Antiulcer Agents. 4. Conformational Considerations and the Antiulcer Activity of Substituted Imidazo[1,2-*a*]pyridines and Related Analogues

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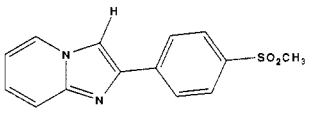
Definition of the interrelationship between the conformational characteristics of a series of substituted imidazo[1,2-*a*]pyridines and their antiulcer activity was investigated by examining the conformational properties of 3-cyano-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**1**), using a variety of experimental and theoretical methods. The results of these studies was the identification of two distinctly different candidates, designated the "folded" and the "extended" conformation, respectively, to represent the two possible minimum-energy conformations of **1**. In order to select the biologically relevant conformer, a group of 3-substituted 2-methylimidazo[1,2-*a*]pyridines, having either a cis or a trans 2-phenylethenyl substituent at the 8-position were designed as conceptually simple and synthetically accessible semirigid analogues of the respective candidate conformers. Gastric antisecretory activity was found to reside only in the trans isomers (compounds **11**, **15**, and **17**), which mimic the "extended" conformation. This observation led to the construction of 8,9-dihydro-2-methyl-9-phenyl-7*H*-imidazo[1,2-*a*]pyrano[2,3-*c*]-pyridine-3-acetonitrile (**40**), a rigid tricyclic analogue that is effectively locked in the "extended" conformation and that exhibited an antiulcer profile comparable to that of prototype **1**. These results unequivocally demonstrate that, in accord with expectation for a drug operating at a specific receptor, the conformational characteristics of the molecule have a substantial effect in determining its antiulcer activity. More precisely, it has been demonstrated that it is the "extended" conformation of **1** that represents the "bioactive" form of the drug. These results constitute the basis for a molecular probe that should aid in the investigation of the as yet uncharacterized gastric proton pump enzyme (H^+/K^+-ATPase), by means of which **1** and its analogues presumably exert their pharmacologic actions.

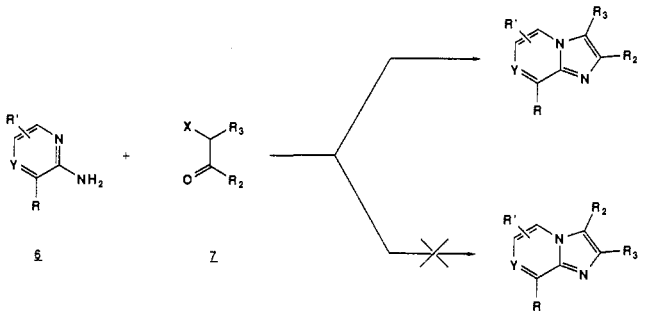
An earlier paper[1] in this series discussed the details of the structure–activity studies that led to the identification and clinical evaluation of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, Sch 28080 (**1**), as a novel antiulcer agent that exhibited both gastric antisecretory and cytoprotective properties in animal models. Observed toxicity led to the withdrawal of **1** from clinical trials.[2,3] Preliminary studies[2] of the pharmacodynamics of **1** have shown that **1** is well absorbed, unchanged **1** is the pharmacologically active species after administration, and **1** is extensively metabolized. Furthermore, the 3-cyanomethyl and 8-phenylmethoxy groups have been established as metabolic sites in **1**, and the pyridyl portion of the imidazo[1,2-*a*]pyridine system has been proposed as a site of metabolism on the basis of the reported metabolism of another imidazo[1,2-*a*]pyridine, zolimidine (**2**).[4-6]



Zolimidine (2)

On the basis of these results, extensive structure–activity studies[2] directed toward discovering a successor to **1** have focused on identification of a bioequivalent for the 3-cyanomethyl function and/or structural alteration of the imidazo[1,2-*a*]pyridine sytem such as to warrant the expectation of a metabolic disposition different from that of **1**. Investigation of the interrelationship between structure, antiulcer activity, and toxicological data derived from a series of analogues of **1** has identified 3-(cyanomethyl)-2,7-dimethyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (**3**), 3-amino-2-methyl-8-(2-phenylethyl)imidazo-[1,2-*a*]pyridine (**4**), and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**5**) as possible successors to compound **1**.[7] These analogues exhibit a combination of antisecretory and cytoprotective activity in animal models without the adverse effects of the prototype **1**. One of these, compound **5**, has a profile meeting all criteria.[7]

Scheme I. General Synthesis of Substituted Imidazo[1,2-*a*]pyridines and Imidazo[1,2-*a*]pyrazines



The present work concerns further structure–activity studies of this series directed toward defining the interrelationship between the conformational requirements, i.e., molecular shape, of the substituted imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyrazines and their antisecretory activity. The compounds described are not histamine (H_2) receptor antagonists, nor are they prostaglandin analogues, yet they exhibit both gastric antisecretory and cytoprotective activities in animal models. The mechanism of their gastric antisecretory activity has been suggested to be competitive and reversible interaction with the high-affinity potassium ion (K^+) binding site of the gastric

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proton pump enzyme (H^+/K^+-ATPase).[8-12]

Chemistry

Condensation of substituted 2-aminopyridines and 2-aminopyrazines with α-halocarbonyl intermediates results in the formation of substituted imidazo[1,2-a]pyridines[13] and imidazo[1,2-a]pyrazines,[14] respectively. When unsymmetrical carbonyl compounds are used, two isomeric products are possible depending upon which nitrogen atom of the pyridine or pyrazine initiates displacement of the halogen (Scheme I). The regiospecificity of the direction of the ring closure in the imidazo[1,2-a]pyridine-forming or imidazo[1,2-a]pyrazine-forming reaction has been established previously,[1,2] and the reaction of other substituted 2-aminopyridines and 2-aminopyrazines with unsymmetrical α-halocarbonyl compounds was presumed to follow the same course.

The substituted imidazo[1,2-a]pyridines and imidazo[1,2-a]pyrazines (Table I) were prepared from the substituted 2-aminopyridines and -pyrazines (**6**) and the α-halocarbonyl intermediates (**7**) specified in the Experimental Section, following the general methods and specific procedures outlined below.

Method A. Condensation of the appropriately substituted 2-aminopyridines or 2-aminopyrazine (**6**) with the appropriate α-halocarbonyl intermediate (**7**) gave the corresponding imidazo[1,2-a]pyridines **9** and **20–22** and imidazo[1,2-a]pyrazine **37**.

Method B. Application of the Mannich reaction to the 3-unsubstituted imidazo[1,2-a]pyridines (**13**, **14**, **31**, and **32**, the preparation of which is also described in the Experimental Section) to produce the corresponding 3-(dimethylamino)methyl derivatives, formation of the trimethylammonium quaternary salts, and subsequent displacement by cyanide gave the corresponding 3-cyanomethyl-substituted imidazo[1,2-a]pyridines **15**, **16**, **33**, and **34**.

Method C. Nitrosation of the appropriately substituted imidazo[1,2-a]pyridine with sodium nitrite and acetic acid and subsequent zinc and acetic acid reduction of the nitroso intermediate gave the corresponding substituted 3-aminoimidazo[1,2-a]pyridines **17**, **18**, and **36**. Compound **35** was prepared by nitrosation using *n*-butyl nitrite followed by zinc and acetic acid reduction of the intermediate nitroso compound.

Method D. Condensation of the N-acetylated derivatives of 4-methyl-2-aminopyridine (**6e**) and 6-methyl-2-aminopyridine (**6c**) with benzaldehyde, followed by deacetylation, gave 4-(2-phenylethenyl)-2-aminopyridine and 6-(2-phenylethenyl)-2-aminopyridine, respectively. Treatment of these olefinic aminopyridines with 3-bromobutan-2-one (**7a**), using method A, gave the substituted imidazo[1,2-a]pyridines **23** and **25**, respectively.

Via the specific procedures described in the Experimental Section, the remaining substituted imidazo[1,2-a]pyridines—**11**, **12**, **19**, **24**, and **26–30**—and substituted imidazo[1,2-a]pyrazines **38** and **39** were prepared.

Treatment of 2,3-dimethyl-8-formylimidazo[1,2-a]pyridine (**10**) with diethyl benzylphosphonate gave 2,3-dimethyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-a]pyridine (**11**), whereas treatment of **10** with benzyltriphenylphosphonium bromide produced the cis isomer of **11**, compound **12**. Preliminary assignments of the double bond geometry were based upon analysis of the coupling constants between the vinylic protons, which were observed to be 16 Hz in **11** and 12 Hz in **12**. These assignments were subsequently confirmed by single-crystal X-ray analysis of the hydrochloride salts of **11** and **12** (Figures 1 and 2, supplementary material). The X-ray studies further established that the site of protonation in compound **11**, which has a pK_a of 6.05, is nitrogen atom 1 (N_1). Similarly, X-ray shows that compound **12** protonates at N_1, as do other members of this series previously examined.[2]

Dehydrochlorination of 2-methyl-8-(1-chloro-3-phenylpropyl)imidazo[1,2-a]pyridine with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave a mixture of 2-methyl-8-((*E*)-3-phenyl-1-propenyl)imidazo[1,2-a]pyridine (**31**) and 2-methyl-8-((*E*)-3-phenyl-2-propenyl)imidazo[1,2-a]pyridine (**32**). The approximately 1:1 composition of the mixture is consistent with the stability of the isomeric products calculated by using the MNDO method. The heat of formation for isomer **31**, in which the carbon–carbon double bond is conjugated to the imidazo[1,2-a]pyridine, is 81.2 kcal/mol, whereas the heat of formation for isomer **32**, in which the carbon–carbon double bond is in conjugation with the phenyl ring, is 81.1 kcal/mol. The difference in the calculated heats of formation for these isomers, 0.1 kcal/mol, predicts a mixture containing approximately 55% of the more stable isomer **32** and 45% of the less stable isomer **31**.

Assignment of the position of the carbon–carbon double bond in **31** and **32** was based on the mass spectral fragmentation patterns. The presence of the tropylium ion ($C_7H_7^+$) in the mass spectrum of **31** and its absence in the mass spectrum of **32** suggested that the carbon–carbon double bond is conjugated to the imidazo[1,2-a]pyridine in **31** and conjugated to the phenyl in **32**. In further support of these assignments, the base peak in the mass spectrum of **32** corresponded to the loss of a phenylethenyl group with proton transfer, $(M - 102)^+$. Application of the Mannich reaction sequence, method B, to **31** and **32** gave 3-(cyanomethyl)-2-methyl-8-((*E*)-3-phenyl-1-propenyl)imidazo[1,2-a]pyridine (**33**) and 3-(cyanomethyl)-2-methyl-8-((*E*)-3-phenyl-2-propenyl)imidazo[1,2-a]pyridine (**34**), respectively. The stereochemical assignment of the configuration about the carbon–carbon double bond in **33** as trans was based on the magnitude of the coupling constant, $J = 16$ Hz, of the vinyl protons. In the case of **34**, the stereochemistry of the carbon–carbon double bond could not be assigned by use of proton magnetic resonance spectroscopy since the vinyl protons in **34** were not resolved even at 600 MHz. However, the positions and trans geometry of the carbon–carbon double bond were unequivocally established by single-crystal X-ray analyses of **33** and **34** (Figures 3 and 4, respectively; supplementary material).

The synthesis of 8,9-dihydro-2-methyl-9-phenyl-7*H*-imidazo[1,2-a]pyrano[2,3-c]pyridine-3-acetonitrile (**40**) is described in Scheme II.

Biological Test Methods

The compounds were evaluated for gastric antisecretory

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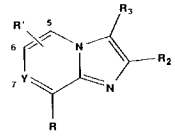
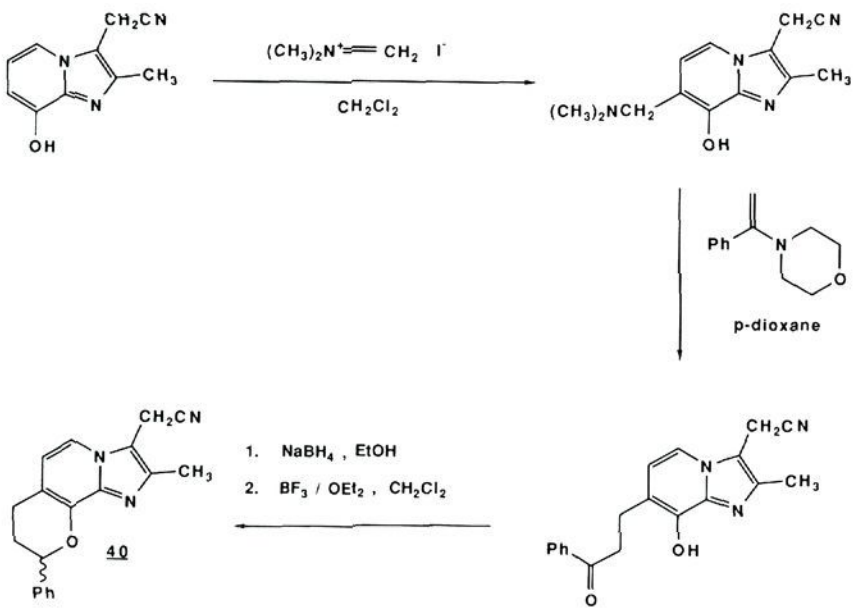
Table I. Substituted Imidazo[1,2-*a*]pyridines and Imidazo[1,2-*a*]pyrazines



compd	R_2	R_3	R	R′	Y	method of synthesis	mp, °C	recryst solvent	yield, %	formula	anal.
1	CH_3	CH_2CN	$PhCH_2O$	H	HC	*a*					
3	CH_3	CH_2CN	$PhCH_2O$	H	CH_3C	*b*					
4	CH_3	NH_2	$PhCH_2CH_2$	H	HC	*b*					
5	CH_3	NH_2	$PhCH_2O$	H	N	*b*					
8	CH_3	CH_3	$PhCH_2O$	H	HC	*a*					
9	CH_3	H	CHO	H	HC	A	140–143	isopropyl ether	24	$C_9H_8N_2O$	C,H,N
10	CH_3	CH_3	CHO	H	HC	*a*					
11	CH_3	CH_3	*E*-PhCH=CH	H	HC	Ex[c]	243–255	methanol	69	$C_{17}H_{18}N_2 \cdot HCl \cdot CH_3OH$	C,H,N,Cl
12	CH_3	CH_3	*Z*-PhCH=CH	H	HC	Ex	174–177	methanol–ether	21	$C_{17}H_{18}N_2 \cdot HCl$	C,H,N,Cl
13	CH_3	H	*E*-PhCH=CH	H	HC	Ex	100–102		89	$C_{16}H_{14}N_2$	C,H,N
14	CH_3	H	*Z*-PhCH=CH	H	HC	Ex	80–87		45	$C_{16}H_{14}N_2 \cdot 0.33H_2O$	C,H,N
15	CH_3	CH_2CN	*E*-PhCH=CH	H	HC	B	133–136		87	$C_{16}H_{18}N_3$	C,H,N
16	CH_3	CH_2CN	*Z*-PhCH=CH	H	HC	B	134–136		49	$C_{16}H_{18}N_3 \cdot 0.1H_2O$	C,H,N
17	CH_3	NH_2	*E*-PhCH=CH	H	HC	C	241–250 dec	methanol–ethyl acetate	40	$C_{16}H_{18}N_3 \cdot HCl \cdot 0.67H_2O$	C,H,N,Cl
18	CH_3	NH_2	*Z*-PhCH=CH	H	HC	C	116–125		43	$C_{16}H_{18}N_3 \cdot 0.33H_2O$	C,H,N[d]
19	CH_3	CH_3CH_2	*E*-PhCH=CH	H	HC	Ex	243–247	methanol–acetonitrile	53	$C_{18}H_{18}N_2 \cdot HCl$	C,H,N,Cl
20	CH_3CH_2	CH_3	*E*-PhCH=CH	H	HC	A	>260	*N,N*-dimethylformamide	25	$C_{18}H_{18}N_2 \cdot HBr$	C,H,N
21	$-(CH_2)_3-$		*E*-PhCH=CH	H	HC	A	173–176	ethyl acetate	22	$C_{18}H_{18}N_2$	C,H,N
22	$-(CH_2)_4-$		*E*-PhCH=CH	H	HC	A	273–276	methanol–ethyl acetate	40	$C_{18}H_{18}N_2 \cdot HCl \cdot 0.75CH_3OH$	C,H,N
23	CH_3	CH_3	H	H	*t*-PhCH=CHC	D	158–160	ethyl acetate	12	$C_{17}H_{16}N_2$	C,H,N
24	CH_3	CH_3	H	6-PhCH=CH	HC	Ex	194–196	ethyl acetate–hexane	31	$C_{17}H_{16}N_2$	C,H,N
25	CH_3	CH_3	H	5-PhCH=CH	HC	D	164–165	ethyl acetate	27	$C_{17}H_{16}N_2 \cdot C_4H_4O_4$	C,H,N
26	CH_3	CH_3	*E*-3-thienyl-CH=CH	H	HC	Ex	255 dec	methanol–water	32	$C_{15}H_{14}N_2S \cdot HCl$	C,H,N,Cl
27	CH_3	CH_3	(*Z*/*E*)-PhCH=C(CH_3)	H	HC	Ex	>200	methanol–ethyl acetate	70	$C_{18}H_{18}N_2 \cdot HCl$	C,H,N,Cl
28	CH_3	CH_3	(*Z*/*E*)-Ph(CH_3)C=CH	H	HC	Ex	73–95		68	$C_{18}H_{18}N_2$	C,H,N
29	CH_3	CH_3	*E*-$PhCH_2CH$=CH	H	HC	Ex	201–204		14	$C_{18}H_{18}N_2 \cdot HCl$	C,H,N,Cl
30	CH_3	CH_3	*E*-PhCH=$CHCH_2$	H	HC	Ex	188.5–190		12	$C_{18}H_{18}N_2 \cdot HCl \cdot 0.5H_2O$	C,H,N
31	CH_3	H	*E*-$PhCH_2CH$=CH	H	HC	Ex	73.5–78	ether	11	$C_{17}H_{16}N_2$	C,H,N
32	CH_3	H	*E*-PhCH=$CHCH_2$	H	HC	Ex	oil		22	$C_{17}H_{16}N_2 \cdot 0.25H_2O$	C,H,N
33	CH_3	CH_2CN	*E*-$PhCH_2CH$=CH	H	HC	B	143–143.5		38	$C_{18}H_{17}N_3$	C,H,N
34	CH_3	CH_2CN	*E*-PhCH=$CHCH_2$	H	HC	B	99–101.5		33	$C_{18}H_{17}N_3$	C,H,N
35	CH_3	NH_2	*E*-$PhCH_2CH$=CH	H	HC	C	222–224 dec		36	$C_{17}H_{17}N_3 \cdot HCl \cdot 0.67H_2O$	C,H,[e]*N*,Cl
36	CH_3	NH_2	*E*-PhCH=$CHCH_2$	H	HC	C	130–132		26	$C_{17}H_{17}N_3 \cdot HCl \cdot 0.33H_2O$	C,H,N,Cl
37	CH_3	CH_3	Cl	H	N	A	169.5–172	ethyl acetate	4	$C_8H_8N_3Cl$	C,H,N,Cl[f]
38	CH_3	CH_3	PhC≡C	H	N	Ex	208.5–210	ethyl acetate	68	$C_{16}H_{13}N_3 \cdot 0.25H_2O$	C,H,N
39	CH_3	CH_3	*E*-PhCH=CH	H	N	Ex	250–256	methanol–ethyl acetate	41	$C_{16}H_{15}N_3 \cdot HCl$	C,H,N,Cl

[a] See ref 1. [b] See ref 2. [c] Ex = experimental procedure described. [d] N: calcd, 16.50; found, 16.09. [e] H: calcd, 6.25; found, 5.64. [f] Cl: calcd, 19.52; found, 19.06.

Scheme II. Synthesis of 3-(Cyanomethyl)-2-methyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine (**40**)



activity in two animal models (Table II). The pylorus-ligated rat[15] was used as the primary screen to assess antisecretory activity and to identify potentially toxic compounds. In this test, compounds were administered at a 40 mg/kg dose intraperitoneally (ip) at the time of ligation and the reduction in acid output was measured at 4 h.

The secondary model was inhibition of histamine-stimulated gastric acid secretion in adult mongrel dogs[16] with surgically prepared Heidenhain pouches. Compounds were first administered in intravenous doses of 0.1–5 mg/kg, and reduction in acid output, relative to the non-drug-treated control value in the same animal, was measured. Selected compounds were also tested against histamine in the Heidenhain pouch dog after oral (po) administration of 2–8 mg/kg doses.

The compounds were tested for gastric cytoprotective activity in the rat (Table II). In this test, the compound was administered orally (po), at doses of 1–30 mg/kg, 30 min before oral administration of absolute ethanol. The effect of the compound against ethanol-induced lesions was determined after 1 h.

Results and Discussion

An empirical structure–activity study based on systematic alteration of the key structural elements of the substituted imidazo[1,2-*a*]pyridine prototype **1**, guided by consideration of established and proposed sites of metabolism, and supported by toxicologic data, has resulted in the identification of three analogues—viz. 3-(cyanomethyl)-2,7-dimethyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (**3**), 3-amino-2-methyl-8-(2-phenylethyl)imidazo-[1,2-*a*]pyridine (**4**), and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**5**)—which exhibit the desirable combination of antisecretory and cytoprotective properties in animal models without the toxic liabilities of compound **1**.[7] The object of the present study was to investigate, by using both experimental and theoretical methods, the potential relationships between the conformational properties of these empirically identified compounds and their antiulcer activity. Assuming that such relationships could be discerned, this information could potentially be utilized to design novel entities that might exhibit an enhanced antiulcer profile.

This study began with an examination of the conformational properties of the prototype, 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**1**).

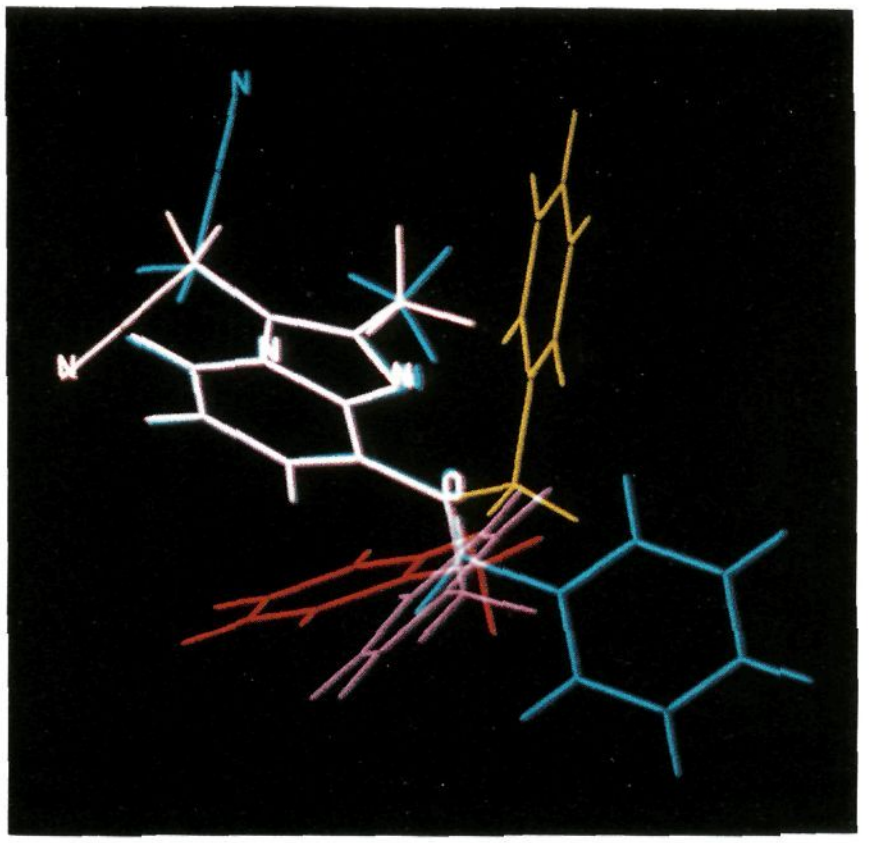


Figure 5. Conformations of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**1**) determined by CAMSEQ: **1a**, RMS = 0.0652 (orange), **1b**, RMS = 0.0652 (yellow), and **1c**, RMS = 0.0652 (magenta), compared to the solid-state conformation **1d** (blue) determined by single-crystal X-ray analysis. The molecules are compared by fitting the atoms of the imidazo-[1,2-*a*]pyridine nuclei with use of the FIT option in SYBYL 5.1 (Tripos Associates, St. Louis, MO).

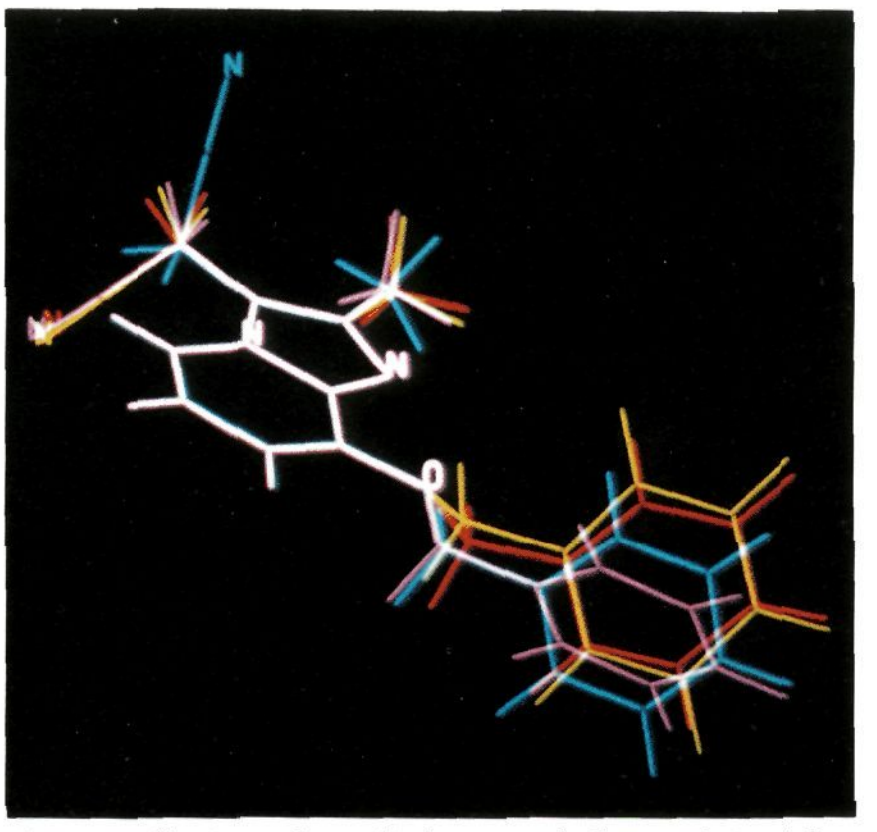


Figure 6. Conformations of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**1f**) determined by MINDO/3, RMS = 0.0470 (orange); MNDO, RMS = 0.0443 (yellow); and AM1, RMS = 0.0425 (magenta), compared to the solid-state conformation **1d** determined by single-crystal X-ray analysis (blue). The molecules are compared by fitting the atoms of the imidazo[1,2-*a*]pyridine nuclei with use of the FIT option in SYBYL 5.1 (Tripos Associates, St. Louis, MO).

Conformational Considerations. The gas-phase conformation of **1** was examined with the CAMSEQ software system.[17,18] A search of the conformational hyperspace of **1** defined about the rotatable bonds described in Table

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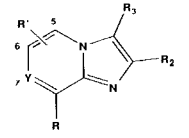
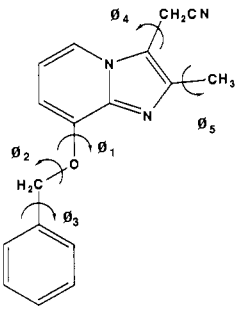
Table II. Gastric Antisecretory and Cytoprotective Activities of Substituted Imidazo[1,2-*a*]pyridines and Imidazo[1,2-*a*]pyrazines



							antisecretory activity[a] Histamine-stimulated Dog									cytoprotective act. ethanol ulcer: ED_{50}, mg/kg
						pylorus-ligated rat: 40 mg/kg, ip	iv dose, mg/kg				iv ED_{50}, mg/kg	po dose, mg/kg			po ED_{50}, mg/kg	
compd	R_2	R_3	R	R′	Y		5	2	1	0.1		8	4	2		
1	CH_3	CH_2CN	$PhCH_2O$	H	HC	98	99	95	83	49	0.09 (0.01–1.2)	77	42	20	4.4 (2.1–14.0)	3.0
3	CH_3	CH_2CN	$PhCH_2O$	H	CH_3C	99		90	74		0.53 (0.22–1.2)[b]	59	20	8	7.8 (3.2–38.3)	13.0
4	CH_3	NH_2	$PhCH_2CH_2$	H	HC	47		71	46	26	1.0[c]	52	41	19	6.7 (2.3–58.2)	9.0
5	CH_3	NH_2	$PhCH_2O$	H	N	79		65	56		0.8 (0.2–6.0)[d]	70	69	63	1.4 (0.6–3.9)[e]	5.0
8	CH_3	CH_3	$PhCH_2O$	H	HC	99			90			26	0			10.0
11	CH_3	CH_3	*E*-PhCH=CH	H	HC	83	86	76	62		0.7 (0.06–2.6)	74	37	25	4.8 (1.6–21.5)	9.5
12	CH_3	CH_3	*Z*-PhCH=CH	H	HC	39		26				3				10.4
15	CH_3	CH_2CN	*E*-PhCH=CH	H	HC	49		76	79			41	0			2.0
16	CH_3	CH_2CN	*Z*-PhCH=CH	H	HC	18	18	0				2				3.0
17	CH_3	NH_2	*E*-PhCH=CH	H	HC	83	67	62	66			4		0		23.0
18	CH_3	NH_2	*Z*-PhCH=CH	H	HC	33	0	24				6				13.0
19	CH_3	CH_3CH_2	*E*-PhCH=CH	H	HC	65	*f*	12				21				0.8
20	CH_3CH_2	CH_3	*E*-PhCH=CH	H	HC	96		42				21				
21	$-(CH_2)_3-$		*E*-PhCH=CH	H	HC	24	8									5.2
22	$-(CH_2)_4-$		*E*-PhCH=CH	H	HC	62		0								7.3
23	CH_3	CH_3	H	H	*t*-PhCH=CHC	40	0					0				
24	CH_3	CH_3	H	6-PhCH=CH	HC	55	0					0				1.7
25	CH_3	CH_3	H	5-PhCH=CH	HC		0						0			5.5
26	CH_3	CH_3	*E*-3-thienyl-CH=CH	H	HC	54		82	64			79	38	5	4.8[c]	24.0
27	CH_3	CH_3	(*Z*/*E*)-PhCH=C(CH_3)	H	HC	71		44				29				5.0
28	CH_3	CH_3	(*Z*/*E*)-Ph(CH_3)C=CH	H	HC	98		65	72			37	17			inactive
29	CH_3	CH_3	*E*-$PhCH_2CH$=CH	H	HC	96		47	24			54	13			6.6
30	CH_3	CH_3	*E*-PhCH=$CHCH_2$	H	HC	58	0					0				5.5
33	CH_3	CH_2CN	*E*-$PhCH_2CH$=CH	H	HC		78		69	9	1.0[c]	82	53	43	4.0[c]	4.0
34	CH_3	CH_2CN	*E*-PhCH=$CHCH_2$	H	HC	27	4									12.0
35	CH_3	NH_2	*E*-$PhCH_2CH$=CH	H	HC	52			32				0			8.6
36	CH_3	NH_2	*E*-PhCH=$CHCH_2$	H	HC	4	20					0				6.4
38	CH_3	CH_3	PhC≡C	H	N	0	0					11				3.7
39	CH_3	CH_3	*E*-PhCH=CH	H	N	74	0					0				5.2
40											0.06 (0.02–0.14)				3.7 (1.6–13.4)	1.7

[a] Confidence limits $\rho = 0.05$ in parentheses. [b] Determination of ED_{50} included the percent inhibition of acid secretion at doses of 0.4 and 0.2 mg/kg which were 39 and 1, respectively. [c] Approximate ED_{50} value. [d] Determination of intravenous ED_{50} included the percent inhibition of acid secretion at doses of 0.4 and 0.2 mg/kg which were 41 and 15, respectively. [e] Determination of oral ED_{50} included the percent inhibition of acid secretion at doses of 16 and 1 mg/kg which were 92 and 39, respectively. [f] Lethalities observed in the pharmacologic evaluation of the test drug.

Table III. Conformational Analysis of 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]-pyridine (1)



conformation	gas-phase stability			
	CAMSEQ[a]	MINDO/3[b]	MNDO[b]	AM1[b]
1a	−28.9	+32.0	+65.8	+99.9
1b	−24.1	+31.4	+65.7	+98.4
1c	−25.5	+31.8	+64.5	+98.1
1d	−20.1	+21.8	+61.5	+95.2
1e		+30.9	+63.8	+98.7
1f		+22.7	+62.0	+95.3
1g		+30.2	+61.6	+95.0
1h		+30.2	+64.1	+95.1
1i		+23.0	+62.9	+95.2

[a] Energy (E) in kilocalories/mole. [b] Heat of formation (H_f) in kilocalories/mole.

III identified three conformations of 1 within 5 kcal/mol of the "global" minimum. All three conformations—**1a**, **1b**, and **1c**—have the phenyl ring of the 8-phenylmethoxy substituent directed toward and over the imidazo[1,2-a]-pyridine ring system (Figure 5). Conformer **1a** was the most stable with a calculated energy of −28.9 kcal/mol, while conformers **1b** and **1c** had energy levels of −24.1 and −25.5 kcal/mol, respectively. The conformational preference of the 8-phenylmethoxy substituent was independent of the 3-cyanomethyl and 2-methyl substituents. We have arbitrarily designated the conformational orientation between the 8-phenylmethoxy substituent and the imidazo[1,2-a]pyridine ring system in these conformers as the "folded" conformation.

Previously, we had examined the solid-state conformation of 1 by single-crystal X-ray analysis,[1] which revealed that the imidazo[1,2-a]ring system is essentially planar with the directly bonded substituent atoms and the oxymethylene carbon atom lying close to this least-squares plane, while the phenyl ring is oriented out and away from the heterocyclic nucleus (Figure 5). This solid-state conformation (**1d**), which contrasts strikingly with the CAMSEQ-generated conformers **1a–c** in the orientation of the phenyl group with respect to the heterocycle, we have arbitrarily designated the "extended" conformation.

Quantitatively, the difference in energy between the "extended" (**1d**) and "folded" (**1a**) conformations using the CAMSEQ method of analysis suggests that the "folded" conformation (**1a**) is more stable than the "extended" conformation (**1d**) by 8.8 kcal/mol (Table III). It was determined that the lattice energies estimated for the two conformations favor the "extended" conformation (supplementary material). This suggests that the intermolecular interactions of the "extended" form more than adequately compensate for the intramolecular interactions of the "folded" form.

The magnitude of the calculated energy difference between the "extended" and "folded" conformations, approximately 9 kcal/mol, is highly significant. Furthermore, resolution of the discrepancy in the estimations of the preferred conformation is extremely important if one is to be guided by the hypothesis that it is the minimum-energy conformation of the drug, or a conformation accessible from the minimum, that approximates the conformation of the drug initially recognized or ultimately bound by the receptor. In either case, the hypothesis holds that it is this conformation that influences, at least in part, the pharmacologic activity of the drug. The design of target molecules and the synthetic strategy employed for their preparation would be highly dependent upon which of the two very different candidate conformations were selected as a model. Thus, further physical and theoretical data were collected and analyzed.

If compound 1 adopts a "folded" conformation in solution, there is a possibility of a charge-transfer interaction between the electron-deficient imidazo[1,2-a]pyridine ring system and the electron-rich phenyl ring of the 8-phenylmethoxy substituent. No evidence of such an interaction could be detected from the ultraviolet spectrum (cyclohexane). Carbon-13 spin–lattice relaxation studies of the ortho or meta and para carbons of the phenyl ring gave no indication of the hindered rotation of the phenyl ring that might be expected in the "folded" conformation. Thus, further computational studies were performed in an attempt to clarify this apparent discrepancy between the CAMSEQ results and the physical data.

The gas-phase stability of the three conformations identified by CAMSEQ—**1a**, **1b**, and **1c**—were determined by using the semiempirical methods MINDO/3, MNDO, and AM1 (Table III). When calculated by any of the three alternative methods, the conformation (**1a**), determined to be most stable by CAMSEQ, appeared to be the least stable. The energy of a completely "folded" conformation, **1e** ($\phi_1 = 90°$, $\phi_2 = 0°$, $\phi_3 = 90°$), was also calculated by using MINDO/3, MNDO, and AM1. With conformation **1e** as the starting point, a new minimum-energy conformer (**1f**) was generated by optimizing all geometric variables (Table III). Regardless of the semiempirical method employed, conformation **1f**, in which the phenyl ring of the 8-phenylmethoxy substituent is "extended" out and away from the imidazo[1,2-a]pyridine ring system (Figure 6), is calculated to be more stable than the starting "folded" conformation **1e** by at least 2–3 kcal/mol (MNDO or AM1) to as much as 8.2 kcal/mol (MINDO/3).

Although the majority of the physical and theoretical data collected would appear to favor the "extended" over the "folded" conformation, an unequivocal case could not be made. Therefore, it was decided to design and synthesize as simple analogues as possible that would mimic, respectively and unambiguously, each of the competing model conformations. The clear differences in molecular shape imposed by the design were intended to address directly the core issue: if the foregoing analysis has validity, it was to be expected that analogues representing one of the conformations would exhibit the desired antisecretory activity, while those mimicking the other conformation should show substantially reduced or no antisecretory activity. Thus, compounds **11**, **15**, and **17**, containing a trans-oriented 2-phenylethenyl group at the 8-position of the imidazo[1,2-a]pyridine ring, were designed to approximate the "extended" conformation of 1, while compounds **12**, **16**, and **18**, containing a cis-oriented 2-phenylethenyl group at the 8-position, would approximate the "folded" conformation of 1. In all cases, the geometric constraints of the carbon–carbon double bond effectively lock in space the conformational position of the phenyl ring with respect to the imidazo[1,2-a]pyridine ring system. Of

(18) Potenzone, R., Jr.; Cavicchi, E.; Weintraub, H. J. R.; Hopfinger, A. J. *Comput. Chem.* **1977**, *1*, 187.

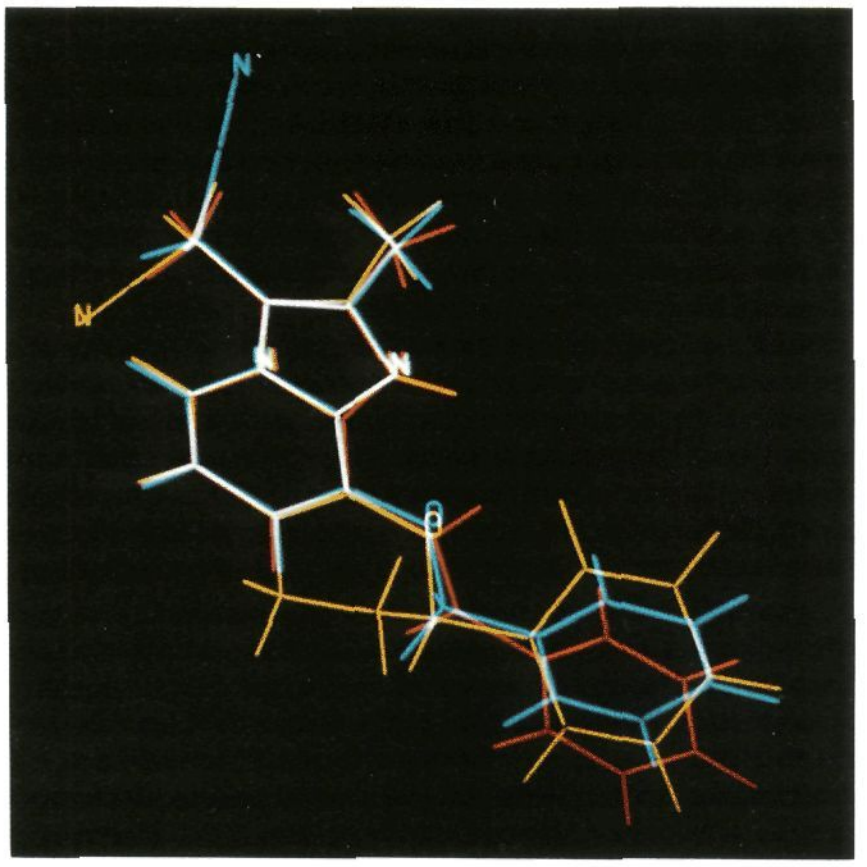


Figure 8. The solid-state conformation (orange) of 2,3-dimethyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine hydrochloride (**11**), RMS = 0.0756, and the "global" minimum-energy conformation (yellow) of 8,9-dihydro-2-methyl-9-phenyl-7*H*-imidazo[1,2-*a*]pyrano[2,3-*c*]pyridine-3-acetonitrile hydrochloride (**40**), RMS = 0.0731, calculated with use of SYBYL and Macromodel,[28] compared to the solid-state conformation **1d** (blue) determined by single-crystal X-ray analysis. The molecules are compared by fitting the atoms of the imidazo[1,2-*a*]pyridine nuclei with use of the FIT option in SYBYL 5.1 (Tripos Associates, St. Louis, MO).

course, there exists flexibility of rotation around the carbon–carbon single bond linking the phenylethenyl group to the heterocyclic nucleus, as is also true with respect to the carbon–oxygen bond linking the phenylmethoxy group to the ring system in prototype compound **1**.

Structure–Activity Relationships. The histamine-stimulated dog data in Table II suggested the following structure–activity relationships. The results of the cytoprotective (rat) assay are also presented in the following discussion, although the effect of structural variations on this mode of activity is not apparent from the available data, and the conclusions drawn apply only to gastric antisecretory activity.

R_8 Substituent. (1) 2-Phenylethenyl Substituents. (a) Geometric Isomers as Models of the "Folded" and "Extended" Conformations of 1. The effect on antisecretory activity of geometric isomerism in the 8-substituent of the imidazo[1,2-*a*]pyridine ring system was examined by comparing a series of analogues (**11**, **12**, **15**, **16**, **17**, and **18**) bearing *cis*- and *trans*-2-phenylethenyl moieties, respectively, at the 8-position. Regardless of the nature of the 3-substituent (methyl, cyanomethyl, or amino), when the compounds were administered intravenously, only the trans isomers (**11**, **15**, and **17**) were active antisecretory agents. The best overall antiulcer profile was exhibited by the 3-methyl analogue **11**. In accordance with the discussion in the previous section, these results suggest that the geometric constraints of the trans carbon–carbon double bond, which effectively lock in space the position of the phenyl ring relative to the imidazo[1,2-*a*]pyridine nucleus and cause these trans-substituted molecules to approximate the "extended" conformation of **1**, may be responsible for the observed antisecretory activity. Conversely, it may be concluded that locking the molecule in the "folded" conformation of **1**, which is approximated by the enforced geometry of the cis carbon–carbon double bond, results in a lack of antisecretory activity.

(b) Structural Modifications of the 2-Phenylethenyl Group. Independent replacement of the α and β hydrogen atoms of the 2-phenylethenyl group with methyl substituents gave Z/E mixtures of 2,3-dimethyl-8-[(1-methyl-2-phenyl)ethenyl]imidazo[1,2-*a*]pyridine (**27**) and 2,3-dimethyl-8-[(2-methyl-2-phenyl)ethenyl]imidazo-[1,2-*a*]pyridine (**28**), respectively. The intravenous and oral antisecretory activity of **27** in the dog was reduced relative to that of **11**. On the other hand, although the intravenous antisecretory activity of **28** was comparable to that of **11**, its relative oral antisecretory activity was significantly reduced. Interestingly, **28** was inactive as a cytoprotective agent in the rat, while **27** retained cytoprotective activity.

Isosteric replacement of the phenyl ring in **11** with a 3-thienyl group produced analogue **26**. The intravenous and oral antisecretory activity of **26** in the dog was comparable to that of **11**. However, the cytoprotective activity of **26** in the rat was reduced relative to that of **11**.

(c) Relocation of the 2-Phenylethenyl Substituent. While the methyl groups at the 2- and 3-positions of the imidazopyridine nucleus were maintained, the 2-phenylethenyl substituent was moved independently around the pyridyl ring to the 5-, 6-, and 7-positions, producing analogues **25**, **24**, and **23**, respectively. All were inactive as antisecretory agents in the dog following either intravenous or oral administration. Although the geometry about the double bonds of these analogues could not be defined from the available spectroscopic data, it is reasonable to suppose that at least some of the "extended" trans isomer was present in all three cases and that for compound **24**, based upon its mode of preparation via a palladium-catalyzed coupling reaction (see the Experimental Section), the trans form was probably the predominant isomer.[23-25]

(2) Phenylpropenyl Substituents. Effect of the Position of the Double Bond. The effect of the position of a trans carbon–carbon double bond in the 8-substituent of the imidazo[1,2-*a*]pyridine ring system on gastric antiulcer activity was tested by examining a series of 8-phenylpropenyl-substituted analogues (**29**, **30**, **33**, **34**, **35**, and **36**) in which the trans-substituted double bond of the propenyl moiety was in conjugation with either the heterocyclic nucleus or the phenyl ring, and the substituent at the 3-position was independently varied among methyl, cyanomethyl, or an amino function. Since the geometry about the carbon–carbon double bond was trans in all cases, the effect of the position of the double bond on antiulcer activity could be discerned in each pair of 3-modified analogues. All the compounds in this phenylpropenyl series were compared with compound **11**, the 3-methylated 8-*trans*-(2-phenylethenyl) analogue, which had exhibited the best antiulcer profile in the phenyl-

(19) Crystallographic calculations were performed on PDP11/44 and MicroVAX II computers by use of the Enraf-Nonius Structure Determination Package incorporating the direct methods program MULTAN11/82.
(20) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = [\sum w (|F_o| - |F_c|^2/\sum w|F_o|^2]^{1/2}$.
(21) *International Tables for X-ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV.
(22) Adams, R.; Schrecker, A. W. *J. Am. Chem. Soc.* **1949**, *71*, 1186. This material is presumed to be a mixture of cis and trans isomers. The olefinic protons could not be discerned in the 80-MHz ^{1}H NMR spectrum.
(23) Heck, R. F. *Pure Appl. Chem.* **1978**, *50*, 691.
(24) Heck, R. F. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 201.
(25) Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2947.

ethenyl series, as discussed above. With a methyl group at the 3-position, only compound **29**, in which the double bond is in conjugation with the imidazo[1,2-*a*]pyridine system, exhibited intravenous and oral antisecretory activity, while compound **30**, with the phenyl-conjugated double bond, was inactive as an antisecretory agent. However, the antisecretory activity of **29** was significantly reduced relative to that of **11**. The results obtained when a cyanomethyl group was placed in the 3-position (compounds **33** and **34**) were similar to those obtained with the 3-methylated pair: only compound **33**, in which the double bond is conjugated with the heterocycle, showed antisecretory activity. In contrast to compound **29**, however, **33** exhibited oral and intravenous potency levels comparable to those of **11**. With an amino group at position 3 (compounds **35** and **36**), the phenyl-conjugated analogue **36** was again inactive, but even the heterocycle-conjugated isomer **35** showed only marginal antisecretory activity upon intravenous administration and was orally inactive. Interestingly, all six compounds in this series exhibited cytoprotective activity in the rat comparable to that of **11**. Thus, the overall antiulcer profile of compound **33** was comparable to that of **11**, while none of the remaining analogues in the 8-phenylpropenyl series approached the level of antisecretory activity exhibited by compounds **11** and **33**.

Modification of the Imidazo[1,2-*a*]pyridine System. The effect of structural alteration of the imidazo[1,2-*a*]-pyridine system on antiulcer activity was examined by testing the imidazo[1,2-*a*]pyrazine congeners **38** and **39**. Both 2,3-dimethyl-8-(2-phenylethynyl)imidazo[1,2-*a*]-pyrazine (**38**), containing an 8-alkynyl substituent, and, more significantly, 2,3-dimethyl-8-((*E*)-2-phenylethenyl)-imidazo[1,2-*a*]pyrazine (**39**), the imidazo[1,2-*a*]pyrazine analogue of **11**, lacked intravenous and oral antisecretory activity in the dog, while maintaining cytoprotective activity in the rat comparable to that of **11**.

Tricyclic Analogue 40, a Rigid Model of the "Extended" Conformation of 1. As discussed above, structure–activity studies in this series using the simplest rigid analogues of the prototype—viz. **11**, **12**, and **15**–**18**—suggested that the conformational requirements of the substituted imidazo[1,2-*a*]pyridine can have a significant effect in determining its antiulcer activity. These observations support the hypothesis that the conformation of the drug molecule initially recognized by the receptor or that conformation which is eventually receptor-bound is approximated by the minimum-energy conformation or by some conformation accessible from that minimum. In either case, it is this conformation that can influence, at least in part, the pharmacologic activity of the drug. Encouraged by these initial results, a rigid tricyclic analogue of **1**, 8,9-dihydro-2-methyl-9-phenyl-7*H*-imidazo[1,2-*a*]-pyrano[2,3-*c*]pyridine-3-acetonitrile hydrochloride (**40**), was prepared. Compound **40** approximates closely the "extended" conformation of prototype **1**, as do the 8-*trans*-phenylethenyl analogues (**11**, **15**, and **17**). Comparison of the X-ray structures of **1** and **11** with the calculated "global" minimum-energy conformation of **40**[28] illustrates the close mutual correspondence of these structures in three-dimensional space (Figure 8). The pyrano ring of **40** contributes the dual virtues of enforcing the requisite "extended" relationship between the phenyl group and the heterocyclic nucleus and mimicking a 7-methyl substituent, the introduction of which has previously been shown[7] to be effective in negating the toxic properties of **1** while retaining its desirable antisecretory and cytoprotective effects. Thus, it seemed reasonable to predict that compound **40** might exhibit an enhanced antiulcer profile, compared to **1**, without the toxic liabilities of the prototype drug. In fact, the intravenous and oral antisecretory potencies of **40**, determined in the histamine-stimulated dog, are equivalent to those of **1**, as is its cytoprotective activity in the rat model. It should be noted that compound **40**, which contains a chiral center, was prepared and tested in racemic form only. Of course, it is possible that one of the enantiomers of **40** might exhibit an enhanced pharmacologic profile compared to that of the racemate. Although these results do not establish the superiority of compound **40** over its progenitor, they are nonetheless strongly supportive of the conformational analysis presented above and represent a significant benchmark in our attempts to elucidate structure–activity relationships in this series. Unfortunately, no data are currently available to establish whether compound **40** is indeed less toxic than **1**.

Conclusion. The pharmacologic observations for compounds **1**, the 2-phenylethenyl series of analogues (**11**, **12**, **15**, **16**, **17**, and **18**), and rigid tricyclic analogue **40** unequivocally demonstrate that, in accord with expectation for a drug operating at a specific receptor, the conformational characteristics of the molecule have a substantial effect in determining its antisecretory activity. More precisely, it has been demonstrated that it is the "extended" conformation of **1** that represents the "bioactive" form of the drug. These results constitute the basis for a molecular probe that should aid in the investigation of the as yet uncharacterized gastric proton pump enzyme (H^+/K^+-ATPase), by means of which **1** and its analogues presumably exert their pharmacologic actions.[28]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Routine ^1H NMR spectra were recorded on a Varian T-60 (60 MHz), CFT-20 (80 MHz), or EM-390 (90 MHz) spectrometer and are expressed as ppm (δ) downfield from Me_4Si internal standard. Higher resolution spectra were obtained at 270 MHz (Bruker), 400 MHz (Varian), and 600 MHz (through the courtesy of Prof. A. A. Bothner-By of Carnegie-Mellon University, Pittsburgh, PA). IR spectra were run on a Perkin-Elmer 221 spectrophotometer, and mass spectra were obtained with a Varian MAT CH5 (EI) or Finnigan Mat 312 double-focusing instrument equipped with a saddle field ion source from Ion Tech (FAB). Microanalyses were performed by the Physical–Analytical Services Department of the Schering-Plough Research Division.

Chemistry. Substituted 2-Aminopyridines and 2-Aminopyrazines 6. The preparation of 2-aminonicotinaldehyde (**6a**) has been described previously.[1] 6-Methyl-2-aminopyridine (**6c**), 5-bromo-2-aminopyridine (**6d**), and 4-methyl-2-aminopyridine (**6e**) were available from the Aldrich Chemical Co. The preparation of 2-amino-3-chloropyrazine (**6f**) has been reported previously.[2]

3-((*E*)-2-Phenylethenyl)-2-aminopyridine (6b). To a mixture of 1.28 g (10.5 mmol) of 2-aminonicotinaldehyde and 2.50 g (11.3 mmol) of diethyl benzylphosphonate in 35 mL of tetrahydrofuran was added 1.0 g (17.8 mmol) of potassium hydroxide. The reaction mixture was stirred under reflux for 1 h and was then allowed to cool. Filtration removed insoluble solids, which were washed with THF. The washings and the original filtrate

(26) Paquette, L. A.; Stucki, H. *J. Org. Chem.* **1966**, *31*, 1232.
(27) ($C_{19}H_{17}N_3O \cdot HCl \cdot H_2O$) Calcd: H, 5.63. Found: 6.10. C, N, and Cl analyses were in accord.
(28) A forthcoming paper will present the details of a modeling study which relates the conformational characteristics of a series of selected imidazo[1,2-*a*]pyridines and -pyrazines, as determined using the SYBYL and MacroModel programs, to their in vitro inhibition of the gastric proton pump enzyme H^+/K^+-ATPase.

were combined, and solvent was removed under reduced pressure. The residual material was dissolved in dilute hydrochloric acid, and the solution was first washed with ether and was then basified by the addition of 15% aqueous sodium hydroxide solution. Extraction with methylene chloride and evaporation of solvent under reduced pressure gave an oil which spontaneously solidified on standing. The resultant solid was dissolved in 20 mL of hot acetonitrile, the solution was allowed to cool, and a small amount of insoluble solid was removed by filtration. The filtrate was concentrated to approximately 10 mL and was cooled to below room temperature. Filtration of the resultant crystals gave 800 mg (39%) of analytically pure title compound **6b**, mp 115–118 °C, identified as the trans isomer on the basis of an observed coupling constant of 16 Hz for the olefinic protons (100 MHz; acetone-d_6). Anal. ($C_{13}H_{12}N_2$) C, H, N.

α-Halo Ketone Intermediates 7. 3-Bromobutan-2-one (**7a**) was available from Eastman Kodak Co. Bromopropan-2-one, as the dimethyl ketal (**7b**), 2-chlorocyclopentanone (**7d**), and 2-chlorocyclohexanone (**7e**) were obtained from the Aldrich Chemical Co. The preparation of 2-bromopentan-3-one (**7c**) has been described previously.[1]

Substituted Imidazo[1,2-*a*]pyridines and Imidazo[1,2-*a*]pyrazines. Method A. 8-Formyl-2-methylimidazo[1,2-*a*]pyridine (9). A mixture of 92.8 g (0.76 mol) of 2-aminonicotinaldehyde and 114.5 g (0.84 mol) of bromopropan-2-one (derived by conventional methods from the commercially available dimethyl ketal **7b**) in 980 mL of dioxane was stirred first at room temperature for 2 h and then at 65 °C for 14 h. The solid which separated was isolated by filtration, dissolved in 800 mL of absolute ethanol, and heated at reflux for 6 h. The reaction mixture was allowed to cool, ethanol was removed under reduced pressure, and the residue was treated with 138 mL of 6 N hydrochloric acid in 750 mL of water for 0.5 h. The acidic aqueous layer was washed with two 300-mL portions of ether, cooled in an ice–water bath, and made basic by the addition of 78 mL of 50% aqueous sodium hydroxide solution and 25 g of solid sodium bicarbonate. The aqueous layer was extracted with methylene chloride, and the combined extracts were dried over anhydrous sodium sulfate. Drying agent was removed by filtration, and solvent was removed from the filtrate under reduced pressure. The residual material was crystallized from isopropyl ether to obtain 29 g (24%) of analytically pure title compound **9**, mp 140–143 °C. Anal. ($C_9H_8N_2O$) C, H, N.

The substituted imidazo[1,2-*a*]pyridines **20–22** and imidazo[1,2-*a*]pyrazine **37** were prepared by reacting the appropriately substituted 2-aminopyridine or -pyrazine and halo ketone according to method A, as described above.

Method B. 3-(Cyanomethyl)-2-methyl-8-((*Z*/*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine (15, 16) via 2-Methyl-8-((*Z*/*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine (13, 14). 8-Trans-Substituted Series. (a) 8-(Hydroxymethyl)-2-methylimidazo[1,2-*a*]pyridine. To a stirred suspension of 30.0 g (0.187 mol) of 8-formyl-2-methylimidazo[1,2-*a*]pyridine (**9**) in 200 mL of isopropyl alcohol, maintained at 0 °C in an ice–water bath, was added portionwise 5.55 g (0.146 mol) of sodium borohydride. When addition was complete, the mixture was allowed to warm to room temperature and was stirred for an additional 2 h. The bulk of the solvent was removed under reduced pressure. The residue was treated with 300 mL of aqueous sodium chloride solution and was then extracted with three 100-mL portions of methylene chloride. The aqueous layer was saturated with sodium chloride and was again extracted with methylene chloride. The combined extracts were dried over anhydrous sodium sulfate. Drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure to afford 26.0 g (88%) of a crude yellow solid, which was dissolved in boiling ethyl acetate and treated with decolorizing carbon. The carbon was filtered out, and the filtrate was allowed to cool to room temperature, which resulted in the precipitation of 21.4 g (73%) of 8-(hydroxymethyl)-2-methylimidazo[1,2-*a*]pyridine with mp 132–137 °C. This material was used without further purification in the following reaction.

(b) 8-(Chloromethyl)-2-methylimidazo[1,2-*a*]pyridine. To a stirred ice-cold solution of 21.4 g (0.132 mol) of 8-(hydroxymethyl)-2-methylimidazo[1,2-*a*]pyridine in 400 mL of methylene chloride was added dropwise 31.4 g (0.264 mol) of thionyl chloride. When addition was complete, the cooling bath was removed, and stirring was continued at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in water. The aqueous solution was adjusted to pH 8 by the addition of concentrated ammonium hydroxide and was then extracted with methylene chloride. The combined extracts were washed successively with water and saturated aqueous sodium chloride solution and were dried over anhydrous sodium sulfate. Drying agent was filtered out, and the filtrate was concentrated under reduced pressure to provide 19.0 g of 8-(chloromethyl)-2-methylimidazo[1,2-*a*]pyridine as a light yellow solid, mp 110–112 °C, which was converted to the phosphonate derivative (see below) without further purification.

(c) Diethyl [(2-Methylimidazo[1,2-*a*]pyridin-8-yl)-methyl]phosphonate. A mixture of 37.7 g (0.209 mol) of 8-(chloromethyl)-2-methylimidazo[1,2-*a*]pyridine and 87.2 g (0.525 mol) of triethyl phosphite was heated at 145–150 °C for 2.5 h and was then allowed to cool to room temperature. Nitrogen gas was bubbled for 15 min through the mixture, which was then cooled to −10 °C and stirred with petroleum ether. The petroleum ether phase, containing excess triethyl phosphite and a relatively nonpolar impurity, was decanted and discarded. This treatment was repeated twice more, and the petroleum ether insoluble oil was dissolved in diethyl ether and filtered through sintered glass to remove a small quantity of dark particulate matter. Ether was removed from the filtrate under reduced pressure to obtain 51.1 g (86%) of the title phosphonate as an oil which was used in the next step of the process without further purification. ^{1}H NMR ($CDCl_3$): δ 7.86 (br d, J = 7 Hz, 1 H), 7.26 (s, 1 H), 7.23–7.03 (m, 1 H), 6.60 (t, J = 7 Hz, 1 H), 4.1 (apparent quintet, J = 7 Hz, 4 H, $POCH_2CH_3$), 3.58 (d, J = 22 Hz, 2 H, PCH_2), 2.51 (s, 3 H), 1.23 (t, J = 7 Hz, 6 H).

(d) 2-Methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine (13). To a mechanically stirred, ice–water-cooled suspension of 11.6 g (0.291 mol) of a 60% dispersion of sodium hydride (prewashed by decantation with petroleum ether) in 50 mL of dimethoxyethane was added dropwise a solution of 48.5 g (0.172 mol) of diethyl [(2-methylimidazo[1,2-*a*]pyridin-8-yl)-methyl]phosphonate and 20.3 g (0.192 mol) of benzaldehyde in 350 mL of dimethoxyethane. The resultant mixture was allowed to warm to room temperature, and stirring was continued overnight. After 18 h solvent was removed under reduced pressure, and the residue was dissolved in water and extracted four times with methylene chloride. The combined extracts were washed successively with water and brine and were dried over anhydrous sodium sulfate. The drying agent was filtered out, the solvent was evaporated from the filtrate under reduced pressure, and the residue was pumped under high vacuum to obtain a crude solid. This crude material was triturated thoroughly with petroleum ether at −10 °C and was then dissolved in diethyl ether and filtered (sintered glass) to remove dark insoluble solids. The filtrate was concentrated under reduced pressure, and the light brown residual solid thus obtained was dried under high vacuum to afford 36.1 g (89%) of the title olefin of sufficient purity to be directly usable in the next step of the synthetic sequence. A portion of this material was flash chromatographed [silica gel; elution with ethyl acetate–petroleum ether (1:3)] to obtain an analytically pure sample of the title compound **13**, mp 100–102 °C, identified as the trans isomer on the basis of an observed coupling constant of 16 Hz for the olefinic protons ($CDCl_3$; 100 MHz). Anal. ($C_{16}H_{14}N_2$) C, H, N.

(e) 3-[(Dimethylamino)methyl]-2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine. To a mixture of 16.0 g (68 mmol) of **13** and 2.24 g (74 mmol) of paraformaldehyde in 300 mL of ethanol was added a solution of 5.60 g (68.7 mmol) of dimethylamine hydrochloride in 50 mL of ethanol. The resultant mixture was refluxed for 2 h. Ethanol was removed under reduced pressure, and the residue was dissolved in chloroform and stirred with an excess of 1.1 M aqueous sodium bicarbonate. The layers were separated, and the chloroform phase was washed with aqueous sodium bicarbonate (2 × 200 mL) and dried over anhydrous sodium sulfate. Drying agent was filtered out, and the filtrate was concentrated under vacuum to obtain a crude product, which was treated with methylene chloride and filtered to remove insoluble solids. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel,

eluting with ethyl acetate–petroleum ether mixtures in a stepped gradient of 80, 83, 86, and 89% ethyl acetate, followed by ethyl acetate containing first 2% and then 10% ethanol. Thus was obtained 15.3 g (77%) of the title compound as a yellow solid, mp 127–130 °C, which was utilized directly in the next synthetic step. A portion of this product was converted to its dihydrochloride salt by treatment with ethereal hydrogen chloride. Recrystallization from methanol–ethyl acetate gave the dihydrochloride as an analytically pure white solid, mp >250 °C. Anal. ($C_{19}H_{21}N_3 \cdot 2HCl$) C, H, N, Cl.

(f) *N,N,N*,2-Tetramethyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine-3-methanaminium Methyl Sulfate. A solution of 11.4 g (39.2 mmol) of 3-[(dimethylamino)methyl]-2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine and 6.18 g (49.0 mmol) of dimethyl sulfate in 400 mL of acetone was stirred at room temperature for 20 h. Volatiles were removed under reduced pressure, and the residue was allowed to triturate in ether for 60 h. Filtration and washing with ether under a blanket of nitrogen yielded 16.2 g (99%) of the title compound as a white solid, which was dried under high vacuum and used without further purification in the preparation of **15**.

(g) 3-(Cyanomethyl)-2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine (15). A mixture of 16.2 g (38.7 mmol) of *N,N,N*,2-tetramethyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]-pyridine-3-methanaminium methyl sulfate salt, 14.3 g (220 mmol) of potassium cyanide, and 2.67 g (10.1 mmol) of 18-crown-6 in 600 mL of acetonitrile was refluxed for 4 h. The resultant suspension was allowed to cool and was then filtered to remove insoluble matter. The filtrate was concentrated under vacuum, and the residual oil was dissolved in chloroform, washed successively with 0.5 M aqueous sodium bicarbonate (2 × 200 mL), water (1 × 200 mL), and brine (1 × 200 mL), and dried over anhydrous sodium sulfate. Drying agent was removed by filtration, and the filtrate was evaporated under reduced pressure to obtain a solid. The crude product was triturated thoroughly with petroleum ether, filtered, and chromatographed on silica gel, eluting with ethyl acetate–petroleum ether (1:1), to obtain 9.27 g (87%) of **15** as a light yellow solid, mp 133–136 °C. Anal. ($C_{18}H_{15}N_3$) C, H, N.

8-Cis-Substituted Series. (a) 2-Methyl-8-((*Z*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine (14). A mixture of 19.4 g (49.8 mmol) of benzyltriphenylphosphonium chloride and 2.0 g (50 mmol) of powdered sodium hydroxide was stirred for 1.5 h at room temperature in 45 mL of dioxane containing 0.4 mL of added water. To the resultant yellow suspension was added 7.68 g (48.0 mmol) of 8-formyl-2-methylimidazo[1,2-*a*]pyridine (**9**), and the mixture was stirred for 19 h at room temperature. Another 5.10 g (0.127 mol) of sodium hydroxide was added in one portion, and the mixture was stirred for an additional 2 h at room temperature. Dioxane was removed at ambient temperature under high vacuum. The residual semisolid was dissolved in ether and diluted with petroleum ether to precipitate triphenylphosphine oxide, which was removed by filtration. The filtrate was evaporated under reduced pressure, and the residue was flash chromatographed on silica gel, eluting with ethyl acetate–petroleum ether (1:3), to obtain 6.29 g (45%) of the title olefin **14**, mp 80–87 °C, identified as the cis isomer on the basis of an observed coupling constant of 12 Hz for the olefinic protons ($CDCl_3$, 100 MHz). Anal. ($C_{16}H_{14}N_2 \cdot 0.33H_2O$) C, H, N. In addition, 1.28 g (11%) of the trans isomer (**13**) was also isolated.

(b) 3-(Cyanomethyl)-2-methyl-8-((*Z*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine (16). By a series of transformations directly analogous to those described for the trans series in steps (e), (f), and (g) above, compound **14** was converted to the corresponding cyanomethyl derivative, title compound **16**, mp 134–136 °C (as a 0.1 hydrate). Anal. ($C_{18}H_{15}N_3 \cdot 0.1H_2O$) C, H, N.

The 3-cyanomethyl moiety of 2-methyl-8-(phenylpropenyl)-imidazo[1,2-*a*]pyridines **33** and **34** was introduced by the application of method B to compounds **31** and **32**, respectively, the preparation of which is described below.

2-Methyl-8-((*E*)-3-phenyl-1-propenyl)imidazo[1,2-*a*]pyridine (31) and 2-Methyl-8-((*E*)-3-phenyl-2-propenyl)imidazo[1,2-*a*]pyridine (32). (a) 2-Methyl-8-(1-hydroxy-3-phenylpropyl)imidazo[1,2-*a*]pyridine. A solution of 25 g (0.14 mol) of 2-phenylethyl bromide in 50 mL of dry ether was added rapidly with vigorous stirring to 20 g (0.82 mol) of magnesium turnings. Five drops of ethylene bromide was added to the mixture. When the reaction mixture began to reflux spontaneously, a solution of 132 g (0.71 mol) of 2-phenylethyl bromide in 350 mL of dry ether was added at such a rate as to maintain gentle reflux. When addition was complete, the mixture was refluxed for another 6 h and was then allowed to stir at room temperature overnight. The clear, dark solution of (2-phenylethyl)magnesium bromide, approximately 2.1 M in concentration, was used without further treatment.

To a mechanically stirred, water-bath-cooled solution of 40 g (0.25 mol) of 8-formyl-2-methylimidazo[1,2-*a*]pyridine (**9**) in 750 mL of tetrahydrofuran (dried over 3A molecular sieves) was added 160 mL (ca. 0.34 mol) of the approximately 2.1 M solution of (2-phenylethyl)magnesium bromide in ether, prepared as described above. The Grignard reagent was added over a 20-min period during which time the temperature rose from 22 to 31 °C. After 18 h of stirring at room temperature, the reaction mixture was cooled to 6–8 °C in an ice–water bath, and 50 mL of a saturated aqueous solution of ammonium chloride was added, followed by 250 mL of water. The layers were separated, and the organic layer was dried over anhydrous sodium sulfate. Drying agent was filtered out, and the filtrate was evaporated under reduced pressure. The residue was partitioned between 150 mL of ether and 290 mL of 0.86 M hydrochloric acid. The phases were separated, and the aqueous phase was washed with ether (2 × 150 mL), basified with 68 mL of 15% (w/v) aqueous sodium hydroxide solution, and extracted with ether (3 × 165 mL). The combined extracts were dried over anhydrous sodium sulfate, the drying agent was removed by filtration, and the filtrate was stripped under reduced pressure to obtain 56 g (84%) of crude title compound. TLC [silica gel; methylene chloride–methanol–ammonium hydroxide (30:10:1)] of this crude material showed one major component and one minor side product. The crude product exhibited the following ^1H NMR spectrum (90 MHz; $CDCl_3$): δ 7.83 (d, $J \cong 7.5$ Hz, 1 H, H-5), 7.25–6.7 (m overlapped by s at 7.11, 7 H, C_6H_5 + H-3 + H-7), 6.51 (t, $J \cong 7.5$ Hz, 1 H, H-6), 4.95 (br t overlapped by br s for OH, $J \cong 7$ Hz, 1 H, CHO), 2.85–2.6 (m, 2 H, $C_6H_5CH_2$), 2.35–1.9 (m, 2 H, $C_6H_5CH_2CH_2$), 2.26 (s, 3 H, CH_3). This crude alcohol was used without further treatment in step (b).

(b) 2-Methyl-8-(1-chloro-3-phenylpropyl)imidazo[1,2-*a*]pyridine. To a magnetically stirred solution of 46 g (0.17 mol) of 2-methyl-8-(1-hydroxy-3-phenylpropyl)imidazo[1,2-*a*]pyridine in 980 mL of methylene chloride was added at room temperature over 0.5 h a solution of 21.1 g (0.19 mol) of thionyl chloride in 200 mL of methylene chloride. The reaction mixture was stirred for 1 h at room temperature and was then poured onto 800 mL of crushed ice and basified to pH 8 by the addition first of 6 M aqueous sodium hydroxide, followed by solid sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with methylene chloride (2 × 150 mL). The combined extracts were washed successively with water (2 × 150 mL) and brine (300 mL) and were dried over anhydrous magnesium sulfate. The drying agent was filtered out, and the filtrate was stripped under reduced pressure to obtain 40 g (81%) of the crude title compound as a dark oil. A 3.74-g (13 mmol) sample of this product was stirred in 50 mL of ethyl acetate and filtered to remove a small amount of insoluble gum. The filtrate was acidified with 3.9 M ethereal hydrogen chloride and diluted with 150 mL of ether to produce a precipitate, which was filtered, washed with ether, and twice recrystallized from methanol–ethyl acetate to obtain 2.42 g (58%) of the hydrochloride salt of the title compound, mp 196.5–197.0 °C dec. Anal. ($C_{17}H_{17}N_2Cl$) C, H, N, Cl.

(c) 2-Methyl-8-((*E*)-3-phenyl-1-propenyl)imidazo[1,2-*a*]pyridine (31) and 2-Methyl-8-((*E*)-3-phenyl-2-propenyl)imidazo[1,2-*a*]pyridine (32). A solution containing 121 g (0.42 mol) of 2-methyl-8-(1-chloro-3-phenylpropyl)imidazo[1,2-*a*]-pyridine and 64.5 g (0.42 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 1.2 L of 1.4-dioxane was refluxed under nitrogen for 21 h. The solvent was removed in vacuo at 40 °C, and the residual oil was dried under vacuum at 50 °C. The residue was extracted by stirring first with 500 mL of ether. The ether was decanted, 500 mL of fresh ether was added, and the mixture was stirred for 18 h at room temperature. This extraction–decantation process was repeated with two successive 600-mL volumes of ethyl acetate.

The extracts were stripped under reduced pressure, the residues were combined and dissolved in 150 mL of ethyl acetate, and this solution was filtered through a 1.5-in. layer of silica gel (Baker 3405) on a 600-mL coarse sintered glass funnel. The silica bed was washed with three 600-mL portions of ethyl acetate, and the filtrates were combined and stripped under reduced pressure to obtain a partially purified mixture of **31** and **32**, present in approximately 1:1 ratio, as ascertained from the ^{1}H NMR spectrum (80 MHz). A rough separation of the two desired components was achieved by flash chromatography of the mixture on silica gel: eluting with ethyl acetate–hexane mixtures containing from 30 to 50% ethyl acetate, 19.1 g (18%) of partially purified **31** was obtained. Increasing the proportion of ethyl acetate in the eluent to 75% effected the isolation 30.2 g (29%) of partially purified **32**. Final purification of the title compounds was conducted as follows: partially purified **31** was triturated with 75 mL of hexane, filtered, and crystallized from 50 mL of ether to obtain 11.3 g (11%) of analytically pure **31**, mp 73.5–78 °C. Anal. ($C_{17}H_{16}N_2$) C, H, N. Partially purified **32** was resubjected to flash chromatography on silica gel, eluting with ethyl acetate–hexane in a stepped gradient starting with 30% ethyl acetate and increasing to 50% and then 75% ethyl acetate. Thus was obtained 23.3 g (22%) of analytically pure **32** as an oil containing 0.25 mol of water. Anal. ($C_{17}H_{16}N_2 \cdot 0.25H_2O$) C, H, N. The mass spectrum (EI) of **31** showed a base peak at (M – 91) (loss of benzyl), whereas the base peak in the spectrum of **32** corresponded to the loss of a phenylethenyl group with proton transfer, $(M - 102)^+$. The ^{1}H NMR spectrum (270 MHz; DMSO-d_6) of **31** revealed the olefinic protons (δ 6.76 and 7.43, respectively), which exhibited a coupling constant of approximately 16 Hz. The olefinic protons could not be discerned in the spectrum of **32**, even at a field strength of 600 MHz. The assignments of the structures of **31** and **32**, based initially on their spectroscopic characteristics and ultimately upon the X-ray analyses of their cyanomethylated derivatives (**33** and **34**, respectively), are discussed in the text.

Method C. 3-Amino-2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine Hydrochloride (17). (a) 2-Methyl-3-nitroso-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine. To a solution of 5.0 g (20 mmol) of 2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine (**13**) in 40 mL of acetic acid and 100 mL of water, maintained at 5 °C, was added portionwise over 10 min 2.7 g (40 mmol) of sodium nitrite. The mixture was stirred at 0–5 °C for 20 min before the cooling bath was removed, and the mixture was allowed to stir for 2 h at room temperature. Another 50 mL of water was then added, and the solid present was isolated by filtration and washed with four 500-mL portions of water. Recrystallization from ethyl acetate gave 4.04 g (73%) of the title nitroso compound, mp 158–160 °C.

(b) 3-Amino-2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine Hydrochloride (17). To a stirred mixture of 3.0 g (10 mmol) of 2-methyl-3-nitroso-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine in 50 mL of glacial acetic acid and 50 mL of water at 0 °C was added in portions 3.0 g (46 mmol) of zinc powder. When addition was complete, the mixture was stirred at 0 °C for 1 h and was then filtered through Celite. The filtrate was diluted with water and methylene chloride and was basified at 10 °C by the addition of 80 mL of 5 N aqueous sodium hydroxide. The resultant emulsion was filtered through Celite, and the Celite pad was washed thoroughly with hot chloroform. The layers of the filtrate were separated, and the aqueous phase was extracted with chloroform. The combined organic extracts were washed successively with water and brine and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was evaporated under reduced pressure to obtain 1.0 g (40%) of the free base form of the title amine. The free base was dissolved in ethyl acetate and treated with 3.4 N ethereal hydrogen chloride. The resultant precipitate was recrystallized from methanol–ethyl acetate to obtain hydrochloride **17** as a 0.67 hydrate, mp 241–250 °C dec. Anal. ($C_{16}H_{15}N_3 \cdot HCl \cdot 0.67H_2O$) C, H, N, Cl.

In an analogous manner, compound **18**, the cis isomer of **17**, was prepared from **14**. Compound **35** was synthesized by the application of method C to 2-methyl-8-((*E*)-3-phenyl-1-propenyl)imidazo[1,2-*a*]pyridine. Compound **36** was prepared via a modification of method C, as described below.

3-Amino-2-methyl-8-((*E*)-3-phenyl-2-propenyl)imidazo[1,2-*a*]pyridine Hydrochloride (36). A solution of 2.54 g (10.0 mmol) of 2-methyl-8-((*E*)-3-phenyl-1-propenyl)imidazo[1,2-*a*]pyridine (**32**) and 5.8 mL (5.3 g, 50 mmol) of *n*-butyl nitrite in 75 mL of tetrahydrofuran (predried over 3A molecular sieves) was heated at 50 °C for 45 min. A second 5.8-mL quantity of *n*-butyl nitrite was added, and heating was continued for another 20 min, whereupon a third 5.8-mL volume of *n*-butyl nitrite was added, and the reaction mixture was maintained at 50 °C for a final 55-min period. Volatiles were removed under reduced pressure. The residue was dissolved in 50 mL of glacial acetic acid, and to the solution was added 10.2 g (160 mmol) of powdered zinc, introduced portionwise over 8 min as the temperature was permitted to rise from 22 to 38 °C. The reaction mixture was cooled to room temperature and stirred for 45 min. It was then poured into 120 mL of ice water, basified by the addition of 96 mL (0.86 mol) of 9 M aqueous sodium hydroxide, and stirred with 150 mL of methylene chloride. The resultant mixture was filtered through Celite, the layers of the filtrate were separated, and the aqueous phase was extracted with three 100-mL portions of methylene chloride. The combined extracts were washed once with 100 mL of brine and were dried over anhydrous sodium sulfate. Drying agent was removed by filtration, and the filtrate was evaporated under reduced pressure to obtain 2.71 g of title compound **36** as the crude free base. The crude product was subjected to flash chromatography on silica gel, eluting with ethyl acetate–ammonium hydroxide (99:1) to obtain 0.81 g (30%) of the pure free base form of **36**. To an ethereal solution of this purified free base was added 0.9 mL (3.06 mmol) of 3.4 M ethereal hydrochloric acid. Filtration of the resulting precipitate and washing with ether yielded 0.81 g (26%) of **36**·HCl as the 0.33 hydrate, mp 130–132 °C dec. Anal. ($C_{17}H_{17}N_3 \cdot HCl \cdot 0.33H_2O$) C, H, N, Cl.

Method D. 2,3-Dimethyl-7-(2-phenylethenyl)imidazo[1,2-*a*]pyridine (23). A mixture of 6.60 g (33.7 mmol) of 2-amino-4-(2-phenylethenyl)imidazo[1,2-*a*]pyridine[22] and 15 mL (21.8 g, 144 mmol) of 3-bromobutan-2-one was stirred at 110–120 °C for 20 min. The reaction mixture was cooled, diluted with 200 mL of an ice–water mixture, and adjusted to pH 8–9 by the addition of aqueous sodium hydroxide. After further dilution with 200 mL of water and filtration to remove insoluble matter, the filtrate was extracted with two 600-mL volumes of chloroform. The combined extracts were washed with 200 mL of water and dried over anhydrous potassium carbonate. Drying agent was filtered out, and the filtrate was evaporated under reduced pressure to obtain 5.6 g of crude product, which was crystallized from ethanol. This yielded 1.4 g (21%) of recovered aminopyridine. The mother liquor was chromatographed on silica gel. Elution with a stepped gradient ranging from methylene chloride to chloroform to chloroform–ethyl acetate (4:1) yielded 2.2 g of partially purified title compound, which was recrystallized from ethyl acetate to obtain 1.0 g (12%) of **23**, mp 158–160 °C. Anal. ($C_{17}H_{16}N_2$) C, H, N. The olefinic protons could not be discerned in the ^{1}H NMR spectrum (80 MHz, $CDCl_3$), and the product was presumed to be a mixture of cis and trans isomers.

Compound **25** was prepared from 2-amino-6-(2-phenylethenyl)pyridine by using method D.

2,3-Dimethyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine Hydrochloride (11). (a) 2,3-Dimethyl-8-formylimidazo[1,2-*a*]pyridine (10). A solution of 207 g (1.7 mol) of 2-aminonicotinaldehyde and 300 g (2.0 mol) of 3-bromobutan-2-one in 150 mL of methylene chloride was heated on a steam bath, allowing the solvent to distill and the residue to heat at approximately 100 °C for 2 h. The reaction mixture was dissolved in dilute hydrochloric acid and was extracted with ether. The aqueous layer was neutralized with 20% sodium hydroxide, and the resultant precipitate was filtered to obtain the crude product. Recrystallization from ethyl acetate gave 73 g (25%) of compound **10**, mp 145–148 °C.

(b) 2,3-Dimethyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine Hydrochloride (11). A stirred solution of 116 g (0.51 mol) of diethyl benzylphosphonate in 300 mL of dimethylformamide was treated with 28 g (0.52 mmol) of sodium methoxide. To the resultant solution, 80 g (0.46 mol) of **10** was added portionwise over 35 min, while the temperature was maintained between 30–35 °C. After stirring at room temperature for 2.5 h, the solvent was removed under reduced pressure, and the residue was partitioned between 300 mL of methylene chloride and 500 mL of water. The methylene chloride layer was separated and

solvent removed under reduced pressure. The residual solid was triturated with three successive 100-mL portions of ether. The trituration mixtures were filtered, and the ether filtrates were combined and treated with ethereal hydrogen chloride. The resultant precipitate was filtered and recrystallized from methanol to obtain 90.5 g (69%) of the title hydrochloride salt **11**, mp 243–255 °C, identified as the trans isomer on the basis of an observed 16-Hz coupling constant for the olefinic protons in the ^{1}H NMR spectrum (100 MHz, $CDCl_3$). As noted in the text, the structure of **11**·HCl has been definitively established by X-ray crystallography. Anal. ($C_{17}H_{16}N_2$·HCl·CH_3OH) C, H, N, Cl.

2,3-Dimethyl-8-((*Z*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine Hydrochloride (12). A stirred mixture of 2.00 g (11.5 mmol) of 2,3-dimethyl-8-formylimidazo[1,2-*a*]pyridine (see section (a) under preparation of **11** above), 4.70 g (12.0 mmol) of benzyltriphenylphosphonium chloride, and 1.5 g (37.5 mmol) of sodium hydroxide in 20 mL of dioxane containing 0.5 mL of water was heated at 75 °C for 2.5 h. The reaction mixture was allowed to cool, solids were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was partitioned between 200 mL of 1 N hydrochloric acid and 300 mL of ethyl acetate, and the mixture was filtered to remove solids. The layers of the filtrate were separated, and the aqueous phase was washed with ethyl acetate and then basified with 10% aqueous sodium hydroxide and extracted with three 40-mL portions of methylene chloride. The combined extracts were evaporated under reduced pressure to obtain a solid, which was chromatographed on silica gel, eluting with methylene chloride–methanol (99:1), to obtain approximately 0.7 g (21%) of **12** as the free base. Initial tentative identification of the product as the cis isomer was based upon the apparent observation (one proton only) of a 12-Hz coupling constant for the olefinic protons in the ^{1}H NMR spectrum (100 MHz, $CDCl_3$). As noted in the text, the assigned structure has been confirmed by an X-ray crystallographic study of the hydrochloride salt. Treatment of the free base with ethereal hydrogen chloride, filtration, and recrystallization of the crude precipitate from methanol–ether yielded the hydrochloride salt of **12**, mp 174–177 °C. Anal. ($C_{17}H_{16}N_2$·HCl) C, H, N, Cl.

3-Ethyl-2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine Hydrochloride (19). (a) 3-Acetyl-2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine. To a stirred, ice-cooled solution of 20.5 g (87.6 mmol) of **13** in 100 mL of acetyl chloride was added portionwise 24.0 g (180 mmol) of aluminum chloride. The resultant mixture was stirred for at 0 °C for 1 h and then at ambient temperature for 2 h, whereupon another 24.0 g (180 mmol) of aluminum chloride was added and stirring continued for an additional hour. Ether (400 mL) was added to the reaction mixtures, resulting in the precipitation of a tarry mass. The solvent was decanted, and the tar was first triturated repeatedly with ether and then treated with 400 mL of an ice–water mixture, which was made strongly alkaline by the addition of 25% aqueous sodium hydroxide. The aqueous suspension was treated with 200 mL of methylene chloride, the mixture was filtered, and the layers of the filtrate were separated. The methylene chloride extract was dried over anhydrous sodium sulfate. Drying agent was filtered out, and the filtrate was evaporated under reduced pressure to obtain 13.0 g (54%) of crude material, which was chromatographed on silica gel, eluting with ethyl acetate. The purified title ketone thus obtained was used without further treatment in the reduction procedure which follows.

(b) 3-Ethyl-2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine Hydrochloride (19). A mixture of 3.6 g (13 mmol) of 3-acetyl-2-methyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine, 2.80 g (50.0 mmol) of powdered potassium hydroxide, and 2.50 g (50 mmol) of hydrazine hydrate in 32 mL of ethylene glycol was heated at 95 °C for 0.5 h and then at 205–210 °C for 1 h. After cooling, the reaction mixture was treated with 350 mL of water, and the resultant mixture was extracted with four 100-mL portions of ether. The combined ether extracts were evaporated under reduced pressure, and the residue was chromatographed on silica gel, eluting with methylene chloride–methanol (90:10), to obtain 1.8 g (53%) of the free base form of **19**. Treatment of the free base with ethereal hydrogen chloride gave the crude salt, which was recrystallized from methanol–acetonitrile to obtain the pure hydrochloride salt of **19**, mp 243–247 °C. Anal. ($C_{18}H_{18}N_2$·HCl) C, H, N, Cl. The trans geometry of the double bond of **19** derives from its method of preparation from **13**, the geometry of which was established by ^{1}H NMR, as noted above.

2,3-Dimethyl-6-(2-phenylethenyl)imidazo[1,2-*a*]pyridine (24). (a) 6-Bromo-2,3-dimethylimidazo[1,2-*a*]pyridine. Commercially available 2-amino-5-bromopyridine (**6d**) and 3-bromobutan-2-one (**7a**) were condensed in refluxing ethanol in accordance with method A and produced the hydrobromide salt of the title imidazo[1,2-*a*]pyridine, mp >260 °C, in 38% yield. The free base derived from this salt was utilized in step (b).

(b) 2,3-Dimethyl-6-(2-phenylethenyl)imidazo[1,2-*a*]pyridine (24). A mixture of 14.3 g (64 mmol) of 5-bromo-2,3-dimethylimidazo[1,2-*a*]pyridine, 16.6 g (160 mmol) of styrene, 9.9 g (118 mmol) of sodium bicarbonate, 0.33 g (1.47 mmol) of palladium acetate, and 1.5 g (5 mmol) of tri-*o*-tolylphosphine, in 250 mL of dry *N*,*N*-dimethylformamide was heated for 16 h at 120–130 °C. The temperature was raised to 135 °C, and the mixture was stirred for another 24 h. The disappearance of starting aryl bromide was monitored by TLC [silica gel; ethyl acetate–hexane; two elutions]. The reaction mixture was allowed to cool, and solvent was removed under reduced pressure. The residue was treated with 300 mL of water and extracted with two 300-mL portions of ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate. Drying agent was filtered out, and the filtrate was evaporated under reduced pressure to obtain 14 g of crude product. Recrystallization from ethyl acetate–hexane yielded 4.9 g (31%) of compound **24**, mp 194–196 °C. Anal. ($C_{17}H_{16}N_2$) C, H, N. The olefinic protons could not be discerned in the ^{1}H NMR spectrum (80 MHz, $CDCl_3$); therefore, a definitive assignment of double-bond geometry could not be made. However, the mechanistic studies and experimental results reported by Heck and co-workers would suggest that predominance of the trans-substituted product is to be expected.[23-25]

2,3-Dimethyl-8-[(*E*)-2-(3-thienyl)ethenyl]imidazo[1,2-*a*]pyridine Hydrochloride (26). (a) Diethyl [(2,3-Dimethylimidazo[1,2-*a*]pyridin-8-yl)methyl]phosphonate. 2,3-Dimethyl-8-formylimidazo[1,2-*a*]pyridine was prepared from 2-aminonicotinaldehyde and 3-bromobutan-2-one in a manner analogous to that described in detail for the preparation of compound **9** The conversion of this 8-formyl derivative to the title phosphonate was accomplished via a three-step reduction–chlorination–phosphonation sequence that was in turn directly analogous to steps (a), (b), and (c) in the syntheses of compounds **13**/**15** and **14**/**16**, as described above. The title phosphonate was an oil which exhibited the following ^{1}H NMR (60 MHz, $CDCl_3$) spectrum: 7.73 (d, $J \cong 6$ Hz, 1 H, H-5), 7.53–7.16 (m, 1 H, H-7), 6.76 (t, $J \cong 6$ Hz, 1 H, H-6), 4.43–3.83 (m, 4 H, OCH_2), 3.66 (d, $J = 22$ Hz, 2 H, PCH_2), 2.43 and 2.38 (2 s, 6 H, 2- + 3-CH_3),, 1.23 (t, $J = 7$ Hz, 6 H, OCH_2CH_3).

(b) 2,3-Dimethyl-8-[(*E*)-2-(3-thienyl)ethenyl]imidazo[1,2-*a*]pyridine Hydrochloride (26). A solution of 3.5 g (11.8 mmol) of the above phosphonate ester in 10 mL of *N*,*N*-dimethylformamide was treated with 0.80 g (14.8 mmol) of sodium methoxide, followed by the portionwise addition of 1.5 g (13.3 mmol) of thiophene-3-carboxaldehyde in 2 mL of DMF over 25 min. After stirring at ambient temperature for 1.25 h, the reaction mixture was treated with 100 mL of brine and 200 mL of ether and stirred for an additional 2 h at room temperature. The mixture was filtered free of a small amount of insoluble matter, and the ether phase of the filtrate was separated and dried over anhydrous sodium sulfate. Drying agent was removed by filtration, and ethereal hydrogen chloride was added to the filtrate. The precipitated salt was isolated by filtration and recrystallized from a mixture of 20 mL of methanol in 130 mL of water to obtain 1.1 g (32%) of the hydrochloride salt of **26**, mp 255 °C dec. Anal. ($C_{15}H_{14}N_2S$·HCl) C, H, N, Cl. The ^{1}H NMR spectrum (100 MHz, $CDCl_3$) of a sample of free base generated from the purified hydrochloride substantiated the trans geometry of the double bond based on an observed coupling constant of 16 Hz for the olefinic protons.

2,3-Dimethyl-8-[(*Z*/*E*)-1-methyl-2-phenylethenyl]imidazo[1,2-*a*]pyridine Hydrochloride (27). (a) Diethyl [1-(2,3-Dimethylimidazo[1,2-*a*]pyridin-8-yl)ethyl]phosphonate. To a suspension of 400 mg (10 mmol) of sodium hydride (60% dispersion in oil; washed with petroleum ether) in 1,2-dimethoxyethane was added a solution of 2.01 g (6.78 mmol)

of diethyl [(2,3-dimethylimidazo[1,2-*a*]pyridin-8-yl)methyl]-phosphonate (see section (a) under preparation of compound **26** above) and 1.14 g (8.03 mmol) of methyl iodide in 20 mL of dimethoxyethane. The mixture was stirred at room temperature for 2 h and then at 35–45 °C for 4 h, during which time three additional 1.14-g (8.03 mmol) portions of methyl iodide were added at intervals. The progress of the reaction was monitored by thin-layer chromatography [silica gel; chloroform–ethanol–ammonium hydroxide (50:3:0.25)]. After cooling to room temperature, the reaction mixture was poured into water and extracted with three successive portions of methylene chloride. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. Drying agent was filtered out, and the filtrate was stripped under high vacuum to obtain 1.96 g (93%) of the title phosphonate as a red oil, which exhibited the following ^{1}H NMR (90 MHz; $CDCl_3$) spectrum: 7.77 (d, J = 6 Hz, 1 H, H-5), 7.51–7.31 (m, 1 H, H-7), 6.84 (t, J = 6 Hz, 1 H, H-6), 4.61–3.68 (m, 5 H, C*H*P(O)(O*CH*$_2$CH$_3$)$_2$), 2.45 and 2.39 (2 s, 6 H, 2- + 3-CH$_3$), 1.61 (dd, J = 7.5, 19 Hz, 3 H, PCHC*H*$_3$), 1.27 and 1.09 (2 t, J = 6 Hz, 6 H, P(O)(OCH$_2$C*H*$_3$)$_2$).

(b) 2,3-Dimethyl-8-[(*Z*/*E*)-1-methyl-2-phenylethenyl]-imidazo[1,2-*a*]pyridine Hydrochloride (27). A mixture of 3.86 g (12.4 mmol) of the above phosphonate and 1.46 g (13.8 mmol) of benzaldehyde in 25 mL of 1,2-dimethoxyethane was added dropwise to a suspension of 0.900 g (22.5 mmol) of sodium hydride (60% dispersion in oil) in 10 mL of dimethoxyethane. After 3 h of stirring at ambient temperature, TLC [silica gel; methylene chloride–methanol–ammonium hydroxide (100:5:0.5)] revealed the presence of a significant amount of unchanged starting material. The reaction mixture was heated for 2 h at 50–55 °C and then allowed to cool. Dimethoxyethane was removed under reduced pressure, and the residue was extracted with methylene chloride. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. Drying agent was filtered out, the filtrate was stripped under vacuum, and the residual oil was chromatographed on silica gel, eluting with methylene chloride to obtain the free base form of compound **27** as a sticky solid with the following ^{1}H NMR (100 MHz, $CDCl_3$) spectral characteristics: 7.75 (d, J = 7 Hz, 1 H, H-5), 7.62–7.21 (m, 6 H, C$_6$H$_5$ + =CH), 7.16 (d, J = 7 Hz, 1 H, H-7), 6.82 (t, J = 7 Hz, 1 H, H-6), 2.50 (d, $J \cong 1$ Hz, 3 H, =CCH$_3$), 2.46 and 2.40 (2 s, 6 H, 2- + 3-CH$_3$). The olefinic proton could not be discerned in the complex multiplet at δ 7.2–7.6, nor could any definitive conclusion be drawn from an analysis of the methyl region of the spectrum regarding the isomeric composition of **27**. However, comparison of the ^{1}H NMR spectrum of **27** with that of the analogous compound **28** (see below), which was an authenticated mixture of cis–trans isomers, suggested that **27** was predominantly one isomer. TLC (silica gel; methylene chloride–methanol–ammonia systems) showed an elongated spot, which was not resolvable into multiple components.

Treatment of an ether solution of free base **27** with 3.4 M ethereal hydrogen chloride gave a solid precipitate which was isolated by filtration and recrystallized from methanol–ethyl acetate to obtain 2.6 g (70%) of the hydrochloride salt of **27**, mp >200 °C. Anal. (C$_{18}$H$_{18}$N$_2$·HCl) C, H, N, Cl.

2,3-Dimethyl-8-[(*Z*/*E*)-2-methyl-2-phenylethenyl]-imidazo[1,2-*a*]pyridine (28). To an ice-cooled suspension of 0.53 g (13.3 mmol) of sodium hydride (60% dispersion in oil) in 6 mL of dimethoxyethane was added dropwise a solution containing 3.0 g (10.1 mmol) of diethyl [(2,3-dimethylimidazo[1,2-*a*]pyridin-8-yl)methyl]phosphonate (see section (a) under preparation of compound **26** above) and 1.32 g (11.0 mmol) of acetophenone in 25 mL of dimethoxyethane. When addition was complete, the cooling bath was removed, and the reaction mixture was allowed to stir at ambient temperature. The progress of the reaction was monitored by TLC [silica gel; methylene chloride–methanol–ammonium hydroxide (100:5:0.5)]. After 2.5 h at room temperature, the reaction was quenched by the addition of water and then evaporated under vacuum. The residue was partitioned between water and methylene chloride, the layers were separated, and the aqueous layer was reextracted with methylene chloride. The combined extracts were washed successively with water and brine and dried over anhydrous sodium sulfate. Drying agent was filtered out, and the filtrate was concentrated under reduced pressure to obtain the crude product. Flash chromatography on silica gel, eluting with ethyl acetate–petroleum ether (2:1), gave 1.81 g (68%) of compound **28** as a mixture (of indeterminante proportions) of cis and trans isomers, mp 73–95 °C. Anal. (C$_{18}$H$_{18}$N$_2$) C, H, N. Biological evaluation of **28** was conducted on this isomer mixture. However, further chromatography [silica gel; ethyl acetate–petroleum ether (1:1)] produced pure samples of the isomers, mp 84–88 °C and 102–111 °C, respectively, but the spectroscopic data did not permit a definitive assignment of geometry. In the ^{1}H NMR spectra, the olefinic protons could not be discerned, and the olefinic methyl groups showed very similar chemical shifts and proton couplings. An attempt to differentiate the isomers on the basis of coupling between the carbon of the olefinic methyl group and the olefinic proton was similarly inconclusive: both isomers exhibited a value of 8 Hz for this coupling.

2,3-Dimethyl-8-((*E*)-3-phenyl-1-propenyl)imidazo[1,2-*a*]-pyridine Hydrochloride (29) and 2,3-Dimethyl-8-((*E*)-3-phenyl-2-propenyl)imidazo[1,2-*a*]pyridine Hydrochloride (30). To a magnetically stirred suspension of 3.73 g (93.3 mmol) of a 60% dispersion of sodium hydride in 65 mL of dry dimethoxyethane was added a solution of 20.5 g (69.3 mmol) of diethyl [(2,3-dimethylimidazo[1,2-*a*]pyridin-8-yl)methyl]phosphonate (prepared as described above under section (a) of the synthesis of compound **26**) in 80 mL of dry dimethoxyethane, and the resultant mixture was stirred for 2.5 h at ambient temperature. The reaction mixture was cooled to approximately 10 °C, and a solution of 11.2 g (93.3 mmol) of phenylacetaldehyde in 30 mL of dry dimethoxyethane was added. The cooling bath was removed, and the reaction mixture was allowed to stir at room temperature for 3 h before diluting with 800 mL of water. The resultant mixture was then extracted with ether (1 × 300 mL and 2 × 200 mL), and the extracts were combined and dried over anhydrous sodium sulfate. Drying agent was filtered out, and the filtrate was evaporated under reduced pressure. The residual amber oil was flash chromatographed on silica gel, eluting with a stepped gradient of hexane, 1:1 ethyl acetate–hexane, and ethyl acetate. Thus were obtained the free base forms of the title compounds: 5.72 g (32%) of **29**, mp 68–82 °C, and 4.00 g (22%) of **30** as an oil. The position of the double bond in the two isomeric products was defined by analysis of their mass spectra, as described above for the 3-unsubstituted analogues, compounds **31** and **32**. The free base of **29** was treated with charcoal and recrystallized from isopropyl ether to obtain 3.02 g (16%) of a solid with mp 87.5–89 °C. This purified free base was dissolved in ether and treated with ethereal hydrogen chloride, thereby converting it to 3.05 g (14% yield) of the analytically pure hydrochloride salt of **29**, mp 201–204 °C. Anal. (C$_{18}$H$_{18}$N$_2$·HCl) C, H, N, Cl. The free base of **30** was similarly converted with ethereal hydrogen chloride to 2.53 g (12%) of the hemihydrate of **30**·HCl, mp 188.5–190 °C. Anal. (C$_{18}$H$_{18}$N$_2$·HCl·0.5H$_2$O) C, H, N. The olefinic proton coupling constants observed in the ^{1}H NMR spectra (400 MHz, CD_3OD) of the hydrochloride salts of **29** (ca. 15 Hz) and **30** (ca. 16 Hz), respectively, defined the geometry as trans in both cases.

2,3-Dimethyl-8-(phenylethynyl)imidazo[1,2-*a*]pyridine (38). (a) 8-Chloro-2,3-dimethylimidazo[1,2-*a*]pyrazine (37). As noted above, following the preparative method described for compound **9**, compound **37** was prepared by the reaction of 2-amino-3-chloropyrazine with 3-bromobutan-2-one.

(b) 2,3-Dimethyl-8-(phenylethynyl)imidazo[1,2-*a*]pyrazine (38). This reaction was run under an atmosphere of argon. The reaction vessel was charged with 546 mg (3.00 mol) of **37**, 1.8 mL (1.31 g, 13.0 mmol) of triethylamine and 735 mg (7.05 mmol, 98%) of phenylacetylene (Aldrich Chemical Co.). To the stirred mixture was added approximately 3 mg (0.015 mmol) of copper(I) iodide, followed by 42 mg (0.06 mmol) of bis(triphenylphosphine)palladium(II) chloride, and the resultant mixture was heated for 2.25 h at 70 °C. The reaction mixture was allowed to cool before treatment with methylene chloride, followed by evaporation under reduced pressure to obtain a slightly tacky, dark brown powder. Flash chromatography of this crude product on silica gel, eluting with ethyl acetate, gave 503 mg (68%) of analytically pure **38**. Crystallization from ethyl acetate gave a 0.25 hydrate, mp 208.5–210 °C dec. Anal. (C$_{16}$H$_{13}$N$_3$·0.25H$_2$O) C, H, N.

2,3-Dimethyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]-pyrazine Hydrochloride (39). A mixture of 3.00 g (12.1 mmol)

of compound **38** and 3.75 g of 5% palladium-on-calcium carbonate poisoned with lead (Lindlar catalyst) in 210 mL of ethanol was hydrogenated on a Parr shaker apparatus at 60 psi for 32 h at room temperature. Catalyst was removed by filtration through Celite, and the filtrate was evaporated under reduced pressure. The crude semisolid thus obtained was flash chromatographed on silica gel, eluting with chloroform–ethanol–ammonium hydroxide (90:1:0.15), to obtain 1.45 g (48%) of purified free base. An ether solution of this material was treated with 3.4 M ethereal hydrogen chloride, and the resultant precipitate was isolated by filtration and recrystallized from methanol–ethyl acetate to render 1.41 g (41%) of **39**·HCl, mp 250–256 °C. Anal. ($C_{16}H_{15}N_3$·HCl) C, H, N, Cl. The ^{1}H NMR spectrum (100 MHz, $CDCl_3$) of this isomerically homogeneous material exhibited two doublets (δ 8.14, 8.34) with a coupling constant of 16 Hz, corresponding to the respective olefinic protons, and thus identified **39** as the trans isomer. There was no evidence for the presence of the cis isomer in this reaction mixture.

8,9-Dihydro-2-methyl-9-phenyl-7*H*-imidazo[1,2-*a*]pyrano[2,3-*c*]pyridine-3-acetonitrile Hydrochloride (40). (a) 7-[(Dimethylamino)methyl]-8-hydroxy-2-methylimidazo[1,2-*a*]pyridine. A mixture of 24.0 g (0.128 mol) of 8-hydroxy-2-methylimidazo[1,2-*a*]pyridine-3-acetonitrile[1] and 26 g (0.141 mol) of *N*,*N*-dimethylmethyleneammonium iodide in 4 L of methylene chloride was stirred at ambient temperature for 4 days. The solids were isolated by filtration, treated with 200 mL of dilute ammonium hydroxide, and extracted continuously for 4 h. Methylene chloride was removed from the extract under reduced pressure to obtain 20.0 g (64%) of the title compound.

(b) 7-(2-Benzoylethyl)-8-hydroxy-2-methylimidazo[1,2-*a*]pyridine-3-acetonitrile Hydrochloride Hemihydrate. A solution of 23.7 g (97.1 mmol) of 7-[(dimethylamino)methyl]-8-hydroxy-2-methylimidazo[1,2-*a*]pyridine-3-acetonitrile and 18.9 g (100 mmol) of 1-morpholino-1-phenylethylene[26] in 400 mL of *p*-dioxane was heated under reflux in a nitrogen atmosphere for 3 h. Upon cooling, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was triturated with hot ethyl acetate (250 mL), and the solids were removed by filtration. The ethyl acetate solution was diluted with 250 mL of ether and filtered, and the filtrate was treated with excess ethereal hydrogen chloride. The resultant precipitate was isolated by filtration, washed with 50 mL of water, and recrystallized from methanol to obtain 4.3 g (14%) of the title compound as a hemihydrate hydrochloride salt, mp 215–220 °C.

(c) 8-Hydroxy-2-methyl-7-(3-phenyl-3-hydroxypropyl)imidazo[1,2-*a*]pyridine-3-acetonitrile. A suspension of 3.5 g (11 mmol) of the above ketone in 200 mL of ethanol and 50 mL of methylene chloride was treated with 2.4 g (63.5 mmol) of sodium borohydride added portionwise over 15 min. After stirring overnight, volatiles were removed under reduced pressure, and the residue was treated with 125 mL of water and acidified with 6 N hydrochloric acid. The solution was brought to pH 8 by the addition of concentrated ammonium hydroxide and extracted with methylene chloride. The extract was evaporated under reduced pressure to obtain the title compound, which was used without further purification in the preparation of compound **40**.

(d) 8,9-Dihydro-2-methyl-9-phenyl-7*H*-imidazo[1,2-*a*]pyrano[2,3-*c*]pyridine-3-acetonitrile Hydrochloride (40). To a solution of 2.70 g (8.41 mmol) of 8-hydroxy-2-methyl-7-(3-phenyl-3-hydroxypropyl)imidazo[1,2-*a*]pyridine in 150 mL of methylene chloride were added 3 mL (3.45 g, 24.3 mmol) of boron trifluoride etherate and a quantity of sand. After the mixture was stirred for 2 h at ambient temperature, another 3 mL (3.45 g, 24.3 mmol) of boron trifluoride etherate was added, and the mixture was refluxed for 3 h. Heating was terminated, and the mixture was allowed to stir at ambient temperature overnight before being treated with dilute ammonium hydroxide (500 mL) and methylene chloride (200 mL). The methylene chloride layer was separated, filtered through Celite, and concentrated under reduced pressure. The residual oil was chromatographed on silica gel, eluting with methylene chloride containing 0.5% (v/v) methanol, to obtain the free base form of compound **40**, mp 158–161 °C. High-resolution MS ($C_{19}H_{17}N_3O$): calcd, 303.1372; found, 303.1383. Treatment of an ether solution of this free base with ethereal hydrogen chloride gave a solid, which was recrystallized from ethanol–ethyl ether, to obtain the hydrochloride of **40** as a monohydrate[27] with mp 220–245 °C.

Biological Test Methods. The methods used for the measurement of antisecretory activity in the rat and dog and gastric cytoprotective activity in the rat have previously been described in detail.[1]

Pylorus-Ligated Rat.[15] The abdomens of anesthetized rats that had been fasted for 24 h were opened and ligatures tied around the pylorus. The stomachs were returned to the abdomens and the incisions closed with autoclips. Test compounds were dissolved in a 2.5% Tween 80 solution and were administered intraperitoneally in doses of 0.5 mL/200 g of body weight. Four hours after drug administration, the animals were killed, and the stomachs were removed. The contents of the stomachs were collected, and the volumes were recorded. Aliquots were removed and titrated against 0.1 N NaOH to determine the acid output (AO). Six rats were used per test compound and eight rats for the control. Percent inhibitions were calculated, and the results were statistically analyzed by the Student's *t* test. The mean plus or minus standard error (SE) acid output in the control studies was 0.61 ± 0.04 mequiv/4 h. The intraperitoneal dose (ED_{50}) of cimetidine that produced a 50% inhibition of the 4-h acid output in the pylorus-ligated rat was 26.1 (12.8-50.9) mg/kg.[3]

Heidenhain Pouch Dog.[16] Mongrel dogs were surgically prepared with Heidenhain pouches. Compounds were dissolved in 3 mL of 0.4% methylcellulose/saline solutions for intravenous studies and in 5 mL for oral studies. Intravenous infusion of histamine at a rate of 0.4 g/kg per min served as the stimulant of gastric secretions, which were collected at 30-min intervals for 0.5–1 h prior to histamine infusion and for 4 and 5 h thereafter. The volume of each 30-min collection was recorded, and an aliquot was titrated to determine acid concentration. One hour after the start of histamine infusion, the test compound was given either intravenously or orally by gavage. The respective 30-min acid outputs were summated for 3 h after drug administration. Each animal served as its own control. In our laboratories the mean plus or minus SE for acid output in control studies was 10.56 ± 1.15 mequiv/3 h. The doses inhibiting histamine-stimulated gastric acid secretion by 50% (ED_{50}) were calculated by linear regression analysis. The intravenous dose (ED_{50}) of cimetidine required to reduce acid output to 50% of control value was 0.66 (0.16–2.60) mg/kg, while the oral dose (ED_{50}) was 1.25 (0.58–2.52) mg/kg.[3]

Cytoprotective Activity in Rats. Rats were fasted and deprived of water for 20 h prior to experiments. Each test drug in 0.4% methylcellulose/saline vehicle was given to individual rats orally 30 min prior to oral administration of 1 mL of absolute ethanol. One hour after ethanol, the rats were sacrificed and the stomachs excised. After the stomach was opened along the greater curvature, the length of each linear hemorrhagic lesion induced by ethanol was measured and totalled for each stomach. Results are expressed as the mean lesion length per rat for each treatment group. The doses inhibiting ethanol-induced lesions by 50% (ED_{50}) were calculated by regression analysis. The estimated oral ED_{50} values for carbenoxolone and PGE_2 against ethanol-induced lesions were 30 and less than 0.1 mg/kg,[3] respectively.

X-ray Crystallographic Studies. Crystal Data. 2,3-Dimethyl-8-((*E*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine hydrochloride dihydrate (**11**·HCl·2H_2O), $C_{17}H_{21}ClN_2O_2$, M_r 320.82, monoclinic, a = 18.803 (6) Å, b = 7.921 (3) Å, c = 25.040 (9) Å, β = 101.49 (2)°, V = 3654.7 Å^3, Z = 8, d_{calcd} = 1.166 g cm^{-3}, μ(Cu Kα radiation, λ = 1.5418 Å) = 19.2 cm^{-1}. Space group $P2_1/c(C^5_{2h})$ uniquely from the systematic absences. $0k0$ when $k \neq 2n$, $h0l$ when $l \neq 2n$. Sample dimensions: 0.10 × 0.15 × 0.70 mm.

2,3-Dimethyl-8-((*Z*)-2-phenylethenyl)imidazo[1,2-*a*]pyridine hydrochloride tetrahydrate (**12**·HCl·4H_2O), $C_{17}H_{25}ClN_2O_4$, M_r 356.85, monoclinic, a = 8.034 (1) Å, b = 19.348 (5) Å, c = 13.492 (2) Å, β = 109.59 (1)°, V = 1975.8 Å^3, Z = 4, d_{calcd} = 1.200 g cm^{-3}, μ(Cu Kα radiation) = 19.0 cm^{-1}. Space group $P2_1/c(C^5_{2h})$ as for **11**·HCl·2H_2O. Sample dimensions: 0.20 × 0.40 × 0.60 mm (sealed inside a thin-walled glass capillary).

3-(Cyanomethyl)-2-methyl-8-((*E*)-3-phenyl-1-propenyl)imidazo[1,2-*a*]pyridine (**33**), $C_{19}H_{17}N_3$, M_r 287.37, monoclinic, a = 10.775 (1) Å, b = 10.131 (2) Å, c = 15.104 (1) Å, β = 109.25 (1)°, V = 1556.6 Å^3, Z = 4, d_{calcd} = 1.226 g cm^{-3}, μ(Cu Kα radiation) = 5.4 cm^{-1}. Space group $P2_1/c(C^5_{2h})$ as for **11**·HCl·2H_2O. Sample dimensions: 0.04 × 0.24 × 0.28 mm.

3-(Cyanomethyl)-2-methyl-8-((*E*)-3-phenyl-2-propenyl)-imidazo[1,2-*a*]pyridine (34), $C_{19}H_{17}N_3$, M_r 287.37, monoclinic, a = 8.667 (1) Å, b = 11.814 (3) Å, c = 15.184 (4) Å, β = 91.19 (1)°, V = 1554.4 Å^3, Z = 4, d_{calcd} = 1.228 g cm^{-3}, μ(Cu Kα radiation) = 5.4 cm^{-1}. Space group $P2_1/c(C^5_{2h})$ as for 11·HCl·2H$_2$O. Sample dimensions: 0.10 × 0.15 × 0.42 mm.

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Supplementary Material Available: Details of the crystallographic measurements and structure analysis; tables (S1–S15) of atomic positional and thermal parameters, interatomic distances, and angles for 11·HCl·2H$_2$O, 12·HCl·4H$_2$O, **33**, and **34**; and corresponding Figures 1–4; tables (S16 and S17) of the estimated lattice energies calculated for the two conformations of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, **1a** and **1d**, and Figure 7 illustrating the packing arrangement of **1d** in the unit cell; SYBYL 5.1 mol files for the conformations of 1 depicted in Figures 5 and 6 and of **1d**, **11**, and **40** shown in Figure 8 (58 pages). Ordering information is given on any current masthead page.

Structure-Activity Relationship of Antiestrogens: A Study Using Triarylbutenone, Benzofuran, and Triarylfuran Analogues as Models for Triarylethylenes and Triarylpropenones†

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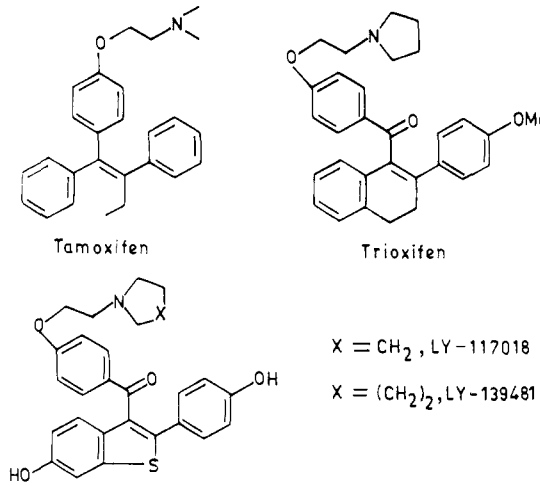
In a study of the structure-activity relationship (SAR) of antiestrogens use has been made of certain 1,2,3-triarylbutenones, of 2-arylbenzofurans carrying aryl or aroyl substituents at C_3, and of 2,3,4-triarylfurans as conformationally constrained models for triarylethylene (TAE) and triarylpropenone (TAP) prototypes. The position-specific contributions of substituents to receptor affinity and to agonist-antagonist profiles were used as aids in characterizing the relative binding orientation of the prototypes. Although most compounds were found to be weak receptor ligands and poorly active in vivo, the following conclusions could be drawn about their SAR: (i) (*Z*)-TAPs and TAEs interact with the receptor in an analogous manner using the *trans*-stilbene core, with their agonist-antagonist profiles depending on the nature of other substructures. (ii) Incorporation into the benzofuran framework introduces a stereoelectronic constraint that compromises the normal binding interactions of TAE, as well as TAP, prototypes, resulting in their poor affinities and weak biological activities. (iii) (*E*)-TAPs can interact with the receptor through their *S*-cis conformation, but such a binding mode is unlikely to account for their behavior as antagonists.

1,2,3-Triarylpropenones (TAPs) have aroused considerable interest as possible leads in the design of newer antiestrogens better than those hitherto known. The motivation for this interest has been the realization that triarylethylenes (TAEs), the best known group of antiestrogens, represented by tamoxifen (Chart I), are associated with partial agonist character, which compromises their effectiveness as antagonist and hence the scope and range of application in research as well as medicine. Certain simple acyclic TAPs were first reported to show antifertility activity with *Z* isomers more effective than (*E*)-TAPs.[1-3] Following this lead, Jones et al. synthesized trioxifen (Chart I) and found it to be a better antiestrogen than tamoxifen, in possessing diminished agonist character.[4] LY-117018[5] and LY-139481,[6] developed later, were found to be progressively better antiestrogens than trioxifen—the latter emerging as a particularly effective antiestrogen with only marginal agonist character. These discoveries have aroused considerable interest in exploring the reasons for improved antagonist activity in (*Z*)-TAPs over TAEs. Since the presence of the intervening carbonyl changes the stereochemical relationship of the aryl bearing the side chain with the *trans*-stilbene core in (*Z*)-TAPs, the analysis of their receptor binding mode in relation to that of the TAEs becomes of interest.

A study on structure-activity relationship (SAR) of acyclic TAPs was thus undertaken by Garg et al.[7] While

Chart I



confirming estrogen antagonist activity in (*Z*)-TAPs, this study also revealed the ability of (*E*)-TAPs to act as an-

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