

BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48(2), 725—726 (1975)

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

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(Received July 1, 1974)

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-occurring antibiotics, Toxoflavin,^{1,2)} Fervenuin,^{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 recently¹¹⁻¹⁴⁾ 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-methylamino¹⁷⁾ and 3-ethylamino¹⁸⁾ analogues (**9**, **10**) were made from **1** and 2-amino-1-methylguanidine or the ethyl homo-

logue respectively *via* the corresponding guanylhydrazones (**4**, **5**).

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 C₉H₁₂N₆O₂: C, 45.8; H, 5.1; N, 35.6%); λ_{max}^{OH} nm (log ε): 338 (3.90), 257 (4.19), and 224 (4.46).

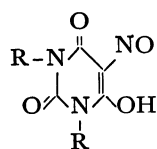
The use of 2-amino-1-methylguanidine·HBr in place of its ethyl homologue in the foregoing condensation gave **6** (36%), mp 290—291 °C (from water) (Found: C, 43.5; H, 4.4; N, 38.0%. Calcd for C₈H₁₀N₆O₂: C, 43.2; H, 4.5; N, 37.8%); λ_{max}^{OH} nm (log ε): 337 (3.92), 255 (4.19), and 223 (4.49).

*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 C₅H₆N₆O₃·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.

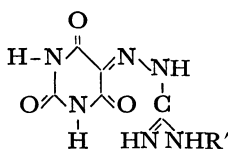
A suspension of **3** (hydrochloride, 2.0 g) in 1% ammonia (100 ml) was boiled under reflux for 2 hr. The subsequent acidification with formic acid gave an ivory powder (1.5 g, 93%) of **8**; mp 300 °C (lit.¹⁷⁾ mp >350 °C) (Found: C, 33.1; H, 1.45; N, 46.8%. Calcd for C₅H₄N₆O₂: C, 33.1; H, 2.2; N, 46.7%); 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).*

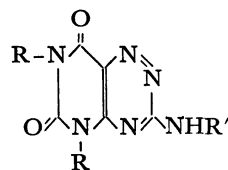
A solution of **1** (3.5 g) and 2-amino-1-methylguanidine·HBr (5.0 g) in 1M-HCl (100 ml) was boiled for 5 hr, and then the solution was treated as above to give **4** as hydrochloride (4.0 g); mp ~300 °C (Found: C, 28.9; H, 3.4;



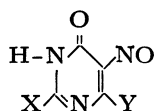
1, R=H

2, R=CH₃

3, R'=H

4, R'=CH₃5, R'=C₂H₅6, R=R'=CH₃7, R=CH₃, R'=C₂H₅

8, R=R'=H

9, R=H, R'=CH₃10, R=H, R'=C₂H₅11, X=NH₂, Y=OH12, X=OH, Y=NH₂13, X=OH, Y=NHCH₃

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 $C_6H_8N_6O_2$: 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%).

References

- 1) A. G. van Veen and W. K. Mertens, *Rec. Trav. Chim. Pays-Bas*, **53**, 257 and 398 (1934).
- 2) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Amer. Chem. Soc.*, **84**, 1724 (1962).
- 3) C. DeBoer, A. Dietz, J. S. Evans, and R. M. Michaels, *Antibiotics Annual*, 220(1959—1960).
- 4) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 5256(1961).
- 5) T. W. Miller, L. Chalet, B. Arison, R. W. Walker, N. R. Trenner, and F. J. Wolf, "Antimicrobial Agents and Chemotherapy," (1963), p. 58.
- 6) E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, **91**, 2143(1969).
- 7) D. J. Brown and R. K. Lynn, *Aust. J. Chem.*, **26**, 1689(1973).
- 8) G. Blankenhorn and W. Pfeiderer, *Chem. Ber.*, **105**, 3334 (1972).
- 9) F. Yoneda and T. Nagamatsu, *Tetrahedron Lett.*, **1973** 1577.
- 10) F. Yoneda and T. Nagamatsu, *J. Amer. Chem. Soc.*, **95**, 5735 (1973).
- 11) D. J. Brown and J. Kershaw, *J. Chem. Soc., Perkin I*, **1972**, 2316.
- 12) E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, **90**, 1374(1968).
- 13) E. C. Taylor and S. F. Martin, *J. Org. Chem.*, **35**, 3792(1970).
- 14) E. C. Taylor and S. F. Martin, *ibid.*, **37**, 3958(1972).
- 15) C. Küchler, W. Küchler, and L. Heinisch, *Arzneim.-Forsch.*, **16**, 1122(1966).
- 16) F. Yoneda, *Kagaku no Ryoiki*, **24**, 1077(1970).
- 17) L. Heinisch, W. Ozegowski, and M. Mühlstädt, *Chem. Ber.*, **97**, 5(1964).
- 18) L. Heinisch, *ibid.*, **100**, 893 (1967).