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3,6-BIS-SUBSTITUTED *s*-TETRAZINES

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The preparation of various substituted *s*-tetrazines is described.

No nitro substituted *s*-tetrazines have been reported in the literature, but substituents in the 3,6 and 1,4 positions which carry nitro groups are known. These are 3,6-bis(4-nitrophenyl)-[1]; 3,6-bis(3-nitrophenyl)-[2]; 1,4-bis(4-nitrophenyl)-1,4-dihydro-[3]; 1,4-bis(2-nitrophenyl)-1,4-dihydro-; 1,4-bis(2-methoxy-5-nitrophenyl)-1,4-dihydro; and 1,4-bis(2-methoxy-4-nitrophenyl)-1,4-dihydro-*s*-tetrazines.[4]

Generally, *s*-tetrazines are prepared from a dihydro derivative by mild oxidation with dilute nitric acid, 3% hydrogen peroxide, bromine or ferric chloride. In many cases the dihydro-*s*-tetrazine, resulting from a cyclization reaction, is oxidized so readily that isolation and purification is difficult. Such dihydro-*s*-tetrazines are thus oxidized to the corresponding fully aromatic compounds without isolation.

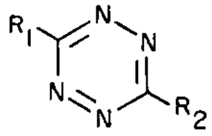
Following the procedure of Müller and Herrdegen[5], 3,6-diphenyl-*s*-tetrazine (Ia) was prepared and successfully hydrolyzed to benzoic acid. In a similar manner, 3,6-bis(4-methoxyphenyl)-*s*-tetrazine (Ib) and 3,6-bis(3-hydroxyphenyl)-*s*-tetrazine (Id) were prepared. Nitration of 3,6-bis(4-methoxyphenyl)-*s*-tetrazine[6] gave 3,6-bis(3-nitro-4-methoxyphenyl)-*s*-tetrazine (Ic).

For the preparation of 3,6-bis(3-aminophenyl)-*s*-tetrazine (Ie) and 3,6-bis(3-acetylaminophenyl)-*s*-tetrazine (If), the procedure of Junghahn and Bunimowicz[7] was followed. Nitration of the acetyl derivative gave 3,6-bis(3-acetylamino-4-nitrophenyl)-*s*-tetrazine (Ig).

Preparation of 3,6-bis(3-nitrophenyl)-*s*-tetrazine (Ih) was accomplished by a variation of Pinner's method[8]. This procedure with ethyl 3,5-dinitrophenylformimidate hydrochloride proceeded only as far as the imino hydrazide instead of the expected 3,6-bis(3,5-dinitrophenyl)-*s*-tetrazine. The imino hydrazide formed a derivative with picryl chloride, thus confirming the structure. Adaptation of the van Es method[9] to 2,4,6-trinitrobenzaldehyde gave picryl cyanide; however, attempts to form the corresponding imino ester failed.

The method of Pulvermacher[10] was used for the preparation of 4-phenylthiosemicarbazide, which was converted to 1,2-dihydro-3,6-dianilino-*s*-tetrazine (IIa) according to the method of Stolle and Gaertner[11]. Treatment of this 1,2-dihydro compound with an excess of acetic anhydride produced the corresponding tetraacetyl derivatives (IIb).

The procedure of Freund and Paradies[12] was followed for the preparation of *S*-methylthiosemicarbazide hydroiodide, which was converted to 3,6-diamino-*s*-tetrazine (Ij) according to the method of Lin, Lieber and Horwitz[13]. All attempts to convert this diamine to 3,6-dinitro-*s*-tetrazine also failed. Concentrated nitric acid readily converted 3,6-diamino-*s*-tetrazine to the dinitrate salt (Ik) at room temperature. Attempts to convert this salt to 3,6-dinitroamino-*s*-tetrazine also failed. The 3,6-diamino-*s*-tetrazine reacted with an equal molar amount of picryl fluoride in dimethylformamide at room temperature to yield 3-amino-6-picrylamino-*s*-tetrazine (Il). This same diamine with an excess of picryl fluoride gave 3,6-bis(picrylamino)-*s*-tetrazine (Ii).



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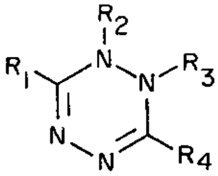

II

$R_1 = R_2$
a) phenyl
b) 4-methoxyphenyl
c) 3-nitro-4-methoxyphenyl
d) 3-hydroxyphenyl
e) 3-aminophenyl
f) 3-acetylaminophenyl
g) 3-acetylamino-4-nitrophenyl
h) 3-nitrophenyl
i) picrylamino
j) amino
k) ammonium nitrate
$R_1 \neq R_2$
l) R_1 = amino; R_2 = picrylamino

$R_1 = R_4$
a) anilino
b) *N*-acetylanilino
$R_2 = R_3$
hydrogen
acetyl

EXPERIMENTAL SECTION

3,6-Diphenyl-*s*-tetrazine (Ia).

To 10 g (0.084 mol) of benzonitrile was added a 15% excess of 95% hydrazine; this solution was heated on the steam bath for 72 hr. The resulting orange-yellow solid was broken up, washed with water, air dried, ground to a fine powder and added to 100 ml of 10% acetic acid. To this solution, small portions of sodium nitrite were added, while warming on the steam bath for 1 hr. The red solid thus produced was collected, washed with water and recrystallized from ethanol, mp 194-195° (lit.[5] mp 195°).

Anal. Calcd. for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 72.02; H, 4.34; N, 24.18.

Hydrolytic Cleavage of Ia.

To 40 ml of concentrated sulfuric acid and 25 ml of water was added 0.5 g (2.14 mmol) of Ia. This mixture was refluxed for 2 hr, cooled, diluted with water and chilled to yield a white solid, mp 121°. A mixed melting point determination with benzoic acid gave no depression.

3,6-Bis(4-methoxyphenyl)-*s*-tetrazine (Ib).

A solution of 5 g (0.0427 mmol) of *p*-anisonitrile in 15 ml of 95% hydrazine was heated on the steam bath for 26 hr. The resulting orange solid was broken up, washed with water and air dried. The solid was then ground to a fine powder and added to 100 ml of 10% acetic acid. This solution was warmed on the steam bath for 1 hr, during which time small amounts of sodium nitrite were added with stirring. After cooling, the red solid was collected, washed with water and recrystallized from ethanol as fine red needles, mp 242-243° (lit.[6] mp 242°).

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.29; H, 4.79; N, 19.04. Found: C, 65.04; H, 4.83; N, 19.38.

3,6-Bis(3-hydroxyphenyl)-*s*-tetrazine (Id).

A mixture of 2 g (16.8 mmol) of *m*-hydroxybenzonitrile and 1 ml of 95% hydrazine was heated at 40-50° for 12 hr and cooled. The resulting yellow-orange solid was broken up, slurried with water, collected by filtration and air dried. This solid was ground to a fine powder, added to 75 ml of 10% acetic acid, warmed on a steam bath and treated with small portions of sodium nitrite over a period of 1 hr. The mixture was then chilled and the resulting red solid was filtered, washed with water and air dried. It was recrystallized from ethanol-water, mp 304-305.5° (21% yield); ir: cm^{-1} 3400 (vb), 1600 (s), 1455 (s), 1400 (s), 1345 (s), 1236 (s), 1175 (b), 1105 (s), 1086 (s), 1057 (m), 994 (m), 930 (s), 893 (s), 879 (s), 800 (s), 689 (s), 645 (s), 536 (w), 510 (m).

Anal. Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.22; H, 3.91; N, 21.11.

3,6-Bis(3-nitro-4-methoxyphenyl)-*s*-tetrazine (Ic).

To 5 ml of concentrated sulfuric acid at 5°, in small portions, 0.5 g (1.7 mmol) of 3,6-bis(*p*-methoxyphenyl)-*s*-tetrazine were added. To this solution, 2 ml of concentrated nitric acid was added dropwise. After standing at room temperature for 1 hr, the mixture was then poured over ice, and the resulting red solid was collected, washed with water and dried. This solid was treated with boiling ethanol, and the insoluble portion (major product) was recrystallized repeatedly from benzene-ethanol as fine red-violet needles, mp 241-243° (23% yield); ir: cm^{-1} 3450 (b), 3090 (m), 2950 (w), 2870 (sh), 2830 (sh), 1625 (s), 1545 (vs), 1448 (m), 1415 (w), 1395 (s), 1355 (s), 1310 (w), 1270 (s), 1210 (w), 1160 (m), 1103 (m), 1065 (s), 972 (s), 912 (s), 892 (m), 802 (m), 782 (s), 750 (w), 732 (w), 720 (s), 656 (m), 610 (m).

Anal. Calcd. for $C_{16}H_{12}N_6O_6$: C, 40.51; H, 2.12; N, 23.63. Found: C, 40.96; H, 2.40; N, 23.92.

3,6-Bis(3-aminophenyl)-*s*-tetrazine (Ic).

A solution of 2 g (13.5 mmol) of *m*-nitrobenzonitrile in 100 ml of ethanol containing 20 ml of yellow ammonium sulfide was heated (sealed in a pop bottle) on a steam bath for 22 hr. The mixture was then cooled and filtered, and the solvent was removed under reduced pressure. The resulting residue was heated with a small amount of water and filtered. To the filtrate, 2.5 ml of 95% hydrazine were added and the resulting mixture was heated on the steam bath for 1.5 hr. The orange-red solid was collected, washed with water and warmed with 50 ml of 3% hydrogen peroxide to yield a red solid, which was collected and dried (18% yield), mp 263-264° (lit.[7] 266-267°).

3,6-Bis(3-acetylaminophenyl)-*s*-tetrazine (If).

To 5 ml of concentrated sulfuric acid, 0.5 g (1.44 mmol) of 3,6-bis(*m*-acetylaminophenyl)-*s*-tetrazine was added at 5°. To this solution kept at 5°, 5 ml of concentrated nitric acid was then added dropwise (stirring) at a rate such that the temperature was maintained at 10° or less. The resulting red-pink solid was collected, washed with water and recrystallized from DMF, mp 277° dec (63% yield); ir: cm^{-1} 3300 (s), 3100 (m), 1690 (s), 1620 (m), 1590 (s), 1555 (s), 1505 (s), 1445 (s), 1370 (s), 1349 (s), 1325 (s), 1255 (b), 1160 (w), 1130 (w), 1110 (w), 1082 (m), 1047 (m), 1010 (m), 967 (w), 898 (m), 841 (s), 758 (s), 722 (w), 700 (m), 678 (w), 646 (w), 586 (w), 542 (w), 459 (m).

Anal. Calcd. for $C_{18}H_{14}N_8O_6$: C, 49.33; H, 3.22; N, 25.55. Found: C, 48.98; H, 3.24; N, 25.25.

Ethyl *m*-Nitrophenylformimidate Hydrochloride.

A slurry of 14.8 g (0.10 mol) of *m*-nitrobenzonitrile in 300 ml of absolute ethanol and 200 ml of absolute ether was treated with dry hydrogen chloride gas for 1.5 hr with stirring and external cooling in an ice-bath. The rate of addition of hydrogen chloride gas was regulated to maintain a temperature of 5-10°. After the addition of hydrogen chloride, the suction flask was stoppered and the side arm equipped with a calcium chloride charged drying tube; the flask was allowed to stand at room temperature overnight. The resulting white needles were collected, mp 140-142° (lit.[2] mp 142°) (41% yield).

In an identical manner, ethyl 3,5-dinitrophenylformimidate hydrochloride was prepared, mp 184-185°.

3,6-Bis(3-nitrophenyl)-*s*-tetrazine (Ih).

A solution of 5 g (23.9 mmol) of ethyl *m*-nitrophenylformimidate hydrochloride in 100 ml of absolute ethanol containing 2.1 ml of 95% hydrazine was allowed to stand at room temperature for 3 days. The resulting solid was collected and the filtrate taken to dryness to give additional crude product. After drying, the product was finely ground, slurried in 10% acetic acid and treated with sodium nitrite. The resulting red-purple solid was collected, washed with water and recrystallized from ethanol-water, mp 199-201° (22% yield); ir: cm^{-1} 3440 (b), 3095 (m), 2915 (w), 2860 (w), 1620 (s), 1535 (vs), 1495 (s), 1420 (m), 1395 (s), 1352 (vs), 1300 (m), 1276 (w), 1240 (w), 1168 (w), 1130 (m), 1110 (w), 1080 (m), 1055 (m), 1000 (w), 968 (w), 928 (m), 918 (m), 880 (m), 810 (m), 758 (s), 740 (s), 719 (s), 701 (w), 681 (s), 660 (w), 600 (s).

Anal. Calcd. for $C_{14}H_8N_6O_4$: C, 51.85; H, 2.49. Found: C, 52.49; H, 2.64

3,5-Dinitrophenylformiminohydrazide.

A solution of 5 g (20.8 mmol) of ethyl 3,5-dinitrophenylformimidate hydrochloride in 100 ml of absolute ethanol and 1.7 ml of 95% hydrazine was allowed to stand at room temperature for 8 days. The resulting dark brown solid was collected and the mother liquor was evaporated to dryness under reduced pressure to leave a dark solid. Both solids had the same melting points and were therefore combined and recrystallized from ethanol, mp 178-180°; ir: cm^{-1} 3460 (s), 3370 (s), 3100 (s), 1645 (s), 1540 (s), 1520 (s), 1470 (m), 1420 (w), 1390 (m), 1350 (vs), 1176 (w), 1105 (m), 1071 (s), 1025 (w), 995 (w), 944 (w), 920 (s), 909 (s), 788 (b), 730 (s), 690 (s), 520 (b), 486 (m).

Anal. Calcd. for $C_7H_7N_5O_4$: C, 37.34; H, 3.13; N, 31.11. Found: C, 37.48; H, 3.26; N, 31.45.

This compound was allowed to react with picryl chloride in refluxing absolute ethanol to yield red-gold plates, mp 245° dec. It was recrystallized from ethanol to give *N*-picryl-3,5-dinitrophenylformiminohydrazide; ir: cm^{-1} 3495 (m), 3395 (s), 3255 (m), 3090 (s), 1650 (s), 1620 (vs), 1590 (s), 1545 (vs), 1440 (s), 1400 (w), 1350 (vs), 1300 (s), 1178 (s), 1118 (m), 1090 (m), 937 (w), 921 (m), 822 (w), 807 (m), 765 (w), 757 (w), 730 (s), 710 (w).

Anal. Calcd. for $C_{13}H_8N_8O_{10}$: C, 35.79; H, 1.85; N, 25.69. Found: C, 35.91; H, 2.29; N, 25.80.

2,4,6-Trinitrobenzonitrile (Picryl Cyanide).

A mixture of 1 g (4.15 mmol) of 2,4,6-trinitrobenzaldehyde, 0.332 g of hydroxylamine hydrochloride, 0.67 g of sodium formate and 15 ml of 97-98% formic acid was refluxed for 1 hr. The reaction mixture was then cooled to room temperature and added slowly with stirring to 100 ml of water. The resulting off-white solid was collected, washed with water and recrystallized from water, mp 133.5-134.5° (0.55 g, 56% yield); ir: cm^{-1} 3100 (s), 3060 (w), 3005 (w), 2890 (w), 1855 (w), 1710 (w), 1640 (s), 1620 (s), 1575 (vs), 1550 (vs), 1460 (w), 1405 (w), 1365 (vs), 1355 (vs), 1350 (vs), 1206 (w), 1188 (w), 1165 (w), 1080 (s), 935 (s), 928 (s), 920 (s), 825 (w), 775 (m), 739 (s), 728 (s), 691 (m), 680 (m), 639 (m), 558 (w), 533 (w), 503 (w).

Anal. Calcd. for $C_7H_2N_4O_6$: C, 35.31; H, 0.85; N, 23.53. Found: C, 34.90; H, 1.16; N, 23.34.

1,2-Dihydro-3,6-dianilino-*s*-tetrazine (IIa).

A mixture of 3.4 g (20.4 mmol) of 4-phenylthiosemicarbazide and 20 g of yellow lead oxide was refluxed in 90 ml of absolute ethanol for 4 hr with stirring. The reaction mixture was then filtered hot, and the red-orange alcoholic solution was evaporated under reduced pressure. The resulting residue was recrystallized at once from ethanol (Norit) to give white needles, which turned pink on exposure to air (yield, 22%) mp 277° (lit.[11] mp 275°).

Acylation of IIa.

A mixture of 0.13 g (0.49 mmol) of IIa and 0.13 g of sodium acetate in 15 ml of acetic anhydride was boiled for 0.25 hr and poured into ice water with stirring. The stirring was continued until all of the excess acetic anhydride was decomposed; the reaction mixture was then allowed to stand 4 hr at room temperature. The resulting off-white solid was collected (0.15 g). It was recrystallized from ethanol-water, mp 196-197°; ir: cm^{-1} 3440 (b), 3055 (w), 2930 (w), 1955 (w), 1750 (s), 1710 (s), 1590 (m), 1545 (s), 1525 (s), 1495 (s), 1452 (s), 1425 (m), 1375 (s), 1352 (s), 1295 (s), 1265 (s), 1236 (s), 1218 (s), 1194 (s), 1168 (w), 1072 (w), 1030 (m), 1015 (m), 1000 (m), 937 (w), 920 (w), 763 (m), 711 (m), 696 (s), 660 (s), 640 (w), 617 (w), 592 (s), 571 (w), 550 (m), 520 (w), 515 (w).

Anal. Calcd. for $C_{22}H_{22}N_6O_4$: C, 60.87; H, 5.10, N, 19.30. Found: C, 60.99; H, 5.17; N, 19.64.

S-Methylthiosemicarbazide Hydroiodide.

A solution of 5 g (55 mmol) of pure thiosemicarbazide and 7.8 g of methyl iodide in 170 ml of absolute ethanol was refluxed for 1 hr. The solvent was removed under reduced pressure and the residue recrystallized from ethanol-ether, mp 139-141° (lit.[12] mp 140°) (85 yield).

3,6-Diamino-*s*-tetrazine (Ij).

To 0.92 g (3.94 mmol) of *S*-methylthiosemicarbazide hydroiodide in 3 ml of water, enough 1*N* sodium hydroxide solution (1.1 ml) was added to achieve *p*H 8. An additional 0.8 ml of water was then added to the solution and pure oxygen was bubbled slowly into it with stirring for 22 hr. The resulting red solid was collected, washed with cold water and recrystallized from water, mp 360° dec) (16% yield).

3,6-Diamino-*s*-tetrazine Dinitrate (Ik).

To 0.2 g (1.786 mmol) of solid Ij, concentrated nitric acid was added dropwise until dissolution was complete. The solution was then allowed to stand at room temperature for 2 hr. The resulting yellow-orange crystalline product was collected, washed with cold water and air dried, mp 164° dec. This product may be recrystallized from water, but due to its explosive nature an elemental analysis was not attempted. Treatment of this compound with dilute sodium hydroxide solution yielded the starting material.

3-Amino-6-picrylamino-*s*-tetrazine (Il).

Compound Ij (0.27 g, 0.0025 mol) and picryl fluoride (0.60 g, 0.0025 mol) were dissolved in DMF (10 ml) and the resulting solution was stirred at 25° for 16 hr. The solution was then diluted with water to precipitate the product, which was collected by filtration, washed with water and dried. Recrystallization from acetone-ethanol provided 0.67 g (83%) of Il, mp 234° dec; nmr (DMSO-d_6): δ 9.10 (2H, picryl protons), 7.80 (2H) and 10.83 (1H) (amino protons).

Anal. Calcd. for $C_8H_5N_9O_6$: C, 29.73; H, 1.56; N, 39.01. Found: C, 29.95; H, 1.56; N, 39.28.

3,6-Bis(picrylamino)-*s*-tetrazine (Ii).

A solution of Ij (0.27 g, 0.0025 mol) and picryl fluoride (2.31 g, 0.01 mol) in DMF (15 ml) was allowed to stir at 25° for 7 days. The product precipitated when the solution was diluted with water; it was filtered, washed with water and dried. Recrystallization from acetone-ethanol gave 0.88 g (66%) of Ii, mp 241° dec; nmr (DMSO-d_6): δ 9.13 (4H, picryl protons), 11.27 (2H, broad, amino protons).

Anal. Calcd. for $C_{14}H_6N_{12}O_{12}$: C, 31.47; H, 1.13; N, 31.46. Found: C, 31.26; H, 1.13; N, 31.24.

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