Fused-*s*-triazino Heterocycles. XI. Displacement Reactions of 7,9-Dichloro-2,5-bis(trichloromethyl)-1,3,4,6,9b-pentaazaphenalene

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The preparation of 7,9-dichloro-2,5-bis(trichloromethyl)-1,3,4,6,9b-pentaazaphenalene (**1e**) by the chlorination of 2-trichloromethyl-5-methyl-1,3,4,6,9b-pentaazaphenalene (**1a**) using molecular chlorine is described. Displacement of one or both trichloromethyl groups of **1e** by a variety of nucleophiles led to the corresponding 7,9-dichloro-2,5-bis-substituted or 7,9-dichloro mixed 2,5-disubstituted derivatives. The reaction of **1a** with *N*-chlorosuccinimide proved not to be a useful route to **1e** but instead led primarily to substitution of positions 7 and/or 9 by chlorine.

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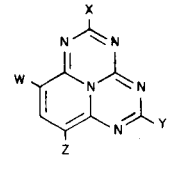
A previous paper [2] described the preparation and nucleophilic displacement reactions of 7,9-dibromo-2-tribromomethyl-5-trichloromethyl-1,3,4,6,9b-pentaazaphenalene (**2a**) and 7,9-dibromo-2,5-bis(tribromomethyl)-1,3,4,6,9b-pentaazaphenalene (**2b**). The brominating conditions (a large excess of bromine and a reaction temperature of 75-80° with acetic acid/sodium acetate as solvent and basic catalyst respectively) used to convert 2-trichloromethyl-5-methyl-1,3,4,6,9b-pentaazaphenalene (**1a**) to **2a** and 2,5-dimethyl-1,3,4,6,9b-pentaazaphenalene (**1w**) to **2b** gave only blue taffy-like resins when chlorine was substituted for bromine in these reactions.

We have since found that 7,9-dichloro-2,5-bis(trichloromethyl)-1,3,4,6,9b-pentaazaphenalene (**1e**) can be prepared under suitable reaction conditions. Thus slow addition of the stoichiometric amount of chlorine gas at ~56° to **1a** dissolved in acetic acid in the presence of sodium acetate gave a 58% yield of **1e**. Use of **1w** as substrate under the same reaction conditions gave only a 22% yield of highly impure **1e**. Attempts to substitute the remaining hydrogen at position 8 of **1e** by the further addition of one equivalent of chlorine during the chlorination of **1a** were in vain. A much lower yield of **1e** together with the formation of an intractable pale green oil resulted.

The use of *N*-chlorosuccinimide (**3a**) in refluxing chloroform to prepare **1e** from **1a** was investigated. While this method only gave very poor yields of **1e**, it did allow the isolation of some of the same intermediates that formed during the reaction of **1a** with molecular chlorine but which were troublesome to obtain under those reaction conditions. For example, reaction of **1a** (1 mole) with **3a** (2 moles) in refluxing chloroform for 2 hours gave three principal products which were isolated using column chromatography. Elemental and nmr analysis completely characterised one of these products as 7,9-dichloro-2-trichloromethyl-5-methyl-1,3,4,6,9b-pentaazaphenalene (**1d**) (12% yield). The remaining two are in doubt as to whether the chlorine atom introduced is at position 7 or 9: 7(or 9)-chloro-2-trichloromethyl-5-methyl-1,3,4,6,9b-pentaazaphenalene (**1b**), melting point 256-258° (10% yield), and 7(or 9)-chloro-2-trichloromethyl-5-methyl-1,3,4,6,9b-pentaazaphenalene (**1c**), melting point 211-213° (9% yield). Increasing the molar ratio of **3a/1a** to 5 and the reflux period to 48 hours gave **1e** and **1d** as the only identifiable products in 8 and 35% yields respectively.

We have found **1e** to be generally more soluble than **2a** or **2b** in chloroform, toluene, *N,N*-dimethylformamide and other organic solvents, thus avoiding the dilute solutions so often required in nucleophilic reactions of **2a** and **2b**. This enhanced solubility of **1e** together with an improved

Figure 1



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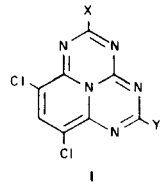
[**1a**, W, Z = H; **1b**, **1c**, (W = Cl, Z = H) or (W = H, Z = Cl); **1d-1v**, W, Z = Cl]

1a, X = CCl_3	Y = CH_3
1b, X = CCl_3,	Y = CH_3
1c, X = CCl_3,	Y = CH_3
1d, X = CCl_3,	Y = CH_3
1e, X = CCl_3,	Y = CCl_3
1f, X = CCl_3,	Y = $NH(CH_2)_3CH_3$
1g, X = CCl_3,	Y = $N(CH_2CH_3)_2$
1h, X = CCl_3,	Y = 1-pyrrolidino
1i, X = CCl_3,	Y = $NHC_6H_4CH_3$-*p*
1j, X = CCl_3,	Y = $NHC_6H_4OCH_3$-*p*
1k, X = CCl_3,	Y = $NHC_6H_4CO_2CH_3$-*o*
1l, X = NH_2,	Y = NH_2
1m, X = $NH(CH_2)_3CH_3$,	Y = $NH(CH_2)_3CH_3$
1n, X = 1-pyrrolidino	Y = 1-pyrrolidino
1o, X = 1-pyrrolidino	Y = $NH(CH_2)_3CH_3$
1p, X = 1-pyrrolidino	Y = $NHC_6H_4OCH_3$-*p*
1q, X = 1-pyrrolidino	Y = OCH_3
1r, X = 1-pyrrolidino	Y = $OCH_2CH_2CH_3$
1s, X = 1-piperidino	Y = 1-piperidino
1t, X = $NHC_6H_4OCH_3$-*p*	Y = OCH_3
1u, X = OCH_3	Y = OCH_3
1v, X = $OCH_2CH_2CH_3$	Y = $OCH_2CH_2CH_3$

Table 1(a)



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Compound No.	X/Y	Method	Reaction Temperature (hours)	Yield % [b]	Mp (°C) [c] Crystallization Solvent	Molecular Formula	Analysis % Calcd./Found C	H	N
1f	CCl_3	A [d]	reflux/1	48	261-263	$C_{13}H_{11}Cl_5N_6$	36.43	2.59	19.61
	$NH(CH_2)_3CH_3$				Carbon tetrachloride		36.15	2.64	19.42
1g	CCl_3	A [e]	rt [f]/24	53	192-193	$C_{13}H_{11}Cl_5N_6$	36.43	2.59	19.61
	$N(CH_2CH_3)_2$				Heptane		36.34	2.42	19.66
1i	CCl_3	B [g]	rt/0.5	59	280-282 dec	$C_{16}H_9Cl_5N_6$	41.54	1.97	18.17
	$NHC_6H_4CH_3$-*p*				Chlorobenzene/heptane		41.28	2.13	17.88
1k	CCl_3	B [h]	rt/2	47	275-276 dec	$C_{17}H_9Cl_5N_6O_2$	40.30	1.79	16.59
	$NHC_6H_4CO_2CH_3$-*o*				Toluene		40.55	1.79	16.33
1l	NH_2	C [i]	rt/1;	31	400	$C_8H_5Cl_2N_7$	35.57	1.87	36.30
	NH_2		reflux/1		DMF/water		35.68	1.69	36.02
1m	$NH(CH_2)_3CH_3$	C [j]	reflux/1,	65	188-190	$C_{16}H_{21}Cl_2N_7$	50.26	5.54	25.65
	$NH(CH_2)_3CH_3$		rt/24		Carbon tetrachloride		49.96	5.61	25.83
1s	1-Piperidino	C	rt/0.25,	75	304-306	$C_{18}H_{21}Cl_2N_7$	53.20	5.21	24.13
	1-Piperidino		reflux/3		Toluene		53.16	5.30	24.37
1p	1-Pyrrolidino	D [k]	reflux/1,	23	218-220 dec	$C_{19}H_{17}Cl_2N_7O$	53.03	3.98	22.79
	$NHC_6H_4OCH_3$-*p*		rt/24		Toluene		52.80	4.08	22.50
1q	1-Pyrrolidino	E [l]	reflux/1.5	73	241-242	$C_{13}H_{12}Cl_2N_6O$	46.03	3.57	24.78
	OCH_3				Toluene		45.82	3.33	24.74
1t	$NHC_6H_4OCH_3$-*p*	E [m]	~70/0.5,	65	305-306	$C_{16}H_{12}Cl_2N_6O_2$	49.12	3.09	21.48
	OCH_3		rt/24		2-Methoxyethanol		49.48	2.88	21.19
1v	$OCH_2CH_2CH_3$	F [n]	~75/2	47	177-179	$C_{14}H_{15}Cl_2N_5O_2$	47.20	4.25	19.66
	$OCH_2CH_2CH_3$				1-Propanol		47.44	4.10	19.42

[a] The ir spectra of the compounds listed supported the structures shown; the pmr spectra of the compounds listed showed the expected signals for the X and Y groups and delta values of 7.3-8.4 for Hg. [b] Crude yields, no attempt was made to optimize yields. [c] Melting point of the recrystallized product. [d] *n*-Butylamine (0.0082 mole) and 10 ml of chloroform served as nucleophile and solvent respectively; after addition of the nucleophile, the remainder of the reaction was carried out at reflux, the crude product being filtered at room temperature without evaporation of solvent. [e] Diethylamine (0.0082 mole) and a solution of dry chloroform and dry toluene, 10 ml each, served as nucleophile and solvent respectively; the crude product was chromatographed over 50 g of silica gel using chloroform-ethyl acetate (95:5) as eluent. [f] Room temperature. [g] The reaction mixture was evaporated to 1/10 volume before filtration. [h] Methyl anthranilate (0.042 mole) and 4-dimethylaminopyridine (0.002 mole) served as nucleophile and acylation catalyst respectively. [i] Twenty ml of dry acetonitrile was the solvent; a gentle stream of ammonia was passed through the reaction mixture, first at room temperature for 1 hour, then at reflux for 1 hour. [j] A solution of dry chloroform and dry toluene, 10 ml each, served as solvent; the crude product was chromatographed over 60 g silica gel using chloroform-ethyl acetate (95:5) as eluent. [k] Compound **1j** (0.002 mole), pyrrolidine (0.008 mole) and 100 ml of dry toluene served as substrate, nucleophile and solvent respectively. [l] Dry methanol and dry toluene, 10 ml each, served as solvent; benzyltrimethylammonium methoxide (0.00033 mole) provided the base catalysis, and crude **1q** was obtained by simple filtration, no chromatography being required. [m] Compound **1j** (0.002 mole), benzyltrimethylammonium methoxide (0.001 mole), and a solution of 175 ml of dry toluene and 20 ml of dry methanol served as substrate, basic catalyst, and solvent respectively; the methoxide catalyst was added over a period of 0.5 hours at 70°; crude **1t** was obtained by simple filtration, no chromatography being required. [n] Sodium 1-propoxide (20% in 1-propanol) (0.0015 mole) and a solution of 63 ml of dry 1-propanol and 10 ml of dry toluene served as basic catalyst and solvent respectively; the catalyst was added over a period of 2 hours at ~75°; crude **1v** was chromatographed over 50 g of silica gel using chloroform-methanol (95:5) as eluent.

stability to heat and what appears to be a higher degree of reactivity toward various nucleophiles made possible the variety of compounds shown in Table 1. As was the case with **2a** or **2b**, displacement of the trichloromethyl groups of **1e** by simple alcohols required the presence of catalytic quantities of the corresponding alkoxide. Displacement of one trichloromthyl group of **1e** by primary or secondary amines(aliphatic or aromatic) was in general rapid; displacement of the second trichloromethyl group depended on the type of amine and varied from rapid displace(pyrrolidine) to no or little displacement accompanied by decomposition and undesired by-products(*p*-anisidine). It should be noted that compounds corresponding to **1g, 1k, 1p** and **1t** had been attempted from **2b** or derivatives of **2b** [2], and could not be prepared.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas-Hoover melting point bath and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 735B spectrophotometer. The pmr spectra

were determined on a Varian EM-360 spectrometer using TMS as an internal reference. Analyses were performed by Micro-analyses Inc., Wilmington, Delaware. All evaporations were carried out on a rotary evaporator at reduced pressure.

N,N-Dimethylformamide (DMF), chloroform and toluene were dried using standard methods and stored over molecular sieves. Woelm silica gel (70-230 mesh) for column chromatography was obtained from ICN Pharmaceutical Inc. Compounds **1a** [3] and **1w** [4] were prepared using methods described in the literature.

7,9-Dichloro-2,5-bis(trichloromethyl)-1,3,4,6,9b-pentaazaphenalene (**1e**).

A stream of chlorine gas was passed through a vigorously stirred solution of 24.6 g (0.3 mole) of anhydrous sodium acetate and 9.06 g (0.03 mole) of **1a** in 150 ml of acetic acid maintained at 53-59°. After 10.8 g (0.15 mole) of chlorine was added (~2 hours) the reaction was stirred for an additional hour at 53-59°, then cooled to room temperature and filtered. The blue filter cake was washed with a small portion of acetic acid and then with petroleum ether (30-60°) until the washings ran clear. The resulting product was heated to boiling with 175 ml of toluene, filtered and the filtrate was evaporated to dryness, 8.23 g (58%), mp 303-305°. Recrystallization from toluene gave beautiful royal blue crystals, mp 306-308°; pmr (deuteriochloroform): δ 7.73 (s, 1H, H_8).

Anal. Calcd. for $C_{10}HCl_8N_5$: C, 25.30; H, 0.21; N, 14.75; Cl, 59.74. Found: C, 25.59; H, 0.30; N, 14.51; Cl, 59.68.

Attempts to shorten the reaction time by increasing the rate of addition of chlorine or raising the temperature resulted in lower yields of **1e**.

Reaction of 2-Trichloromethyl-5-methyl-1,3,4,6,9b-pentaazaphenalene (**1a**) (1 mole) with *N*-Chlorosuccinimide (**3a**) (2 moles).

A solution of 2.0 g (0.0066 mole) of **1a**, 1.77 g (0.0133 mole) of **3a** and 30 ml of chloroform was refluxed for 2 hours. The solution was evaporated to dryness and the residue, which was chromatographed over 120 g of silica gel using methylene chloride-ethyl acetate (90/10) as eluent, gave the following products:

The first fraction (blue) yielded 0.29 g (12%) of crude **1d**, mp 145-150°. Recrystallization from toluene-petroleum ether (60-90°) gave blue crystals, mp 157-158°; pmr (deuteriochloroform): δ 2.10 (s, 3H, CH_3), 7.70 (s, 1H, H_8).

Anal. Calcd. for $C_{10}H_4Cl_5N_5$: C, 32.33; H, 1.09; N, 18.86. Found: C, 32.58; H, 1.20; N, 18.93.

The second fraction (purple) yielded 0.23 g (10%) of crude **1b**, mp 245-249°. Recrystallization from toluene gave purple crystals, mp 256-258°; pmr (deuteriochloroform): δ 2.17 (s, 3H, CH_3), 6.29 [d (J = 8 Hz), 1H, H_7 or H_9], 7.52 [d (J = 8 Hz), 1H, H_8].

Anal. Calcd. for $C_{10}H_5Cl_4N_5$: C, 35.64; H, 1.50; N, 20.79. Found: C, 35.73; H, 1.32; N, 20.66.

The third fraction (purple) yielded 0.19 g (9%) of crude **1c**, mp 203-206°. Recrystallization from toluene-hexane gave purple crystals mp 211-213°; pmr (deuteriochloroform): δ 2.11 (s, 3H, CH_3), 6.35 [d (J = 8 Hz), 1H, H_7 or H_9], 7.60 [d (J = 8 Hz), 1H, H_8].

Anal. Calcd. for $C_{10}H_5Cl_4N_5$: C, 35.64; H, 1.50; N, 20.79. Found: C, 35.59; H, 1.56; N, 20.60.

There was considerable tarry material retained by the column.

Reaction of 2-Trichloromethyl-5-methyl-1,3,4,6,9b-pentaazaphenalene (**1a**) (1 mole) with *N*-Chlorosuccinimide (**3a**) (5 moles).

A solution of 2.0 g (0.0066 mole) of **1a**, 4.4 g (0.033 mole) of **3a** and 30 ml of chloroform was refluxed for 48 hours. The solution was evaporated to dryness and the residue, which was chromatographed over 120 g of silica gel using methylene chloride-ethyl acetate (90/10) as eluent gave the following products:

The first fraction (blue) gave 0.24 g (8%) of crude **1e**, mp 295-298°. Recrystallization from toluene gave royal blue crystals whose physical properties were identical to **1e** prepared by chlorination of **1a** using molecular chlorine as given above.

The second and third fractions (both blue) yielded small amounts (0.05 g and 0.08 g respectively) of resinous materials which resisted further purification.

The fourth fraction (blue) gave 0.86 g (35%) of crude **1d**, mp 149-153°. Recrystallization from toluene-petroleum ether (60-90°) gave blue crystals, mp 157-158°, and with other physical properties identical to **1d** prepared above.

There was considerable tarry material retained by the column.

Increasing the molar ratio of **3a/1a** to 6 or 10 gave essentially the same result.

The following examples are illustrative of the methods used to prepare the compounds listed in Table 1.

Method A.

7,9-Dichloro-2-trichloromethyl-5-(1-pyrrolidino)-1,3,4,6,9b-pentaazaphenalene (**1h**).

A stirred solution of 1.0 g (0.0021 mole) of **1e** in 100 ml of dry toluene was treated dropwise over a period of 30 minutes at 8-10° with a solution of 0.15 g (0.0021 mole) of pyrrolidine in 20 ml of dry toluene. Following an additional 10 minute reaction period, the mixture was evaporated to almost dryness and the residue was collected by filtration with the aid of petroleum ether (30-60°), 0.85 g (95%); mp 268-270° dec. Recrystallization from carbon tetrachloride gave red crystals, mp 270-271° dec; pmr (deuteriochloroform): δ 1.90 (m, 4H, CH_2CH_2), 3.65 (m, 4H, CH_2NCH_2), 7.57 (s, 1H, H_8).

Anal. Calcd. for $C_{15}H_9Cl_5N_6$: C, 36.60; H, 2.13; N, 19.71. Found: C, 36.42; H, 1.92; N, 19.54.

Method B.

2-(*p*-Anisidino)-7,9-dichloro-5-trichloromethyl-1,3,4,6,9b-pentaazaphenalene (**1j**).

A stirred solution of 1.0 g (0.0021 mole) of **1e** in 10 ml of dry DMF was treated in one portion at room temperature with a solution of 2.46 g (0.02 mole) of *p*-anisidine. Following an additional 30 minute reaction period, the thick red mixture was filtered and the filter cake was washed with ether, 0.50 g (49%), mp 283-287° dec. Recrystallization from DMF gave pale-red crystals, mp 288-290° dec; ir λ (nujol): μm 2.94 (NH); pmr (very low solubility precluded pmr analysis).

Anal. Calcd. for $C_{16}H_9Cl_5N_6O$: C, 40.15; H, 1.90; N, 17.56. Found: C, 39.86; H, 1.63; N, 17.59.

Method C.

7,9-Dichloro-2,5-bis(1-pyrrolidino)-1,3,4,6,9b-pentaazaphenalene (**1n**).

A stirred solution of 1.0 g (0.0021 mole) of **1e** in 10 ml of dry toluene was treated at room temperature with 0.6 g (0.0084 mole) of pyrrolidine (in one portion). A mild exotherm (10°) was noticed and the mixture was stirred for an additional 15 minutes followed by a 35 minute reflux period. The brownish-orange solid that had formed was collected at room temperature by vacuum filtration and washed with petroleum ether (30-60°), 0.65 g (82%), mp 330-333° dec. Recrystallization from toluene gave golden crystals, mp 330-332° dec; pmr (deuteriochloroform): δ 1.87 [m, 8H, bis(CH_2CH_2)], 3.59 [m, 8H, bis(CH_2NCH_2)], 7.32 (s, 1H, H_8).

Anal. Calcd. for $C_{16}H_{17}Cl_2N_7$: C, 50.80; H, 4.53; N, 25.93. Found: C, 50.56; H, 4.78; N, 25.70.

Method D.

2-(*n*-Butylamino)-7,9-dichloro-5-(1-pyrrolidino)-1,3,4,6,9b-pentaazaphenalene (**1o**).

A stirred mixture of 1 g (0.0023 mole) of **1h**, 0.67 g (0.0092 mole) of *n*-butylamine and 10 ml of dry chloroform was refluxed for 1 hour and then allowed an additional 22 hours of reaction time at room temperature. The insoluble material was filtered at room temperature and washed with ether, 0.69 g (79%), mp 268-270°. Recrystallization from toluene gave very fluffy yellow crystals with the same melting point; ir λ (nujol): μm 3,08 (NH); pmr (very low solubility precluded pmr analysis).

Anal. Calcd. for $C_{16}H_{19}Cl_2N_7$: C, 50.53; H, 5.04; N, 25.78. Found: C, 50.34; H, 4.89; N, 25.72.

Method E.

7,9-Dichloro-2-(1-propoxy)-5-(1-pyrrolidino)-1,3,4,6,9b-pentaazaphenalene (**1r**).

A stirred solution of 1.0 g (0.0023 mole) of **1h** in 10 ml of dry 1-propanol and 10 ml of dry toluene was treated at 75° with 0.16 g (0.00039 mole) of sodium propoxide (20% in 1-propanol) and maintained at this temperature for 15 minutes to complete the reaction (tlc). The residue obtained after evaporating the reaction mixture to dryness was chromatographed over 30 g of silica gel using chloroform-ethyl acetate (95:5) as eluent. The yellow fraction was collected and yielded 0.69 g (82%), mp 191-194°. Recrystallization from 1-propanol gave bright yellow crystals, mp 200-202°; pmr (deuteriochloroform): δ 0.98 [t (J = 6 Hz), 3H, CH_3], 1.78 [m, 6H, propoxy (CH_2) and pyrrolidino (CH_2CH_2)], 3.6 [m, 4H, (CH_2N-CH_2)], 4.28 [t, (J = 6 Hz), 2H, CH_2O], 8.18 (s, 1H, H_8).

Anal. Calcd. for $C_{15}H_{16}Cl_2N_6O$: C, 49.06; H, 4.39; N, 22.89. Found: C, 49.23; H, 4.21; N, 22.64.

Method F.

7,9-Dichloro-2,5-dimethoxy-1,3,4,6,9b-pentaazaphenalene (**1u**).

After refluxing a stirred mixture of 1.0 g (0.0021 mole) of **1e** in 25 ml of dry methanol for 10 minutes, the *p*H was adjusted to ~8 by the addition of 0.065 g (0.00036 mole) of benzyltrimethylammonium methoxide (40% in methanol). Analysis (tlc) showed that after 20 minutes additional refluxing there was no longer any **1e** present. The precipitate that formed on chilling the reaction mixture was filtered and washed with a little cold methanol, 0.52 g (83%), mp 238-239°. Recrystallization from toluene gave brownish-orange crystals with the same melting point; pmr (DMSO-d_6): δ 3.73 [s, 6H, 2(OCH_3)], 7.98 (s, 1H, H_8).

Anal. Calcd. for $C_{10}H_7Cl_2N_5O_2$: C, 40.02; H, 2.35; N, 23.34. Found: C, 40.06; H, 2.50; N, 23.48.

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