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The Preparation of Amino-*s*-triazines with Amino- or Nitrophenyl Groups

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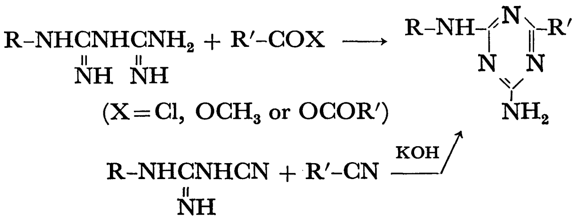
Amino-*s*-triazines with nitro groups were prepared by the reaction of biguanide derivatives with appropriate carboxylic acid derivatives (acyl chloride, anhydride, or ester) or by reaction between dicyanodiamide derivatives and nitrile. Amino-*s*-triazines with aminophenyl groups were prepared by the reduction of the corresponding nitro-compounds. Acylamino-*s*-triazines have been found to be formed when an excess of acyl chloride or anhydride is used.

The amino-*s*-triazines bearing extra amino groups attached to the side chain are interesting since these compounds can serve as possible intermediates for the synthesis of new triazine derivatives.

In this paper the preparation of amino-*s*-triazines bearing phenyl substituents with nitro or amino groups will be described.

In general,[1] amino-*s*-triazine derivatives have been prepared by the reaction of appropriate biguanide derivatives with acyl chloride, anhydride, or ester, or from appropriate dicyanodiamide derivatives with nitrile in the presence of strong alkali. These two methods were used in the present work.

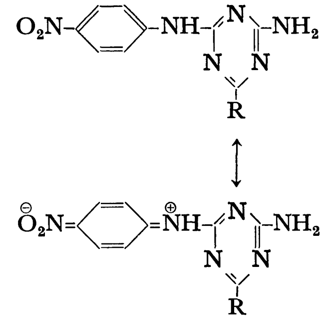


Results and Discussion

The synthetic results are summed up in Table 1. The reaction of biguanide derivatives with methyl formate proceeded rapidly, but the corresponding reaction with methyl acetate was slow and gave poor yields of the desired materials.[2] With methyl benzoate, the reaction was found to proceed even more slowly than in the cases of methyl acetate and methyl formate. Therefore, acyl chloride or acid anhydride was used to obtain *s*-triazine from biguanide derivatives. In the present work, when an excess of acetic anhydride or benzoyl chloride was used as the acylation reagent, it was found that acylated amino-*s*-triazines were obtained as the by-products. On the other hand, when excesses of biguanide derivatives were used, it was found that no acylamino-*s*-triazines were obtained.

UV Spectra. The UV spectra of *s*-triazines have been reported by several investigators.[3-7] *s*-Triazines without phenyl or anilino groups attached directly to the triazine ring have ε values of around 10^3.[3]

The UV spectral data of *s*-triazines described in Table 1 are summed up in Table 2. These triazines have ε values of about 10^4. It can be seen from Table 2 that, while it has been known that 2,4-diamino-6-phenyl-*s*-triazine and 2-amino-4-anilino-6-phenyl-*s*-triazine have their absorption maxima at 245 mμ[8] ($\varepsilon=22.2\times10^3$) and at 260 mμ[8] ($\varepsilon=43.4\times10^3$), *s*-triazines with *p*-nitroanilino substituents and those with *p*-aminophenyl substituents were found to reveal their absorption maxima at 344—352 mμ and at 315—320 mμ respectively. The comparisons of the absorption maxima of 4- or 6-substituted-*s*-triazines are described in Table 3. That is, the introduction of a nitro group into the *para* position of a 4-anilino-substituent, or that of an amino group into the *para* position of a 6-phenyl-substituent, of the 2-amino-*s*-triazine ring results in a large bathochromic shift, as expected. This is due to the resonance interaction involving contributions from the following structures:



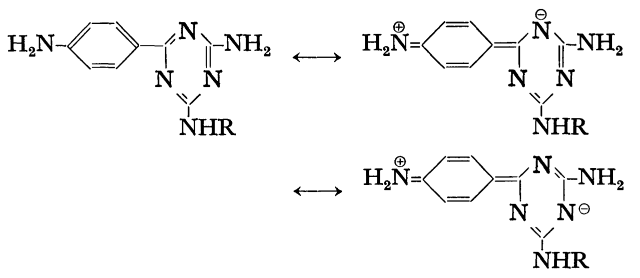


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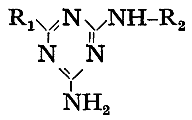
TABLE 1. *s*-TRIAZINE DERIVATIVES



Compounds	R_1	R_2	Method[a]	Yield (%)	mp[b] (lit.) (°C)	Found (Calcd) C(%)	H(%)	N(%)
1	$C_6H_4NO_2$(*p*)	H	A	89	322 (330—331[c])			
2	$C_6H_4NO_2$(*m*)	H	A	82	240—241 (243—245[d])			
3	H	$C_6H_4NO_2$(*p*)	B	48	335 (325[e], 347[f])	47.80 (46.55	3.23 3.47	37.08 36.19; $C_9H_8N_6O_2$)
4	H	$C_6H_4NO_2$(*m*)	B	43	226—227	46.17 (46.55	3.43 3.47	35.66 36.19; $C_9H_8N_6O_2$)
5	CH_3	$C_6H_4NO_2$(*p*)	C	90	269	49.07 (48.78	4.02 4.09	34.10 34.13; $C_{10}H_{10}N_6O_2$)
6	CH_3	$C_6H_4NO_2$(*m*)	C	55	224—225	48.94 (48.78	3.80 4.09	34.62 34.13; $C_{10}H_{10}N_6O_2$)
7	C_6H_5	$C_6H_4NO_2$(*p*)	C A	75 58	230—231	58.68 (58.44	3.66 3.92	26.39 27.26; $C_{15}H_{12}N_6O_2$)
8	C_6H_5	$C_6H_4NO_2$(*m*)	C	90	213—215	59.33 (58.44	3.57 3.92	27.27 27.26; $C_{15}H_{12}N_6O_2$)
9	$C_6H_4NO_2$(*p*)	C_6H_5	C	77	223—224	58.25 (58.44	4.13 3.92	27.43 27.26; $C_{15}H_{12}N_6O_2$)
10	$C_6H_4NO_2$(*m*)	C_6H_5	C	93	205—206 (212—213[g])	57.99 (58.44	4.32 3.92	27.11 27.26; $C_{15}H_{12}N_6O_2$)
11	$C_6H_4NO_2$(*p*)	$C_6H_4NO_2$(*p*)	C	98	364	50.72 (51.00	2.92 3.14	26.78 27.75; $C_{15}H_{11}N_7O_4$)
12	$C_6H_4NO_2$(*p*)	$C_6H_4NO_2$(*m*)	C	69	266	51.83 (51.00	3.30 3.14	26.76 27.75; $C_{15}H_{11}N_7O_4$)
13	$C_6H_4NO_2$(*m*)	$C_6H_4NO_2$(*p*)	C A	89 41	278	50.28 (51.00	3.87 3.14	26.86 27.75; $C_{15}H_{11}N_7O_4$)
14	$C_6H_4NO_2$(*m*)	$C_6H_4NO_2$(*m*)	C	82	277	51.29 (51.00	3.08 3.14	26.92 27.75; $C_{15}H_{11}N_7O_4$)
15	$C_6H_3(NO_2)_2$-3,5	C_6H_5	C	77	297	51.43 (51.00	3.43 3.14	27.21 27.75; $C_{15}H_{11}N_7O_4$)
16	$C_6H_3(NO_2)_2$-3,5	H	C	90	361	39.52 (39.00	2.65 2.55	34.74 35.37; $C_9H_7N_7O_4$)
17	$C_6H_4NH_2$(*p*)	H	A	56	196—197 (206[d])			
18	$C_6H_4NH_2$(*m*)	H	A	85	206—208 (212—213[d])			
19	$CH_2C_6H_4NH_2$(*p*)	H	A	56	255—256.5	55.84 (55.54	5.17 5.60	39.56 38.86; $C_{10}H_{12}N_6$)
20	H	$C_6H_4NH_2$(*p*)	D	54	288	53.50 (53.46	4.80 4.98	42.28 41.56; $C_9H_{10}N_6$)
21	H	$C_6H_4NH_2$(*m*)	D	78	215—216	54.24 (53.46	4.76 4.98	42.80 41.56; $C_9H_{10}N_6$)
22	CH_3	$C_6H_4NH_2$(*p*)	D	90	246—247	55.14 (55.54	5.16 5.59	38.05 38.86; $C_{10}H_{12}N_6$)
23	CH_3	$C_6H_4NH_2$(*m*)	D	90	176—177	55.89 (55.54	5.66 5.59	38.45 38.86; $C_{10}H_{12}N_6$)
24	C_6H_5	$C_6H_4NH_2$(*p*)	D	84	195.5—196	65.37 (64.75	4.77 5.03	30.39 30.22; $C_{15}H_{14}N_6$)
25	C_6H_5	$C_6H_4NH_2$(*m*)	D	69	190—191	64.99 (64.75	4.83 5.03	30.79 30.22; $C_{15}H_{14}N_6$)
26	$C_6H_4NH_2$(*p*)	C_6H_5	D	78	203—204	64.91 (64.75	5.75 5.03	29.34 30.22; $C_{15}H_{14}N_6$)
27	$C_6H_4NH_2$(*m*)	C_6H_5	D	67	162—163	65.08 (64.75	4.81 5.03	30.72 30.22; $C_{15}H_{14}N_6$)

a) A, from dicyanodiamide and nitrile; B, from biguanide and ester; C, from biguanide and acyl chloride or anhydride; D, reduction of the corresponding nitro-*s*-triazine. b) The mp above 250°C was measured by DSC. c) V. A. Titkov and I. D. Pletnev, *Zh. Obshch. Khim.*, **33**, 1983 (1963); *Chem. Abstr.*, **59**, 15408f (1963). d) Ref. 1. e) J. T. Thurston and D. W. Kaiser, US 2493703 (1950); *Chem. Abstr.*, **44**, 2574d (1950) f) I. Groth, Brit. 794398 (1958); *Chem. Abstr.*, **53**, 420e (1959). g) Ref. 5.

Table 2. UV Spectra of *s*-triazines

Compounds	$\lambda_{max}^{(m\mu)}$ ($\varepsilon \times 10^{-3}$)	solvent[a]
1	280 (19.5)	MCS
2	232 (22.8), 270s(7.7)	MCS
3	344 (19.1)	MCS
4	261 (21.4), 274 (21.6), 340s(1.4)	MCS
5	345 (15.4)	MCS
6	260s(25.1), 273 (27.0), 340 (1.6)	MCS
7	248 (28.9), 348 (23.8)	Et
8	261 (41.6)	Et
9	272 (33.0), 290s(29.6)	MCS
10	245s(27.7), 259 (34.4), 310s(6.6)	MCS[b]
11	279 (17.0), 352 (20.0)	MCS
12	268 (26.3), 275s(25.7)	MCS
13	245 (31.6), 350 (20.0)	MCS
14	245s(35.6), 258 (41.3)	MCS
15	245s(27.3), 257 (31.2)	MCS
16	243 (23.4), 300s(3.1)	MCS
17	315 (23.7)	Et
18	233 (32.7), 263s(12.0), 328 (2.4)	Et
19	242 (13.7), 290s(2.5)	Et
20	245s (9.6), 282 (14.3)	MCS
21	245 (20.0), 270s(13.9), 300s(7.6)	MCS
22	245s(9.5), 283 (16.3)	MCS
23	244 (19.4), 270s(13.7), 300s(6.7)	MCS
24	255 (26.9), 265s(26.5)	Et
25	227s(28.5), 247 (31.8), 258s(30.0) 300s(8.0)	Et
26	257 (16.7), 316 (25.4)	Et
27	233 (28.1), 258 (31.0), 310s(9.2)	Et
28[c]	316 (39.7)	MCS
29[c]	320 (39.7)	MCS
30[c]	237 (53.9), 256s(35.4), 306 (10.7)	MCS

a) Solvent: MCS, methyl cellosolve: Et, ethanol.

b) Shapiro has reported 255 mμ (ε, 39.7×10^3) in methanol (Ref. 5).

c) Reported previously (Y. Yuki, S. Sakurai, T. Kakurai, and T. Noguchi, This Bulletin, **43**, 2130 (1970)).
28: 2-amino-4-*p*-aminoanilino-6-*p*-aminophenyl-*s*-triazine,
29: 2-amino-4-*m*-aminoanilino-6-*p*-aminophenyl-*s*-triazine,
30: 2-amino-4-*m*-aminoanilino-6-*m*-aminophenyl-*s*-triazine.

Table 3. Comparisons of the ultraviolet absorption maxima of substituted *s*-triazines

4 or 6-Substituent	λ_{max}(mμ)	Compound
p-Nitroanilino	344—352	3,5,7,11, and 13
m-Nitroanilino	258—274	4,6,8,12, and 14
p-Nitrophenyl	275—290	1,9,11, and 12
m-Nitrophenyl	232—259	1,10,13, and 14
p-Aminoanilino	265—283	20,22, and 24
m-Aminoanilino	258—270	21,23, and 25
p-Aminophenyl	315—320	17,26,28, and 29
m-Aminophenyl	233—237 256—265	18,27, and 30

On the other hand, the introduction of a nitro or amino group into the *meta* position of a phenyl or anilino group attached to the 2-amino-*s*-triazine ring leads to little or no bathochromic effect, as is shown in Table 3.

Experimental

All the melting points were uncorrected, and mps above 250°C were measured by means of a Differential Scanning Calorimeter (DSC). MCS denotes methyl cellosolve.

*2-Amino-4-*m*-nitroanilino-*s*-triazine (4).* This product was predpared by the procedure detailed by Overberger and Shapiro.[9] When *m*-nitrophenylbiguanide (*m*-NPB) was treated with methyl formate in methanol, it gave **4** (43%). The removal of the solvent from the filtrate gave a residue which was then recrystallized from a methanol-ethanol mixture to afford formic acid salt of *m*-NPB, mp 186—187°C (decomp).

Found: C, 40.25; H, 4.31; N, 30.80%. Calcd for $C_9H_{12}N_6O_4$: C, 40.30; H, 4.51; N, 31.33%.

*2-Amino-4-*p*-nitroanilino-6-methyl-*s*-triazine (5).* Into a solution of 8.9 g (40 mmol) of *p*-nitrophenylbiguanide (*p*-NPB) in 100 m*l* of acetone, we slowly stirred 2.0 g (20 mmol) of acetic anhydride with ice-cooling. After 1 hr, the precipitate (8.73 g) was separated and washed with hot water to yield 3.0 g of the product, which was then treated with methanol-MCS mixture to give 0.2 g of insoluble, crude 2-acetamido-4-*p*-nitroanilino-6-methyl-*s*-triazine (*31*), mp 275°C. This was recrystallized from DMF, mp 286°C. The filtrates (acetone and methanol-MCS) were combined, and from this there were obtained 4.5 g (90%) of **5**, recrystallized from MCS, mp 269°C.

*2-Acetamido-4-*p*-nitroanilino-6-methyl-*s*-triazine (31).* To a solution of 1.23 g (5 mmol) of **5** suspended in 10 m*l* of dioxane, we added 3 m*l* of acetic anhydride, and then the solution was refluxed for 5 hr. We thus obtained 1.10 g (76%) of the product, which was subsequently recrystallized from DMF, mp 287°C.

Found: C, 50.03; H, 3.92; N, 28.84%. Calcd for $C_{12}H_{12}N_6O_3$: C, 50.00; H, 4.20; N, 29.15%. UV: λ_{max}^{MCS}mμ ($\varepsilon \times 10^{-4}$) 234(2.64) and 343(2.03).

*2-Amino-4-*m*-nitroanilino-6-methyl-*s*-triazine (6).* This compound was previously prepared by the reaction of *m*-NPB with methyl acetate.[2] In the present work the reaction of *m*-NPB with acetic anhydride was carried out as above. Acetic anhydride (1.02 g) and 4.44 g of *m*-NPB gave 1.34 g (55%) of **6**, mp 224—225°C, and 0.30 g of 2-acetamido-4-*m*-nitroanilino-6-methyl-*s*-triazine, recrystallized from DMF mp 259°C.

Found: C, 49.66; H, 4.04; N, 29.56%. Calcd for $C_{12}H_{12}\cdot N_6O_3$: C, 50.00; H, 4.20; N, 29.15%. UV: λ_{max}^{MCS}mμ ($\varepsilon \times 10^{-4}$), 231(2.13) and 271(3.00).

*2-Amino-4-*p*-nitroanilino-6-phenyl-*s*-triazine (7).* a) When *p*-NPB (6.66 g, 30 mmol) was treated with 4.20 g (30 mmol) of benzoyl chloride and 2.0 g (36 mmol) of sodium hydroxide, it gave 2.95 g (32%) of **7** and 1.45 g of 2-benzamido-4-*p*-nitroanilino-6-phenyl-*s*-triazine, which was recrystallized from DMF, mp 265°C.

Found: C, 63.20; H, 3.73; N, 20.64%. Calcd for $C_{22}H_{16}N_6O_3$: C, 64.07; H, 3.91; N, 20.38%. UV: λ_{max}^{MCS}mμ ($\varepsilon \times 10^{-4}$) 256(2.98) and 347(1.86).

b) *p*-NPB (4.70 g, 21 mmol) was treated with 1.40 g (10 mmol) of benzoyl chloride in acetone to give 2.30 g (75%) of the product, mp 228—229°C.

Found: C, 56.13; H, 3.94; N, 26.28%. Calcd for $C_{15}H_{12}N_6O_2\cdot 1/2\ H_2O$: C, 56.78; H, 4.13; N, 26.49%.

c) *p*-Nitrophenyldicyanodiamide (*p*-NPD) (1.0 g, 5 mmol) was treated with 1 m*l* of benzonitrile and 0.1 g of sodium

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[9] C. G. Overberger and S. L. Shapiro, *J. Amer. Chem. Soc.*, **76**, 93 (1954).

hydroxide in MCS under reflux for 5 hr. There was thus obtained 0.89 g, (58%) of **7**, which was recrystallized from MCS-water, mp 230—231°C.

Found: C, 58.15; H, 3.63; N, 26.73%. Calcd for $C_{15}H_{12}N_6O_2$: C, 58.44; H, 3.92; N, 27.26%.

*2-Amino-4-*m*-nitroanilino-6-phenyl-*s*-triazine (8).* a) *m*-NPB (6.66 g, 30 mmol) was treated with 4.60 g (33 mmol) of benzoyl chloride and 2.0 g (36 mmol) of sodium hydroxide give to 5.02 g (54%) of **8** and 2.76 g of 2-benzamido-4-*m*-nitroanilino-6-phenyl-*s*-triazine, which was recrystallized from DMF, mp 266—267°C.

Found: C, 63.86; H, 3.66; N, 20.53%. Calcd for $C_{22}H_{16}N_6O_3$: C, 64.07; H, 3.91; N, 20.38%. UV: $\lambda_{\text{max}}^{\text{MCS}}$ mμ ($\varepsilon \times 10^{-4}$) 261(3.77).

b) Into 4.50 g (20.3 mmol) of *m*-NPB dissolved in 50 m*l* of acetone, we stirred, drop by drop, 1.27 g (9.1 mmol) of benzoyl chloride in 50 m*l* of acetone with ice-cooling over a half-hour period. As the precipitate, 2.03 g of hydrochloride of *m*-NPB were thus obtained. The filtrate was condensed and poured into water. A yellow product, 2.52 g (90%) of **8**, was obtained.

*2-Amino-4-anilino-6-*p*-nitrophenyl-*s*-triazine (9).* Phenylbiguanide (30 g, 0.17 mol) was treated with 25 g (0.13 mol) of *p*-nitrobenzoyl chloride. The precipitate was filtered to yield 27.5 g of the pure product.

Found: C, 57.72; H, 4.06; N, 27.09%. Calcd for $C_{15}H_{12}N_6O_2$: C, 58.44; H, 3.89; N, 27.27%.

From the filtrate we obtained 4.5 g of **9** and 4.0 g of *p*-nitrobenzoic acid. The total yield of the product was 32 g (77%), recrystallized from a water-MCS mixture, mp 223-224°C.

*2-Amino-4-*p*-nitroanilino-6-*m*-nitrophenyl-*s*-triazine (13).*

a) *p*-NPB (15 g, 68 mmol) was treated with 9.3 g (50 mmol) of *m*-nitrobenzoyl chloride. We thus obtained 15.7 g (87%) of the product, mp 275°C.

b) The reaction of *p*-NPD (2.15 g 10.5 mmol) with *m*-nitrobenzonitrile (1.56 g, 11 mmol) was carried out using 0.2 g of potassium hydroxide in MCS under reflux for 5 hr; it gave 1.52 g (41%) of **13**, which was recrystallized from a DMF-MCS mixture, mp 278°C.

*2-Amino-4-*m*-aminoanilino-*s*-triazine (21).* Tin (0.6 g) and 0.55 g (2.36 mmol) of **4** were suspended in 10 m*l* of ethanol containing 3.0 m*l* of 12 N hydrochloric acid, after which the solution was refluxed for 1 hr. On cooling, the precipitate was filtered and dissolved in hot water. A further amount of sodium hydroxide was added. There was thus obtained 0.37 g of a product (78%) which was recrystallized from methanol, mp 215—216°C.

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