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New Routes to Heterobicyclic Ring Systems via Meta-Bridging. 4. Reactions of Nitroquinoline and Dinitropyridine

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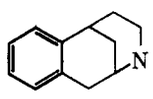
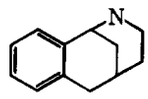
The first examples of heteroaromatic meta-bridging of pyridines and quinolines with amidines and carbanions are described. The effect of aza functionality on the mode of reaction is discussed. Reactions of the corresponding *N*-oxides are also described. The meta-bridged products, highly functionalized aza and diaza bicyclics, result from bis nucleophilic addition of amidines or carbanions to the electron-deficient heterocycles.

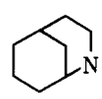
The formation of highly functionalized derivatives of the ring systems **1a, 1b,** and **2** from reaction of electron-deficient



1a



1b



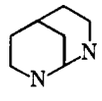
2

naphthalenes and benzenes with amidines has recently been reported.[2,3] Such products are readily formed by cyclization of anionic σ complex (Meisenheimer complex) intermediates which result from nucleophilic addition of amidine to the aromatic, a reaction we have termed "meta-bridging".[13] This type of reaction proceeds in two steps and is distinctly different from the 1,3-dipolar cycloadditions reported by Katritzky[1b] which also yield meta-bridged products.

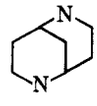
Electron-deficient pyridines form anionic σ complexes[4-7]

3a

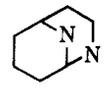
3b



4a



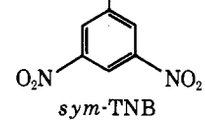
4b



4c

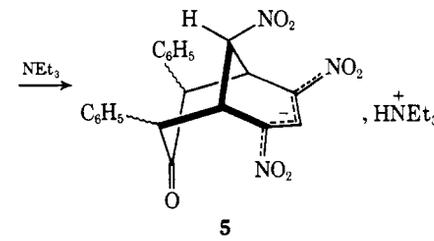
and the activating effect of heterocyclic nitrogen in nucleophilic aromatic substitution has been of interest in this regard.[8] It was thus of interest to investigate the meta-bridging reactions of electron-deficient pyridines. With such substrates, meta-bridging with carbanions could yield either of the ring systems **3a** or **3b,** whereas with amidines **4a, 4b,** or **4c** could result.

The meta-bridging reactivity of dibenzyl ketone with *sym*-trinitrobenzene (TNB) in the presence of triethylamine has been studied in some detail.[9] The reaction occurring has been well characterized and leads to the bridged product **5.** Isomers with both cis and trans phenyls have been isolated,[9]



sym-TNB

+ $(C_6H_5CH_2)_2C{=}O$



5

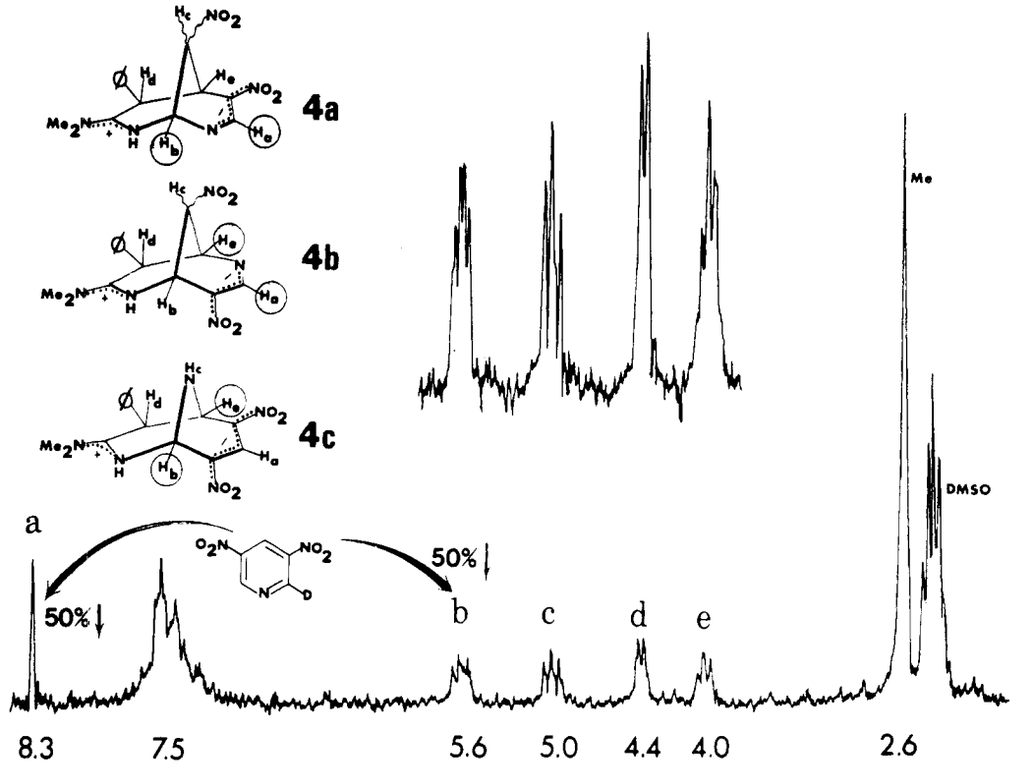
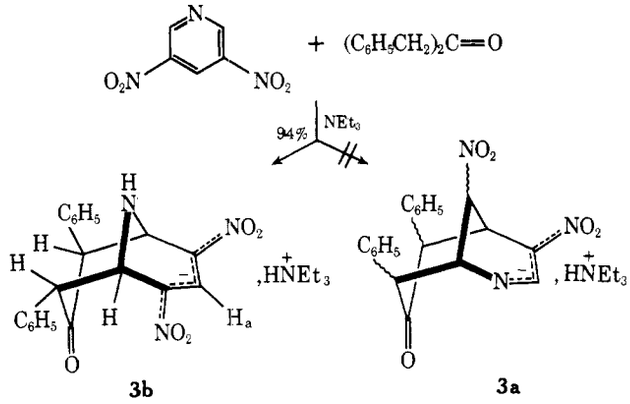


Figure 1.

and stereochemistry at the one carbon bridge has been determined by x-ray crystallography in the cis isomer.[10]

Reaction of 3,5-dinitropyridine (DNP) with dibenzyl ketone and triethylamine under conditions similar to those used in the reaction with TNB gave bridged ion **3b** in 94% yield. There was no evidence for **3a**. The visible spectrum of **3b** showed a characteristic 517-nm maximum of the nitropropene nitronate function.[4,9] Confirmation of structure **3b** is provided by the

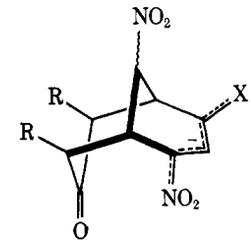


3b **3a**

^1H NMR spectrum, which shows the expected low-field singlet for H_a at δ 8.6. Trans orientation of the phenyl groups is evidenced by one distinct five-proton multiplet at δ 7.2, as well as two- and three-proton multiplets centered at δ 7.8 and 7.4. The remainder of the spectrum is recorded in the Experimental Section.

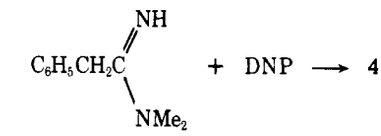
It is of interest that not even a trace of **3a** could be detected in the product. All the 1-X-substituted 3,5-dinitrobenzenes (X less electron withdrawing than NO_2) bridged previously *always* yielded ions in which the X function was part of the delocalized negative charge, i.e., as in **6**.[1] At present we have no explanation for this change in reactivity pattern.

Mixing equivalent quantities of DNP and α-phenyl-*N,N*-dimethylacetamidine in ethanol results in an orange solution with a visible maximum at 506 nm characteristic of



6

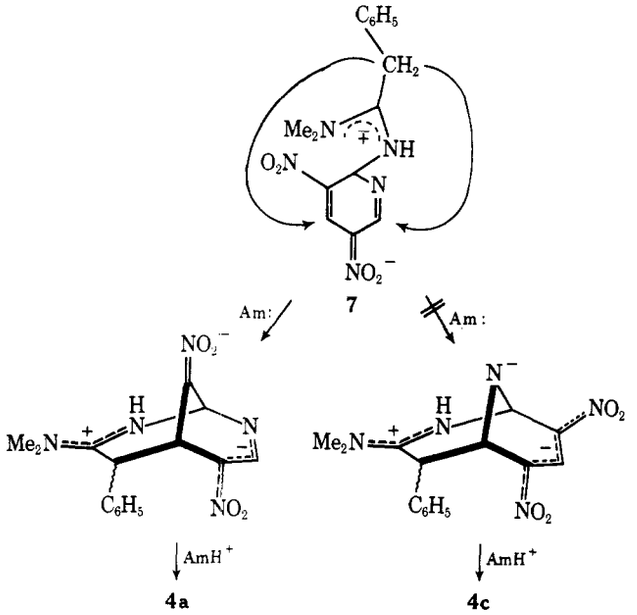
dinitropyridine σ complex intermediates.[4-7] Crystals of **4** are formed after 3 h and these analyze correctly for a 1:1 adduct of the amidine and DNP. They have a strong maximum at 365 nm (Me_2SO).



The ^1H NMR spectrum of **4** (Me_2SO-d_6) is shown in Figure 1. Based on analogous reactions of α-phenyl-*N,N*-dimethylacetamidine with electron-deficient benzenes[2,3] **4a, 4b,** and **4c** are all possible products. Structure **4c** can be ruled out because the nitropropene nitronate functionality in such a product would absorb strongly in the region of 500 ± 20 nm.[2,3,11] Deuterium substitution at C-2 in DNP confirms that the product is not **4c** (vide infra). A distinction between **4a** and **4b** cannot be made on the basis of the visible and ^1H NMR spectra as the chemical shift assignments, made from comparisons with spectra of the adduct of α-phenyl-*N,N*-dimethylacetamidine and TNB,[3] will fit either structure. Only in **4a,** however, do both H_a and H_b diminish by 50% when 2-deuterio-DNP is used as the starting material. These peaks do diminish in intensity as expected (see Figure 1 and Experimental Section).

The formation of **4a** is in accord with the reactivity of DNP in nucleophilic addition reactions[7] and it is formed via the expected cyclization pathway.[1] In alcoholic solutions, nu-

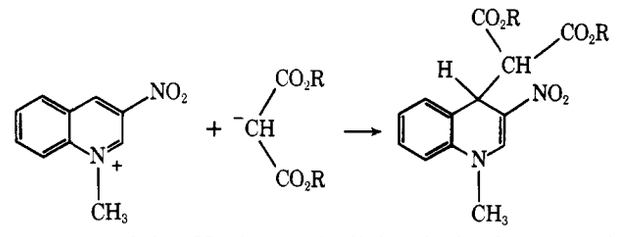
cleophilic addition to C-4 of DNP is difficult to detect.[7] The adducts formed result from attack at C-2. We have previously established that α-phenyl-*N,N*-dimethylacetamidine attacks electron-deficient aromatics initially via nitrogen,[3] and the intermediate complex expected is thus **7**. All our previous studies on related systems,[1,11] i.e., reactions of 1-X-substituted 3,5-dinitrobenzenes, show that the mode of cyclization in unsymmetrical complexes such as **7** is controlled by the ability of the ortho substituent (NO_2 or =N— in **7**) to accommodate accumulating negative charge in the transition state for the cyclization step.[1] This yields the kinetically controlled product. The observation that all 1-X-3,5-dinitrobenzenes thus bridge to yield ions in which the X function bears formal charge in the *final* product, i.e., **6** (X = CN, CO_2R, COR), is



in accord with the formation of **4a** rather than **4c**.[1,11] It is in this regard that the reaction of DNP and dibenzyl ketone, which gives the unexpected product, i.e., **3b** and not **3a**, seems puzzling.

The reactions of both α-phenoxy-*N,N*-dimethylacetamidine and *N,N*-dimethylpropionamidine with DNP yield bridged ions which are in all respects analogous to that obtained with α-phenyl-*N,N*-dimethylacetamidine (see Experimental Section).

In considering the reactivity of dinitropyridines in meta-bridging, we supposed that a single nitro group would be adequate to activate quinoline in such a bridging reaction. It has been reported previously that 3-nitroquinolinium methiodide reacts with carbanions to yield addition products.[12] It has also



been reported that *N*-ethoxyquinolinium iodide **8** reacts with the enamine of cyclohexanone and morpholine, **9**, to give **10**.[13] Examination of **10** shows that it is a quinoline which has been meta-bridged by the enamine. Since there is no nitro group on C-3 in **8**, charge localization at this site associated with the intramolecular cyclization step is accommodated by reaction with a second equivalent of starting quinolinium salt. We presumed that the presence of a nitro group at C-3 of the quinoline ring system would provide a substrate, **11**, which was

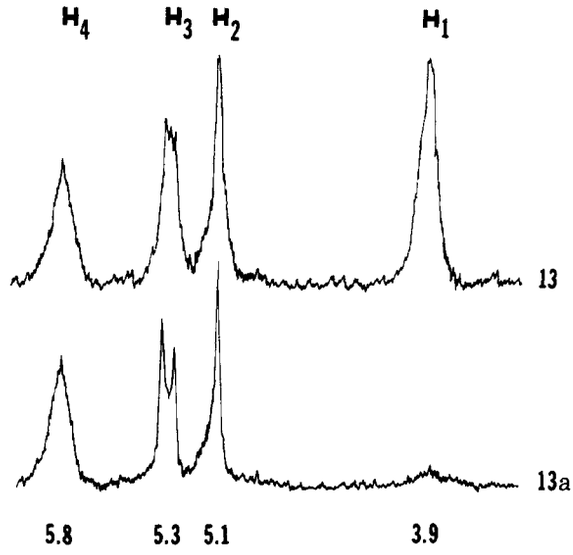
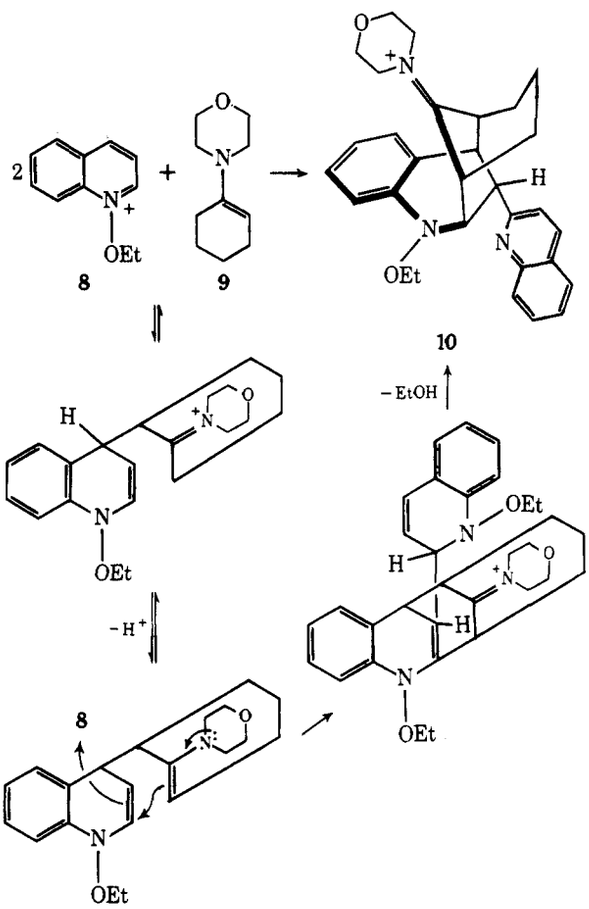
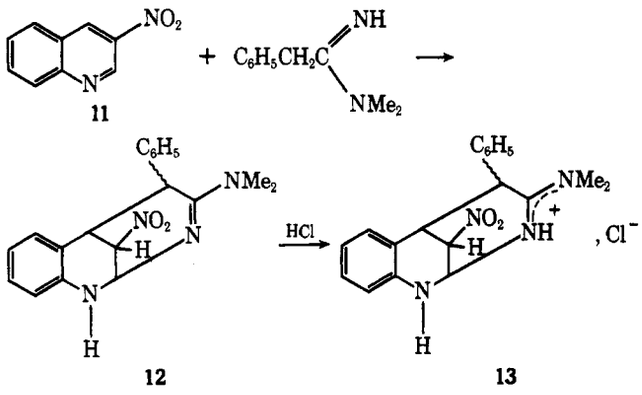


Figure 2.

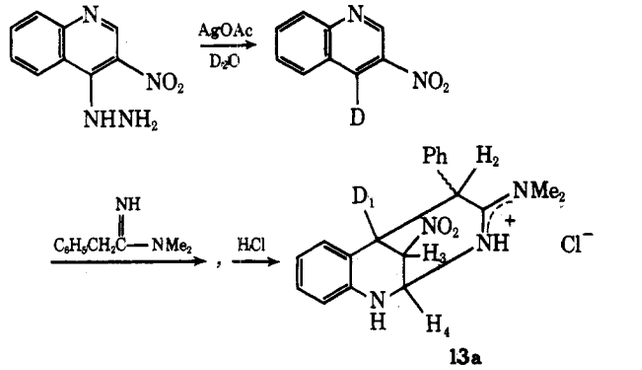


sufficiently reactive to undergo bridging without first being quaternized, and which would not add a second equivalent of electrophilic aromatic. Reaction of **11** with α-phenyl-*N,N*-dimethylacetamidine yielded the bridged product **12** as white crystals, mp 138–139 °C. These readily reverted to starting material when dissolved in Me_2SO. Addition of methanolic HCl to **12** yields the stable hydrochloride salt **13**, mp 195–196 °C. The assignment of structures **12** and **13** is based on the ^1H NMR spectra (see Experimental Section), elemental analyses, and comparative spectral data with naphthalene and pyridine adducts.[3] Such comparative analysis has been extensive[3] and it provides substantial evidence that amidine nitrogen has attacked C-2 of quinoline and not C-4.

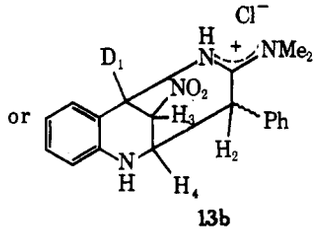


11 12 13

In order to confirm the structural assignment for **13**, C-4 deuterated **11** was prepared from 4-hydrazino-3-nitroquinoline[22] by reaction of the latter with AgOAc in D_2O. The two possible products resulting from reaction of this deuterated analogue are **13a** and **13b**. The four one-proton absorptions (H_1–H_4) in **13** which appear between δ 3.9 and 6.0 are shown in Figure 2. The H-1 and H-4 peaks are respectively the high- and low-field absorptions.[3] The partial spectrum of the adduct



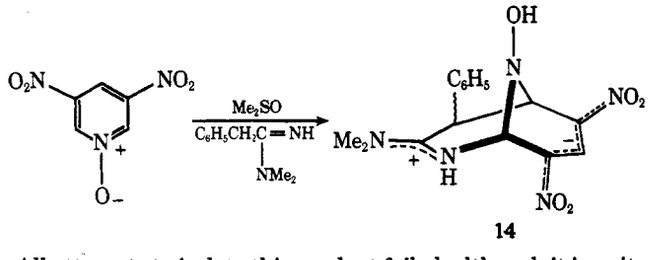
13a



13b

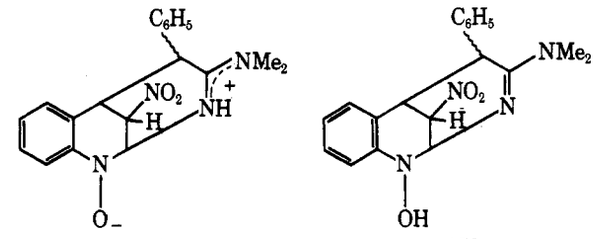
prepared from C-4 deuterated **11** is shown beneath that of **13** in Figure 2. It is clearly consistent only with **13a**, confirming amidine nitrogen attack at C-2 of **11**. The adduct **13** is a strong CNS depressant in mice.[14] Pharmacological data will be reported elsewhere.

It might be expected that 3,5-dinitropyridine and 3-nitroquinoline *N*-oxides would also serve as reactive heteroaromatics, and thus be quite susceptible to nucleophilic attack and meta-bridging. Thus, reaction of 3,5-dinitropyridine *N*-oxide with α-phenyl-*N*,*N*-dimethylacetamidine in Me_2SO yields a solution with ^1H NMR absorptions consistent with formation of the bridged ion **14** (see Experimental Section).



14

All attempts to isolate this product failed, although it is quite stable in Me_2SO in the absence of air. The analogous ion, **15**,



15a 15b

readily forms when 3-nitroquinoline *N*-oxide reacts with α-phenyl-*N*,*N*-dimethylacetamidine in Me_2SO. This product could be either **15a** or **15b** as the ^1H NMR spectrum is consistent with either structure.

Experimental Section

All melting points are uncorrected. ^1H NMR spectra were run on JEOL C-60 HL and MH-100 spectrometers with Me_4Si as an internal reference. Visible and ultraviolet spectra were recorded on a Perkin-Elmer Model 402 UV–visible spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 237 B infrared spectrophotometer. Elemental analyses were cross checked by Galbraith Laboratories, Inc., Knoxville, Tenn., G. I. Robertson Laboratories, Florham Park, N.J., and Integral Microanalytical Laboratories, Inc., Raleigh, N.C.

Preparation of Precursor Aromatics. Both 3,5-dinitropyridine and 2-deuterio-3,5-dinitropyridine were prepared by reported methods.[15,16] There are three published procedures for the preparation of 3-nitroquinoline.[17–19] We have prepared it by each method and found that the cyclization of 2-nitro-2-formylethylideneaniline as described by Morley and Simpson[17] gave the best yields (41%).

Both 3,5-dinitropyridine *N*-oxide and 3-nitroquinoline *N*-oxide were also prepared by published methods.[20,21]

Meta-Bridging Reactions. Preparation of 3b. To a stirred mixture of 0.383 g of 3,5-dinitropyridine and 1.36 g of dibenzyl ketone at 60 ° C was added 0.5 mL of triethylamine. In about 5 min the mixture gelled. Heating to 75 °C with an additional 0.3 mL of amine did not effect dissolution. After an additional 72 h at 50 °C anhydrous ether was added to the gel and the mixture was rapidly stirred for 2 h. The ether was decanted from the solid and a fresh portion of ether was added. After stirring for an additional 2 h the mixture was filtered to give 1.01 g (94%) of an orange powder which when recrystallized from methanol gave orange crystals, mp 119.5–120.5 °C, analyzing correctly $C_{26}H_{32}N_4O_5$: C, 64.98; H, 6.71; N, 11.66. Found: C, 64.85; H, 6.88; N, 11.57.

In Me_2SO **3b** shows absorption maxima at 304 and 517 nm. IR absorption bands occur at 3315, 3020, 1690, 1555, 1470, 1425, 1305, 1250, 1215, 1190, 1130, 1090, 825, 745, and 695 cm^{-1}. The ^1H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 8.55 (1 H, s), 7.78 (2 H, m), 7.43 (3 H, m), 7.17 (5 H, m), 5–6 (2 H, br), 4.94 (1 H, d), 4.85 (1 H, br, s), 4.31 (1 H, d), 3.76 (1 H, br, s), 3.12 (6 H, q), and 1.18 (9 H, t).

Preparation of 4a. Solutions of 0.214 g of DNP in 30 mL of anhydrous EtOH and 0.232 g of α-phenyl-*N*,*N*-dimethylacetamidine in 10 mL of anhydrous EtOH were mixed at room temperature. After a few hours yellow crystals precipitated from the solution. These were filtered, washed with anhydrous Et_2O, and dried to give 0.292 g (68%) of **4a**, mp 178–182 °C. In Me_2SO **4a** shows a single absorption maxima at 365 nm. IR absorption bands (KBr) occur at 2700–3200, 1625, 1525, 1450, 1375, 1225, and 1005 cm^{-1}. The ^1H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 2.71 (6 H, s), 3.98 (1 H, t), 4.40 (1 H, d), 4.98 (1 H, t), 5.55 (1 H, t, br), 7.41 (5 H, m), and 8.33 (1 H, s). Anal. Calcd for $C_{15}H_{16}N_5O_4$: C, 54.37; H, 5.17; N, 21.14. Found: C, 54.34; H, 5.23; N, 21,12.

Formation of **4a** also occurs readily in Me_2SO. A solution of 0.23 g of amidine and 0.21 g of DNP in 1 mL of this solvent was allowed to stand for several days. Ether was then added and the solution was stirred for several hours. The crystals which separated were filtered and dried, and melted at 176–179 °C. The electronic, IR, and ^1H NMR spectra are identical with those of **4a** prepared in ethanol.

Deuterated **4a** was prepared using 2-deuterio-3,5-dinitropyridine in the same fashion as with 3,5-dinitropyridine. A solution of 0.054 g of the amidine in 5 mL of anhydrous ethanol was added to 0.058 g of 2-deuterio-DNP in 10 mL of ethanol. After 3 h the crystals which formed were filtered, washed with ethanol, and dried (0.1 mm) at 80 °C for 4 h to give 0.037 g (33%) of product. The ^1H NMR spectrum of this material in Me_2SO-d_6 shows absorptions at δ 2.76 (6 H, s), 4.03 (1 H, t, J = 1 Hz), 4.43 (1 H, d), 5.00 (1 H, t), 5.58 (0.5 H, dd), 7.41 (5 H, m), and 8.31 (0.5 H, s).

Reaction of DNP and α-Phenoxy-*N,N*-dimethylacetamidine. A solution of 0.33 g of DNP in 0.5 mL of Me_2SO was added to a solution of 0.71 g of the amidine in 1.5 mL of Me_2SO. The mixture was stirred at room temperature for 24 h and then added to 200 mL of anhydrous ether. After stirring for 2 h the ether was decanted off and the residue was stirred with fresh ether. Repeating this procedure two more times provided a brown powder which was filtered and recrystallized from ethanol to yield tan crystals. On standing, the collected ether washings also deposited crystals identical with those obtained from the ethanol recrystallization. A combined yield of 0.54 g (81%) was obtained after drying. The product had mp 183–185 °C and analyzed correctly for $C_{15}H_{16}N_5O_5$: C, 51.87; H, 4.93; N, 20.16. Found: C, 51.93; H, 5.07; N, 20.04. In Me_2SO it shows an absorption at 361 nm. Absorption bands in the IR (KBr) are observed at 2400–3200, 1610, 1580, 1550, 1325, 1230, 1215, and 980 cm^{-1}. The ^1H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 2.88 (6 H, s), 4.35 (1 H, m), 5.46 (3 H, m), 7.42 (5 H, br, s), and 8.30 (1 H, s).

Reaction of DNP and *N,N*-Dimethylpropionamidine. A solution of 0.203 g of DNP in 30 mL of EtOH was added to 0.13 g of amidine. After 48 h the crystals which formed were filtered, stirred in anhydrous Et_2O, and recrystallized from EtOH to give 0.13 g of product, mp 167–168 °C, which analyzed correctly for $C_{10}H_{16}N_5O_4$: C, 44.61; H, 5.62; N, 26.01. Found: C, 44.51; H, 5.64; N, 25.97. The product shows a maximum at 361 nm in Me_2SO and has IR absorptions (KBr) at 1605, 1565, 1540, 1435, 1400, 1375, 1310, 1280, 1235, 1150, 1065, and 885 cm^{-1}. The ^1H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 1.34 (d, 3 H), 2.86 (6 H, s), 3.08 (1 H, m), 3.82 (1 H, m), 5.43 (m, 2 H), and 8.19 (1 H, s).

Preparation of 12. To 0.103 g of 3-nitroquinoline dissolved in 1 mL of Me_2SO was added 0.192 g of α-phenyl-*N,N*-dimethylacetamidine. After 48 h at room temperature the white crystals were filtered off, washed with methanol, and dried at 50 °C to yield 0.14 g (75%) of **12**, mp 138–139 °C. The material rapidly reverted to 3-nitroquinoline and starting amidine when heated in Me_2SO in an attempt to dissolve it in order to take a ^1H NMR spectrum. The IR spectrum (KBr) shows absorption bands at 3190, 2960, 1580, 1540, 1490, 1393, 1305, 1260, 1115, 1030, 915, 750, and 700 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.48; H, 5.94; N, 16.47.

Preparation of 13. The adduct **12**, undissolved, was stirred in methanol and methanolic hydrogen chloride was added dropwise until dissolution was complete. The solvent was evaporated under vacuum and the residue was stirred in ether, filtered, and recrystallized from ethanol–chloroform to give a quantitative yield of **13**, mp 195–196 °C. The IR (KBr) showed absorptions at 2500–3400, 1630, 1600, 1550, 1480, 1260, 1235, 1020, and 750 cm^{-1}. The ^1H NMR spectrum in Me_2SO-d_6 showed absorptions at δ 2.82 (3 H, s), 3.25 (3 H, s), 3.92 (1 H, m), 4.20 (1 H, br), 5.07 (1 H, br, s), 5.30 (1 H, m), 5.80 (1 H, m), 6.85 (2 H, m), 7.19 (2 H, m), 7.54 (5 H, br, s), and 10.98 (1 H, br). Anal. Calcd for $C_{19}H_{21}N_4O_2Cl \cdot \frac{1}{2}H_2O$: C, 59.76; H, 5.81; N, 14.67. Found: C, 59.67; H, 5.47; N, 14.52.

Formation of 14 and 15. Addition of ~0.5 mL of a saturated Me_2SO solution of DNP *N*-oxide to 0.5 mL of a solution containing 2 equiv of α-phenyl-*N,N*-dimethylacetamidine results in a dark orange mixture which has ^1H NMR absorptions consistent with the formation of **14** or its amidinium salt. Resonances for the bridged ion are observed at δ 8.52 (1 H, s), 5.82 (1 H, br, s), and 4.24 (2 H, m). The phenyl and *N*-methyl absorptions overlap those of free amidine (or the cation). Since the phenyl protons integrate for more than 10 H, it is likely that the hydroxyl and amino protons fall in the aromatic multiplet.

Reaction of 3-nitroquinoline *N*-oxide with α-phenyl-*N,N*-dimethylacetamidine in a fashion similar to that for DNP *N*-oxide results in a solution showing single proton multiplets at δ 5.69, 4.91, 4.43, and 3.66 consistent with formation of **15**. Other absorptions overlap free amidine.

Preparation of C-4 Deuterated 11 and Formation of 13a. To a stirred mixture of 3.0 g of AgOAc in 30 mL of D_2O was added 0.8 g of 4-(3-nitroquinolyl)hydrazine.[22] The resulting mixture was refluxed for 2 h and then cooled to room temperature. The mixture was made alkaline with dilute ammonia and extracted with four 50-mL portions of chloroform. After drying the extracts with sodium sulfate and removal of the chloroform the residue obtained was recrystallized from ethanol to give 0.48 g of product, mp 125–127 °C. The ^1H NMR spectrum (Me_2SO-d_6) shows only a sharp singlet at δ ~9.5 and a four-proton multiplet centered at δ 8.0. The undeuterated 3-nitroquinoline shows two coupled doublets (J = 2.5 Hz) at δ 9.5 and 8.5 as well as the four-proton multiplet centered at δ 8.0.

The preparation of **13a** was carried out in the same way as that for **13**, using C-4 deuterated **11** as the starting aromatic.

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Registry No.—**3b**, 62375-61-5; **4a**, 62375-62-6; **4a** deuterated, 62375-63-7; **4a** phenoxy analogue, 62375-64-8; **4a** α-methyl analogue, 62375-65-9; **11**, 17676-53-3; **11** C-4 deuterated, 62375-66-0; **12**, 62375-67-1; **13**, 62375-68-2; **14**, 62375-69-3; **15b**, 62375-70-6; **22**, 23589-54-0; 3,5-dinitropyridine, 940-06-7; dibenzyl ketone, 102-04-5; triethylamine, 121-44-8; α-phenyl-*N,N*-dimethylacetamidine, 56776-16-0; 2-deuterio-3,5-dinitropyridine, 62375-71-7; α-phenoxy-*N,N*-dimethylacetamidine, 59054-96-5; *N,N*-dimethylpropionamidine, 56776-14-8; DNP *N*-oxide, 62375-72-8; 3-nitroquinoline *N*-oxide, 7433-86-5.

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