A New Synthesis of *s*-Triazines (1a)

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The anions of urea, guanidine, thiourea, biguanide, and biuret were reacted with aromatic nitriles to yield *s*-triazines. *Ortho*-chloro substituted aromatic nitriles gave other products or did not react because of steric factors.

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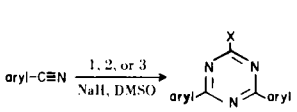
In the past few years symmetrical triazines have developed in importance both in biochemical research (3) and for industrial applications. We have continued the study initiated by Collins (4) of the facile one-step synthesis of 2-hydroxy-4,6-bis-aryl-*s*-triazines from urea and aryl cyanides (Scheme 1). By a similar reaction 2-amino-4,6-bis-aryl-*s*-triazines have been formed from arylnitriles and guanidine (5). The versatility of this synthesis is further explored in this paper by additional studies with urea and guanidine and also by replacing them with either thiourea, biguanide, or biuret (Schemes 1 and 2). Some of the limitations of this general method are examined.

The initial object of this study was to develop water-soluble *s*-triazines with bactericidal or fungicidal activity. Unfortunately all the 2-hydroxy-4,6-bis-aryl-*s*-triazines developed in this study were water-insoluble. Consequently dimethylsulfoxide was used as the solvent for the bactericidal and fungicidal tests. Compounds **1b**, **1c**, and **1e** proved to be inactive.

The synthesis of 2-hydroxy-4,6-bis-aryl-*s*-triazines is shown for **1a**, **1b**, **1c**, **1d**, and **1e** (Scheme 1).

Scheme 1



anion	X
1 urea	OH
2 guanidine	NH_2
3 thiourea	SH

aryl

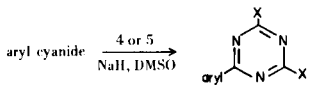
a phenyl
b 4-chlorophenyl
c 4-bromophenyl
d 4-fluorophenyl
e 3,5-dichlorophenyl

All yields are based on sodium hydride and the yields increase as the sodium hydride to aryl nitrile mole ratio increases. The mole ratio of aryl cyanide to urea was held at two to one. The low yield for **1d** may be due to benzyne formation. *o*-Chlorobenzonitrile, urea, and sodium hydride gave *o*-chlorobenzamide rather than a triazine. Apparently the chlorine atom *ortho* to the cyano group sterically prevents cyclization. With 2,6-dichlorobenzonitrile, urea and sodium hydride only unreacted nitrile was recovered from the reaction mixture. The steric effect of two *ortho* chlorine atoms prevents any reaction.

The reaction of guanidine carbonate, benzonitrile, and enough sodium hydride to both neutralize the salt as well as form the anion of guanidine gave an excellent yield of **2a**. This latter reaction was carried out with a mole ratio for benzonitrile and guanidine carbonate of two to one. By a similar technique thiourea gave **3b**.

Use of this procedure with biguanide, benzonitrile and two equivalents of sodium hydride gave 2,4-diamino-6-phenyl-*s*-triazine (**4a**). (Scheme 2) In this reaction two

Scheme 2



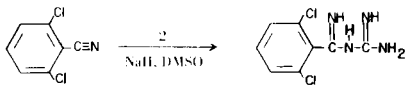
anion	X
4 biguanide	NH_2
5 biuret	OH

equivalents of hydride were used to ensure that at least one of the terminal nitrogen atoms of biguanide was present as the anion. Benzoguanamine (**4a**) has been prepared from benzonitrile and dicyandiamide (6). When biuret was reacted with benzonitrile and either one or two equivalents of sodium hydride, a mixture of products was

obtained which was not **5a**. Mass spectrometry suggests the presence of 2,4,6-trisphenyl-*s*-triazine and **1a**.

The reaction of guanidine carbonate with 2,6-dichlorobenzonitrile gave 2,6-dichlorobenzimdoyl guanidine, (**6f**), (Scheme 3).

Scheme 3



Guanidine, a better nucleophile than urea, gives **6f**; however, steric hindrance prevents cyclization to the diarylamino-*s*-triazine. The formation of an acylimidoguanidine has been observed previously for *p*-toluonitrile using guanidine, sodium, and boiling alcohol (5).

Further work will involve a study of the effect of structure and reactant ratios on the products.

EXPERIMENTAL

Melting points are not corrected. Infrared spectra were measured with Perkin-Elmer 237 and mass spectra with Jeol (JMS-01-SC). The pharmacological tests were performed at Sterling Winthrop Laboratories, Rensselaer, New York.

The compounds were tested against eight microorganisms, five bacteria, and three fungi. The bacteria were: *Staphylococcus aureus*, Smith; *Escherichia coli*, Vogel; *Klebsiella pneumoniae* 39645 (S.W. #); *Proteus mirobilis* MGH-1, and *Pseudomonas aeruginosa* MGH-2. The fungi were: *Condida albacans*, *Aspergillis niger*, and *Trichophyton mentagrophytes*.

The solvent used for the tests was dimethylsulfoxide and the drugs were tested in concentrations ranging from 500 γ (1,000 γ = 1 mg./1 ml.) to 7.8 γ. Depending on the organism, the incubation temperature and period was varied (example: *C. albicans* 37°, 48 hours).

2-Hydroxy-4,6-bisphenyl-*s*-triazine (**1a**).

A mixture of benzonitrile (5.14 g., 0.05 mole), urea (1.5 g., 0.025 mole), sodium hydride (1.05 g. of 57% oil dispersion, 0.025 mole), and dimethylsulfoxide (100 ml.) was stirred at room temperature for two hours. After heating at 75° for twenty-five hours, the solution was poured into ice water and neutralized with sulfuric acid. The product, (2.1 g., 60%) was recrystallized from pyridine, m.p. 288-290° (reported m.p. 289°, (7)); ir (potassium bromide): 1650, 1550, 1420, 820 cm^{-1}.

2-Hydroxy-4,6-bis-4-chlorophenyl-*s*-triazine (**1b**).

A mixture of *p*-chlorobenzonitrile (26.1 g., 0.19 mole), urea (3.8 g., 0.095 mole), sodium hydride (2.28 g. of 57% oil dispersion, 0.054 mole), and dimethylsulfoxide (200 ml.) was reacted as above to give **1b** (12.5 g., 74%), m.p. 358°. After recrystallization from pyridine, **1b** had m.p. 368° (reported m.p., 374°, (8)); ir (potassium bromide) γ: 1665, 1540, 1410, 795 cm^{-1}; mass spectrum: 317 (m^+), 138 (base), 111.

Anal. Calcd. for $C_{15}H_9Cl_2N_3O$: C, 56.62; H, 2.85; N, 13.21. Found: C, 56.92; H, 2.94; N, 13.05.

2-Hydroxy-4,6-bis-4-bromophenyl-*s*-triazine (**1c**).

From *p*-bromobenzonitrile, urea, and 57% of the theoretical amount of sodium hydride by the procedure of **1b**, compound **1c** was obtained as crystals (1.45 g., 25%). After recrystallization from pyridine, **1c** had m.p. 380-383°; ir (potassium bromide) γ: 1670, 1545, 1410, 795 cm^{-1}; mass spectrum: 405 (m^+), 182, 155, 102 (base).

Anal. Calcd. for $C_{15}H_9Br_2N_3O$: C, 44.26; H, 2.63; N, 10.32. Found: C, 44.55; H, 2.43; N, 10.02.

A repetition of the above reaction with the theoretical amount of sodium hydride gave 34% yield.

2-Hydroxy-4,6-bis-4-fluorophenyl-*s*-triazine (**1d**).

A mixture of *p*-fluorobenzonitrile (5 g., 0.041 mole), urea, (1.58 g., 0.0205 mole), sodium hydride (1.05 g. of 57% oil dispersion, 0.012 mole), and dimethylsulfoxide (40 ml.) was reacted and worked up as described above to give **1d** (0.16 g., 5%), m.p. 265°; ir (potassium bromide) γ: 1660, 1550, 1410, 795 cm^{-1}.

2-Hydroxy-4,6-bis-3,5-dichlorophenyl-*s*-triazine (**1e**).

A mixture of 3,5-dichlorobenzonitrile (5 g., 0.029 mole), urea (0.87 g., 0.0145 mole), sodium hydride (0.35 g. of 57% oil dispersion, 0.0083 mole), and dimethylsulfoxide (40 ml.) was reacted and worked up as for **1b**. The product (2.96 g., 93%) was recrystallized from pyridine to a substance whose mass spectrum corresponded to **1e**; mass spectrum: 385 (m^+), 350, 198, 174 (base), 158, 145, 136. However, the elementary analysis suggests a one-to-one complex of **1e** and pyridine.

Anal. Calcd. for $C_{15}H_7Cl_4N_3O.C_5H_5N$: C, 51.53; H, 2.59; N, 12.02; Cl, 30.42. Found: C, 51.08; H, 2.47; N, 11.72; Cl, 30.03.

After heating for three hours at 180° in a vacuum oven, the pyridine complex formed **1e**, m.p. 355°; ir (potassium bromide) γ: 1625, 1545, 1410, 800 cm^{-1}.

Anal. Calcd. for $C_{15}H_7Cl_4N_3O$: C, 46.55; H, 1.82; N, 10.86. Found: C, 46.2; H, 2.6; N, 10.9.

2-Amino-4,6-bisphenyl-*s*-triazine (**2a**).

A mixture of benzonitrile (20.6 g., 0.2 mole), guanidine carbonate [9.3 g., 0.05 mole of $(CH_5N_3)_2{\cdot}H_2CO_3$], sodium hydride (8.4 g. of 57% oil dispersion, 0.2 mole), and dimethylsulfoxide (200 ml.) was stirred for two hours and heated for an additional thirty hours at 75°. The solution was poured into ice water to yield a product (22.7 g., 91%). Recrystallization from alcohol-water gave **2a**, m.p. 168° (reported m.p. 167°, (5)); ir (potassium bromide) γ: 3325, 1650, 1600, 1520, 1445, 835, 765 cm^{-1}; mass spectrum: 248 (m^+), 103 (base), 97, 95, 83, 71, 69, 57, 55.

Anal. Calcd. for $C_{15}H_{12}N_4$: C, 72.56; H, 4.87; N, 22.56. Found: C, 72.58; H, 4.87; N, 22.41.

2-Mercapto-4,6-bis-4-chlorophenyl-*s*-triazine (**3b**).

Compound **3b** was prepared from *p*-chlorobenzonitrile (6.98 g., 0.05 mole), thiourea (1.9 g., 0.025 mole), sodium hydride (1.05 g. of 57% oil dispersion, 0.025 mole), and dimethylsulfoxide (100 ml.). After stirring for two hours and heating for twenty-seven hours at 85° the yield of **3b** was 3.6 g. (43%). After three recrystallizations from pyridine, **3b** had m.p. of 210-213°; ir (potassium bromide) γ: 3340, 3180, 1660, 1545, 1435, 1200, 840 cm^{-1}; mass spectrum: 333 (m^+), 316, 298, 257, 239, 179, 163, 137 (base), 111, 102.

Anal. Calcd. for $C_{15}H_9Cl_2N_3S$: N, 12.57. Found: N, 12.4.

2,4-Diamino-6-phenyl-*s*-triazine (**4a**).

For this reaction benzonitrile (2.57 g., 0.025 mole), biguanide (2.52 g., 0.025 mole), and sodium hydride (2.1 g. of 5.7% oil dispersion, 0.05 mole) was added to dimethylsulfoxide (100 ml.).

After heating for thirty hours at 80° the solution was poured into ice water to give crystals of **4a** (2.87 g., 61%). Two recrystallizations from 50% aqueous ethanol gave **4a**, m.p. 244.5° (reported m.p. 226-228°, (6)); ir (potassium bromide) γ: 3320, 3150, 1670, 1620, 1530, 1450, 1430, 830, 775 cm^{-1}.

The Reaction of Benzonitrile with Biuret.

The reaction of benzonitrile (10.3 g., 0.1 mole), biuret (17.4 g., 0.1 mole), and sodium hydride (4.8 g. of 99% sodium hydride, 0.2 mole) in 150 ml. of dimethylsulfoxide for two hours at room temperature followed by thirty hours at 75° gave white crystals (4.3 g.) when added to ice water and acidified. After recrystallization from pyridine and a methanol wash, the product melted at 288-291°; ir (potassium bromide) γ: 2850, 1365, 1360-1300, 980 cm^{-1}. The carbon, hydrogen, acid nitrogen analysis did not agree with a structure of 2,4-dihydroxy-6-phenyl-*s*-triazine, **5a**. The mass spectrum: m/e 309 corresponded to the cyclic trimers of benzonitrile and m/e 248 corresponded to 2-hydroxy-4,6-phenyl-*s*-triazine.

2,6-Dichlorobenzimidoylguanidine (**6f**).

A mixture of 2,6-dichlorobenzonitrile (4.3 g., 0.025 mole), guanidine carbonate (2.25 g., 0.0125 mole), sodium hydride (1.05 g. of 57% oil dispersion, 0.025 mole) and dimethylsulfoxide (100 ml.) was stirred for two hours and heated for twenty-six hours at 90°. When this solution was poured into ice water a tar separated out. The next day yellow crystals of **6f** (1.0 g., 35%) were filtered off from the aqueous layer. Recrystallization from 50% aqueous alcohol gave **6f**, m.p. 231°; ir (potassium bromide) γ: 3350-3150, 1670, 1630, 1580 cm^{-1}; mass spectrum: 194 (base), 177, 152, 90, 63, 36, 28, 18; m/e 194 compounds to 2,4-diamino-5-chlorobenzopyrimidine.

Anal. Calcd. for $C_8H_8Cl_2N_4$: C, 41.4; H, 3.5; N, 24.3. Found: C, 40.1; H, 3.7; N, 23.2.

The Reaction of *o*-Chlorobenzonitride with Urea.

A mixture of 2-chlorobenzonitrile (6.88 g., 0.05 mole), urea (1.5 g., 0.025 mole), sodium hydride (1.05 g. of 57% oil dispersion, 0.025 mole), and dimethylsulfoxide (100 ml.) was stirred for two hours and then heated for thirty hours at 65°; after pouring into ice water, acidifying, and evaporating to dryness, a residue was obtained which was worked with water and dissolved in hot alcohol. After recrystallization from alcohol 2-chlorobenzamide was obtained m.p. 137°; ir (potassium bromide): 3380, 3190, 1660, 1640, 1420, 1140, 820, 780, 750, 720, 680, 630 cm^{-1}.

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(1a) Taken from theses submitted by Alsofrom and Grossberg for B.S. degree at Union College; (b) New York State Medical School, New York, New York.

(2) To whom all correspondence should be addressed.

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