Ethanolamine Reduction of Nitrophenanthridine Derivatives to Amines

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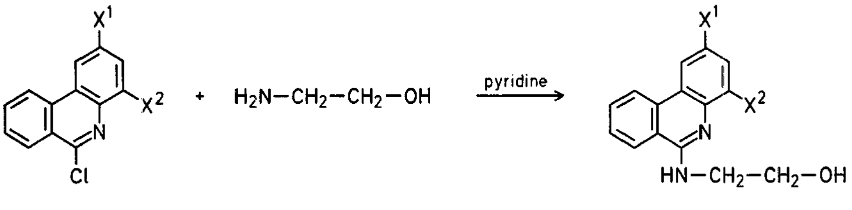
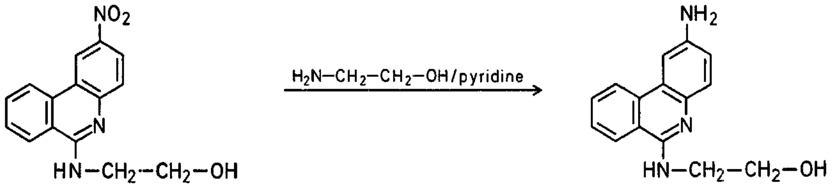
Although hydroxyalkylamines (in particular ethanolamine) are known as reducing agents[1], there are few instances in the literature where these substances have been used to reduce aryl nitro groups[2,3]; even in these cases mixtures were produced with substantial amounts of azo and azoxy derivatives, and generally only small yields of the amine.

We wish to report, however, that in a series of nitrophenanthridine derivatives, in which we had replaced a 6-chloro with the 2-hydroxyethylamino group, a reaction (**1**→**2**) that is complete in an hour on the steam bath, the use of excess ethanolamine and an equivalent of pyridine,

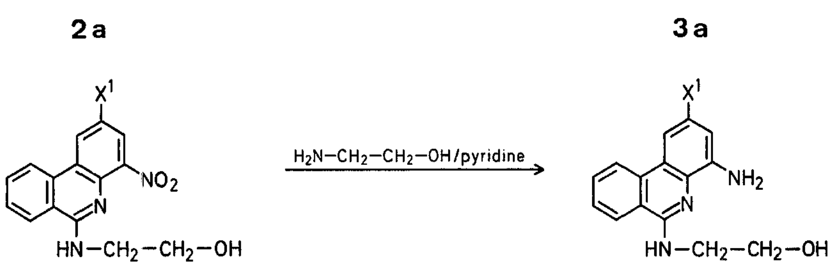


1 **2**

a $X^1 = NO_2$, $X^2 = H$
b $X^1 = Cl$, $X^2 = NO_2$
c $X^1 = Br$, $X^2 = NO_2$



2a **3a**

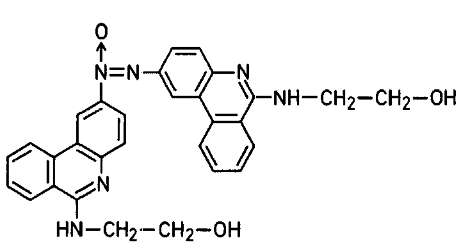


2b $X^1 = Cl$
c $X^1 = Br$

3b $X^1 = Cl$
c $X^1 = Br$

at somewhat elevated temperatures for a prolonged period, leads to high yields of the corresponding aminophenanthridines (3).

When 6-(2-hydroxyethylamino)-2-nitrophenanthridine (**2a**) was isolated (1 hr, steam bath) and then reacted with excess ethanolamine (24 hr, 110°) and an equivalent of pyridine (with no hydrogen chloride available as it is in the case of the overall reaction), the yield of amine (**3a**) was lower (60 %). When **2a** was reacted with ethanolamine alone the yield was still lower (40 %), and a small amount (5 %) of the azoxy compound, **4**, was obtained.



4

The identity of the amines was established by reduction of the corresponding nitro derivatives by conventional methods (e.g. with hydrazine hydrate and either palladium on carbon or Raney nickel, or with stannous chloride and hydrochloric acid), with I.R. comparison, and mixture m.p. determination. Stannous chloride was used in the reduction of **2c**, since partial debromination occurred even with Raney nickel/hydrazine hydrate[4], and a compound having an empirical formula of $C_{30}H_{27}BrN_6O_2$ (583.5) was obtained. Reduction-debromination[5] of **2c** with palladium on carbon/hydrazine hydrate gave **3d** ($X^1 = H$).

2-Nitro-, 2-Chloro-4-nitro, and 2-Bromo-4-nitro-6-chlorophenanthridine (1a, 1b, 1c):

The 6-(5*H*)-phenanthridinone (2-nitro-[6], 2-chloro-4-nitro-[6], or 2-bromo-4-nitro[6]) was mixed with one molar equivalent of phosphorus pentachloride and ~30 parts of phosphorus oxychloride. The mixture was refluxed for 20–24 hr and the oxychloride was distilled off. The product, after trituration in crushed ice and water, was collected by filtration, and recrystallized from benzene.

2-Nitro-, 2-Chloro-4-nitro-, and 2-Bromo-4-nitro-6-(2-hydroxyethylamino)-phenanthridine (2a, 2b, 2c):

A mixture of **1a**, **1b**, or **1c**, one equivalent of pyridine, and an excess of ethanolamine (25 ml per 0.01 mol of the nitrophenanthridine) was heated on a steam bath with occasional shaking for 1 hr. The product was isolated by dilution with aqueous sodium chloride and filtration, and purified by recrystallization from benzene.

2-Amino-, 2-Chloro-4-amino-, and 2-Bromo-4-amino-6-(2-hydroxyethylamino)-phenanthridine (3a, 3b, 3c):

The mixture, as described in the preceding procedure, was heated under reflux with stirring at 110–120° for 24–32 hr, cooled, and triturated in saturated aqueous sodium chloride. The solid material was separated by filtration or by decantation and washed with water. Recrystallization from dilute ethanol or benzene gave the product.

6,6'-Bis-[2-hydroxyethylamino]-2,2'-azoxyphenanthridine (4):

Ethanolamine (25 ml) and **2a** (1.4 g) were heated at 110° for 24 hr and then triturated in saturated aqueous sodium chloride. The solid was recrystallized twice from ethanol/water giving the product as light yellow crystals; yield of 4: 5%. The ethanol-water filtrates, when worked up, gave **3a** (40%).

Table 1. Substituted Phenanthridines

Compound	Yield %	m.p.[a]	Analytical Data[b]						
1a	90	255–256°	$C_{13}H_7ClN_2O_2$	calc.	C 60.36	H 2.73			N 10.83
			(258.7)	found	60.27	2.75			10.69
1b	91	214.5–215.5°	$C_{13}H_6Cl_2N_2O_2$	calc.					N 9.56
			(293.1)	found					9.43
1c	91	236.5–237°	$C_{13}H_6BrClN_2O_2$	calc.	C 46.26	H 1.79	Br 23.67	Cl 10.50	N 8.30
			(337.6)	found	46.35	1.75	23.68	10.34	8.12
2a	100	244–245°	$C_{15}H_{13}N_3O_3$	calc.	C 63.60	H 4.63			N 14.83
			(283.3)	found	63.34	4.62			15.02
2b	96	193.5–194.5°	$C_{15}H_{12}ClN_3O_3$	calc.	C 56.70	H 3.81			N 13.23
			(317.7)	found	56.88	3.87			13.15
2c	92	181–182°[c]	$C_{15}H_{12}BrN_3O_3$	calc.	C 49.74	H 3.34			N 11.60
			(362.2)	found	49.91	3.48			11.49
3a	90	151–152°	$C_{15}H_{15}N_3O$	calc.	C 71.13	H 5.97			N 16.59
			(253.3)	found	70.96	5.80			16.45
3b	56	182–183°	$C_{15}H_{14}ClN_3O$	calc.	C 62.61	H 4.90		Cl 12.32	
			(287.8)	found	62.83	4.99		12.20	
3c	67	189–190°	$C_{15}H_{14}BrN_3O$	calc.	C 54.23	H 4.25	Br 24.05		N 12.65
			(332.2)	found	54.34	4.17	24.23		12.52
3d	90	159–160°	$C_{15}H_{15}N_3O$	calc.	C 71.13	H 5.97			N 16.59
			(253.3)	found	71.17	5.79			16.77
4	5	273–274°	$C_{30}H_{26}N_6O_3$	calc.	C 69.48	H 5.05			N 16.21
			(518.6)	found	69.65	5.31			16.39

[a] Melting points below 250° were taken on a Fisher-Johns block and are corrected to standards. Those above 250° were taken in a capillary on the Hoover apparatus and are uncorrected.

[b] Analyses were performed by Alfred Bernhardt, D-5251 Elbach, West Germany.

[c] Taken on a preheated block. The melt solidifies when pressed, remelting at 192–193°.

4-Amino-6-(2-hydroxyethylamino)-phenanthridine (3d, $X^1 = H$):
A mixture of **2c** (1.8 g, 5 mmol), 99% hydrazine hydrate (3 ml), 5% palladium on carbon (0.2 g), and 95% ethanol (150 ml) was refluxed for 3 hr, and filtered. The filtrate was concentrated to a small volume and diluted with water. The precipitated product was separated and recrystallized from benzene giving glistening yellowish-white needles.

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[4] See footnote [14] in M. J. Namkung, T. L. Fletcher, W. H. Wetzel, J. Med. Chem. **8**, 551 (1965), for a comparison of the effects of palladium on carbon and Raney nickel with hydrazine hydrate on the aryl halogen atoms.

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