

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

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(Received February 3, 1975)

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 guanylhyazone (**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 pyrimidotriazines (**5p**, **r**); similarly, their 5,7-dimethyl homologues (**5i**, **j**, **k**)¹⁾ were made from **1a** and the respective aminoguanidine (**3c**, **d**, or **e**). The 3-ethylthio- and 3-benzylthio-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 oxide³⁾ to give the 3-unsubstituted 6-aminopyrimidotriazin-8-one (**6h**).

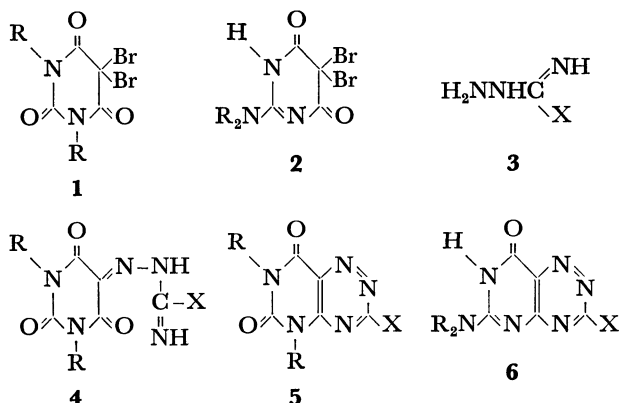
Experimental

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 $\lambda_{\max}$ 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 C₉H₁₄N₆O₃·HCl·0.5H₂O: 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 C₉H₁₄N₆O₃·HCl·0.5H₂O: 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 C₇H₈N₆O₂: C, 40.4; H, 3.9; N, 40.4%; $\lambda_{\max}^{\text{MeOH}}$: 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); $\lambda_{\max}^{\text{MeOH}}$: 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 H₂O-EtOH) (Found: C, 53.4; H, 3.95; N, 22.5%). Calcd for C₁₄H₁₃N₅O₂S: C, 53.3; H, 4.15; N, 22.2%; $\lambda_{\max}^{\text{MeOH}}$:



	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 ₂ Ph
f:	—	SEt	p:	Me	NH ₂
g:	—	SCH ₂ Ph	q:	Me	NHMe
h:	H	H	r:	Me	NHEt
i:	H	NH ₂	s:	Me	SEt
j:	H	NHMe	t:	Me	SCH ₂ Ph

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 $C_6H_7N_7O \cdot 0.2H_2O$: 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 $C_7H_9N_7O \cdot 0.3H_2O$: 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 $C_7H_9N_7O \cdot 0.2H_2O$: 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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