# Fused *s*-Triazino Heterocycles. X. Displacement Reactions of 7,9-Dibromo-2-tribromomethyl-5-trichloromethyl-1,3,4,6,9b-pentaazaphenalene and 7,9-Dibromo-2,5-bis(tribromomethyl)-1,3,4,6,9b-pentaazaphenalene



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The preparation of 7,9-dibromo-2-tribromomethyl-5-trichloromethyl-1,3,4,6,9b-pentaazaphenalene (**1c**) and 7,9-dibromo-2,5-bis(tribromomethyl)-1,3,4,6,9b-pentaazaphenalene (**1d**) is described. Reaction of **1c** with various nucleophiles converted it to the corresponding 7,9-dibromo-2,5-bis-substituted derivatives, the trihalomethyl groups serving as leaving groups. Displacement, first of one tribromomethyl group on **1d** by pyrrolidine, and then by various nucleophiles on the remaining tribromomethyl group led to several mixed 2,5-disubstituted derivatives.

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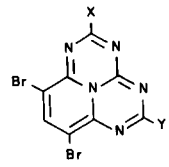
A recent paper [2] reported on the preparation of certain 2-amino and 2-alkoxy-substituted derivatives of the 1,3,4,6,9b-pentaazaphenalene ring system **1**. The reactions involved nucleophilic displacement on 2-trichloromethyl-5-methyl-1,3,4,6,9b-pentaazaphenalene (**1a**) by various alkoxides or primary and secondary amines, the trichloromethyl group serving as a useful leaving group.

It was of interest to attempt the preparation of similar 2,5-disubstituted amino, alkoxy or mixed-amino alkoxy derivatives of **1**. An investigation of ring-closure methods for the preparation of 2,5-bis(trichloromethyl)-1,3,4,6,9b-pentaazaphenalene (**1b**); a possible starting material for such displacement reactions has not been promising. Attempts to prepare **1b** by selective chlorination of **1a** using molecular chlorine has led to a host of products and much resinous material. However, base catalyzed (sodium acetate) bromination of **1a** using excess bromine (10 equivalents per mole of **1a**) in acetic acid gave a 77% yield of 7,9-dibromo-2-tribromomethyl-5-trichloromethyl-1,3,4,6,9b-pentaazaphenalene (**1c**), a compound potentially suitable for the preparation of the desired derivatives, albeit with bromine groups at positions 7 and 9 of **1**. Use of the stoichiometric amount of bromine under the same conditions led to much lower yields of **1c** together with troublesome amounts of difficultly removable multibrominated products. Analysis (tlc) of the bromination reaction in its very early stages revealed a multitude of products indicating random substitution of the hydrogens of the methyl side-chain and 7,9-positions. Bromination of **1a** using bromine/carbon tetrachloride or *N*-bromosuccinimide was not investigated as previous work [3] has shown these conditions would not brominate the methyl side-chains of 2,5-dimethyl-1,3,4,6,9b-pentaazaphenalene; instead ring positions 7 and 9 were brominated. The number and location of the bromine atoms in **1c** follows primarily from elemental analysis, pmr data and the results of the displacement reactions on **1c**. Thus typical pmr values [3] for $H_7$, $H_9$ ($\delta$ 6.0-6.3) and $H_8$ (7.4-8.2) of the ring system **1** show that the latter correspond better to the only resonance signal shown by **1c**, a 1-proton singlet ($\delta$ 8.54).

Displacement of both leaving groups of **1c** by simple alcohols (base catalyzed), ammonia and aliphatic amines was achieved with varying success as shown in Table 1 and the experimental section. It has been possible to displace only one of the two leaving groups of **1c** using a reasonably reactive aromatic amine like *p*-anisidine. Attempts to force the reaction by use of elevated temperature or the use of the acylation catalyst 4-dimethylaminopyridine, which had proved useful in related earlier work [2], was not successful. In addition, it was not possible to get a good elemental analysis on the mono-anisidino product, a result shared by other mono-substituted derivatives attempted from **1c**. Apparently displacement of the tribromomethyl and trichloromethyl groups takes place at a similar rate with the resultant formation of two products with very close physical properties. To circumvent these difficulties, we prepared 7,9-dibromo-2,5-bis(tribromomethyl)-1,3,4,6,9b-pentaazaphenalene (**1d**) in 44% yield from 2,5-dimethyl-1,3,4,6,9b-pentaazaphenalene, following essentially the same bromination procedure used to prepare **1c**.

A few preliminary experiments showed it was much easier to control the formation of a mono-substituted derivative obtained from **1d** using a reactive amine like pyrrolidine than from reactive alkoxide like sodium methoxide. Thus, 7,9-dibromo-2-tribromomethyl-5-(1-pyrrolidino)-1,3,4,6,9b-pentaazaphenalene (**1e**) was obtained in 42% yield by the addition of an equimolar amount of pyrrolidine to a very dilute solution of **1d**. Table 1 shows the results of efforts to displace the remaining tribromomethyl

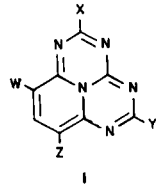
Table 1 (a)



| Compound No. | X/Y | Method | Reaction Temperature (hours) | Yield % (b) | Mp (°C) (c) Crystallization Solvent | Molecular Formula | Analysis % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **1f** | *p*-$NHC_6H_4OCH_3$ $CBr_3$ | C (d) | 25°/0.33 | 15 | 266-268 dec toluene/hexane | $C_{16}H_9Br_5N_6O$ | 27.42<br>27.15 | 1.30<br>1.59 | 11.99<br>11.73 |
| **1g** | $OCH_3$ $OCH_3$ | A (e) | reflux/0.5 | 51 | 232-233 dec toluene | $C_{10}H_7Br_2N_5O_2$ | 30.87<br>31.21 | 1.81<br>2.01 | 18.00<br>17.75 |
| **1i** | $NH_2$ $NH_2$ | B (f) | reflux/3.0 | 12 | >400 DMF/water | $C_6H_5Br_2N_7$ | 26.76<br>27.03 | 1.40<br>1.13 | 27.31<br>27.58 |
| **1j** | $NH(CH_2)_3CH_3$ $NH(CH_2)_3CH_3$ | B (g) | reflux/48 | 8 | 210-212 carbon tetrachloride | $C_{16}H_{21}Br_2N_7$ | 40.78<br>40.62 | 4.49<br>4.38 | 20.81<br>20.76 |
| **1m** | 1-pyrrolidino $NH(CH_2)_3CH_3$ | D (h) | reflux/22 | 43 | 228-230 toluene | $C_{16}H_{18}Br_2N_7$ | 41.05<br>41.43 | 3.87<br>4.17 | 20.94<br>20.75 |
| **1n** | 1-pyrrolidino $OCH_3$ | D (i) | reflux/0.5 | 41 | 251-253 acetonitrile | $C_{13}H_{12}Br_2N_6O$ | 36.47<br>36.61 | 2.83<br>3.01 | 19.63<br>19.39 |
| **1o** | 1-pyrrolidino $OCH_2CH_2CH_3$ | D (j) | 75°/2 | 44 | 217-218 1-propanol | $C_{15}H_{16}Br_2N_6O$ | 39.49<br>39.72 | 3.54<br>3.79 | 18.43<br>18.35 |

(a) The ir spectra of the compounds listed support the structures shown; the pmr spectra of the compounds listed showed the expected signals for the X and Y groups and delta values of 7.73-8.2 for $H_8$. (b) Crude yields, no attempt was made to optimize yields. (c) Melting point of the recrystallized product. (d) Thirty ml of dry DMF was used as solvent and 0.02 mole of *p*-anisidine dissolved in 10 ml of dry DMF served as nucleophile; crude **1f** was obtained by ordinary filtration, no addition of hexane being needed. (e) Twenty-five ml of dry methanol served as solvent and 0.00018 mole of benzyltrimethylammonium methoxide provided the base catalysis; crude **1g** was obtained by ordinary filtration, no chromatography being needed. (f) Twenty ml of dry acetonitrile was the solvent; a gentle stream of ammonia was passed through the reaction mixture. (g) Five ml each of dry chloroform and dry toluene served as solvent; the crude **1j** was chromatographed over 15 g of silica gel using chloroform-methanol (95:5) as eluent. (h) The crude product was chromatographed over 70 g of silica gel using chloroform-methanol (95:5). (i) One hundred ml of dry methylene chloride and 25 ml of dry methanol served as solvent; 0.00054 mole of benzyltrimethylammonium methoxide provided the base catalysis. (j) Thirty-five ml of dry toluene and 15 ml of dry 1-propanol served as solvent, and 0.0008 mole of sodium propoxide provided the base catalysis; the crude **1o** was chromatographed over 70 g of silica gel using chloroform-ethyl acetate (95:5).

Figure 1



I

(**1a**, **1b**, W, Z = H; **1c-1o**, W, Z = Br)

**1a**, X = $CCl_3$, Y = $CH_3$
**1b**, X = $CCl_3$, Y = $CCl_3$
**1c**, X = $CBr_3$, Y = $CCl_3$
**1d**, X = $CBr_3$, Y = $CBr_3$
**1e**, X = $CBr_3$, Y = 1-pyrrolidino
**1f**, X = $CBr_3$, Y = $NHC_6H_4OCH_3$-*p*
**1g**, X = $OCH_3$, Y = $OCH_3$
**1h**, X = $O(CH_2)_2CH_3$, Y = $O(CH_2)_2CH_3$
**1i**, X = $NH_2$, Y = $NH_2$
**1j**, X = $NH(CH_2)_3CH_3$, Y = $NH(CH_2)_3CH_3$
**1k**, X = 1-pyrrolidino, Y = 1-pyrrolidino
**1ℓ**, X = 1-pyrrolidino, Y = $NHNH_2$
**1m**, X = 1-pyrrolidino, Y = $NH(CH_2)_3CH_3$
**1n**, X = 1-pyrrolidino, Y = $OCH_3$
**1o**, X = 1-pyrrolidino, Y = $O(CH_2)_2CH_3$

group of **1e** by several nucleophiles.

We were also able to obtain a rather low yield (15%) of 2-(*p*-anisidino)-7,9-dibromo-5-tribromomethyl-1,3,4,6,9b-pentaazaphenalene (**If**) from **1d**. Here, in contrast to preparation of **1e**, a large excess of the weaker nucleophile *p*-anisidine under much more concentrated reaction conditions was required. However, clean and complete displacement of the remaining tribromomethyl group of **1f** was not possible, very largely due to its very low solubility which required such long reaction times at elevated temperatures.

Interestingly, use of **1d** in place of **1c** in the preparation of any of the 7,9-dibromo-2,5-bis(substituted) derivatives listed in Figure 1 invariably gave lower yields.

## 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. Compound **1a** [2] and 2,5-dimethyl-1,3,4,6,9b-pentaazaphenalene [4] were prepared using methods described in the literature.

7,9-Dibromo-2-tribromomethyl-5-trichloromethyl-1,3,4,6,9b-pentaazaphenalene (**1c**).

A stirred solution of 24.61 g (0.30 mole) of anhydrous sodium acetate and 9.08 g (0.03 mole) of **1a** in 120 ml of acetic acid was treated dropwise at 75-80° with a solution of 47.94 g (0.30 mole) of bromine in 30 ml of acetic acid over a 20 minute period. The reaction mixture was maintained at this temperature interval for 30 minutes additional, then cooled to 20°, filtered, the filter cake being washed with petroleum ether (30-60°) until the washings were free of bromine. The crude product which was contaminated with inorganic salts was recrystallized from toluene to give 16 g (77%) of blue crystals, mp 300-305° (compound loses bromine, no melting observed up to 400°); pmr (DMSO-$d_6$): δ 8.57 (s, 1H, $H_8$).

*Anal.* Calcd. for $C_{10}HBr_5Cl_3N_5$: C, 17.23; H, 0.14; N, 10.05. Found: C, 17.57; H, 0.55; N, 9.86.

7,9-Dibromo-2,5-bis(tribromomethyl)-1,3,4,6,9b-pentaazaphenalene (**1d**).

A stirred solution of 39.6 g (0.48 mole) of anhydrous sodium acetate and 5.97 g (0.03 mole) of 2,5-dimethyl-1,3,4,6,9b-pentaazaphenalene in 120 ml of acetic acid was treated dropwise at 80-85° with a solution of 76.7 g (0.48 mole) of bromine in 20 ml of acetic acid over a 20 minute period. The reaction mixture was maintained at this temperature interval for 1 additional hour, then cooled to 15°. The precipitate which had formed was filtered and washed with petroleum ether (30-60°) until the washings were free of bromine. Recrystallization from toluene (rapidly as the product undergoes some decomposition at the boiling point of toluene) gave 11 g (44%) of a pale blue solid, mp indeterminate; tlc (silica gel/chloroform) showed one blue spot; pmr (DMSO-$d_6$): δ 8.54 (s, 1H, $H_8$).

*Anal.* Calcd. for $C_{10}HBr_8N_5$: C, 14.46; H, 0.12; N, 8.43. Found: C, 14.62; H, 0.21; N, 8.44.

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

Method A. 7,9-Dibromo-2,5-bis(1-propoxy)-1,3,4,6,9b-pentaazaphenalene (**1h**).

A stirred solution of 1 g (0.0014 mole) of **1c** in 10 ml of dry 1-propanol and 10 ml of dry toluene was treated dropwise with 0.73 (0.0019 mole) of 21% sodium propoxide over 6 hours, the temperature being held at about 75°. The amber solution was then stirred at room temperature overnight, after which time the reaction was found to be complete (tlc). The residue obtained after evaporation of the reaction mixture to dryness was chromatographed over 70 g of silica gel using chloroform-ethyl acetate (95:5) as eluent. The yellow fraction was collected and yielded 0.35 g (55%) of crude **1h**, mp 181-183°. Recrystallization from 1-propanol gave brownish orange crystals, mp 183-185°; pmr (deuteriochloroform): δ 0.96 [t (J = 6 Hz), 6H, 2 ($CH_3$)], 1.78 [m, 4H, 2 ($CH_2$)], 4.32 (t [J = 6 Hz), 4H, 2 ($CH_2O$)], 7.94 (s, 1H, $H_8$).

*Anal.* Calcd. for $C_{14}H_{15}Br_2N_5O_2$: C, 37.77; H, 3.40; N, 15.74. Found: C, 37.53; H, 2.95; N, 16.06.

Method B. 7,9-Dibromo-2,5-bis(1-pyrrolidino)-1,3,4,6,9b-pentaazaphenalene (**1k**).

A stirred solution of 1.0 g (0.0014 mole) of **1c** in 10 ml of dry toluene was treated at 75° with 0.40 (0.0056 mole) of pyrrolidine and the mixture was allowed to cool to room temperature over 1 hour. The precipitate that formed was collected by filtration and washed with acetone, 0.33 g (50%), mp 228-230° dec. Recrystallization from toluene gave yellow crystals, with the same decomposition point; pmr (deuteriochloroform): δ 1.85 [m, 8H, 2 ($CH_2CH_2$)], 3.55 [m, 8H, 2 ($CH_2NCH_2$)], 7.73 (s, 1H, $H_8$).

*Anal.* Calcd. for $C_{16}H_{17}Br_2N_7$: C, 41.13; H, 3.67; N, 20.99. Found: C, 41.10; H, 3.72; N, 20.76.

Method C. 7,9-Dibromo-2-tribromomethyl-5-(1-pyrrolidino)-1,3,4,6,9b-pentaazaphenalene (**1e**).

A stirred solution of 3.32 g (0.004 mole) of **1d** in 290 ml of dry toluene was treated dropwise over a period of 10 minutes at 40-45° with a solution of 0.28 g (0.004 mole) of pyrrolidine in 10 ml of toluene. Following an additional 10 minute reaction period, the mixture was evaporated to one-third volume and caused to precipitate by the addition of 110 ml of hexane and chilling. The red solid was collected by filtration and washed with petroleum ether (30-60°), 1.1 g (42%), mp 194-197° dec. Recrystallization from toluene/hexane gave red crystals, mp 203-205° dec; pmr (DMSO-$d_6$): δ 1.93 (m, 4H, $CH_2CH_2$), 3.55 (m, 4H, $CH_2NCH_2$), 8.20 (s, 1H, $H_8$).

*Anal.* Calcd. for $C_{13}H_9Br_5N_6$: C, 24.07; H, 1.40; N, 12.95. Found: C, 24.36; H, 1.75; N, 13.23.

Method D. 7,9-Dibromo-2-hydrazino-5-(1-pyrrolidino)-1,3,4,6,9b-pentaazaphenalene (**1ℓ**).

A stirred refluxing solution of 1 g (0.0015 mole) of **1e** and 70 ml of dry chloroform was treated with 1 g (0.02 mole) of hydrazine monohydrate. The reaction mixture after refluxing for 1 hour was cooled to room temperature, filtered and the filter cake was washed with acetone and then petroleum ether (30-60°), 0.44 g (69%), mp 247-248° dec (Note: to obtain this melting point, a sample in a capillary tube was plunged into a melting point bath at 240° and then rapidly heated to the decomposition point). Recrystallization from 2-methoxyethanol did not alter the decomposition point; ir (nujol): λ μm 3.02 (NH); (very low solubility precluded pmr analysis).

*Anal.* Calcd. for $C_{12}H_{12}Br_2N_8$: C, 33.67; H, 2.83; N, 26.18. Found: C, 33.38; H, 3.13; N, 25.94.

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