

Synthesis and Properties of Some Aryl-*s*-Triazines (1a)

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The synthesis and reactions of several substituted *s*-triazines were studied in attempts to prepare 4,6-bis(4-chlorophenyl)-*s*-triazine-2-carboxylic acid (**2**) and 2-aldehyde (**8**). The 4,6-bis(4-chlorophenyl)-*s*-triazine derivatives were surprisingly inert to a variety of reagents. 4,6-Bis(4-chlorophenyl)-2-methyl-*s*-triazine (**1**) could not be oxidized with any of a variety of oxidants. On bromination **1** gave 4,6-bis(4-chlorophenyl)-2-dibromomethyl-*s*-triazine (**4**) which was resistant to hydrolysis but on oxidation with selenium dioxide gave **2**. Compound **2** was also prepared by the oxidation of 4,6-bis(4-chlorophenyl)-2-hydroxymethyl-*s*-triazine (**7**) with potassium permanganate. Other reagents did not oxidize **7** to **8**. 4,6-Bis(4-chloroanilino)-2-methyl-*s*-triazine (**3**) was also resistant to oxidizing agents. 2-Diazomethyl-4,6-dichloro-*s*-triazine (**11**) on reaction with 4-chloroaniline gave 4,6-bis(4-chloroanilino)-2-chloromethyl-*s*-triazine (**12**). All efforts to prepare **8** were unsuccessful.

Diaryl-*s*-triazine carboxylic acids or aldehydes were required as intermediates in the preparation of triazine aminoalcohols for evaluation as possible antimalarial agents. This communication describes various approaches, partially successful, to particular compounds of these types.

Aryl-*s*-triazinecarboxylic acids have been prepared by oxidation of the corresponding methyl compounds. For example, 4,6-diphenyl-*s*-triazine-2-carboxylic acid was prepared by oxidation of 4,6-diphenyl-2-methyl-*s*-triazine (**2**) and by oxidation of 4,6-diphenyl-2-hydroxymethyl-*s*-triazine with alkaline permanganate (**3**).

4,6-Bis(4-chlorophenyl)-2-methyl-*s*-triazine (**1**), prepared from 4-chlorobenzamidine and acetic anhydride (**4**), could not be oxidized to 4,6-bis(4-chlorophenyl)-*s*-triazine-2-carboxylic acid (**2**) with any of a variety of oxidants, unchanged **1** being recovered in every case. Possibly related to its inertness towards oxidation is the fact that **1** did not react with benzaldehyde to form the styryl derivative, a reaction which 4,6-diphenyl-2-methyl-*s*-triazine undergoes (**2**).

Since it has been reported (**2**) that electron withdrawing groups at the 4 and 6 positions of *s*-triazine prevent the oxidation of a 2-methyl group and electron donating groups at these positions facilitate oxidation, we prepared 4,6-bis(4-chloroanilino)-2-methyl-*s*-triazine (**3**) by a known procedure (**5**) and studied its oxidation. All attempts to oxidize **3** to the corresponding acid failed.

Bromination of **1** with one molar equivalent of bromine

or *N*-bromosuccinimide invariably gave 4,6-bis(4-chlorophenyl)-2-dibromomethyl-*s*-triazine (**4**). When **4** was treated with silver nitrate in DMSO, a product whose physical properties and ir spectrum indicated that it was the silver salt of **2** was obtained, but it did not react with methyl iodide (**6**) nor could **2** be obtained from it by acidification. With two molar equivalents of bromine, **1** gave **4** in very good yield. Compound **4** on oxidation with selenium dioxide gave **2**.

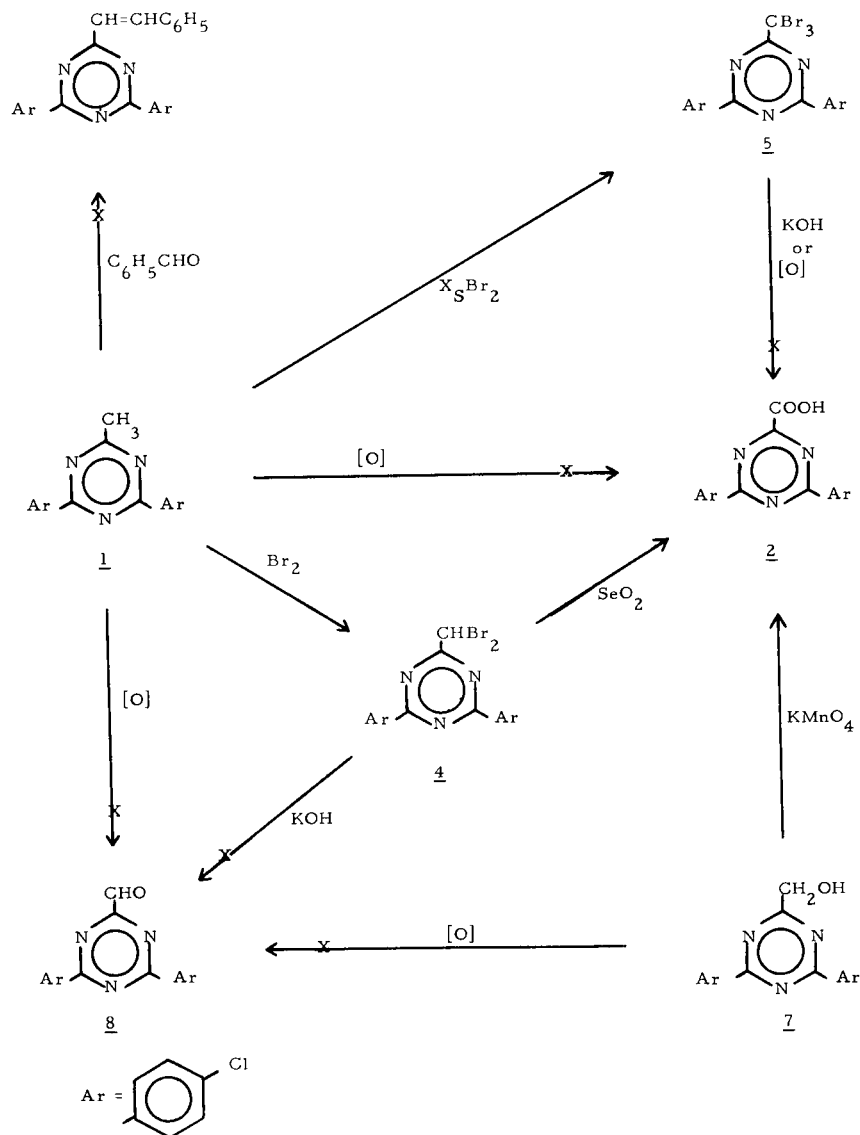
Bromination of **1** with excess bromine gave 4,6-bis(4-chlorophenyl)-2-tribromomethyl-*s*-triazine (**5**) which could not be hydrolyzed nor oxidized to **2**.

4,6-Bis(4-chlorophenyl)-2-ethyl-*s*-triazine (**6**) was prepared from 4-chlorobenzamidine and propionic anhydride (**4**). Compound **6** could not be oxidized to the methyl ketone with a variety of oxidants and on bromination gave a mixture of products.

4,6-Bis(4-chlorophenyl)-2-hydroxymethyl-*s*-triazine (**7**) was prepared from 4-chlorobenzamidine and glycolonitrile (**3**). On oxidation with alkaline permanganate **7** gave the acid **2**.

Grundman and Kober (**7**) successfully synthesized *s*-triazine aldehydes by reduction of diazomethyl-*s*-triazines and cleavage of the hydrazones with 2,4-dinitrobenzaldehyde. Since in earlier work (**8**) these authors had shown that diazomethane reacts with 2,4-dichloro-6-phenyl-*s*-triazine but not with 2-chloro-4,6-diphenyl-*s*-triazine, we proceeded as described below to attempt the synthesis of 4,6-bis(4-chlorophenyl)-*s*-triazine-2-aldehyde (**8**).

SCHEME I



One equivalent of 4-chlorophenyl magnesium bromide when allowed to react with cyanuric chloride by known procedures (5) gave 6-(4-chlorophenyl)-2,4-dichloro-*s*-triazine (9) which with diazomethane (8) gave 4-chloro-6-(4-chlorophenyl)-2-diazomethyl-*s*-triazine (10). Attempts to replace the 4-chloro group in 10 with a 4-chloroanilino or a 4-chlorophenyl group met with failure.

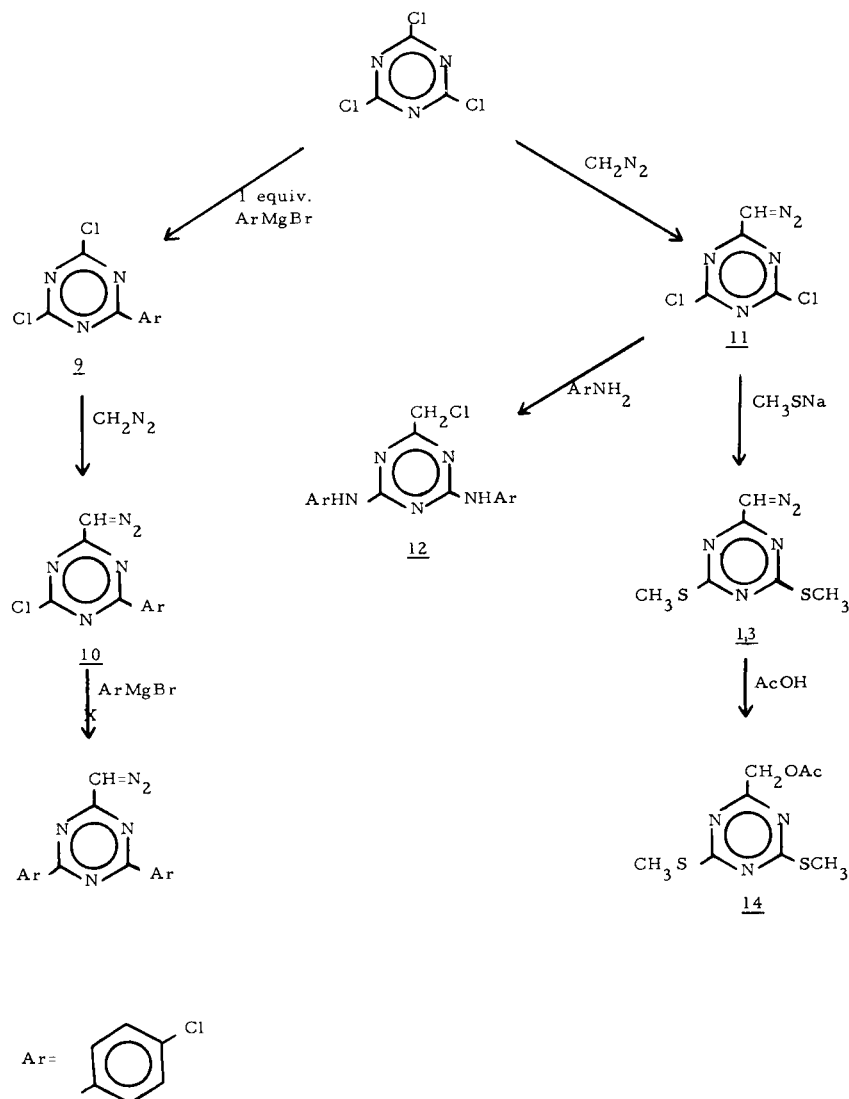
Cyanuric chloride with diazomethane gave 2-diazomethyl-4,6-dichloro-*s*-triazine (11) (8), which on reaction with 4-chloroaniline in an attempt to prepare 2-diazomethyl-4,6-bis(4-chloroanilino)-*s*-triazine, yielded 4,6-bis(4-chloroanilino)-2-chloromethyl-*s*-triazine (12). Grundmann (8) reported that the analogous reaction with aliphatic amines gave 4,6-bis(alkylamino)-2-diazomethyl derivatives. Evidently, 4-chloroaniline is too weak a base to compete

effectively with the diazomethyl group for the hydrogen chloride formed in the reaction.

2-Diazomethyl-4,6-bis(thiomethyl)-*s*-triazine (13) (8) with acetic acid produced the acetate of 4,6-bis(thiomethyl)-2-hydroxymethyl-*s*-triazine (14). Our intention was to convert this ester into 4,6-bis(4-chlorophenyl)-2-hydroxymethyl-*s*-triazine (7) but 7 was more readily prepared in one step as described previously.

It may be inferred from Grundmann and Kober's work (7) that substitution of two aryl groups modifies the acyl chloride character of the remaining chloro group in a diarylmonochloro-*s*-triazine since it does not react with diazomethane. Proceeding with this assumption we attempted to prepare a Grignard reagent and a lithium derivative from 2-chloro-4,6-bis(4-chlorophenyl)-*s*-triazine

SCHEME II



(15) for carbonation or aldehyde preparation by Pearson's method (9). Neither reaction yielded identifiable products.

Other routes investigated for preparation of the desired triazine aldehyde (8) were unsuccessful. 2-Dibromomethyl-4,6-bis(4-chlorophenyl)-*s*-triazine (4) could not be hydrolyzed to the aldehyde even by fusion with potassium hydroxide. The hydroxymethyl compound (7) was surprisingly stable towards oxidizing agents. Pyridine-sulfur dioxide-DMSO reagent (10) failed to oxidize it or its tosylate. When 7 was allowed to react with ceric ammonium nitrate (11), a product which showed the presence of an aldehyde group in its ir spectrum was obtained, but the mass spectrum of this material indicated that the triazine ring had been destroyed in the reaction.

EXPERIMENTAL (12)

4,6-Bis(4-chlorophenyl)-2-methyl-*s*-triazine (1).

Acetic anhydride (5 ml.) and 4-chlorobenzamidine (2 g., 14.4 mmoles) were mixed in a flask and heated to reflux. A crystalline mass precipitated out of the initially clear solution after 15 minutes. Reflux was continued for 2 hours more, and the mixture was cooled and filtered. The solid was washed with ether and crystallized from benzene, yield 1.68 g. (74%), m.p. 200-202°.

Anal. Calcd. for $C_{16}H_{11}Cl_2N_3$: C, 60.78; H, 3.51; N, 13.29. Found: C, 60.67; H, 3.42; N, 12.93.

4,6-Bis(4-chlorophenyl)-*s*-triazine-2-carboxylic Acid (2).

4,6-Bis(4-chlorophenyl)-2-dibromomethyl-*s*-triazine (4), (14 g., 44.3 mmoles) was dissolved in refluxing glacial acetic acid (200 ml.) and to this refluxing solution selenium dioxide (7 g., 63.6 mmoles)

in water was added slowly. The reaction mixture was refluxed for 1 hour and the dark red solution was distilled. To the residue more acetic acid was added and distilled. The solid residue was washed with petroleum ether until the washings were colorless and then with ether. The residue was crystallized from acetic acid, yield 9 g. (crude, 90%), m.p. 231-231.5°.

Anal. Calcd. for $C_{16}H_9Cl_2N_3O_2$: C, 55.52; H, 2.62; Cl, 20.48; N, 12.14. Found: C, 55.67; H, 2.77; Cl, 20.40; N, 11.91.

4,6-Bis(4-chloroanilino)-2-methyl-s-triazine (3).

4,6-Dichloro-2-methyl-s-triazine (5) (3 g., 18.3 mmoles) was dissolved in acetone (15 ml.) and cooled in ice water. To this cold solution 4-chloroaniline (5 g., 39.1 mmoles) in acetone (25 ml.) was added slowly with stirring. When the addition was over the reaction mixture was stirred at room temperature for 45 minutes and at 40° for 30 minutes. The precipitate was filtered and washed with acetone and ether, m.p. 295-305°. An additional 1 g. of compound was obtained from the concentrated mother liquor, giving a total yield of 6.66 g. (90%). The base was liberated with sodium hydroxide, crystallized from methanol and recrystallized from ether, m.p. 208.5-209°.

Anal. Calcd. for $C_{16}H_{13}Cl_2N_5$: C, 55.51; H, 3.79; Cl, 20.48; N, 20.23. Found: C, 55.29; H, 3.66; Cl, 20.50; N, 19.96.

4,6-Bis(4-chlorophenyl)-2-dibromomethyl-s-triazine (4).

Compound 1 (2 g., 6.3 mmoles) was dissolved in refluxing acetic acid (50 ml.) and bromine (2 g., 12.5 mmoles) in acetic acid (25 ml.) was added slowly. When all the bromine was added, the reaction mixture was refluxed until most of the hydrogen bromide was removed. Acetic acid was distilled, and the compound was crystallized from ether, yield 3 g. (100%), m.p. 153-155°.

Anal. Calcd. for $C_{16}H_9Br_2Cl_2N_3$: C, 40.54; H, 1.91; N, 8.84. Found: C, 41.02; H, 1.82; N, 8.59.

4,6-Bis(4-chlorophenyl)-2-tribromomethyl-s-triazine (5).

Bromine (6.6 g., 82.6 mmoles) in acetic acid was added to a refluxing solution of 1 (3.78 g., 12 mmoles) in acetic acid (100 ml.) and refluxing was continued until most of the hydrogen bromide was removed. The solid was filtered and washed with hot acetic acid, yield 3.78 g. (58%), crystallized from chloroform, m.p. 212-216°.

Anal. Calcd. for $C_{16}H_8Br_3Cl_2N_3$: C, 34.79; H, 1.45; N, 7.60. Found: C, 35.59; H, 1.59; N, 7.78.

4,6-Bis(4-chlorophenyl)-2-ethyl-s-triazine (6).

Propionic anhydride (100 ml.) and 4-chlorobenzamidine (25 g., 180 mmoles) were mixed and refluxed for 3 hours. The excess anhydride and formed propionic acid were distilled. The residue was crystallized from acetone, yield 15.32 g., m.p. 130-132°.

Anal. Calcd. for $C_{17}H_{13}Cl_2N_3$: C, 61.83; H, 3.97; N, 12.72. Found: C, 61.59; H, 3.90; N, 12.43.

4,6-Bis(4-chlorophenyl)-2-hydroxymethyl-s-triazine (7).

Glycolonitrile (20 ml., 70% aqueous solution) was added to an ice cold solution of 4-chlorobenzamidine (31 g., 200 mmoles) in 120 ml. of methanol followed by water (100 ml.). The reaction mixture was allowed to stand at room temperature for 3 days. The precipitate was filtered and crystallized from acetone, yield 3.5 g. (10%), m.p. 201-203°.

Anal. Calcd. for $C_{16}H_{11}Cl_2N_3O$: C, 57.85; H, 3.34; Cl, 21.34; N, 12.65. Found: C, 57.64; H, 3.27; Cl, 21.48; N, 12.81.

6-(4-Chlorophenyl)-2,4-dichloro-s-triazine (9).

An ether solution of 4-chlorophenylmagnesium bromide, pre-

pared from magnesium (2.68 g., 0.11 g.-atom) and 4-bromochlorobenzene (23 g., 0.12 mole) was added slowly to cyanuric chloride (18.5 g., 0.10 mole) in THF (175 ml.) at room temperature. The resultant dark reaction mixture was stirred at room temperature for 2 hours, poured into water (1500 ml.) and extracted with ether. The ether extract was dried (sodium sulfate) and solvents were removed. The solid residue was crystallized from acetone, yield 14.6 g. (56%). A sample was recrystallized from acetone, m.p. 149-150.5°.

Anal. Calcd. for $C_9H_4Cl_3N_3$: C, 41.50; H, 1.55; N, 16.13. Found: C, 41.70; H, 1.66; N, 15.85.

4,6-Bis(4-chloroanilino)-2-chloromethyl-s-triazine (12).

4-Chloroaniline (4 g., 31 mmoles) in acetone (15 ml.) was added to a solution of 2-diazomethyl-4,6-dichloro-s-triazine (8) (3 g., 15.3 mmoles) in acetone (15 ml.). The reaction mixture was refluxed on a water bath for 2 hours and acetone was removed. The residue was diluted with ether and the precipitate was filtered and washed with ether, m.p. 230-235°. The base was liberated with sodium hydroxide and crystallized from ether, m.p. 138-139°.

Anal. Calcd. for $C_{16}H_{12}Cl_3N_5$: C, 50.48; H, 3.18; Cl, 27.94; N, 18.40. Found: C, 50.66; H, 3.26; Cl, 28.10; N, 18.19.

Acetate of 4,6-Bisthiomethyl-2-hydroxymethyl-s-triazine (14).

4,6-Bisthiomethyl-2-diazomethyl-s-triazine (8) (3 g., 14 mmoles) was stirred with 90% aqueous acetic acid (50 ml.). As the temperature of the solution was raised, the solid dissolved, and a gas was evolved. The solution was refluxed for 15 minutes, cooled and neutralized with sodium carbonate solution. The aqueous suspension was extracted with ether. The ether extract was dried (sodium sulfate) and ether was removed. The residue was extracted with naphtha, and the extract was concentrated. The first precipitate was a gummy solid which was discarded. After the filtrate stood for a short time a white fluffy material precipitated and was discarded. The desired compound precipitated as white crystals after 2 days, yield 0.5 g. (14%), m.p. 74-77.5°.

Anal. Calcd. for $C_8H_{11}N_3O_2S_2$: C, 39.17; H, 4.52; N, 17.13. Found: C, 39.31; H, 4.60; N, 16.80.

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