nical assistance of C. Hotowy, E. Mlynar, and A. van Lierde is greatly appreciated.

Registry No. **1a**, 23956-12-9; **1c**, 90301-77-2; **1d**, 108008-58-8; **1e**, 90301-68-1; **3a**, 108008-55-5; **3b**, 108008-56-6; **3c**, 108008-57-7; **4a**, 108008-59-9; **4b**, 108008-61-3; **4c**, 108008-62-4; **4d**, 90301-71-6; **4e**, 90301-70-5; **4f**, 90301-72-7; **4g**, 108034-57-7; **4h**, 108008-63-5; **4i**, 90301-73-8; **4k**, 108008-64-6; **5a**, 108008-60-2; **5b**, 108034-76-0; 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-*erythro*-pentofuranosyl chloride, 3601-89-6; 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride, 4060-34-8; 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide, 56632-81-6.

Synthesis and Biological Properties of Some 6*H*-Pyrido[4,3-*b*]carbazoles

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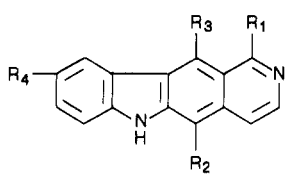
The effect of methyl substitution on the biological properties of the ellipticines was reexamined. 9-Hydroxy-6*H*-pyrido[4,3-*b*]carbazole was synthesized and shown to be devoid of antitumor activity in murine P388 lymphocytic leukemia in mice. 5-(Hydroxymethyl)-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (**46**) and its *N*-methylcarbamate (**48**) were synthesized and their effect on macromolecular synthesis in HeLa cells and their antitumor properties were compared with those of ellipticine. In contrast to the alkaloid **1** and the hydroxymethyl derivative **46**, which produced partially reversible inhibition of [^{3}H]thymidine incorporation, the carbamate ester irreversibly blocked incorporation of the tritiated pyrimidine. The ester was also a more potent antitumor agent in P388 lymphocytic leukemia than **1** or **46**.

A great deal of interest has been shown in the alkaloids ellipticine (**1**, 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) and its regioisomer olivacine (**2**, 1,5-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) because of their antitumor properties in animals and humans.[1] Ellipticine has been shown to react with DNA by an intercalation process,[2] which may account for its cytotoxicity. Li and Cowie[3] found that **1** markedly inhibited DNA polymerase but not RNA polymerase. At concentrations of 0.2 and 1.0 μg/mL, the drug inhibited DNA and RNA synthesis as measured by the incorporation of [^{3}H]thymidine and [^{3}H]uridine. At these concentrations there was little effect on protein synthesis. The authors concluded that inhibition of nucleic acid synthesis was an important contribution to the cytotoxic effect of ellipticine. Sethi[4] was able to show that **1** did inhibit RNA polymerase but at concentrations far higher than those of other antitumor agents such as dactinomycin, adriamycin, and daunomycin.

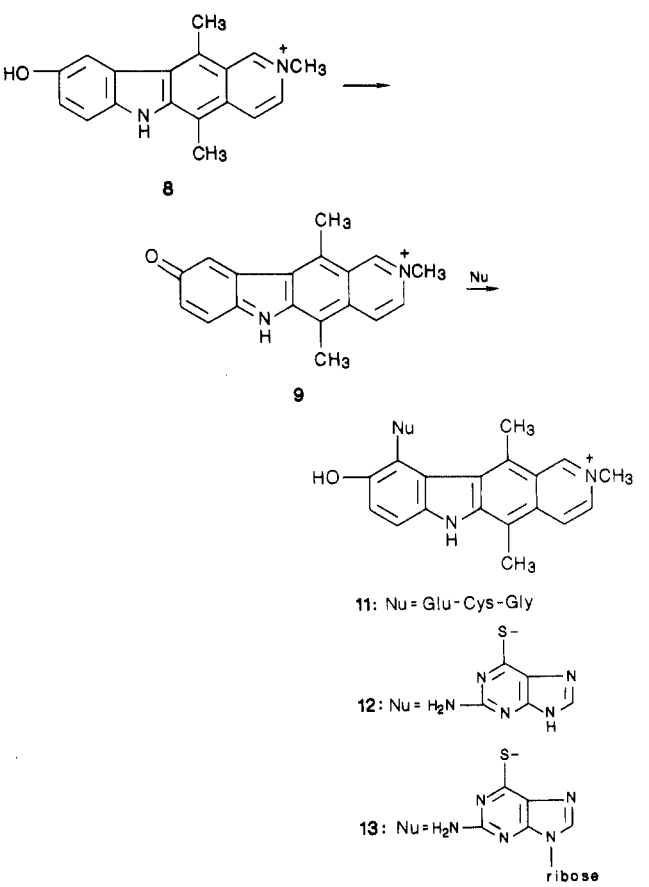


1 (ellipticine): $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$
2 (olivacine): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$
3 (9-hydroxyellipticine): $R_1 = H$, $R_2 = R_3 = CH_3$, $R_4 = OH$
4: $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
5: $R_1 = R_2 = R_3 = R_4 = H$
6: $R_1 = R_2 = CH_3$, $R_3 = H$, $R_4 = OH$
7: $R_1 = R_3 = H$, $R_2 = CH_3$, $R_4 = OH$

Ellipticine, 9-hydroxyellipticine (**3**), and its corresponding methoacetate **8** were shown to produce DNA double and single strand breaks in L1210 cells exposed to these drugs.[5,6] The double strand breaks resulting from the interaction with mammalian topoisomerase II were reversible in L1210 cell cultures and in cell-free systems.[6-9]

9-Hydroxyellipticine (**3**) is the major metabolite of ellipticine in the rat.[10,11] LePecq et al.[2] have shown that this metabolite is a better intercalating and a more active antitumor agent than ellipticine. It was also reported that 5-methyl-6*H*-pyrido[4,3-*b*]carbazole (**4**) and 6*H*-pyrido-[4,3-*b*]carbazole (**5**) were not cytotoxic in in vitro L1210 systems.[2] 9-Hydroxyolivacine (**6**) was found to be more

Scheme I



† Cogswell Laboratory.
‡ Laboratory for Cell Biology.

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cytotoxic in vitro than olivacine.[2] Gouyette et al.[12] reported that 9-hydroxy-5-methyl-6*H*-pyrido[4,3-*b*]carbazole (**7**) was inactive in vivo against murine L1210 leukemia. They attributed the lack of cytotoxic activity of **4** and **5** to their relatively weak intercalating properties.

Auclair and Paoletti[13] have shown that ellipticine and some of its congeners are oxidized either enzymically or with molecular oxygen via a free-radical intermediate. In the case of the quaternary salt **8**, the product is the quinone imine **9**. This is a powerful electrophile that can add nucleophiles covalently as shown in Scheme I.

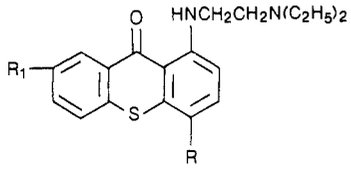
In support of this hypothesis, they have shown that a metabolite of **8** is the glutathione derivative **11** presumably formed by addition of the tripeptide to the quinone imine **9**. It was implied that the cytotoxic effect of **8** is due to covalent binding of **9** to an essential macromolecule such as DNA.

In the presence of stoichiometric amounts of H_2O_2 ($H_2O_2/8 = 1$), the quinone imine **9** reacts with DNA to produce a fluorescent compound irreversibly linked to the DNA.[14] Recently Dugué and his collaborators[15] have found that incubation of **8** with L1210 murine leukemia cells at 37 °C for 8 h resulted in covalent binding of **8** to DNA and RNA but not to proteins. At 0.1 μM concentrations, the ratio of mole of drug bound per mole of nucleotide was 3.5×10^{-6} for DNA and 2.5×10^{-6} for RNA. In the case of *N*-methylellipticinium (**8** minus the 9-OH) the ratios were 0.16×10^{-6} and 0.14×10^{-6} for DNA and RNA, respectively. The IC_{50} for the cytotoxicity of NMHE in L1210 cells was 0.05 μM whereas that for *N*-methylellipticine was 1.68 μM. The 9-deoxy compound was about 30-fold less potent in both test systems.[16]

When **8** was incubated with L1210 cells at 37 °C for 1 h, single and double strand DNA breaks occurred in a reversible manner.[6] After 1 h Dugué et al.[15] found that only about 25% of the maximum possible covalent binding takes place. These authors suggest that "two effects may be responsible for cytotoxicity, DNA breaks and covalent binding".

Despite the impressive array of experimental evidence marshalled to support the mechanism suggested in Scheme I, some concerns remain. For example, if the quinone imine **9** is the reactive species in the experiments of Dugué et al., then it is surprising that no covalent binding to proteins occurred since it has been shown that **9** reacts regiospecifically at C-10 with N, O, and S nucleophiles such as pyridine, methanol, and cysteine.[17] Thioguanine and thioguanosine add to **9** to give **12** and **13**, respectively. These adducts are equally cytotoxic as **8** in L1210 murine leukemia cells cultured in vitro.[18] Since C-10 is already occupied in these adducts, it is not clear how they can exert their cytotoxicity via the quinone imine mechanism. Condensation of **8** with valine and leucine in the presence of horseradish peroxidase furnished "amino acid adducts"[19] whose structure was later shown to be **35** and **36**.[20] These compounds show significant cytotoxicity in L1210 cell cultures and also in vivo.[19] It is difficult to see how **35** and **36** can exert their biological effects via the quinone imine **9**.

In our studies[21-23] on the mode of antischistosomal and antitumor action of lucanthone (**14**) and hycanthone (**15**) and its congeners, we have adduced evidence that the methyl group of lucanthone (**14**) is metabolized in the mammalian host to hycanthone (**15**), which then may be enzymically esterified to either **16** or **17**. These may dissociate nonenzymically to the carbonium ion **18**, which alkylates DNA to form the adduct **19**. The carbamate ester **20** acted as a surrogate for **16** or **17**. The enhanced antitumor action of **21**, in which the 7-OH is regiochemically analogous to the 9-OH in **6**, was attributed to stronger intercalation into DNA as compared with hycanthone.[24]



14 (lucanthone): R = CH_3, R_1 = H
15 (hycanthone): R = CH_2OH, R_1 = H
16: R = $CH_2OPO_3H^-$, R_1 = H
17: R = $CH_2OSO_3^-$, R_1 = H
18: R = CH_2^+, R^1 = H
19: R = CH_2-DNA, R_1 = H
20: R = $CH_2OOCNHCH_3$, R_1 = H
21: R = CH_2OH, R_1 = OH

In view of these results, it was felt that the role of the methyl groups in the ellipticine series ought to be reexamined. Although Gouyette and his associates[12] reported that **7** was inactive in vivo in murine L1210 leukemia, Mosher and her co-workers[25] reported that **4** and olivacine (**2**) were active antitumor agents in vivo. In their study, the French investigators administered the drug only once, whereas in Mosher's case, following an NCI protocol, the drugs were administered once a day over a 9-day period. Such prolonged administration would allow active metabolites to accumulate.

If it is assumed that 6*H*-pyrido-[4,3-*b*]carbazole (**5**) does reach the tumor cell target as do the homologues **1** and **4**, then the lack of activity can be rationalized in at least two

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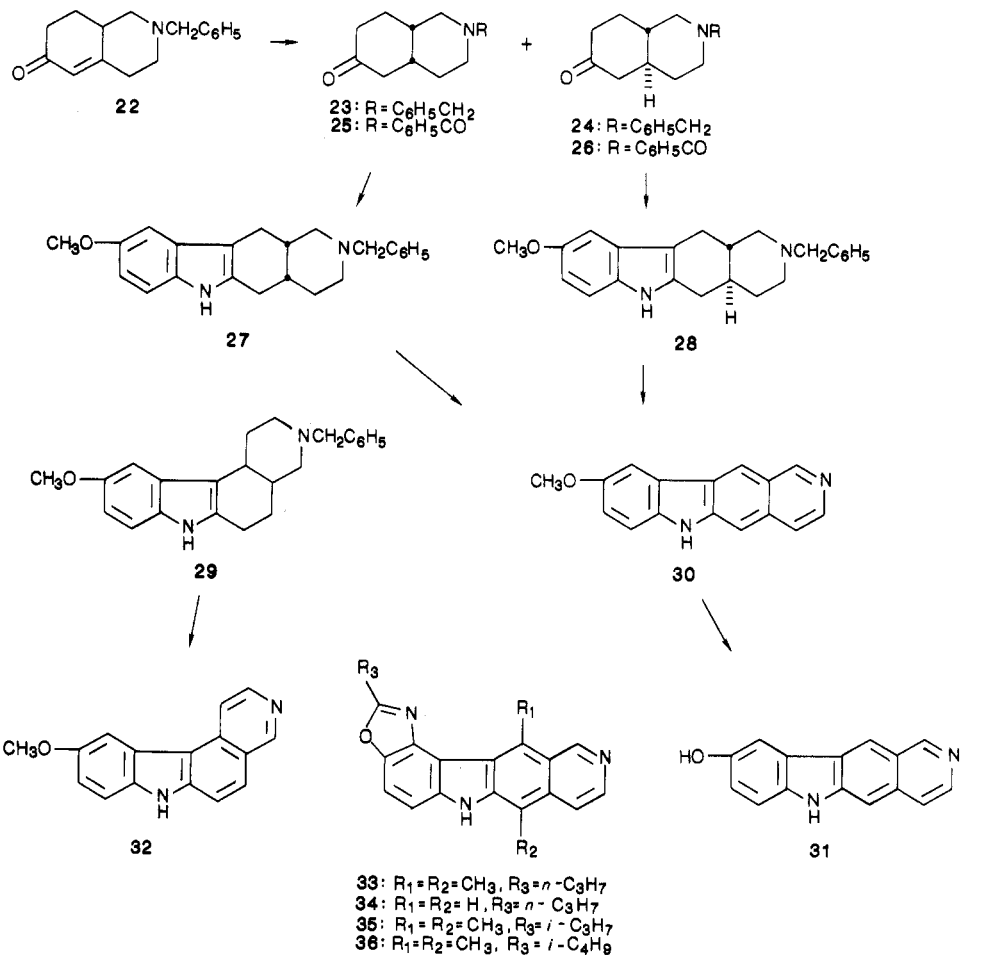
Scheme II



ways: (1) the compound is not a substrate for the appropriate hydroxylase enzyme, thus preventing the eventual formation of a quinone imine or (2) the lack of a C-5 methyl group does not permit the metabolic conversion to an hydroxymethyl group, which on enzymic esterification would be converted to an alkylating agent similar to **16** or **17**. To test the first possibility, we prepared 9-hydroxy-6*H*-pyrido[4,3-*b*]carbazole (**31**) and submitted the drug to the NCI for antitumor testing using the NCI protocol.[35] To examine the hypothesis that metabolic conversion of the 5-methyl group would lead to covalent binding to DNA, we synthesized 5-(hydroxymethyl)-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (**46**) and its *N*-methylcarbamate[26] (**48**) and studied the effect of these drugs on DNA synthesis in HeLa cells and their antitumor activity in murine P388 lymphocytic leukemia.

Chemistry

The synthesis of 9-hydroxy-6*H*-pyrido[4,3-*b*]carbazole (**31**) was carried out as shown in Scheme II. It is similar to the method used to prepare **7**.[12]

N-Benzyl-4-piperidone was converted to the known[27] pyrrolidino eneamine by the procedure of Stork.[28] The latter was treated with methyl vinyl ketone to give the hexahydroisoquinoline **22**, catalytic reduction of which furnished an easily separable mixture of the cis and trans isomers **23** and **24**. In order to assign the proper structures to these isomers, the known[29] *cis*- and *trans*-*N*-benzoyl-octahydroisoquinolones **25** and **26** were converted to **23** and **24**, respectively. The cis and trans isomers **23** and **24** were converted individually to the *cis*- and *trans*-octahydro-6*H*-pyrido[4,3-*b*]carbazoles **27** and **28** by a Fischer indole synthesis using (*p*-methoxyphenyl)hydrazine. In the case of the cis isomer, a significant amount of the nonlinear isomer **29** was isolated. The structure of this compound was secured by catalytic debenzylation and dehydrogenation in boiling diphenyl ether with palladium on charcoal to furnish the known[30] 10-methoxy-7*H*-pyrido[3,4-*b*]carbazole (**32**). Similar treatment of a mixture of **27** and **28** gave the linear carbazole **30**, which was demethylated with pyridine hydrochloride to give the desired 10-hydroxy-6*H*-pyrido[4,3-*b*]carbazole (**31**).

9-Hydroxyellipticine is readily oxidized with MnO_2 to **36** in the presence of *n*-butylamine to give the oxazole **33**.[31] Treatment of **31** under similar conditions furnished the corresponding oxazole **34**. The absence of the methyl groups had no discernible influence on the course of the reaction.

The preparation of 5-(hydroxymethyl)-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (**46**) was accomplished by using a modification of the Weller synthesis of ellipticine[32] as shown in Scheme III.

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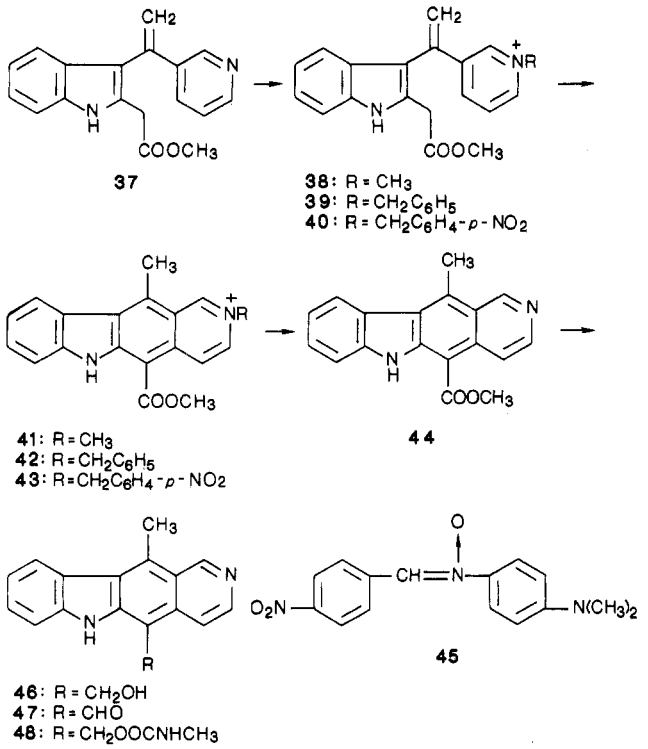
Scheme III



Acid-catalyzed condensation of methyl indole-2-acetate, with 3-acetylpyridine, furnished the vinylindole **37**. This was converted to the quaternary ammonium salts **38–40** with the appropriate halides. Cyclization in methanol containing sodium methoxide, followed by treatment with a quaternary salt of ethyl nicotinate resulted in ring closure and aromatization to afford **41–43**. Heating either **41** or **42** with a number of nucleophiles (e.g., thiophenoxide ion) did not furnish the required ester **44** in usable yield. Catalytic hydrogenation of **42** gave **44** in very low yields; the major product contained a reduced pyridine ring with the benzyl group still attached to the nitrogen. Treatment of **43** with nitrosodimethylaniline, as described by Kröhnke[33] to gave the nitrone **45** and the desired ester **44** in 47% yield, accompanied by a red by-product, which was difficult to remove chromatographically.[26] Reduction of the crude ester with LAH gave the required alcohol **46** in greater than 50% yield for the two steps. Oxidation of **46** with MnO_2 gave the aldehyde **47**, a natural product whose synthesis was reported recently by Gribble.[34] Direct comparison of the infrared spectrum of **47** with the natural alkaloid showed that the spectra were identical. Treatment of **46** with methyl isocyanate afforded the carbamate **48**.

Biological Results

9-Hydroxy-6*H*-pyrido[4,3-*b*]carbazole (**31**) was tested for antitumor activity at the National Cancer Institute[35] against murine P388 lymphocytic leukemia and was found to be inactive (T/C < 122 at 25.0–200 mg/kg). Thus, whatever the reason for the lack of antitumor activity of **5**, it cannot be due to the fact that it is not enzymically hydroxylated. The formation of the oxazole **34** indicates that **31** can form a quinone imine analogous to **9**, which gives **33**.[31]

Ellipticine (**1**), 5-(hydroxymethyl)-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (**46**), and its corresponding *N*-methylcarbamate (**48**) were tested for antitumor activity at the Lederle Laboratories.[36] The results are summarized in Table I.

Ellipticine and the carbinol **46** were about equipotent, but the carbamate **48** was more toxic and more active than either. The latter exhibited significant antitumor activity at a dose of 2.5 mg/kg and was toxic at the 80 mg/kg dose level. The effect of these drugs on [^{3}H]thymidine incorporation in HeLa cells is summarized in Table II. The measurement of the incorporation of [^{3}H]uridine was complicated by the fact that the drugs partially inhibited [^{3}H]uridine uptake by the HeLa cells.

Table I. Activity against P388 Lymphocytic Leukemia of Ellipticine, 5-(Hydroxymethyl)-11-methyl-6*H*-pyrido[4,3-*b*]carbazole, and Its Carbamate in Mice[a]

compound	dose	MST[b]	% ILS[c]
placebo		10	control
ellipticine (**1**)	40	16.0	60
	20	13.0	30
	10	13.0	30
	5	12.0	20
46			
	80.	18	80
	40.	16.5	65
	20.	16.5	65
	10	14.5	45
	5	13	30
	2.5	12.5	25
48			
	80.	6.0	toxic
	40.	10.0	0
	20.	15.0	50
	10	21.0	110
	5	16.0	60
	2.5	18.0	80

[a] The compounds were administered ip on days 1, 5, and 9 in a 9-day protocol at Lederle Laboratories. BDFR-1 mice were inoculated ip with 10^6 P388 cells at day 0. [b] MST = median survival time. [c] % ILS = percent increase in life span relative to controls.

Table II. Effect of Ellipticine, 5-(Hydroxymethyl)-11-methyl-6*H*-pyrido[4,3-*b*]carbazole, and Its Carbamate on [^{3}H]Thymidine Incorporation by HeLa Cells[a]

		% incorporation of [^{3}H]thymidine compared to control	
compound	concn, μg/mL	in presence of drug	3 h after washing
ellipticine	5	65	78
	10	56	47
	25	8	25
46	5	67	88
	25	22	52
48	5	59	18
	25	27	3

[a] The drugs **1**, **46**, and **48** were added to growing cultures of HeLa cells and 1 h later [^{3}H]thymidine was added. After another 1 h the amount of the labeled base incorporated by the cells was determined. In another experiment HeLa cells were exposed to the drugs for 1 h and then washed thoroughly. Three hours later [^{3}H]thymidine was added and the above procedure was repeated.

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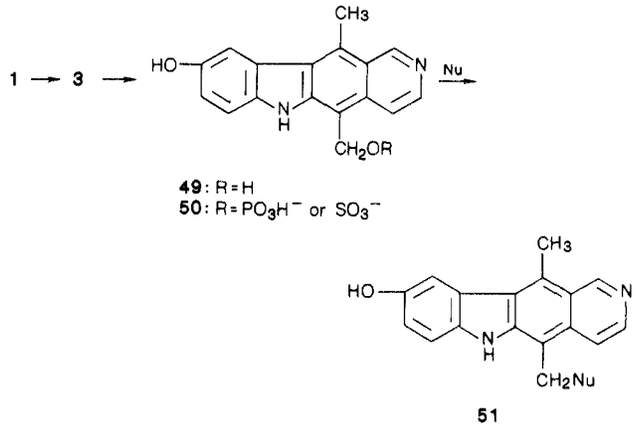
(36) We express our thanks to Dr. Stanley Lang, Head, Chemistry Department Infectious and Neoplastic Disease Research Laboratory of Lederle Laboratories for arranging the testing of our compounds and communicating the results to us.

Scheme IV



Ellipticine and the carbinol **46** blocked [^{3}H]thymidine incorporation, but the inhibition was partially reversible 3 h after washing. The carbamate **48** blocked [^{3}H]thymidine incorporation also, but in this instance the blockade was irreversible. This result is similar to that obtained with hycanthone (**15**) and its carbamate **20** in schistosomes[22] and HeLa cells.[23] Hycanthone blocked incorporation of [^{3}H]uridine, but, after washing, incorporation resumed, whereas the carbamate **20** was effective in preventing [^{3}H]uridine incorporation in washed and unwashed cells.

On the basis of the evidence presented in this paper, we propose an alternate mechanism (Scheme IV) to account for the antitumor activity of ellipticine and some of its active congeners.

Ellipticine is metabolically converted to 9-hydroxyellipticine (**3**), a known metabolite of **1**,[10,11] as suggested originally by LePecq et al.[2] This species, in turn, is enzymically converted first to the carbinol **49**, which then is transformed enzymically to **50**. This compound, which now possesses a good leaving group, alkylates a nucleophilic macromolecule such as DNA or possibly topoisomerase II to give **51**. The carbamate **48** acts as a surrogate for **50** just as hycanthone *N*-methylcarbamate (**20**) does for the corresponding phosphate **16** or sulfate **17**.[22]

Such a mechanism can account for the greater antitumor potency and toxicity of **48** if it assumed that the observed irreversible binding in HeLa cells is due to alkylation of a macromolecule. Ross[37] has pointed out that ellipticine causes a higher frequency of DNA strand breaks than adriamycin, yet it is far less cytotoxic. He suggests that ellipticine-induced breaks are rapidly repaired when the drug is removed from the surrounding medium whereas the adriamycin-induced breaks are retained much longer. If the carbamate **48** forms covalent bonds with macromolecules as in **51**, it should be retained much longer than ellipticine or the carbinol **46**; consequently, repair should occur more slowly, if at all.

Experimental Section

Melting points were taken on a Mel-Temp capillary melting point apparatus and are corrected. NMR spectra were recorded on a Hitachi R-600 or a Varian XL-200 spectrometer. All NMR values are reported in ppm downfield from $(CH_3)_4Si$, the internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 298 spectrometer and mass spectra were determined on a Hewlett-Packard 5987A GC/MS spectrometer. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, or Galbraith Laboratories, Knoxville, TN.

2-Benzyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolone (22). To a solution of 8.7 g (0.124 mol) of methyl vinyl ketone in 150 mL of dry dioxane there was added 27.4 g (0.11 mol) of the enamine derived from pyrrolidine and *N*-benzyl-4-piperidone,[27] and the whole was heated under reflux in a nitrogen atmosphere for 17 h. Then 30 mL of H_2O was added and heating was continued for an additional hour. To the cooled solution there was added 400 mL of 5% HCl and then it was extracted with ether. The aqueous phase was separated, made basic with NH_4OH, and extracted with ether. The combined, dried ether solutions were treated with HCl gas. The gummy precipitate was dissolved in EtOH–EtOAc (1:1), and after the mixture was allowed to stand for several days, crystals separated. They were collected, washed with EtOAc, and dried; wt 11.6 g. The filtrate was concentrated and the residue was converted to the free base, which was purified by chromatography over silica gel to furnish 10.4 g of the free base of **22** as a yellow oil: NMR ($CDCl_3$) δ 7.32 (br s, 5 H, aromatic H), 5.85 (s, 1 H, vinyl H), 3.55 (s, 2 H, $C_6H_5CH_2$), 3.20–1.50 (m, 11 H); IR (film) 2940, 2800, 1675 cm^{-1}. The HCl salt crystallized from EtOH–EtOAc as white needles, mp 164–165 °C. Anal. ($C_{16}H_{19}NO$·HCl) C, H, N.

***cis*- and *trans*-2-Benzyloctahydro-6(2*H*)-isoquinolone (23, 24).** A solution of 10.56 g (43.7 mmol) of **22** in 200 mL of 95% EtOH was hydrogenated in the presence of 2.1 g of 5% Rh on Al_2O_3. After 4 h the catalyst was removed and the solution concentrated to leave 9.7 g of a mixture of cis and trans isomers. This was combined with 8.26 g of a similar mixture obtained from another run and the resulting mixture was chromatographed on silica gel with hexane–EtOAc (3:1) as the eluting solvent. There was obtained 6.4 g (35%) of pure cis and 5.36 g (29%) of the pure trans isomers isolated as oils. An additional 2.77 g of a mixture of isomers was obtained also.

The cis isomer **23** formed a hydrochloride salt, mp 234–235 °C, after crystallization from EtOH–EtOAc. Free base: NMR ($CDCl_3$) δ 7.29 (br s, 5 H, aromatic H), 3.50 (d, 1 H, J = 13 Hz, $C_6H_5CH_2$), 3.47 (d, 1 H, J = 13 Hz, $C_6H_5CH_2$), 2.39–1.32 (m, 12 H); IR 1715, 1245, 1105 cm^{-1}. Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

The trans isomer **24** furnished a crystalline methiodide in acetone: mp 237–237.5 °C dec; NMR (free base in $CDCl_3$) δ 7.31 (br s, 5 H, aromatic H), 3.55 (d, 1 H, J = 13 Hz, $C_6H_5CH_2$), 3.47 (d, 1 H, J = 13 Hz, $C_6H_5CH_2$), 2.39–1.32 (m, 12 H); IR (film) 1715, 1245, 1105 cm^{-1}. Anal. ($C_{17}H_{24}INO$) C, H, N.

Conversion of *cis*- and *trans*-*N*-Benzoyloctahydro-6-(2*H*)-isoquinolones (25 and 26) to 23 and 24. *cis*-*N*-Benzoyloctahydro-6(2*H*)-isoquinolone, mp 150–150.5 °C (lit.[29] mp 148–149 °C) (200 mg) was dissolved in 60 mL of dry toluene containing 50 mg of ethylene glycol and 20 mg of *p*-toluenesulfonic acid, and the solution was heated under reflux for 17 h under N_2. The solution was evaporated to dryness and the residue was dissolved in 30 mL of dry ether. To this solution was added 50 mg of LAH and the suspension was refluxed for 3 h. Dilute HCl was added and the solution ws stirred for 30 min and made alkaline. The ether solution was separated and the aqueous phase was extracted with ether. The combined ether solutions were evaporated, and the residue was chromatographed to give an oil whose IR was identical with that of **23**.

A similar set of reactions was carried out on the *trans*-*N*-benzoyl isomer **26**. The resulting oil had the same IR spectra as that of **24**. The methiodide prepared from this sample was identical in all respects with the material prepared from **24**.

***trans*-2-Benzyl-9-methoxy-1,2,3,4,4a,5,11,11a-octahydro-6*H*-pyrido[4,3-*b*]carbazole (28).** Two grams of the HCl salt of **24** and 1.50 g of (*p*-methoxyphenyl)hydrazine hydrochloride was suspended in 100 mL of EtOH containing 1 mL of concentrated HCl, and the mixture was stirred at room temperature under N_2. After 30 min a clear solution resulted. After 24 h a new crystalline solid appeared. It was collected and dried; wt 1.68 g (61%). After crystallization from toluene–hexane, the free base melted at 164.5–166 °C: NMR ($CDCl_3$) δ 7.70 (s, 1 H, NH), 7.31 (br s, 5 H, aromatic H), 7.20–6.60 (m, 3 H, aromatic H), 3.80 (s, 3 H, OCH_3), 3.65 (s, 2 H, $C_6H_5CH_2$), 3.25–1.35 (m, 12 H); IR (KBr) 3385, 1470, 1210, 740, 690 cm^{-1}; MS (CI, CH_4), m/e 347 (M + 1). Anal. ($C_{23}H_{26}N_2O$) C, H, N.

***cis*-2-Benzyl-9-methoxy-1,2,3,4,4a,5,11,11a-octahydro-6*H*-pyrido[4,3-*b*]carbazole (27).** When similar quantities of the *cis*-isoquinolone **23** was treated with (*p*-methoxyphenyl)hydrazine and stirred with HCl in EtOH overnight, the desired indole crystallized as the HCl salt in 38% yield. After crystallization

(37) Ross, W. E. *Biochem. Pharmacol.* **1985**, *34*, 4191.

from EtOH, the white plates melted at 259–260 °C: NMR (free base, $CDCl_3$) δ 7.57 (s, 1 H, NH), 7.38–7.24 (m, 5 H, aromatic H), 7.16 (d, 1 H, J = 8.7 Hz, C-7H), 6.95 (d, 1 H, J = 2.2 Hz, C-10 H), 6.75 (dd, 1 H, J = 2.3, 8.7 Hz, C-8 H), 3.85 (s, 3 H, OCH_3), 3.59 (d, 1 H, J = 13.4 Hz, $C_6H_5CH_2$), 3.41 (d, 1 H, J = 13.4 Hz, $C_6H_5CH_2$), 3.00–2.60 (m, 5 H), 2.50–1.60 (m, 7 H); MS (CI, CH_4), m/e 347 (M + 1); IR (HCl salt in KBr) 1470, 1205, 740, 690 cm^{-1}. Anal. ($C_{23}H_{26}N_2O$·HCl) C, H, N.

10-Methoxy-1,2,3,4,4a,5,6,11c-octahydro-7*H*-pyrido[3,4-*c*]carbazole (29). After filtration of the above HCl salt, the filtrate was taken to dryness, the residue was shaken with diluted NaOH and CH_2Cl_2, and the CH_2Cl_2 was evaporated to leave a residue which, after chromatography on silica gel (hexane–EtOAc–EtOH) (15:15:1), furnished the free base in 17% yield: mp 152–153 °C after crystallization first from EtOAc and then MeOH; NMR ($CDCl_3$) δ 7.57 (s, 1 H, NH), 7.41–7.24 (m, 5 H, aromatic), 7.18 (d, 1 H, J = 8.6 Hz, C-8 H), 6.96 (d, 1 H, J = 1.9 Hz, C-11 H), 6.80 (dd, 1 H, J = 8.6, 2.4 Hz, C-9 H), 3.97 (s, 3 H, OCH_3), 3.68 (s, 2 H, $C_6H_5CH_2$), 3.20–1.45 (m, 12 H); MS (CI, CH_4), m/e 347 (M + 1); IR (KBr) 3350, 1455, 1200, 1020, 860, 735, 695 cm^{-1}. Anal. ($C_{23}H_{26}N_2O$) C, H, N.

9-Methoxy-6*H*-pyrido[3,4-*b*]carbazole (30). A mixture of 2.26 g (5.9 mmol) of the HCl salts of the *cis*- and *trans*-octahydropyridocarbazoles **27** and **28** and 2.5 g of 10% Pd/C were suspended in 120 mL of diphenyl ether, and the suspension was refluxed in an atmosphere of N_2 for 2 h. The suspension was allowed to cool to about 100 °C and was filtered (sintered glass). The catalyst was washed with hexane, and the combined filtrates were shaken thoroughly with 5% HCl. The organic phase was discarded and the acid solution was made alkaline to precipitate 1.07 g (73%) of the crude carbazole **30**, which was contaminated with a small amount of the hydroxypyridocarbazole **31**. The material was suitable for use in the next step.

The pure methoxy derivative was obtained by crystallization of the crude solid from aqueous MeOH and then MeOH: mp 276 °C; NMR (Me_2SO-d_6) δ 11.57 (s, 1 H, NH), 9.48 (s, 1 H, C-1 H), 9.02 (s, 1 H, C-11), 8.37 (d, 1 H, C-3 H), 7.99, 7.97 (overlapping d, 2 H, C-4 H, C-10 H), 7.90 (s, 1 H, C-5 H), 7.50 (d, 1 H, C-7 H), 7.21 (dd, 1 H, C-8 H), 3.10 (s, 3 H, OCH_3); MS (CI, CH_4), m/e 248 (M + 1); IR (KBr) 3300–2200, 1605, 1475, 1210, 890, 840, 805 cm^{-1}. Anal. Calcd for $C_{16}H_{12}N_2O$·H_2O: C, 72.10; H, 5.29; N, 10.52. Found: C, 72.08; H, 4.91; N, 10.38.

9-Hydroxy-6*H*-pyrido[4,3-*b*]carbazole (31). To a slurry of 25 g of pyridine hydrochloride in 10 mL of MeOH there was added 1.50 g (6.04 mmol) of the methyl ether **30**. The mixture was heated slowly to 220 °C in an atmosphere of N_2 as the CH_3OH distilled off. After 4 h the solution was cooled and treated with 150 mL of ether. After the ether was removed, the aqueous phase was made acidic with HOAc and then slightly alkaline with NH_4OH to precipitate a green powder; wt 1.00 g. The crude material was purified by vacuum sublimation at 325 °C (0.02 mm). There was obtained 740 mg (52%) of bright yellow crystals: mp ca. 350 °C dec; NMR (Me_2SO-d_6) δ 11.23 (s, 1 H, NH), 9.37 (s, 1 H, C-1 H), 9.21 (s, 1 H, OH), 8.82 (s, 1 H, C-11 H), 8.33 (d, 1 H, C-3 H), 7.81 (d, 1 H, C-4 H), 7.77 (s, 1 H, C-5 H), 7.66 (d, 1 H, C-10 H), 7.36 (d, 1 H, C-7 H), 7.04 (dd, 1 H, C-8 H); MS (EI), m/e 234 (M^+) 205, 217; IR (KBr) 3410, 3200–2200, 1445, 1205, 850, 790 cm^{-1}. Anal. ($C_{15}H_{10}N_2O$) C, H, N.

10-Methoxy-7*H*-pyrido[3,4-*c*]carbazole (32). The free base **29** was treated with 10% Pd/C in refluxing diphenyl ether as in the case of the linear isomer. The crude product was purified by vacuum sublimation to give the desired compound **32** in 29% yield: mp 244–246 °C (lit.[30] value 254 °C); NMR (Me_2SO-d_6) δ 9.27 (s, 1 H, C-3 H), 8.61 (d, 1 H, C-2 H), 8.55 (d, 1 H, C-1 H), 8.00–7.98 (overlapping of 2 H, C-5 H, C-10 H), 7.81 (d, 1 H, C-4 H), 7.57 (d, 1 H, C-7 H), 7.09 (dd, 1 H, C-8 H), 3.96 (s, 3 H, OCH_3). Anal. ($C_{16}H_{22}N_2O$) C, H, N.

Oxazole Derived from 9-Hydroxy-6*H*-pyrido[4,3-*b*]carbazole (34). A solution of 70 mg of the carbazole **31**, 59 μL of *n*-butylamine, 15 mL of dimethoxyethane, and 1.5 mL of absolute EtOH was treated with 1.04 g of MnO_2, and the suspension was stirred at room temperature for 7 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was flash chromatographed on 16 g of silica gel with EtOAc as the eluant. The combined fractions (57 mg) were crystallized from EtOAc; wt 27 mg; mp 275–279 °C. Anal. Calcd for $C_{19}H_{15}N_3O$·0.25H_2O: C, 74.61; H, 5.11; N, 13.74. Found: C, 74.66; H, 5.14; N, 13.72.

1-[2-(Carbomethoxymethyl)-3-indolyl]-1-(3-pyridyl)ethene (37). A solution of 6.13 g (0.032 m) of methyl indole-2-acetate, 7.16 g (7.0 mL, 0.059 m) of 3-acetylpyridine, and 10 mL of concentrated H_2SO_4 in 200 mL of dry MeOH was refluxed for 2 h in an atmosphere of N_2. The clear red solution was poured onto 600 g of ice. It was made alkaline with NH_4OH and extracted with 2 × 500 mL portions of ether. The ether solution was washed with H_2O, dried, and concentrated to dryness. The residue was triturated with hexane–ether (1:1), and the crystals that formed were collected and dried; wt 8.0 g; mp 154–157 °C (lit.[32] mp 160–161 °C). The material was suitable for the next step. An additional 110 mg separated from the ether–hexane filtrate. Total yield 8.17 g.

2-(*p*-Nitrobenzyl)-5-carbomethoxy-11-methyl-6*H*-pyrido[4,3-*b*]carbazolium Bromide (43). Three grams (0.01 mol) of the ester **37** and 12.0 g (0.05 mol) of *p*-nitrobenzyl bromide in 140 mL of reagent grade acetone was stirred for 24 h. The crystals of **40** were collected, washed with ether, and dried; wt 4.72 g (92%). To a solution of 150 mg of metallic sodium in 40 mL of dry MeOH there were added 2.67 g (5.25 mmol) of crude **40** and 4.52 g (18.4 mmol) of ethyl nicotinate methobromide. The solution was stirred for 22 h at room temperature in a nitrogen atmosphere. The crystallize solid that separated was filtered, washed with methanol, and dried; wt 2.31 g (80%) of the desired *p*-nitrobenzyl quaternary salt **43**. The analytical sample was obtained by crystallization from CH_2Cl_2–MeOH (1:1): mp 284–289 °C dec; NMR (Me_2SO-d_6) δ 12.13 (s, 1 H), 10.40 (s, 1 H), 9.31 (d, 1 H), 8.69 (d, 1 H), 8.49 (d, 1 H), 8.33 (d, 2 H), 7.86 (m, 3 H), 7.7–7.65 (m, 1 H), 7.50–7.47 (m, 1 H), 6.20 (s, 2 H), 4.13 (s, 3 H), 3.41 (s, 3 H); IR (KBr) 3240, 3045, 2945, 1717, 1590, 1420 cm^{-1}. Anal. ($C_{25}H_{20}N_3O_4$) C, H, N.

5-Carbomethoxy-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (44). To a solution of 200 mg (13 mmol) of metallic sodium in 600 mL of dry MeOH there were added 2.70 g (5.3 mmol) of the quaternary salt **43**, 1.06 g (6.3 mmol) of *p*-nitrosodimethylaniline, and 300 mL of dry $CHCl_3$. The suspension was stirred overnight at room temperature in a nitrogen atmosphere and then evaporated to dryness. The residue was suspended in a solution of 30 mL of $CHCl_3$ and 5 mL of MeOH and flash chromatographed on a column of 40 g of silica gel (37–55 μm) with ether–triethylamine (20:1) as the eluant. The purest fraction was set aside and the less pure material was rechromatographed. The process was repeated, and the purest fractions which showed essentially only one spot on TLC were combined; wt 715 mg (47%). After crystallization from EtOAc–CH_2Cl_2 (5:1), the yellow needles melted at 203–204 °C dec: NMR (Me_2SO-d_6) δ 11.56 (s, 1 H), 9.73 (s, 1 H), 8.87 (d, 1 H), 8.53 (d, 1 H), 8.38 (d, 1 H), 7.80 (d, 1 H), 7.60–7.52 (m, 1 H), 7.30–7.29 (m, 1 H), 4.10 (s, 3 H), 3.33 (s, 3 H); IR (KBr) 3300, 2950, 1675, 1600, 1465 cm^{-1}. Anal. ($C_{18}H_{14}N_2O_2$) C, H, N.

5-(Hydroxymethyl)-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (46). A solution of 170 mg (0.74 mmol) of metallic sodium in 150 mL of MeOH, 1.78 g (3.5 mmol) of the quaternary salt **43**, 581 mg (3.5 mmol) of *p*-nitrosodimethylaniline, and 75 mL of dry $CHCl_3$ was stirred for 5 h at room temperature in an atmosphere of N_2. The suspension was evaporated to dryness and the dried residue was dissolved in 100 mL of dry THF. To the resulting solution there was added 300 mg of LAH. After the mixture was stirred for 1 h at room temperature, 600 mg of LAH was added. After 20 min the reaction was judged to be complete (TLC). The mixture was worked up in the usual way, and the solid that was collected was washed thoroughly with five portions of hot CH_2Cl_2–MeOH (1:1). The aqueous filtrate was extracted with 3 × 200 mL portions of CH_2Cl_2. The combined organic layers were concentrated to dryness, and the residue was suspended in 30 mL of CH_2Cl_2 and 5 mL of MeOH. The suspension was flash chromatographed on silica gel, first with EtOAc as the eluant and then with EtOAc–MeOH (5:1). The purest fractions were combined, concentrated to a small volume, and cooled, whereupon the desired carbinol crystallized to give 518 mg (56% for the two steps) of **46**, which melted at 257–258 °C dec after one crystallization from EtOAc–MeOH (5:1): NMR (Me_2SO-d_6) δ 11.46 (s, 1 H), 9.71 (s, 1 H), 8.43 (d, 1 H), 8.39 (d, 1 H), 8.08 (d, 1 H), 7.62–7.48 (m, 2 H), 7.30–7.22 (m, 1 H), 5.25 (s, 3 H), 3.32 (s, 3 H).

Anal. Calcd for $C_{17}H_{14}N_2O \cdot 0.25H_2O$: C, 76.52; H, 5.48; N, 10.52. Found: C, 76.78; H, 5.49; N, 10.40.

5-Formyl-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (17-Oxoellipticine) (47). A suspension of 40 mg of the carbinol **46** and 200 mg of MnO_2 in 35 mL of $CHCl_3$ was heated under reflux for 3.5 h. The hot suspension was filtered and the collected solid was washed with $CHCl_3$. The combined filtrates were evaporated to dryness to leave a residue, which was chromatographed on silica gel. Elution with EtOAc furnished 23 mg of the desired aldehyde **48**, which melted at 274–276 °C (lit.[34] mp 275–276 °C) after crystallization from $CHCl_3$–hexane. The IR spectrum was identical in all respects with that of an authentic sample.[34] Further elution of the column with EtOAc–MeOH (19:1) gave 11 mg of recovered starting material.

5-(Hydroxymethyl)-11-methyl-6*H*-pyrido[4,3-*b*]carbazole *N*-Methylcarbamate (48). To a solution of 400 mg (1.53 mmol) of the carbinol **46** in 25 mL of dry pyridine and 20 mL of reagent grade acetone there was added 900 μL of MeNCO. The solution was magnetically stirred at room temperature in a stoppered flask until all the starting alcohol had disappeared as judged by TLC (ca. 3 days). The solvents were removed in vacuo, and the residue was crystallized from EtOAc–CH_2Cl_2–MeOH to give 152 mg of the desired carbamate, mp 213–214.5 °C. The filtrate was concentrated to dryness and the remaining solid was flash chromatographed to give an additional 145 mg of material of similar purity: wt 307 mg (61%); NMR (Me_2SO-d_6) δ 11.62 (s, 1 H), 9.71 (s, 1 H), 8.46 (d, 1 H), 8.39 (d, 1 H), 7.97 (d, 1 H), 7.61–7.54 (m, 2 H), 7.32–7.29 (m, 1 H), 7.04 (d, 1 H), 5.77 (s, 2 H), 3.34 (s, 3 H), 2.60 (s, 3 H). Anal. ($C_{19}H_{17}N_3O_2$) C, H, N.

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6-Alkoxy-*N*,*N*-disubstituted-2-pyridinamines as Anticonvulsant Agents

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The anticonvulsant effect of a series of 6-alkoxy-*N*,*N*-disubstituted-2-pyridinamines is described. An investigation was carried out to optimize the activity/side-effect ratio in this series of compounds. The most desirable profile was seen with 1-[6-(2-methylpropoxy)-2-pyridinyl]piperazine, **6**, and this compound was selected for a more complete pharmacological evaluation. Overall, **6** has a pharmacological profile that is very similar to that of diphenylhydantoin (phenytoin). While nearly equipotent to phenytoin, animal studies suggest a fairly short duration of action. In addition, **6** exhibited some troublesome side effects including central nervous system depression and hypothermia.

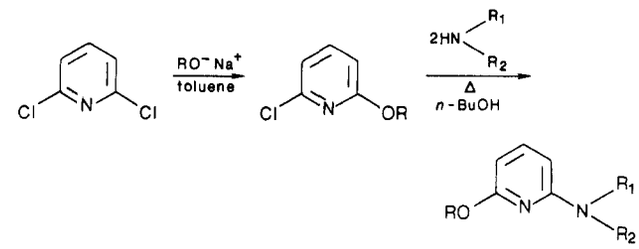
The need for improved agents for the treatment of seizure disorders is widely recognized[1] since currently available antiepileptic drugs are effective in only 60–80% of patients. While absence (petit mal) seizures are well treated in most instances, significant therapeutic improvement is necessary for the treatment of partial-complex (focal) seizures and generalized tonic-clonic (grand mal) epilepsy.[2]

Most marketed anticonvulsants suffer from a broad range of undesirable side effects[3] such as sedation, teratogenicity, cognitive dulling, blood dyscrasia, and liver damage. Failure to achieve control of seizures is frequently due to use-limiting side effects seen with increasing doses of the drugs before a satisfactory therapeutic dose is reached.

Precise mechanisms by which most clinically available anticonvulsants act are unknown.[2a] However, current theories generally agree that several control mechanisms function in normal neuronal tissues and loss of these inhibitory mechanisms causes excitatory mechanisms (that are necessary for normal neuronal function) to "run away" in an uncontrolled neuronal discharge. The result is synchronized and spreading waves of excitation resulting in seizures. Potentially, anticonvulsants could operate by any number of mechanisms that would limit uncontrolled discharges. Consequently, compounds from a wide range of structural classes are known to exhibit anticonvulsant activity.[4] Among these are hydantoins, succinimides, ureas, benzodiazepines, and amides.

Through our drug discovery program and in collaboration with the NIH–NINCDS Antiepileptic Drug Discovery Program,[5] we have recently discovered the anticonvulsant effects of a series of 6-alkoxy-*N*,*N*-disubstituted-2-pyridinamines.

Scheme I



Various 1-(6-alkoxy-2-pyridinyl)piperazines have been reported in the patent and medicinal chemistry literature. Compound **3** (Table I), 1-(6-methoxy-2-pyridinyl)-piperazine, has been reported as an intermediate in the preparation of analgesic, antianaphylactic, antihypertensive, antiinflammatory, broncholytic, central nervous system (CNS) depressant and stimulant, contraceptive, tranquilizing and vasodilatory agents. The active agents

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