4-(1-methyl-2-phenyl-1*H*-indol-3-yl)-1,1-cyclohexanedicarboxylate (**16** Me ester): mp 134–135 °C (crystallized from EtOH). Anal. ($C_{25}H_{27}NO_4$) C, H, N.

To a solution of 3.2 g (0.049 mol) of KOH in 50 mL of MeOH and 5 drops of H_2O was added 2.0 g (0.0049 mol) of **16** Me ester. This solution was heated under reflux for 1 h and then concentrated in vacuo at room temperature. The residue was suspended in H_2O, made acidic with 3 N HCl, and extracted with Et_2O. The Et_2O extract was washed with brine two times, dried ($MgSO_4$), concentrated in vacuo, and crystallized from Et_2O:hexane to give 0.8 g (42%) of **16**: mp 192–193 °C. Anal. ($C_{24}H_{25}NO_4$) C, H, N.

4-(2-Phenyl-1*H*-indol-3-yl)benzoic Acid (17). To a solution of 43.4 g (0.13 mol) of **5** Me ester in 400 mL of dioxane was added 63.6 g (0.28 mol) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) followed by 50 mL of dioxane. The resulting pea-green suspension was stirred and heated under reflux for 19 h. The reaction mixture was coooled in an ice bath and the insoluble 2,3-dichloro-5,6-dicyanohydroquinone was collected, washed with hot dioxane:hexane, and dried to give 51.3 g (80%): mp 302-305 °C. The reaction mixture filtrate was concentrated and partitioned between EtOAc:toluene and ice H_2O. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to give 40 g of a semisolid. This semisolid was subjected to column chromatography on 1000 g of SiO_2 with toluene and toluene:EtOAc (9:1) as eluting solvents and gave 27.0 g of a red-orange solid: mp 163-165 °C. Purification of this material by HPLC on SiO_2 using hexane:toluene (1:4) as eluting solvent, followed by crystallization from EtOAc:hexane, gave 25.2 g (59%) of **17** Me ester: mp 165–166 °C. Anal. ($C_{22}H_{17}NO_2$) C, H, N.

A mixture of 13.2 g (0.040 mol) of **17** Me ester and 11.2 g (0.17 mol) of KOH in 250 mL of EtOH was stirred and heated under gentle reflux for 4 h to give a solution. The cooled solution was concentrated in vacuo and partitioned between cold H_2O and Et_2O, and the aqueous layer was separated, made acidic with 6 N HCl, and extracted with EtOAc. The EtOAc extract was dried (Na_2SO_4), concentrated in vacuo, and triturated with hexane to give a solid which was collected and recrystallized three times from acetone:EtOAc:hexane to give 8.9 g (71%) of **17**: mp 252–253 °C. Anal. ($C_{21}H_{15}NO_2$) C, H, N.

4-(1-Methyl-2-phenyl-1*H*-indol-3-yl)benzoic Acid (18). By use of the method described for the preparation of **17**, except that **18** was recrystallized from dioxane:H_2O, 10.2 g (0.030 mol) of **8** Me ester was transformed into 7.3 g (74%) of **18**: mp 232–235 °C. Anal. ($C_{22}H_{17}NO_2$) C, H, N.

Acknowledgment. We thank Allan G. Hlavac for assistance in spectra determinations.

Registry No. **1**, 948-65-2; **2**, 3558-24-5; **3**, 874-61-3; **4**, 58230-12-9; **5**, 93503-50-5; **5** Me ester, 93503-51-6; **6**, 93503-52-7; **6** diMe ester, 93503-53-8; **7**, 93503-54-9; **7** diMe ester, 93503-55-0; **8**, 93503-56-1; **8** Me ester, 93503-57-2; **8**·K, 93503-58-3; **9**, 93503-59-4; **9** Me ester, 93503-60-7; **10**, 93503-61-8; **11**, 93503-62-9; **11** diMe ester, 93503-63-0; **12**, 93503-64-1; **13**, 93503-65-2; **14**, 93503-66-3; **14** Me ester, 93503-67-4; **15**, 93503-68-5; **15** Me ester, 93503-69-6; **16**, 93503-70-9; **16** Me ester, 93503-71-0; **16** Me ester didehydro, 93503-55-0; **16**·K, 93503-72-1; **17**, 93503-73-2; **17** Me ester, 93503-74-3; **18**, 93503-75-4; 2,3-dichloro-5,6-dicyanohydroquinone, 4640-41-9; EtI, 75-03-6; PrBr, 106-94-5; DDQ, 84-58-2.

Imidazo[1,5-*a*]pyridines: A New Class of Thromboxane A_2 Synthetase Inhibitors

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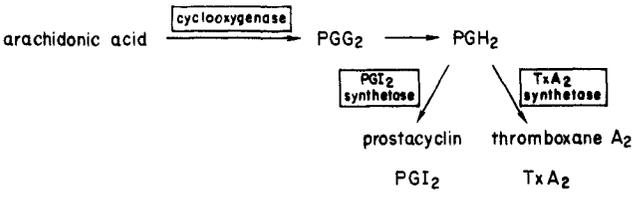
The synthesis and structure–activity profile of a new class of potent and highly specific thromboxane A_2 synthetase inhibitors is described. The most potent member of this series in vitro is determined to be imidazo[1,5-*a*]-pyridine-5-hexanoic acid (**9**).

Thromboxane A_2 (TxA_2) is an extremely unstable natural product with potent vasoconstricting, bronchoconstricting, and platelet aggregating activities.[2] It has been implicated in the etiology of a variety of disorders including vasospasm, stroke, ischemia, and myocardial infarction.[3] The biosynthesis of TxA_2 from arachidonic acid is blocked by classical nonsteroidal antiinflammatory drugs which prevent the formation of its precursors prostaglandin G_2 and prostaglandin H_2 by inhibiting cyclooxygenase (Scheme I).

Since TxA_2 and prostacyclin (PGI_2) share PGG_2 as a common precursor, inhibition of cyclooxygenase necessarily blocks the formation of the antiaggregatory vasodilator, PGI_2. A selective inhibitor of TxA_2 synthetase, which has no inhibitory effect on prostacyclin synthetase, would appear to have therapeutic potential especially in the treatment of platelet-mediated disorders.[4] Thromboxane synthetase inhibitors may have therapeutic utility in several conditions where platelets are believed to play a role in the disease process, e.g., thromboembolic disorders,[5] pulmonary hypertension,[6] cardiac ischemia,[7] endotoxin shock,[8] and tumor metastasis.[9]

Scheme I. Biosynthesis of Prostacyclin and Thromboxane A_2



Imidazole and pyridine, and especially their N- and 3-substituted derivatives, respectively, are the only re-

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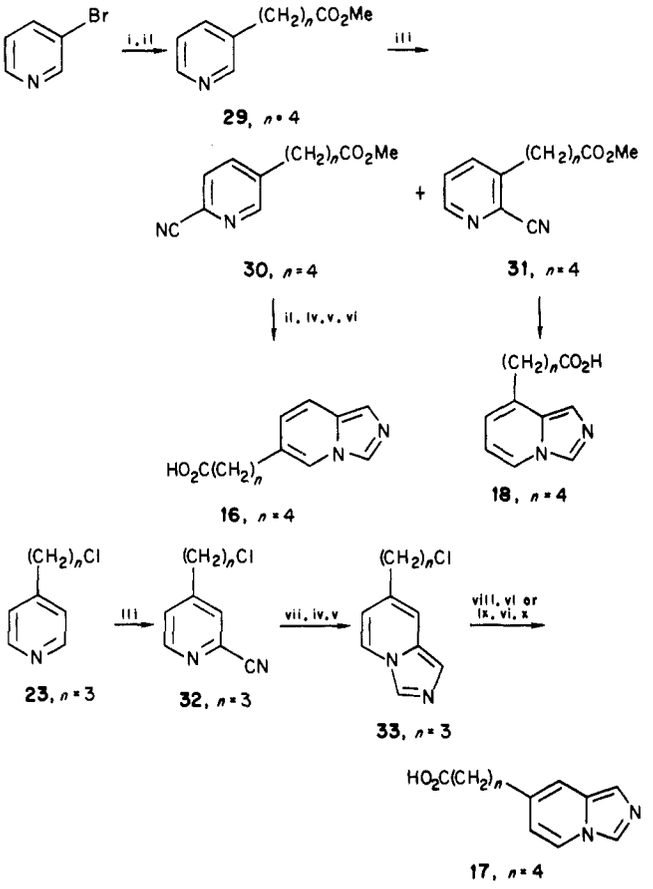
Scheme II. Synthetic Route A to Imidazo[1,5-*a*]pyridines[a]



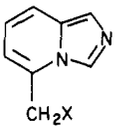
[a] (i) $Pd(OAc)_2$, P(*o*-Tol)$_3$, $CH_2{=}CH(CH_2)_{n-2}CO_2Et$, (ii) H_2/Pd, (iii) CH_3CO_3H, Me_2SO_4, KCN, (iv) HCO_2H, (v) $POCl_3$, (vi) OH^-/H_2O, (vii) BH_3-Me_2S, (viii) KCN, 18-crown-6, (ix) NaH/$CH(CO_2Et)_2$, (x) Δ.

ported heteroaromatic nuclei which potently and noncompetitively inhibit thromboxane synthetase.[10] To further investigate this activity, a series of imidazo[1,5-*a*]pyridines has been synthesized and has proven to possess members which are both potent and highly selective inhibitors of thromboxane synthetase. On the basis of previous findings,[11] ω-(carboxyalkyl)imidazo[1,5-*a*]-pyridines have been the main objective of this work, but alternative alkyl termini have been evaluated.

Chemistry. The chemistry of imidazo[1,5-*a*]pyridines is not extensively documented.[12] Two main approaches to their synthesis have been employed in these laboratories.

Route A. The first route has involved the synthesis of suitably substituted 2-cyanopyridines from the corresponding substituted pyridines by N-oxidation, *O*-methylation, and cyanation. Catalytic reduction of the nitrile to the (aminomethyl)pyridine was best achieved at atmospheric pressure with 5% palladium on charcoal in the presence of 2 equiv of hydrochloric acid. Under these conditions, less than 10% of dimer formation was observed. This circumvented the high pressures and temperatures frequently advocated for carrying out this transformation.[13] Formylation with formic acid and subsequent phosphorus oxychloride induced cyclization yielded the desired imidazo[1,5-*a*]pyridines (Scheme II). When reactive functionality prevented catalytic hydrogenation, borane–dimethyl sulfide was successfully employed.[14]

Route B. The second approach involved the alkylation of 5-methylimidazo[1,5-*a*]pyridine which can be prepared from 6-cyano-2-picoline by transformations iii, iv, and v described in Scheme II. Selective C_5-methyl deprotonation of **24** with *n*-butyllithium in tetrahydrofuran between 0 and −78 °C provides an ambident anion **25**, which alkylates at the C_5-methyl but reacts with other electrophiles, e.g., aldehydes, ketones, acid chlorides, dialkyl sulfides, and trimethylsilyl chloride, at C_3. This reactivity provides a versatile route to ω-(carboxyalkyl)imidazo[1,5-*a*]pyridines as well as other derivatives. Alkylation can be affected routinely with use of appropriate ω-bromoalkyl orthoesters and bromochloroalkanes to yield **26** and **27**, respectively. Nucleophilic displacement by cyanide or malonate anions and subsequent hydrolysis yields homologous ω-(carboxyalkyl)imidazo[1,5-*a*]pyridines (**28**). The rate of alkylation, which was slow with unactivated alkylating agents, could be increased by the addition of hexamethylphosphoramide immediately before adding the electrophile (see experimental details).



24, X = H
25, X = Li
26, X = $(CH_2)_nC(OEt)_3$
27, X = $(CH_2)_nCH_2Cl$
28, X = $(CH_2)_{n+1}CO_2H$, $(CH_2)_{n+2}CO_2H$

Carboxylic acid equivalents, such as tetrazoles, hydroxamic acids, amides, and esters, were obtained as precursors to the free acids or were prepared from them by standard methods, as described in the Experimental Section.

Unsaturated derivatives in the above series were prepared by Wittig–Horner olefination[15] of the corresponding aldehydes followed by hydrolysis (**19–22**).

Biology. The in vitro inhibition of thromboxane A_2 synthetase was measured by the method of Sun. With use of a preparation of lysed human platelets as the enzyme source,[17] TxB_2, PGE_2, and $PGF_{2\alpha}$ formed from [1-^{14}C]arachidonic acid (4 μM) were measured after separation by thin-layer chromatography. A partially purified preparation of PGH_2 synthetase[18] served to generate radiolabeled endoperoxide substrate from [1-^{14}C]arachidonic acid in situ.

The activities of prostacyclin and prostaglandin synthetase were measured as described in the Experimental Section.

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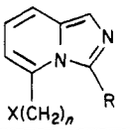
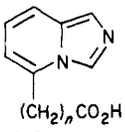
Table I. Variation of TxA_2 Synthetase Inhibition with Terminal Functionality



no.	R	X	n	IC_{50},[b] nM	mp, °C	formula[a]
1	H	CH_3	6	3300	158–160	$C_{14}H_{20}N_2$
2	H	CO_2H	6	5.2	137–139	$C_{14}H_{18}N_2O_2$
3	H	CN	5	630	178–180	$C_{13}H_{15}N_3 \cdot HCl$
4	H	CO_2Et	5	330	170–175 (0.12 mm)	$C_{15}H_{20}N_2O_2$
5	H	$CON(CH_3)_2$	5	550	166–171	$C_{15}H_{21}N_3O \cdot HCl$
6	H	$CONHCH_3$	5	270	115–122	$C_{14}H_{19}N_3O$
7	H	CH_2OH	5	280	174–179	$C_{13}H_{18}N_2O \cdot HCl$
8	H	$CONH_2$	5	77	131–132	$C_{13}H_{17}N_3O$
9	H	CO_2H	5	3.2	142–145	$C_{13}H_{16}N_2O_2$
10	CH_3	CO_2H	5	25000	170–173	$C_{14}H_{18}N_2O_2$
11	H	CONHOH	5	20	138–140	$C_{13}H_{17}N_3O_2$
12	H		4	11	158–160	$C_{12}H_{14}N_6 \cdot HCl$
13	H		5	19	188–190	$C_{13}H_{16}N_6 \cdot HCl$

[a] All C, H, N within ±0.4% of the theoretical values. [b] IC_{50} values are averages of two or more experiments.

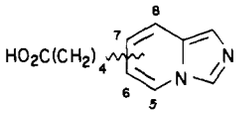
Table II. Variation of TxA_2 Synthetase Inhibition with Side-Chain Length



no.	n	IC_{50},[b] nM	mp, °C	log P	formula[a]
14	4	41	161–163	0.70	$C_{12}H_{14}N_2O_2$
9	5	3.2	142–145	1.10	$C_{13}H_{16}N_2O_2$
2	6	5.2	137–139	1.54	$C_{14}H_{18}N_2O_2$
15	7	21	97–101	2.01	$C_{15}H_{20}N_2O_2$

[a] All C, H, N within ±0.4% of the theoretical values. [b] IC_{50} values are averages of two or more experiments.

Table III. Variation of TxA_2 Synthetase Inhibition with Side-Chain Position



no.	position	IC_{50},[b] nM	mp, °C	formula[a]
14	5	41	161–163	$C_{12}H_{14}N_2O_2$
16	6	3300	173–175	$C_{12}H_{14}N_2O_2$
17	7	4700	162–164	$C_{12}H_{14}N_2O_2$
18	8	390	195–197	$C_{12}H_{14}N_2O_2$

[a] All C, H, N within ±0.4% of the theoretical values. [b] IC_{50} values are averages of two or more experiments.

Structure–Activity Relationships

1. Terminal Functionality. The imidazo[1,5-*a*]pyridine ring system inhibits thromboxane synthetase with an IC_{50} value of 10^{-6} M. However, as shown by Yoshimoto,[11] a side chain with a polar terminus capable of hydrogen bonding is necessary for optimum activity. This is illustrated by the superior activity of imidazo[1,5-*a*]pyridine-5-heptanoic acid (**2**) over 5-heptylimidazo[1,5-*a*]pyridine (**1**) as an enzyme inhibitor. Furthermore, varying the terminus in the 5-hexyl series produces an increase in activity where X = CN ≃ CO_2Et < $CON(CH_3)_2$ < $CONHCH_3$ ≃ CH_2OH < $CONH_2$ < CO_2H (compounds **3–9**). The importance of an unsubstituted C_3 carbon is emphasized by a 10000-fold difference in activity between **9** and its 3-methyl analogue **10** (see Table I). Carboxylic acid equivalents, such as the tetrazole **13** and the hydroxamic acid **11** retain excellent and essentially equivalent activities in vitro.

2. Side-Chain Length. The length of the alkanoic acid side chain had a marked effect on potency. Variation from the optimum chain length of the hexanoic acid decreased the activity. Since no correlation was observed between activity and partition coefficient[19] (Table II), the change in activity in vitro may be independent of the lipophilic character of this series of inhibitors. This variation of inhibitor potency with chain length is consistent with a secondary interaction between the carboxylic acid and a basic amino acid residue in or near the active site. It is attractive to speculate that arginine may be the focus of this interaction which would be strongest when two parallel hydrogen bonds are possible. Deviation from the optimum chain length would not eliminate activity but would reduce the multiplicity of the hydrogen bonding and hence the potency of the compounds as enzyme inhibitors. Such a sliding mechanism[20] is postualted for the interaction of carboxyalkyl-substituted trimethoprim analogues with dihydrofolate reductase.[21]

3. Side-Chain Position. The variation of activity with side-chain position on the imidazo[1,5-*a*]pyridine nucleus showed that 5-alkanoic acids are 10 times more active than 8-substituted derivatives which are 10 times more active than the equipotent 6- and 7-substituted analogues (Table III).

The low activity of 6- or 7-substituted imidazo[1,5-*a*]pyridines **16** and **17** and the good activity of 5-(imidazopyridinyl)pentanoic acid (**14**) suggest a site of secondary interaction above or below the plane of the ring in closer

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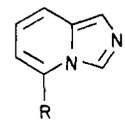
Table IV. Variation of TxA_2 Synthetase Inhibition with Side-Chain Unsaturation



no.	R	IC_{50},[b] nM	mp, °C	formula[a]
19	$(CH_2)_3CH{=}CHCO_2H$	4.8	142–144	$C_{13}H_{14}N_2O_2$
20	$(CH_2)_5CH{=}CHCO_2H$	40	110–111	$C_{15}H_{18}N_2O_2$
21	$(CH_2)_5CH{=}C(CH_3)CO_2H$	19	104–105	$C_{16}H_{20}N_2O_2$
22	$(CH{=}CH)_2CO_2H$	28	243–245	$C_{12}H_{10}N_2O_2$

[a] All C, H, N within ±0.4% of the theoretical values. [b] IC_{50} values are averages of two or more experiments.

proximity to the imidazo portion than the pyridine portion of the heterocycle.

4. Introduction of Unsaturation into the Side Chain. Having verified that a ω-carboxyalkyl, especially pentyl, side chain in the 5-position provided optimum activity, the effect of introducing unsaturation was evaluated (Table IV). By comparison of **19** with **9** and **20** and **21** with **15**, it is apparent that α,β unsaturation does not improve in vitro potency. Furthermore, extended conjugation, as exemplified by **22**, reduced inhibitory activity in this series. This is presumably due to reduced side-chain flexibility when all sp^3 centers have been eliminated. This observation further supports the notion that the secondary interaction involving the carboxyl is out of the plane of the imidazopyridine ring. Consequently, simple measurement of the distance between the carboxyl and the imidazole groups is an unreliable means of predicting activity.[10a]

In conclusion, the activity of these imidazo[1,5-*a*]-pyridines in inhibiting thromboxane A_2 synthetase is a function of side-chain position, length, rigidity, and terminal functionality.

The most potent member of the series, **9**, has an in vitro IC_{50} value of 3.2×10^{-9} M, whereas it inhibits prostacyclin synthetase and cyclooxygenase at 10^{-4} and 10^{-5} M, respectively. It is therefore an extremely potent and highly selective inhibitor of thromboxane A_2 synthetase.[22]

Experimental Section

Biological Methods. Materials. [1-^{14}C]Arachidonic acid, [^{3}H]TxB_2, [^{3}H]6-keto-$PGF_{1\alpha}$ and [^{3}H]PGE_2 were obtained from New England Nuclear. TxB_2, 6-keto-$PGF_{1\alpha}$, and PGE_2 were purchased from Upjohn Diagnostics or Sigma Chemical Co. The calcium ionophore A-23187 (free acid) was supplied by Calbiochem-Behring Corp. Antisera for TxB_2, 6-keto-$PGF_{1\alpha}$, and PGE_2 were obtained from Seragen, Inc., Boston, or from Dr. J. B. Smith, Thomas Jefferson University, Philadelphia. TLC plates were silica gel 60 F-254 from Merck, Darmstadt, Germany.

Enzyme Preparations and Assays. Tx synthetase was prepared from human platelets as described by Needleman et al.[17] A radiometric TLC assay similar to that reported by Sun et al.[16] was used to measure the formation of TxB_2, PGE_2, and $PGF_{2\alpha}$ from radiolabeled endoperoxide substrate. [1-^{14}C]Arachidonic acid (2 nmol) was incubated in 0.5 mL of 0.1 M Tris-HCl buffer, pH 7.5, containing tryptophan (5 mM), hemoglobin (0.2 μM), and an enzyme mixture consisting of crude microsomal Tx synthetase and a solubilized, partially purified preparation of PGH_2 synthetase from sheep seminal vesicles.[18] The latter enzyme served to generate radiolabeled endoperoxide substrate from [1-^{14}C]arachidonic acid in situ, thus eliminating the need to maintain an exogenous supply of PGH_2. Test drugs were present in a wide range of concentrations. At the end of the incubation period (30 min at 37 °C), PGE_2 was reduced to $PGF_2(\alpha+\beta)$ by the addition of $NaBH_4$. The reaction mixtures were acidified and the products extracted into ethyl acetate. The extracts were evaporated to dryness, dissolved in acetone, spotted on TLC plates, and chromatographed in the solvent system toluene–acetone–glacial acetic acid (100:100:3). The radioactive zones were located with a Berthold TLC Scanner; areas corresponding to TxB_2 and $PGF_2(\alpha+\beta)$ were scraped off and counted in a Beckman liquid scintillation counting system. Owing to kinetic complexities introduced by nonenzymic conversion of endoperoxide substrate to PGE_2 and $PGF_{2\alpha}$, results were calculated in terms of ratios of counts for $TxB_2/PGF_2(\alpha+\beta)$, which are better than simple measurements of TxB_2 formation as estimates of Tx synthetase activity under the assay conditions employed. IC_{50} values were determined graphically as the concentrations of test drugs at which the ratios were reduced to 50% of the control value. The ratio under control conditions ranged from 1 to 4 in different experiments. IC_{50} values were the average of two or more experiments.

PGH_2 synthetase was obtained from sheep seminal vesicles by the method of Takeguchi et al.[23] The incubation mixture (0.5 mL) in 0.1 M Tris-HCl, pH 8.3, contained [1-^{14}C]arachidonic acid (2 μM), epinephrine (1 mM), glutathione (1 mM), and test drug in a wide range of concentrations. The reaction was started by addition of enzyme and continued for 10 min at 25 °C. The reaction mixtures were acidified, extracted, and chromatographed as described above for the Tx synthetase assay. Spots corresponding to PGE_2 were counted. IC_{50} values were determined graphically as the concentrations of test drugs at which the counts for PGE_2 were reduced to 50% of the control value.

Prostacyclin synthetase was prepared from bovine aorta according to the method of Gryglewski et al.[24] The assay was identical with the Tx synthetase assay except for substitution of the latter enzyme by crude microsomal prostacyclin synthetase, omission of the $NaBH_4$ reduction step, and chromatography in the organic phase of ethyl acetate–2,2,4-trimethylpentane–glacial acetic acid–water (110:50:20:10). Again, owing to nonenzymic conversions of endoperoxide substrate and the attendant kinetic complexities, results were expressed as ratios of counts for 6-keto-$PGF_{1\alpha}/PGE_2$. IC_{50} values were determined graphically as the concentrations of test drugs at which the ratios were reduced to 50% of the control value. The control ratio ranged from 1 to 10 in different experiments.

Chemistry. The melting points were measured with a Thomas melting point apparatus and are uncorrected. The NMR spectra were recorded on Hitachi Perkin-Elmer R-600 or a Perkin-Elmer R-12 instrument. The IR spectra were recorded on a Perkin-Elmer 281B infrared spectrophotometer. Chromatographies were carried out with 70–230-mesh silica gel from E. Merck, Darmstadt, as stationary phase, or 2000 μm, 20 × 20 cm silica chromatography plates from Analtech. Metalations were carried out in tetrahydrofuran distilled from lithium aluminum hydride with *n*-butyllithium in hexane from Alfa. Alkylating agents were freshly distilled prior to use.

Methyl 5-(3-Pyridyl)pentanoate (29). A solution of 4.8 mL of 3-bromopyridine (7.9 g, 50 mmol), 7.15 g of methyl 4-pentenoate (7.15 g, 62.5 mmol), 0.11 g of palladium acetate (0.5 mmol), and 0.6 g of tri-*o*-tolylphosphine (2.0 mmol) in 50 mL of triethylamine was refluxed for 24 h under argon and the solvent evaporated. The residue was taken up in 50 mL of methylene chloride and washed with water (2 × 40 mL). The organic phase was dried and evaporated to yield 9.5 g of 3-[4-(methoxycarbonyl)but-1-enyl]pyridine containing a small amount of contaminant, as a colorless liquid which was carried on without further purification. NMR ($CDCl_3$) δ 3.72 (s, 3 H), 6.40 (s, 1 H); IR (film) 1725 cm^{-1}.

A solution of 9.5 g of the oil containing 3-[4-(methoxycarbonyl)but-1-enyl]pyridine was hydrogenated in 100 mL of methanol at 3 atm for 3.5 h with 0.5 g of 5% palladium on charcoal. The reaction mixture was filtered and evaporated to yield an oil which is chromarographed on 400 g of silica with 3:1 toluene–ethyl acetate to yield 8.75 g (90%) of methyl 5-(3-

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pyridyl)pentanoate (29): NMR ($CDCl_3$) δ 1.50–1.95 (m, 4 H), 2.10–2.90 (m, 4 H), 3.70 (s, 3 H), 7.22 (dd, J = 4.5, 7.5 Hz, 1 H), 7.55 (d, J = 7.5 Hz, 1 H), 8.48 (d, J = 4.5 Hz, 1 H), 8.5 (s, 1 H); IR (film) 1725 cm^{-1}.

Methyl 5-(2-Cyanopyrid-3-yl)pentanoate (30), Methyl 5-(2-Cyanopyrid-5-yl)pentanoate (31). Peracetic acid (40%) (8.3 mL, 63.9 mmol) was added dropwise to methyl 5-(3-pyridyl)pentanoate (10.81 g, 55.9 mmol) (29), so as to maintain the reaction temperature between 80 and 85 °C. After the addition was complete, the temperature was allowed to fall to 30 °C and excess peracid was destroyed with aqueous sodium sulfite. The acetic acid was distilled at reduced pressure, and the residue was taken up in methylene chloride (50 mL), filtered, and evaporated. The residue was treated with dimethyl sulfate (7.7 g, 61.3 mmol) in 40 mL of toluene at 90 °C for 1 h and the solvent was evaporated. The methyl sulfate salt was dissolved in 16.7 mL of ice-cold water and a solution of 8.3 mL of 1 N sodium hydroxide and potassium cyanide (11.21 g, 172 mmol) in 16.7 mL of ice-cold water was added slowly so as to keep the reaction temperature below 0 °C. After 24 h at 0 °C, extraction with methylene chloride (3 × 30 mL), drying over sodium sulfate, and evaporation of solvent yielded 9.02 g of isomeric cyanopyridines, from which 3.4 g (28%) of methyl 5-(2-cyanopyrid-3-yl)pentanoate (Rf 0.56) (30) and 2.64 g (22%) of methyl 5-(2-cyanopyrid-5-yl)pentanoate (Rf 0.5) (31) were obtained by column chromatography (300 g of SiO_2, 3:2 ether:pentane). **30**: NMR ($CDCl_3$) δ 1.70–2.20 (m, 4 H), 2.40–3.10 (m, 4 H), 3.85 (s, 3 H), 3.8 (s, 1 H), 3.86 (s, 1 H), 8.72 (s, 1 H); IR (CH_2Cl_2) 1720 cm^{-1}; MS, 218 (M^+), 187, 157, 145. **31**: NMR ($CDCl_3$) δ 1.60–1.95 (m, 4 H), 2.40–2.90 (m, 4 H), 3.60 (s, 3 H), 6.48 (d of d, J = 8.0, 4.5 Hz, 1 H), 6.70 (d of d, J = 8.0, 2.2 Hz, 1 H), 8.52 (d of d, J = 4.5, 2.2 Hz, 1 H); IR 1715 cm^{-1}; MS, 218 (M^+), 187, 157, 145.

Methyl 5-[2-(Aminomethyl)pyrid-3-yl]pentanoate Hydrochloride. Methyl 5-(2-cyanopyrid-3-yl)pentanoate (2.40 g, 11 mmol) was dissolved in 92 mL of methanol containing 2.4 mL of concentrated hydrochloric acid and hydrogenated at atmospheric pressure with 1.2 g of 10% palladium on charcoal for 3 h. Filtration, evaporation, and recrystallization from ether–methylene chloride yielded 1.65 g (67%) of methyl 5-[2-(aminomethyl)pyrid-3-yl]pentanoate hydrochloride (mp 79–81 °C): NMR (Me_2SO) δ 1.40–1.80 (m, 4 H), 2.20–2.90 (m, 4 H), 3.60 (s, 3 H), 4.18 (br s, 2 H), 7.15–7.85 (m, 2 H), 8.42 (br s, 1 H); IR (Me_2SO) 1725 cm^{-1}.

8-[4-(Methoxycarbonyl)butyl]imidazo[1,5-*a*]pyridine. Methyl 5-[2-(aminomethyl)pyrid-3-yl]pentanoate (0.1 g, 0.45 mmole) was heated to 90 °C in 0.6 mL of formic acid for 18 h. The mixture was cooled to 0 °C, made basic with saturated ammonium hydroxide solution, and extracted with methylene chloride (4 × 10 mL). Drying, filtration, and evaporation of the extracts yielded 67 mg (60%) of the low-melting formamide (43–45 °C), which was redissolved in 1 mL of toluene and heated to 90 °C for 17 h with phosphorus oxychloride (75 mg, 0.49 mmol). Evaporation of excess phosphorus oxychloride with toluene, basification at 0 °C with saturated ammonium hydroxide solution, extraction with methylene chloride (4 × 15 mL), and drying over sodium sulfate yielded 54 mg of an oil which was chromatographed (SiO_2, ethyl acetate) to yield 36 mg (68%) of 8-[4-(methoxycarbonyl)butyl]imidazo[1,5-*a*]pyridine (R_f 0.29): NMR ($CDCl_3$) δ 1.60–2.00 (m, 4 H), 2.39 (t, J = 5.5 Hz, 2 H), 2.80 (t, J = 6.0 Hz, 2 H), 3.70 (s, 3 H), 6.50 (d, J = 4.4 Hz, 2 H), 7.43 (s, 1 H), 7.83 (t, J = 4.4 Hz, 1 H), 8.22 (s, 1 H); IR (CH_2Cl_2) 1725 cm^{-1}; MS, 232 (M^+), 201, 173, 159, 145, 132.

8-(4-Carboxybutyl)imidazo[1,5-*a*]pyridine (18). A solution of 8-[4-(methoxycarbonyl)butyl]imidazo[1,5-*a*]pyridine (30 mg, 0.13 mmol) in 0.3 mL of ethanol and 0.3 mL of 1 N sodium hydroxide was refluxed for 2 h, cooled, diluted with 2 mL of water, and extracted with ethyl acetate (1 × 5 mL). The aqueous phase was brought to pH 6 and was extracted with methylene chloride (4 × 10 mL). The extracts were dried and evaporated to yield 28 mg (98%) of 8-(4-carboxybutyl)imidazo[1,5-*a*]pyridine as pale yellow crystals (mp 195–197 °C): NMR ($CDCl_3$) δ 1.50–2.20 (m, 4 H), 2.20–3.05 (m, 4 H), 6.65 (d, J = 4.0 Hz, 2 H), 7.53 (s, 1 H), 8.13 (t, J = 4.0 Hz, 1 H), 8.55 (s, 1 H); IR (CH_2Cl_2) 1710 cm^{-1}; MS, 218 (M^+), 173, 132.

Methyl 5-[2-(Aminomethyl)pyrid-5-yl]pentanoate. Methyl (2-cyanopyrid-5-yl)pentanoate (31) (1.48 g, 6.8 mmol) was dissolved in 56 mL of methanol containing 1.5 mL of concentrated hydrochloric acid and hydrogenated at atmospheric pressure with 0.75 g of 10% palladium on charcoal for 18 h. Filtration, evaporation, chromatography on 20 g of silica gel with 1:1 methanol–ethyl acetate, and crystallization from ether–methylene chloride yielded 0.89 g (59%) of methyl 5-[2-(aminomethyl)-pyrid-5-yl]pentanoate as its carbonate (mp 79–80 °C): NMR ($CDCl_3$) δ 1.50–1.95 (m, 4 H), 2.15–2.80 (m, 4 H), 3.67 (s, 3 H), 4.24 (s, 2 H), 7.28 (d, J = 7.0 Hz, 1 H), 7.53 (d, J = 7.0 Hz, 1 H), 8.44 (s, 1 H); IR (CH_2Cl_2) 1725 cm^{-1}; MS, 222 (M^+), 205, 194, 191, 135.

6-[4-(Methoxycarbonyl)butyl]imidazo[1,5-*a*]pyridine. Methyl 5-[2-(aminomethyl)pyrid-5-yl] pentanoate (0.20 g, 0.9 mmol) was heated to 90 °C in 0.6 mL of formic acid for 18 h. The mixture was cooled to 0 °C, made basic with saturated ammonium hydroxide solution, and extracted with methylene chloride (4 × 15 mL). Drying, filtration, and evaporation of the extracts yielded 0.124 g of an oily formamide (ν 1720, 1675 cm^{-1}), which was redissolved in 1 mL of toluene and heated to 90 °C for 18 h with phosphorus oxychloride (0.166 g, 1.08 mmol). Evaporation of excess phosphorus oxychloride with toluene, basification at 0 °C with saturated ammonium hydroxide solution, extraction with methylene chloride (4 × 15 mL), and drying over sodium sulfate yielded 126 mg of an oil which was chromatographed (SiO_2, ethyl acetate) to yield 107 mg (51%) of 6-[4-(methoxycarbonyl)butyl]imidazo[1,5-*a*]pyridine (R_f 0.26): NMR ($CDCl_3$) δ 1.40–1.90 (m, 4 H), 2.00–2.65 (m, 4 H), 3.58 (s, 3 H), 6.45 (d, J = 9.0 Hz, 1 H), 7.25 (d, J = 9.0 Hz, 1 H), 7.38 (s, 1 H), 7.62 (s, 1 H), 7.94 (s, 1 H); IR (CH_2Cl_2) 1730 cm^{-1}; MS, 232 (M^+), 201, 145, 131.

6-(4-Carboxybutyl)imidazo[1,5-*a*]pyridine (16). A solution of methyl 5-(6-imidazo[1,5-*a*]pyridyl)pentanoate (92 mg, 0.8 mmol) in 0.3 mL of ethanol and 0.9 mL of 1 N sodium hydroxide was refluxed for 2 h, cooled, diluted with 2 mL of water, and extracted with ethyl acetate (5 mL). The aqueous phase was brought to pH 6 and was extracted with chloroform. The extracts were dried and evaporated to yield 55 mg (63%) of 6-(4-carboxybutyl)-imidazo[1,5-*a*]pyridine as white crystals (mp 168–171 °,c): NMR ($CDCl_3$) δ 1.40–1.80 (m, 4 H), 2.05–2.75 (m, 4 H), 6.69 (d, J = 9.6 Hz, 1 H), 7.52 (d, J = 9.6 Hz, 1 H), 8.16 (s, 2 H), 8.33 (s, 1 H); IR (CH_2Cl_2) 1700 cm^{-1}; MS, 218 (M^+), 145, 131.

4-(3-Chloropropyl)-2-cyanopyridine (32). Peracetic acid (40%, 5.0 mL, 38.7 mmol) was added to 4-(3-chloropropyl)-pyridine[25] (5.18 g, 33.3 mmol) at such a rate as to keep the reaction temperature at 80 °C. The mixture was stirred until the temperature fell to 30 °C. Excess peracid was destroyed with sodium sulfite solution and the solvent was vacuum distilled. The residue was redissolved in methylene chloride (50 mL), filtered, and evaporated to yield the crude N-oxide, which was heated to 80 °C in dimethyl sulfate (4.66 g, 37 mmol) for 2 h. The resulting methyl sulfate salt was dissolved in 10 mL of water, cooled to 0 °C, and reacted with an ice-cold solution of potassium cyanide (6.7 g, 100 mmol) in 20 mL of 0.25 N sodium hydroxide for 22 h. The product was extracted with methylene chloride (3 × 30 mL) and dried over sodium sulfate. The solvent was evaporated and the residue filtered through 45 g of silica gel with ether to yield 1.26 g (21%) of 4-(3-chloropropyl)-2-cyanopyridine as a yellow oil (R_f 0.61): NMR ($CDCl_3$) δ 2.0–2.40 (m, 2 H), 2.90 (t, J = 6.0 Hz, 2 H), 3.56 (t, J = 6.0 Hz, 2 H), 7.40 (d, J = 5.0 Hz, 1 H), 7.57 (s, 1 H), 8.60 (d, J = 5.0 Hz, 1 H); IR (CH_2Cl_2) 2210 cm^{-1}.

2-(Aminomethyl)-4-(3-chloropropyl)pyridine. A solution of borane–dimethyl sulfide (0.83 mL, 7.7 mmol) in 7 mL of tetrahydrofuran was added slowly to a refluxing solution of 4-(3-chloropropyl)-2-cyanopyridine (1.24 g, 6.9 mmol) in 7 mL of tetrahydrofuran. Dimethyl sulfide was simultaneously distilled off through a 10-cm vigreux column. The mixture was refluxed for 15 min after the addition was complete and cooled to 30 °C and 6 mL of 6 N hydrochloric acid was added. After hydrogen evolution had ceased, the mixture was refluxed for 30 min, cooled to 0 °C, and saturated with solid sodium carbonate before extracting with methylene chloride (4 × 50 mL). The organic extracts were dried over sodium sulfate and evaporated to yield 0.99 g of an oil which was filtered through 10 g of silica gel (1:1 EtOAc–MeOH) to yield 0.53 g (12%) of 2-(aminomethyl)-4-(3-chloropropyl)pyridine as a yellow oil: NMR ($CDCl_3$) δ 1.60–2.40 (m, 2 H), 2.82 (t, J = 8.0 Hz, 2 H), 3.55 (t, J = 7.0 Hz, 2 H), 4.20

(s, 2 H), 7.07 (d, J = 4.5 Hz, 1 H), 7.27 (s, 1 H), 8.46 (d, J = 5.7 Hz, 1 H); MS, 184 (M^+), 169, 155.

7-(3-Chloropropyl)imidazo[1,5-*a*]pyridine (33). A solution of 2-(aminomethyl)-4-(3-chloropropyl)pyridine (0.47 g, 2.5 mmol) in 1 mL of formic acid was heated to 90 °C for 18 h, cooled to 0 °C, and made basic by the addition of saturated ammonium hydroxide solution. Extraction with methylene chloride (4 × 10 mL), drying over sodium sulfate, and evaporation yielded 0.51 g of the formamide (ν 1674 cm^{-1}), which was heated to 90 °C in phosphorus oxychloride (0.75 g, 4.9 mmol) for 15 h. Excess phosphorus oxychloride was evaporated with toluene and the residue was suspended in 15 mL of methylene chloride, cooled to 0 °C, and made basic with saturated ammonium hydroxide. Extraction with methylene chloride (4 × 15 mL), drying over sodium sulfate, and preparative thin-layer chromatography (SiO_2, EtOAc) yielded 42 mg (86%) of 7-(3-chloropropyl)imidazo[1,5-*a*]pyridine (R_f 0.24, EtOAc) as a yellow gum: NMR ($CDCl_3$) δ 1.8–2.4 (m, 2 H), 2.72 (t, J = 8.0 Hz, 2 H) 3.58 (t, J = 8.5 Hz, 2 H), 6.42 (d of d, J = 3.8, 1.8 Hz, 1 H), 7.21 (s, 1 H), 7.32 (s, 1 H), 7.88 (d, J = 3.8 Hz, 1 H), 8.07 (s, 1 H); IR (CH_2Cl_2) 3050 cm^{-1}.

7-[4,4-Bis(methoxycarbonyl)butyl]imidazo[1,5-*a*]pyridine. A solution of 7-(3-chloropropyl)imidazo[1,5-*a*]pyridine (50 mg, 0.26 mmol), dimethyl malonate (0.14 g, 1.05 mmol), and potassium carbonate (144 mg, 1.04 mmol) in 2 mL of dimethylformamide was heated between 80 and 90 °C under nitrogen for 9 h. The solvent was evaporated and the residue taken up in 10 mL of water and extracted with ethyl acetate (2 × 10 mL). The organic extracts were washed with 2 N hydrochloric acid (2 × 10 mL). Basification of the aqueous extracts with solid sodium bicarbonate, extraction with methylene chloride (3 × 10 mL), drying over sodium sulfate, and evaporation yielded 68 mg (91%) of the dimethyl ester: NMR ($CDCl_3$) δ 1.2–1.9 (m, 4 H), 2.30 (t, J = 8.0 Hz, 2 H), 2.9–3.2 (m, 1 H), 3.40 (s, 6 H), 6.06 (d, J = 7.0 Hz, 1 H), 6.82 (s, 1 H), 6.94 (s, 1 H), 7.55 (d, J = 7.0 Hz, 1 H), 7.75 (s, 1 H); IR (CH_2Cl_2) 1725 cm^{-1}; MS, 290 (M^+), 259, 145, 144, 131.

7-(4-Carboxybutyl)imidazo[1,5-*a*]pyridine (17). A solution of 7-[4,4-bis(methoxycarbonyl)butyl]imidazo[1,5-*a*]pyridine (65 mg, 0.22 mmol) in 8.0 mL of 1 N sodium hydroxide and 0.5 mL of ethanol was heated at reflux for 2 h. The solvent was evaporated and 0.8 mL of 1 N hydrochloric acid was added. After the water was evaporated, the residue was redissolved in 3 mL of xylene and heated to 137 °C for 4 h. The xylene was evaporated and replaced with 2 mL of 1 N sodium hydroxide. Extraction of the aqueous phase with 5 mL of ethyl acetate, acidification to pH 6, reextraction with chloroform (3 × 15 mL), and evaporation yielded 20 mg (42%) of 7-(4-carboxybutyl)imidazo[1,5-*a*]pyridine (mp 158–161 °C): NMR ($CDCl_3$) δ 1.2–1.9 (m, 4 H), 2.1–2.6 (m, 4 H), 6.55 (d of d, J = 6.0, 1.4 Hz, 1 H), 7.32 (br s, 2 H), 8.30 (d, J = 6.0 Hz, 1 H), 8.37 (s, 1 H); IR (CH_2Cl_2) 1705 cm^{-1}; MS, 218 (M^+). 145, 131.

5-[5-(Ethoxycarbonyl)pentyl]imidazo[1,5-*a*]pyridine (4). To a solution of 5-methylimidazo[1,5-*a*]pyridine (24) (50.0 g, 0.378 mol) in 625 mL of tetrahydrofuran at −78 °C under nitrogen was added 175 mL of 2.4 N *n*-butyllithium (0.42 mol) in hexane. The temperature was maintained below −50 °C during the addition. The solution of 5-(lithiomethyl)imidazo[1,5-*a*]pyridine was recooled to −78 °C and a solution of 5-bromo-1,1,1-triethoxypentane (121.8 g, 0.43 mol) in 125 mL of tetrahydrofuran was added rapidly. The reaction was allowed to warm to −4 °C over a 45-min period, and the solvents were evaporated to yield a residue which was partitioned between 500 mL of ether and 240 mL of 3 N hydrochloric acid. The ether solution was extracted twice with 60 mL of 3 N hydrochloric acid, and the combined aqueous extracts were basified with 100 mL of concentrated ammonium hydroxide solution. The aqueous phase was extracted with 200 mL of ether, and the extracts were dried ($MgSO_4$) and evaporated to an oil which yielded 51.0 g (52%) of 5-[5-(ethoxycarbonyl)-pentyl]imidazo[1,5-*a*]pyridine on distillation at 180–185 °C (0.12 mmHg): NMR ($CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3 H), 1.3–2.2 (m, 6 H), 2.34 (t, J = 6.5 Hz, 2 H), 2.85 (t, J = 6.5 Hz, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 6.36 (d, J = 5.9 Hz, 1 H), 6.70 (d of d, J = 5.9, 9.5 Hz, 1 H), 7.42 (d, J = 9.5 Hz, 1 H), 7.48 (s, 1 H), 8.10 (s, 1 H); IR (CH_2Cl_2) 1724 cm^{-1}.

5-(5-Carboxypentyl)imidazo[1,5-*a*]pyridine (9). A suspension of 5-[5-(ethoxycarbonyl)pentyl]imidazo[1,5-*a*]pyridine (26.0 g, 0.11 mol) in 100 mL of 1 N aqueous sodium hydroxide solution was heated on a steam bath for 2 h. Ethanol (10 mL) was added and heating was continued for 45 min. The reaction mixture was cooled, washed with 300 mL of ether, and adjusted to pH 5.5 with concentrated hydrochloric acid. The resulting solid was filtered, washed with 50 mL of water to yield 21.8 g (95%) of 5-(5-carboxypentyl)imidazo[1,5-*a*]pyridine (mp 144–147 °C): NMR (Me_2SO) δ 1.20–2.05 (m, 6 H), 2.28 (t, J = 6.0 Hz, 2 H), 2.95 (t, J = 7.5 Hz, 2 H), 6.54 (d, J = 6.0 Hz, 1 H), 6.82 (d of d, J = 6.0, 9.0 Hz, 1 H), 7.48 (s, 1 H), 7.51 (d, J = 9.0 Hz, 1 H), 8.40 (s, 1 H); IR (Nujol) 1707 cm^{-1}.

5-(6-Hydroxyhexyl)imidazo[1,5-*a*]pyridine (7). 5-(5-Carboxypentyl)imidazo[1,5-*a*]pyridine (9) (1.0 g 4.2 mmol) was suspended in 5 mL of tetrahydrofuran with trimethyl borate (2.35 g) and borane–dimethyl sulfide (1.0 mL, 10.0 mmol) was added dropwise. The reaction mixture was refluxed for 2 h, cooled, and quenched by the addition of 2.6 mL of methanol, 9.5 mL of water, and 2 mL of 50% sodium hydroxide. After heating under reflux for 1 h, the mixture was diluted with water and extracted twice with methylene chloride. The methylene chloride extracts were dried and evaporated to yield an oil which was treated with ethanolic hydrochloric acid in ether to yield 0.55 g (60%) of 5-(6-hydroxyhexyl)imidazo[1,5-*a*]pyridine hydrochloride melting at 174–179 °C: NMR (Me_2SO) 1.25–2.10 (m, 8 H), 2.90–3.25 (m, 2 H), 3.30–3.70 (m, 2 H), 7.04 (d, J = 7.6 Hz, 1 H), 7.29 (d of d, J = 7.6, 9.6 Hz, 1 H), 7.82 (d, J = 9.6 Hz, 1 H), 8.23 (s, 1 H), 9.88 (s, 1 H); IR (Nujol) 3280 cm^{-1}.

5-[5-(Methylcarbamoyl)pentyl]imidazo[1,5-*a*]pyridine (6). A solution of 5-[5-(ethoxycarbonyl)pentyl]imidazo[1,5-*a*]pyridine (4) (3.9 g, 16.5 mmol) in 40 mL of 1-butanol was saturated with methylamine and heated on a steam bath for 56 h in a pressure bottle. The solvent was evaporated and resulting solid was recrystallized from 1:1 ethyl acetate–ether to yield 2.1 g (51%) of 5-[5-(methylcarbamoyl)pentyl]imidazo[1,5-*a*]pyridine melting at 118–122 °C: NMR ($CDCl_3$) δ 1.40–2.10 (m, 6 H), 2.24 (t, J = 6.0 Hz, 2 H), 2.60–3.10 (m, 2 H), 2.85 (d, J = 5.0 Hz, 3 H), 5.50–6.20 (m, 1 H), 6.43 (d, J = 6.0 Hz, 1 H), 6.76 (d of d, J = 6.0, 9.4 Hz, 1 H), 7.43 (d, J = 9.4 Hz, 1 H), 7.52 (s, 1 H), 8.13 (s, 1 H); IR (CH_2Cl_2) 3230, 1662 cm^{-1}.

5-(5-Chloropentyl)imidazo[1,5-*a*]pyridine. A solution of 1-bromo-4-chlorobutane (3.0 g, 0.16 mol) in 20 mL of dry tetrahydrofuran was added to a solution of 5-(lithiomethyl)imidazo-[1,5-*a*]pyridine, prepared from 5-methylimidazo[1,5-*a*]pyridine (16.2 g, 0.15 mol) and 70 mL of *n*-butyllithium (0.16 mol) in hexane in 200 mL of tetrahydrofuran at −50 °C. After 3 h at −50 °C and 15 h at room temperature, the solvent was evaporated. The residue was taken up in 100 mL of 3 N hydrochloric acid and washed with 100 mL of ether. The aqueous phase was adjusted to pH 10 and extracted with methylene chloride to yield 24 g (67%) of 5-(5-chloropentyl)imidazo[1,5-*a*]pyridine which was used without further purification.

5-[5-(Dimethylcarbamoyl)pentyl]imidazo[1,5-*a*]pyridine (5). A solution of 5-[5-(methylcarbamoyl)pentyl]imidazo[1,5-*a*]pyridine (6) (2.45 g, 1.03 mmol) in 25 mL of dimethylformamide was warmed to 50 °C for 30 min with 0.011 mol of sodium hydride (obtained by washing 0.53 g of 50% NaH dispersion in mineral oil with hexane). Methyl iodide (1.56 g, 1.04 mmol) was added to the cooled solution which was stirred at room temperature for 2 h, diluted with water, and extracted with a 1:1 mixture of ethyl acetate and ether and with chloroform. Drying and evaporation of solvents yielded an oil which was dissolved in ether and treated with ethanolic hydrochloric acid. The precipitated salt was collected and recrystallized from ethanol/ether to yield 2.03 g (71%) of 5-[5-(dimethylcarbamoyl)pentyl]imidazo[1,5-*a*]pyridine hydrochloride melting at 166–171 °C: NMR (Me_2SO) δ 1.40–2.05 (m, 6 H), 2.20–2.50 (m, 2 H), 2.70–3.10 (m, 2 H), 2.84 (s, 3 H), 2.98 (s, 3 H), 7.00–7.30 (m, 2 H), 7.65–7.92 (m, 1 H), 8.17 (s, 1 H), 9.68 (s, 1 H); IR (CH_2Cl_2) 1626, 1637 cm^{-1}.

5-(5-Cyanopentyl)imidazo[1,5-*a*]pyridine (3). A solution of 5-(5-chloropentyl)imidazo[1,5-*a*]pyridine (37.0 g, 0.2 mol), potassium cyanide (21.7 g), and dibenzo-18-crown-6 (3.0 g) in acetonitrile was heated to reflux for 20 h. The acetonitrile was evaporated and the residue was partitioned between water and methylene chloride. The methylene chloride extract was evaporated to dryness to yield 34.1 g of 5-(5-cyanopentyl)imidazo-[1,5-*a*]pyridine as an oil (mp 178–180 °C hydrochloride): NMR ($CDCl_3$) δ 1.55–2.20 (m, 6 H), 2.4 (t, J = 5.5 Hz, 2 H), 2.92 (t, J

= 6.5 Hz, 2 H), 6.40 (d, J = 6.0 Hz, 1 H), 6.75 (d of d, J = 6.75, 9.2 Hz, 1 H), 7.41 (d, J = 9.2 Hz, 1 H), 7.51 (s, 1 H), 8.13 (s, 1 H); IR (film) 1634 cm^{-1}.

5-(5-Carbamoylpentyl)imidazo[1,5-*a*]pyridine (8). A solution of 5-(5-cyanopentyl)-3-methylimidazo[1,5-*a*]pyridine hydrochloride (3) (3.0 g, 13.3 mmol) in 20 mL of ethanol and 5 mL of 1 N sodium hydroxide was treated with 10 mL of 30% hydrogen peroxide solution. The pH of the solution was adjusted to 10 with 1 N sodium hydroxide. After the solution was stirred at room temperature overnight, the ethanol was evaporated, water was added, and the mixture was extracted with methylene chloride. The resulting product crystallized from ether and was recrystallized from acetonitrile to yield 2.03 g (69%) of 5-(5-carbamoylpentyl)imidazo[1,5-*a*]-pyridine (mp 131–132 °C): NMR ($CDCl_3$) δ 1.30–2.05 (m, 6 H), 2.28 (t, J = 5.5 Hz, 2 H), 2.92 (t, J = 7.6 Hz, 2 H), 5.50–6.10 (m, 2 H), 6.41 (d, J = 6.4 Hz, 1 H), 6.75 (d of d, J = 6.4, 9.8 Hz, 1 H), 7.40 (d, J = 9.8 Hz, 1 H), 7.49 (s, 1 H), 8.13 (s, 1 H); IR (CH_2Cl_2) 3335, 1660 cm^{-1}.

5-[5-(Hydroxycarbamoyl)pentyl]imidazo[1,5-*a*]pyridine (11). A solution of hydroxylamine (from 2.06 g of hydroxylamine hydrochloride and 2.02 g of sodium hydroxide) and 5-[5-(methoxycarbonyl)pentyl]imidazo[1,5-*a*]pyridine (6.08 g, 27.4 mmol) in 25 mL of methanol was allowed to stand at room temperature for 20 h. The methanol was evaporated and the residue was taken up in 5 mL of water and adjusted to pH 7. The resulting oil crystallized and the solid was collected, yielding 5.0 g (82%) of 5-[5-(hydroxycarbamoyl)pentyl]imidazo[1,5-*a*]pyridine: mp 138–140 °C; NMR (Me_2SO) δ 1.20–2.20 (m, 8 H), 2.84 (t, J = 6.2 Hz, 2 H), 6.40 (d, J = 6.0 Hz, 1 H), 6.70 (d of d, J = 6.0, 9.0 Hz, 1 H), 7.36 (s, 1 H), 7.40 (d, J = 9.0 Hz, 1 H), 8.29 (s, 1 H); IR (Nujol) 1632 cm^{-1}.

5-[5-(5-Tetrazolyl)pentyl]imidazo[1,5-*a*]pyridine (13). A solution of 5-(5-cyanopentyl)imidazo[1,5-*a*]pyridine (3) (5.26 g, 27.8 mmol) in 16 mL of dry dimethylformamide was heated at 120 °C for 15 h with sodium azide (2.15 g, 33.0 mmol), lithium chloride (0.2 g), and ammonium chloride (1.80 g). After cooling and filtration, the solvent was evaporated and the residue was dissolved in 50 mL of water, extracted with 25 mL of ethyl acetate, and brought to pH 5 with concentrated hydrochloric acid. The precipitated solid was filtered, washed with water, and dried to yield 1.62 g (23%) of 5-[5-(5-tetrazolyl)pentyl]imidazo[1,5-*a*]-pyridine hydrochloride: mp 197–199 °C; NMR (Me_2SO) δ 1.20–2.10 (m, 6 H), 2.70–3.30 (m, 4 H), 6.96 (d, J = 6.0 Hz, 1 H), 7.32 (d of d, J = 6.0, 9.2 Hz, 1 H), 7.79 (d, J = 9.2 Hz, 1 H), 8.20 (s, 1 H), 9.85 (s, 1 H); IR (Nujol) 3124, 1641, 1560, 1540 cm^{-1}.

5-(5-Formylpentyl)imidazo[1,5-*a*]pyridine. To a cooled solution of 5-[5-(methoxycarbonyl)pentyl]imidazo[1,5-*a*]pyridine (4.9 g, 22.1 mmol) (obtained by esterification of 5-(5-carboxypentyl)imidazo[1,5-*a*]pyridine with diazomethane in methylene chloride) in 140 mL of methylene chloride at −60 °C was added dropwise 40 mL of a 1.75 M solution of diisobutylaluminum hydride in toluene. On completion of the addition, the reaction was allowed to stir at −60 °C for a further 20 min. Methanol (10 mL), followed by 100 mL of water, was then added. The reaction was stirred at room temperature for 15 min, the methylene chloride layer was separated and dried over sodium sulfate and the solvent was evaporated under reduced pressure to yield 4.0 g (94%) of 5-(5-formylpentyl)imidazo[1,5-*a*]pyridine: NMR ($CDCl_3$) δ 1.20–1.95 (m, 6 H), 2.80 (t, 2 H, J = 6.0 Hz), 3.65 (t, 2 H, J = 6.0 Hz), 6.28 (d, J = 6.2 Hz, 1 H), 6.65 (d of d, J = 6.2, 9.0 Hz, 1 H), 7.1 (s, 1 H), 7.15 (d, J = 9.0 Hz, 1 H), 7.45 (s, 1 H), 8.02 (s, 1 H), 9.71 (t, J = 1.2 Hz, 1 H); IR (CH_2Cl_2) 1700 cm^{-1}.

5-(7-Carboxy-6-heptenyl)imidazo[1,5-*a*]pyridine (20). A solution of 5-(5-formylpentyl)imidazo[1,5-*a*]pyridine (2.75 g, 14.3 mmol) in 180 mL of chloroform was stirred at room temperature for 18 h with (carbethoxymethylene)triphenylphosphorane (6.5 g, 18.6 mmol). The solvent was evaporated and the residue was redissolved in 30 mL of methanol and 15 mL of 1 N sodium hydroxide solution was added. The mixture was stirred for 3 h at room temperature and the methanol was evaporated. The residue was diluted with 30 mL of water, adjusted to pH 7 with concentrated hydrochloric acid, and extracted with chloroform (2 × 50 mL). The organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 0.7 g (19%) of 5-(7-carboxy-6-heptenyl)imidazo[1,5-*a*]pyridine: mp 110–111 °C; NMR ($CDCl_3$) δ 1.2–3.1 (m, 10 H), 5.92 (d, J = 15.5 Hz, 1 H), 6.44 (d, J = 6.0 Hz, 1 H), 6.78 (d of d, J = 6.0, 9.2 Hz, 1 H), 7.05 (d, J = 15.5 Hz, 1 H), 7.4 (d, J = 9.2 Hz, 1 H), 7.54 (s, 1 H), 8.29 (s, 1 H), 8.29 (s, 1 H); IR (CH_2Cl_2) 1695 cm^{-1}.

5-[4-(Ethoxycarbonyl)-1,3-butadienyl]imidazo[1,5-*a*]-pyridine. To a stirred suspension of sodium hydride (0.15 g, 3.1 mmol) in 25 mL of toluene was added dropwise triethyl 4-phosphonocrotonate (0.55 g, 2.2 mmol). The reaction was maintained at 5 °C while 5-formylimidazo[1,5-*a*]pyridine (0.24 g, 2.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, poured into 100 mL of ice water, and extracted with 2 × 100 mL of ethyl acetate. The ethyl acetate extracts were combined and dried over magnesium sulfate, filtered, and evaporated to dryness to yield an oil which was purified on silica gel (ether–ethyl acetate, 1:1) to yield 5-[4-(ethoxycarbonyl)-1,3-butadienyl]imidazo[1,5-*a*]pyridine melting at 101–103 °C: NMR ($CDCl_3$) δ 1.36 (t, J = 6.8 Hz, 3 H), 4.27 (q, J = 6.8 Hz, 2 H), 6.24 (d, J = 14.5 Hz, 1 H), 6.70–7.70 (m, 7 H), 8.33 (s, 1 H); IR (Nujol) 1707 cm^{-1}.

5-(4-Carboxy-1,3-butadienyl)imidazo[1,5-*a*]pyridine (22). A solution of 5-[4-(ethoxycarbonyl)-1,3-butadienyl]imidazo[1,5-*a*]pyridine (0.2 g, 0.9 mmol) in 20 mL of methanol and 5 mL of 1 N sodium hydroxide was stirred at room temperature for 18 h. The methanol was evaporated under reduced pressure and the residue diluted with 10 mL of water. The solution was adjusted to pH 5 with hydrochloric acid and 0.16 g (95%) of 5-(4-carboxy-1,3-butadienyl)imidazo[1,5-*a*]pyridine (mp 243–245 °C) was collected by filtration: NMR (Me_2SO) δ 6.22 (d, J = 14.5 Hz, 1 H), 6.70–7.80 (m, 7 H), 8.77 (s, 1 H); IR (Nujol) 1685 cm^{-1}.

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Registry No. 1, 93806-43-0; 2, 85691-75-4; 3, 91624-65-6; 3·HCl, 91624-58-7; 4, 85691-73-2; 4 (methyl ester), 85692-02-0; 5, 85691-85-6; 5·HCl, 91624-59-8; 6, 85691-84-5; 7, 85691-87-8; 7·HCl, 91624-60-1; 7 (aldehyde), 85691-44-7; 8, 85691-83-4; 9, 85691-74-3; 10, 85691-82-3; 11, 93178-53-1; 12, 93806-45-2; 12·HCl, 93178-51-9; 13, 93178-52-0; 13·HCl, 93198-45-9; 14, 85691-81-2; 15, 85691-76-5; 16, 85692-06-4; 16 (methyl ester), 85692-05-3; 17, 85692-09-7; 18, 91624-71-4; 18 (methyl ester), 85692-04-2; 19, 85692-00-8; 20, 85692-03-1; 21, 93806-44-1; 22, 85691-69-6; 22 (ethyl ester), 85691-72-1; 23, 5264-02-8; 23 (*N*-oxide), 69603-66-3; 23 (*N*-oxide·Me_2SO_4), 93806-42-9; 24, 6558-64-1; 27 (n = 3), 91624-57-6; 29, 85691-50-5; 29 (*N*-oxide·Me_2SO_4, 85703-86-2; 30, 91624-69-0; 30 (amine), 85691-53-8; 30 (formamide), 85691-46-9; 31, 85691-52-7; 31 (amine), 93806-40-7; 31 (formamide), 85691-45-8; 32, 85691-59-4; 32 (amine), 85691-48-1; 32 (formamide), 91624-74-7; 33, 85691-60-7; CH_2=$CH(CH_2)_2CO_2Me$, 818-57-5; $CH_2(CO_2Me)_2$, 108-59-8; $Br(CH_2)_4C(OEt)_3$, 85691-40-3; $Br(CH_2)_4Cl$, 6940-78-9; Ph_3P=$CHCO_2Et$, 1099-45-2; $(EtO)_2P(O)CH_2CH$=$CHCO_2Et$, 10236-14-3; TxA_2 synthetase, 60832-04-4; 3-bromopyridine, 626-55-1; 3-[4-(methoxycarbonyl)but-1-enyl]]pyridine, 85691-49-2; 7-[4,4-bis(methoxycarbonyl)butyl]imidazo[1,5-*a*]pyridine, 85691-58-3.