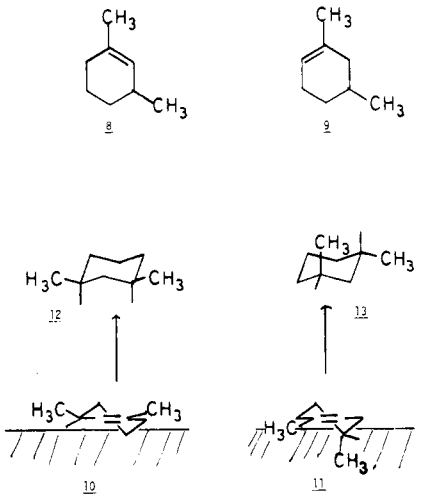
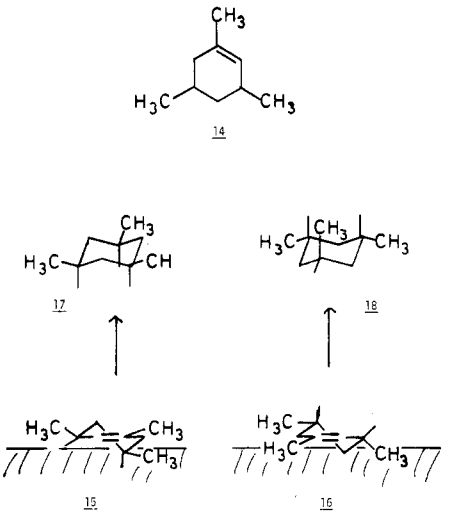


product compositions obtained from 8 and 9 it appears that double bond isomerization is not occurring during these hydrogenations, but this cannot be completely ruled out on the basis of the available data. Further, it would seem that a substituent in the allylic position as in **10** and **11** exerts more steric control over the hydrogenation than does one in the homoallylic position as in **2** and **3**.

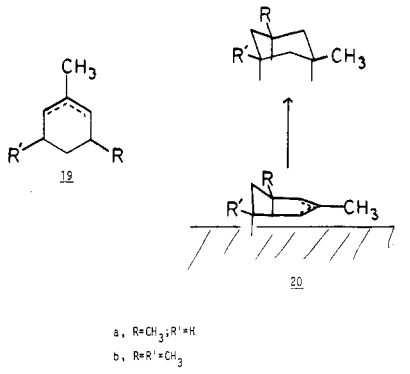
To determine whether this was the case or not the catalytic hydrogenation of 1,3,5-trimethylcyclohexene (**14**) was run over Pt, Rh, and Pd catalysts in ethanol under ambient conditions with the results listed in Table I. This molecule was chosen for two reasons. In the first place all double bond positions are equivalent so if double bond isomerization does take place it will have no influence on the outcome of the reaction. Second, as shown by the



adsorption modes **15** and **16** both allylic and homoallylic substituents are present so one should be able to determine which is the more critical in determining product stereochemistry.

From the data in Table I it can be seen that hydrogenation of **14** over Pt and Rh gives essentially the same amount of cis product as is obtained on hydrogenation of **1a** and **9**. This indicates that the homoallylic methyl group as in **2** and **3** is more influential in determining product stereochemistry than is the allylic methyl. Further, the close correspondence of results between **14** and **9** also indicates that there is little, if any, double bond isomerization taking place on hydrogenation of **9**.

The hydrogenations of **8**, **9**, and **14** over Pd all give predominantly the cis product **12** from **8** and **9** and **17** from **14**. This is not surprising since these three alkenes would form the π-allyl **19**, which would have its primary adsorption mode as depicted in **20**.



a, R=CH_3; R'=H
b, R=R'=CH_3

Experimental Section

1,3,5-Trimethylcyclohexene (**14**) was prepared by the addition of *cis*-3,5-dimethylcyclohexanone to a solution of methylmagnesium iodide and the product alcohol dehydrated by using standard procedures:[7] bp 141–143 °C (lit. 142.5–143.5 °C).[8]

The hydrogenations were run with 0.5 mL of **14** in 20 mL of purified ethanol over 50 mg of either 5% Pt/C, 5% Rh/C, or 5% Pd/C catalyst under ambient conditions in a sloping manifold hydrogenator using previously published procedures.[6] The catalysts used were the same as those used in previous studies.[6,7] After completion of the hydrogenation a sample of the product mixture was analyzed by gas chromatography through a 45 ft × $^1/_4$ in. column of 10% DEGS on Chromosorb P at 130 °C and a flow rate of 45 mL He/min. The products were identified by comparison of their retention times with authentic materials prepared by the hydrogenation of 1,3,5-trimethylbenzene under reported conditions.[9]

Acknowledgment. This work was supported, in part, by Grant DE-FG 0284ER45120 from the U.S. Department of Energy, Office of Basic Energy Sciences.

Registry No. **14**, 3643-64-9; Pt, 7440-06-4; Rh, 7440-16-6; Pd, 7440-05-3.

(7) Augustine, R. L.; Beutelman, H. P. *J. Catal.* **1986**, *97*, 59.
(8) Mohmoud, B. H. *J. Indian Chem. Soc.* **1968**, *45*, 303.
(9) Liberman, A. L.; Pryanishinkova, M. A.; Kazamskii, B. A. *Isv. Akad. Nauk SSSR, Ser. Khim.* **1956**, 1142.

Synthesis of Novel 8-Arylimidazo[1,2-*a*]pyridines and 8-Arylimidazo[1,5-*a*]pyridines

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As part of a program intended to study novel heterocycles related to purine,[1] we required synthetic methodology that could be used to conveniently prepare 8-arylimidazo[1,2-*a*]pyridines and -imidazo[1,5-*a*]pyridines. In addition, we were interested in methodology that could be general in its scope such that several derivatives could be obtained for use in structure–biological activity studies.

While several methods for preparing imidazo[1,2-*a*]-pyridines (**1**) have been reported,[2,3] the most common method remains that first reported by Tschitschibabin,[4]

(1) Erhardt, P. W. *J. Med Chem.*, in press.
(2) Mosby, W. L. *Heterocyclic Systems with Bridgehead Nitrogen Atoms*; Interscience: New York, 1961; Vol. XV, Part 1.
(3) Lumma, W. C., Jr.; Springer, J. P. *J. Org. Chem.* **1981**, *46*, 3735.

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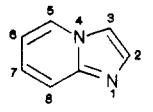

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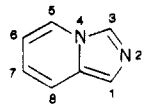


2

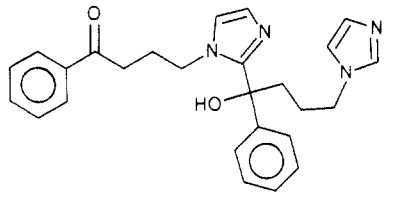
which involves the reaction of 2-aminopyridines with α-halo aldehydes or ketones. To prepare 8-aryl derivatives by this route requires the corresponding 2-amino-3-arylpyridines. These compounds are not readily prepared; the parent compound, 2-amino-3-phenylpyridine, has not been reported.

Imidazo[1,5-*a*]pyridines (**2**) are readily prepared by the method of Bower and Ramage,[5] which involves the acylation of 2-(aminomethyl)pyridines, followed by cyclization with phosphorus oxychloride. In order to prepare 8-aryl derivatives by this route, the corresponding 2-(aminomethyl)-3-arylpyridines would be required. No examples of these compounds have been reported.

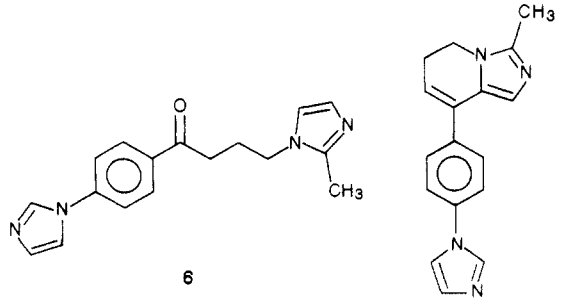
We now report a two-step method for preparing both 8-arylimidazo[1,2-*a*]pyridines and 8-arylimidazo[1,5-*a*]-pyridines from imidazoles and 4-halobutyrophenones or aryl cyclopropyl ketones. For the 1,2-*a* ring system, this method involves the reaction of 4-chlorobutyrophenones (or the corresponding aryl cyclopropyl ketone) with excess imidazole followed by dehydrogenation of the resulting 5,6-dihydro intermediates. The 1,5-*a* ring system is similarly prepared by substituting 2-methylimidazole for the imidazole.

Table I lists several of the 5,6-dihydroimidazopyridines prepared by this method. Compound **3** was prepared in 42% yield from 1 equiv of cyclopropyl phenyl ketone and 4.5 equiv of imidazole at 200 °C for 18 h (Scheme I). Compound **3** has also been prepared in 79% yield from 1 equiv of cyclopropyl phenyl ketone and 2 equiv of imidazole in refluxing decalin containing a catalytic amount of polyphosphoric acid; however, this method was not general for all compounds. Similarly, **4** was prepared from 1 equiv of 4-chloro-1-phenylbutan-1-one and 6 equiv of 2-methylimidazole at 200 °C for 48 h (Scheme II).

For the preparation of both ring systems, the reactions are monitored by TLC. Initially, an intermediate is formed that slowly disappears with the gradual formation of the 5,6-dihydroimidazopyridine, which has a slightly higher R_f. During a preparation of **3**, this intermediate (**5**) was



5



6

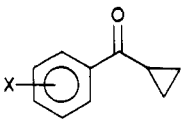
7

isolated and its structure assigned by the ^{1}H NMR and mass spectra. For the 1,5-*a* series, a similar intermediate (**6**) was isolated during a preparation of **7**. In both cases, when these intermediates were resubmitted to the original reaction conditions, they were cleanly converted to the corresponding 5,6-dihydroimidazopyridines (TLC data).

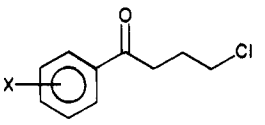
Treatment of cyclopropyl 4-methoxyphenyl ketone with imidazole at 225 °C resulted in a 1:1 mixture of the phenolic compounds **8** and **9** (Scheme III). TLC data suggest that demethylation occurs before ring closure, which could account for the relatively high temperature required for the condensation. The high temperature also appears to be responsible for the disproportionation reaction, since similar results were observed when other aryl cyclopropyl ketones were treated with imidazole at this temperature. Treatment of cyclopropyl 4-methoxyphenyl ketone with 2-methylimidazole at 220 °C gave compound **10** in 36% yield with no disproportionation. Compounds **11** and **12** were obtained in approximately a 1:1 ratio by treatment of cyclopropyl 3-methoxyphenyl ketone with imidazole at 175 °C (Scheme IV).

Compounds **13** and **14** were prepared in one step by treating 4-chloro-1-(4-fluorophenyl)butan-1-one with imidazole and 2-methylimidazole, respectively. Displacement

Table I



34a-e

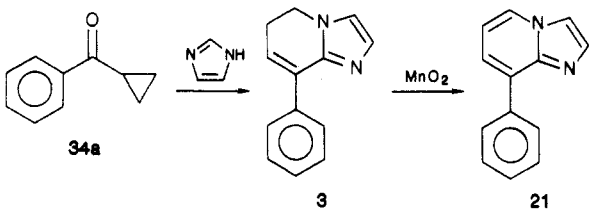


35a-d

entry	X	subst on imidazole	time, h	temp, °C	product	% yield
34a	H		18	200	3	45
34a	H		48	200	3	79
35a	H	2-methyl	24	180	4	41
34b	4-Im[a]	2-methyl	14	175	7	57
34c	4-CH_3O		16	225	8	17
34c	4-CH_3O	2-methyl	16	220	10	36
34d	3-CH_3O		18	175	11	26
35b	4-F		18	175	13	43
35b	4-F	2-methyl	18	200	14	44
35c	4-CH_3		22	175	15	34
35c	4-CH_3	2-methyl	70	175	16	71
34e	4-Cl	2-methyl	20	200	18	39
34e	4-Cl	2-ethyl-4-methyl	40	175	19	45
35d	4-C_2H_5O	2-methyl	18	175	20	45

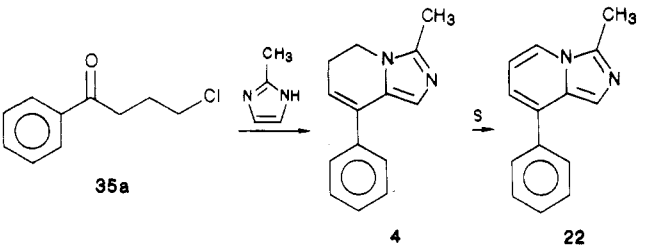
[a] Im = imidazol-1-yl.

Scheme I



34a 3 21

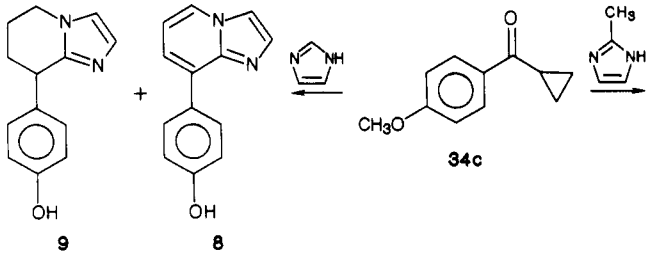
Scheme II



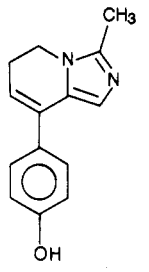
35a 4 22

(4) Tschitschibabin, A. E. *Chem. Ber.* **1925**, *58*, 1704.
(5) Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1955**, 2834.

Scheme III

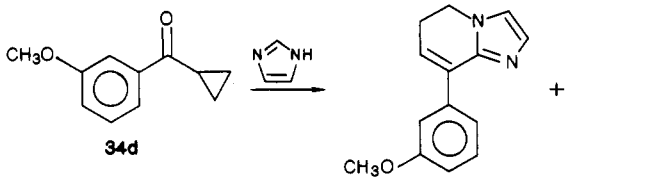


9 8 34c

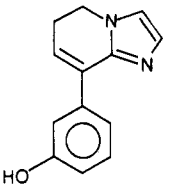


10

Scheme IV



34d 11



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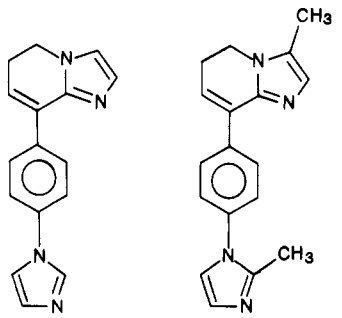
of fluorine occurs, as expected, before cyclization (TLC data).



13 14

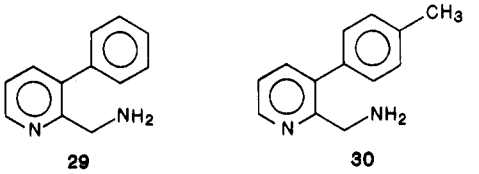
In the ^{1}H NMR spectrum of **3**, the assignments of the 2- and 3-positions were established to be 7.10 and 6.89 ppm, respectively, by a nuclear Overhauser effect (NOE) experiment, in which the 5-position methylene protons were irradiated. This result is in agreement with the parent compound **1**[6] and rules out the possible 1,5-*a* isomer, which would show a singlet at approximately 8 ppm for the 3-position. The ^{1}H NMR spectrum of **4** is also in accord with **2**,[7] with further evidence provided by a similar NOE experiment.

Table II

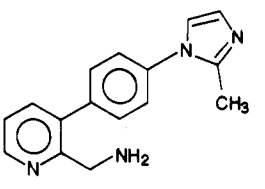
entry	dehydrog agent	solvent	time, h	temp, °C	product	% yield
3	MnO_2	CH_2Cl_2	14	44	21	78
4	S	decalin	6	190	22	69
13	MnO_2	CH_2Cl_2	20	44	23	75
14	S	1,2-$Cl_2C_6H_4$	13	175	24	58
15	MnO_2	CH_2Cl_2	5	44	25	90
16	S	decalin	5	190	26	74
17	MnO_2	CH_2Cl_2	5	44	27	75
20	MnO_2	CH_2Cl_2	24	44	28	21

The dehydrogenation of **3** was readily accomplished by treatment with excess "activated" MnO_2[8] in methylene chloride to give **21** in 78% yield (Scheme I). While this method proved to be general for the 1,2-*a* series, it gave poor results for the 1,5-*a* series. Other reagents such as $BaMnO_4$ and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) also failed to give a clean reaction. Dehydrogenation of **4** was finally accomplished with sulfur at 180 °C in decalin, to give **22** in 69% yield (Scheme II). The results for both series are listed in Table II.

By a procedure by Dunham[9] for converting imidazo[1,5-*a*]pyridine to 2-(aminomethyl)pyridine and formic acid by treatment with refluxing dilute HCl, compounds **22**, **24**, and **26** were converted in good yield to the corresponding 2-(aminomethyl)-3-arylpyridines **29–31**. These compounds represent the first reported examples for this class of substituted pyridines and are valuable intermediates for other 8-arylimidazo[1,5-*a*]pyridines not readily prepared by the process presented here. The 8-arylimidazo[1,2-*a*]pyridines proved to be insensitive to the hydrolysis conditions.

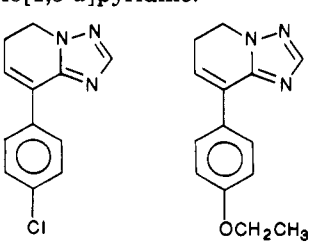


29 30



31

In attempts to generalize the condensation reaction, other heterocycles were substituted for imidazole. The triazolo[1,5-*a*]pyridines **32** and **33** were isolated in low yields by reaction of 1,2,4-triazole with 4-chlorophenyl cyclopropyl ketone and 4-chloro-1-(4-ethoxyphenyl)butan-1-one, respectively. Reaction of pyrazole with 4-chlorophenyl cyclopropyl ketone failed to give any of the desired pyrazolo[1,5-*a*]pyridine.



32 33

(6) Paudler, W. W.; Blewitt, H. L. *Tetrahedron* **1965**, *21*(2), 356.
(7) Black, P. J.; Hefferman, M. L.; Jackman, L. M.; Porter, Q. N.; Underwood, G. R. *Aust. J. Chem.* **1964**, *17*, 1128.
(8) Manganese(IV) oxide, activated, black, was used as purchased from Aldrich Chemical Co., Catalog No. 22, 432-4.
(9) Taylor, E. C.; Weissberger, A. *Special Topics in Heterocyclic Chemistry*; Interscience: New York, 1977; Vol. 30, Part II, pp 164–165.

Several attempts were also made to react cyclopropyl methyl ketone with imidazole and 2-methylimidazole. In both cases, none of the desired products were obtained.

Several of the compounds presented here, together with some compounds not presented here, were found to possess a wide range of biological activities. Those possessing cardiovascular activity are the subject of a current paper in a companion publication.[10]

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Sargent/Welch 3-300 spectrophotometer and a Beckman Aculab 2 spectrophotometer. ^1H NMR spectra were recorded on a Varian XL-300 spectrometer. Mass spectra were measured on a Kratos MS25 mass spectrometer. Elemental analyses were performed by the Berlex Analytical Department and by Galbraith Laboratories, Inc. Column chromatography was carried out on Merck silica gel 60, 230–400 mesh. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 plates.

General Procedure for the Preparation of 8-Aryl-5,6-dihydroimidazo[1,2-*a*]pyridines. Method A. 5,6-Dihydro-8-phenylimidazo[1,2-*a*]pyridine (3). Cyclopropyl phenyl ketone (100g, 0.68 mol), imidazole (100g, 1.47 mol), and 2.0 g of polyphosphoric acid were combined in 1 L of decalin, and the resultant mixture was heated at reflux under nitrogen for 48 h. After cooling to room temperature, the reaction mixture was extracted 2× with 1-L portions of 2 N H_2SO_4. The combined extracts were made basic with K_2CO_3 and extracted with 2× 1-L portions of methylene chloride. The combined extracts were dried over Na_2SO_4 and charcoal treated, and the solvent was removed under vacuum. The residue was crystallized with ether to provide 106 g (79%) a white solid: mp 65–67° C; IR (CH_2Cl_2) 1485, 1445 cm^{-1}; NMR ($CDCl_3$) δ 2.68 (q, 2), 4.10 (t, 2), 6.16 (t, 1), 6.89 (s, 1), 7.10 (s, 1), 7.34 (m, 3), 7.66 (d, 2); mass spectrum, *m/e* 196 (M^+). Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.76; H, 6.02; N, 14.25.

Method B. Cyclopropyl phenyl ketone (25 g, 0.17 mol) and imidazole (50 g, 0.73 mol) were combined, and the resultant mixture was heated to 200 °C under nitrogen for 18 h. The reaction mixture was cooled to 80 °C, and 500 mL of ethyl acetate was added. The ethyl acetate mixture was washed with 500 mL of 10% K_2CO_3 and 3× with 500 mL of water and dried over Na_2SO_4, and the solvent was removed under vacuum. The residue was chromatographed on 200 g of silica gel with methylene chloride. Crystallization from ether provided 14 g (42%) of **3**.

General Procedure for the Preparation of 8-Aryl-5,6-dihydroimidazo[1,5-*a*]pyridines. 5,6-Dihydro-3-methyl-8-(4-methylphenyl)imidazo[1,5-*a*]pyridine (16). A mixture of 4-chloro-1-(4-methylphenyl)butan-1-one (50 g, 0.25 mol) and 2-methylimidazole (124 g, 1.5 mol) was heated at 175 °C under nitrogen for 70 h. After the mixtrure was cooled to 80 °C, 200 mL of ethyl acetate was added, and the reaction mixture was poured into an additional 1 L of ethyl acetate, which was washed with 1 L of 10% K_2CO_3 and 2 L of water. The organic portion was dried over $MgSO_4$ and charcoal treated and the solvent removed under vacuum. The residue was crystallized from ether to afford **16** as an off-white solid: yield 40.4 g (71%); mp 112–113 °C; IR (CH_2Cl_2) 1545, 1490, 1410 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3), 2.41 (s, 3), 2.63 (q, 2), 3.92 (t, 2), 5.77 (t, 1), 6.84 (s, 1), 7.19 (d, 2), 7.38 (d, 2). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.50; H, 7.17; N, 12.51.

5,6-Dihydro-3-methyl-8-phenylimidazo[1,5-*a*]pyridine (4): mp 83–84 °C (ether); IR (CH_2Cl_2) 1540, 1485, 1250 cm^{-1}; NMR ($CDCl_3$) δ 2.41 (s, 3), 2.65 (m, 2), 3.94 (t, 2), 5.80 (t, 1), 6.84 (s, 1), 7.30 (m, 5); mass spectrum, *m/e* 210 (M^+). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.05; H, 6.82; N, 13.15.

5,6-Dihydro-8-[4-(1*H*-imidazol-1-yl)phenyl]-3-methylimidazo[1,5-*a*]pyridine (7): mp 195–197 °C (CH_3CN); IR (CH_2Cl_2) 1605, 1550, 1515, 1495 cm^{-1}; NMR ($CDCl_3$) δ 2.43 (s, 3), 2.68 (q, 2), 3.97 (t, 2), 5.86 (t, 1), 6.85 (s, 1), 7.24 (d, 1), 7.31 (d, 1), 7.41 (d, 2), 7.61 (d, 2), 7.92 (s, 1). Anal. Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.73; H, 5.83; N, 20.15.

8-(4-Hydroxyphenyl)imidazo[1,2-*a*]pyridine (8): mp 199–201 °C (CH_3OH); IR (KBr) 1625, 1610, 1580, 1255 cm^{-1}; NMR (Me_2SO) δ 6.92 (m, 3), 7.47 (d, 1), 7.62 (d, 1), 8.05 (m, 3), 8.56 (m, 1). Anal. Calcd for $C_{13}H_{10}N_{20}$: C, 74.27; H, 4.79; N, 13.32. Found: C, 73.90; H, 4.95; N, 13.29.

5,6,7,8-Tetrahydro-8-(4-hydroxyphenyl)imidazo[1,2-*a*]pyridine (9): mp 258–261 °C (CH_3OH); IR (KBr) 1615, 1600, 1520, 1245 cm^{-1}; NMR (Me_2SO) δ 1.84 (m, 3), 2.05 (m, 1), 3.35 (m, 1), 3.95 (m, 3), 6.65–7.10 (m, 6). Anal. Calcd for $C_{13}H_{14}N_{20}$: C, 72.87; H, 6.55; N, 13.07. Found: C, 72.57; H, 6.71; N, 13.02.

5,6-Dihydro-8-(4-hydroxyphenyl)-3-methylimidazo[1,5-*a*]pyridine (10): mp 257–259 °C (CH_3CN); IR (Nujol) 1610, 1590, 1415, 1240 cm^{-1}; NMR (CF_3CO_2D) δ 2.70 (m, 5), 4.15 (t, 2), 6.30 (t, 1), 7.02–7.65 (m, 5). Anal. Calcd for $C_{14}H_{14}N_{20}$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.67; H, 6.25; N, 12.42.

5,6-Dihydro-8-(3-methoxyphenyl)imidazo[1,2-*a*]pyridine (11): mp 84–85 °C (ether); IR (CH_2Cl_2) 1600, 1575, 1325, 1270 cm^{-1}; NMR ($CDCl_3$) δ 2.45 (m, 2), 3.85 (s, 3), 3.95 (t, 2), 6.18 (t, 1), 6.84–7.50 (m, 6). Anal. Calcd for $C_{14}H_{14}N_{20}$: C, 74.31; 6.24; N, 12.38. Found: C, 74.29; H, 6.27; N, 12.29.

5,6-Dihydro-8-(3-hydroxyphenyl)imidazo[1,2-*a*]pyridine (12): mp 208–210 °C (CH_3OH); IR (KBr) 3440, 1595, 1480, 1245 cm^{-1}; NMR (CF_3CO_2D) δ 2.80 (m, 2), 4.30 (t, 2), 6.65–7.70 (m, 7). Anal. Calcd for $C_{13}H_{12}N_{20}$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.30; H, 5.75; N, 13.10.

5,6-Dihydro-8-[4-(1*H*-imidazol-1-yl)phenyl]imidazo[1,2-*a*]pyridine (13): mp 139–141 °C (ether); IR (CH_2Cl_2) 1610, 1520, 1485, 1260 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (m, 2), 4.00 (t, 2), 6.15 (t, 1), 6.95 (d, 2), 7.10–8.00 (m, 7). Anal. Calcd for $C_{16}H_{14}N_4 \cdot 0.2H_2O$: C, 72.27; H, 5.46; N, 21.07. Found: C, 72.45; H, 5.34; N, 21.25.

5,6-Dihydro-3-methyl-8-[4-(2-methyl-1*H*-imidazol-1-yl)phenyl]imidazo[1,5-*a*]pyridine (14): mp 221–223 °C (CH_3CN); IR (CH_2Cl_2) 1615, 1550, 1495, 1270 cm^{-1}; NMR (Me_2SO) δ 2.32 (s, 3), 2.33 (s, 3), 2.62 (q, 2), 3.97 (t, 2), 5.98 (t, 1), 6.74 (s, 1), 6.93 (d, 1), 7.30 (d, 1), 7.47 (d, 2), 7.63 (d, 2). Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.29. Found: C, 74.28; H, 6.30; N, 19.07.

5,6-Dihydro-8-(4-methylphenyl)imidazo[1,2-*a*]pyridine (15): mp 81–82 °C (ether); IR (CH_2Cl_2) 1420, 1270, 1250 cm^{-1}; NMR ($CDCl_3$) δ 2.36 (s, 3), 2.68 (m, 2), 4.11 (t, 2), 6.14 (t, 1), 6.89 (s, 1), 7.09 (s, 1), 7.22 (d, 2), 7.55 (d, 2). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.06; H, 6.71; N, 13.30.

8-(4-Chlorophenyl)-5,6-dihydroimidazo[1,2-*a*]pyridine (17): mp 97–98 °C (ether); IR (CH_2Cl_2) 1585, 1505, 1425, 1255 cm^{-1}; NMR ($CDCl_3$) δ 2.70 (m, 2), 4.15 (t, 2), 6.20 (t, 2), 6.92 (s, 1), 7.15 (s, 1), 7.51 (m, 4). Anal. Calcd for $C_{13}H_{11}ClN_2$: C, 67.68; H, 4.81; N, 12.14. Found: C, 67.84; H, 4.76; N, 21.25.

8-(4-Chlorophenyl)-5,6-dihydro-3-methylimidazo[1,5-*a*]pyridine (18): mp 112–113 °C (ether); IR (CH_2Cl_2) 1660, 1550, 1415, 1270 cm^{-1}; NMR($CDCl_3$) δ 2.45 (s, 3), 2.48 (m, 2), 3.80 (t, 2), 5.75 (t, 1), 6.90 (s, 1), 7.30 (m, 4). Anal. Cacld for $C_{14}H_{13}ClN_2$: C, 68.71; H, 5.35; N, 11.45. Found: C, 68.43; H, 5.40; N, 11.39.

8-(4-Chlorophenyl)-1-ethyl-5,6-dihydro-3-methylimidazo-[1,5-*a*]pyridine (19): mp 81–82 °C (ether); IR (CH_2Cl_2) 1545, 1475, 1410 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (t, 3), 1.77 (s, 3), 2.55 (q, 2), 2.70 (q, 2), 3.88 (t, 2), 5.64 (t, 1), 7.25 (m, 4). Anal. Calcd for $C_{16}N_{17}ClN_2$: C, 70.45; H, 6.28; N, 10.27. Found: C, 70.80; H, 6.25; N, 10.32.

8-(4-Ethoxyphenyl)-5,6-dihydro-3-methylimidazo[1,5-*a*]pyridine (20): mp 137–138 °C (ether); IR (CH_2Cl_2) 1615, 1515, 1425, 1270 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (t, 3), 2.41 (s, 3), 2.61 (q, 2), 3.92 (t, 2), 4.05 (q, 2), 5.77 (t, 1), 6.84 (s, 1), 7.09 (d, 2), 7.41 (d, 2). Anal. Calcd for $C_{16}H_{18}N_{20}$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.53; H, 7.11; N, 10.92.

General Procedures for the Dehydrogenation of 8-Aryl-5,6-dihydroimidazopyridines. Method A. "Activated" Manganese Dioxide. 8-Phenylimidazo[1,2-*a*]pyridine (21). To a solution of **3** (9 g, 46 mmol) in 200 mL of methylene chloride was added 50 g of activated manganese(IV) oxide, and the mixture was heated to reflux for 14 h. The reaction mixture was filtered over Celite, and the filtrate was concentrated to dryness under vacuum. The residue was crystallized from ether to provide 7 g (78%) of **21**: mp 69–70 °C; IR (CH_2Cl_2) 1490, 1300, 1140 cm^{-1}; NMR ($CDCl_3$) δ 6.85 (t, 1), 7.27 (d, 1), 7.40 (m, 3), 7.63 (d, 1), 7.70

(10) Davey, D. D.; Erhardt, P. W.; Lumma, W. C., Jr.; Wiggins, J.; Sullivan, M. E.; Pang, D.; Cantor, E. H. *J. Med Chem.*, in press.

(d, 1), 7.99 (d, 2), 8.10 (d, 1). Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.43; H, 5.33; N, 14.29.

8-[4-(1*H*-Imidazol-1-yl)phenyl]imidazo[1,2-*a*]pyridine (23): mp 136–137 °C (ether); IR (CH_2Cl_2) 1640, 1520, 1425 cm^{-1}; NMR ($CDCl_3$) δ 7.03 (t, 1), 7.16 (s, 1), 7.56 (d, 1), 7.66 (s, 1), 7.82 (d, 2), 7.84 (s, 1), 8.07 (s, 1), 8.34 (d, 2), 8.35 (s, 1), 8.60 (d, 1). Anal. Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.40. Found: C, 73.92; H, 4.67; N, 21.40.

8-(4-Methylphenyl)imidazo[1,2-*a*]pyridine (25): mp 120–122 °C (ether); IR (CH_2Cl_2) 1495, 1420, 1325 cm^{-1}; NMR ($CDCl_3$) δ 2.41 (s, 3), 6.83 (t, 1), 7.27 (d, 2), 7.30 (d, 2), 7.62 (s, 1), 7.68 (s, 1), 7.89 (d, 1), 8.08 (d, 1). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.96; H, 5.79; N, 13.45.

8-(4-Chlorophenyl)imidazo[1,2-*a*]pyridine (27): mp 118–120 °C (ether); IR (CH_2Cl_2) 1625, 1590, 1485, 1310 cm^{-1}; NMR ($CDCl_3$) δ 6.86 (t, 1), 7.25 (d, 1), 7.46 (d, 2), 7.64 (s, 1), 7.69 (s, 1), 7.96 (d, 2), 8.12 (d, 1). Anal. Calcd for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.18; H, 3.86; N, 12.20.

8-(4-Ethoxyphenyl)-3-methylimidazo[1,5-*a*]pyridine (28): mp 97–98 °C (ether); IR (CH_2Cl_2) 1600, 1570, 1275, 1245 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (t, 3), 2.62 (s, 3), 4.11 (q, 2), 6.70 (m, 2), 7.14 (d, 2), 7.36 (s, 1), 7.75 (d, 2), 8.12 (d, 1). Anal. Calcd for $C_{16}H_{16}N_2O{\cdot}0.7H_2O$: C, 72.54; H, 6.62; N, 10.57. Found: C, 72.34; H, 6.48; N, 10.45.

Method B. Sulfur. 3-Methyl-8-phenylimidazo[1,5-*a*]pyridine (22). Sulfur (75 g, 2.34 mol) and **4** (250 g, 1.19 mol) were combined in 1.5 L of decalin, and the resultant mixture was heated at 180–190 °C under nitrogen for 6 h. After the mixture was cooled to room temperature, 1 L of ethyl acetate was added and the reaction mixture extracted 2× with 1.5 L of 2 N H_2SO_4. The combined extracts were washed with 2 L of methylene chloride, made basic with KOH, and extracted 2× with 1-L portions of methylene chloride. The combined extracts were dried over $MgSO_4$ and charcoal treated, and the solvent was removed under vacuum. Crystallization of the residue with ether provided 170 g (69%) of **22**: mp 70–71 °C; IR (CH_2Cl_2) 1485, 1420, 1375, 1245 cm^{-1}; NMR ($CDCl_3$) δ 2.69 (s, 3), 6.66 (m, 2), 7.46 (m, 4), 7.68 (m, 3). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.75; H, 5.80; N, 13.45. Found: C, 80.63; H, 5.78; N, 13.38.

3-Methyl-8-[4-(2-methyl-1*H*-imidazol-1-yl)phenyl]imidazo[1,5-*a*]pyridine (24): mp 194–195 °C (EtOAc); IR (CH_2Cl_2) 1510, 1495, 1405, 1250 cm^{-1}; NMR ($CDCl_3$) δ 2.45 (s, 3), 2.71 (s, 3), 6.72 (m, 2), 7.07 (d, 1), 7.08 (d, 1), 7.42 (d, 2), 7.49 (s, 1), 7.75 (s, 1), 7.81 (d, 2). Anal. Calcd for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.12; H, 5.57; N, 19.42.

3-Methyl-8-(4-methylphenyl)imidazo[1,5-*a*]pyridine (26): mp 134–135 °C (ether); IR (CH_2Cl_2) 1615, 1485, 1410 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3), 2.62 (s, 3), 6.75 (m, 2), 7.33 (m, 3), 7.61 (d, 2), 8.07 (d, 1). Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.77; H, 6.35; N, 12.40.

General Procedure for the Hydrolysis of 8-Arylimidazo[1,5-*a*]pyridines. 2-(Aminomethyl)-3-phenylpyridine (29). A solution of 160 g (0.78 mol) of **22** and 1.3 L of 6 N HCl was heated at reflux for 24 h. After cooling to room temperature, the reaction mixture was made basic with NaOH and extracted with 3× with 600-mL portions of methylene chloride. The combined extracts were dried over $MgSO_4$, and the solvent was removed under vacuum. The residue was Kugelrohr distilled at 100–110 °C (0.5 mmHg) to provide 114 g (79%) of **29** as a colorless liquid: IR (CH_2Cl_2) 3370, 1595, 1560, 1415 cm^{-1}; NMR ($CDCl_3$) δ 1.78 (s, 2), 3.92 (s, 2), 7.23–7.54 (m, 7), 8.60 (d, 1). Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20. Found: C, 77.94; H, 6.64; N, 15.01.

2-(Aminomethyl)-3-(4-methylphenyl)pyridine (30): bp 110–115 °C (0.2 mmHg); IR (CH_2Cl_2) 3360, 1545, 1415 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (s, 2), 2.41 (s, 3), 3.92 (s, 2), 7.20 (m, 5), 7.52 (d, 1), 8.57 (d, 1). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.85; H, 7.11; N, 13.73.

2-(Aminomethyl)-3-[4-(2-methyl-1*H*-imidazol-1-yl)phenyl]pyridine (31): mp 115–117 °C (ether); IR (CH_2Cl_2) 3040, 1560, 1510, 1250 cm^{-1}; NMR (Me_2SO) δ 2.35 (s, 3), 2.50 (s, 2), 3.76 (s, 2), 6.94 (d, 1), 7.36 (d, 1), 7.38 (m, 1), 7.56 (d, 2), 7.59 (d, 2), 7.61 (d, 1), 8.60 (d, 1). Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.86; H, 6.25; N, 21.03.

Preparation of Compounds 5, 6, 32, 33, and 34b. 4-[2-[1-Hydroxy-4-(1*H*-imidazol-1-yl)-1-phenylbutyl]-1*H*-imidazol-1-yl]-1-phenylbutan-1-one (5). Cyclopropyl phenyl ketone (25 g, 0.17 mol) and imidazole (50 g) were combined, and the resultant mixture was heated at 150 °C under nitrogen for 18 h. The reaction mixture was cooled to ~80 °C, poured into 500 mL of methylene chloride, washed 3× with 200-mL portions of 10% NaOH, dried over $MgSO_4$, and charcoal treated, and the solvent was removed under vacuum. The residue was crystallized with ether to provide 17 g of a white solid: mp 67–68 °C; IR (CH_2Cl_2) 3050, 1690, 1510, 1450, 1230, 1075 cm^{-1}; NMR ($CDCl_3$) δ 1.85 (m, 1), 2.10–2.30 (m, 6), 2.94 (t, 2), 4.07 (m, 4), 6.83 (m, 4), 7.25 (m, 3), 7.47 (m, 6), 7.89 (d, 2); mass spectrum, *m/e* 428 (M^+). Anal. Calcd for $C_{26}H_{28}N_4O_2{\cdot}0.7H_2O$: C, 70.79; 6.57; N, 12.70. Found: C, 70.93; H, 6.57; N, 12.70.

1-[4-(1*H*-Imidazo-1-yl)phenyl]-4-(2-methyl-1*H*-imidazol-1-yl)butan-1-one (6). A mixture of 25 g (0.12 mol) of **34b** and 100 g of 2-methylimidazole was heated at 150 °C under nitrogen for 18 h. After cooling to 70 °C, the reaction mixture was added to 1 L of methylene chloride, washed 3× with 2-L portions of water, dried over $MgSO_4$, and charcoal treated, and the solvent was removed under vacuum. The residue was crystallized from ethyl acetate to provide 18 g (52%) of a white solid: mp 152–153 °C; IR (Nujol) 1690, 1620, 1535 cm^{-1}; NMR (Me_2SO) δ 2.01 (m, 2), 2.29 (s, 3), 3.09 (t, 2), 3.94 (t, 2), 6.73 (s, 1), 7.07 (s, 1), 7.16 (s, 1), 7.84 (d, 2), 7.90 (s, 1), 8.07 (d, 2), 8.44 (s, 1). Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.40; H, 6.22; N, 18.74.

8-(4-Chlorophenyl)-5,6-dihydrotriazolo[1,5-*a*]pyridine (32). A mixture of 25 g (0.14 mol) of **34e** and 50 g of 1,2,4-triazole was heated at 200 °C for 18 h under nitrogen. After cooling to 70 °C, the reaction mixture was dissolved in 300 mL of methylene chloride, washed with two 500-mL portions of 1 N NaOH, dried over $MgSO_4$, and column chromatographed on 250 g of silica with methylene chloride to provide, after crystallization from ether, 6.2 g (19%) of a white solid: mp 117–118 °C; IR (CH_2Cl_2) 1595, 1520, 1485 cm^{-1}; NMR ($CDCl_3$) δ 2.61 (m, 2), 4.26 (t, 2), 6.36 (t, 1), 7.31 (m, 4), 8.00 (s, 1). Anal. Calcd for $C_{12}H_{10}ClN_3$: C, 62.21; H, 4.35; N, 18.14. Found: C, 62.09; H, 4.40; N, 18.25.

8-(4-Ethoxyphenyl)-5,6-dihydrotriazolo[1,5-*a*]pyridine (33). A mixture of 5 g (22.1 mmol) of **35d** and 15 g of 1,2,4-triazole was heated at 200 °C under nitrogen for 16 h. The reaction mixture was cooled to 60 °C, dissolved in 200 mL of methylene chloride, washed with 300 mL of 2 N NaOH, dried over $MgSO_4$, and charcoal treated, and the solvent was removed under vacuum. The residue was crystallized with ether to provide 1.5 g (28%) of a white solid: mp 132–134 °C; IR (CH_2Cl_2) 1620, 1515, 1485, 1250 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (t, 3), 2.85 (m, 2), 4.06 (q, 2), 4.36 (t, 2), 6.35 (t, 1), 6.92 (d, 2), 7.61 (d, 2), 7.92 (s, 1). Anal. Calcd for $C_{14}H_{15}N_{30}$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.56; H, 6.16; N, 17.20.

Cyclopropyl[4-(1*H*-imidazol-1-yl)phenyl]methanone (34b). To a mixture of 7 g (0.1 mol) of imidazole and 12 g of K_2CO_3 in 30 mL of dimethyl sulfoxide was added 14 g (85 mmol) of cyclopropyl(4-fluorophenyl)methanone. After being heated at 100 °C for 12 h, the reaction mixture was poured into 500 mL of ice water with good mixing. The resulting solids were filtered, washed with water, and recrystallized from ether to provide 11.3 g (62%) of a white solid: mp 96–97 °C; IR (CH_2Cl_2) 1665, 1600, 1515 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (m, 4), 2.53 (m, 1), 7.31 (m, 4), 8.15 (m, 3). Anal. Calcd for $C_{13}H_{12}N_{20}$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.34; H, 5.70; N, 12.91.

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Registry No. **3**, 104271-32-1; **4**, 107454-13-7; **5**, 107454-14-8; **6**, 107454-15-9; **7**, 107454-16-0; **8**, 104271-34-3; **9**, 104271-35-4; **10**, 107454-17-1; **11**, 104271-40-1; **12**, 104271-42-3; **13**, 104271-43-4; **14**, 107454-18-2; **15**, 104271-52-5; **16**, 107454-19-3; **17**, 104271-30-9; **18**, 107454-20-6; **19**, 107454-21-7; **20**, 107454-22-8; **21**, 104271-33-2; **22**, 107454-23-9; **23**, 104271-44-5; **24**, 107454-24-0; **25**, 104271-53-6; **26**, 107454-25-1; **27**, 104271-31-0; **28**, 107454-26-2; **29**, 107454-27-3; **30**, 107454-28-4; **31**, 107454-29-5; **32**, 107454-30-8; **33**, 107454-31-9; **34a**, 3481-02-5; **34b**, 107454-32-0; **34c**, 7152-03-6; **34d**, 104271-41-2; **34e**, 6640-25-1; **35a**, 939-52-6; **35b**, 3874-54-2; **35c**, 38425-26-2; **35d**, 75343-08-7; imidazole, 288-32-4; 2-methylimidazole, 693-98-1; 2-ethyl-4-methylimidazole, 931-36-2; 1,2,4-triazole, 288-88-0; cyclopropyl(4-fluorophenyl)methane, 772-31-6.