80	40	*j*, A	40-43	27	$C_{11}H_8ClNO$
6	3-Cl	H				60	60	0	*j*, A	148-150 (12)	32	$C_{11}H_8ClNO$
7	4-Cl	H	55	65	70	80	30	65	*j*, A	35-36	22	$C_{11}H_8ClNO$
8	2-Br	H				65	50	*k*	*h*, B	148-150 (1)	60	$C_{11}H_8BrNO$
9	4-Br	H	75	75	70	90	70	85	*h*, C	33-35	80	$C_{11}H_8BrNO$
10	$2\text{-}C_2H_5O$	H				70	70	65	A	102-104 (0.15)	56	$C_{13}H_{13}NO_2$
11	$3\text{-}CH_3O$	H				55	55	20	*l*, A	163-164 (10)	67	$C_{12}H_{11}NO_2$
12	$4\text{-}CH_3O$	H				78	75	35	A	163-164 (10)	30	$C_{12}H_{11}NO_2$
13	H	$2\text{-}CH_3$				75	65	80	D	119-120 (10)	14[m]	$C_{12}H_{11}NO$
14	H	$3\text{-}CH_3$				70	80	45	*n*, A	150-152 (18)	60	$C_{12}H_{11}NO$
15	H	$4\text{-}CH_3$				75	85	15	*i*, A	145-146 (18)	75	$C_{12}H_{11}NO$
16	H	$6\text{-}CH_3$[o]		60	50	85	85	*k*	E	138-140 (10)	27	$C_{12}H_{11}NO$
17	$3\text{-}CF_3$	H				30	55	*k*	A	105-108 (6)	62	$C_{12}H_8F_3NO$
18	$3\text{-}CO_2CH_3$	H				70	60	55	F	173-175 (10)	70	$C_{13}H_{11}NO_3$
19	$2\text{-}NH_2$	H			70	80	65	55	G	68-70	33	$C_{11}H_{10}N_2O$
20	$2\text{-}NO_2$	H				60	90	50	H	140-142 (0.6)	59	$C_{11}H_8N_2O_3$
21	$2\text{-}NH_2$	$6\text{-}CH_3$[p]				65	45	40	G	60-63	95	$C_{12}H_{12}N_2O$
22	$2\text{-}NO_2$	$6\text{-}CH_3$[q]		70	70	85	70	35	H	138-140 (0.2)	48	$C_{12}H_{10}N_2O_3$

[a] Where no value is given, the compound was not tested at this dose. Numbers are the percent retention. [b] The original reference is indicated by the first small letter. The capital letters refer to the methods mentioned under Experimental Section. [c] All samples were analyzed for C, H, and N, and the results were within ±0.4% of the theoretical values with the exception of 5 (C: calcd, 64.25; found, 63.22), 7 (C: calcd, 64.25; found, 63.49), and 18 (C: calcd, 68.11; found, 67.54). [d] Compound 1 was tested at two additional dose levels with the following results: 10 mg/kg = 80% retention and 40 mg/kg = 50% retention. [e] R. R. Renshaw and R. C. Conn, *J. Am. Chem. Soc.*, 59, 297 (1937). [f] D. E. Butler, U.S. Patent 4 179 563 (1979). [g] The other major product in this synthesis was found to be 3-[2-(2-fluorophenoxy)phenoxy]pyridine (30), bp 123-125 °C (0.15 mm), 20% yield. Anal. ($C_{17}H_{12}FNO_2$) C, H, N. [h] K. A. Nowatny, U.S. Patent 3 567 616 (1971); *Chem. Abstr.*, 75, P35758*d* (1971). [i] F. J. Villani, T. A. Mann, E. A. Wefer, J. Hannon, L. L. Larca, M. J. Landon, W. Spivak, D. Vashi, S. Tozzi, G. Danko, M. del Prado, and R. Lutz, *J. Med. Chem.*, 18, 1 (1975). [j] K. Fujikawa, K. Kondo, I. Yokomichi, F. Kimura, T. Haga, and R. Nishiyama, *Agr. Biol. Chem.*, 34, 68 (1970). [k] Animals untrainable because of depression. [l] D. E. Butler, U.S. Patent 4 187 379 (1980). [m] Compound 13 contained 6% of Compound 16 as determined by VPC analysis. [n] D. E. Butler, U.S. Patent 4 187 311 (1980). [o] This is named by Chemical Abstracts as 2-methyl-5-phenoxypyridine. [p] This is named by Chemical Abstracts as 2-[(6-methyl-3-pyridinyl)oxy]benzenamine. [q] This is named by Chemical Abstracts as 2-methyl-5-(2-nitrophenoxy)pyridine.

Table III. Related Pyridines



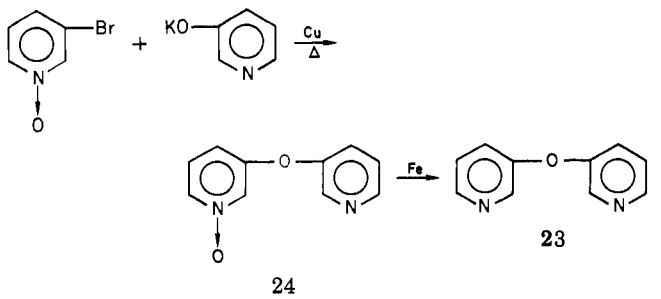
no.	name	retention test test doses,[a] mg/kg sc (free base) 0.63	1.25	2.5	5.0	20	80	ref & expl[b] method	bp (mmHg) or mp, °C	yield, %	formula[c]
23	3,3′-oxybis(pyridine)				85	100	55	I	145-147 (0.14)	64.5	$C_{10}H_8N_2O$
24	3,3′-oxybis(pyridine) 1-oxide	60	45	65	85	85	85	J	116-118	32	$C_{10}H_8N_2O_2$
25	3,3′-oxybis(pyridine) 1,1-dioxide	65	75	60	90	90	60	K	220-222	33	$C_{10}H_8N_2O_3$
26	3-phenoxypyridine 1-oxide				40	20	0	c	80-82		$C_{11}H_9NO_2$
27	2-phenoxypyridine				65	50	30	P			$C_{11}H_9NO$
28	4-phenoxypyridine				70	65	0	d	46-48		$C_{11}H_9NO$
29	3-(phenylthio)pyridine				80	85	85	*c*, A	164-165 (19)	95	$C_{11}H_9NS$

[a] Where no value is given the compound was not tested at this does. Numbers indicate the percent retention. All samples analyzed for C, H, and N within ±0.4%. [b] The original reference is indicated by the small letter and the method the compound was synthesized unless accompanied by a capital letter indicating the methods mentioned in the Experimental Section, except that P stands for purchased. [c] D. E. Butler, P. Bass, I. C. Nordin, F. P. Hauck, Jr., and Y. J. L'Italien, *J. Med. Chem.*, 14, 575 (1971). [d] E. Koenigs and H. Greiner, *Chem. Ber.*, 64, 1049 (1931). [e] K. F. King and L. Bauer, *J. Org. Chem.*, 36, 1641 (1971).

activity over a wide dose range, and a series of analogues was prepared for testing (Tables II and III). Most of the compounds were synthesized by known methods and are referenced in the footnotes to Table II and III. Compound 18 [methyl 3-(3-pyridinyloxy)benzoate] was synthesized from compound 17 [3-[3-(trifluoromethyl)phenoxy]-pyridine], by the hydrolysis method of Hansl.[23] Re-

(22) D. E. Butler, P. Bass, I. C. Nordin, F. P. Hauck Jr., and Y. J. L'Italien, *J. Med. Chem.*, 14, 575 (1971).

Scheme I



24 23

placement of the 3-phenoxy group with a (3-pyridinyloxy) residue was unsuccessful using standard methods and the compound was obtained as shown in Scheme I.

A compound had to show at least 80–85% retention at a minimum of two dose levels to be considered to have any activity and to show over 90% retention at a minimum of two doses to be of real interest. Clearly the spatial and electronic characteristics are very specific in this series with only 2- and 4-fluoro substitution (compounds **2** and **4**) and, possibly, replacement of the phenoxy moiety by a (3-pyridinyloxy) (**23**) or (3-pyridinyloxy) 1-oxide group (**24**) giving *broad* inverted U-shaped dose–effect curves. Some potential cognition activation activity was retained in the compounds substituted by 2-chloro (**5**) and 4-bromo (**8**) and the compound in which the oxygen atom was replaced by a sulfur atom (**29**). Nuclear substitution of the pyridine with a methyl group caused loss of activity, with the possible exception of 2-methyl-5-phenoxypyridine (**13**). In contrast with the earlier reported antisecretory series,[22] the compounds with phenoxy groups in the 2 (**27**) or 4 position (**28**) and the 1-oxide of compound **1** (**26**) were inactive. Other substitutions on the phenoxy group, such as 3- and 4-chloro, 2-, 3-, and 4-alkoxy, 3-(trifluoromethyl), and 3-carbomethoxy residues, also destroyed activity.

Compound **1** was clearly superior to all of the analogues in Tables I and II in terms of the level of retention, grammometric potency, and the breadth of its inverted U-shaped dose–response curve. Compound **1** was considered to be a unique cognition activator. It was given the designation of CI-844 and was submitted for preclinical toxicological workup. Its utilities are the subject of two United States Patents.[24,25] A detailed study of its pharmacological profile will be the subject of a separate publication.

Experimental Section

Pharmacology. Retention Testing. The method described by Essman and Alpern[18] was modified as follows: 80 naive male mice (Carworth, CF-1 strain, 19–21 g at the time of shipment) were divided into four groups of 20 mice each. Each animal was used only once. One hour prior to training the mice were injected intraperitoneally with an aqueous solution or methocel suspension of the chemical. Usually three doses of the chemical and one of normal saline were tested at a time. The initial screening doses were 5, 20, and 80 mg/kg. Active compounds were retested at lower and intermediate doses.

One hour after the above dosing, the mice were placed, one at a time, on the small shelf attached to the outside wall of the test box. In this position, the mouse was suspended in space and was motivated to step from the shelf through a conveniently placed small hole into the interior of the box. As soon as the mouse had all four feet within the semidarkened interior of the box, the grid floor of the box was electrified (1.5 MA, 3-s duration), producing a strong pain/fear reaction from the animal. Approximately 5 s later the mouse was removed from the test box and placed in a group holding cage until the entire group had received the single training trial. Then the entire group was returned to the home cages.

One week later the mice were tested for retention (memory) of the painful footshock received within the shelf-box apparatus. This testing was accomplished by once again placing each mouse on the small shelf attached to the test box. Any mouse that stayed on the shelf for 60 seconds without entering the box was counted as remembering the painful footshock received within the box 1 week earlier. Any mouse entering the box within the 60-s period was counted as having forgotten the training or as never having learned it in the first place.

Control experiments showed that about 65–75% of placebo-treated mice demonstrated memory for the footshock according to the above criteria. Control groups were run along with each drug tested. If the control scores did not fall within this range on any given day, the tests for that day were discarded. The activity of each dose of drug tested was rated as follows: 86% or more, active; 80 to 85%, borderline active; less than 80%, inactive. Statistical tests using the binomial distribution, with $N = 20$ and $p = 0.65$ or 0.70, indicated that a rating of active would have an expected probability of 0.01 or 0.04, respectively. The probability of finding two active doses of the same drug by chance alone was, of course, much lower.

Chemistry. The melting points were determined in open capillary tubes in a Thomas-Hoover apparatus and are uncorrected. IR spectra were determined with a Beckman IR-9 spectrophotometer. NMR spectra were recorded with a Varian A-60 instrument with Me_4Si as the internal standard. Concentration was carried out under reduced pressure. IR and NMR spectra were obtained for all compounds and were consistent with the assigned structures. C, H, and N analyses were performed on all compounds prepared and, unless otherwise noted, checked within ±0.4%.

Method A. These 3-(aryloxy)pyridines (Table II) were prepared by the procedure used by Renshaw and Conn.[21]

Method B. 3-(2-Bromophenoxy)pyridine (8). A solution of 2-(3-pyridinyloxy)benzenamine (**19**), 18.6 g (0.1 mol), in 48% HBr, 160 g (1 mol), was cooled to −6 °C with stirring under a N_2 atmosphere and a solution of $NaNO_2$, 7.5 g (0.11 mol), in H_2O, 50 mL, was added dropwise below 0 °C. Copper bronze, 250 mg, was added and the mixture cautiously warmed. N_2 evolution was vigorous at 35 °C, and the temperature was held below 45 °C by cooling. The reaction was finally heated to 60 °C for 30 min, cooled, and extracted (CH_2Cl_2). The extracts were treated with saturated $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and distilled to yield 8, 15 g (60%), bp 148–150 °C (1 mm). Anal. ($C_{11}H_8BrNO$) C, H, N.

Method C. 3-(4-Bromophenoxy)pyridine (9). A solution of 3-phenoxypyridine (**1**), 34.2 g (0.2 mol), and NaOAc, 32.8 g (0.4 mol), in glacial HOAc, 300 mL, was stirred and treated with Br_2, 35.2 g (0.22 mol), dropwise. The reddish mixture was poured into H_2O and extracted (Et_2O). The extracts were washed with sodium thiosulfate solution and dried (KOH pellets). The extracts were concentrated and distilled to yield **9**, 40 g (80%) bp 104–105 °C (0.15 mm), crystallized mp 33–35 °C. Anal. ($C_{11}H_8BrNO$) C, H, N.

Method D. 2-Methyl-3-phenoxypyridine (13). A solution of CH_3Li was prepared from Li chips, 14.8 g (2.1 G.A.), and iodomethane, 142 g (1.0 mol), in Et_2O, 1 L, and under N_2 a solution of 3-phenoxypyridine (**1**), 86 g (0.5 mol), in toluene, 1 L, was added. The mixture was heated to 110 °C by distilling Et_2O and refluxed for 16 h. After the mixture cooled, H_2O was added, and the organic phase was separated, dried ($MgSO_4$), filtered, and distilled to yield 52 g, bp 115–125 °C (10 mm). Careful fractionation yielded **13**, 15 g (16%), bp 119–120 °C (10 mm). Anal. ($C_{12}H_{11}NO$) C, H, N. Gas chromatography indicated the presence of 6% of compound **16**.

Method E. 2-Methyl-5-phenoxypyridine (16). A solution of 6-methyl-3-pyridinol, 109 g (1 mol; Aldrich Chemical Co.), in 2-methoxyethyl ether, 500 mL, was treated with potassium *tert*-butoxide, 112 g (1 mol), and heated to 160 °C with distillation

(23) N. R. Hansl, U.S. Patent 3792048 (1974); *Chem. Abstr.*, **80**, 108202*h* (1974).
(24) B. P. H. Poschel and D. E. Butler, U.S. Patent 4067983 (1978); *Chem. Abstr.*, **88**, P141706*p* (1978).
(25) S. G. Hastings, B. P. H. Poschel, and D. E. Butler, U.S. Patent 4061756 (1977); *Chem. Abstr.*, **88**, 110535*c* (1978).

of *t*-BuOH. Copper bronze, 1 g, and iodobenzene, 204 g (1 mol), were added, and the mixture was refluxed for 48 h. The mixture was filtered and distilled to yield 141 g of **16**, bp 120–140 °C (10 mm). The distillate was dissolved in *i*-PrOH and treated with an excess of 70% $HClO_4$ and diluted (Et_2O). The Et_2O layer was discarded, and the aqueous and oil layers were treated with an excess of NaOH solution and extracted (Et_2O). The extracts were dried (KOH pellets), filtered, and distilled to yield **16**, 50 g (27%), bp 138–140 °C (10 mm). Anal. ($C_{12}H_{11}NO$) C, H, N.

Method F. Methyl 3-(3-Pyridinyloxy)benzoate (18). A solution of 3-[3-(trifluoromethyl)phenoxy]pyridine (**17**), 10 g (0.042 mol), in concentrated H_2SO_4, 52 g (0.5 mol), was heated on the steam bath for 16 h. The solution was cooled and poured into MeOH, 1 L. The solution was refluxed for 2 h and poured into a large excess of solid $NaHCO_3$. Et_2O was added and the mixture was filtered through filter aid. The organic layer was dried ($MgSO_4$), filtered, and distilled to yield **18**, 6.7 g (70%), bp 173–175 °C (10 mm). Anal. ($C_{13}H_{11}NO_3$) H, N; C: calcd, 68.11; found, 67.54.

Method G. 2-(3-Pyridinyloxy)benzenamine (19). A solution of 3-(2-nitrophenoxy)pyridine (**20**), 43 g (0.2 mol), in glacial HOAc, 250 mL, held between 95 and 100 °C, was treated with four portions of Fe filings, 56 g (1 G.A.), and H_2O, 105 mL, with stirring. The mixture was held at 100 °C for 1 h and poured into H_2O. The aqueous mixture was extracted (CH_2Cl_2). The extracts were dried ($MgSO_4$), filtered, and distilled to yield 27 g, bp 125–127 °C (0.3 mm). Recrystallization (Et_2O) yielded **19**, 13 g (33%), mp 68–70 °C. Anal. ($C_{11}H_{10}N_2O$) C, H, N.

Method H. 3-(2-Nitrophenoxy)pyridine (20). A solution of 3-pyridinol, 47.5 g (0.5 mol; Aldrich Chemical Co.), in Me_2SO, 350 mL, was treated with NaH, 21 g (0.5 mol, 57% in mineral oil), in portions under a N_2 atmosphere. Copper bronze, 100 mg, and 1-chloro-2-nitrobenzene, 88 g (0.5 mol), were added and, with stirring, the mixture was heated cautiously to 110 °C. The reaction became moderately exothermic and the temperature rose to 145 °C. The mixture was heated at 165 °C for 1 h, cooled, and poured into H_2O. The mixture was extracted (Et_2O). The extracts were dried ($MgSO_4$), filtered, and distilled to yield **20**, 54 g (50%), bp 140–142 °C (0.6 mm). Anal. ($C_{11}H_8N_2O_3$) C, H, N.

Method I. 3,3'-Oxybis(pyridine) (23). A solution of 3,3'-oxybis(pyridine) 1-oxide (**24**), 16.5 g (0.088 mol), in glacial HOAc was heated to 100 °C and Fe, 6.0 g (0.106 G.A.), was added in two equal portions with stirring. The mixture was heated at 100 °C for 1 h, cooled, poured into H_2O, and filtered through filter aid. The mixture was treated with a large excess of solid NaOH and extracted repeatedly (Et_2O). The extracts were dried ($MgSO_4$), filtered, and distilled to yield **23**, 9.75 g (64.5%), bp 145–147 °C (14 mm). Anal. ($C_{10}H_8N_2O$) C, H, N.

Method J. 3,3'-Oxybis(pyridine) 1-Oxide (24). A solution of 3-pyridinol, 29.5 g (0.3 mol), in H_2O (100 mL) was treated with KOH, 16.8 g (0.3 mol). Toluene, 500 mL, was added and the mixture was refluxed and stirred, removing H_2O with a Dean–Stark trap until dry. The toluene was removed at reduced pressure. The dry salt was mixed with 3-bromopyridine 1-oxide,[26] 65 g (0.37 mol), and heated cautiously to 140 °C. The reaction became moderately exothermic and warmed to 175 °C. When the exotherm had subsided, the mixture was heated at 180 °C for 0.25 h. After the mixture cooled, $CHCl_3$ and H_2O were added and the mixture was filtered through filter aid. The $CHCl_3$ layer was separated, dried ($MgSO_4$), filtered, and distilled to yield 20.7 g, bp 145–150 °C (0.2 mm). Recrystallization (*i*-PrOH–Et_2O) yielded **24**, 18 g (32%), mp 116–118 °C. Anal. ($C_{10}H_8N_2O_2$) C, H, N.

Method K. 3,3'-Oxybis(pyridine) 1,1'-Dioxide (25). This is essentially the method of Ochiai.[27] A solution of 3,3'-oxybis(pyridine) 1-oxide (**24**), 4.2 g (0.0223 mol), in glacial HOAc, 20 mL, was treated with an excess of 30% H_2O_2 and heated on the steam bath for 16 h. The mixture was cooled, *i*-PrOH was added, and the solution was evaporated at reduced pressure. The residue was treated with excess NaOH and extracted ($CHCl_3$). The extracts were dried ($MgSO_4$), filtered, and evaporated to yield **25**, 2.1 g (45%), mp 216–218 °C. Sublimation at 180 °C (0.1 mm) yielded **25**, 1.5 g (33%), mp 220–222 °C. Anal. ($C_{10}H_8N_2O_3$) C, H, N.

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Nucleosides Containing Chemically Reactive Groups

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5'-Amino-5'-deoxyinosine (1) and 1-(6-amino-2,5,6-trideoxy-β-D-*erythro*-hexofuranosyl)thymine (**9**) were prepared and substituted on the amino group with chemically reactive functions in an effort to find inhibitors of enzymes that metabolize the corresponding nucleotides. The resulting 5'-substituted methylnitrosoureas **3**, **11a**, and **11b**, bromoacetamides **4** and **13**, phenyl carbamates **5** and **14**, and 4-(fluorosulfonyl)benzamides **6** and **15** were tested for cytotoxicity to H.Ep-2 cells in culture and as inhibitors of incorporation of precursors into nucleic acids of L1210 cells. The inosine derivatives were also evaluated as inhibitors of hypoxanthine phosphoribosyltransferase. Compounds **4**, **6** and **13** showed moderate inhibition of formation of nucleic acids, and compound **4** demonstrated significant cytotoxicity ($ED_{50} < 5$ μg/mL).

A detailed rationale has been presented for the preparation of nucleosides containing a chemically reactive function attached to C-5' that may act as irreversible inhibitors of enzymes that act on the corresponding nucleotide.[1] This paper describes the synthesis and evaluation of certain derivatives of inosine and thymidine. The reactive functions chosen were the methylnitrosoureido, bromoacetamide, phenyl carbamate, and phenylsulfonyl fluoride.

5'-Amino-5'-deoxyinosine[2] (1) and 1-(6-amino-2,5,6-trideoxy-β-D-*erythro*-hexofuranosyl)thymine[3] (**9**) were prepared by literature procedures. These compounds were

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