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The Syntheses of Several Pyrimido[4,5-*e*][1,2,4]triazines

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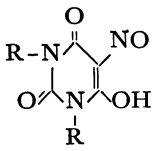
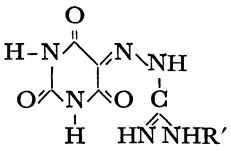
Synopsis. A new synthetic method for some derivatives of pyrimido[4,5-*e*][1,2,4]triazine, using 5-nitrosopyrimidines as the starting materials, was studied. That is, the condensation of 5-nitrosopyrimidin-2,4,6-trione and its methyl derivative with amino- or alkylamino-guanidine gave several 3-aminopyrimidotriazin-6,8-diones.

The discovery and identification of three naturally-occuring antibiotics, Toxoflavin,[1,2] Fervenulin,[3,4] and MSD-92,[5,6] derivatives of pyrimido[5,4-*e*][1,2,4]triazine, have aroused considerable interest in the syntheses and chemistry of these antibiotics and related compounds.[7–10] The isomeric pyrimido[4,5-*e*][1,2,4]-triazine series is also of increasing interest recently[11–14] because certain derivatives of this series have been found to have antiviral activities.[15,16] In this paper we wish to report a convenient method for the synthesis of several derivatives of the latter series, using readily-available 5-nitrosopyrimidines as the starting material.

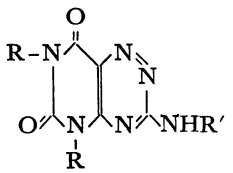
Heating 1,3-dimethyl-5-nitrosopyrimidin-2,4,6-trione (**2**) with 2-amino-1-ethylguanidine in dimethylformamide(DMF) under reflux gave 3-ethylamino-5,7-dimethylpyrimido[4,5-*e*][1,2,4]triazin-6,8-dione(**7**) in a single step. A similar procedure afforded its 3-methylamino analogue(**6**), but failed to give their 5,7-demethyl homologues (**9**, **10**); when 5-nitrosopyrimidin-2,4,6-trione(**1**) was boiled in DMF with 2-amino-1-ethyl(or methyl)guanidine, only dark-colored materials were obtained. However, the treatment of **1** in boiling dil. hydrochloric acid with aminoguanidine afforded alloxane guanylhydrazone(**3**) in a good yield; this cyclized to 3-aminopyrimidotriazin-6,8-dione(**8**)[17] in boiling ammonia. Similarly, its 3-methylamino[17] and 3-ethylamino[18] analogues(**9**, **10**) were made from **1** and 2-amino-1-methylguanidine or the ethyl homologue respectively *via* the corresponding guanylhydrazones(**4**, **5**).



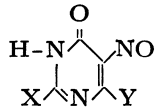
1, R=H
2, R=CH_3



3, R′=H
4, R′=CH_3
5, R′=C_2H_5



6, R=R′=CH_3
7, R=CH_3, R′=C_2H_5
8, R=R′=H
9, R=H, R′=CH_3
10, R=H, R′=C_2H_5



11, X=NH_2, Y=OH
12, X=OH, Y=NH_2
13, X=OH, Y=$NHCH_3$

Attempts to make the 6-amino analogue of **8** from 2-amino-5-nitrosopyrimidin-4,6-dione(**11**) and aminoguanidine in a similar manner resulted only in the formation of **8**; the starting aminopyrimidine inevitably suffered hydrolysis at the initial condensation step under the conditions employed and gave **3**. Similarly, the reaction of 4-amino-5-nitrosopyrimidin-2,6-dione (**12**) or its 4-methylamino analogue(**13**) with aminoguanidine again gave only the same guanylhydrazone (**3**).

Experimental

The analyses were done by the Analytical Section, Meijo University, Nagoya; the UV spectra were measured with a JASCO model ORD/UV-5 spectrophotometer.

*3-Ethylamino-5,7-dimethylpyrimido[4,5-*e*][1,2,4]triazin-6,8-dione (**7**) and its 3-Methylamino Analogue (**6**).* A solution of **2** (3.5 g) and 2-amino-1-ethylguanidine·2HCl (3.5 g) in DMF (40 ml) was boiled under reflux for 1 hr. The subsequent removal of the solvent under reduced pressure and the trituration of the residue with water (10 ml) gave colorless needles (1.3 g) of **7**; mp 267—267.5 °C (from methanol) (Found: C, 45.8; H, 5.0; N, 35.7%. Calcd for $C_9H_{12}N_6O_2$: C, 45.8; H, 5.1; N, 35.6%); λ_{max}^{MeOH} nm (log ε): 338 (3.90), 257 (4.19), and 224 (4.46).

The use of 2-amino-1-methylguanidine·HBr in place of its ethyl homologue in the foregoing condensation gave **6** (36%), mp 290—291 °C (from water) (Found: C, 43.5; H, 4.4; N, 38.0%. Calcd for $C_8N_{10}N_6O_2$: C, 43.2; H, 4.5; N, 37.8%); λ_{max}^{MeOH} nm (log ε); 337 (3.92), 255 (4.19), and 223 (4.49).

*3-Aminopyrimido[4,5-*e*][1,2,4]triazin-6,8-dione (**8**).* A solution of **1** (1.6 g) and aminoguanidine bicarbonate (1.5 g) in 1M–HCl (100 ml) was boiled under reflux for 1 hr. The subsequent concentration under reduced pressure to *ca.* 30 ml and chilling gave **3** as hydrochloride (1.7 g); mp >300 °C (Found: C, 25.6; H, 2.9; N, 36.1%. Calcd for $C_5H_6N_6O_3$·HCl: C, 25.6; H, 3.0; N, 35.8%). The same compound was also obtained from **11** (52% yield), **12** (58% yield), and **13** (55% yield) when these aminopyrimidines were treated with aminoguanidine as above; the structure of the product was confirmed by satisfactory elemental analyses.

A suspension of **3** (hydrochloride, 2.0 g) in 1% ammonia (100 ml) was boiled under reflux for 2 hr. The subsequent acidification with formic acid gave an ivory powder (1.5 g, 93%) of **8**; mp 300 °C (lit,[17] mp>350 °C) (Found: C, 33.1; H, 1.45; N, 46.8%. Calcd for $C_5H_4N_6O_2$: C, 33.1; H, 2.2; N, 46.7%); pK_a 7.08±0.03; λ_{max} nm (log ε) at pH 4.0: 327(3.85) and 244(4.11); at pH 9.3: 335(3.93), 255(sh., 3.93), and 229(4.56).

*3-Methylaminopyrimido[4,5-*e*][1,2,4]triazin-6,8-dione (**9**).* A solution of **1** (3.5 g) and 2-amino-1-methylguanidine·HBr (5.0 g) in 1M–HCl (100 ml) was boiled for 5 hr, and then the solution was treated as above to give **4** as hydrochloride (4.0 g); mp ~300 °C (Found: C, 28.9; H, 3.4;

N, 33.7%. Calcd for $C_6H_8N_6O_3 \cdot HCl$: C, 29.0; H, 3.65; N, 33.8%). Similar treatments of **11**, **12**, and **13** with 2-amino-1-methylguanidine gave the same product (**4**) in 77, 79, and 73% yields respectively.

A suspension of **4** (hydrochloride, 2.5 g) in 1% ammonia (100 ml) was refluxed for 2.5 hr. The resulting solution was acidified with formic acid and chilled to give a colorless powder (1.2 g, 63%) of **9**; mp>300 °C (lit,[17] mp>350 °C) (Found: C, 36.7; H, 3.0; N, 43.5%. Calcd for $C_6H_6N_6O_2$: C, 37.1; H, 3.1; N, 43.3%); pK_a 7.24±0.04; λ_{max} nm (log ε) at pH 4.0: 360(sh., 3.74), 335(3.83), and 254(4.20); at pH 9.6: 360(sh., 3.89), 341(3.96), 265(sh., 3.91), and 235(4.57).

*3-Ethylaminopyrimido[4,5-e][1,2,4]triazin-6,8-dione (**10**).* A solution of **11** (4.0 g) and 2-amino-1-ethylguanidine·HBr (7.0 g) in 1M–HCl (100 ml) was boiled for 5 hr. The subsequent chilling of the solution gave yellow leaflets (2.0 g) of **5** as hydrochloride; mp>300 °C (Found: C, 31.8; H, 4.1; N, 32.3%. Calcd for $C_7H_{10}N_6O_3HCl$: C, 32.0; H, 4.2; N, 32.0%). The heating of **5** with 1% ammonia as above gave **10** (75% yield); mp>300 °C (lit,[18] mp >350 °C) (Found: C, 40.9; H, 3.7; N, 41.2%. Calcd for $C_7H_8N_6O_2$: C, 40.4; H, 3.9; N, 40.4%).

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