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Annelations of Amidines on Halonitroaromatics. A One-Step Route to Quinoxaline and Imidazoquinoxaline *N*-Oxides and Related Structures

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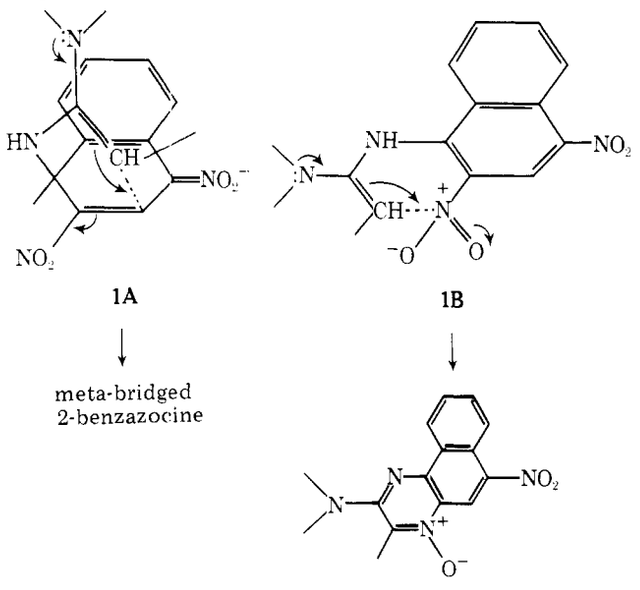
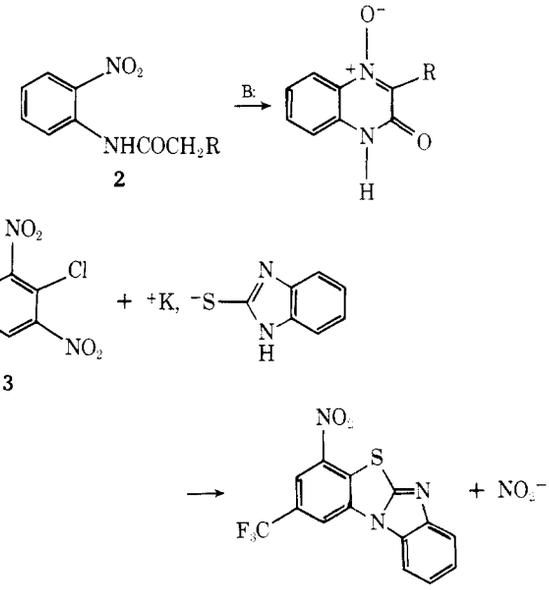
The reactions of α-phenylacetamidines with *o*-nitrohaloaromatics and related substrates have been shown to yield displacement–addition products in which the amidine is annelated across the ring carbon and nitrogen of an adjacent nitro group in the aromatic. The products are quinoxaline and imidazoquinoxaline *N*-oxides. The reactivity of amidines in meta-bridging reactions vs. ortho substituent annelations is discussed.

We have previously found that the nitrogen and α carbon of α-phenylacetamidines act as nucleophilic centers in meta-bridging reactions[1] (eq 1) of polynitrobenzenes, pyridines, and naphthalenes.[2-4] For example, reaction of α-phenyl-*N*,*N*-dimethylacetamidine with 1,3-dinitronaphthalene yields products in which a CCN moiety from the amidine is annelated across the 2 and 4 positions of the aromatic substrate.[3] The amidine in this reaction acts as a bifunctional nucleophile. Because of tetrahedral geometry at the C-1 carbon of anionic sigma complexes[5] we have previously proposed that geometrical constraints in the intermediate precursor to benzazocines (the addition complex **1A**) favor nucleophilic attack of amidine carbon at the 3 position in the cyclization step,[1,2] i.e.,



Consideration of geometry in a planar SnAr displacement "intermediate" **1B** (resulting from amidine attack on an aromatic bearing a good leaving group) led us to suppose that attack on an ortho substituent would be favored. This supposition is supported by the observed cyclization of nitroanilides like **2**.[6] *o*-Nitrite displacement could also occur, however, as observed in the reaction of **3** with 2-mercapto-



benzimidazole.[7] We have carried out reactions of several amidines with various 1-substituted 2-nitroaromatics in order to further explore patterns of amidine reactivity.

As noted above, while 1,3-dinitronaphthalene yields a 2-benzazocine with α-phenyl-*N*,*N*-dimethylacetamidine, 1-methoxy-2,4-dinitronaphthalene yields an entirely different

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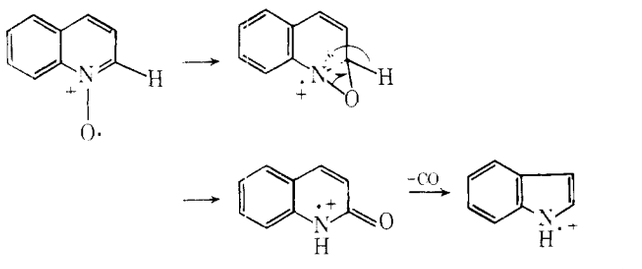
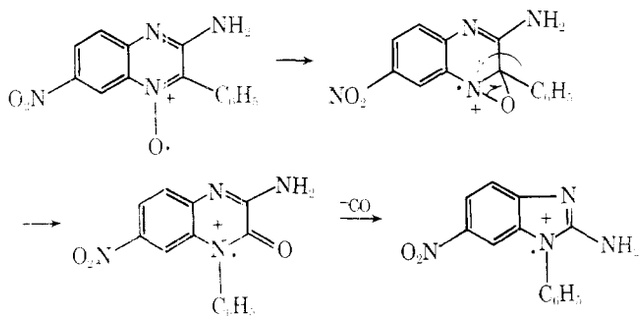
product which is not simply the result of SnAr displacement. The yellow crystalline product obtained from this reaction analyzes correctly for a 1:1 adduct of amidine and aromatic less an equivalent each of methanol and water. No absorptions between δ 3.5 and 7.0 are observed in the ^{1}H NMR spectrum of this material as would be expected if **4** had been formed (H_a, H_b, and H_c).[3] The parent peak in the mass spectrum at *m/e* 360 as well as the M-16 peak at 344 are characteristic of the *N*-oxide **5**.[8] The rest of the spectral data (see Experimental Section) also support this structure. Although the isomeric structure **5a** cannot be ruled out on the basis of spectral and analytical data, mechanistic considerations[9,10] support a structure in which amidine nitrogen attack occurs on carbon bearing methoxy in the aromatic substrate. Formation of **5** is analogous to the previously reported two-step synthesis of 2-amino-6-nitronaphtho[1,2-*e*]triazene 4-oxide **6** from guanidine and 1-chloro-2,4-dinitronaphthalene.[11]

The reaction with 1-methoxy-2,4-dinitronaphthalene was carried out with the intention of clarifying how meta-bridging, **1A**, and ortho substituent cyclization, **1B**, might compete in an aromatic substrate which had structural prerequisites suitable for each type of reaction. It was of interest to carry out the annelation reaction on a substrate which could not be expected to undergo meta bridging. Meta bridging has been shown to occur only on benzenes bearing a minimum of two nitro groups plus one additional electron withdrawing group (not halogen) or a benzofusion.[1] Sangor's reagent (1-fluoro-2,4-dinitrobenzene) reacts after a few minutes in warm ethanol solution with α-phenylacetamidine to yield a yellow insoluble crystalline solid. The elemental analyses, ^{1}H NMR, and mass spectral data are all consistent with **7**. These are summarized in the Experimental Section. A strong parent peak at *m/e* 282 as well as an M − 16 peak characteristic of heterocyclic *N*-oxides (**8**) are present in the mass spectrum. In addition, a strong M − 17 peak is also present which has been reported as characteristic of quinoxaline *N*-oxides,[12a] thus supporting structure **7** rather than the isomeric **7a**. Quinoline *N*-oxide decomposes upon electron impact to yield a major peak at *m/e* 117 which is accounted for by the following rearrangement process followed by loss of CO.[12b] A similar process can occur with **7** which leads to the stable delocalized radical ion **8** which is the largest peak in the mass spectrum of **7** except for M^+ (100%). This lends further support to structure **7** rather than **7a**. The reaction leading to **7** requires a relatively acidic amidine methylene, for the analogous reaction with propionamidine does not occur. This is consistent with the mechanism proposed for the formation of **5** (and presumably **7**). The position of tautomeric equilibrium of the amidine side chain in the initial displacement product (i.e., C ⇌ D) may well determine the rate at which cyclization occurs.

The preparation of the quinoxaline ring system via a one-step annelation with amidines would be useful if it could be adapted to other related heterocyclic compounds of interest. The limited but intriguing patent literature dealing with the imidazo[1,2-*a*]quinoxalines as antiinflammatory,[13-15] antibacterial,[15] and antiviral agents[13] prompted us to attempt a one-step preparation of this interesting ring system using an



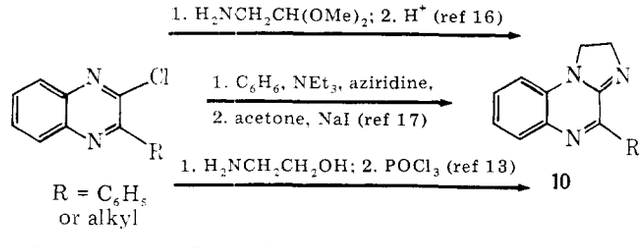
9 (*m/e* 117 (10%))



8 (*m/e* 254 (30%))

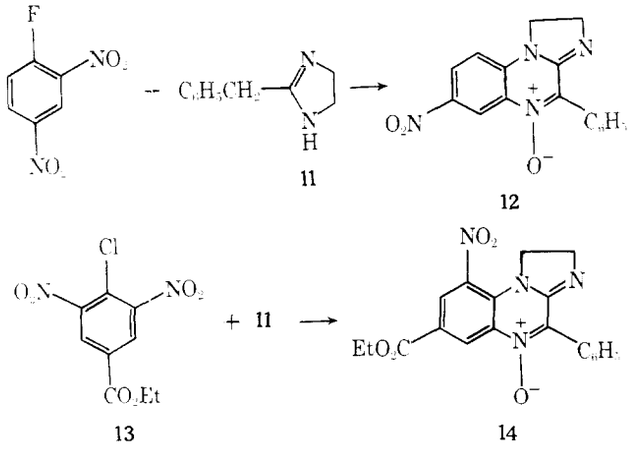
amidine annelation. All previously described routes to imidazo[1,2-*a*]quinoxalines involve chloroquinoxalines as precursors in a two-step sequence involving nucleophilic displacement followed by intramolecular cyclization.[13,16,17]

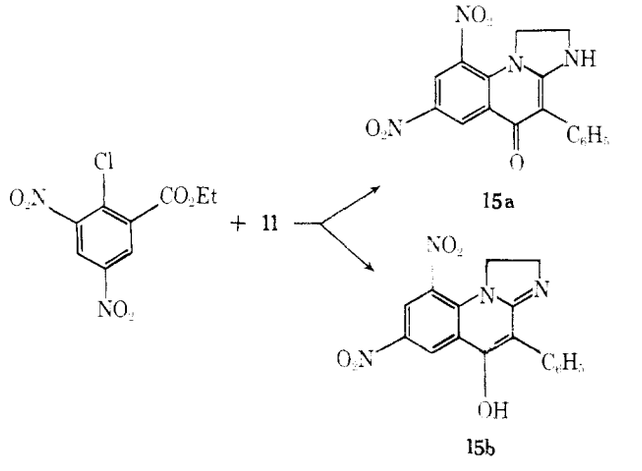
The use of cyclic amidines could provide a potentially useful one-step preparation of imidazo[1,2-*a*]quinoxaline *N*-oxides. These could easily be deoxygenated if desired.[8]



Reaction of 1-fluoro-2,4-dinitrobenzene with the cyclic amidine **11** (Tolazoline) yields a yellow crystalline solid **12** which analyzes correctly for a 1:1 adduct of amidine and aromatic less an equivalent of HF and H_2O (see Experimental Section). The ^1H NMR and mass spectrum are consistent with structure **12**. A similar product, **14**, is formed when 1-chloro-2,6-dinitro-4-carboethoxybenzene (**13**) is the aromatic substrate.

Interestingly, when the carboethoxy group is interchanged with a nitro group ortho to chlorine in **13**, reaction with Tolazoline gives an entirely different product. This material analyzes correctly for an adduct of amidine and aromatic less an equivalent each of HCl and ethanol. The M − 16 peak characteristic of heterocyclic *N*-oxides is not present in the mass spectrum and the ^1H NMR spectrum does not contain a triplet and quartet for the carboethoxy function. All the spectral data are consistent with the imidazoquinoline **15**.





Annelation has apparently occurred by attack on the ester carbonyl rather than on a nitro group. There is no carbonyl absorption in the IR spectrum of **15** but strong absorption does appear from 3100 to 3500 cm^{-1}, which does not appear in the analogues **12** or **14**. This is consistent with the formation of **15b** rather than the tautomeric **15a**.

These interesting bis nucleophilic reactions further elaborate the utility of amidine annelations in the preparation of heterocyclic ring systems.

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. Mass spectra were obtained on a Perkin-Elmer RMU-6D mass spectrometer. 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 Amidines. α-Phenyl-*N*,*N*-dimethylacetamidine was prepared as reported previously.[2] α-Phenylacetamidine was prepared by a method similar to that for the preparation of *N*-cyano-*N'*-phenylacetamidine.[18] To 2.0 g of ethyl phenylacetimidate[19] in 5 mL of MeOH was added 15 mL of a saturated solution of ammonia in EtOH. After 3 days the solvent was removed under vacuum at room temperature. The residue was added to 20 mL of a saturated ammonia solution and the mixture was stored for 3 days. Removal of the alcohol gave a residue which was recrystallized from ether–pentane mixtures. The white crystals melted at 62–63 °C. The picrate melted at 224–225 °C (lit.[20] mp 225–226 °C).

Tolazoline hydrochloride was purchased from Aldrich and was converted to the free base as follows. A solution of 14.5 g (0.098 mol) of the hydrochloride in 100 mL of MeOH was added to a solution of 2.28 g (0.099 mol) of Na in 75 mL MeOH at −70 °C. A white precipitate of NaCl formed immediately and the dry ice–acetone bath boiled vigorously indicating an exothermic reaction. The mixture was allowed to stand overnight, the NaCl was filtered off, and the filtrate was stripped on a rotary evaporator to yield a yellow oil. Dry Et_2O was then added. The resulting white solid was filtered off and the filtrate was again stripped on a rotary evaporator to yield 11.2 g of a yellow-white waxy solid, mp 65–68 °C (lit.[21] mp 67 °C). The free base was used without further purification.

Preparation of 5. To a solution of 0.34 g (0.0014 mol) of 1-methoxy-2,4-dinitronaphthalene in 100 mL of MeOH was added 0.53 g (0.003 mol) of α-phenyl-*N*,*N*-dimethylacetamidine. After 5 days the resulting yellow crystals were filtered off, washed with methanol and ether, and then vacuum dried to give 0.29 g (0.001 mol) of product, mp 277–279 °C. The IR spectrum (KBr) shows absorption bands at

1600, 1750, 1520, 1395, 1370, 1340, 1300, 1245, and 1215 cm^{-1}. The ^1H-NMR spectrum in $CDCl_3$ shows absorptions at δ 3.02 (6 H, s, MNe_2), 7.69 (5 H, m, C_6H_5), 7.92 (2 H, m), 8.78 (1 H, dd, J = 6 and 2 Hz, peri to N), 9.28 (1 H, dd, J = 6 and 2 Hz, peri to NO_2), and 9.35 (1 H, s, peri to N-oxide). The mass spectrum shows a parent peak at m/e 360 as well as peaks at 344 ($M^+ - O$), 343, and 314. Anal. Calcd for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55. Found: C, 66.77; H, 4.74; N, 15.59.

Preparation of 7. This compound was prepared in a fashion analogous to that for **5.** It was also prepared by generating the amidine from the hydrochloride in situ as follows. To a solution of 1.82 g (0.011 mol) of α-phenylacetamidine hydrochloride in 60 mL of EtOH was added 0.25 g (0.011 mol) of Na. A white precipitate of NaCl formed immediately. The mixture was filtered through a fine frit sintered glass funnel and the filtrate was added directly to 1.0 g (0.005 mol) of 1-fluoro-2,4-dinitrobenzene. The solution was refluxed for about 8 h and after cooling the resulting yellow solid was filtered off and recrystallized from acetonitrile to give 0.2 g of orange crystals, mp 279–282 °C. The crystals changed from orange to yellow at ~265 °C but did not otherwise change at this temperature. The ^1H-NMR spectrum (Me_2SO-d_6) shows absorptions at δ 7.10 (2 H, br, NH), 7.55 (5 H, m, C_6H_5), 7.68 (1 H, d, J = 8 Hz, peri to N), 8.39 (1 H, dd, J = 8 and 3 Hz, para to N-oxide), and 8.92 (1 H, d, J = 3 Hz, ortho to N-oxide). The mass spectrum shows a parent peak at m/e 282 as well as strong peaks at 266, 265, 254, 235, 219, and 207. Anal. Calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.80; H, 3.53; N, 19.71.

An attempt was made to run this reaction under identical conditions using propionamidine hydrochloride instead of phenylacetamidine hydrochloride. No trace of an adduct analogous to **7** could be isolated, however.

Preparation of 12. A solution of 1.28 g (0.008 mol) of Tolazoline in 10 mL absolute ethanol was added to 0.74 g (0.004 mol) of 1-fluoro-2,4-dinitrobenzene in this same solvent. After 5 min an orange solid precipitated. After 24 h the solid was filtered off, washed with a small portion of ethanol, and vacuum dried to yield 1.08 g of **12,** mp 212–213 °C. Recrystallization of a small portion of these crystals from ethanol and then again from acetone yielded crystals melting at 230–231 °C. The ^1H-NMR spectrum (Me_2SO-d_6) shows absorptions at δ 4.07 (4 H, br s, $-CH_2CH_2-$), 7.05 (1 H, d, J = 9 Hz, peri to N), 7.45 (3 H, m, Ar), 7.95 (2 H, m, Ar), 8.32 (1 H, dd, J = 2 and 9 Hz, para to N-oxide), and 8.75 (1 H, d, J = 9 Hz, ortho to N-oxide). The mass spectrum shows a parent peak at m/e 308 as well as strong peaks at 292 and 291 (M − 16 and M − 17) characteristic of the N-oxide functionality. The IR spectrum shows strong absorptions at 1600 (C=N), 1508 (NO_2), 1425, 1320, 1275, and 1145 cm^{-1}. Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.93; N, 18.17. Found: C, 62.24; H, 3.96; N, 18.34.

Preparation of 14. A solution of 2.40 g (0.009 mol) of 1-chloro-2,6-dinitro-4-carboethoxybenzene in 40 mL of hot EtOH was mixed with a solution of 2.79 g (0.018 mol) of Tolazoline in 10 mL of EtOH. The solution was refluxed gently and turned very dark yellow. After 2 more h of refluxing and 2 h at room temperature, the reaction mixture was cooled to 0 °C. The resulting yellow crystals were filtered off and recrystallized twice from ETOH to yield 1.0 g of product, mp 201–202 °C. The ^1H-NMR spectrum (Me_2SO-d_6) shows absorptions at δ 1.50 (3 H, t, J = 7.5 Hz, CH_3CH_2), 4.21 (4 H, m, CH_2CH_2), 4.68 (2 H, q, J = 7.5 Hz, CH_3CH_2), 7.80 (3 H, m, Ar), 8.20 (2 H, m, Ar), 8.77 (1 H, d, J = 3 Hz, para to N-oxide), and 9.17 (1 H, d, J = 3 Hz, ortho to N-oxide). The mass spectrum shows a parent peak at m/e 380 as well as a very strong peak at m/e 364 ($M^+ - O$). These are the most intense peaks in the spectrum. The IR spectrum shows a strong carbonyl absorption at 1700 cm^{-1} as well as strong absorptions at 1600, 1520, 1370, 1310, 1280, 1220, 1190, and 1020 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_4O_5$: C, 60.00; H, 4.24; N, 14.73. Found: C, 60.15; H, 4.18; N, 15.01.

Preparation of 15b. A solution of 1.72 g (0.006 mol) of 1-chloro-2,4-dinitro-6-carboethoxybenzene in 30 mL of EtOH was added to a solution of 2.0 g (0.012 mol) of Tolazoline in 10 mL of EtOH. The reaction mixture was refluxed for 5 min and a voluminous yellow precipitate formed. This was filtered off and recrystallized from CH_3CN to yield 0.9 g of **15b,** mp 291–293 °C. The ^1H-NMR spectrum (Me_2SO-d_6) shows absorptions at δ 3.80 (2 H, m, CH_2CH_2), 4.28 (2 H, m, CH_2CH_2), 7.65 (5 H, m, Ar), 8.00 (1 H, br s, OH), 9.16 (1 H, d, J = 2 Hz, nitroaromatic ring proton), and 9.28 (1 H, d, J = 2 Hz, nitroaromatic ring proton). The mass spectrum shows a parent peak at m/e 352. No peaks are observed at all in the M − 16 or M − 17 region confirming the absence of the N-oxide function. The IR spectrum shows broad absorption in the region from 3100 to 3500 cm^{-1} (OH) and no other absorption above 1610 cm^{-1} (absence of C=O). Anal Calcd for $C_{17}H_{12}N_4O_5$: C, 57.95; H, 3.43; N, 15.90. Found: C, 57.83; H, 3.17; N, 16.03.

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Registry No.—**5,** 65392-15-6; **7,** 65392-16-7; **12,** 65392-17-8; **13,** 19649-81-1; **14,** 65392-18-9; **15b,** 65392-19-0; α-phenylacetamidine, 5504-24-5; ethyl phenylacetimidate, 4971-77-1; 1-methoxy-2,4-dinitronophthalene, 13772-69-5; α-phenyl-N,N-dimethylacetamidine, 56776-16-0; α-phenylacetamidine hydrochloride, 2498-46-6; 1-fluoro-2,4-dinitrobenzene, 70-34-8; tolazoline, 59-98-3; 1-chloro-2,4-dinitro-6-carboethoxybenzene, 7251-28-7.

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