

of 2-Halopyridines and 1,2-Benzenediamines.

Scope and Mechanism of the Reaction

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Received November 23, 1981

The scope and mechanism of acid-catalyzed cyclizative condensation of 2-halopyridines with 1,2-benzenediamines has been explored. The reaction requires a 2-halopyridine which is activated toward nucleophilic substitution. Evidence in favor of a mechanism involving pyridine ring opening is presented. Of three substituted 1,2-benzenediamines which were examined, the 4-nitro compound gave a single cyclization product whereas 4-chloro and 4-methyl derivatives gave isomeric mixtures. The structure of the product from 2-chloro-5-nitropyridine and 4-nitro-1,2-benzenediamine is shown to be 2,8-dinitropyrido[1,2-*a*]benzimidazole.

J. Heterocyclic Chem., **19**, 585 (1982).

We undertook the synthesis of a number of amino-substituted pyrido[1,2-*a*]benzimidazoles in order to assess their potential for intercalative binding with DNA and related biological activity. A review of potential synthetic methods indicated the applicability of the Graebe-Ullman reaction (1) to nitro-substituted pyrido[1,2-*a*]benzimidazoles but also revealed a single example of a novel cyclizative condensation between 2-chloro-5-nitropyridine and 1,2-benzenediamine to give 2-nitropyrido[1,2-*a*]benzimidazole, **1a** (2). The relative ease of access to the starting materials for this latter reaction prompted an exploration of the scope and mechanism of this reaction.

A. Scope of the Reaction.

Stephenson and Warburton (2) reported the formation of a 58% yield of 2-nitropyrido[1,2-*a*]benzimidazole when 1,2-benzenediamine and 2-chloro-5-nitropyridine were heated at $\sim 100^\circ$ for 22 hours in aqueous 2*N* hydrochloric acid containing $\sim 20\%$ ethanol. Various modifications of this reaction in our laboratory provided yields consistently on the order of 35%. Condensation of 4-nitro-1,2-benzenediamine with 2-chloro-5-nitropyridine proceeded in 80% yield under these conditions. 4-Nitro-1,2-benzenediamine

also condensed successfully with 2-chloro-3-nitropyridine. 2-Chloropyridine was completely unreactive toward 1,2-benzenediamines under these conditions. These results, and Stephenson and Warburton's prior demonstration that 2-(*o*-aminoanilino)-5-nitropyridine, **2**, cyclizes under the hydrolytic conditions is consistent with the view that the first step in the reaction is displacement of an *activated* 2-chloro substituent and that only such activated halopyridines are suitable substrates.

In contrast to 4-nitro-1,2-benzenediamine which gave a single condensation product, two other substituted 1,2-benzenediamines, the 4-chloro and 4-methyl derivatives, gave approximately 1:1 mixtures of two isomeric products when condensed with 2-chloro-5-nitropyridine. Mechanistic considerations (*vide infra*) and spectroscopic data indicated that these mixtures are 2,7 and 2,8-disubstituted pyrido[1,2-*a*]benzimidazoles.

Table I summarizes the yield data.

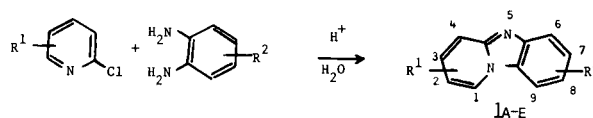


Table I

Yields from Cyclizative Condensation of 2-Chloropyridines with 1,2-Benzenediamines

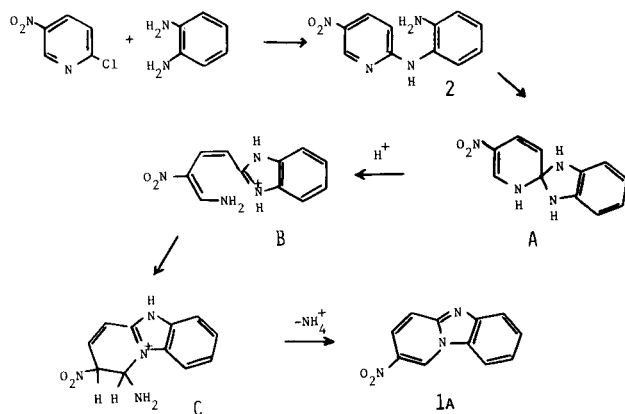
2-Chloropyridine Substituent	1,2-Benzenediamine Substituent	Pyrido[1,2- <i>a</i>]benzimidazole Substituents		Product	Yield %
		R ¹	R ²		
none	none	--	--	--	0
none	4-nitro	--	--	--	0
5-NO ₂	none	2-NO ₂	H	1a	35
5-NO ₂	4-nitro	2-NO ₂	8-NO ₂	1b	80
5-NO ₂	4-chloro	2-NO ₂	7,8-Cl (a)	1c	70
5-NO ₂	4-methyl	2-NO ₂	7,8-CH ₃ (a)	1d	40
3-NO ₂	4-nitro	4-NO ₂	8-NO ₂	1e	62

(a) Mixture of isomers.

B. Mechanism of the Reaction.

Stephenson and Warburton (2) did not comment on the mechanism of formation of 2-nitropyrido[1,2-*a*]benzimidazole under the hydrolytic conditions. A recent review of pyrido[1,2-*a*]benzimidazole synthesis suggests a displacement of one of the amino groups from the 1,2-benzenediamine (3), an inherently unlikely process. It seemed more likely the reaction was of the $S_NANRORC$ class (4), involving a ring-opening-reclosure of the pyridine ring. Although several other variations in the sequence of protonation and hydrolysis steps are conceivable, we suggest that the mechanism probably proceeds as in Scheme I.

Scheme I



As a test of this mechanism the reactivity of a quaternary pyridinium salt was investigated. 1-Ethyl-2-chloro-5-nitropyridinium tetrafluoroborate was prepared by quaternization of the neutral chloropyridine. This salt reacted with 1,2-benzenediamine in the course of 2 hours to give 2-nitro[1,2-*a*]benzimidazole in 63.5% yield. This result proves that it is the pyridine nitrogen which is lost in the course of the cyclization.

Efforts to detect intermediate species A, B, or C by monitoring the reaction by nmr failed. These experiments were carried out using intermediate 2 as the starting material in acidified DMSO. Disappearance of this material and appearance of product and the ammonium ion were observed readily but no peak attributable to any of the intermediates was observed, indicating that once the spiro intermediate A is formed subsequent steps are too rapid to permit substantial accumulation of intermediates.

C. Product Structure Determination.

The proposed mechanism, as well as other conceivable ones, suggest that substituted phenylenediamines such as the 4-chloro-, 4-methyl- and 4-nitro derivatives which were studied, could give rise to product mixtures. This possibility was confirmed with 4-chloro-1,2-benzenediamine and

4-methyl-1,2-benzenediamine, the product in each case being a nearly 1:1 mixture of the 7- and 8-substituted pyrido[1,2-*a*]benzimidazoles. For the methyl case this was evident from the proton nmr spectrum, whereas in the chloro case the C-13 spectrum was more definitive. These mixtures could not be effectively separated by either chromatography or crystallization and the yields and analytical data refer to the ~ 1:1 mixtures.

In contrast, 4-nitro-1,2-benzenediamine gave a single condensation product in 80% yield and it was of interest to establish the location of the nitro group.

An unambiguous chemical structure proof was achieved by the reactions shown in Scheme II.

Scheme II

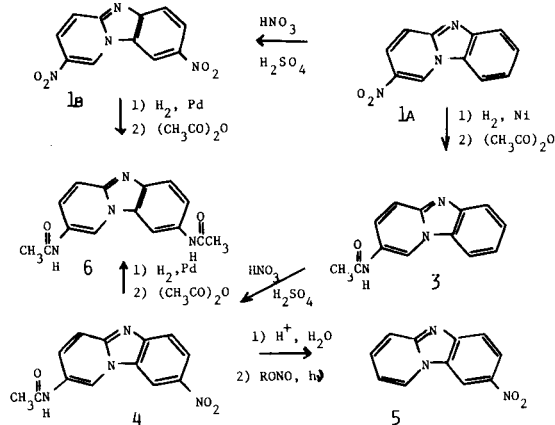


Table II

Proton NMR Data for Pyrido[1,2-*a*]benzimidazoles (a)

1a (b)	10.2 d (J = 2 Hz), 8.95 dd (J = 8, 2 Hz), 8.5 dd (J = 8, 2 Hz), 8.25 d (J = 8 Hz), 7.8-8.1 m (3H)
1b (b)	10.5 d (J = 2 Hz), 9.65 d (J = 2 Hz), 9.13 dd (J = 7, 2 Hz), 8.92 dd (J = 7, 2 Hz), 8.46 d (J = 7 Hz), 8.30 d (J = 7 Hz)
1e (b)	9.3 d (J = 7 Hz), 9.1 d (J = 2 Hz), 8.9 d (J = 7 Hz), 8.42 dd (J = 7, 2 Hz), 7.85 d (J = 7 Hz), 7.58 t (J = 7 Hz)
3 (c)	10.0 (bs), 9.5 d (J = 2 Hz), 7.9 d (J = 7 Hz), 7.8 d (J = 7 Hz), 7.2-7.6 m (4H), 2.2 s (3H)
4 (b)	10.3 d (J = 2 Hz), 9.45 d (J = 2 Hz), 9.33 bs, 8.8 dd (J = 7, 2 Hz), 8.0-8.3 m (3H), 2.45 s (3H)
5 (d)	8.95 d (J = 2 Hz), 8.58 d (J = 7 Hz), 8.42 dd (J = 7, 2 Hz), 7.9 d (J = 7 Hz), 7.6-7.8 m (2H), 7.02 t (J = 7 Hz)
6 (b)	9.9 s, 9.3 bs, 8.85 s, 8.25 dd (J = 7, 2 Hz), 7.9 s (2H), 2.45 s (6H)
7 (c)	10.65 d (J = 2 Hz), 10.7 s, 8.4 dd (J = 7, 2 Hz), 8.3 s, 7.9 d (J = 7 Hz)

(a) All signals are for single protons unless otherwise specified. (b) In trifluoroacetic acid. (c) In DMSO- d_6 . (d) In deuteriochloroform.

The product from 4-nitro-1,2-benzenediamine proved to be identical to a dinitro compound derived from 2-nitropyrido[1,2-*a*]benzimidazole by nitration. After converting 2-nitropyrido[1,2-*a*]benzimidazole to 2-acetamido[1,2-*a*]benzimidazole, it was nitrated and then deaminated by the technique of Nair and Richardson (5). The deamination product was the known 8-nitropyrido[1,2-*a*]benzimidazole (6). Finally, it was proven that both of the nitration products were 2,8-disubstituted by converting them to the same 2,8-diacetamido compound.

The preferred position for electrophilic substitution in the protonated pyrido[1,2-*a*]benzimidazole ring is therefore C-8. In agreement with this conclusion, it was found that the 1:1 mixture of 2-nitro-7-chloro and 2-nitro-8-chloropyrido[1,2-*a*]benzimidazole gave a single pure nitro derivative, 2,8-dinitro-7-chloropyrido[1,2-*a*]benzimidazole (7).

The proton nmr spectra of the various pyrido[1,2-*a*]benzimidazoles are recorded in Table II.

EXPERIMENTAL

2-Nitropyrido[1,2-*a*]benzimidazole (1a).

The following procedure, adapted from that of Stephenson and Warburton (2), routinely gave yields of about 35%. A mixture of 1,2-benzenediamine (16 g), 2-chloro-5-nitropyridine (24 g), 2*N* hydrochloric acid (100 ml), ethanol (64 ml) and water (225 ml) were mixed together in a one liter flask. The solution was then heated in an oil bath at 105-110° for 20-24 hours. The solution was then cooled and a precipitate, which was mainly *N,N'*-bis(5-nitro-2-pyridyl)-1,2-benzenediamine, was removed by filtration. The filtrate was then made alkaline by addition of ammonium hydroxide at which point the product precipitated and was isolated by filtration. The precipitate was then redissolved in 250 ml of 2*N* hydrochloric acid, any undissolved solid being removed by filtration. The solution was again made alkaline with ammonium hydroxide and the precipitate collected. Finally the product was recrystallized from ~100 ml of ethanol using charcoal for decoloration and filtering hot through Celite. After reducing the volume of the solution to one half, it was cooled and the precipitate collected. The solid was then washed thoroughly on the funnel to remove ammonium chloride and dried.

2-Acetamidopyrido[1,2-*a*]benzimidazole (3).

Reduction of 2-nitropyrido[1,2-*a*]benzimidazole (1.0 g) in ethanol (200 ml) over Raney Nickel at 42 psi proceeded to completion in about 2 hours. The solution was filtered and evaporated to dryness. The residual solid was then dissolved in chloroform (50 ml) and treated with acetic anhydride (2 ml) and pyridine (0.25 ml). The solution was stirred overnight and evaporated to dryness. The residue was mixed with aqueous sodium hydroxide and extracted with chloroform. The chloroform was dried and evaporated to give 2-acetamidopyrido[1,2-*a*]benzimidazole (0.7 g, 65%), mp 226-227° after recrystallization from ethanol, lit (2) mp 230-231°.

8-Acetamidopyrido[1,2-*a*]benzimidazole.

8-Nitropyrido[1,2-*a*]benzimidazole (6) (1.0 g, 4.7 mmoles) was dissolved in ethanol (200 ml) and Raney nickel (~0.50 g) was added. After shaking under 42 psi of hydrogen for 2 hours, the solution was filtered through Celite, and evaporated to dryness, giving a yellow powder. Without purification, the solid was dissolved in chloroform and treated with acetic anhydride (20 ml) and pyridine (0.2 ml) and stirred overnight. After eva-

porating the chloroform, the residue was carefully mixed with 15% aqueous sodium hydroxide solution and then extracted with chloroform. After drying and evaporation the acetamide was obtained as a white solid (0.70 g, 66%). The analytical sample was recrystallized from ethanol, mp 230-232°.

Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 68.04; H, 5.04; N, 18.29. Found: C, 67.98; H, 5.05; N, 18.27.

2,8-Dinitropyrido[1,2-*a*]benzimidazole by Cyclizative Condensation (1b).

A mixture of 2-chloro-5-nitropyridine (2.1 g) and 4-nitro-1,2-benzenediamine (2.0 g) in a solution made from 12.5 ml of 2*N* hydrochloric acid, 28 ml of water and 8 ml of dioxane was heated at 105° in an oil bath for 22 hours. The reaction mixture was cooled and the pale green precipitate was collected (2.7 g, 80%). The compound gave bright yellow needles on recrystallization from dimethylformamide, mp > 330°.

Anal. Calcd. for $C_{11}H_8N_4O_4$: C, 51.17; H, 2.34; N, 21.70. Found: C, 51.24; H, 2.37; N, 21.66.

2-Nitro-7-chloro and 2-Nitro-8-chloropyrido[1,2-*a*]benzimidazole (1c).

A mixture of 2-chloro-5-nitropyridine (3.0 g) and 4-chloro-1,2-benzenediamine (2.7 g) in a solution of 12.5 ml 2*N* hydrochloric acid, 28 ml of water and 8 ml of ethanol was heated at 105° in an oil bath for 22 hours. The greenish precipitate which formed during the reaction was collected by filtration. No additional product precipitated upon making the solution alkaline with ammonium hydroxide. Recrystallization of the precipitate gave yellow plates, mp 231-232° (3.2 g, 70%) which were shown by C-13 nmr to be an approximately 1:1 mixture of the 2,7- and 2,8-isomers.

Anal. Calcd. for $C_{11}H_8ClN_4O_2$: C, 53.35; H, 2.44; N, 16.97. Found: C, 53.18; H, 2.49; N, 16.89.

2-Nitro-7-methyl- and 2-Nitro-8-methylpyrido[1,2-*a*]benzimidazole (1d).

A mixture of 2-chloro-5-nitropyridine (1.0 g) and 4-methyl-1,2-benzenediamine (0.77 g) was heated at 105° for 22 hours in a solution of 4.2 ml of 2*N* hydrochloric acid, 9 ml of water and 10 ml of ethanol. The solution deposited a precipitate shown by ¹H-nmr to be *N,N'*-bis(5-nitro-2-pyridyl)-4-methyl-1,2-benzenediamine. The filtrate was made alkaline with aqueous sodium hydroxide and filtered to give a yellow solid (0.60 g, 41%), mp 185-186° after recrystallization from ethanol. The ¹H-nmr spectrum showed this solid to be a 1:1 mixture of the 2,7- and 2,8-isomers.

Anal. Calcd. for $C_{12}H_9N_5O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.57; H, 4.07; N, 18.37.

The same mixture was isolated by first allowing 4-methyl-1,2-benzenediamine to react in aqueous ethanol to give *N*(5'-nitro-2-pyridyl)-4-methyl-1,2-benzenediamine, mp 202-204°, followed by heating under the same conditions as for the direct procedure.

4,8-Dinitropyrido[1,2-*a*]benzimidazole (1e).

2-Chloro-3-nitropyridine (3.0 g) and 4-nitro-1,2-benzenediamine (2.0 g) were heated together at 105° for 22 hours in a solution of 12.5 ml 2*N* hydrochloric acid, 28 ml of water and 8 ml of dioxane. After cooling, a brown precipitate was collected. Additional product precipitated when the filtrate was made alkaline with ammonium hydroxide. The combined precipitate was recrystallized from dimethylformamide to give 3.9 g (68%) of pure product, mp > 330°.

Anal. Calcd. for $C_{11}H_8N_6O_4$: C, 51.17; H, 2.34; N, 21.70. Found: C, 51.17; H, 2.37; N, 21.66.

1-Ethyl-2-chloro-5-nitropyridinium Tetrafluoroborate.

2-Chloro-5-nitropyridine (0.5 g, 3.2 mmoles) was dissolved in dry dichloromethane (10 ml). To this solution there was added dropwise 9.5 mmoles of triethyloxonium tetrafluoroborate as a 1 *M* solution in methylene chloride. The solution was refluxed overnight. A white precipitate formed on cooling (0.75 g, 68%), mp 168-171° after recrystallization from ethanol.

Reaction of this salt with 1,2-benzenediamine gave 2-nitropyrido[1,2-*a*]benzimidazole in 63% yield after 2 hours.

Nitration of 2-Nitropyrido[1,2-*a*]benzimidazole.

A solution of 2-nitropyrido[1,2-*a*]benzimidazole (1.0 g) in concentrated sulfuric acid was cooled to -5°. There was then slowly added a solution of 41% nitric acid (0.56 ml) dissolved in 5 ml of concentrated sulfuric acid. After stirring 2 hours at 0°, the mixture was poured on to crushed ice and the precipitated yellow powder collected and dried (0.79 g, 65%). The material, after recrystallization from dimethylformamide, was identical to the material **1b** prepared by the cyclization method.

2-Acetamido-8-nitropyrido[1,2-*a*]benzimidazole (**4**).

2-Acetamidopyrido[1,2-*a*]benzimidazole (1.4 g) was dissolved in concentrated sulfuric acid (15 ml) and the solution cooled to -5°. A solution of 41% nitric acid (0.6 ml) in sulfuric acid (5 ml) was added dropwise. The reaction mixture was then stirred at 0° for 2 hours. The solution was diluted and carefully neutralized with aqueous sodium hydroxide and an orange precipitate collected by filtration. The material was recrystallized from ethanol (74% yield, mp 205-210 dec).

Anal. Calcd. for $C_{13}H_{10}N_4O_3 \cdot \frac{1}{2}H_2O$: C, 55.91; H, 3.97; N, 20.06. Found: C, 55.99; H, 4.00; N, 20.11.

Hydrolysis and Deamination of 2-Acetamido-8-nitropyrido[1,2-*a*]benzimidazole.

2-Acetamido-8-nitropyrido[1,2-*a*]benzimidazole (1.0 g) was suspended in 12 ml of 2*N* hydrochloric acid and refluxed for 2 hours, during which time the reaction mixture became homogeneous. Evaporation of the solution gave a quantitative recovery of the expected hydrochloride which was neutralized by shaking with potassium carbonate solution and isolated by filtration. After drying, a portion of this solid (0.175 g) was dissolved in dry THF (20 ml) and heated to reflux. Dropwise addition of isopentyl nitrite (2.7 ml, 20 mmoles) in THF (20 ml) to the refluxing solution was carried out over a period of 20 minutes. The solution was then irradiated with two 100 W clear incandescent lamps for 6 hours. At this point, tlc indicated the reaction was complete and the reaction mixture was evaporated to dryness. The residue was purified by chromatography on silica gel using 1% methanol chloroform for elution. The product (0.082 g, 61%) was identical by tlc, nmr and ir with authentic 8-nitropyrido[1,2-*a*]benzimidazole (**6**).

2,8-Diacetamidopyrido[1,2-*a*]benzimidazole (**6**).A. From 2,8-Dinitropyrido[1,2-*a*]benzimidazole.

The dinitro compound (2.30 g) was suspended in 95% ethanol (50 ml) and hydrochloric acid (2 equivalents) and 10% palladium/charcoal (0.05 g) was added. The mixture was stirred under 1 atmosphere of hydrogen for several hours and stopped at 90-95% of the theoretical uptake of hydrogen. The mixture was filtered and the yellow solution evaporated to dryness. This material, presumably the hydrochloride of 2,8-diaminopyrido[1,2-*a*]benzimidazole, was moderately stable but attempts to obtain

the neutral free base were unsuccessful because of extreme instability toward oxygen. The hydrochloride was dissolved in carefully degassed pyridine (5 ml) under nitrogen and treated with acetic anhydride (1.5 ml). After stirring overnight and evaporating the pyridine at 40-50° *in vacuo*, the residual solid was triturated with a small amount of absolute ethanol. This material, which could be recrystallized from ethanol, mp 295-300°, was the hydrochloride of the diacetamido derivative.

Anal. Calcd. for $C_{15}H_{13}ClN_4O_2$: C, 56.52; H, 4.74; N, 17.48. Found: C, 56.24; H, 4.79; N, 17.45.

B. From 2-Acetamido-8-nitropyrido[1,2-*a*]benzimidazole.

Reduction of 2-acetamido-8-nitropyrido[1,2-*a*]benzimidazole under similar conditions, followed by acetylation under oxygen-free conditions gave 2,8-diacetamidopyrido[1,2-*a*]benzimidazole hydrochloride in 30% yield. The nmr and ir of this material was identical to the material prepared from 2,8-dinitropyrido[1,2-*a*]benzimidazole.

Nitration of a Mixture of 2-Nitro-7-chloro- and 2-Nitro-8-chloropyrido[1,2-*a*]benzimidazole (**7**).

A solution of the isomer mixture was dissolved in concentrated sulfuric acid (10 ml) and cooled to 0° in an ice-salt bath. There was then added 41% nitric acid (0.25 ml) dissolved in 5 ml of concentrated sulfuric acid over a period of 20 minutes. The reaction mixture was kept at 0° for 3 hours before being poured on ice. The acidic solution was then made weakly basic with aqueous sodium hydroxide and the orange precipitate was collected. The compound appeared to be sensitive to strongly alkaline solution. The product (0.08 g, 35%) was recrystallized from dimethylformamide, mp > 330°.

Anal. Calcd. for $C_{11}H_7ClN_4O_2$: C, 45.14; H, 1.72; N, 19.14. Found: C, 45.25; H, 1.79; N, 19.19.

Acknowledgement.

This research was carried out under the auspices of the Walter Reed Army Institute of Research, Medical Research and Development Command, Contract DAMD 17-78-C-8016. This paper is designated contribution No. 1636 to the Army Research Program on Antiparasitic Drugs.

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