Heterocycles. LXXXII. Some Investigations on 1,2,3-Benzotriazines

B. Stanovnik and M. Tišler

Department of Chemistry, University of Ljubljana, Ljubljana, Yugoslavia

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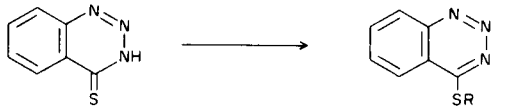
Various 4-substituted 1,2,3-benzotriazines (**2**, **6**, **7**) have been prepared and of particular interest was the 4-azido derivative (**11**) as a potential azidotetrazolo tautomerism exhibiting compound. However, no such interconversion could be established and this compound exists exclusively in the azido form. 2,5-bis-(Arylamino)-1,3,4-thiadiazoles (9) have been found to result from the reaction between 4-hydrazino-1,2,3-benzotriazine and aryl isothiocyanates. In addition, a ring opening reaction between 4-hydrazino-1,2,3-benzotriazine gave 2-(tetrazol-5″-yl)-2′,4′-dihydroxyazobenzene (**10**) and photochemical conversion of the 4-azido derivative gave *s*-tetrazino-[2,3-*b*:5,6-*b*′]diindazole (12).

Previous investigations on azido-tetrazolo isomerizations of various heterocyclic systems (1) prompted us to investigate the possibility of such interconversions in the hitherto unknown 4-azido-1,2,3-benzotriazine. In view of the predisposition of 1,2,3-benzotriazines to undergo reactions of ring cleavage (the ring system is frequently referred as to possess masked diazonium character) (2), some reactions involving a 4-substituent were also investigated.

1,2,3-Benzotriazine-4(3*H*)thione (**1**) was converted into several *S*-alkylated derivatives (**2**). Eventual substitution at the nitrogen atom at position 3 was excluded on grounds of negative iodine-azide reaction (3) with all these compounds. 4-Carboxymethylthio-1,2,3-benzotriazine (**2**, R = CH_2COOH), which was not obtainable by direct alkylation of the 4-thione, could be prepared by careful hydrolysis of the corresponding 4-carbethoxymethylthio derivative (**2**, R = CH_2COOEt) at room temperature. Attempted hydrolysis with hot alkali caused complete elimination of the sulfur function and the corresponding 4-oxo compound (**3**) was obtained. In such cases an intramolecular mechanism or intermolecular bifunctional catalysis has been postulated (4).

In an attempt to prepare the parent heterocyclic system, several methods were tried. In one of them, the 4-benzylthio compound (**2**, R = CH_2Ph) was treated with palladium on charcoal at room temperature for 24 hours, but the compound remained unchanged. Similarly, the catalytic elimination of the 4-hydrazino group, as described by Albert (5), led only to decomposition. Several attempts to oxidize *S*-alkyl derivatives failed to give identifiable products, an exception being the 4-(2′,4′,6′-trinitrophenylthio) compound (**2**, R = $C_6H_2(NO_2)_3$) which afforded with hydrogen peroxide a product, characterized by the uptake of one oxygen atom. Since the ir spectrum showed no bands characteristic for the presence of a sulfoxy



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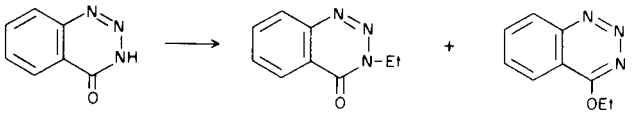

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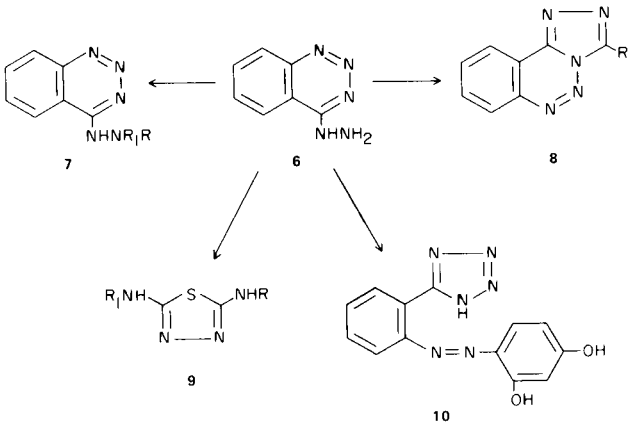
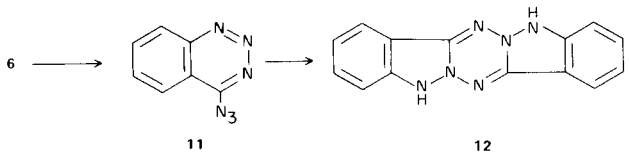
group (6) and the mass spectrum showed an intense peak at m/e = M-244, corresponding to the loss of the 2,4,6-trinitrophenylthio moiety, the product is most adequately represented as the *N*-oxide. This reaction is understandable also if one takes into account both the shielding of the sulfide *S*-atom by both *ortho* nitro groups and the calculated electron density (7) which predicts positions 3 and 1 to be most susceptible to such attack.

Alkylation of cyclic amides with oxonium salts has been claimed (8) to furnish exclusively the corresponding *O*-alkyl derivatives. In our hands, however, reaction between 1,2,3-benzotriazin-4(3*H*)one (**3**) and triethyloxonium fluoroborate led to a mixture of the *N*-ethyl (**4**) and *O*-ethyl (**5**) compounds in a ratio of about 3:1 as evaluated from the nmr spectrum of the product.

4-Hydrazino-1,2,3-benzotriazine (**6**) could be transformed into *s*-triazolo[4,3-*c*]-1,2,3-benzotriazine (**8**, R = H) or its 3-amino analog (**8**, R = NH_2) by means of





diethoxymethyl acetate or cyanogen bromide. This ring system was recently obtained by Potts and Brugel (9), however from a triazole precursor. A similar attempt to generate the fused imidazo ring from 4-amino-1,2,3-benzotriazine was unsuccessful. Although 4-hydrazino-1,2,3-benzotriazine reacted with phenyl isocyanate as anticipated to give the corresponding semicarbazide derivative (**7**, R = H, R_1 = CONHPh), an analogous reaction with phenyl isothiocyanate took a completely different route and 2,5-bis-(anilino)-1,3,4-thiadiazole (**9**, R = R_1 = Ph) was identified as the final product. Its formation can be envisaged by the formation of a thiosemicarbazide derivative which is then decomposed to **9**. This is consistent with the finding that with *p*-methylphenyl isothiocyanate the corresponding unsymmetrical thiadiazole (**9**, R = Ph, R_1 = *p*-Me-C_6H_4-) was obtained. An intermediate benzoazetine can be postulated and this formation from 1,2,3-benzotriazines has been observed by Burgess and McCullagh (10) who obtained stable *N*-phenylbenzoazetine from 3-phenyl-4*H*-1,2,3-benzotriazine upon irradiation.

Application of the common procedure for conversion of a hydrazino into the azido group by reaction of nitrous acid on 4-hydrazino-1,2,3-benzotriazine did not give the expected azide. Instead, a solution of the diazonium salt, generated by ring opening of the triazine ring, was obtained and after addition of resorcinol the red azo dye (**10**) was precipitated. It is rather surprising that ring opening occured under relatively mild conditions since it is known that for the formation of a diazonium group with related 1,2,3-benzotriazines heating at about 100° in polar organic solvents is required (11). 4-Azido-1,2,3-benzotriazine (**11**) was finally obtained by treating the hydrazino derivative (**6**) with amyl nitrite in glacial acetic acid. The azido compound revealed a strong azide band in its ir spectrum and the azidotetrazolo equilibrium is completely on the azide side as judged from the nmr spectrum which revealed no changes when different solvents were used. The azide group could be displaced in a nucleophilic reaction with sodium ethyl thioglycollate. When irradiated it was transformed into a colourless product, which is best represented with structure **12**. It is worthwhile to mention that similar products, triazinoindazoles, were observed to result from thermal decomposition of an azido group of *o*-azidophenyl-*s*-triazines (12).

EXPERIMENTAL (13)

2-Aminothiobenzamide was best prepared by a modification of the procedure by Fairfull *et al.* (14). Into a solution of 2-aminobenzonitrile (24 g.) in pyridine (16 ml.) and triethylamine (33 ml.) hydrogen sulfide was introduced for 2 hours, the mixture was poured into water (200 ml.) under stirring and the crystals which were separated were filtered and washed with water. The crude product (yield 26 g., 81%) was enough pure for further work; m.p. 116-120°. It could be crystallized from benzene to give the pure compound with m.p. 120-121° (lit. (15) gives m.p. 121.5°).

1,2,3-Benzotriazine-4(3*H*)-thione (**1**) was prepared according to the procedure of Reissert and Grube (15) with such a modification that the crude product was purified by dissolution in 10% aqueous sodium hydroxide solution and precipitation with 2*N* hydrochloric acid under vigorous stirring. M.p. of this product was 192° and a sample, crystallized from ethanol had m.p. 205-206° (lit. (15) m.p., 187.5°).

4-Methylthio-1,2,3-benzotriazine (**2**, R = Me).

A solution of the thione (**1**, 3.26 g.) in a methanolic solution of sodium methoxide (prepared from 0.46 g. of sodium and 20 ml. methanol) was treated with methyl iodide (1.5 ml.) and the solution was heated under reflux for 10 minutes. Upon cooling and filtration, the solution was evaporated to dryness and the residue was extracted several times with hot benzene. The combined extracts were heated with charcoal, filtered and the solution evaporated to dryness. The product could be purified by dissolution in benzene and precipitation with petrol ether, yield 2.8 g., m.p. 100-101° (lit. (15) m.p., 101-103°).

4-Benzylthio-1,2,3-benzotriazine (**2**, R = $PhCH_2$).

A solution of the thione (**1**, 3.26 g.) in ethanolic sodium ethylate (prepared from 0.46 g. sodium and 40 ml. ethanol) and benzyl chloride (2.52 g.) was heated under reflux for 30 minutes and the solvent was then removed *in vacuo*. The residue was treated with water (50 ml.), the aqueous layer was decanted and the residual red oil crystallized slowly, m.p. 109-110° (from ethanol), yield 2.0 g.

Anal. Calcd. for $C_{14}H_{11}N_3S$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.39; H, 4.57; N, 16.82.

4-Phenacylthio-1,2,3-benzotriazine (**2**, R = CH_2COPh).

A solution of the 4-thione (**1**, 4.1 g.) in methanolic sodium methoxide (prepared from 0.6 g. sodium and 20 ml. methanol) was treated with phenacyl bromide (5 g.) and the mixture was

heated under reflux for 10 minutes. Upon evaporation *in vacuo* to dryness, iced water (20 ml.) was added and the product was collected. For analysis the product was crystallized several times from ethanol using charcoal, m.p. 175°; ir spectrum: 1689 cm^{-1} (CO).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.04; H, 4.09; N, 15.08.

4-Carbethoxymethylthio-1,2,3-benzotriazine (**2**, R = CH_2COOEt).

The compound was obtained in a similar way as described above from the thione (3.26 g.) and ethyl chloroacetate (2.45 g.) in the presence of sodium ethylate. The reaction mixture was filtered hot and from the cold ethanolic solution (10 ml.) the product separated (2.5 g.), m.p. 138-139°; ir spectrum 1730 cm^{-1} (COOEt). For analysis it was crystallized from water, m.p. 139°.

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.94; H, 4.49; N, 16.89.

The same compound was obtained from 4-azido-1,2,3-benzotriazine (**11**) after treatment with the sodium salt of ethyl thioglycollate.

4-Carboxymethylthio-1,2,3-benzotriazine (**2**, Rc = CH_2COOH).

The above ester (**2**, R = CH_2COOEt, 1.25 g.) was left to stand in 2 ml. of aqueous sodium hydroxide (prepared from 0.2 g. in 10 ml. water) at room temperature for 60 hours. Upon filtration the filtrate was acidified with hydrochloric acid (1:1) and the separated product (0.7 g.) was crystallized from water, m.p. 163-165° dec.; ir spectrum: 1721 (COOH) and 2525 cm^{-1} (broad, bonded OH).

Anal. Calcd. for $C_9H_7N_3O_2S$: C, 48.87; H, 3.19; N, 19.00. Found: C, 49.06; N, 3.32; N, 19.09.

If in the above procedure heating was applied, upon acidification of the solution the corresponding 4-one (**3**) was isolated.

2',4',6'-Trinitrophenylthio-1,2,3-benzotriazine (**2**, R = $C_6H_2(NO_2)_3$).

A solution of the thione (**1**, 3.26 g.) in ethanolic sodium ethylate (prepared from 0.46 g. sodium and 25 ml. ethanol) was treated with a solution of picryl chloride (4.95 g.) in tetrahydrofuran (10 ml.) and the mixture was heated under reflux for 5 minutes. The product which separated was collected, washed with ethanol, suspended in water and filtered again. It was crystallized from tetrahydrofuran with addition of some water, m.p. 185° dec.; nmr spectrum (in DMSO-d_6): τ = 0.80 (s, H_3' and H_5') and 1.70 (m, H_5H_6, H_7 and H_8).

Anal. Calcd. for $C_{13}H_6N_6O_6S$: C, 41.71; H, 1.62; N, 22.46. Found: C, 42.18; H, 2.05; N, 22.62.

2',4',6'-Trinitrophenylthio-1,2,3-benzotriazine 3-(or 1-)-Oxide.

The above sulfide (1.42 g.) was suspended in acetic acid (10 ml.), treated with hydrogen peroxide (1.5 ml. of 75%) and warmed to 50°. After standing at room temperature for 4 hours, water was added and the mixture was evaporated to dryness and the residue was then crystallized from acetonitrile and water. The compound had no definite m.p. and upon heating to 275° it slowly charred and decomposed. Nmr spectrum (in deuterio DMSO-d_6) at 99°: τ = 0.85 (s, $H_3'H_5'$) and 2.05 (m, H_5, H_6, H_7, H_8). Mass spectrum: m/e 390 (M^+), m/e 146 (M-244 = trinitrophenylthio).

Anal. Calcd. for $C_{13}H_6N_6O_7S$: C, 39.99; H, 1.55; N, 21.54. Found: C, 40.05; H, 2.03; N, 21.82.

Alkylation of 1,2,3-Benzotriazin-4(3*H*)one with Triethyloxonium Fluoroborate.

To a stirred suspension of 1,2,3-benzotriazin-4(3*H*)one (**15**) (**3**) (0.74 g.) in methylene chloride (50 ml.) triethyloxonium fluoroborate (1.0 g.) in methylene chloride (20 ml.) was added at room temperature. Stirring was continued for 3 hours and the mixture was then set aside for 3 hours. While stirring a solution of potassium carbonate (10 ml. of 50%) was added dropwise, the mixture was filtered, separated and the organic layer was dried over sodium sulfate. The solvent was removed *in vacuo* and the residual oil crystallized (yield 75 mg.); nmr revealed the presence of about 75% of the *N*-ethyl compound (4) and 25% of the *O*-ethyl compound (**5**).

An authentic 3-ethyl-1,2,3-benzotriazin-4(3*H*)one (**4**) (16) had the following nmr spectrum (in deuteriochloroform): τ = 2.05 (m, H_5, H_6, H_7, H_8), 5.46 (q, CH_2CH_3), and 8.45 (t, CH_2CH_3); J_{Et} = 7.5 Hz.

4-Hydrazino-1,2,3-benzotriazine (**6**).

The *S*-methyl compound (**2**, R = Me) (1.77 g.) was dissolved in hot ethanol (10 ml.) and hydrazine hydrate (1 ml. of 100%) was added. Upon short warming the product began to separate (0.85 g.). For analysis it was crystallized from a large volume of ethanol, m.p. 195-196°. (Lit. (17) gives m.p. 188° and lit. (18) gives m.p. 191-192°). The compound is also conveniently prepared directly from 1,2,3-benzotriazin-4(3*H*)thione and hydrazine hydrate (17). The following hydrazones were prepared:

Benzylidene derivatives, m.p. 180° (from ethanol).

Anal. Calcd. for $C_{14}H_{11}N_5$: C, 67.45; H, 4.45; N, 28.10. Found: C, 67.21; H, 4.45; N, 28.10.

Hydrazone of ethyl pyruvate, m.p. 104-105° (from aqueous ethanol).

Anal. Calcd. for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.02. Found: C, 55.61; H, 4.90; N, 27.00.

Hydrazone of glyoxylic acid, m.p. 144-146° dec. (from ethanol).

Anal. Calcd. for $C_9H_7N_5O_2$: C, 49.77; H, 3.25; N, 32.25. Found: C, 49.52; H, 3.28; N, 32.01.

s-Triazolo[4,3-*c*]-1,2,3-benzotriazine (**8**, R = H).

A mixture of (**6**) (2.4 g.), triethyl orthoformate (10 ml.) and diethoxymethyl acetate (3 ml.) was heated under reflux for 5 minutes. Upon cooling the separated product was collected and crystallized from ethanol, m.p. 138° (lit. (9) m.p. 135-136°). Nmr spectrum (in deuteriochloroform): τ = 1.60 (s, H_3) and two multiplets at 2.05 and 1.60 (H_7, H_8, H_9, H_{10}) (ABCD pattern).

3-Amino-*s*-triazolo[4,3-*c*]-1,2,3-benzotriazine (**8**, R = NH_2).

A suspension of **6** (1.61 g.) in methanol (30 ml.) was treated with cyanogen bromide (1.06 g.) and the mixture was heated under reflux for 5 minutes. Upon cooling, triethylamine (1.5 ml.) was added and the product was collected. For purification it was dissolved in hot morpholine, charcoaled and precipitated with addition of water, yield 0.46 g., m.p. 245-246°.

Anal. Calcd. for $C_8H_6N_6$: C, 51.61; H, 3.25; N, 45.14. Found: C, 52.10; H, 3.39; N, 45.67.

1-(1',2',3'-Triazin-4-yl)-4-phenylsemicarbazide (**7**, R = H, R_1 = CONHPh).

A solution of compound **6** (0.8 g.) in *N*,*N*-dimethylformamide (30 ml.) was treated with phenyl isocyanate (0.6 g.) and the mixture was left at room temperature for 24 hours. The solvent was removed *in vacuo* and the residue was crystallized from ethanol, m.p. 204-205°; mass spectrum: M^+ = 280.

Anal. Calcd. for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.99. Found: C, 60.14; H, 4.46; N, 29.82.

2,5-Dianilino-1,3,4-thiadiazole (**9**, R = R_1 = Ph).

A hot suspension of compound **6** (3.22 g.) in ethanol (40 ml.) was treated with a solution of phenyl isothiocyanate (2.7 g.) in ethanol (10 ml.) and the mixture was heated under reflux for 10 minutes. The product was filtered, washed with some ethanol and crystallized from ethanol, yield 3.1 g., m.p. 246°, mixed m.p. with an authentic specimen (19) was undepressed and ir spectra were identical; mass spectrum: $M^+ = 268$. Alternatively *N,N*-dimethylformamide could be used as solvent for this reaction.

Anal. Calcd. for $C_{14}H_{12}N_4S$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.43; H, 4.64; N, 20.98.

2-Anilino-5-(*p*-toluidino)-1,3,4-thiadiazole (**7**, R = Ph, R_1 = *p*-Me-C_6H_4-).

The compound was prepared in the same way as the dianilino analog with the aid of *p*-toluyl isothiocyanate, m.p. 219-220.5° (from ethanol); nmr spectrum (in deuterio dimethylsulfoxide-d_6), τ = 2.48 (d, H_2', H_6'), 2.95 (d, H_3', H_5'), 3.05 (m, C_6H_5), 7.73 (s, CH_3); $J_{2'3'} = J_{5'6'}$ = 9.0 Hz; mass spectrum: $M^+ = 282$.

Anal. Calcd. for $C_{15}H_{14}N_4S$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.63; H, 5.03; N, 20.03.

2-(Tetrazol-5″-yl)-2′,4′-dihydroxyazobenzene (**10**).

A stirred and cooled suspension of finely powdered compound **6** (1.61 g.) in glacial acetic acid (20 ml.) was treated with sodium nitrite (0.7 g.). The resulting solution was filtered and the filtrate was added to an alkaline solution of resorcinol. The red precipitate was collected, dissolved in hot ethanol and precipitated with addition of water, m.p. 220-225° dec.; nmr spectrum (in deuterio dimethylsulfoxide-d_6), τ = 2.20 (m, H_3, H_4, H_5, H_6), 3.42 (d, H_3'), 3.68 (q, H_5'), 3.62 (d, H_6'); $J_{3'5'}$ = 2.5 Hz, $J_{5'6'}$ = 8.2 Hz. Mass spectrum: $M^+ = 282$.

Anal. Calcd. for $C_{13}H_{10}N_6O_2$: C, 55.31; H, 3.57; N, 29.78. Found: C, 55.12; H, 3.49; N, 29.79.

4-Azido-1,2,3-benzotriazine (**11**).

A suspension of compound **6** (1.61 g.) in glacial acetic acid (10 ml.) was treated with amyl nitrite (1.5 ml.). Gentle external cooling was applied when the reaction became too vigorous. The reddish brown solution was left to stand on ice overnight. The solid mass was transferred to a Büchner funnel and suction was applied until the accompanying glacial acetic acid melted and was filtered. The residue was dissolved in hot benzene and the compound precipitated with addition of petrol ether, yield 0.5 g. The compound had no definite m.p. and decomposed at about 118° with charring; ir spectrum: 2273 cm^{-1} (N_3); nmr spectrum (in dimethylsulfoxide-d_6), τ = 1.80 and 1.35 (m, $H_5H_6H_7H_8$) (ABCD pattern). In deuteriochloroform no change in spectrum is observed.

Anal. Calcd. for $C_7H_4N_6$: C, 48.84; H, 2.34; N, 48.82. Found: C, 48.98; H, 2.71; N, 48.87.

Photochemical Transformation of 4-Azido-1,2,3-benzotriazine.

The azido compound (**11**, 50 mg.) was dissolved in ethanol (20 ml.) and the solution was irradiated in a Rayonet photochemical reactor at a wavelength of 350 nm until evolution of nitrogen had ceased (about 6 hours). The solvent was removed *in vacuo*, the residue was dissolved in chloroform and purified by thin layer chromatography (on PSC-Fertigplatten Kieselgel 2 mm, F 254, Merck, and a mixture of methanol and chloroform, 1:9). Three spots could be detected: the main with R_f = 0.11 and R_f = 0.64 (trace of 4-azido-1,2,3-benzotriazine) and R_f = 0.81 (traces of unidentified product). The main product was extracted from silica gel with chloroform and the residue, after evaporation of the solvent (32 mg., 85%) had m.p. over 320°; ir spectrum: no azide band; mass spectrum: $M^+ = 262$ (*s*-tetrazino/2,3-*b*:5,6-*b*′/diindazole, **12**).

Anal. Calcd. for $C_{14}H_{10}N_6$: C, 64.11; H, 3.84; N, 32.05. Found: C, 64.02; H, 4.04; N, 32.34.

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