The acidified aq soln was extd with EtOAc. These extracts were washed with H_2O and dried before evapn. The residue was treated with Et_2O, and the solid obtd weighed 210 mg (15%). Analysis by tlc (SGH, solvent K) indicated the two solids were of nearly identical compn and of excellent purity. Their repptn from Et_2O–EtOAc did not yield material having satisfactory elemental analyses, and the remaining product was subjected to column chromatography (SGH, 20 g; developed with solvent K). The best fractions were combined: 339 mg, 24% yield; tlc (SGH, solvent K) indicated slight impurity; uv max (0.1 *N* NaOH) 256 (ϵ 33,900), 351 (7440). *Anal.* ($C_{26}H_{30}N_8O_8$) C, H, N.

B. Acetylation of the Product of Reductive Condensation of 2 and 4.—Compd **4** (3.55 g, 11 mmoles), **2** (2.33 g, 10 mmoles), and *p*-toluenethiol (8.7 g, 70 mmoles) in 300 ml of anhyd methoxyethanol were utilized in the reductive condensation procedure previously described (B, synthesis of **10**). Celite (10 g) was added to the product suspended in Et_2O, and the total filter cake was air-dried before acetylation as previously described (A, synthesis of **3c**). The solid phase was removed by filtration and washed with Ac_2O and Me_2CO. The filtrates were combined and evapd, and the residue was triturated with Et_2O. The insol fraction was extd with warm EtOAc several times, and the combined exts were washed with H_2O and dried. Evapn yielded 3.3 g of solid (57% crude yield).

This solid was chromatographed on a column of SGH (150 g) by development with solvent K. Product-containing fractions were rechromatographed (SGH, 75 g, solvent K). The best fractions were combined and evapd, and the residue obtd was triturated with Et_2O. The product was isolated by filtration: 740 mg, 13% yield; tlc was identical with that of the analytical sample; uv max (0.1 *N* NaOH) 256 (ϵ 33,700), 351 (7680); pmr (DMSO-d_6) δ 2.22 (s, 3 H, $COCH_3$), 2.24 (s, 3 H, $COCH_3$), 5.36 (s, 2 H, NCH_2), 7.87 (d, 1 H, C_5'-H), 8.32 (d of doublets, 1 H, C_6'-H), 8.88 (d, 1 H, CONH of glutamic acid), 8.89 (d, 1 H, C_2'-H), 8.95 (s, 1 H, C_7-H), 12.10 (m, 2 H, CONH). Other pmr spectral data obtd for this sample were equiv to those given for **4**. *Anal.* ($C_{26}H_{30}N_8O_8$) H; C: calcd, 53.60; found, 52.27; N: calcd, 19.24; found, 18.76.

***N*-(6-{[(2-Amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino}nicotinoyl)glutamic Acid (3′-Azafolic Acid).**—Compd **8b** (759 mg, 1.3 mmoles) was dissolved in 390 ml of deaerated 0.1 *N* NaOH, and the soln was allowed to stir at room temp under N_2. At the end of 16 hr, the soln was acidified to pH 3.5, and the ppt was isolated and washed with dil HCl by centrifugation. The gelatinous mass was dried (P_2O_5) *in vacuo*, and the solid obtd was dissolved in H_2O contg 2 equiv of NH_4OH. This soln was diluted to 1 l. and was made 0.1 *M* in mercaptoethanol; the resulting soln (pH <7) was applied to a DEAE-cellulose column (22 g, std capacity, phosphate form). The column was eluted with a linear NaCl gradient (1000 ml of 0.7 *M* NaCl in the reservoir and 1000 ml of 0.0 *M* NaCl in the mixing bottle; both soln were 0.1 *M* in mercaptoethanol). Elution of the fractions was monitored by uv absorption, and the desired fractions were combined and acidified to pH 3.5 with HCl.

The ppt was collected and washed with dil HCl by centrifugation. The gelatinous mass was dried (P_2O_5) *in vacuo*, and the product was pulverized before final drying (P_2O_5) for 24 hr at room temp and 0.5 mm. The yellow solid weighed 384 mg, 63% yield (8% yield from **2**); a comparable reaction had previously afforded 53% yield (13% from **2**); tlc: **6** appeared homogeneous (uv detection) on SGH (solvent A), Cell-A (solvent A), Cell-B (solvents C, D, E). On Cell-B (solvent A), **6** produced a pattern of 2 overlapping spots; repetition of this same pattern from each of the original 2 spots on 2-dimensional tlc indicated the pattern was a chromatographic artifact. On Cell-DEAE (solvent F), **6** appeared to contain two blue-fluorescent impurities. Side-by-side comparison of **6** with **10** in this tlc system indicated that the amount of **11** present in **6** was much less than 1%; the amount of the second impurity appeared comparable; uv max (0.1 *N* HCl) 261 (ϵ 24,800), 316 (15,500); uv max (pH 7) 277 (32,000), 347 (8020); uv max (0.1 *N* NaOH) 258 (28,200), 275 (29,000), 365 (8900); pmr (CF_3CO_2D) δ 2.62 (m, 4 H, CH_2CH_2), 5.13 (m, 1 H, NCH), 5.18 (s, 2 H, NCH_2), 7.42 (d, 1 H, C_5'-H), 8.58 (d of doublets, 1 H, C_6'-H), 8.84 (d, 1 H, C_2'-H), 9.05 (s, 1 H, C_7-H). *Anal.* ($C_{15}H_{18}N_8O_6 \cdot 1.5H_2O$) C, H, N.[19]

Acknowledgments.—The authors express their appreciation to Dr. W. C. Coburn, Jr., and associates for microanalytical and spectral determinations and to Mrs. Martha Thorpe for pmr data. Some of the analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Choline Acetyltransferase Inhibitors. Styrylpyridine Analogs with Nitrogen-Atom Modifications

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Among steric and electronic features of styrylpyridine analogs previously associated with their activity as inhibitors of choline acetylase were molecular coplanarity and the π-electron-deficient cationic pyridinium moiety. Azomethines, capable of assuming, but presumably not preferring, molecular coplanarity, are represented by both active and inactive trans isomer types. The active inhibitor is less potent than the styrylpyridine analog. An aminomethylstilbene had no inhibitory activity; the cationic and steric features are believed favorable, but the absence of a π-electron-deficient moiety is not. 2-Pyridoneimines were intermediate in potency and ionization between corresponding pyridine and pyridinium analogs. These observations are consistent with previously reported structure–activity relationships and proposed enzyme receptor interactions.

In previous articles,[2,3] a variety of steric and electronic parameters of analogs of styrylpyridines were assessed in relation to influences on potency and specificity as inhibitors of choline acetylase (ChA) (choline acetyltransferase). A simple, potent prototype is the *trans*-*N*-methyl-4-(1-naphthylvinyl)pyridinium salt, I. There are now described analogs that include azomethines, in which the α and β carbon atoms are selectively replaced by N, 2-pyridoneimine (1,2-dihydro-2-iminopyridine) species, and *trans*-4-aminomethylstilbene. For the reasons next outlined, these have been designed

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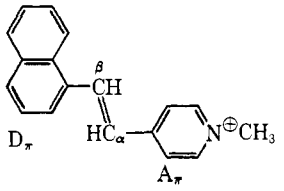
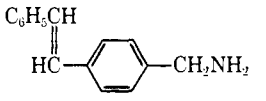


I

to permit more critical evaluation of projected hypotheses.[2,3]

Earlier evidence pointed to molecular coplanarity as a feature favoring ChA inhibitory activity among the styrylpyridine analogs. The trans isomers of stilbene, azobenzene, styrylpyridine, and their unhindered derivatives energetically favor coplanarity. Azomethines (Schiff bases), on the other hand, have been described as nonplanar.[4-7] In benzylideneanilines, the phenyl ring attached to N has been proposed as existing at an angle of from 30° to 40–60° from the plane of the PhCH=N unit.[5,6] These azomethines are stated to be more stable as trans isomers and to photoisomerize to cis forms.[8] Although an unhindered *trans*-azomethine in solution may not preferentially assume coplanarity, there appears to be no barrier to existence of the coplanar form. Assuming electronic factors remain favorable, an azomethine should be less potent than styrylpyridine but not necessarily inert as a ChA inhibitor if coplanarity favors potency.

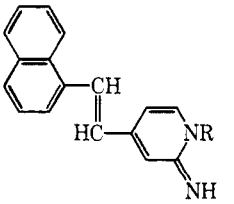
Previous studies showed that ChA inhibitory potency was favored by a cationic charge on the pyrido component of I. Such a structural feature endows this part of the molecule with both π-electron-acceptor (A_π) qualities and ionic-bonding potential. Earlier variations, such as styrylpyridine *N*-oxide and *trans*-stilbene-4-carboxylic acid, are neither cationic nor π-electron deficient, and their inactivity as inhibitors cannot be unequivocally associated with only one of these variables. There is considerable evidence that little specificity is associated with the nature of substituents in the vicinity of the pyrido-N.[2,3,9] A compound with dimensional, hydrophobic and conjugation features comparable to *trans*-styrylpyridine, and possessing a basic group in the structurally nonspecific locus, is *trans*-4-aminomethylstilbene (VIII). It should be at least as potent as the



VIII

pyridine base if cationic charge alone is sufficient, but inactive if π-electron-acceptor properties are required.

The quaternized pyridinium derivatives, such as I, are considerably more potent inhibitors of ChA than are the weakly basic pyridine forms. A 2-pyridoneimine analog of I would be a much stronger base[10] than a pyridine, presumably a π-electron acceptor in the ionized state, and predicted as intermediate in potency between the pyridine and its quaternized derivative. Compounds IXa and IXb were prepared and, consistent with spectral and other physical characteristics and evidence in the literature,[11] are assigned the 1,2-dihydro-2-iminopyridine (2-pyridoneimine) structure.



IXa, R = CH_3
b, R = CH_2CH_2OH

Discussion and Results

Two isomeric pairs of azomethines were compared with the styrylpyridine analogs, I and II. Although I and II are only about three times as potent as the corresponding azomethine pair III and IV, the isomeric azomethines V and VI are essentially inert. Anils as a group are more susceptible to hydrolytic cleavage[12] than are styrylpyridines. Aqueous solutions of IV and VI at pH 7.4 in the dark showed, respectively, no change in the uv spectrum of VI after 3 hr, and a progressive change in IV measured from 0.5 to 4 hr. Inactive VI is more stable than inhibitory IV, so the difference in potency cannot be attributed to hydrolysis. Both IV and VI were photolabile, and uv spectral characteristics changed after 30-min exposure to fluorescent light. This is characteristic of trans isomers of azomethines[8] as well as of styrylpyridines. The uv spectra of IV and VI are markedly different from one another and may reflect electronic differences between this pair of structural isomers which also may influence their relative tendency to favor molecular coplanarity. The isomer VI is about as inert as the nonconjugated, noncoplanar VII. The differences between IV and VI which influence ChA inhibitory activity may be steric as well as electronic.

The *trans*-4-aminomethylstilbene, VIII, not only was inactive as a ChA inhibitor, but was found to be slightly stimulating for this enzyme.[13] This strongly supports the contention that the π-electron-deficient (acceptor) moiety in the styrylpyridine analogs is important for ChA inhibitory activity. If cationic charge were sufficient, VIII should have a ChA I_{50} value between that of *trans*-4-styrylpyridine (6×10^{-4} *M*) and its *N*-Me quaternary derivative (1.5×10^{-5}).[2] A much lower rate of photoisomerization was found for VIII than for the *trans*-styrylpyridines under ionizing conditions, further supporting the view[14] that the π-electron-acceptor character of the pyridinium moiety contributes to cis isomer stabilization by intramolecular charge transfer interaction.

In contrast to the noninhibitory nature of the stilbene derivative, VIII, the two 2-pyridoneimines, IXa and IXb

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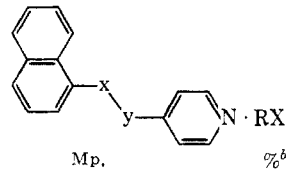
TABLE I
CHOLINE ACETYLASE INHIBITORY ACTIVITIES



No.	x–y[a]	RX	Mp, °C	%[b] yield	ChA I_{50}, *M*	Formula
II[c]	CH=CH	HCl			2.5×10^{-5}	$C_{17}H_{14}Cl\,N$
I[c]	CH=CH	MeI			4.7×10^{-7}	$C_{18}H_{16}IN$
III	N=CH		111–112	87	7.5×10^{-5}	$C_{16}H_{12}N_2$
IV	N=CH	MeI	209–212 dec	27	1.5×10^{-6}[d]	$C_{17}H_{16}IN_2$
V	CH=N		65–67	75	$15\%/10^{-4}$	$C_{16}H_{12}N_2$
VI	CH=N	MeI	187–189	12	$15\%/10^{-4}$	$C_{17}H_{15}IN_2$
VII	CH_2CH_2	MeI	193–195		$10\%/10^{-4}$	$C_{18}H_{18}IN$

[a] Where x–y is a double bond link, the configuration is trans. [b] Yield as analytically satisfactory material. [c] Compound reported earlier,[2,3] included to facilitate comparisons. [d] Molar I_{50} against crude rat brain acetylcholinesterase is 3.8×10^{-4}.

had molar I_{50} values against ChA of 5×10^{-6} and 8×10^{-6}, respectively. These values, as was predicted, are intermediate between those of the more ionized I and weaker base II. The relative nonspecificity of substituents in the pyrido-N region is again confirmed. The hydroxyethyl derivative, IXb, is more water soluble than IXa and may be particularly appropriate for animal pharmacology studies.

Recently, a variety of anthelminthic 1-arylvinylpyridinium derivatives have been described.[15] One of these, 1-(phenylvinyl)pyridinium bromide, in our tests showed less than 20% inhibition of ChA at 10^{-4} *M*. This is relatively inactive compared with the (4-phenylvinyl)-1-methylpyridinium derivatives.[2,3] This may result from an unfavorable localization of the cationic charge or from deviation from coplanarity, or both, in the 1-arylvinylpyridinium system.

Experimental Section

The final compds usually were dried *in vacuo* at 80°. Yields were of secondary importance to purity. Melting points were taken with a Fisher-Johns apparatus; reported values are corrected. Analyses were performed by M-H-W Laboratories, Garden City, Mich. Found anal. conform to within 0.3% of the calcd values.

Inhibition measurements against rat brain ChA and AChE enzyme prepns were conducted as described previously.[2] The ChA values also were checked by a second method.[14] Subdued or pink light illumination was used during experimental exposure of solns of the test compds.

***N*-(1-Naphthyl)-1-(4-pyridyl)methylenimine (III) and Its Methiodide (IV).**—A mixture of 2.8 g (0.02 mole) of 1-naphthylamine and 2.1 g (0.02 mole) of 4-pyridinecarboxaldehyde in 40 ml of EtOH was refluxed for 5 hr. The solvent was evapd off, and the crude material recrystd from hot *i*-PrOH to yield 4.0 g of product (III). *Anal.* ($C_{16}H_{12}N_2$) C, H.

A soln of 0.46 g (0.002 mole) of III in 5 ml of MeI was allowed to stand at room temp for 3 hr. The crude reaction material which pptd on addn of Et_2O was collected by filtration and recrystd from hot EtOH to yield 0.2 g of IV. *Anal.* ($C_{17}H_{15}IN_2$) C, H.

1-(1-Naphthyl)-*N*-(4-pyridyl)methylenimine (V) and Its Methiodide (VI).—A mixture of 4.7 g (0.05 mole) of 4-aminopyridine and 7.8 g (0.05 mole) of 1-naphthaldehyde in 70 ml of dry PhMe was heated to reflux for approx 30 hr with a catalytic amount of $PhSO_3H$, and the H_2O formed was distd off azeotropically. The solvent then was distd off, and the residue was crystd by dissolving in hot ligroin and cooling to −5° to yield V. *Anal.* ($C_{16}H_{12}N_2$) C, H.

A soln of 2.3 g (0.01 mole) of V in 10 ml of MeI was allowed to stand at room temp overnight. The MeI was evapd off, the residue was triturated with warm EtOH, the soln was filtered, and the filtrate was cooled to yield product. Recrystn from hot EtOH was repeated to yield pure VI. *Anal.* ($C_{17}H_{15}IN_2$) C, H, N.

4-(1-Naphthylethyl)pyridine Methiodide (VII).—4-(1-Naphthylvinyl)pyridine was reduced with 50% HI[16] to the Et analog, purified as the HCl salt. The liberated base treated with MeI yielded VII, recrystd from hot *i*-PrOH. *Anal.* ($C_{18}H_{18}NI$) C, H.

***trans*-4-Aminomethylstilbene Hydrochloride (VIII).**—A soln of 4.2 g (0.02 mole) of stilbene-4-carbonitrile[17] in Et_2O was treated with LAH.[18] The product was pptd from Et_2O by addn of ethereal HCl. Two recrystns from *i*-PrOH gave 1.6 g of white solid: mp 268–269.5°; ir (KBr), 2800–3400 (NH_3^+), 1610 (stilbene C=C), 975 cm^{-1} (*trans* RC(H)=(H)CR); uv, λ_{max} (H_2O), 308 mμ (ε 30,000), 298 (30,100), 216 (14,100); nmr (DMSO-d_6, Me_4Si) *s*, 2, τ 5.98 (C), m, 5, 2.48–2.68 (A), s, 6, 2.35 (b), b, 3, −1.0 (D). *Anal.* ($C_{15}H_{15}ClN$) C, H.

A melting point of 300–305° has been reported[19] for VIII and is not in agreement with our finding. The ir, uv, and nmr spectra of our product are consistent with the structure.

Photoisomerization of VIII.—The uv spectrum of a sample of VIII in H_2O was determined using a Cary Model 15 spectrophotometer. The sample in the cuvette was then irradiated with a 275-W Westinghouse sun lamp at a distance of 1 m for 1-, 6-, and 66-min total exposures. The uv spectrum was determined after each exposure. The two bands at 308 and 298 mμ were replaced by one band at 283 mμ after 66-min exposure (Table II). This rate of photoisomerization is considerably lower than that observed with the styrylpyridines under identical conditions.

TABLE II
INFLUENCE OF IRRADIATION ON UV SPECTRUM OF *trans*-4-AMINOMETHYLSTILBENE HYDROCHLORIDE IN WATER

	Absorbance		
Exposure, min	308 mμ	298 mμ	216 mμ
0	0.75	0.74	0.34
1	0.67	0.67	0.34
6	0.35	0.39	0.40
		283 mμ	
66		0.26	0.40

1-Methyl-2-imino-4-(1-napthylethenyl)-1,2-dihydropyridine (IXa) and HI Salt.—A soln of 2- amino-4-methylpyridine in MeI was refluxed for 10 min, excess MeI evapd off, and the residue recrystd from hot *i*-PrOH to yield 2-imino-1,4-dimethyl-1,2-dihydropyridine·HI.[20] To 2.5 g (0.01 mole) of this product in 30

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ml of MeOH was added 1.6 g (0.01 mole) of 1-naphthaldehyde and 3 drops of piperidine. After 30-hr refluxing, solvent was evapd off, and the residue was washed with Et_2O and then recrystd from hot 1:1 water–MeOH to yield 2.8 g (75%) of IXa·HI, mp 278–281°, dec. *Anal.* ($C_{18}H_{17}IN_2$) C, H.

Treatment of the HI salt at room temp with 10% aq NaOH yielded the base; recrystd from hot CH_3CN, mp 200–203°. Treatment of the base with HI regenerated the original salt (same mp and ir spectrum).

1-Hydroxyethyl-2-imino-4-(1-naphthylethenyl)-1,2-dihydropyridine (IXb) and HBr Salt. A soln of 5.3 g (0.05 mole) of 2-amino-4-methylpyridine and 6.2 g (0.05 mole) of bromoethanol in 30 ml of *i*-PrOH was refluxed overnight. Crude product sepd on cooling and was recrystd from hot MeCN to yield 9.2 g (80%) of 1-hydroxyethyl-2-imino-4-methyl-1,2-dihydropyridine·HBr, mp 132–134°. This was treated with 1-naphthaldehyde and the product recrystd as described for IXa, mp 214–217°. *Anal.* ($C_{19}H_{19}BrN_2O$) C, H.

Treatment of the HBr salt with 10% aq NaOH at room temp yielded the base; recrystd from hot *i*-PrOH, mp 162–163. *Anal.* ($C_{19}H_{18}N_2O$) C, H, N.

Acknowledgments.—The choline acetyltransferase and AChE inhibition studies at Montefiore Hospital and Medical Center were supported in part by U. S. Public Health Service Grants MHI3331 and NBO5541. The research at the University of North Carolina was supported in part by U. S. Public Health Service Grant NBO7932. Compound VIII was prepared by M. L. Edwards while supported by a fellowship from Bristol Laboratories, Syracuse, New York. We are indebted to Pfizer Medical Research Laboratories, Groton, Conn., for a sample of 1-(phenylvinyl)pyridinium bromide.

Inhibitors of Blood Platelet Aggregation. 1. Biphenylyloxyalkylamines

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Certain biphenylyloxyalkylamines (**2**) inhibit ADP-induced platelet aggregation *in vitro*. The most active compounds, 5-(4-chloro-2-phenylphenoxy)-*N*-ethyl-*N*-(2-hydroxyethyl)amylamine·HCl (**14**) and the homologous butylamine·HCl (**11**), afford 50% inhibition of ADP-induced platelet aggregation at 4.8×10^{-5} *M* and 7.1×10^{-6} *M*, respectively. The structural requirements for activity are rather general. Thus, a compound having a large lipophilic moiety separated from a basic N by 2–10 elements will usually inhibit, to some degree, this type of platelet aggregation. The activity of these compounds appears to be related to that exhibited by "membrane-active" drugs such as the tricyclic antidepressants and certain antihistamines. The mechanism of action appears to be mediated through a nonspecific adsorption of these lipophilic amines onto the platelet membranes, causing a general disruption of membrane function.

One of the earliest events in the formation of an intravascular thrombus is the aggregation of blood platelets.[1] This intravascular aggregation has been described as a pathological exaggeration of the normal role of platelets in hemostasis and repair.[2] It is generally conceded that an agent which would reduce abnormally high platelet adhesiveness to, but not below, that level required for adequate hemostasis may be useful in the treatment and prophylaxis of thrombotic diseases.

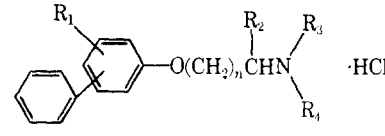
The role of adenosine diphosphate (ADP) as an important and biologically omnipresent initiator of platelet aggregation has been well documented.[3] Thus, agents that will inhibit ADP-induced platelet aggregation are of interest as potential drugs.

A number of lipophilic amines have been reported to inhibit ADP-induced platelet aggregation *in vitro*. Among these are tricyclic antidepressants,[4] antihistamines,[4c,5] and phenothiazine antipsychotic agents.[5a,c,6]

We explored the structure–activity relationship of a series of biphenylyloxyalkylamines. The general structure (**2**) of this series can be derived from **1** by moving the side chain to one of the rings and eliminating the methylene bridge. Two methods were used to prepare

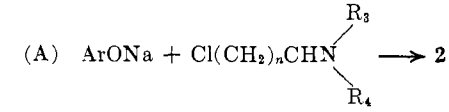
$(C_6H_5)_2CHO(CH_2)_2N(CH_3)_2$

1

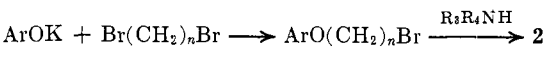


2

the compounds listed in Tables I and II.



(A) $ArONa + Cl(CH_2)_nCHN(R_3)(R_4) \longrightarrow$ **2**



(B) $ArOK + Br(CH_2)_nBr \longrightarrow ArO(CH_2)_nBr \xrightarrow{R_3R_4NH}$ **2**

Both methods involve a Williamson ether synthesis for coupling phenols and side chains. In method A the amine moiety was introduced using an aminoalkyl halide, whereas in method B an ω-bromoalkoxybiphenyl was prepared and used to alkylate the appropriate amine.

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