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A New Synthesis of Pyrimido[4,5-*e*][1,2,4]triazines from 5,5-Dibromopyrimidines

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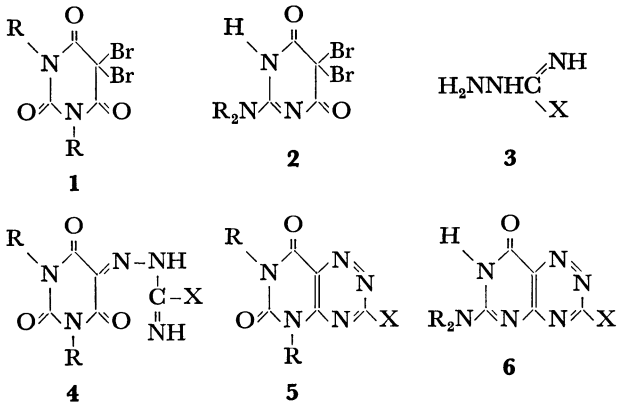
Synopsis. A new method for the synthesis of pyrimido-[4,5-*e*][1,2,4]triazines from 5,5-dibromopyrimidines was studied. Condensation of dibromopyrimidines (**1a, b**) with aminoguanidine or its analogues gave the 6,8-dioxo series (**5**) of the pyrimidotriazine, and aminodibromopyrimidines (**2a, b**) gave the 6-amino-8-oxo series (**6**).

An approach to a pyrimido[4,5-*e*][1,2,4]triazine from a pyrimidine may usually find difficulties in introducing a hydrazino group into the 5-position of the pyrimidine nucleus. In continuing our investigation in the synthesis of pyrimido[4,5-*e*][1,2,4]triazines as a potential antiviral agent,[1] we studied a new synthetic method of the series starting from 5,5-dibromopyrimidines.

The dibromopyrimidine(**1b**)[2] condensed with 1-amino-3-methylguanidine(**3d**) to give a guanylhydrazone(**4q**); this cyclized to 3-methylamino-5,7-dimethylpyrimido[4,5-*e*][1,2,4]triazin-6,8-dione (**5q**)[1] when heated with aqueous ammonia. The analogous treatments of **1b**[2] with **3c** or **3e** gave the corresponding pyrimitriazines(**5p,r**); similarly, their 5,7-demethyl homologues(**5i,j,k**)[1] were made from **1a** and the respective aminoguanidine(**3c,d**, or **e**). The 3-ethylthio- and 3-benzyltio-pyrimidotriazines(**5s,t**) were made from **1b** and *S*-ethyl or *S*-benzyl isothiosemicarbazide(**3f,g**); the use of pyridine in stead of ammonia in the cyclization step gave better yields.

Then, we extended this method to the preparation of 6-aminopyrimidotriazin-8-ones(**6**), which could not be made by other method.[1] The required dibromopyrimidines(**2a,b**) were obtained by the action of bromine on 2-amino(or dimethylamino)-5-nitrosopyrimidin-4,6-dione in ice-cold water. The aminopyrimidine(**2a**), on condensation with **3f** or **3g** in DMF and subsequent cyclization in boiling pyridine, afforded the expected products(**6n,o**); also the dimethylaminopyrimidine(**2b**) and **3d** yielded a pyrimidotriazine (**6q**). The ethylthio ether(**6n**) readily underwent aminolysis to give the 3-amino analogues(**6i,j,k,l**) on heating with an appropriate amine. Similarly, **6o** and hydrazine gave the 3-hydrazino derivative(**6m**); the hydrazino group was easily removed from **6m** by silver oxide[3] to give the 3-unsubstituted 6-aminopyrimidotriazin-8-one(**6h**).



1 **2** **3**

4 **5** **6**

	R	X		R	X
a:	H	—	**k:**	H	NHEt
b:	Me	—	**l:**	H	NMe_2
c:	—	NH_2	**m:**	H	$NHNH_2$
d:	—	NHMe	**n:**	H	SEt
e:	—	NHEt	**o:**	H	SCH_2Ph
f:	—	SEt	**p:**	Me	NH_2
g:	—	SCH_2Ph	**q:**	Me	NHMe
h:	H	H	**r:**	Me	NHEt
i:	H	NH_2	**s:**	Me	SEt
j:	H	NHMe	**t:**	Me	SCH_2Ph

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 and the λ_{max} are given in nm with a log ε in parentheses.

*3-Methylamino-5,7-dimethylpyrimido[4,5-*e*][1,2,4]triazin-6,8-dione (5q) and its analogues (5p, r).* A solution of **1b**[2] (2.8 g) and **3d**·2HCl (1.6 g) in HOAc (50 ml) was stirred at 20 °C for 30 min, then boiled for 5 min. After cooling, the needles were collected and crystallized from 1M-HCl to give **4q**·HCl (3.5 g), mp>300 °C (Found: C, 33.6; H, 4.9; N, 29.4%. Calcd for $C_9H_{14}N_6O_3HCl\cdot0.5H_2O$: C, 33.6; H, 4.9; N, 29.4%). Refluxing of **4q** (3.0 g) in 1% ammonia (150 ml) for 3 hr gave **5q** (1.3 g), mp 290—291 °C (from water) (lit.[1] mp 290—291 °C). The same treatments of **1b** with **3e** gave **4r** (79%), mp >300 °C (Found: C, 35.5; H, 5.6; N, 27.7%. Calcd for $C_9H_{14}N_6O_3HCl\cdot0.5H_2O$: C, 35.6; H, 5.45; N, 27.7%); **4r** was converted to **5r** (31%), mp 267—268 °C (from MeOH) (lit,[1] mp 267—268 °C). In the analogous manner, **5p** was obtained in 37% yield, mp>300 °C (lit,[4] mp 363—365 °C dec.) (Found: C, 40.0; H, 3.2; N, 40.3%. Calcd for $C_7H_8N_6O_2$: C, 40.4; H, 3.9; N, 40.4%); λ_{max}^{MeOH}: 221 (4.57), 247 (4.14), and 329 (3.99).

*3-Aminopyrimido[4,5-*e*][1,2,4]triazin-6,8-dione (5i) and its analogues (5j, k).* These compounds were made from **1a**[2] and the respective aminoguanidines (**3c, d, e**) by an analogous method as above in 40, 55, and 34% yields respectively; all gave satisfactory elemental analyses and were identified with the authentic samples.[1]

*3-Ethylthio(and benzylthio)-5,7-dimethylpyrimido[4,5-*e*][1,2,4]-triazin-6,8-diones (5s, t).* A suspension of **1b** (0.60 g) and **3f**·HBr (0.50 g) in HOAc (20 ml) was treated as above. Evaporation under reduced pressure gave a yellow solid; this compound was heated in pyridine (40 ml) under reflux for 20 min. Evaporation and recrystallization from water gave **5s** (0.30 g), mp 146.5—147.5 °C (lit,[5] mp 146—147 °C); λ_{max}^{MeOH}: 237 (4.32), 260 (sh., 4.06), and 340 (4.00). A similar treatment of **1b** with **3g** gave **5t** (85%), mp 201—202 °C (from H_2O–EtOH) (Found: C, 53.4; H, 3.95; N, 22.5%. Calcd for $C_{14}H_{13}N_5O_2S$: C, 53.3; H, 4.15; N, 22.2%); λ_{max}^{MeOH}:

238 (4.36), 260 (sh., 4.13), and 339 (4.05).

6-Amino-3-ethylthio(and benzylthio)pyrimido[4,5-e][1,2,4]triazin-8-ones (6n, o). Bromine (26 g) was added dropwise to a vigorously stirred suspension of 2-amino-5-nitrosopyrimidin-4,6-dione (12 g) in ice-cold water (50 ml) during 30 min. The colorless solid (17.2 g) was collected, washed with water, and dried over P_2O_5. The product could not be purified satisfactorily for elemental analysis owing to its instabilities. A solution of the dibromopyrimidine (9.0 g) and **3f**·HBr (6.5 g) in DMF (100 ml) was stirred at 20 °C for 30 min. The solution was diluted with pyridine (100 ml) and refluxed for 2 hr, followed by filtration while hot. The filtrate, on evaporation under reduced pressure and subsequent trituration with water, gave **6n** (3.2 g), mp>300 °C (by reprecipitation)(Found: C, 37.6; H, 3.4; N, 37.75%. Calcd for $C_7H_8N_6OS$: C, 37.5; H, 3.6; N, 37.5%); pK_a 6.72±0.06; λ_{max} at pH 4.1: 261 (4.48) and 353 (3.99); at pH 10.4: 253 (4.53) and 352 (3.99).

Replacing **3f** by **3g** in the foregoing condensation gave **6o** (73%), mp >300 °C (by reprecipitation) (Found: N, 28.4%. Calcd for $C_{13}H_{10}N_6OS$: N, 28.2%); pK_a 6.72±0.03; λ_{max} at pH 4.0: 261 (4.47) and 354 (4.03); at pH 11: 255 (4.54) and 354 (4.04).

6-Dimethylamino-3-methylaminopyrimido[4,5-e][1,2,4]triazin-8-one (6q). 5,5-Dibromo-2-dimethylaminopyrimidin-4,6-dione (**2b**) was made from its 5-nitroso precursor and bromine in 70%. The dibromopyrimidine (**2b**) and **3d**, on treatments in a similar way for the 2-oxy analogue (**5j**), gave **6q** (37%), mp>300 °C (from water) (Found: C, 43.6; H, 5.0; N, 44.2%. Calcd for $C_8H_{11}N_7O$: C, 43.4; H, 5.0; N, 44.3%); pK_a 7.60±0.02; λ_{max} at pH 4.0: 247 (4.62) and 352 (4.02); at pH 10.0: 238 (4.56), 265 (sh., 4.04), and 368 (4.11).

3,6-Diaminopyrimido[4,5-e][1,2,4]triazin-8-one (6i) and its 3-alkylamino analogues (6j, k, l). A solution of **6n** (0.50 g) in 30% ammonia (10 ml) was heated in a sealed tube at 140 °C for 10 hr. Evaporation and subsequent trituration with dil. formic acid gave **6i** (0.30 g), mp >300 °C (from water) (Found: C, 33.5; H, 2.8%. Calcd for $C_5H_5N_7O$: C, 33.5; H, 3.2%); pK_a 8.05±0.05; λ_{max} at pH 4.0: 232 (4.54) and 346 (3.91); at pH 10.2: 227 (4.46), 245 (sh, 4.25), and 339 (4.00). The use of methylamine, ethylamine, or dimethylamine in the foregoing aminolysis gave the corresponding analogues: **6j** (93%), mp >300 °C (Found: C, 36.55; H, 3.5; N, 49.2%. Calcd for $C_6H_7N_7O\cdot0.2H_2O$: C, 36.6; H, 3.8; N, 49.8%); pK_a 7.86±0.05; λ_{max} at pH 4.1: 241 (4.59) and 345 (3.90); at pH 12: 237 (4.63) and 347 (3.99). The 3-ethylamino derivative (**6j**) was obtained in 76% yield, mp >300 °C (Found: C, 39.8; H, 4.4; N, 45.4%. Calcd for $C_7H_9N_7O\cdot0.3H_2O$: C, 39.55; H, 4.55; N, 46.1%); pK_a 8.08±0.04; λ_{max} at pH 11.0: 249 (4.60) and 346 (3.98). The 3-dimethylamino analogue (**6l**), obtained in 65% yield, had mp >300 °C (Found: C, 40.05; H, 4.3; N, 46.5%. Calcd for $C_7H_9N_7O\cdot0.2H_2O$: C, 39.9; H, 4.5; N, 46.5%); pK_a 7.94±0.02; λ_{max} at pH 4.0: 250 (4.50), 270 (sh., 4.19), 353 (3.77), and 380 (sh., 3.68); at pH 10.1: 242 (4.58) and 351 (3.87).

6-Aminopyrimido[4,5-e][1,2,4]triazin-8-one (6h). A mixture of **6o** (1.5 g), hydrazine hydrate (10 ml), and pyridine (100 ml) was refluxed for 6 hr. Chilling gave a solid (0.70 g), which was stirred with silver oxide (4 g) in water (300 ml) at 30 °C for 10 hr. Filtration and concentration to *ca.* 30 ml gave **6h** (0.18 g), mp >300 °C (from water) (Found: C, 32.7; H, 2.7; N, 45.6%. Calcd for $C_5H_4N_6O$: C, 33.0; H, 3.3; N, 46.1%); pK_a 6.37±0.03; λ_{max} at pH 4.1: 277 (3.90) and 332 (3.68); at pH 10.4: 258 (4.15) and 339 (3.73).

References

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