Synthesis of 1*H*-Imidazo[1,2-*a*]pyrazolo[3,4-*c*]pyridines

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The reactions of nitrosyl chloride with 6- and 8-acetamido-7-methylimidazo[1,2-*a*]pyridine (7g—i) reveal clear differences of reactivity of these isomeric structures. After bifunctionalization of the imidazolic moiety, the 6-acetamido derivatives do not yield the 1*H*-imidazo[1,2-*a*]pyrazolo[4,5-*d*]pyridine (4) system, but undergo a Gomberg–Bachman reaction complicated by Dimroth rearrangement. In contrast, upon similar treatment, the 8-acetamido compounds (17, 19) yielded the *N*-nitrosoacetamides (18a, b), which were converted into 1*H*-imidazo[1,2-*a*]pyrazolo[3,4-*c*]pyridines (20a, b) in 22 and 34% yields, respectively, without rearrangement.

Keywords imidazo[1,2-*a*]pyridine; nitrosyl chloride; Gomberg–Bachman reaction; 1*H*-imidazo[1,2-*a*]pyrazolo[3,4-*c*]pyridine

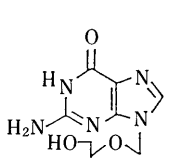
Several series of heterocyclic compounds have been found to exhibit antiherpetic and antiviral activities.[1] Modifications of the guanine moiety of acyclovir (**1**) have received relatively minor attention[2] compared to those of the acyclic side chain.[3] Recently Nakanishi *et al.* determined the structure of Y base (**2**) as a component of $tRNA^{Phe}$ [4] and Boryski *et al.* showed that new acyclovir analogs having the tricycle of **2** exhibited a marked antiherpetic activity (HSV-1 and -2).[5] On the other hand, De Wald reported the synthesis and the anti-psychotic activity of 1*H*-imidazo[1,2-*c*]pyrazolo[3,4-*e*]pyrimidine (**3**).[6]

As a part of our studies on the reactivity of nitrogen bridgehead systems, we have investigated the possibility of obtaining the 1*H*-imidazo[1,2-*a*]pyrazolo[3,4-*c*]-(**4**) or [4,5-*d*]pyridine (**5**) as an isostere of the fluorescent Y base.

The approach used for the synthesis of **4**, **5** was based on the thermal intramolecular heterocyclization of *N*-nitroso-6 (or 8)-acetamido-7-methylimidazo[1,2-*a*]pyridines.

The starting 2-amino-4-methylnitropyridines (**6a**, **b**) used in the present work were prepared from the corresponding 2-aminopicolines according to the reported method.[7] Treatment of **6a**, **b** with phenacyl bromide or ethyl bromopyruvate yielded azaindolizines (**7a—c**). Reduction of **7a—c** with H_2/Pd on charcoal or Sn/HBr produced the corresponding amines (**7d—f**). These products were acetylated by a standard method to give (**7g—i**) (Chart 1). Attempts to prepare the *N*-nitrosoacetamides from **7g—i** by using nitrosyl chloride in acetic acid (by analogy with successful syntheses of other related heterocycles[8] were unproductive. Only tars were obtained, probably due to polynitrosation on the imidazole moiety. Nitrosation at the 3-position of the azaindolizines had been described in the case of 2-phenyl compounds[9] but failed with 2-carboxylic acid esters. Effective nitrosation of the ester (**8a**) was achieved with $NOCl/(CH_3CO)_2O)/CH_3CO_2H$ at $-10\,^{\circ}C$, and was generalized with the methyl derivatives (**8b—d**) to give (**9b—d**) (Chart 2).

An alternative route for obtaining the tricyclic structure (**4**) was developed as follows. The secondary reaction was stopped by blocking the 3-position with a suitable functionalized group (NO_2, Br). Attempted conversion of the nitroso derivative (**11**) prepared by condensation of **10**



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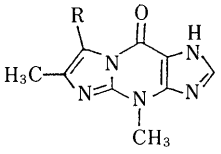

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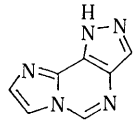

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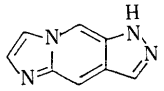

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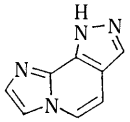

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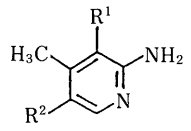
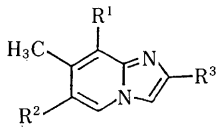


6a, b

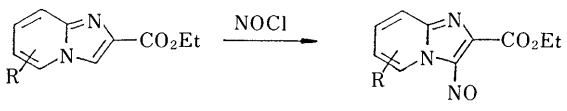
a : $R^1=NO_2$, $R^2=H$
b : $R^1=H$, $R^2=NO_2$



7a—j

a : $R^1=H$, $R^2=NO_2$, $R^3=C_6H_5$
b : $R^1=NO_2$, $R^2=H$, $R^3=CO_2Et$
c : $R^1=H$, $R^2=NO_2$, $R^3=CO_2Et$
d : $R^1=H$, $R^2=NH_2$, $R^3=C_6H_5$
e : $R^1=NH_2$, $R^2=H$, $R^3=CO_2Et$
f : $R^1=H$, $R^2=NH_2$, $R^3=CO_2Et$
g : $R^1=H$, $R^2=NHCOCH_3$, $R^3=C_6H_5$
h : $R^1=NHCOCH_3$, $R^2=H$, $R^3=CO_2Et$
i : $R^1=H$, $R^2=NHCOCH_3$, $R^3=CO_2Et$
j : $R^1=H$, $R^2=H$, $R^3=CO_2Et$

Chart 1



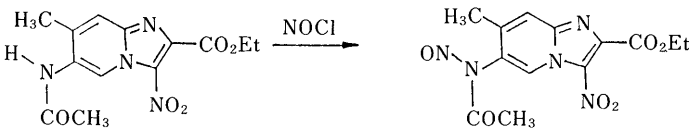
8a—d

a : R=H
b : R=8-CH_3
c : R=7-CH_3
d : R=6-CH_3

9a—d

a : R=H
b : R=8-CH_3
c : R=7-CH_3
d : R=6-CH_3

Chart 2



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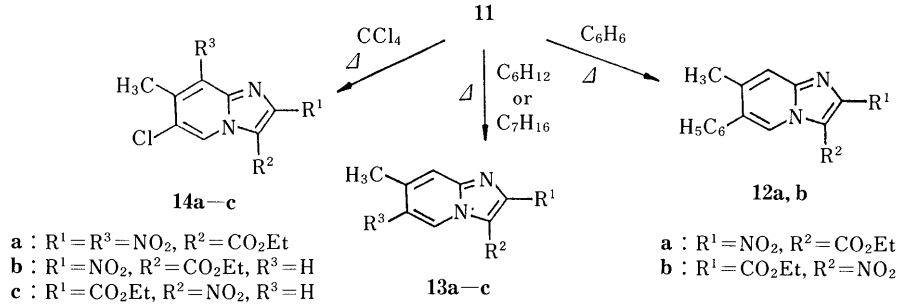


14a—c

a : $R^1=R^3=NO_2$, $R^2=CO_2Et$
b : $R^1=NO_2$, $R^2=CO_2Et$, $R^3=H$
c : $R^1=CO_2Et$, $R^2=NO_2$, $R^3=H$

13a—c

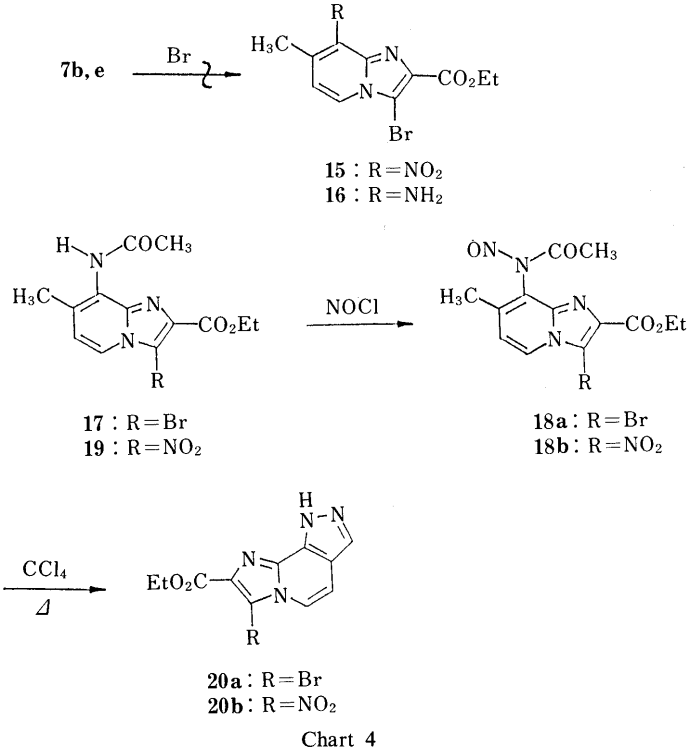
a : $R^1=NO_2$, $R^2=CO_2Et$, $R^3=H$
b : $R^1=CO_2Et$, $R^2=NO_2$, $R^3=H$
c : $R^1=NO_2$, $R^2=CO_2Et$, $R^3=NNOCOCH_3$

12a, b

a : $R^1=NO_2$, $R^2=CO_2Et$
b : $R^1=CO_2Et$, $R^2=NO_2$

Chart 3

with nitrosyl chloride did not give the desired heterocycle, but gave two products (**12a, b**) due to a Gomberg–Bachman reaction between diazonium acetate and benzene complicated by a Dimroth rearrangement. Comparison of the chemical shift of the C-3 signal of **12a, b** with the typical shift of C-3 of imidazo[1,2-*a*]pyridines[10] lead to the required information regarding the structures **12a, b**. The signal of the quaternary carbons C-2 at δ 153.2 for **12a** and C-3 at δ 134.4 for **12b** were consistent with the deshielding effect of the NO_2 group. Among various reaction conditions examined, replacement of benzene with cyclohexane or hexane yielded **13a, b**. Furthermore, in heptane, ethyl 6-*N*-nitrosoacetamido-7-methyl-2-nitroimidazo[1,2-*a*]pyridine-3-carboxylate (**13c**) was isolated. These results suggested that Dimroth rearrangement of the *N*-nitrosoacetamide occurs. An attempt to form the ring system (**4**) from the isolated *N*-nitroso compound (**11**) with Na_2CO_3 in carbon tetrachloride unexpectedly gave the dinitroester (**14a**) together with monochlorinated derivatives (**14b, c**). Isolation of **14a—c** from the reaction mixture by flash chromatography gave yields of 2, 11 and 6%, respectively. The relation between the CO_2Et and NO_2 groups of **13a, b** was confirmed by comparison of **13b** with the same product from the reaction of **7j** with HNO_3–H_2SO_4. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of **14b, c** were in accord with the proposed structures. The strong deshielding of the quaternary carbons C-3 at δ 134.3 for **14c** and C-2 at δ 152.2 for **14b** (carbon substituted by the NO_2 group) led to the required information by comparison with similar assignments for imidazopyridines.[10] In mass spectrometry, compound **14a** showed *m/z* 330—328 (100—33% respectively), with one aromatic signal at δ 9.57 in the proton nuclear magnetic resonance spectrum (^{1}H-NMR). Taking the chemical shift of the H-8 and H-5 signals in the imidazopyridine series into account, the C-5 position was concluded to be free from a nitro group, which is considered to be located at the C-8 position. Structure **14a** was confirmed by downfield shifts due to the NO_2 group (δ 152.1 for C-2 and δ 139.1 for C-8) and by the presence



15 : R=NO_2
16 : R=NH_2

17 : R=Br
19 : R=NO_2

18a : R=Br
18b : R=NO_2

20a : R=Br
20b : R=NO_2

Chart 4

of the quaternary carbon C-3 signal (δ 108.5) in the ^{13}C-NMR spectra (Chart 3).

When compounds **7b, e** were treated with bromine, compounds **15** and **16** were formed in 39 and 59% yields, respectively.

The application of the heterocyclization to the 8-acetamido derivative (**17**) obtained by bromination of **7h** gave, in contrast, the desired 1*H*-imidazo[1,2-*a*]pyrazolo[3,4-*c*]pyridine (**20a**) from the *N*-nitroso derivative (**18a**) in 22% yield. Similarly, nitration of **7h** gave **19**, which, when added to NOCl, forms **18b** and this in turn cyclizes to give **20b** (Chart 4). The individual structures were assigned on the basis of mass spectrum (MS) and ^{1}H-NMR

spectral data. The structures of **20a**, **b** were identified by direct comparisons of their spectral data with those of the 3-CO_2Et and 3-NO_2 group of imidazo[1,2-*a*]pyridines.[10] The bromine of **20a** is considered to be located at the C-7 position from the ^{1}H-NMR upfield shift of the H-5 signal (δ 8.2). The ^{1}H-NMR spectrum of **20b** indicated that the nitro group is also connected to the C-7 position, in view of the presence of the H-5 signal at low field (δ 9.38).

Experimental

Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. Elemental analyses were performed by the Microanalytical Center, ENSCM, Montpellier. Spectral measurements were taken with the following instruments: ^{1}H-NMR spectra were recorded on a Varian EM 360 (60 MHz) or a Bruker MSL 300. Chemical shifts are expressed relative to internal tetramethylsilane in $CDCl_3$ at a concentration of *ca.* 5%. Assignements marked with an asterisk may be reversed. MS were recorded on a LKB 2091 spectrometer at 70 eV [(θ_{source}) = 180 °C]. Compounds were purified by chromatography on alumina or silica gel columns. When necessary, solvents and reagents were dried prior to use. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated neutral alumina plates.

7-Methyl-6-nitro-2-phenylimidazo[1,2-*a*]pyridine (7a) A solution of 15 g (75 mmol) of phenacyl bromide in 200 ml of dry ethanol, was added to a solution of **6b**[7] (11 g, 72 mmol) in 500 ml of dry ethanol. The reaction mixture was refluxed for 4 h, then cooled to room temperature. The precipitate was collected by filtration, washed with ethanol and dissolved in water (40 ml). The aqueous solution was basified with sodium carbonate and extracted with dichloromethane. The organic layers were dried and the solvent removed *in vacuo* to give **7a** as yellow plates (4 g, 22%); mp 192—193 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.70 (3H, s), 7.50 (4H, m), 7.93 (3H, m), 9.13 (1H, s). *Anal.* Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.35; N, 16.60. Found: C, 66.28; H, 4.38; N, 16.51.

Ethyl 7-Methyl-8-nitroimidazo[1,2-*a*]pyridine-2-carboxylate (7b) A solution of **6a** (20 g, 0.137 mol) and ethyl bromopyruvate (40 g, 0.207 mol) in 500 ml of dry ethanol was refluxed for 4 h. The solvent was removed *in vacuo*, and the residue was dissolved in water. This solution was made alkaline with sodium carbonate and extracted with dichloromethane. After drying of the organic solution, chromatography on neutral alumina eluted with dichloromethane gave **7b** as yellow plates (30 g, 92%); mp 116—118 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.40 (3H, t, J = 7 Hz), 2.48 (3H, s), 4.42 (2H, q), 6.83 (d, J = 7 Hz 6-H), 8.23 (s, 3-H), 8.23 (d, 5-H). *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.42; N, 16.87. Found: C, 52.93; H, 4.39; N, 16.92.

Ethyl 7-Methyl-6-nitroimidazo[1,2-*a*]pyridine-2-carboxylate (7c) A solution of **6b** (20 g, 0.137 mol) and ethyl bromopyruvate (40 g, 0.207 mol) was refluxed for 4 h in dry ethanol (600 ml). After cooling, the precipitate was treated as described above to give **7c** (20 g, 61.5%) as pale yellow needles; mp 146—148 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.43 (3H, t, J = 7 Hz), 2.68 (3H, s), 4.48 (2H, q), 7.57 (s, 8-H), 8.35 (s, 3-H), 9.23 (s, 5-H). *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.42; N, 16.87. Found: C, 52.89; H, 4.38; N, 16.77.

6-Amino-7-methyl-2-phenylimidazo[1,2-*a*]pyridine (7d) Following the introduction of hydrogen gas into a solution of 2.5 g (10 mmol) of 7a in 100 ml of ethanol in the presence of 150 mg of 5% Pd/C, the suspension was stirred for 3 h at room temperature and the Pd/C was filtered off. The filtrate was evaporated *in vacuo*, leaving a residue. This crude product was purified by flash chromatography on silica gel, eluted with dichloromethane with a methanol gradient (final: 5%). The product (**7d**; 1.3 g, 59%) was isolated as a white powder; mp 239—241 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.27 (3H, s), 2.83 (br s, NH_2), 7.43 (6H, m), 7.90 (2H, m).

Ethyl 8-Amino-7-methylimidazo[1,2-*a*]pyridine-2-carboxylate (7e) Compound **7b** (5 g, 0.02 mol) was added portionwise to a suspension of 6 g of zinc in 50 ml of concentrated hydrobromic acid at −10 °C. The reaction mixture was stirred for 3 h at room temperature, then the suspension was filtered and the solid dissolved in water. The solution was basified with sodium carbonate and the precipitate was filtered off to give the amine (**7e**; 3.4 g, 70%); mp 169—171 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.40 (3H, t, J = 7 Hz), 2.18 (3H, s), 4.45 (2H, q), 4.58 (2H, s, NH_2), 6.58 (d, J = 7 Hz, 6-H), 7.53 (d, J = 7 Hz, 5-H), 8.05 (s, 3-H).

Ethyl 6-Amino-7-methylimidazo[1,2-*a*]pyridine-2-carboxylate (7f) Compound **7c** (5 g, 20 mmol) was added portionwise to a mixture of zinc powder (7 g) and concentrated hydrochloric acid (100 ml) at such a rate that the temperature did not rise above 0 °C. After the addition, the reaction mixture was left at room temperature overnight, basified with aqueous ammonia and extracted with dichloromethane. The organic layers were dried and the solvent was removed *in vacuo* to give **7f** (3.8 g, 87%) as a white powder; mp 209—211 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.42 (3H, t, J = 7 Hz), 2.28 (3H, s), 3.63 (2H, s, NH_2), 4.47 (2H, q), 7.50 (s, 8-H), 7.63 (s, 5-H), 8.03 (s, 3-H).

6-Acetamido-7-methyl-2-phenylimidazo[1,2-*a*]pyridine (7g) A solution of compound **7d** (1 g, 4.5 mmol) in acetic anhydride (5 ml) and toluene (20 ml) was refluxed for 15 min and then evaporated to dryness. The residual oil was dissolved in aqueous ammonia and the pH was adjusted to 8. The 6-acetamido derivative (**7g**; 1 g, 84%); mp 258—260 °C; was filtered off, washed with water and dried. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 2.25 (3H, s), 2.36 (3H, s), 7.43 (4H, m), 7.93 (3H, m), 9.00 (1H, s). *Anal.* Calcd for $C_{16}H_{15}N_3O$: C, 72.45; H, 5.66; N, 15.85. Found: C, 72.37: H. 5.69; N, 15.94.

Ethyl 8-Acetamido-7-methylimidazo[1,2-*a*]pyridine-2-carboxylate (7h) The amine **7e** (3 g, 13.7 mmol) was dissolved in 25 ml of dry toluene and treated with 5 ml of acetic anhydride. The mixture was refluxed for 15 min and then evaporated to dryness. The residue was dissolved in 50 ml of water, and the solution made alkaline with ammonia then filtered to give the acetamide 7 h as yellow plates (3 g, 84%); mp 108—110 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.37 (3H, t, J = 7 Hz), 2.17 (3H, s), 2.37 (3H, s), 4.40 (2H, q), 6.80 (d, J = 7 Hz, 6-H), 7.93 (d, 5-H), 8.10 (s, 3-H), 10.08 (s, NH). *Anal.* Calcd for $C_{13}H_{15}N_3O_3$: C. 59.77; H, 5.75; N, 16.09. Found: C, 59.85; H, 5.73; N, 16.03.

Ethyl 6-Acetamido-7-methylimidazo[1,2-*a*]pyridine-2-carboxylate (7i) A solution of **7f** (2 g, 9 mmol) in 10 ml of acetic anhydride and 40 ml of toluene was refluxed for 15 min. The reaction mixture was treated and worked up as described above to give 2.4 g (100%) of **7i** as white plates; mp 195—197°C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.42 (3H, t, J = 7 Hz), 2.22 (3H, s), 2.30 (3H, s), 4.47 (2H, J = 7 Hz, q), 7.35 (s, 8-H), 8.02 (s, NH), 8.08 (s, 3-H), 8.85 (s, 5-H). *Anal.* Calcd for $C_{13}H_{15}N_3O_3$: C, 59.77; H, 5.75; N, 16.09. Found: C, 58.65; H, 5.77; N, 16.13.

Ethyl 3-Nitrosoimidazo[1,2-*a*]pyridine-2-carboxylate (9a) Ethyl imidazo[1,2-*a*]pyridine-2-carboxylate[11] (**8a**) (1 g, 5.26 mmol) was dissolved in a solution of acetic acid–acetic anhydride (1.5 : 3) and the solution was cooled to −10 °C. Nitrosyl chloride solution (0.37 g/ml) (2 ml, 11.2 mmol) in acetic anhydride, was added slowly so that the temperature did not rise above −5 °C. After the addition, the solution was poured onto ice (100 g), and the precipitate was collected, washed with water and purified on silica gel eluted with Et_2O to give **9a** as green plates (0.76 g, 66%); mp 157—159°C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.52 (3H, t, J = 7Hz), 4.77 (2H, q), 7.53 (pseudo t, 6-H), 8.03 (m, 7-H, 8-H), 9.80 (dd, $J_{5,6}$ = 7 Hz, 5-H); MS *m/z*: M^+: 219, 190, 174, 159, 146, 131, 104, 78 (base peak). *Anal.* Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.11; N, 19.18. Found: C, 54.88; H, 4.15; N, 19.11.

By the same procedure **9b**, **9c** and **9d** were also prepared.

Ethyl 8-Methyl-3-nitrosoimidazo[1,2-*a*]pyridine-2-carboxylate (9b) Yield: 55%; mp 170—172°C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.53 (3H, t, J = 7 Hz), 2.80 (3H, s), 4.72 (2H, q), 7.33 (pseudo t, $J_{5,6}$ = 7 Hz, $J_{6,7}$ = 8 Hz, 6-H), 7.43 (dd, $J_{7,6}$ = 8 Hz, $J_{5,7}$ = 1 Hz, 7-H), 9.75 (dd, $J_{5,6}$ = 7 Hz, $J_{5,7}$ = 1 Hz, 5-H). *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.72; N, 18.03. Found: C, 56.53: H, 4.70; N, 18.19.

Ethyl 7-Methyl-3-nitrosoimidazo[1,2-*a*]pyridine-2-carboxylate (9c) Yield: 32%; mp 131—133 °C, ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.52 (3H, t, J = 7 Hz), 2.45 (3H, s), 4.67 (2H, q, J = 7 Hz), 7.29 (dd, $J_{5,6}$ = 7 Hz, $J_{6,8}$ = 1 Hz, 6-H), 7.72 (m, 8-H), 9.59 (d, $J_{5,6}$ = 7 Hz, 5-H). *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.72; N, 18.03. Found: C, 55.82; H, 4.65; N, 17.95.

Ethyl 6-Methyl-3-nitrosoimidazo[1,2-*a*]pyridine-2-carboxylate (9d) Yield: 69%; mp 125—127 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.52 (3H, t, J = 7 Hz), 2.45 (3H, s), 4.67 (2H, q, J = 7 Hz), 7.70 (d, $J_{7,8}$ = 9 Hz, 8-H), 7.95 (dd, $J_{7,8}$ = 9 Hz, $J_{7,5}$ = 1.5 Hz, 7-H), 9.58 (d, $J_{7,5}$ = 1.5 Hz, 5-H). *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.72; N, 18.03. Found: C, 56.51; H, 4.76; N, 18.19.

Ethyl 6-Acetamido-7-methyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxylate (10) Nitric acid (d = 1.38, 2 ml) was slowly added to a solution of **7i** (1.2 g, 4.6 mmol) in 20 ml of ice-cooled concentrated sulfuric acid. The reaction mixture was stirred for 1 h at 0 °C and 2 h at room temperature, and then poured into an excess quantity of ice-water. The precipitate formed was extracted with dichloromethane. The organic layers were washed with water, dried with magnesium sulfate, and evaporated *in vacuo* to leave a residue, which was chromatographed on neutral alumina using

dichloromethane as the eluent to give **10** (1.05 g, 75%) as yellow plates; mp 214—216 °C ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.43 (3H, t, J=7 Hz), 2.27 (3H, s), 2.43 (3H, s), 4.57 (2H, q, J=7 Hz), 7.57 (s, 8-H), 7.72 (s, NH), 9.70 (s, 5-H). *Anal.* Calcd for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.58; N, 18.30. Found: C, 50.87; H, 4.65; N, 18.43.

Cyclization of 10 Method A: A cold (−10 °C) solution of nitrosyl chloride in acetic anhydride (0.37 g/ml) (7 ml, 39.5 mmol) was slowly added to a solution of **10** (1 g, 3.3 mmol) and dried potassium acetate (1 g, 10.2 mmol) in acetic anhydride (25 ml) and acetic acid (12.5 ml) such that the temperature of the mixture did not rise above 5°C, under cooling at 0 °C. After completion of the addition, stirring was continued for 15 min at 0 °C. The absence of the starting material was verified by TLC on silica gel (eluent: pentane–ether–methanol, 50 : 49 : 1). The mixture was poured into a suspension of sodium carbonate (13 g, 0.123 mol) in dry benzene (100 ml) and stirred until gas evolution ceased. After filtration, the filtrate was evaporated *in vacuo* and the resultant crude *N*-nitrosoacetamide (**11**) (1.09 g, 100%) was crystallized from ether–pentane (50 : 50); ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.45 (3H, t, J=7 Hz), 2.07 (3H, s), 3.05 (3H, s), 4.57 (2H, q, J=7 Hz), 7.77 (s, 8-H), 9.00 (s, 5-H). The *N*-nitrosoacetamide (**11**) was dissolved in dry benzene (100 ml) and refluxed for 2 h. The solvent was evaporated off *in vacuo* and the oily residue was taken up in ether–dichloromethane (50 : 50). Filtration and evaporation gave 0.92 g of a crude product which was flash-chromatographed on silica gel (eluent: dichloromethane with methanol gradient: final 5%). Three products were isolated. The first fraction gave ethyl 7-methyl-2-nitro-6-phenylimidazo[1,2-*a*]pyridine-3-carboxylate **12a** (0.22 g, 21%); mp 97—99 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.36 (3H, t, J=7 Hz), 2.36 (3H, s), 4.40 (2H, q, J=7 Hz), 7.34 (m, 2′-H, 6′-H), 7.47 (m, 3′-H, 4′-H, 5′-H), 7.63 (s, 8-H), 9.09 (s, 5-H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ: 13.9 (CH_3), 20.9 (CH_3), 61.8 (CH_2), 106.9 (C-3), 117.7 (C-8), 126.4 (C-5), 128.5, 128.7, 129.3 (C-H arom.), 133.4 (C*-6), 135.9 (C* arom.), 141.1 (C-7), 142.9 (C-8a), 153.2 (C-2), 158.5 (CO). MS *m/z* (%): 325 (M^+, 100), 295(M^+ − NO, 6), 280 ($M^+ - OC_2H_5$, 4), 252 ($M^+ - CO_2C_2H_5$, 49), 235 (34), 207 (25), 195 (27), 168 (17), 153 (21), 141 (16), 128 (12), 115 (14), 77 (12). *Anal.* Calcd for $C_{17}H_{15}N_3O_4$: C, 62.77; H, 4.62; N, 12.92. Found: C, 62.69; H, 4.59; N 12.97. The second fraction gave ethyl 7-methyl-3-nitro-6-phenylimidazo[1,2-*a*]pyridine-2-carboxylate **12b** (0.08 g, 8%); mp 112—114°C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.47 (3H, t, J=7 Hz), 2.40 (3H, s), 4.58 (2H, q, J=7 Hz), 7.53 (5H, m), 7.82 (s, 8-H), 9.28 (s, 5-H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ: 14.0 (CH_3), 21.0 (CH_3), 62.8 (CH_2), 118.2 (C-8), 125.7 (C-5), 128.8, 128.9, 129.3 (C-H arom.), 130.8 (C-2), 134.4 (C-3), 135.5 (C*-6), 137.4 (C* arom.), 142.5 (C-7), 144.3 (C-8a), 158.3 (CO): MS *m/z* (%): 325 (M^+, 40), 265 (15), 235 (18), 194 (20), 168 (100), 153 (17), 141 (20), 128 (10), 115 (13), 77 (15). *Anal.* Calcd for $C_{17}H_{15}N_3O_4$: C, 62.77; H, 4.62. Found: C, 62.86; H, 4.63. The third fraction gave the amide (**10**) (0.27 g, 27%).

Method B: A solution of **10** (2 g, 6.5 mmol) and dried potassium acetate (4 g, 40.8 mmol) in acetic anhydride (25 ml) and acetic acid (25 ml), cooled to −10°C, was treated as above with nitrosyl chloride/acetic anhydride (0.37 g/ml) (3 ml, 17 mmol). The mixture was poured into a suspension of sodium carbonate–cyclohexane–pentane (25 g : 150 ml : 50 ml) at −10 °C. After neutralization, the precipitate was filtered off and washed with cyclohexane (2 × 50 ml). After evaporation of the pentane, the combined organic layers were refluxed for 1 h. The mixture was evaporated to dryness and the oily residue was submitted to flash chromatography on silica gel eluted with pentane–ether–methanol (50 : 49 : 1) then with dichloromethane with a methanol gradient (final %: 5%). The first fraction gave ethyl 7-methyl-2-nitroimidazo[1,2-*a*]pyridine-3-carboxylate **13a** (0.26 g, 16%) as an orange powder; mp 133—135 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.38 (3H, t, J=7 Hz), 2.50 (3H, s), 4.43 (2H, q, J=7 Hz), 7.08 (dd, $J_{5,6}$=7 Hz, $J_{6,8}$=2 Hz, 6-H), 7.52 (d, $J_{6,8}$=2 Hz, 8-H), 9.12 (d, $J_{5,6}$=7 Hz, 5-H). MS *m/z* (%): 250 (M^++1.13), 249 (M^+, 100), 204 ($M^+ - OC_2H_5$, 12), 177 ($M^+ - CO_2C_2H_5$ − H, 73), 159 (40), 131 (56), 119 (73), 104 (33), 92 (83), 77 (30). *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.42; N, 16.87. Found: C, 52.87; H, 4.38; N, 16.78. Further elution gave ethyl 7-methyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxylate **13b** (0.08 g, 5%); mp 138—140 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.45 (3H, t, J=7 Hz), 2.52 (3H, s), 4.55 (2H, q, J=7 Hz), 7.23 (d, J=7 Hz, 6-H), 7.68 (s, 8-H), 9.30 (d, J=7 Hz, 5-H). This compound was identical with an authentic sample prepared by nitration of ethyl 7-methylimidazo[1,2-*a*]pyridine-2-carboxylate.[12] The final fraction (0.35 g, 17%) gave the acetamide **10**.

Method C: A solution of **10** (2 g, 6.5 mmol) and dried potassium acetate (4 g, 40.8 mmol) in acetic anhydride (25 ml) and acetic acid (25 ml), cooled to −10 °C, was treated in the same manner as above with nitrosyl chloride/acetic anhydride (0.37 g/ml) (2 ml, 11.3 mmol). The mixture was poured into a solution of sodium carbonate in water (70 g/250 ml) at 0 °C. After neutralization, 200 ml of water was added and the reaction product was extracted with dichloromethane. The organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The crude *N*-nitrosoacetamide was diluted in carbon tetrachloride (120 ml). Molecular sieves 4 Å (1 g) were added and the solution was refluxed for 1 h. After evaporation of the solvent, the crude reaction mixture was flash chromatographed on silical gel with pentane–ether–methanol (50 : 49 : 1 v/v) and then with dichloromethane with a methanol gradient (final 5%). Four fractions were collected. The first fraction gave ethyl 6-chloro-7-methyl-2,8-dinitroimidazo[1,2-*a*]pyridine-3-carboxylate (**14a**) as pale yellow needles (0.05 g, 2%); mp 157—159 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.40 (3H, t, J=7 Hz), 2.58 (3H, s), 4.50 (2H, q, J=7 Hz), 9.57 (s, 5-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 13.8 (CH_3), 16.0 (CH_3), 62.9 (CH_2), 108.5 (C-3), 126.5 (C-6), 127.6 (C-5), 133.7 (C-7), 135.0 (C-8a), 139.1 (C-8), 152.1 (C-2), 157.7 (CO). MS *m/z* (%): 330 (M^++2, 33), 328 (M^+, 100), 311 (11), 283 (25), 256 (22), 239 (17), 211 (13), 193 (42), 180 (16), 149 (26), 125 (25), 117 (21), 90 (26), 78 (20), 77 (16). *Anal.* Calcd for $C_{11}H_9ClN_4O_6$: C, 40.18; H, 2.74. Found: C, 40.31; H, 2.69. Further elution gave ethyl 6-chloro-7-methyl-2-nitroimidazo[1,2-*a*]pyridine-3-carboxylate **14b** as a white powder which became green on exposure to daylight (0.2 g, 11%); mp 116—118 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.38 (3H, t, J=7 Hz), 2.53 (3H, s), 4.47 (2H, q, J=7 Hz), 7.63 (s, 8-H), 9.35 (s, 5-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 13.6 (CH_3), 20.2 (CH_3), 60.0 (CH_2), 106.6 (C-3). 117.7 (C-8), 125.4 (C-5), 127.0 (C-6), 140.7 (C-7), 141.9 (C-8a), 152.2 (C-2), 157.9 (CO). MS *m/z* (%): 285 (M^++2, 33), 283 (M^+, 100), 255 (12), 238 (15), 211 (80), 195 (62), 153 (62), 126 (53), 117 (23), 90 (49), 78 (12), 77 (18). *Anal.* Calcd for $C_{11}H_{10}ClN_3O_4$: C, 46.56; H, 3.53; N, 14.81. Found: C, 46.41; H, 3.59; N, 14.94. Further elution gave ethyl 6-chloro-7-methyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxylate **14c** as pale yellow needles (0.1 g, 6%); mp 108—110 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.47 (3H, t, J=7 Hz), 2.60 (3H, s), 4.58 (2H, q, J=7 Hz), 7.77 (s, 8-H), 9.47 (s, 5-H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ: 13.9 (CH_3), 20.5 (CH_3), 62.9 (CH_2), 118.4 (C-8), 124.9 (C-5), 127.2 (C-6), 128.1 (C-2), 134.3 (C-3), 140.6 (C-8a), 142.0 (C-7), 159.5 (CO). MS *m/z* (%): 285 (M^++2, 11), 283 (M^+, 36), 194 (10), 153 (22), 129 (33), 127 (100), 102 (16), 99 (14), 90 (32), 77 (7). *Anal.* Calcd for $C_{11}H_{10}ClN_3O_4$: C, 46.56; H, 3.53; N, 14.81. Found: C, 46.52; H, 3.52; N, 14.81. The final fraction (0.20 g, 10%) gave the acetamide **10**.

Method D: *N*-Nitrosoacetamide **11** (0.5 g, 1.5 mmol), obtained by the method described above, was suspended in dry heptane (50 ml) and the suspension was refluxed for 45 min. After evaporation of the solvent *in vacuo*, the crude reaction mixture was subjected to flash chromatography on silica gel with pentane–dichloromethane–methanol (50 : 49 : 1 v/v). Three fractions were collected. The first fraction gave a mixture 75 : 25 (0.04 g, 11%) of **13a** and **13b**. Further elution gave 35 mg of ethyl 6-*N*-nitrosoacetamido-7-methyl-2-nitro-imidazo[1,2-*a*]pyridine-3-carboxylate (**13c**). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.38 (3H, t, J=7 Hz), 2.28 (3H, s), 2.46 (3H, s), 4.50 (2H, q, J=7 Hz), 7.65 (s, 8-H), 9.83 (s, 5-H), and (**11**) (65 mg). The third fraction gave **10** (0.25 g, 54%).

Ethyl 3-Bromo-7-methyl-8-nitroimidazo[1,2-*a*]pyridine-2-carboxylate (15) and Ethyl 8-Amino-3-bromo-7-methylimidazo[1,2-*a*]pyridine-2-carboxylate (16) A solution of **7b** (7 g, 28.1 mmol) in 100 ml of acetic acid was treated with 2.9 ml of bromine (56.2 mmol) and the mixture was stirred for 3 h at 20°C, then basified with ammonia and extracted with dichloromethane. After being dried, the organic layers were evaporated *in vacuo* and the residue was subjected to chromatography on neutral alumina eluted with dichloromethane to give **15** (3.6 g, 39%) as yellow plates; mp 148—150°C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.43 (3H, t, J=7 Hz), 2.53 (3H, s), 4.50 (2H, q, J=7 Hz), 7.08 (d, J=7 Hz, 6-H), 8.37 (d, 5-H). *Anal.* Calcd for $C_{11}H_{10}BrN_3O_4$: C, 40.24; H, 3.05; N, 12.80. Found: C, 40.07; H, 3.01; N, 12.93.

A procedure similar to that used for **7e** was also employed to obtain **16** in 59% yield; mp 108—110 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.43 (3H, t, J=7 Hz), 2.18 (3H, s), 4.47 (2H, q, J=7 Hz), 4.75 (s, NH_2), 6.68 (d, J=7 Hz, 6-H), 7.52 (d, J=7 Hz, 5-H). *Anal.* Calcd for $C_{11}H_{12}BrN_3O_2$: C, 44.30; H, 4.03; N, 14.09. Found: C, 44.52; H, 4.11; N, 13.89.

Ethyl 8-Acetamido-3-bromo-7-methylimidazo[1,2-*a*]pyridine-2-carboxylate (17) The method used to obtain **7h** was applied to prepare **17** from **16** as yellow plates in 62% yield; mp 219—221 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.33 (3H, t, J=7 Hz), 2.10 (3H, s), 2.23 (3H, s), 4.38 (2H, q, J=7Hz), 6.90 (d, J=7 Hz, 6-H), 7.90 (d, J=7 Hz, 5-H), 11.32 (s, NH), *Anal.* Calcd for $C_{13}H_{14}BrN_3O_3$: C, 45.88; H, 4.12; N, 12.35. Found: C, 45.69; H, 4.14; N, 12.19.

Ethyl 8-Acetamido-7-methyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxylate (19) A solution of **7h** (3 g, 11.5 mmol) in 50 ml of concentrated

sulfuric acid was cooled to −10 °C and then 4.7 ml of nitric acid (d=1.38) was slowly added such that the temperature remained below 0 °C. The mixture was poured into ice, and the solid was collected by filtration, then dissolved in dichloromethane. The organic layers were dried and evaporated *in vacuo* to give **19** (3.1 g, 88%); mp 157—159 °C. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.38 (3H, t, J=7 Hz), 2.28 (3H, s), 2.43 (3H, s), 4.47 (2H, q, J=7 Hz), 7.27 (d, J=7 Hz, 6-H), 9.08 (d, J=7 Hz, 5-H), 9.75 (s, NH). *Anal.* Calcd for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.58; N, 18.30. Found: C, 50.79; H, 4.52; N, 18.18.

Ethyl 7-Bromo-1*H*-imidazo[1,2-*a*]pyrazolo[3,4-*c*]pyridine-8-carboxylate (20a) Potassium acetate (4 g) was added to a solution of **17** (2 g, 5.88 mmol) in acetic anhydride–acetic acid (25:25) and the mixture cooled to −10 °C. Nitrosyl chloride (2 ml) (0.37 g/ml) was added dropwise and the mixture was stirred for 15 min at −15 °C. Then 2 ml of nitrosyl chloride was added and the whole was stirred for another 10 min until the acetamide was no longer detectable on TLC. The mixture was poured into a solution of 70 g of sodium carbonate in 250 ml of water. The solution was extracted with dichloromethane, dried and evaporated *in vacuo*. Recrystallization of the residu from ether–pentane gave 2.16 g of the *N*-nitrosoacetamide **18a** (99.5%). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.38 (3H, t, J=7 Hz), 2.08 (3H, s), 3.05 (3H, s), 4.40 (2H, q, J=7 Hz), 6.95 (d, J=7 Hz, 6-H), 8.20 (d, J=7 Hz, 5-H). The *N*-nitrosoacetamide (**18a**) was suspended in 180 ml of carbon tetrachloride with 1 g of Molecular sieves 4 Å and refluxed for 1 h. After evaporation, the residue was chromatographed on alumina. Elution with dichloromethane–methanol (95 : 5) gave **20a** (400 mg, 22%) as yellow plates; mp 209—211 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.45 (3H, t, J=7 Hz), 4.53 (2H, q, J=7 Hz), 7.31 (d, J=8 Hz, 4-H), 7.89 (d, J=8 Hz, 5-H), 8.15 (s, 3-H). *Anal.* Calcd for $C_{11}H_9BrN_4O_2$: C, 42.72; H, 2.91; N, 18.12. Found: C, 42.59; H, 2.95; N, 18.19.

Ethyl 7-Nitro-1*H*-imidazo[1,2-*a*]pyrazolo[3,4-*c*]pyridine-8-carboxylate (20b) Potassium acetate (4 g) was added to a solution of **19** (2 g, 6.53 mmol) in acetic anhydride/acetic acid (25/25 ml) and the mixture cooled to −10 °C. Nitrosyl chloride (2 ml) (0.37 g/ml) was added dropwise and the whole was stirred for 15 min at −15 °C. Then 2 ml of nitrosyl chloride was added and the whole was stirred for another 10 min until the acetamide had disappeared on TLC. The mixture was poured into a solution of 70 g of sodium carbonate in 250 ml of water, and extracted with dichloromethane. The organic layer was dried and evaporated *in vacuo*. Recrystallization in ether–pentane gave 2.16 g of the *N*-nitrosoacetamide (**18b**) (99%); ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.44 (3H, t, J=7 Hz), 2.26 (3H, s), 3.25 (3H, s), 4.49 (2H, q, J=7 Hz), 7.32 (d, J=7 Hz, 6-H), 9.38 (d, J=7 Hz, 5-H). The *N*-nitroso-acetamide was suspended in 180 ml of carbon tetrachloride with 1 g of Molecular sieves 4 Å and refluxed for 1 h. The precipitate was collected by filtration to give 200 mg of pure **20b**. After evaporation of the mother liquor, the residue was chromatographed on alumina. Elution with dichloromethane–methanol (95 : 5) gave 400 mg of **20b** as yellow plates (the total yield was 34%); mp 237—239 °C; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.47 (3H, t, J=7 Hz), 4.63 (2H, q, J=7 Hz), 7.62 (d, J=8 Hz, 4-H), 8.30 (s, 3-H), 8.95 (d, J=8 Hz, 5-H). MS m/z (%): 275 (M^+, 41), 247 ($M^+ - N_2$, 4), 230 ($M^+ - OEt$, 4), 214 (3), 187 (13), 170 (8), 157 (19), 145 (25), 130 (15), 118 (100), 91 (15), 78 (7). *Anal.* Calcd for $C_{11}H_9N_5O_4$: C, 48.00; H, 3.27; N, 25.46. Found: C, 48.22; H, 3.20; N, 25.39.

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