Condensed 1,3,5-Triazines: 1,3,4-Thiadiazolo[3,2-*a*]-1,3,5-triazines and Isoxazolo[2,3-*a*]-1,3,5-triazines

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A convenient route is reported for the synthesis of substituted 1,3,4-thiadiazolo[3,2-*a*]-1,3,5-triazine-5,7-diones and isoxazolo[2,3-*a*]-1,3,5-triazines. Condensation of the appropriately substituted 2-amino-1,3,4-thiadiazole and 3-aminoisoxazole with phenoxycarbonyl isocyanate provides the desired target compounds in fair yield.

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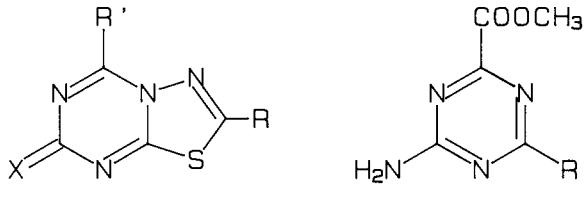
Introduction.

Certain heteroaryl-fused pyrimidinediones (*e.g.* fervenulin), 1,3,5-triazinediones, and structurally related agents display antimicrobial activity, *e.g.* [1-5]. The heteroaryl moiety of these compounds has usually been a six-membered ring. The purpose of this present study was to prepared several new heteroaryl-fused 1,3,5-triazinones where the fused ring is five-membered. Specifically, we undertook the synthesis of several derivatives of 1,3,4-thiadiazolo[3,2-*a*]-1,3,5-triazine (of which very few examples are known) [4,6,7], and of the new ring system isoxazolo[2,3-*a*]-1,3,5-triazine, for purposes of studying their chemical properties, and for their evaluation as antifungal agents. In the one instance where thiadiazolotriazines have been evaluated as potential antimicrobials, 5-substituted 1,3,4-thiadiazolo[3,2-*a*]-1,3,5-triazine-7-thiones were demonstrated to possess significant antifungal activity [4]. We report here some of the preliminary results of our work.

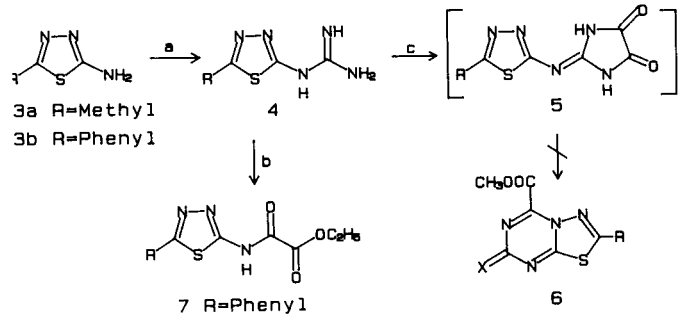
Results and Discussion.

One of the initial targets was **1** where R' = O or substituted NH. Several monocyclic triazines with this substitution pattern have been synthesized *via* 4-carboalkoxy-2-amino-1,3,5-triazine intermediates (*e.g.* **2**) which, in turn, have been prepared by the cyclization of the appropriately substituted guanidines [8-10]. Consequently, **4** was prepared and allowed to react with diethyl oxalate; however, rather than obtaining the desired fused heterocycle **6**, compound **7** was the sole product of this reaction (Scheme 1) as identified by spectral means. In one instance (**7**, R = phenyl), the product was isolated and compared with an authentic sample. A variety of reaction conditions (*e.g.* variation of reaction times and temperatures, different bases to liberate the free base of **4** either prior to the reaction or *in situ*) led us to the conclusions that **4** was prone to decompose to **3** (or was unreactive) under each of the conditions examined, and that once **3** was formed it was probably rapidly acylated to afford **7**. Free bases of guanidine salts are known to be unstable and can decompose to their parent amines upon heating and upon prolonged contact with alkaline media [11]; thus, these results were not totally unanticipated. However, imidazoline-4,5-diones have been proposed as intermediates in the cyclization of guanidines to 1,3,5-triazines with diethyl oxalate [9,10,12]; upon heating in absolute ethanol, these unstable intermediates rearrange to afford the desired triazines. In one instance (*i.e.* Scheme 1, R = CH_3), we were able to prepare what appears to be such an intermediate (*i.e.* **5**, R = CH_3),



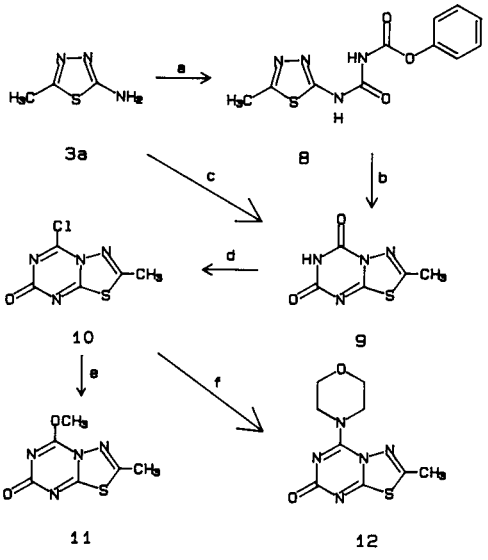
1 X=NH, O

2



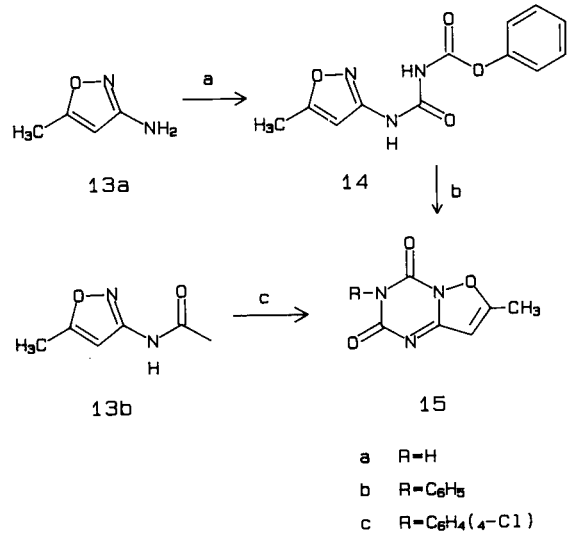
Scheme 1. a: 1) H_2N-CN/HCl, 2) NH_4NO_3. b: NaOEt, $(COOC_2H_5)_2$. c: 1) isolation of **4** as free base, 2) $(COOC_2H_5)_2$.

at 0°, as a white crystalline solid. All attempts to cyclize this intermediate to **6** were unsuccessful. Neither heating nor ethanolysis of **5** provided **6**, but resulted in **3**. However, the ethanolysis reaction was followed by thin layer chromatography (tlc) and it was noted that shortly after the initiation of the reaction, a transient product was formed that co-chromatographed with the free base of **4** (R = CH_3). Consequently, the free base of **4** was prepared by treatment of an aqueous solution of the salt with dilute sodium bicarbonate and extraction with chloroform; tlc analysis of this solution revealed that even at room temperature (in the absence of diethyl oxalate), the presence of **3** was evident within an hour. The inability to prepare **6**, then, is probably related more to the instability of the free base of **4** than to any other factor.



Scheme 2. a: PhOCON=C=O/CH_3CN/heat 2 hours. b: xylenes/heat 6 hours. c: PhO-CO-N=C=O/xylenes/heat 16 hours. d: $PCl_5/POCl_3$. e: CH_3OH/heat 30 minutes. f: morpholine/room temperature.

A more useful approach to the synthesis of the desired compounds is shown in Scheme 2. Addition of phenoxycarbonyl isocyanate to a refluxing solution of the appropriate 2-amino-1,3,4-thiadiazole in acetonitrile affords a product which was identified on the basis of spectral data and elemental analysis as the uncyclized intermediate **8**. The triazine **9** could be prepared by replacing the acetonitrile in the above reaction with xylenes and allowing the reaction to heat at reflux overnight, or by heating the intermediate **8** for 6 hours in xylenes. Compound **9** was converted to the chloro derivative **10** by treatment with a mixture of phosphorus pentachloride and phosphorus oxychloride. Whereas the infrared spectrum of **9** displays carbonyl absorption bands at 1650 and 1770 cm^{-1}, **10** displays a single band at 1760 cm^{-1}. These results are similar to those observed for the spectra of 7-substituted 1,3,4-thiadiazolo-[3,2-*a*]-1,3,5-triazine-5-ones (*i.e.* 1700-1715 cm^{-1}) relative to their 5,7-diones (1680-1700 and 1750-1770 cm^{-1}) [6,7], and structural assignment was made on this basis. The chloro derivative **10** is quite reactive as evidenced by its conversion to **11** upon attempted recrystallization from methanol. The morpholino derivative **12** was also readily prepared by treatment of **10** with morpholine at room temperature.



Similarly, the isoxazolotriazine **15a** was prepared by treatment of 3-amino-5-methylisoxazole (**13**) with phenoxycarbonyl isocyanate (Scheme 3); with acetonitrile as solvent, the intermediate **14** could be isolated. This method of preparation results in triazines that are unsubstituted at the N6-position. Gizycki and Oertel [13] have demonstrated that arylisocyanates react with *N*-acetyl heteroarylamines to produce 1,3,5-triazines (presumably *via* 1,4-dipolar cycloaddition of the arylisocyanate with the isocyanato-heterocycle formed in the course of the reaction). Consequently, we were able to prepare the N6-phenyl (*i.e.* **15b**) and N6-(4-chlorophenyl) (*i.e.* **15c**) derivatives of **15** using this method.

Thus, condensation of appropriately substituted heteroarylamines with phenoxycarbonyl isocyanate provides the corresponding condensed 1,3,5-triazines in one step. Although these compounds are unsubstituted at the N6-position, the method of Gizycki and Oertel [13] can be employed if N6-substituents are desired.

The fused triazine analogs were evaluated for antifungal activity against *Cryptococcus neoformans, Candida albicans, C. tropicalis, C. parasilosis, Aspergillus fumigatus, A. flavus, A. fuma, Sporothrix schenckii, Epidermatophyton floccusum, Trichophyton mentagrophytes, T. tonsurans,* and *T. rubrum* using an agar dilution method [14]. All compounds were inactive at concentrations of up to 100 μg/ml.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared and ^{1}H-nmr spectra were obtained using a Perkin-Elmer 257 spectrophotometer, and a JEOL FX 90Q spectrometer with tetramethylsilane as an internal standard, respectively. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA.

N-(5-Methyl-1,3,4-thiadiazol-2-yl)guanidinium Nitrate (**4a**).

A solution of cyanamide (2.6 g, 60 mmoles), of concentrated hydrochloric acid (3.3 g), and 2-amino-5-methyl-1,3,4-thiadiazole (**3a**) (3.4 g, 30 mmoles) in absolute ethanol (30 ml) was heated at reflux for 6 hours. The solvent was removed under reduced pressure and the resultant viscous liquid was triturated with water (20 ml); after filtration, ammonium nitrate (90 mmoles) was gradually added to the filtrate and the desired product precipitated as a white solid. Recrystallization from water afforded 1.1 g of **4a** as white crystals, mp 128-130°.

Anal. Calcd. for $C_4H_7N_5S\cdot HNO_3$: C, 21.82; H, 3.66; N, 38.17. Found: C, 21.51; H, 3.53; N, 37.98.

N-(5-Phenyl-1,3,4-thiadiazol-2-yl)guanidinium Nitrate (**4b**).

Compound **4b** was prepared from 2-amino-5-phenyl-1,3,4-thiadiazole (**3b**) [15] in the same manner used for the preparation of **4a** and after recrystallization from water, it had mp 153°.

Anal. Calcd. for $C_9H_9N_5S\cdot HNO_3$: C, 38.29; H, 3.57; N, 29.77. Found: C, 37.98; H, 3.50; N, 29.71.

Ethyl *N*-(5-Phenyl-1,3,4-thiadiazol-2-yl)oxamate (**7**, R = Phenyl).

Ethyl oxalyl chloride (1.3 g, 1 mmole) was added dropwise to a stirred solution of **3b** [15] (0.2 g, 1 mmole) and triethylamine (0.2 g, 2 mmoles) in THF (50 ml) at 0°, and the reaction mixture was allowed to stir overnight at room temperature. The solvent was removed *in vacuo* and the residue was recrystallized from ethanol/water (7/3) to give 0.13 g (47%) of the product, mp 190°; ir (potassium bromide): 3270-3300 cm^{-1} (NH), 1750-1680 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.5 (t, 3H, CH_3), 4.5 (q, 2H, CH_2), 7.5-8.1 (m, 5H, aromatic protons), 10.2 (br s, 1H, NH).

Anal. Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.98; H, 3.97; N, 15.16. Found: C, 52.00; H, 4.03; N, 15.06.

N-(Phenoxycarbonyl)-*N'*-(5-methyl-1,3,4-thiadiazol-2-yl)urea (**8**).

Phenoxycarbonyl isocyanate [16] (1.5 g, 9 mmoles) was added dropwise with stirring under a nitrogen atmosphere to a refluxing solution of 2-amino-5-methyl-1,3,4-thiadiazole (**3a**) (0.9 g, 8 mmoles) in acetonitrile (100 ml). After the addition was complete, a thick white precipitate had formed. Heating was continued for another 2 hours, the reaction mixture was filtered hot, and the collected precipitate was washed with hot acetonitrile (50 ml). Recrystallization from ethyl acetate afforded 0.7 g (32%) of **8** as shiney platelets, mp 273-275°; ir (potassium bromide): 3060, 3200 cm^{-1} (NH), 1720-1740 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 2.5 (s, 3H, C_5-CH_3), 3.25 (br s, 1H, NH deuterium oxide-exchangeable), 7.2-7.3 (m, 5H, aromatic protons), 11.1 (br s, 1H, NH deuterium oxide-exchangeable).

Anal. Calcd. for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.62; N, 20.13. Found: C, 47.55; H, 3.65; N, 20.10.

6*H*-2-Methyl-1,3,4-thiadiazolo[3,2-*a*]-1,3,5-triazine-5,7-dione (**9**).

Method A.

A solution of **8** (0.1 g, 0.3 mmoles) in xylene (30 ml) was heated at reflux for 6 hours. The reaction mixture was filtered hot and the collected solid was recrystallized from DMF to give 0.07 g (70%) of **9** as white crystals, mp 279-280°.

Method B.

Phenoxycarbonyl isocyanate (3 g, 18 mmoles) was added dropwise with stirring to a refluxing solution of 2-amino-5-methyl-1,3,4-thiadiazole (**3a**) (1.8 g, 15 mmoles) in xylene (150 ml) under a nitrogen atmosphere. The reaction mixture was heated at reflux overnight, and filtered hot to give 1.5 g (52%) of **9** mp 279° after recrystallization from DMF. The products obtained by method A and method B were identical with respect to chromatographic and spectral properties; ir (potassium bromide): 1650, 1770 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 2.60 (s, 3H, C_2-CH_3), 11.50 (br s, 1H, NH exchangeable with deuterium oxide).

Anal. Calcd. for $C_5H_4N_4O_2S$: C, 32.61; H, 2.18; N, 30.43. Found: C, 32.70; H, 2.19; N, 30.40.

5-Chloro-2-methyl-7-oxo-1,3,4-thiadiazolo[3,2-*a*]-1,3,5-triazine (**10**).

A mixture of **9** (0.4 g, 2 mmoles), phosphorus pentachloride (0.44 g, 2.5 mmoles) and phosphorus oxychloride (50 ml) was heated at reflux for 4 hours. The dark red solution was cooled and the excess phosphorus oxychloride was removed *in vacuo*; ice (100 g) was added to the gummy residue with stirring for 30 minutes. The yellow precipitate that formed was collected by filtration. This solid material was dissolved in chloroform (100 ml) and the solution was filtered. The filtrate was dried (magnesium sulfate) and evaporated to dryness *in vacuo* to give 0.1 g of crude **10**, mp 130-132°; ir: 1760 cm^{-1} (C=O), ^{1}H-nmr (deuteriochloroform): δ 2.6 (s, 3H). This crude product was used without further purification.

5-Methoxy-2-methyl-7-oxo-1,3,4-thiadiazolo[3,2-*a*]-1,3,5-triazine (**11**).

Compound **10** (0.2 g) was heated in methanol (15 ml) for 30 minutes and the clear solution was then allowed to stand at room temperature for 48 hours. The separated yellow solid was collected and recrystallized from methanol to give 0.1 g (50%) of **11** as yellow crystals, mp 150°; ir (potassium bromide): 1765 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 2.6 (s, 3H, C_2-CH_3), 3.35 (s, 3H, OCH_3).

Anal. Calcd. for $C_6H_6N_4O_2S$: C, 36.36; H, 3.05; N, 28.27. Found: C, 36.19; H, 3.07; N, 28.14.

5-Morpholino-2-methyl-7-oxo-1,3,4-thiadiazolo[3,2-*a*]-1,3,5-triazine (**12**).

Morpholine (0.2 g, 2.4 mmoles) was added with stirring to a solution of **10** (0.5 g, 2.5 mmoles) in ethanol (20 ml) at 0°. The reaction mixture was stirred at room temperature overnight. The ethanol was removed *in vacuo* and the brown residue was recrystallized from water to give 0.2 g (33%) of **12** as a yellow powder, mp 170-173°; ir (potassium bromide): 3480-3100, 1750 (C=O) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.4 (s, 3H, C_2-CH_3), 2.6 (q, 4H), 3.4 (q, 4H).

Anal. Calcd. for $C_9H_{11}N_5O_2S\cdot H_2O$: C, 39.85; H, 4.83; N, 25.82. Found: C, 39.69; H, 4.88; N, 25.72.

6*H*-2-Methylisoxazolo[2,3-*a*]-1,3,5-triazine-5,7-dione (**15a**).

Phenoxycarbonyl isocyanate (4.8 g, 30 mmoles) was added dropwise to a stirred solution of **13a** (3 g, 30 mmoles) in acetonitrile (90 ml) under a nitrogen atmosphere. A thick white precipitate formed almost immediately. The reaction mixture was heated at reflux for 2 hours and was allowed to cool to room temperature. The precipitated solid was collected by filtration and recrystallized from acetonitrile to give 2.8 g (37%) of **14** as a white crystals, mp 170°; ir (potassium bromide): 2900-3200 (NH), 1700-1750 (C=O) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 2.4 (s, 3H, CH_3), 6.7 (s, 1H, C_4-H), 7.35 (m, 5H, aromatic protons), 10.0-10.2 (br s, NH).

Compound **14** (2.5 g) was heated at reflux in toluene for 4 hours and the reaction mixture was filtered hot to give 1 g (40%) of **15a** as a white solid, mp 208-210° after recrystallization from methanol; ir (potassium bromide): 1680, 1750 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 6.5 (s, 1H, C_5-H), 9.8-10.0 (br s, 1H, NH).

Anal. Calcd. for $C_6H_5N_3O_3$: C, 43.11; H, 3.01; N, 25.14. Found: C, 43.15; H, 3.14; N, 25.24.

6*H*-2-Methyl-6-phenylisoxazolo[2,3-*a*]-1,3,5-triazine-5,7-dione (**15b**).

A mixture of *N*-acetyl-2-amino-5-methylisoxazole (**13b**) [17] (2.5 g, 1.8 mmoles), phenyl isocyanate (5.3 g, 44.6 mmoles) and anhydrous pyridine (3.5 g) was heated in an oil-bath at 135° for 4 hours. After cooling, anhydrous ether (150 ml) was added and the reaction mixture was stirred for 1 hour. The yellow precipitate was collected and washed thoroughly with

cold ether to give 0.3 g (7%) of **15b** as a white amorphous powder after recrystallization from absolute ethanol, mp 157°; ir (potassium bromide): 1760, 1690 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 2.5 (s, 3H, C_2-CH_3), 6.1 (s, 1H, C_3-H), 7.2-7.4 (m, 5H, aromatic protons).

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.25; H, 3.73; N, 17.27. Found: C, 59.17; H, 3.77; N, 17.24.

6*H*-2-Methyl-6-(4-chlorophenyl)isoxazolo[2,3-*a*]-1,3,5-triazine 5,7-dione (**15c**).

The title compound was prepared in 51% yield using 4-chlorophenyl isocyanate with the procedure described for the preparation of **15b**. The product was obtained as a yellow powder after recrystallization from absolute ethanol, mp 166-168°; ir (potassium bromide): 1750-1690 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d_6): δ 2.6 (s, 3H, C_2-CH_3), 6.45 (s, 1H, C_3-H), 7.4 (m, 4H aromatic protons) ppm.

Anal. Calcd. for $C_{12}H_8ClN_3O_3$: C, 51.90; H, 2.90; N, 15.13. Found: C, 51.97; H, 2.95; N, 15.08.

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REFERENCES AND NOTES

[1] The work presented herein is in partial fulfillment of the requirements for doctoral degree in Pharmaceutical Chemistry from the University of Mansoura for IAS.

[2] H. E. Latuasan and W. Berrends, *Biochem. Biophys. Acta*, **52**, 502 (1961).

[3] R. Samuels and D. J. Stouder, *J. Protozool.*, **9**, 249 (1962).

[4] S. Singh, L. D. S. Yadov and H. Singh, *Indian J. Chem.*, **20B**, 518 (1981).

[5] R. A. Coburn, M. D. Taylor and W. L. Wright, *J. Pharm. Sci.*, **70**, 1322 (1981).

[6] F. Russo, M. Santagati and A. Santagati, *Farmaco, Ed. Sci.*, **33**, 26 (1978).

[7] F. Russo, M. Santagati and A. Santagati, *Farmaco, Ed. Sci.*, **33**, 972 (1978).

[8] M. Furukawa and T. Uede, *Chem. Pharm. Bull.*, **11**, 596 (1963).

[9] S. Hayashi, M. Furukawa, J. Yamamoto and Y. Nishizima, *Chem. Pharm. Bull.*, **16**, 471 (1968).

[10] S. Hayashi, M. Furukawa, Y. Fujino and H. Morishita, *Chem. Pharm. Bull.*, **19**, 1789 (1971).

[11] H. Krall, *J. Chem. Soc.*, **107**, 1396 (1915).

[12] S. Hayashi, M. Furukawa, J. Yamamoto and Y. Nishizima, *Chem. Pharm. Bull.*, **16**, 474 (1968).

[13] U. v. Gizycki and G. Oertel, *Angew. Chem., Int. Ed. Engl.*, **7**, 380 (1968).

[14] S. Shadomy, A. Ingroff and A. Gebhart, *J. Med. Vet. Mycol.*, **23**, 125 (1985).

[15] E. Hoggarth, *J. Chem. Soc.*, 1918 (1949).

[16] A. E. Speziale, L. R. Smith and J. E. Fedder, *J. Org. Chem.*, **30**, 4306 (1965).

[17] K. Hideo and M. Yasuo, *Chem. Pharm. Bull.*, **3**, 270 (1955).