Antiulcer Agents. 3. Structure-Activity-Toxicity Relationships of Substituted Imidazo[1,2-*a*]pyridines and a Related Imidazo[1,2-*a*]pyrazine

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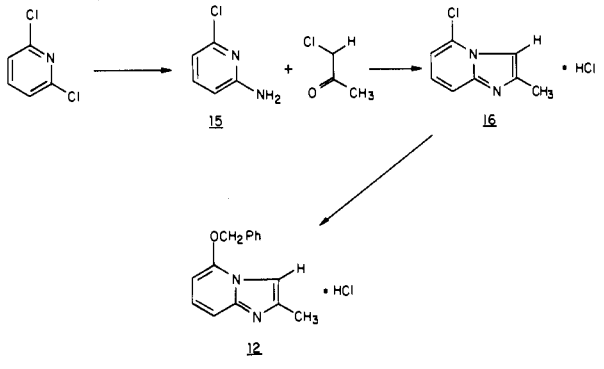
Investigation of the interrelationship between structure, antiulcer activity, and toxicology screening data derived from a series of compounds selected from structure–activity studies directed toward identifying a successor to 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, Sch 28080 (1), has identified 3-(cyanomethyl)-2,7-dimethyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (5), 3-amino-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyridine (6), and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (7). These analogues exhibit a combination of antisecretory and cytoprotective activity in animal models, while eliminating the adverse effects of the prototype 1. One of these, 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine, Sch 32651 (7), has a profile meeting all criteria.

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 antisecretory and cytoprotective properties in animal models. Observed toxicity led to the withdrawal of 1 from clinical trials.[2] Hepatic changes evident in animals during continued drug safety studies identified the liver as a target organ of toxicity. Concomitant with this finding was the observation of elevated serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels in human volunteers during a rising dose tolerance study. In addition, gastric morphologic alterations caused by our clinical candidate in animals led us to initiate a study directed toward the identification of a successor that would retain the desirable combination of antisecretory and cytoprotective properties of 1, but be devoid of these toxic effects. We also wanted the successor to exhibit a longer duration of action when given orally. The significant disparity between the oral and intravenous gastric antisecretory potency (ED_{50}) determined for 1 in the histamine-stimulated dog suggested that either 1 is poorly absorbed following oral administration or 1 is extensively metabolized.

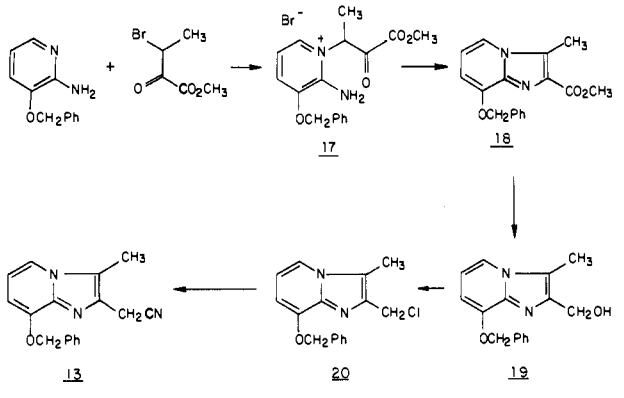
Preliminary studies[3] of the pharmacodynamics and metabolism of 1, performed with the aid of cyano carbon labeled versions of the drug, have shown that 1 is well-absorbed, unchanged 1 is the pharmacologically active species after administration, and 1 is extensively metabolized. Furthermore, the 3-cyanomethyl 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 (21).

On the basis of these results, extensive structure–activity studies directed toward discovering a successor to 1 have focused on the identification of a bioequivalent for the 3-cyanomethyl function and/or structural alteration of the imidazo[1,2-*a*]pyridine system such as to warrant the expectation of a metabolic disposition different from that of 1.[3]

Scheme I. 2-Methyl-5-(phenylmethoxy)imidazo[1,2-*a*]pyridine (12)



Scheme II. Synthesis of 2-(Cyanomethyl)-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (13)



The present work concerns the investigation of the interrelationship between structure, antiulcer activity, and toxicology screening data derived from a series of compounds selected from our structure–activity studies[1,3] directed toward identifying a successor to 1. Three compounds, 3-(cyanomethyl)-2,7-dimethyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (5), 3-amino-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyridine (6), and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (7), exhibiting the requisite profile have been identified. One of these, 3-amino-2-methyl-8-(henylmethoxy)imidazo[1,2-*a*]pyrazine, Sch 32651 (7), has a profile meeting all criteria.

Chemistry

The preparation of all of the compounds discussed here except 12 and 13 has been reported previously.[1,3]

The syntheses of 12 and 13, as outlined in Schemes I and II, respectively, are discussed below, and details of their preparation are presented in the Experimental Section.

(1) Kaminski, J. J.; Bristol, J. A.; Puchalski, C.; Lovey, R. G.; Elliott, A. J.; Guzik, H.; Solomon, D. M.; Conn, D. J.; Domalski, M. S.; Wong, S. C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; Steinberg, M.; McPhail, A. T. *J. Med. Chem.* **1985**, 28, 876.
(2) Long, J. F.; Chiu, P. J. S.; Derelanko, M. J.; Steinberg, M. *J. Pharmacol. Exp. Ther.* **1983**, 226(1), 114.
(3) Kaminski, J. J.; Hilbert, J. M.; Pramanik, B. N.; Solomon, D. M.; Conn, D. J.; Rizvi, R. K.; Elliott, A. J.; Guzik, H.; Lovey, R. G.; Domalski, M. S.; Wong, S. C.; Puchalski, C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; McPhail, A. T. *J. Med. Chem.*, preceding paper in this issue.

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Treatment of 2,6-dichloropyridine with ammonium hydroxide at elevated temperature in a bomb gave 2-amino-6-chloropyridine (**15**), which was condensed with chloroacetone to obtain 2-methyl-5-chloroimidazo[1,2-*a*]-pyridine hydrochloride (**16**). The nuclear chlorine of **16** was displaced by the sodium salt of benzyl alcohol in *N,N*-dimethylformamide to produce 2-methyl-5-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**12**).

Condensation of 2-amino-3-(phenylmethoxy)pyridine with methyl 3-bromo-2-oxobutyrate[4] in dimethoxyethane produced the quaternary salt 2-amino-1-(1-methoxalylethyl)-3-(phenylmethoxy)pyridinium bromide (**17**), which without purification was heated under reflux in methanol in the presence of type 3A molecular sieves to obtain 2-carbomethoxy-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**18**). The ester function of **18** was reduced with lithium aluminum hydride in tetrahydrofuran, and the resultant alcohol **19** was converted to the corresponding chloride **20** by the action of thionyl chloride in chloroform. Treatment of the chloride with potassium cyanide in dimethyl sulfoxide yielded 2-(cyanomethyl)-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**13**).

Structure–Activity–Toxicity Relationships

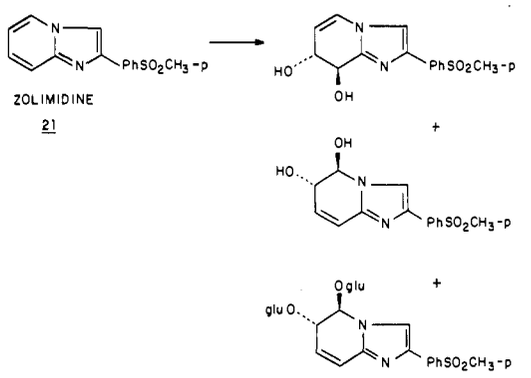
A summary of the relevant structure, activity, and toxicology screening data is presented in Table I. Antiulcer *activity* has been represented in terms of ED_{50} values for oral antisecretory activity in the histamine-stimulated Heidenhain pouch dog and by oral cytoprotective efficacy in rats against gastric lesions induced by absolute ethanol. Compound **1** exhibits substantial levels of potency in both these assays. For purposes of this discussion, "toxicity" is defined in terms of gross and microscopic effects on the stomachs of mice that were dosed with the test compounds for 2 weeks.[5] Adverse effects on mouse stomach caused by some members of this series included increased stomach weight and alterations in gastric morphology. Those compounds that caused a significant increase in stomach weight relative to control, with concomitant hyperplasia of the glandular mucosa, were regarded as toxic (**1–4**, **8**, **13**).

To gain insight into the relatively complex and subtle relationships among structure, activity, and toxicity exhibited by this series of substituted imdiazo[1,2-*a*]pyridines and a related imidazo[1,2-*a*]pyrazine, it is useful to assign compounds manifesting a dual combination of antisecretory and cytoprotective activity (**1–7**), (b) those compounds that are cytoprotective only (**9–12**), and (c) those compounds that are inactive (**14**). Although compounds **8** and **13** may be assigned to either category a or b, certain generalizations are nonetheless substantiated by the data, as discussed below.

All compounds exhibiting dual activity, antisecretory and cytoprotective, have either a cyanomethyl or amino function at the 3-position. The presence of these substituents may or may not be associated with toxicity, depending upon other structural parameters.

All *toxic, dually active* compounds have an arylmethylene or heteroarylmethylene substituted heteroatom group at the 8-position (**1–4**). *Nontoxic, dually active* compounds may (a) retain this XCH_2-aryl substituent at position 8, but incorporate a significant structural change at position 7 (**5** and **7**, respectively), or (b) replace the 8-XCH_2-aryl with 8-CH_2CH_2-aryl (**6**). The effectiveness

Scheme III. Human Urinary Metabolites of Zolimidine (**21**)



of this latter isosteric replacement at position 8 in eliminating toxicity in the dually active series is controversial if **8** is classified as a member of this series. However, the lack of a definitive antisecretory ED_{50} value for **8** makes this assignment arbitrary. Moreover, even if **8** were classified as being *cytoprotective only*, it would still constitute an anomaly, being the only toxic example in this category.

None of the compounds exhibiting *cytoprotective activity only* (**9–12**) contain the combination of a 3-cyanomethyl or 3-amino group with an 8-XCH_2-aryl function common to the dually active series, but may have one of these two structural features. However, the structural parameters associated with cytoprotective activity per se, irrespective of associated antisecretory activity, are diverse and not readily amenable to strict definition. All *cytoprotective-only* compounds are nontoxic.

Since the metabolic disposition of a compound may have a profound effect on both its activity and its toxicologic profile, the design of analogues of **1** incorporating structural variations that might differentiate their metabolic fate from that of **1** was regarded as crucial to identify congeners that would retain the desired antiulcer activities and be devoid of the observed toxicity of **1**. The principal metabolites of the antiulcer agent zolimidine (2-[4-(methylsulfonyl)phenyl]imidazo[1,2-*a*]pyridine) (**21**), isolable in human urine after oral administration of the drug, have been identified as the 5,6- and 7,8-dihydroxylated dihydro derivatives, respectively, as well as the bisglucuronidated adduct of the former compound, Scheme III.[6] The only identified imidazo[1,2-*a*]pyridine-containing metabolite of **1** was the debenzylated derivative **14**. Compound **14** contributes to neither the activity nor the toxicity of **1** (Table I). On the assumption that ring hydroxylation analogous to that demonstrated to occur in the metabolism of **21** might be operative in our series, the effect of structural modifications designed to alter the extent and/or nature of the metabolism of the pyridyl portion of the imidazo[1,2-*a*]pyridine ring system was examined. Three compounds (**5–7**) that exhibit the desired dual activity profile without toxicity all incorporate modifications of this type. Indeed, with respect to toxicity only, all compounds in which a structural variation from **1** has been introduced at position 5, 6, or 7, albeit in one instance (**12**) in concert with changes in substitution on the imidazole ring, have been rendered nontoxic (**5–7**, **9**, and **10**).

The effect of replacement of the heteroatom at the 8-position is noteworthy: changing oxygen to methylene retains dual activity and eliminates toxicity when the 3-

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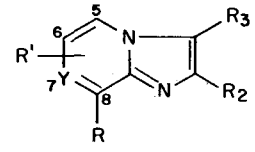
(5) Perkins, D. G.; Frantz, J. D.; Murphy, B. F.; Szot, R. J.; Black, H. E.; Schwartz, E. *The Toxicologist* **1984**, Abstract 685.

(6) (a) Almirante, L.; Picco, S.; Bonaldi, A.; Cattaneo, R. *Farmaco, Ed. Sci.* **1974**, *29*(12), 841. (b) Picco, S.; Bonaldi, A.; Frigerio, A.; Danieli, B., Almirante, L. *Farmaco, Ed. Sci.* **1974**, *29*(12), 848. (c) Almirante, L.; Danieli, B.; Frigerio, A.; Mugnaini, A.; Picco, S. *Farmaco, Ed. Sci.* **1974**, *29*(12), 941.

Table I. Structure–Activity–Toxicity Relationships of Substituted Imidazo[1,2-*a*]pyridines and a Related Imidazo[1,2-*a*]pyrazine



no.	R_2	R_3	R	R′	Y	antisecretory act.: % inhibn of acid secretion, histamine-stimulated dog, ED_{50}^{po}, mg/kg	cytoprotective act.: EtOH ulcer, ED_{50}^{po}, mg/kg	organ wt[a] (g), stomach: analogue ± SE	organ wt[a] (g), stomach: control ± SE	organ wt ratio, stomach: analogue:control	organ wt ratio, stomach: analogue:1	organ wt ratio, stomach: histopathology, stomach
1	CH_3	CH_2CN	$PhCH_2O$	H	HC	4.4 (2.1–14.0)[b]	3.0	1.13 ± 0.02	0.80 ± 0.02	1.4	1.0	HGM[c]
2	CH_3	CH_2CN	3-thienyl-CH_2O	H	HC	2.7[d]	2.0	1.12 ± 0.05	0.75 ± 0.05	1.5	1.0	HGM
3	CH_3	CH_2CN	$PhCH_2NH$	H	HC	6.7[d]	2.0	0.90 ± 0.14	0.75 ± 0.05	1.2	0.8	HGM
4	CH_3	NH_2	$PhCH_2O$	H	HC	2.0[d]	6.0	1.09 ± 0.05	0.88 ± 0.03	1.2	1.0	HGM
5	CH_3	CH_2CN	$PhCH_2O$	H	CH_3C	7.1 (3.2–50.6)	13.0	0.90 ± 0.02	0.83 ± 0.02	1.1	0.8	N[e]
6	CH_3	NH_2	$PhCH_2CH_2$	H	HC	6.8 (2.3–59.2)	9.0	0.88 ± 0.02	0.80 ± 0.02	1.1	0.8	N
7	CH_3	NH_2	$PhCH_2O$	H	N	1.4 (0.6–3.9)	5.0	0.86 ± 0.02	0.78 ± 0.02	1.1	0.8	N
8	CH_3	CH_2CN	$PhCH_2CH_2$	H	HC	>4.4[f,h]	7.0	0.99 ± 0.02	0.80 ± 0.02	1.2	0.9	HGM
9	CH_3	CH_2CN	H	6-$PhCH_2CH_2$	HC	inactive[i]	2.7	0.81 ± 0.02	0.80 ± 0.02	1.0	0.7	N
10	CH_3	NH_2	H	6-$PhCH_2CH_2$	HC	inactive	5.7	0.81 ± 0.02	0.83 ± 0.02	1.0	0.7	N
11	CH_3	H	$PhCH_2O$	H	HC	inactive	4.0	0.84 ± 0.02	0.82 ± 0.02	1.0	0.7	N
12	CH_3	H	H	5-$PhCH_2O$	HC	inactive	1.0	0.76 ± 0.02	0.82 ± 0.02	0.9	0.7	N
13	CH_2CN	CH_3	$PhCH_2O$	H	HC	>4.4[g,h]	inactive[j]	0.98 ± 0.02	0.82 ± 0.02	1.2	0.9	HGM
14	CH_3	CH_2CN	HO	H	HC	inactive	inactive	0.80 ± 0.02	0.82 ± 0.02	1.0	0.7	N

[a] Organ weight in grams ± standard error (SE). [b] Confidence limits, $\rho = 0.05$. [c] HGM = hyperplasia of glandular mucosa. [d] Approximate ED_{50}; the regression was not significant. [e] N = within normal variation. [f] The percent inhibition of histamine-stimulated gastric acid secretion was 83 and 3 at oral doses of 8 and 4 mg/kg, respectively. [g] The percent inhibition of histamine-stimulated gastric acid secretion was 91 and 19 at oral doses of 8 and 4 mg/kg, respectively. [h] Although a definitive ED_{50}^{po} has not been established for this compound, it is regarded as less potent and may also be less active than those tabulated compounds for which an ED_{50}^{po} value has been quoted. [i] Inactive when tested at oral dose of 8 mg/kg. [j] Inactive when tested at an oral dose of 30 mg/kg.

substituent is the amino group (compare 4 and 6), but fails to eliminate toxicity and apparently reduces antisecretory activity when the cyanomethyl group occupies the 3-position (compare 1 and 8).

That none of the structural variables can be considered to be independent is further evidenced by the observation that compounds having in common the 2-methyl-3-cyanomethyl array may be either toxic (1–3, 8) or nontoxic (5, 9, 14) and may exhibit dual activity (1–3, 5) or cytoprotection only (9) or be totally inactive (14), depending upon the nature of the substitution in the pyridyl portion of the nuclear ring system (positions 6, 7, or 8).

The crucial effect on activity of the position of each substituent is illistrated by the difference in that activity profiles of 1 and 13: reversing the 2- and 3-position substituents effectively eliminates cytoprotective activity and has a substantial effect on antisecretory potency, as well. In contrast, toxicity is not significantly altered by this isomeric change.

In summary, toxicity, as defined above, has been succesfully separated from the desired dual activity profile exhibited by the 3-cyanomethyl (1) or 3-amino (4) analogues by structural alteration of the pyridyl portion of the imidazo[1,2-*a*]pyridine ring system. These changes derive conceptually from an attempt to alter the proposed metabolic disposition of these compounds, based on the known metabolic fate of another imidazo[1,2-*a*]pyridine, zolimidine (21).

Experimental Section

Chemistry. 2-Methyl-5-(phenylmethoxy)imidazo[1,2-*a*]pyridine Hydrochloride (12). 2,6-Dichloropyridine, 60.0 g (0.41 mol), dissolved in 300 mL of 20% ammonium hydroxide was heated at 180 °C in a bomb for 40 h. Upon cooling, the solid that formed was isolated by filtration and dried. Recrystallization from hexanes–isopropyl ether gave 16.9 g (0.13 mol), 32%, of 2-amino-6-chloropyridine (15), mp 72–74.5 °C. Anal. ($C_5H_5ClN_2$) C, H, N, Cl.

A mixture of 14.0 g (0.10 mol) of 2-amino-6-chloropyridine (15) and 11.3 g (0.11 mol) of chloroacetone in 70 mL of ethanol was heated under reflux for 48 h. Most of the ethanol was removed by distillation, and 30 mL of ether was added. The solid that formed was isolated by filtration and dried.

Recrystallization from ethanol gave 10.2 g (0.05 mol), 50%, of 5-chloro-2-methylimidazo[1,2-*a*]pyridine hydrochloride (16), mp 335 °C dec. Anal. ($C_8H_8Cl_2N_2$) C, H, N, Cl.

To a stirred suspension of 0.96 g (0.02 mol) of sodium hydride in mineral oil (50%) and 10 mL of *N*,*N*-dimethylformamide at 0 °C was added 2.2 g (0.02 mol) of benzyl alcohol, and the mixture was stirred at room temperature for 1.5 h. 5-Chloro-2-methylimidazo[1,2-*a*]pyridine hydrochloride (16), 2.0 g (0.01 mol), was added in portions while the temperature was maintained at 0–5 °C. The reaction mixture was stirred at ambient temperature overnight. The mixture was added to water (50 mL), and the aqueous solution was extracted with dichloromethane (3 × 50 mL). The dichloromethane extracts were combined and dried. Following filtration, the dichloromethane was removed under reduced pressure to give an oil, 2.3 g. The oil was dissolved in ether and treated with 30 mL of ethereal hydrogen chloride (1 M). The ether was removed under reduced pressure to give a solid. Recrystallization from dichloromethane–acetone gave 2.2 g (0.008 mol), 80%, of 2-methyl-5-(phenylmethoxy)imidazo[1,2-*a*]pyridine hydrochloride (12), mp 135–137 °C. Anal. ($C_{15}H_{15}ClN_2O$) C, H, N, Cl.

2-(Cyanomethyl)-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (13). To 20.0 g (0.10 mol) of 2-amino-3-(phenylmethoxy)pyridine dissolved in 200 mL of dimethoxyethane was added dropwise with stirring 19.5 g (0.10 mol) of methyl 3-bromo-2-oxobutyrate[4] in 100 mL of dimethoxyethane. The suspension was stirred at ambient temperature for 48 h under a nitrogen atmosphere. The solid that formed was isolated by filtration and washed thoroughly with ether. After drying, there was obtained 36.2 g (0.092 mol), 92%, of 2-amino-1-(1-methoxalylethyl)-3-(phenylmethoxy)pyridinium bromide (17), mp 150 °C dec. Anal. ($C_{17}H_{19}BrN_2O_4$) C, H, N, Br.

To a solution of 34.0 g (0.086 mol) of 2-amino-1-(1-methoxalylethyl)-3-(phenylmethoxy)pyridinium bromide (17) in 300 mL of methanol was added 25 g of molecular sieves (3A), and the mixture was heated under reflux for 24 h. Upon cooling, the molecular sieves were removed by filtration and the methanol was removed under reduced pressure. The solid obtained was partitioned between dichloromethane (100 mL) and 10% sodium bicarbonate (100 mL). The layers were separated, and the basic aqueous solution was extracted with dichloromethane (2 × 100 mL). The dichloromethane extracts were combined and dried (Na_2SO_4).

Following filtration, the dichloromethane was removed under reduced pressure to give a solid. Recrystallization from ethyl acetate gave 21.6 g (0.073 mol), 85%, of 2-carbomethoxy-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (18), mp 108.5–109.5 °C. Anal. ($C_{17}H_{16}N_2O_3$) C, H, N.

To a stirred suspension of 1.03 g (0.03 mol) of lithium aluminum hydride in 200 mL of tetrahydrofuran at 0 °C was added 13.3 g (0.045 mol) of 2-carbomethoxy-3-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (18) in portions over 0.3 h while the temperature was maintained below 8 °C. When the addition was complete, the mixture was stirred at 0 °C for 0.5 h and at ambient temperature for an additional 1 h. The reaction mixture was cooled to 0 °C, and to the stirred mixture were added 1 mL of water, then 2 mL of 10% sodium hydroxide, and finally 3 mL of water. The mixture was allowed to warm to room temperature with stirring, and the solids were removed by filtration. The solids were thoroughly washed with hot tetrahydrofuran (2 × 100 mL) and hot chloroform (4 × 100 mL). The filtrate and washings were combined and dried (K_2CO_3). Following filtration, the solvents were removed under reduced pressure to give a solid. Recrystallization from chloroform gave 8.6 g (0.032 mol), 71%, of 2-(hydroxymethyl)-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (19), mp 172–175 °C dec. Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

To a stirred suspension of 9.4 g (0.035 mol) of 2-(hydroxymethyl)-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (19) in 50 mL of chloroform was added 8.4 g (0.07 mol) of thionyl chloride. After stirring at ambient temperature for 4 h, the suspension was poured into a mixture of ice, 10% sodium bicarbonate (250 mL), and chloroform (200 mL). The layers were separated, and the aqueous layer was extracted with chloroform (2 × 100 mL). The chloroform extracts were combined and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give a solid. Recrystallization from ethyl acetate gave 9.2 g (0.032 mol), 91%, of 2-(chloromethyl)-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (20), mp 260 °C. Anal. ($C_{16}H_{15}ClN_2O$) C, H, N, Cl.

To a stirred suspension of 0.87 g (0.013 mol) of potassium cyanide in 30 mL of dimethyl sulfoxide was added 3.5 g (0.012 mol) of 2-(chloromethyl)-3-methyl-8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine (20). The mixture was stirred at ambient temperature for 5 h and at 45–50 °C for 0.75 h. Upon cooling, the reaction mixture was partitioned between chloroform (125 mL) and water (200 mL). The layers were separated, and the aqueous layer was extracted with chloroform (2 × 200 mL). The chloroform extracts were combined and dried (Na_2SO_4).

Following filtration, the chloroform was removed under reduced pressure to give a solid. Recrystallization from methanol gave 2.2 g (0.008 mol), 66%, of 2-(cyanomethyl)-3-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (13), mp 169–170.5 °C. Anal. ($C_{17}H_{15}N_3O$) C, H, N.

Pharmacology. The compounds were evaluated for gastric antisecretory activity in the dog and gastric cytoprotective activity in the rat by using the protocol that has been described previously.[1]

Toxicology/Pathology. In a series of studies, each analogue was administered to a group of 20 male CD-1 mice (Charles River) weighing 25–35 g. In each study, one group of 20 untreated male mice of comparable age and body weight range served as controls. All animals were weighed weekly during the pretreatment and dosing periods, and quantitative food consumption was determined weekly. Doses of the test compounds were given via dietary admixture at 400 mg/kg for 14 consecutive days. Mean daily intake of each test compound was calculated weekly from the food consumption data. Consistent dosage on a milligram/kilogram

basis was maintained by adjusting the concentration of the test compound in the diet weekly.

On day 15 all animals were necropsied. The stomachs were excised and weighed, and sections of each were fixed in neutral buffered 10% formalin for histological processing. The tissues were then cut, blocked, sectioned, and stained with hematoxylin and eosin prior to microscopic examination.

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Registry No. 1, 76081-98-6; 2, 91849-04-6; 3, 79707-13-4; 4, 85333-23-9; 5, 91848-94-1; 6, 85333-50-2; 7, 85333-46-6; 8, 91848-84-9; 9, 85332-64-5; 10, 85332-81-6; 11, 79707-53-2; 12, 85333-09-1; 13, 110270-88-7; 14, 79707-49-6; 15, 45644-21-1; 16, 110270-89-8; 17, 110270-90-1; 18, 79707-22-5; 19, 79707-21-4; 20, 110294-56-9; 2,6-dichloropyridine, 2402-78-0; chloroacetone, 78-95-5; 2-amino-3-(phenylmethoxy)pyridine, 24016-03-3; methyl 3-bromo-2-oxobutyrate, 34329-73-2.

Metabolic Synthesis of Arylacetic Acid Antiinflammatory Drugs from Arylhexenoic Acids. 2. Indomethacin

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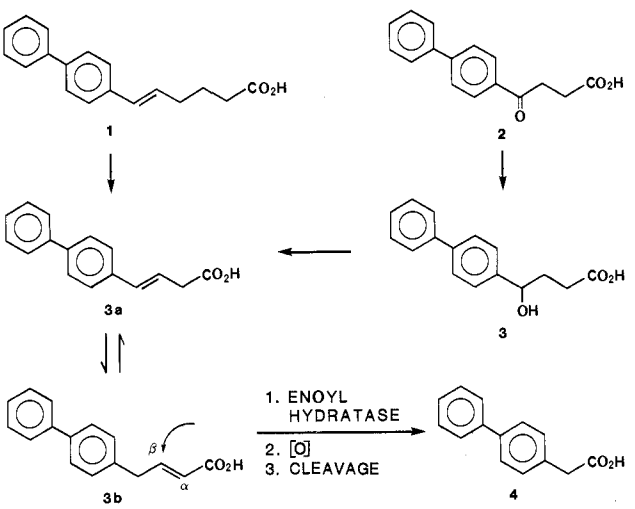
Arylacetic acid antiinflammatory drugs can be metabolically produced by β-oxidation of a 6-arylhex-5-enoic acid side chain. Such a mechanism provides for an in vivo sustained release of the active principle indomethacin from 6-[*N*-(*p*-chlorobenzoyl)-2-methylindol-3-yl]hex-5-enoic acid (**7**). Similarly, biphenylacetic acid was produced from both 6-(4′-biphenylyl)hex-5-enoic acid and its lower even homologue, 4-(4′-biphenylyl)but-3-enoic acid. The indole derivative produced sustained analgesia in a yeast-induced hyperalgesia model over a 12-h period. Indomethacin plasma levels of 2 μg/mL were observed for up to 24 h. Such levels were less than those achieved for the analogous case in which biphenylacetic acid was produced from biphenylylhex-5-enoic acid, suggesting metabolic discrimination between hex-5-enoic substrates. When indomethacin was dosed in equipotent analgesic levels, the level of circulating drug was considerably higher than that seen for metabolically derived drug. Hence 6-hex-5-enoic acid derivatives of indomethacin are metabolized to indomethacin in vivo to give sustained analgesia at low apparent circulating plasma levels of free drug. The possibility of tissue compartmentalization enhancing biological efficacy is suggested by these observations.

Toxicity resulting from acutely elevated drug concentrations following oral administration has provoked considerable research into drug delivery systems that facilitate zero-order kinetics in the absorption or distribution of the active principle. Numerous means are currently employed to achieve even drug distribution. They range from the relatively simple ester prodrug[1] stratagem to advanced pharmaceutical preparations that employ osmotic pumps, acting through polymeric membranes, to diffuse drug at a fixed rate via high-precision, laser-drilled holes.[2]

Metabolic production of a drug is one of the phenomena that can be exploited to unmask an inert prodrug and release its active form. Certain enzyme systems that are involved in ubiquitous metabolic processes can be exploited to effect systemic drug distribution. The most commonly used enzymes in prodrug design are the hydrolases, although oxidoreductases and lipases also serve. Furthermore, if distinct biochemical differences exist between pathological and normal cells, then selective toxicity may be achieved by either targeted drug delivery or site-specific activation.[3]

This paper will present evidence that indicates that arylhexenoic acids may act as arylacetic acid prodrugs, which in certain cases convey useful pharmacological characteristics to the parent drug. Initial evidence for such an assertion was found when *trans*-6-(4′-biphenylyl)hex-5-enoic acid (**1**) was found to have significant, long-duration, antiinflammatory and antiplatelet aggregatory properties in vivo[4] or ex vivo. The compound was essentially devoid of in vitro activity in appropriate models. It was found that the compound was undergoing metabolic activation in vivo by conversion to the known cyclooxygenase inhibitor biphenylacetic acid[5] (**4**), which was responsible for the observed biological activity. The metabolically produced drug profile, as determined by

Scheme I



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(5) See *Chem. Eng. News* **1967**, *45* (Feb 13), 10.

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