Synthesis of 9-Substituted-1,4,5,8-tetraazaphenanthrenes

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The synthesis of 9-substituted-1,4,5,8-tetraazaphenanthrenes was undertaken in the course of a study aimed at the preparation of organometallic complexing agents.

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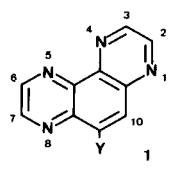
We have described previously that 1,4,5,8-tetraazaphenanthrene, hereafter abbreviated as TAP (**1a**) gave stable complexes with zerovalent transition metals (1). In order to extend this study to substituted ligands and to refine the understanding of substituent effects, we undertook the synthesis of 2- and 3-substituted TAP's (2). We now describe the preparation of 9-substituted-TAP (**1b-1g**). A specific scheme had to be devised for each derivative (Scheme I & II).



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1a	Y =	H
1b		OCH_3
1c		NC_5H_{10}
1d		NO_2
1e		NH_2
1f		F
1g		Cl

We have mentioned earlier (3) that 6,7-dinitroquinoxaline leads almost to quantitative normal substitution of a nitro group with sodium methoxide, whereas the same substrate gives rise essentially to cine substitution when reacted with concentrated piperidine in boiling ethanol.

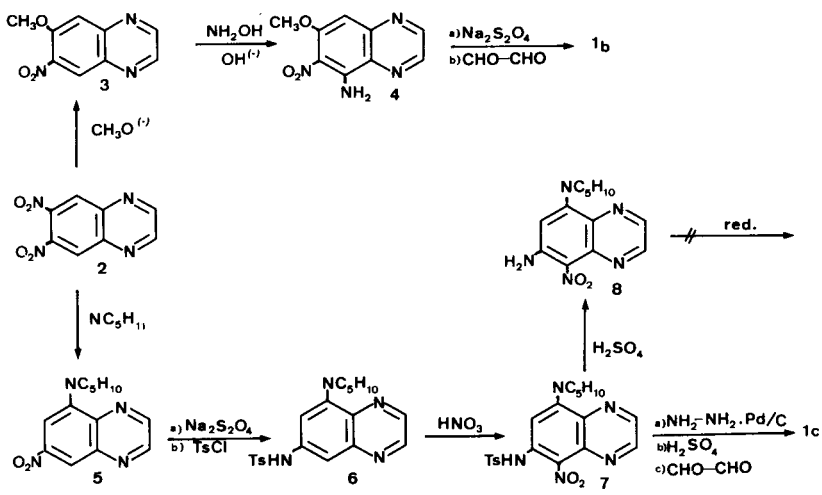
Direct amination of a fine suspension of 6-methoxy-7-nitroquinoxaline with hydroxylamine hydrochloride in alcoholic potassium hydroxide gave 5-amino-7-methoxy-6-nitroquinoxaline (**4**). The nitro amine **4** was reduced with sodium hydrosulfite (4) in water at 80° to yield 5,6-diamino-7-methoxyquinoxaline; the latter was ultimately condensed with glyoxal in boiling ethanol to afford 9-methoxy-TAP (**1b**) with an overall yield of 32% starting from **2**.

After the failure of the direct amination of **5** with hydroxylamine in alkaline medium, we resorted to an indirect route. The reduction of the nitro substituent was followed by tosylation of the amino group. After many exploratory experiments, the touchy nitration of **6** could be achieved in acetic acid with concentrated nitric acid giving 5-nitro-6-*N*-*p*-toluenesulfonamido-8-piperidinoquinoxaline (**7**) together with a small amount of the presumed isomeric 6-nitro-7-*N*-*p*-toluenesulfonamido-5-piperidinoquinoxaline. The reduction of **7** was carried out by hydrazine hydrate in ethanol using palladium on charcoal as catalyst; the hydrolysis of the sulfonamide and subsequently the condensation of the diaminoquinoxaline with glyoxal afforded 9-piperidino-TAP (**1c**) in 61% yield.

Unsuccessful attempts were made to reduce 6-amino-5-nitro-8-piperidinoquinoxaline (**8**) obtained quantitatively from **7**. Despite the use of different experimental conditions (catalytic hydrogenation, sodium polysulfide, sodium hydrosulfite, stannous chloride), we always have obtained complex mixtures.

The double tosylation of 5,6-diaminoquinoxaline (**9**)

Scheme I



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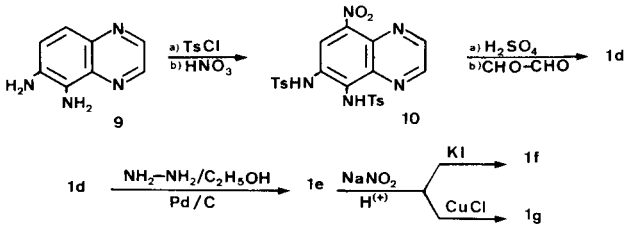
required prolonged heating in concentrated refluxing pyridine to be successful. The nitration has been performed with fuming nitric acid in acetic acid at 60° to yield 5,6-bis(*N*-*p*-toluenesulonamido)-8(7)-nitroquinoxaline (**10**). The hydrolysis and ring closure have been realized in the same conditions as mentioned previously and lead to 9-nitro-TAP (**1d**). The reduction of the nitro group could easily be achieved with an excess of hydrazine hydrate in the presence of palladium on charcoal. The diazotization of **1e** with sodium nitrite in acetic acid, followed by treatment with potassium iodide gave **1f** with 50% yield. When the same procedure was applied for the preparation of the chloro derivative, the yield was lower and some deamination occured. Finally 9-chloro-TAP (**1g**) has been obtained conducting the diazotization reaction in hydrochloric acid. Incidentally, **1g** has also been prepared starting from 6-chloro-7-nitroquinoxaline, by the classical amination reaction. The sequence of the following steps was identical to those described previously.

Scheme II



All new synthesized TAP form complexes with iron (II). When irradiated in benzene or THF solution in the presence of chromium hexacarbonyl, they give the corresponding metal tetracarbonyl chelate. These results will be described elsewhere. The table summarizes the nmr data of the newly synthesized tetraazaphenanthrenes, including the parent TAP for comparison. Having no specifically deuterated compounds, we have not been able to assign the signals to each proton of the outer rings. The only possible step is to detect in the eight lines the pairs of interacting protons on the same rings. This was usually possible by simple inspection, as for 9-amino- and 9-piperidino-TAP, where the two four-line AB systems are fairly well separated and where such assignments are straightforward. For 9-iodo- and 9-nitro-TAP, the two AB systems overlap badly, and selection of well-behaved four-line sets had to be substantiated by 270 MHz spectra. In most cases, it appears that one ring is more shielding than the other; in 9-nitro-TAP, the protons in one ring bracket those in the other, suggesting that the nitro group induces more anisotropy than the other substituents. The H_{10} shifts require no special comment, since they follow known electronic effects; the iodo group, however, seems to induce an unexpectedly high deshielding.

EXPERIMENTAL

Melting points measured on a Reichert hot stage microscope are uncorrected. Proton magnetic resonance spectra were determined on a Jeol 100 spectrometer. Chemical shifts are reported as δ units with tetramethylsilane as an internal standard.

6-Methoxy-7-nitroquinoxaline (**3**).

A solution of sodium methoxide (8 g., 150 mmoles) in 125 ml. of anhydrous methanol was added over 15 minutes to a suspension of 6,7-dinitroquinoxaline (**2**) (11 g., 50 mmoles) in 375 ml. of boiling methanol. After being refluxed an additional 60 minutes, the reaction mixture was cooled. The crude product (9.89 g., 96%) was recrystallized from 1-propanol, in the presence of charcoal, giving 9 g. (88%) of a pale yellow solid, m.p. 195-197°.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.86; H, 3.29; N, 20.69.

5-Amino-7-methoxy-6-nitroquinoxaline (**4**).

Hydroxylamine hydrochloride (18 g., 259 mmoles) was added to a well

Table

Proton Nmr Data for 9-Substituted-TAP's

Substituent	Solvent	Outer Rings Protons (a)			H_{10} (b)	(c)
-NH_2	DMSO-d_6	[9.22,	9.11	(2.0)]	7.16	6.75 (broad)
		[8.83,	8.71	(2.0)]		
-NC_5H_{10}	DMSO-d_6	[9.16,	9.14	(2.0)]	7.39	1.76 (broad, 6H)
		[8.97,	8.90	(2.0)]		3.40 (broad, 4H)
-OCH_3	DMSO-d_6	[9.21,	9.14	(2.0)]	7.56	4.12 (s, 3H)
		[9.02,	8.97	(2.0)]		
-H	DMSO-d_6	[9.23,	9.20	(2.0)]	8.35	—
-Cl	Deuteriochloroform	[9.21,	9.20	(2.0)]	8.49	—
		[9.12,	9.06	(2.0)]		
-I	Deuteriochloroform	[9.15,	9.05	(2.1)]	9.02	—
		[9.15,	9.12	(2.1)]		
-NO_2	DMSO-d_6	[9.38,	9.28	(2.0)]	9.02	—
		[9.35,	9.31	(2.0)]		

(a) All protons appear as doublets; the AB spin systems for interacting protons in the same ring are given in brackets (see text). J values in Hz are given in parentheses. (b) All sharp singlets. (c) Shifts for substituents.

stirred mixture of nitrocompound **3** (9 g., 44 mmoles) in 400 ml. of dioxane-ethanol 1:1. The temperature was maintained between −15° and −10° during the addition of a solution of potassium hydroxide (21 g., 375 mmoles) in 100 ml. of methanol over a period of 90 minutes. The dark mixture was allowed to warm to room temperature (120 minutes) and poured in 4 l. of iced-water. After one night, the yellow precipitate was filtered, rinsed with water and dried. The crude solid (6 g.) was recrystallized from 1-propanol giving 4.95 g. (50%) of bright yellow needles, m.p. 225-227°.

Anal. Calcd. for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.46. Found: C, 49.36; H, 3.76; N, 25.09.

9-Methoxy-TAP (**1b**).

Nitro compound **4** (4.95 g., 22.5 mmoles) was stirred vigorously in 270 ml. of water to produce a fine suspension. After heating to 75-80°, sodium hydrosulfite (20 g., 115 mmoles) was added in one portion. Out of the resulting orange solution, a yellow solid immediately separated. After cooling, 3.82 g. (89%) was filtered, washed with water, dried and the 5,6-diamino-7-methoxyquinoxaline (m.p. 180-181°) was used without further purification. The product suspended in 65 ml. of ethanol was treated with 30% aqueous glyoxal (6 ml.). The mixture, heated on a steam-bath for 60 minutes gave a dark green solution. The alcohol was evaporated, the residue dissolved in water and the solution was extracted with chloroform. Drying and evaporation of the organic washes left a crude solid which was triturated with acetone giving 3 g. (70%) of **1b** as a white solid. An analytical sample was sublimed at 150° (10^{-3} torr), m.p. 298-300°.

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 61.98; H, 3.66; N, 26.16.

7-Nitro-5-piperidinoquinoxaline (**5**).

Piperidine (30 ml., 300 mmoles) was added to a well stirred suspension of **2** (6.6 g., 30 mmoles) in ethanol (100 ml.). The mixture was kept at 80° for 60 minutes, during which time a precipitate settled. After cooling, the solid (6.62 g.) was filtered and rinsed with alcohol. The mother liquors were evaporated, the residue dissolved in benzene and washed with 0.5*N* hydrochloric acid. The organic layer was dried (magnesium sulfate) and evaporated to dryness giving 0.96 g. of an orange yellow solid. The total yield of **5** reached 98%. Recrystallization in ethanol afforded orange needles, m.p. 147-148°.

Anal. Calcd. for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.70. Found: C, 60.64; H, 5.39; N, 21.50.

7-*N*-*p*-Toluenesulonamido-5-piperidinoquinoxaline (**6**).

A fine suspension of **5** (4.33 g., 16.7 mmoles) in 20 ml. of ethanol and 150 ml. of water was heated to 70°. Sodium hydrosulfite (25 g., 143 mmoles) was added in one portion; a yellow cristalline solid immediately separated out of the solution. After cooling at 0°, the mixture was filtered and the precipitate rinsed with water and dried yielding 2.23 g. (58%) of 7-amino-5-piperidinoquinoxaline, m.p. 197-199°. The homogeneity was confirmed by tlc (silica gel/ethyl acetate). To a solution of 1.36 g. (5.95 mmoles) of the above product in 20 ml. of dry pyridine, there was added slowly *p*-toluenesulfonyl chloride (1.20 g., 6.31 mmoles) dissolved in 15 ml. of pyridine. The stirring was maintained at room temperature for a further 15 minutes after the addition and the mixture was poured into ice-water containing 15 ml. of concentrated hydrochloric acid (density 1.19). The yellow precipitate was removed by filtration, washed with water and dried. Crystallization from toluene-cyclohexane yielded 76% of **6**, m.p. 162-164°.

Anal. Calcd. for $C_{20}H_{22}N_4O_2S$: C, 62.81; H, 5.79; N, 14.65. Found: C, 62.92; H, 5.75; N, 14.45.

5-Nitro-6-*N*-*p*-toluenesulfonamido-8-piperidinoquinoxaline (**7**).

To a solution of **6** (1.79 g., 4.68 mmoles) in 60 ml. of glacial acetic acid at 35°, was added slowly a mixture of 0.4 ml. of concentrated nitric (density 1.4) and 4 ml. of acetic acid. The temperature raised to 40° and a dark red color developed. After disappearance of the starting material, as followed by tlc (silica gel/chloroform-ether 1:1), the reaction mixture was poured on ice and the *p*H adjusted to ~ 9 by ammonium hydroxide. The resulting brown precipitate (2 g.) was isolated, dissolved in acetone, adsorbed on cellulose (4 g.) and chromatographed on a silica-gel column. Elution with chloroform-ether gave first 0.62 g. (31%) of a yellow compound identified as **7**, m.p. 201-203° dec; nmr (DMSO-d_6): H_2, H_3, 8.93 (d), 8.85 (d), J = 2, H_2, 6.80 (s). Recrystallization in benzene-ethanol afforded an analytical sample.

Anal. Calcd. for $C_{20}H_{21}N_5O_4S$: C, 56.20; H, 4.95; N, 16.39. Found: C, 56.65; H, 4.90; N, 16.25.

Further elution gave 0.1 g. (6%) of red 6-nitro-7-*N*-*p*-toluenesulfonamido-5-piperidinoquinoxaline, m.p. 184-186°; nmr (DMSO-d_6): H_2, H_3, 8.95 (s), H_7 7.37 (s), ms: m/e 427 $M^{\cdot+}$.

9-Piperidino-TAP (**1c**).

A suspension of **7** (1.84 g., 4.3 mmoles) in 80 ml. of ethanol and 0.2 g. of palladium on charcoal (5%) was stirred at 65°. Hydrazine hydrate 98% (0.4 ml.) was introduced dropwise. The slowly evolving reduction was followed by tlc (chloroform-acetone, 8:2). When the starting material had disappeared the catalyst was eliminated by filtration (Celite). After evaporation of most of the solvent under vacuum, iced water was introduced and the red-brick solid (1.21 g.) removed by filtration and dried. The crude product was heated in concentrated sulfuric acid (12 ml.) on the steam-bath for 30 minutes, then poured into ice-water. The solution was made alkaline (*p*H ~ 9) by addition of ammonium hydroxide and further extracted three times with chloroform. The organic washes were dried (magnesium sulfate) and evaporated to dryness leaving a red oil which slowly crystallized. The semi-solid residue was immediately dissolved in 25 ml. of ethanol, treated with 30% aqueous glyoxal, and the mixture kept on the steam-bath for 30 minutes. Elimination of the solvent, left 1 g. of a dark brown solid; it was dissolved in chloroform, adsorbed on cellulose (2 g.) and percolated through a silicagel column (elution with chloroform-acetone, 8:2). Elimination of the solvents gave an homogeneous yellow powder (0.7 g., 61%). A specimen crystallized from ethanol had m.p. 163-167°.

Anal. Calcd. for $C_{15}H_{15}N_5$: C, 67.91; H, 5.69; N, 26.39. Found: C, 67.70; H, 5.81; N, 26.71.

6-Amino-5-nitro-8-piperidinoquinoxaline (**8**).

Concentrated sulfuric acid (10 ml.) containing 2.22 g. (5.2 mmoles) of **7** was heated during 30 minutes. After pouring on ice, the red solution was made alkaline (*p*H ~ 9) and the resulting yellow precipitate was removed by filtration. Compound **8** (1.39 g.) was dried and could be precipitated by adding hexane to a chloroform solution; its homogeneity was checked by tlc (silica gel/ethyl acetate), m.p. 200-205° dec; nmr (DMSO-d_6): H_2, H_3, 8.75 (d), 8.55 (d), J = 2.0, H_7, 6.69 (s); ms: m/e 273 $M^{\cdot+}$.

The addition of a saturated ethanol solution of picric acid to a solution of **8** precipitated a red picrate. Recrystallization from ethanol gave an analytical sample, m.p. 198-200° dec.

Anal. Calcd. for $C_{19}H_{18}N_8O_9$: C, 45.42; H, 3.61; N, 22.30. Found: C, 45.40; H, 3.80; N, 22.15.

5,6-Bis(*N*-*p*-toluenesulfonamido)-8(7)-nitroquinoxaline (**10**).

To a stirred cold solution of **9** (8 g., 50 mmoles) dissolved in 25 ml. of dry pyridine, was added, by portions, 19 g. (100 mmoles) of *p*-toluenesulfonyl chloride. The mixture was then heated at 125° for 24 hours and after cooling poured on ~ 400 g. of ice containing 15 ml. of hydrochloric acid. The brown oil solidified slowly and the crude solid was recrystallized from boiling aqueous acetic acid after treatment with charcoal. On cooling bright needles separated giving 20 g. (85%) of 5,6-bis(*N*-*p*-toluenesulfonamido)quinoxaline, m.p. 204-206°. The nitration of the preceding bis-tosylaminoquinoxaline was performed on batches of 7 g. About one third of a solution of fuming nitric acid (1 ml.) in glacial acetic acid (10 ml.) was added to a stirred suspension of 5,6-bis(*N*-*p*-toluenesulfonamido)quinoxaline in acetic acid (60 ml.) at 60°. After the

initial reaction, dissolution occurred, the temperature rose to ~ 65° and a tan solid separated. Addition of the nitration reactants was completed (6 ml.) and the reaction mixture was allowed to cool at 0°. Crystallization of the precipitate from glacial acetic acid yielded 5.27 g. of **10** (69%), m.p. 215-217° dec.

Anal. Calcd. for $C_{22}H_{19}N_5O_6S_2$: C, 51.46; H, 3.73; N, 13.64. Found: C, 51.50; H, 3.70; N, 13.39.

9-Nitro-TAP (**1d**).

A mixture of **10** (17.7 g., 34 mmoles) and 100 ml. of concentrated sulfuric acid was heated for 15 minutes on the steam-bath. It was then poured in ice and made alkaline (*p*H ~ 9). The resulting dark-red cristalline precipitate (7.1 g.) was thoroughly rinsed with water, dried and used without further purification. It was transferred into a mixture of 670 ml. of boiling ethanol containing 25 ml. of acetic acid. Glyoxal (21 ml. of a 30% aqueous solution) was added and the reflux maintained during 120 minutes. After evaporation of most of the alcohol, addition of water and neutralization with ammonium hydroxide, the brown precipitate was filtered, rinsed and dried. The well pulverized crude 9-nitro-TAP was continuously extracted during 24 hours with refluxing acetone. The solvent was removed under vacuum in the presence of cellulose (15 g.) and the product was percolated through a silica gel column (elution with chloroform-acetone, 8:2). Evaporation left 4.5 g. of an homogeneous yellow solid. The yield of **1d** reached 57% and an analytical sample recrystallized from 1-propanol gave bright yellow needles, m.p. 259-261°.

Anal. Calcd. for $C_{10}H_5N_5O_2$: C, 52.87; H, 2.22; N, 30.83. Found: C, 52.66; H, 1.99; N, 30.50.

9-Amino-TAP (**1e**).

Hydrazine hydrate 98% (4.5 ml.) diluted in 50 ml. of ethanol was added dropwise over 120 minutes to a hot solution (70°) of 9-nitro-TAP (5.28 g., 23 mmoles) in 500 ml. of dioxane-ethanol (1:1) containing 1.3 g. of palladium on charcoal (10%). Progress of the reduction was monitored by tlc (ethanol) followed by spraying an aqueous solution of iron(II). Stirring and refluxing were maintained until the several spots reduce to a single one; this may require several hours. The catalyst was removed by filtration and the solvent evaporated. The residue was rinsed and dried affording 4.18 g. of a bright yellow solid. Recrystallization from 1-propanol gave 75% of **1e**, m.p. 290-300° (sublimes).

Anal. Calcd. for $C_{10}H_7N_5$: C, 60.91; H, 3.57; N, 35.51. Found: C, 60.77; H, 3.58; N, 35.68.

9-Iodo-TAP (**1f**).

A finely divided suspension of 0.71 g. (3.6 mmoles) of 9-amino-TAP (**1e**) in 10 ml. of acetic acid was added to a well stirred cold (0°) solution of one equivalent of sodium nitrite (0.25 g.) in 7 ml. of concentrated sulfuric acid. During the diazotization the temperature was kept below 5°. The dark mixture was then diluted with iced-water to 40 ml. This blood-red solution was poured in one portion into a cold solution of potassium iodide (7 g.) dissolved in 70 ml. of water containing 5 ml. of sulfuric acid. When the evolution of gas subsided (30 minutes), ammonium hydroxide was added to *p*H ~ 9 and **1f** was extracted with chloroform. After drying and treatment of the organic layer with decolourizing carbon, the solvent was evaporated giving 0.55 g. (50%) of a white solid. An analytical sample crystallized from toluene melted at 238-240°.

Anal. Calcd. for $C_{10}H_5IN_4$: C, 38.98; H, 1.63; N, 18.18. Found: C, 38.90; H, 1.80; N, 17.70.

9-Chloro-TAP (**1g**).

To a cold solution (−5°) of 0.72 g. (3.6 mmoles) of **1e** in 20 ml. of concentrated hydrochloric acid (density 1.19) were added two equivalents (0.52 g.) of sodium nitrite dissolved in 10 ml. of water. The temperature was kept below 0°. Stirring was maintained for a further 5 minutes and the mixture was poured, portionwise, into a freshly prepared solution of cuprous chloride (0.42 g.) in 15 ml. of hydrochloric acid. After 120 minutes at room temperature, a brown precipitate was formed with evolution of gas. A sodium hydroxide solution (30%) was added (*p*H ~ 8) and extraction with chloroform gave 0.54 g. of a crude solid. Purification on silica gel column chromatography (elution with chloroform-acetone 7:3) afforded 0.42 g. (55%) of a white solid. An analytical sample was recrystallized from benzene-ethanol, m.p. 249-251° dec.

Anal. Calcd. for $C_{10}H_5ClN_4$: C, 55.44; H, 2.33; N, 25.86. Found: C, 55.51; H, 2.27; N, 25.91.

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